HANDBOOK OF VENOUS AND LYMPHATIC DISORDERS

FOURTH EDITION

Guidelines of the American Venous Forum

Edited by
Peter Gloviczki

Associate Editors
Michael C. Dalsing, Bo Eklöf,
Fedor Lurie, Thomas W. Wakefield

Assistant Editor
Monika L. Gloviczki

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This book is dedicated to

John J. Bergan, MD
FACS, FACPh, FRCS Hon. (Eng.)
1927–2014

Founding Father and First President of the American Venous Forum,
Past President of the Society for Vascular Surgery,
President-Elect of the American College of Phlebology,
An inspiring mentor, innovating scholar, captivating speaker,
and prolific author and editor,
for his visionary leadership and for serving as an
international ambassador of venous and lymphatic disorders.

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Foreword

This fourth edition of the *Handbook of Venous and Lymphatic Disorders: Guidelines of the American Venous Forum* provides a current review and reference source for managing venous and lymphatic clinical challenges. Arranged in seven parts and including 68 chapters, it is comprehensive and up to date. An example is the inclusion of the management of venous trauma under Special Venous Problems. Editor Peter Gloviczki, a widely recognized world leader in managing vascular problems, including those of the venous and lymphatic systems, is assisted ably by co-editors Michael Dalsing, Bo Eklöf, Fedor Lurie, Thomas Wakefileld, and Monika Gloviczki, all of whom have established worldwide credibility in managing venous and lymphatic diseases. Through four editions, this effort has been championed by the American Venous Forum over the past 20 years now, with the support of other organizations, including the Society for Vascular Surgery. Comparison to the first edition emphasizes the expansion and progress in managing venous and lymphatic diseases. It is most appropriate that the editors have dedicated this fourth edition of the *Handbook of Venous and Lymphatic Disorders* to John J. Bergan, the First President of the American Venous Forum. Of many productive members of the American Venous Forum in recent years, John J. Bergan stands at the forefront in championing the management of lymphatic and venous diseases as recognized around the world. As the second President of the American Venous Forum, it was a distinct privilege and pleasure to work closely with and to learn from John J. Bergan.

The first meeting of the European–American Symposium on Venous Diseases in Montreaux, Switzerland, in 1974 revealed the domination of surgeons and physicians from Europe and Latin America in treating venous and lymphatic diseases. Of course, there were a few Americans, including Geza de Takats, John Homan, Robert Linton, and Karl Lofgren, who had an interest in venous diseases in the early part of the twentieth century; however, they were the exceptions. Subsequently, the second meeting of the European–American Symposium of Venous Diseases in Zurich, Switzerland, in 1978 and the third meeting in Acapulco, Mexico, in 1981 stimulated additional interest among physician and surgeons in North America, leading to the fourth meeting in Bethesda, Maryland, in 1987 when, with the support of European leaders, including Leo Widmer of Switzerland and others, in managing venous and lymphatic diseases, the American effort to establish the American Venous Forum was supported under the presidency of John J. Bergan. A fifth European–American Symposium on Venous Diseases was held in 1990 in Vienna, Austria, under the leadership of Hugo Partsch, and it was agreed that this would be the last with phlebological societies established throughout the world.

With the majority of the contributors to the fourth edition of the *Handbook of Venous and Lymphatic Disorders* coming from the membership of the American Venous Forum, this is a testament of the progress made over the past 25 years. Nevertheless, international contributions from long-established experts, including Eberhardt Rabe, Ramesh Tripathi, Peter Neglén, Alun Davies, and Philip Coleridge-Smith, augment and complement the American experience. Just as editors Peter Gloviczki, Bo Eklöf, Fedor Lurie, and others have contributed from both European and American bases, the United States as a "melting pot" continues to welcome contributions from multiple sources. Byung-Boong Lee has had extensive experience in both South Korea and in the United States with diagnosing and managing arteriovenous malformations. International cooperation is noted in this fourth edition, including that of Hugo Partsch, Thomas Proebstle, Oscar Maleti, Marzia Lugli, and Patrick Carpentier.

Everyone involved can be justifiably proud of their accomplishments as represented over the past 25 years and included in this fourth edition of the *Handbook of Venous and Lymphatic Disorders*. As interest in global medicine continues to expand, cooperative international activities such as this will benefit patients around the world.

Norman M. Rich, MD, FACS, DMCC

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Preface

It is with excitement and great anticipation that we present to you the fourth edition of the *Handbook of Venous and Lymphatic Disorders*. Twenty years after the publication of the first edition, jointly edited with James S.T. Yao, the current volume serves as testimony to the remarkable progress that occurred during the past two decades in the evaluation and treatment of acute and chronic venous and lymphatic disorders. From cover to cover, the fourth edition logically progresses from basic considerations, epidemiology, classification, diagnostic evaluation, and imaging studies to current management of the most prevalent venous and lymphatic disorders.

Almost 1 million people in the United States are affected by acute venous thromboembolism, and a third of these will have a frequently fatal pulmonary embolism. This book discusses the latest advances in the evaluation and treatment of these conditions. Medical therapy, including indications and the efficacies of new antithrombotic medications, are presented. Attention is focused on effective, minimally invasive, endovascular techniques to treat acute deep vein thrombosis and pulmonary embolism with catheter-directed thrombolysis, pharmacomechanical and aspiration thrombectomy, and, when needed, venous stenting. Few areas in medicine have progressed as quickly as the minimally invasive outpatient treatment of chronic venous disease. Almost a quarter of the adult United States population has varicose veins, and millions have advanced chronic venous insufficiency. Treatment of this frequently painful and disabling illness has advanced by leaps and bounds by applying endovenous therapies, laser and radiofrequency ablation, liquid and foam sclerotherapy, minimally invasive surgery, or the latest technologies using cyanoacrylate embolization or mechanico-chemical ablations, among others.

An estimated 6–7 million women in the United States suffer from chronic pelvic congestion syndrome. Evaluation and management of this highly prevalent venous syndrome, together with other special venous pathologies, such as May–Thurner syndrome and axillary subclavian venous thrombosis, are presented in great detail in this edition. Chapters on vascular malformation, venous trauma, and the management of venous tumors are included, and the up-to-date management of chronic lymphedema, chylous effusions, and chylous complications is discussed.

Evidence-based clinical practice guidelines for managing the day-to-day practice of venous specialists are the hallmark of this book. This fourth edition includes 300 new guidelines, 105 dealing with the management of chronic venous disorders. The guidelines are aligned with recently published recommendations of the American Venous Forum, the Society for Vascular Surgery, the American College of Chest Physicians, and other important and relevant organizations. An increasing number of randomized controlled studies, many with follow-up periods of five or more years, provide high levels of evidence to guidelines on the management of acute and chronic venous disorders.

Written by the world's foremost venous specialists, leaders of the American Venous Forum, and international authorities, the handbook has become the most important encyclopedic and practical reference for both information and the day-to-day management of venous and lymphatic disorders. Together with our enthusiastic and hard-working group of Associate Editors, including Michael C. Dalsing, Bo Eklöf, Fedor Lurie, and Thomas W. Wakefield, we express our most sincere gratitude to those who have contributed to this volume. We are grateful to our publisher, CRC Press, Taylor & Francis Group in England, to Medical Editor Miranda Bromage, Editorial Assistant Cherry Allen, and to Nick Barber, Project Manager at Techset Composition in Chennai, India, for their efforts, proficiency, and for producing such a beautiful book in such a short time. For her expertise, dedication and unwavering commitment to this project, I am most indebted to Monika L. Gloviczki. Her support and love inspired me enormously.

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Evidence-based guidelines

Evidence-based medicine is the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients.[1] Listing the evidence-based guidelines of the American Venous Forum has been a hallmark of this handbook, and the fourth edition is no exception. At the end of each chapter, a table summarizes the relevant guidelines. The grade of recommendation of a guideline can be **Strong (1)** or **Weak (2)**, depending on the risk and burden of a particular diagnostic test or a therapeutic procedure to the patient versus the expected benefit. The words "**we recommend**" are used for **Grade 1,** strong recommendations, if the benefits clearly outweigh risk and burdens, or vice versa, and the words "**we suggest**" are used for **Grade 2,** weak recommendations, when the benefits are closely balanced with risks and burden. Letters A, B, and C mark the level of evidence (**A: high quality; B: moderate quality; C: low or very low quality**).[2] These guidelines of the American Venous Forum are based on the GRADE system, as was reported previously by Guyatt et al. (Table 0.1).[2] When there are no comparable alternatives to a recommendation or evidence is lacking, the authors and editors have relied on case series supplemented by the best opinion of a panel of experts, and the recommendation was labeled **Best Practice**. Chapter 68 gives a summary of all 300 guidelines presented in this book.

The American Venous Forum, the first academic organization in the United States dedicated exclusively to venous and lymphatic disorders, is committed to promoting research, education, awareness, prevention, and delivery of care. The American Venous Forum, jointly with the Society for Vascular Surgery and other organizations, has long recognized the need to formulate clinical practice guidelines based on scientific evidence in order to aid physicians and patients to receive the best and latest information regarding venous and lymphatic disorders.[4–6] Clinical guidelines, as published in the fourth edition of this handbook, however, should not be used as dogma when a diagnostic test is selected or a therapeutic procedure is performed. Scientific evidence should always be combined with the clinical experience of the physician and the patient's preference (Figure 0.1).[7,8] The correct decision on care requires patient-centered communication skills from the physician, who is well aware of the informed preferences of his or her patient. Optimal patient care requires both evidence-based medicine and shared decision making.[9] The intentions of the authors and editors of this volume were to help with the evaluation and treatment of patients, with the ideals in mind, which were suggested by Dr. William J. Mayo already in 1910, that "The best interest of the patient is the only interest to be considered."

Peter Gloviczki

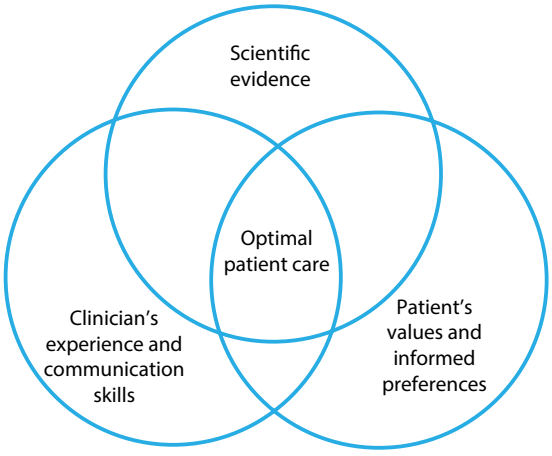

Figure 0.1 A shared clinical decision to select optimal patient care is based on scientific evidence, the clinician's experience and communication skills, and the patient's values and informed preferences.

Table 0.1 Grading recommendations according to evidence

Grade of recommendation/ description	Benefit vs. risk and burdens	Methodological quality of supporting evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very-low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher-quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Source: From Guyatt G, Gutterman D, Baumann MH et al. *Chest* 2006;29:174–81. With permission.
Note: RCT, randomized clinical trials.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
AAGSV	anterior accessory great saphenous vein
AASV	anterior accessory saphenous vein
ACA	anticardiolipin antibodies
ACCP	American College of Chest Physicians
ACH	acetylcholine
ACP	activated protein C
ACT	activated clotting time
ACVRL1	activin receptor-like kinase-1
ADP	adenosine diphosphate
AF	atrial fibrillation
AHA	American Heart Association
AK	above the knee
AM	arterial malformation
AMP	adenosine monophosphate
AP	anterior–posterior
aPE	antiphosphatidylethanolamine
APG	air plethysmography
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
ASA	aspirin
ASD	atrial septal defect
ASVAL	Ablation Selective des Varices sous Anesthesie Locale
ATTRACT	Acute Venous Thrombosis: Thrombosis Removal with Adjunctive Catheter-Directed Thrombolysis trial
AV	axillary vein
AVF	American Venous Forum
AVF	arteriovenous fistula
AVL	anterior vein of the leg
AVM	arteriovenous malformation
AVVS/AVVQ	Aberdeen Varicose Vein Scores or Questionnaire
b.i.d.	*bis in die* = twice daily
BC/BCE	before the current (common) era
bFGF	basic fibroblast growth factor
BK	below the knee
BMI	body mass index
BNP	brain natriuretic peptide
BV	brachial vein
C4b-BP	C4b-binding protein
CA	cyanoacrylate
CAE	cyanoacrylate embolization
cAMP	cyclic adenosine monophosphate
CAPS	catastrophic antiphospholipid antibody syndrome
CaVenT	Catheter-Directed Thrombolysis in Acute Iliofemoral Vein Thrombosis trial
CBS	cystathione β synthase
CBT	catheter-based treatment
CCJ	costoclavicular junction
CD-31	cluster of differentiation-31
CDT	catheter-directed thrombolysis
CDT	complex decongestive therapy
CE	common era
CE	contrast-enhanced
CEAP	C, clinical; E, etiology; A, anatomy; P, pathophysiology
CFD	color-flow duplex ultrasonography
cFN	fibronectin
CFV	common femoral vein
CHIVA	conservative hemodynamic ambulatory treatment of venous insufficiency
CHIVA	Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire
CI	confidence interval
CIV	common iliac vein
CIVIQ	Chronic Venous Insufficiency Questionnaire
CLF	ClosureFast
CM	capillary malformations
cm	centimeter
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CP	ClosurePlus
CPT	current procedural terminology code book
CrCl	creatinine clearance
CRP	C-reactive protein
CS	conventional surgery
CT	computed tomography
CTV	computed tomography venography
CUS	compression ultrasound

CV	contrast venography
CVA	cerebrovascular accident
CVC	central venous catheter
CVD	chronic venous disease
CVI	chronic venous insufficiency
CVM	congenital vascular malformation
CVT	central venous thrombosis
Cx43	Connexin43
CXVUQ	Charing Cross Venous Ulceration Questionnaire
dceMRI	dynamic contrast-enhanced magnetic resonance imaging
DIC	disseminated intravascular coagulation
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DP	dynamic pressure
DTI	direct thrombin inhibitor
DUS	duplex ultrasound
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging
ECG	electrocardiogram
ECM	extracellular matrix
ECMO	extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
ECTR	endothelial cell turnover rate
EGF	epidermal growth factor
EHIT	endovenous heat-induced thrombosis or thrombi
EIV	external iliac vein
EKG	electrocardiography
ELISA	enzyme-linked immunosorbent assay
ELS	elastic compressive stockings
EMMPRIN	extracellular matrix metalloproteinase inducer
EN	enteral nutrition
ENG	endoglin
EPCR	endothelial cell protein C receptor
EPC	endothelial progenitor cell
ePTFE	expanded polytetrafluoroethylene graft
EQ-5D	EuroQol questionnaire
ERK	extracellular signal-regulated kinase
ETA	endothermal ablation
EVF	European Venous Forum
EVL	endovenous laser ablation
EVOH	ethylene copolymer and vinyl alcohol
EVRF	endovenous radiofrequency
FDA	Food and Drug Administration
FGFR-2	fibroblast growth factor receptor-2
FPDL	flashlamp pumped dye laser
FPNI	ferroportin gene
FS	foam sclerotherapy
FSE	free precession sequence
FV	femoral vein
FVIII	factor VIII
FVL	factor V Leiden mutation
FXIII	factor XIII
gal3	galectin 3
gal3bp	galectin 3 binding protein
GFR	glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony stimulating factor
GPIbα	glycoprotein Ibα
GRE	standard gradient recalled echo
GSV	great saphenous vein
GVM	glomuvenous malformation
GWOT	global war on terrorism
HFE	hemochromatosis C282Y
HFVM	high-flow vascular malformation
HGF	hepatocyte growth factor
HHC	hyperhomocysteinemia
HHT	hereditary hemorrhagic telangiectasia
HIF-1	hypoxia inducible factor-1
HIT	heparin-induced thrombocytopenia
HITT	heparin-induced thrombocytopenia and thrombosis
HL/S	high ligation and stripping
HLM	hemolymphatic malformation
HOPE	Heart Outcomes Prevention Evaluation trial
HP	hydrostatic pressure
HR	hazard ratio
HRQL	health-related quality of life
HRT	hormone-replacement therapy
Ht	height
IAC	Intersocietal Accreditation Commission
IBD	inflammatory bowel disease
ICAM-1	intercellular adhesion molecule-1
ICG	indocyanine green
ICU	intensive care unit
IED	improvised explosive device
IF	iliofemoral
IFN-γ	interferon-γ
Ig	immunoglobulin
IJV	internal jugular vein
IL-12p40	interleukin-12p40
IL-1α	interleukin-1α
IL-1β	interleukin-1β
INR	international normalized ratio of prothrombin time of blood coagulation
IPC	intermittent pneumatic compression
IPG	impedance plethysmography
IPL	intense pulsed light
IRR	incidence rate ratio
ISCVS	International Society for Cardiovascular Surgery
ISS	Injury Severity Score
ISSVA	International Society for the Study of Vascular Anomalies
ISTH	International Society of Thrombosis and Hemostasis
ITGA9	integrin α9
IUA	International Union of Angiology
IUP	International Union of Phlebology

IV	iliac vein
IV	intravenous injection
IVC	inferior vena cava
IVUS	intravenous or intravascular ultrasound
JNK	c-Jun N-terminal kinases
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
kDa	kilo-Dalton
kg	kilogram
KO	knockout
KTP	potassium titanyl phosphate
L	liter
LA	lupus anticoagulant
LA-ICGFA	laser-assisted indocyanine green fluorescence angiography
LARA	Laser and Radiofrequency Ablation study
LDS	lipodermatosclerosis
LDUH	low-dose unfractionated heparin
LE	lower extremity
LEDVT	lower extremity deep vein thrombosis
LFA-1	lymphocyte function-associated antigen-1
LFT	liver function test
LFVM	low-flow vascular malformation
LGV	left gonadal vein
LM	lymphatic malformation
LMWH	low-molecular-weight heparin
LRV	left renal vein
LS	liquid sclerotherapy
LV	left ventricle
LVA	lymphaticovenous anastomosis
LVR	lymphovenous reconstruction
MAP kinase/MAPK	mitogen-activated protein kinase
MAUDE FDA	Manufacturer and User Facility Device Experience database
MCP-1	monocyte chemoattractant protein-1
MCT	medium-chain triglyceride
MDCT	multiple detector computed tomography
MHz	megahertz, unit of frequency
MIP-1β	macrophage inflammatory protein-1β
MKK	MAPK kinase
mL	milliliter
MLD	manual lymphatic drainage
mm	millimeter
mmHg	millimeters of Mercury
MMP-1, -2 …	matrix metalloproteinase-1, -2 …
MOCA	mechanochemical endovenous ablation or mechanical occlusion chemically assisted
MRI	magnetic resonance imaging
MRL	magnetic resonance lymphangiography
mRNA	messenger ribonucleic acid
MRV	magnetic resonance venogram
ms	miliseconds
MTFR	methylenetetrahydrofolate reductase
MTHFR	methylenetetrahydrofolate reductase
MT-MMP	membrane-type matrix metalloproteinase
mTOR	mammalian target of rapamycin
MTS	May–Thurner syndrome
MVT	mesenteric venous thrombosis
nBCA or NBCA	N-butyl cyanoacrylate
NCNS	non-central nervous system
Nd:YAG	neodymium-doped yttrium aluminum garnet lasers
NETS	neutrophil extracellular traps
NGAL	neutrophil gelatinase-associated lipocalin
NHS-TAS	National Health Services Health Technology Assessment Survey
NIH	National Institutes of Health
NIVL	non-thrombotic iliac vein lesion
NLN	National Lymphedema Network
nm	nanometer
NOAC	novel oral anticoagulant
NORVIT	Norwegian Vitamin trial
NPV	negative predictive value
NR	non-reported
NS	nutcracker syndrome
NSF	nephrogenic sclerosing fibrosis
NSQIP	National Surgical Quality Improvement Project database
NTNT	non-thermal non-tumescent technique
OC	oral contraceptive
OCP	oral contraception
OR	odds ratio
OTC	over-the-counter drug
PA	pulmonary artery
PAI-1	plasmin activator inhibitor-1
PASTE	post-ablation superficial thrombus extension
PAV	posterior arch vein
PCDT	pharmacomechanical catheter-directed thrombolysis
PCP	pneumatic compression pump
PCP	pre-test clinical probability score
PCS	pelvic congestion syndrome
PCV	post-capillary venule
PD	polidocanol
PDA	patent ductus arteriosus
PDGFR-α and -β	platelet-derived growth factor receptor-α and -β
PE	pulmonary embolism
PEM	polidocanol endovenous microfoam
PERT	Pulmonary embolism response team
PFO	patent foramen ovale
PFV	profunda femoris vein
PIC or PICC	peripherally inserted central catheter
PIN	perforate–invaginate technique of stripping
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis study

PISA-PED	Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis
PMN	polymorphonuclear neutrophil
PN	parenteral nutrition
PP	primary patency rate
PPG	photoplethysmography
ppRb	phosphorylated protein retinoblastoma
PPV	positive predictive value
pRb	protein retinoblastoma
PREVAIT	PREsence of Varices After InTervention study
PRF	pulse repetition frequency
proBNP	prohormone of BNP
PROM	patient-reported outcome measure
PSGL-1	P-selectin glycoprotein ligand-1
PSVs	peak systolic velocities
PT	prothrombin time
PTA	percutaneous transluminal angioplasty
PTFE	polytetrafluoroethylene
PTS	post-thrombotic syndrome
PTT	partial thromboplastin time
PV	perforating vein
PV	popliteal vein
PVI	primary venous insufficiency
PVL	primary venous leiomyosarcoma
PVS	peritoneovenous shunt
PWS	Parkes–Weber syndrome
q.d.	*quaque die* = every day
QoL	quality of life
qPCR	quantitative real-time polymerase chain reaction
RA	right atrium
RBC	red blood cell
RCC	renal cell cancer
RCT	randomized controlled trial
REVAS	recurrent varices after surgery
RF	radiofrequency
RFA	radiofrequency ablation
RFiTT	radiofrequency-induced thermotherapy
RIETE	Computerized Registry of Patients with Venous Thromboembolism
RIJV	right internal jugular vein
rPSGL	PSGL-1 receptor
RR	relative risk
RV	right ventricle
rVCSS	revised Venous Clinical Severity Score
RVF	residual volume fraction
RVO	residual venous obstruction
S&L	stripping and ligation
SA-β-Gal	β-galactosidase
SALP	suction-assisted protein lipectomy
SBP	systolic blood pressure
s-CT	spiral computed tomography
SDF-1	stromal cell-derived factor-1
SEPS	subfascial endoscopic perforator surgery
SEV	superficial epigastric vein
SF-36	Short Form 36-Item health survey
SFJ	saphenofemoral junction
SGP	strain-gauge plethysmography
SIR	Society of Interventional Radiology
SLE	systemic lupus erythematosus
SMA	superior mesenteric artery
SMC	smooth muscle cell
SNP	single nucleotide polymorphism
SNR	signal-to-noise ratio
SOB	shortness of breath
SP	secondary patency rate
SPE	surgical pulmonary embolectomy
SPGR	spoiled gradient recalled echo
SPJ	saphenopopliteal junction
SQ	subcutaneous injection
SSFP	steady-state free precession
SSV	small saphenous vein
STS	sodium tetradecyl sulfate
SVC	superior vena cava
SVI	secondary venous insufficiency
SVS	Society for Vascular Surgery
SVT	superficial vein thrombosis
TAFI	thrombin activatable fibrinolysis inhibitor
Tc-fSC	^{99m}Tc–sulfur colloid
TD	thoracic duct
TDD	mechanical needle disruption technique
TDE	thoracic duct embolization
TED	thromboembolic deterrent stocking
TEE	transesophageal echocardiogram
TF	tissue factor
TGC	time gain compensation
TGF-β1	transforming growth factor-β1
TIA	transient ischemic attacks
TIMP-1	tissue inhibitor of metalloproteinases-1
TIPP	transilluminated powered phlebectomy
TIPS	transjugular intrahepatic portosystemic shunt
TLPS	transarterial lung perfusion scintigraphy
TNF-α	tumor necrosis factor-α
TORPEDO	Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion trial
tPA	tissue plasminogen activator
TREAT	echo-shared angiographic technique
TRICKS	time-resolved imaging of contrast kinetics
TRISS	Trauma Injury Severity Score
TRPV	transient receptor potential vanilloid channel
TSOAC	target-specific oral anticoagulant
TT	thermal tumescent
TVI	total vascular isolation
UE	upper extremity
UEDVT	upper extremity deep vein thrombosis
UFH	unfractionated heparin
UGFS	ultrasound-guided foam sclerotherapy
uPA	urokinase plasminogen activator

uPAR	urokinase plasminogen receptor
US	ultrasound
VAS	visual analog scale
VATS	video-assisted thoracoscopy
VBAS	V block-assisted sclerotherapy
VCAM-1	vascular adhesion molecule-1
VCSS	Venous Clinical Severity Score
VDS	Venous Disability Score
VEGF	vascular endothelial growth factor
VEINES-QOL/Sym	venous insufficiency epidemiologic and economic study of quality of life
VESPA	Venous Enhanced Subtracted Peak Arterial study
VFI_{90}	venous filling $index_{90}$
VFT	venous filling time
VISP	Vitamin Intervention for Stroke Prevention trial
VITRO	Vitamins and Thrombosis trial
VKA	vitamin K antagonist
VLA-4	very late antigen-4
VLNT	vascularized lymph node transfers
VLU	venous leg ulcer
VM	venous malformation
Vn	vitronectin
VP	ventilation–perfusion
VQ	ventilation and perfusion scintigraphy
VSDS	Venous Segmental Disease Score
VT	vein thrombosis
VTE	venous thromboembolism
VTOS	venous thoracic outlet syndrome
VV	varicose vein
VVSymQ	Varicose Vein Symptom Questionnaire
vWF	von Willebrand's factor
WBC	white blood cell
β2-GPI	β2-glycoprotein I
μm	micrometer

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PART 1

Basic Considerations of Venous Disorders

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1

Venous and lymphatic disease: A historical review

CHRISTINE M. DUBBERKE AND RUTH L. BUSH

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…it shows what a distance we have travelled in surgery during the last quarter of a century (19th) and finally it should make us very careful of our written statements, for in a few years they look very ridiculous.

Jerry Moore

1.1 INTRODUCTION

This chapter is an updated historical overview that describes the progression of discoveries and subsequent advancements in both the diagnosis and treatment of venous and lymphatic diseases. Reflection on the historical evolution of medical knowledge is important in order to appreciate how far we have truly come and to realize how far we have left to go. As with all scientific progress, our current understanding of venous and lymphatic diseases is inextricably connected and built upon the advancements of our predecessors. We have the luxury of thousands of years of observation, scientific trials, errors, and discoveries, which have sequentially culminated in creating our current expertise in the field today. We are in an unprecedented era of medical economic conscientiousness superimposed with exponential advancements in technology and medical therapies. Comprehensive data collection is utilized to instantaneously evaluate the unlimited variables in our concerted efforts to discern the efficacy and efficiency of medical interventions, and design the best overall evidence-based, patient-centered therapies. How to promote and execute the continuous improvement of patient care, management, and prevention practices is the challenge we currently face. We are at the frontier of knowledge, yet medical uncertainties, unknown etiologies, and lack of definitive treatments for and prophylaxis of common venous disease is a true testament to how far we have left to go. Before we can address how to produce significant change in the future, we will take a step back and review the major historical chronology in the medical management of venous diseases.

1.2 VARICOSE VEINS AND CHRONIC VENOUS INSUFFICIENCY

1.2.1 Venous disease throughout antiquity

The first descriptions of varicose veins and manifestations of chronic venous insufficiency date back thousands of years. Since the human race has walked on two legs, gravity opposed the venous return of blood to the heart, leading to the development of acute venous thrombosis, varicose veins, and chronic venous insufficiency. Thus, the basic principles underlying the treatment of varicose veins today are shockingly reminiscent of the methods used to treat varicosities in ancient times.

The Ebers Papyrus was written by the ancient Egyptians in around 1550 BCE and is one of the oldest and most important medical papyri. It contains medical descriptions and treatments of varices and describes them as "tortuous, [and] solid with many knots, as if blown up by air."[1] Later, the first surgical textbook was written by Sushruta, an Indian surgeon who lived between 800 and 600 BCE. Several translations from the original Sanskrit reveal that he discussed *siragranthi* or "aneurysms of the veins," and that "straining or exertion by pressure" caused the described varicosities to develop. He also provided one of the first recorded accounts

on the difficulty in treating the associated condition of thrombophlebitis. In his attempts to cure varices, he developed phlebotomy, and described using tree bark-derived astringents (*sandhana*), freeze-induced blood thickening (*skandana*), ash-induced dehydration (*pachana*), and vein cauterization-induced singeing (*dahana*) as ways of achieving hemostasis. Ultimately, he concluded that varices were incurable.[1,2]

The first illustration of varicose veins dates back to the fourth century BCE and is displayed on an ancient Greek votive tablet (Figure 1.1). The stone carving discovered in Acropolis (Athens) shows a twisted swelling extending up the medial side of a massive leg and is believed to have been dedicated to Doctor Amynos, one of the first phlebotomists.

The ancient Greek Corpus Hippocraticum is evidence that Hippocrates (460–377 BCE), the renowned "father of medicine," recognized a correlation between varicose veins and ulceration. Even at a time when the understanding of pathophysiology was extremely limited, he discouraged standing for patients with lower extremity ulcers, explained that varicosities represented "an influx of blood into the veins," and appreciated the importance of firm leg compression treatment by his prescription of bandages.[1,3–5] The doctrine of the four humors (blood, phlegm, yellow bile, and black bile) was the foundation of Hippocrates' medicine and an extremely primitive understanding of circulation physiology, as both veins and arteries were believed to carry air.[3] He recommended alternative treatments, such as small punctures in varicose veins and the use of cautery. Hippocrates faced the same difficulties in treating varices as his predecessor, Sushruta, and wrote,

Figure 1.1 Votive offering leg with varicose veins. Epidauros, Greece, third century BCE. (Available at http://www.hkma.org.)

> What cannot be cured by medications is cured by the knife, what cannot be cured by the knife is cured by the searing iron, whatever this cannot cure must be considered incurable.[3]

One of the earliest attempts at compiling a complete history of medicine was completed in the first century CE by Aurelius Cornelius Celsus (25 BCE–50 CE), a famous Roman encyclopedist. He described the use of compression linen bandages and various types of plaster to treat leg ulcers, and even performed operative phlebectomy via avulsion with a blunt hook or cautery.[1,3] The widely accepted etiology during this era was continuous bidirectional movement of blood and its spirits, which resulted in varices that stored the toxic humors safely outside of the body. The varicosities harboring evil spirits were believed to be benign unless pressed back into the circulation.[1]

Lack of anesthesia and a distorted view of blood circulation did not stop Claudius Galen, a first century (130 CE) Greek physician, from attempting surgical interventions on unsightly varicose veins. Galen elaborated on Celsus's description of varicose vein surgeries, described venesection, and promoted operative avulsion with a blunt hook. He is also credited with advancing the theory of humoral dynamics in a text that would influence Western medicine and surgery for the next 1500 years.[1,5,6] An excerpt of his writing explains:

> In varicose veins of the legs we mark out the whole extent of them by scratches on the outside, then put them on their backs, take hold of the skin surface, and divide that first, then lift up the varicosity with a hook and tie it off, and do the same thing at all the incisions. Or we pull them out with a varicocele hook and cut off the ends, or we pass thread through the coil of the veins with a probe and pull them up and take them out.[2]
>
> If a vein is straight, or though crooked, is yet not twisted, and if of moderate size, it is better cauterized. If a vein is curved and twisted, as it were into intricate coils and involutions, it is better to cut it out.[7]

Byzantine physicians studied the medical treatments and surgical techniques proposed by previous Greek and Roman physicians at the famous Egyptian Alexandrian school of medicine. Finding a surgical cure for varicose veins was of great interest to ancient physicians, despite the relatively limited knowledge concerning the pathophysiology of the disease process. Medical practice and surgery were highly developed from the fourth to sixth centuries CE. As Byzantine medical texts demonstrate, several surgical techniques for varices were widely studied, shared, and practiced by all eminent Byzantine physicians, including Oribasius, Aetius, Alexander of Tralles, and Paul of Aegina. Their collective experiences through study and practice

enabled them to establish the basic principles of vascular surgery and develop new and innovative techniques.[3,7]

Oribasius was one of these notable fourth century CE physicians who advanced the study of varicose veins by consolidating the wisdom learned from the Alexandrian medical school with his own observations, descriptions, and experiences. He wrote two famous medical texts with extensive chapters that meticulously depicted varices and surgical treatment techniques. His works were some of the earliest texts to define varices and detail physical distribution patterns in the head, abdomen, scrotum, and the legs.[7] In his chapter entitled "About the Difficulty in Curing Ulcers which are above Varicose Veins," he suggested venesection via incision along the vein in order to completely empty its contents and allow inflammation and resulting scar tissue to eventually obliterate the vein. This procedure was then followed by the administration of purgatives.[7]

Succeeding Byzantine physicians evaluated the usefulness of previously proposed procedures and advanced their own modifications and observations, developing surgical techniques further. Aetius, a great sixth century CE Byzantine medical writer, was the first to ligate varicose veins.[1] In the seventh century CE, Paulus Aegineta (607–690 CE) improved Aetius's ligation technique by recognizing the importance of great saphenous vein (GSV) ligation and removal.[1] He also advanced other novel modalities, such as the use of tourniquets in preparation for surgery.[3,7] He was followed by Albucasis de Cordova (936–1013 CE), a Muslim surgeon, who was one of the first to report the use of a rudimentary external stripper.[3,6]

1.2.2 From the middle ages to the Renaissance: Abandonment of the humoral theory of disease

By the middle ages, the lack of successful surgical outcomes, along with significant associated morbidity, brought attention to the anatomy of the structures involved in pathophysiologic processes. Guy de Chalice (1298–1368), a French Renaissance surgeon, studied anatomy through dissections, led by Galen's anatomy textbooks.[5] To treat leg ulcers, he developed the predecessor of the modern-day multilayer compression dressing using compression bandages composed of linen and an adhesive plaster made of lead oxide, olive oil, and water.[5] This process, described in his dissertation entitled *Chirurgical Magna*, remained a standard reference in Europe for almost four centuries.[8]

Later, in his detailed anatomy drawings, Leonardo Da Vinci (1452–1519) accurately illustrated the venous system of the legs, including the superficial veins (Figure 1.2).

1.2.3 Sixteenth century

Jeronimus Fabricius d'Aquapendente (1533–1619), a renowned professor of anatomy at the Padua medical school, provided one of the first full descriptions of valves, which he

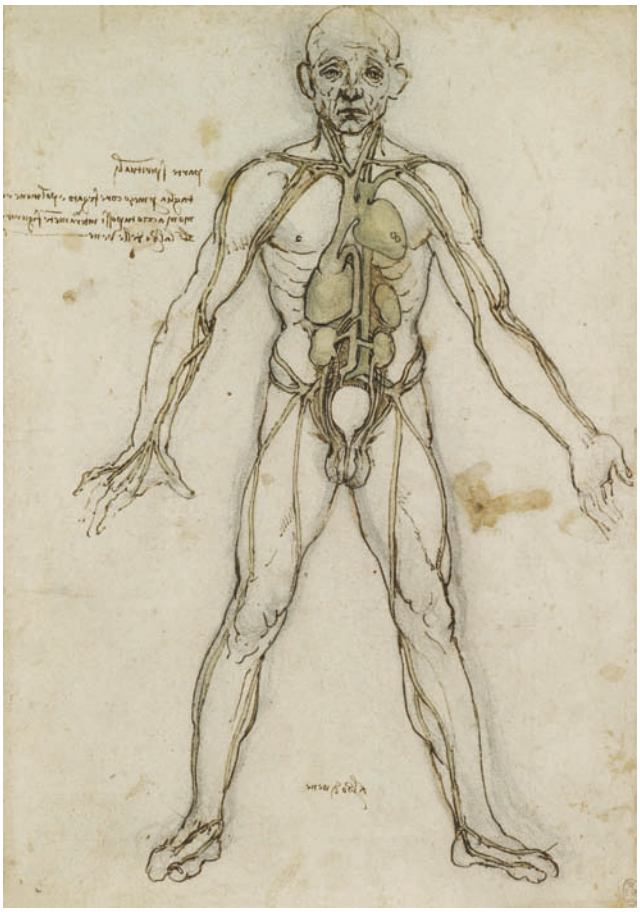

Figure 1.2 Leonardo da Vinci. (From da Vinci L. The major organs and vessels c. 1485–1490 (RCIN 912597). Royal Collection Trust/© Her Majesty Queen Elizabeth II 2016.)

demonstrated at public dissections in 1579. His formal work on venous valves, *De Venarum Ostiolis*, was published in 1603.[3] In 1593, in another text entitled *Opera Chirurgica*, he described the surgical approach to varicose veins. Jeronimus reported the use of multiple ligations above and below the varicosity, and since ligation alone was not adequate, he advocated complete removal of the "gross" blood from the vein via puncture to achieve a successful treatment.[3]

A brilliant French Renaissance surgeon Ambroise Paré (1510–1590) published texts about the treatment of varicose veins.[1] He was one of the first aesthetically conscientious surgeons, as he expressed concern regarding long scars.[3] He was also the first to perform ligation of the internal saphenous vein, described the ligation of varicose veins and the GSV in the thigh, and advocated the use of escharotics to the skin overlying the varix in order to produce thrombosis.[3] The immense pain and lethal complications of sepsis significantly affected the popularity of surgical treatment during this era, so Paré came back to Galen's strategy of noninvasive compressive ulcer treatments. His modifications included local debridement, topical treatment, and cleaning of the ulcer, followed by bandaging of the leg from the foot upwards with a lead plate in his dressing in order to increase local compression.[5] He also incorporated a rigid

diet, purgatives, bleeding, and bedrest into his treatments. However, Paré expressed concern that the healing of an ulcer may cause noxious humors to go elsewhere and cause other serious diseases such as cancer, in contrast to open ulcers, in which the harmful humors had the opportunity to escape the body.

When Paré, the surgeon of Henri II of France, was taken prisoner by Lord Vaudeville at the siege of Hesdin,[5,9] he was promised freedom if he could cure Vaudeville's leg ulcer that had persisted for 6 or 7 years. Paré used his compression method to almost completely heal the ulcer in 15 days, and he was released from captivity.[5,9]

1.2.4 Seventeenth and eighteenth centuries

The monumental discovery that forever changed the understanding of venous physiology came from William Harvey (1578–1657). After extensive study of anatomy under Fabricius d'Aquapendente, he presented the first accurate description of the circulation in 1628. He proved that blood circulates with the heart acting as a pump, and established unidirectional blood flow, made possible by venous valves (Figure 1.3).[3,5] This understanding essentially disproved the theory of humors and influenced further investigation into more sound pathophysiological causes of varicose veins.[5]

Like Hippocrates, Richard Wiseman (1622–1676) believed in an association between varicose veins and ulceration, and is credited with coining the term "varicose ulcer" in 1696.[3,5] He deviated from the tradition of writing about the accredited work of preceding surgeons and focused on describing his personal treatment methods and case histories.[5,10] Early in his career, he performed relatively simple operations of the division and ligation of varicosities above leg ulcers, but was greatly disturbed by the morbidity and suffering that patients endured from surgery. Wiseman realized that not all cases were appropriate for surgical operation, and generally opposed surgical treatment except for extremely severe cases. By searching for noninvasive alternative treatments, he invented the first permanent laced compression stockings, constructed from dog skin leather, which was preferred for its softness and comfort (Figure 1.4). The novelty of these stockings resided in the lace-up feature that provided operator-controlled, variable degrees of compression pressure. Wiseman reported on several patients who were successfully treated with his device, and recognized the palliative nature of the treatment when ulcers recurred after discontinuation of the stockings.[3,5]

An expansion of more sound pathophysiological theories came from Jean Louis Petit (1674–1750), the first director of the Academy of Surgery in Paris. He believed that varicosities were caused by "anything that obstructed the rising blood in the veins."[6] The association of pregnancies as a causative factor of varicosities was also an observation that was made during this era.[3]

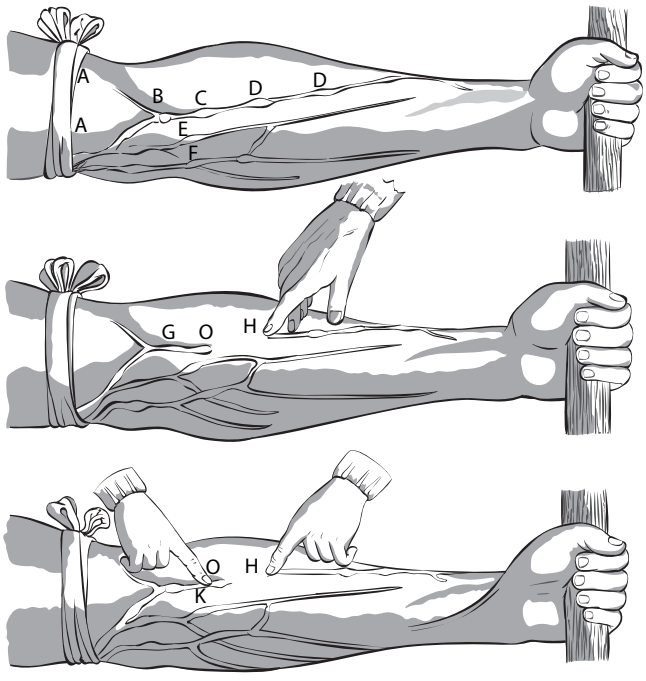

Figure 1.3 Harvey's little vein experiment. (From De Motu Cordis HW. *Scientific Papers: Physiology, Medicine, Surgery, Geology, with Introductions, Notes and Illustrations*, translated by Willis R. The Harvard Classics. P. F. Collier and Son, New York, 1910, vol. 38.)

1.2.5 Nineteenth century

Nineteenth-century scientists and surgeons expressed an increasing need to investigate the underlying pathophysiological causes of varicose veins. Identified mechanisms became the bases of newly developed surgical concepts and resulted in rapid treatment evolution towards the end of the century.

The invention of the hypodermic needle facilitated the very first intravenous sclerotherapy reported by Charles-Gabriel Pravaz in 1840. These experiments, with injections of absolute alcohol and ferric chloride into varicose veins,[3]

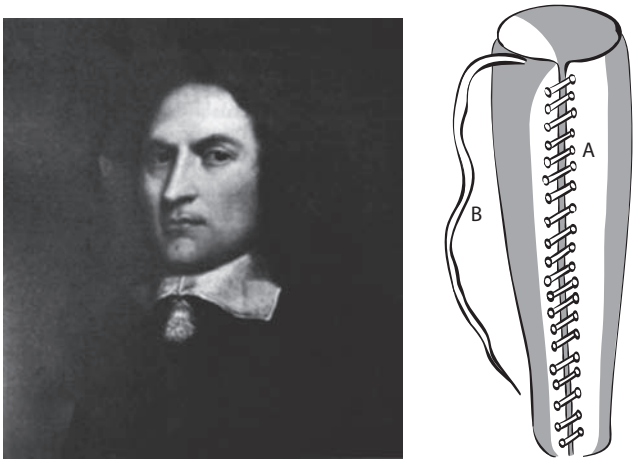

Figure 1.4 Richard Wiseman (1622–1676) and his laced stocking. (From Royle J and Somjen GM. *ANZ J Surg*, 77(12), 1120–1127, 2007.)

were unsuccessful, being complicated by suppurative infection, and were eventually banned. The idea was revisited again at the turn of the twentieth century.

By 1867, the idea of the "varicose ulcer" was adamantly refuted by a London surgeon, John Gay, who publically criticized the causal relationship between varicose veins and ulceration in his famous Lettsomian Lectures. During his meticulous dissections of cadavers with varicose veins, ulceration, pigmentation, and induration, he assimilated considerable knowledge on venous insufficiency. He concluded that ulcers were not invariably associated with visible varicose veins, and emphasized the role of other abnormalities, including arterial disease, as well as the involvement of the deep or communicating venous systems.[1,5] John Gay wrote that the term "varicose ulcer" was misleading, subsequently reclassifying ulcers into three groups in 1868: simple ulcers, venous ulcers (a term he first coined), and arterial ulcers. He was also the first to accurately describe perforating veins of the leg, which paved the way for the modern treatment of varicose veins.[1,5,11]

Until the end of the nineteenth century, the most effective therapy for all forms of venous disease remained leg elevation and compression, as advocated by Wiseman.[12] Even the simplest surgical varicosity operations carried significant danger of infection, commonly followed by septic complications and venous thrombosis. Evaluation of proposed surgical procedures became possible after the acceptance of aseptic surgical techniques and the introduction of safe anesthesia.[5] In 1867, Joseph Lister developed surgical antisepsis, which greatly increased the safety of groin incision by substantially reducing the risk of infection.[3] Around the same time, anesthesiology had greatly improved, with the introduction of spinal and gas anesthesia. The progress of anesthesia and antiseptic techniques advanced the surgical treatment of varicose veins at an unprecedented pace.[3]

Friedrich Trendelenburg (1844–1925), a famous German surgeon, published the original landmark paper on the GSV ligation in 1890, establishing the foundation for modern-day venous surgery.[5] He identified the incompetent GSV as the source of reflux and resultant venous hypertension, which could be eliminated by ligation of the GSV (Figure 1.5). Early ambulation was not enforced due to a fear of mobility causing pulmonary emboli, thus Trendelenburg kept his patients in bed for more than 10 days. Patients were often hospitalized for 5–6 weeks after the procedure, often due to frequent thrombophlebitis and infectious complications.[3,6]

William "Jerry" Moore (Figure 1.5), a surgeon from Melbourne, Australia, modified Trendelenburg's original GSV ligation procedure to a high ligation and division of the GSV just distal to the saphenofemoral junction (SFJ), which is very similar to how it is still performed today (Figure 1.6). He also recommended a short transverse incision 1–2 inches below the Poupart ligament, where the anatomical position of the GSV is relatively constant. He was one of the first surgeons to faithfully use Lister's aseptic surgery principles in order to perform his operations with minimal infectious complications. In 1896, he published an extraordinary paper

Figure 1.5 William Moore, circa 1903. (From Royle J and Somjen GM. *ANZ J Surg*, 77(12), 1120–1127, 2007.)

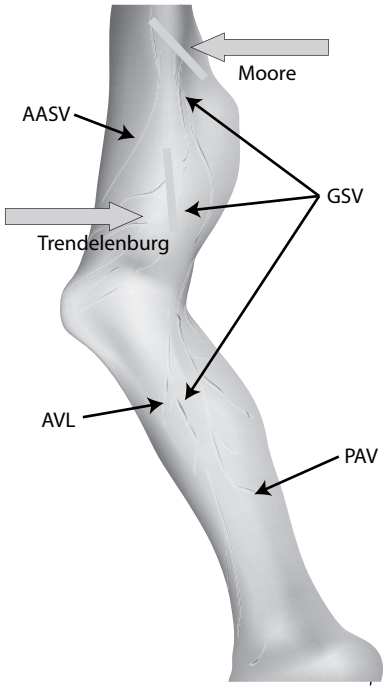

Figure 1.6 The recommended levels of great saphenous vein ligation according to Trendelenburg and Moore. AASV, anterior accessory saphenous vein; AVL, anterior vein of the leg; GSV, great saphenous vein; PAV, posterior arch vein. (From Royle J and Somjen GM. *ANZ J Surg*, 77(12), 1120–1127, 2007.)

in which he quoted Trendelenburg's procedure as an inspiration for his intervention. The article was a comprehensive description of the etiology of varicose veins, listing venous reflux, gravitational force leading to vein dilation, and incompetent, faulty valves of the saphenous vein as factors in the development of varicosities. An important question on of the pathological process was also raised: do faulty valves lead to venous dilatation or does venous dilatation lead to valvular incompetence?[5,12] He reported successful results in the healing of leg ulcers, and that previously engorged veins nearly vanished when surgical elastic bandages were employed after the interventions.[5]

1.2.6 Twentieth century

By the twentieth century, saphenous vein ligation at the SFJ, known as "crossectomy," was routinely practiced, but it was soon realized that recurrence rates were high. In the early 1900s, interest was again peaked in terms of the development of sclerosing agents, and many concoctions were tried but abandoned, due side effects such as allergic reactions, skin sloughing, pain, and even death. Eventually, saphenous vein stripping was added to proximal GSV ligation, which was found to significantly reduce the number of recurrences.[3]

In 1916, John Homans further advanced the pathophysiological classification system of venous diseases originally proposed by Gay. Contrary to popular belief, Homans believed that the surgical treatment of varicose veins and ulcers should be based upon the specific causative anatomical defect.[3] He wrote:

> Surface varix complicated by varicosity of the perforating veins requires for its cure not only eradication of the great saphenous vein, but a thorough exploration of the lower leg in order to ligate varicose perforating veins.[1]

In the 1930s, an engineer named Conrad Jobst, who suffered from varicose veins and chronic ulcerations refractory to sclerotherapy, noticed that his symptoms improved considerably while standing in a pool of water. He realized that graduated pressure counteracted excessive hydrostatic pressure, relieving his symptoms. He designed his own ambulatory gradient compression stockings, and to this day, his invention remains the most important treatment for venous insufficiency.[1,13]

Later, in 1938, Robert Linton significantly advanced the understanding of venous diseases by describing communicating veins and incompetent perforators and their roles in venous ulcer development. He ardently studied the anatomy of these veins, and developed the surgical approaches for the subfascial ligation of medial lower leg communicating veins, known as the "Linton procedure."[1,3] His technique was eventually abandoned due to the unacceptable morbidity associated with the necessary extensive skin incisions.[1,3]

The first use of phlebography by Beberich and Hirsch in 1923 was an important breakthrough in the diagnosis of venous disorders. The first attempt to quantify the degree of venous insufficiency was made using Barber's "blood manometer" in 1925. In this method, an 18-gauge needle was used to obtain direct measurements of lower extremity venous pressure. In 1948, Gunnar Bauer of Sweden developed descending phlebography, which confirmed the high incidence of deep venous system abnormalities in patients with varicose veins and leg ulcers, and showed that abnormalities other than varicosities predisposed individuals to venous insufficiency.[1]

The use of foamed sclerosing agents was introduced in 1939 by Stuard McAusland, when he accidentally produced foam by shaking a bottle that was filled with sodium morrhuate and treated spider veins and telangiectasias with the froth.[3] Sclerotherapy became an accepted treatment for venous insufficiency after his report on using sclerotherapy in 10,000 patients.[1] Egmont James Orbach's 1944 publication entitled *Air-block Technique* described the injection of a small amount of air into the venous segment, displacing the blood in the vein that was to be treated, and inspired today's "foam-block" (air-block with large-bubbled foams), which is still used to treat small veins. The ensuing several decades were peppered with several variations and improvements on sclerosing foams.[3]

Since initial attempts in 1906 by Carrel and Guthrie, the evolution of venous reconstructive surgery remained relatively stagnant until the 1950s, during which arterial surgical techniques were developed, but its progress was still much slower than arterial surgery. Venous disorders have a relatively tolerable insidious development, making them less acute, and not urgently life or limb threatening. Additionally, the pathophysiology of venous insufficiency is complicated and varies with each individual patient, often requiring more than a single, simple procedure. Furthermore, the delicate venous anatomy (collapsible thin-walled vessels with paper-fine valves) added to the complexity and difficulty encountered in venous reconstructive surgery. The first graft using a saphenous vein to bypass an obstructed external iliac vein was performed in 1952. It thrombosed after 3 weeks, but was followed by various other attempts throughout the 1960s. In 1968, Psathakis transformed a segment of the gracilis tendon in order to construct what he called a "substitute valve" for the popliteal vein. This inspired the first reported attempt by Kistner to directly repair incompetent femoral valves in 1975, with successful long-term results. Eventually, in 1979, prosthetic grafts were used in the venous system. Surgeons also began to transplant segments of veins with normal valves in order to replace the diseased veins in the 1980s. Prosthetic grafts were used in the 1990s to reconstruct large veins, including the superior vena cava and iliac veins.[1] Today, venous valve reconstruction treatments, such as valve transplant, valvuloplasty, and endograft valves, are used only selectively. However, surgical vein bypass is an option for patients with severe proximal venous reflux or obstruction after percutaneous intervention has failed, or if percutaneous intervention is not possible. Sclerosing agents became popular again in the 1960s due to the failings and invasiveness

of surgery. The technique of sclerotherapy continued to be adapted and improved upon; however, the lack of consistently reproducible techniques and the variety of preparations made it difficult to compare results and determine the ideal technique.[3]

The treatment of residual varicosities after surgery remained an issue, inspiring Robert Muller, a Swiss dermatologist, to reinvent the stab avulsion phlebectomy technique using instruments that he developed in 1967, initially from half of a broken hemostat. This procedure, known as the "Mullerian ambulatory phlebectomy," was taught to hundreds of physicians. Robert Muller is regarded as the father of modern-day ambulatory phlebectomy and his hooks are still used today.[3]

Duplex scanning, which was introduced in the mid-1980s, rapidly surpassed phlebography as the gold standard for investigating venous reflux. Color duplex imaging arrived in the early 1990s, which required less time for performing scans and demonstrated improved reliability. It facilitated the noninvasive diagnosis and study of the natural history and pathophysiology of venous disease.[3] In 1994, the CEAP classification was developed, with the recognition of the different etiologies and locations of lower extremity venous disease. This classification system defined seven clinical classes according to the clinical signs (C), the etiology (E), the anatomic (A) distribution, and the pathologic (P) mechanism of the venous disease. Severity and disability rating scales were also designated.[1]

1.2.7 Modern varicose vein treatment

Prior to the twenty-first century, varicose veins were conventionally treated with open operations. Today, most venous disorders and resultant venous insufficiency are treated without the need for open procedures. Minimally invasive techniques have forever changed the clinical landscape of varicose vein surgery, and include ultrasound-guided foam sclerotherapy, endovenous laser therapy, and radiofrequency ablation. Newer interventions are continually being developed and will be discussed in later chapters. These procedures can be performed on an outpatient basis and do not require general anesthesia. High patient satisfaction rates are related to the improved quality of life, reduced postoperative pain, fewer complications, and quicker return to work and normal activities.[14] Albeit slightly adjusted, the core surgical principles in the treatment of varicose veins and venous ulcers are applied today in much the same way as they were over 100 years ago. On occasion, traditional surgical methods may be required for patients with recurrent or refractory venous ulceration.[15] Use of foamed sclerotherapy resumed in the late 1990s. Today, sclerotherapy is the treatment of choice for lower extremity telangiectasias, reticular veins, and small varicose veins. The modern sclerosing agents include sodium tetradecyl sulfate, polidocanol, and, occasionally, hypertonic saline.[16] Laser therapy is also used for the treatment of small or facial (cosmetic) telangiectasias.[15]

1.2.8 Modern economic implications of varicose veins and chronic venous insufficiency

The management of venous diseases and their associated sequelae consumes a significant proportion of today's health care budget. Venous diseases should not be considered to be a benign, cosmetic issue. The enormous costs associated with venous diseases are associated with the management of subsequent venous ulceration and complications. Minimally invasive procedures have greatly improved the therapeutic efficiency and health-related quality of life by reducing serious side effects, costs, and postoperative pain.[3] The importance of venous reflux treatment for reducing the risk of recurrent venous ulceration has been clearly demonstrated, and subsequent systematic reviews of health economic analyses have suggested that the early treatment of varicose veins using endovenous procedures performed under local or tumescent anesthesia in the outpatient setting is more cost effective than conservative management in the long run.[17,18] Continued research and economic analyses in this area are needed to confirm this assessment and deliver cost-effective, quality treatment options for patients.[17]

1.2.9 Venous thromboembolism

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Unlike the long history of varicose veins and chronic venous insufficiency, the identification, diagnosis, and treatment of VTE have been relatively recent in the history of medicine. Due to its equivocal clinical findings and its rapidly lethal nature, VTE was unrecognized and untreated for thousands of years, and continues to be a diagnostic and therapeutic challenge today. Although humans have undoubtedly suffered from VTE for thousands of years, the recorded history of DVT treatment begins much more recently in the past 700 years, with major discoveries and progress occurring within the past 100 years.[2,8]

1.2.10 First cases and treatments of DVT: 1271–1700s

It is speculated that the earliest reference to venous thrombosis came from Avicenna (980–1037), an oriental scientist who noted a risk of "particle migration" during vein surgery.[8] In 1271, the first formal description of DVT was written by Guillaume de Saint Pathus. His manuscript describes a 20–year-old Norman cobbler, named Raoul, who presented to a surgeon, Henri de Perche, with unilateral pain and swelling of the right calf. He was initially advised to wait for clinical improvement; however, the pain and swelling progressively extended up to his thigh. After several unsuccessful treatment attempts, the symptoms continued to worsen until the patient eventually developed a leg ulcer. Finally, he was advised to visit the tomb of King Saint

Louis. The cobbler was miraculously healed by applying the Saint's tomb dust directly onto his ulcer, making this the first known case report of DVT.[8]

The number of notified DVT cases increased rapidly, along with proposed pathological hypotheses and treatment attempts. Throughout the middle ages and Renaissance, physicians widely subscribed to the humoral disease theory, and it was believed that DVT was caused by an accumulation of "evil humors." Similarly to many other diseases in the seventeenth to nineteenth centuries, treatment was focused on eliminating these evil humors and restoring the body's natural humoral balance via bloodletting.[8] In spite of a generally erroneous understanding of pathophysiology, Renaissance physicians did notice a correlation between DVT and pregnancy, which was the leading cause of reported DVT during this era. The advised prophylaxis for pregnancy-related DVT was breast feeding, since the cause was suspected to be the retention of unconsumed milk in the legs, commonly referred to as "milk leg."[8,19]

Eventually, the lack of therapeutic efficacy led to the abandonment of the humoral theory of disease. Physicians were puzzled by the large blood clots discovered upon autopsy in the lungs of patients after sudden death. Recognition and scientific interest emerged in 1676 when Richard Wiseman suggested that DVT was caused by an alteration of blood.[2,8,19] In the mid-nineteenth century, Jean Cruveilhier, a renowned French pathologist, elaborated on the exact nature of the blood alteration and published his theory that "phlebitis dominates all of pathology."[2,8,20]

This notion was widely accepted throughout the nineteenth century, with therapy aimed at the symptomatic treatment of infection and associated venous inflammation.[8] DVT management included bloodletting, leech application, cupping, purging, ice application, and cold baths, all in an effort to reduce limb congestion. Targeted anti-infectious agents were quinquona (quinine) used for malaria, mercury used for syphilis, and autumn crocus (colchicine) used for gout. Finally, anti-inflammatory medications and general antiseptics such as zinc chloride were also tried in order to prevent DVT.[8]

Known as the father of modern pathology, Rudolph Virchow (Figure 1.7) made tremendous contributions to our understanding of VTE pathophysiology and initiated the era of cellular pathology. After graduation from medical school and surgical appointment, he was instantly attracted to the autopsy room. At the recommendation of his anatomy professor, he intensely studied Cruveilhier's theory of phlebitis as the cause of all disease. He was curious as to exactly how venous inflammation led to clot formation, and was determined to establish a method of discerning clots formed while living from blood clots formed after death. After extensive laboratory studies, he accurately identified two distinctly different types of thrombus in 1856: the thrombus that forms within a vessel at the site of occlusion and the thrombus that breaks away from its origin and forms an embolus traveling through the bloodstream to occlude pulmonary vessels. Just two years out of medical school, he had discovered the relationship between DVT and fatal PE, coining the term

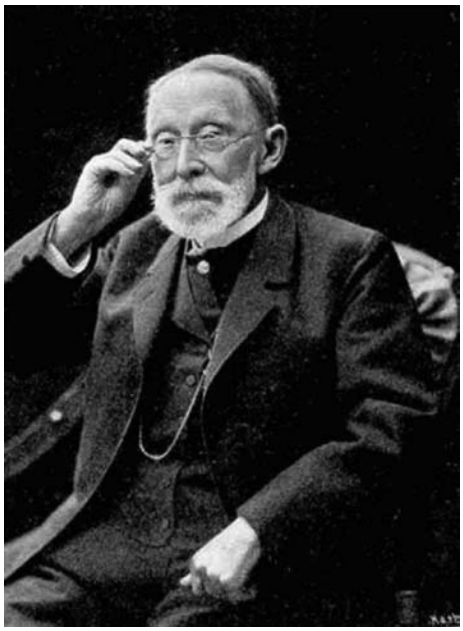

Figure 1.7 Rudolf Virchow, 1902, in the year of his death at the age of 81. (From Bagot CN, Roopen A. *Br J Haematol*, 143(2), 180–190, 2008, four black and white photographs, two diagrams. Database: Image Quick View Collection.)

"embolism." His famous triad (venous stasis, trauma, and hypercoagulability) is still taught and recognized as the most comprehensive explanation of VTE etiology.[2]

Prior to the discovery of anticoagulants, strict bed rest for many weeks was the cornerstone of VTE treatment. The rationale behind this treatment was that during the "acute phase" of DVT, the thrombus was not fixed to the vessel and was at high risk of migration,[8] and the thrombus could be secured in place by restricting movement of the limb. Patients' lower limbs were set in iron splints to prevent movement, and special reclining orthopedic beds were used to optimize venous return. The application of a warm compress was also used to reduce vasospasm and increase collateral circulation.[8] Unfortunately, in addition to actually promoting thrombus formation and extension, prolonged immobilization was frequently associated with serious unpleasant consequences, such as lower extremity joint stiffness (ankyloses) and muscle atrophy (amyotrophia).[8] Late in the nineteenth century, after observing that superficial vein thrombosis quickly vanished with the use of compression bandages, two German phlebologists (Fischer and Lasker) started prescribing compression bandages to their DVT patients. Despite their foresight and the appropriateness of their therapy, their approach was not popular due to the widespread teaching of prolonged bed rest as the most important treatment for DVT.[8]

1.2.11 Evolution of surgical and endovascular VTE treatments

In 1793, John Hunter proposed that DVTs were caused by blood clots causing vein occlusion and attempted the

first surgical treatment in 1784 utilizing venous ligation above a thrombus in an effort to prevent extension of the clot, leading to fatal PE. Subsequently, in 1868, Armand Trousseau, a French surgeon, suggested ligation of the inferior vena cava (IVC) in cases of recurrent PE. This approach was also adopted by Enrico Bottini in 1893.[2] Surgical venous ligations continued to be practiced into the twentieth century, despite their association with a high fatality rate (14%).[8] In 1908, Friedrich Trendelenburg of Leipzig, Germany, performed the very first pulmonary embolectomy via left anterior thoracotomy. This operation was unsuccessfully performed on two patients who were dying from massive PEs.

In the early twentieth century, physicians lacked a truly effective treatment and prophylaxis for fatal PEs. Almost 20 years after Trendelenburg's failed attempts, Marin Kirschner, a student of Trendelenburg, completed the first successful pulmonary embolectomy on March 28, 1924, and thus ushered in the era of surgical PE correction. The intervention was extremely risky, rarely successful, and very few cases were performed worldwide over the next 40 years. However, the invention of the heart–lung machine by John H. Gibbon, Jr. in 1931 made a surgical PE approach more realistic.

On April 18, 1961, Denton Cooley (Figure 1.8) from Houston, Texas, accomplished the first pulmonary embolectomy under extracorporeal circulation in a 37-year-old woman recovering from abdominal hysterectomy.[2] However, even with extracorporeal circulation, there continued to be a tremendous risk of mortality secondary to fatal intraoperative embolisms and high rates of rethrombosis.[8,21] It remained a measure of last resort reserved only for massive, acute PEs or chronic, recurrent PEs resulting in large thrombi wedged in the pulmonary arteries and causing severe pulmonary hypertension.[2] A few years later, in 1969, Dr. Lazar Greenfield suggested a less invasive method of pulmonary embolectomy using a catheter introduced into the femoral vein under fluoroscopic guidance. This technique, known as transvenous catheter embolectomy or thrombo-fragmentation, was associated with a 25% mortality rate and similar indications as open pulmonary embolectomy.[2]

Although the fibrinolytic properties of some substances were studied and reported in the late nineteenth century, thrombolytic agents have been available for medical use only during the past 50 years. In 1947, the first partially purified streptokinase was produced for the treatment of myocardial infarctions; however, the associated toxicity of thombolytics during this era greatly precluded their systemic use.[8,22] In 1953, plasmin and streptokinase were intravascularly infused for the first time in order to treat acute thromboses, including isolated DVTs in volunteer cancer patients with advanced metastasis.[8] Currently, pharmacological thrombolytic agents are the main treatment that is initiated for early thrombus removal. The optimal approach for catheter-directed versus systemic thrombolytic use has yet to be defined, and there are ongoing research studies in this area.[8,23]

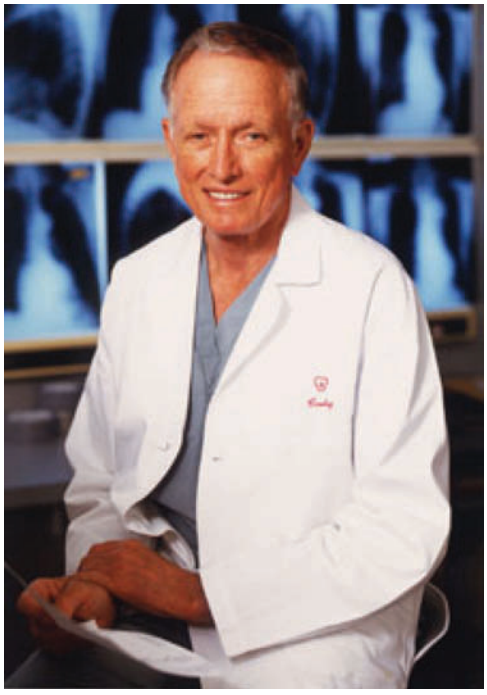

Figure 1.8 Denton A. Cooley, MD, pioneering cardiovascular surgeon and founder of the Texas Heart Institute (http://www.examiner.com/article/a-tribute-to-dr-denton-cooley).

1.2.12 Therapeutic and prophylactic progress—the anticoagulant era: 1920s–1950s

The most important advances in the medical management of DVT occurred in the early twentieth century. Concern shifted from fear of sudden death due to fatal DVT embolism to the less severe complications of VTE, including recurrence and major bleeding. By this time, physicians had finally formed a consensus on Virchow's triad as the pathologic basis of VTE. Before the revolutionary anticoagulation breakthroughs of the 1920s, numerous other ineffective therapeutic options had been tried. Experimental use of antibiotics (sulfanilamide, sulfapyradine, and sulfathiazole), application of leeches, X-ray therapy, mecholyl iontophoresis, and paravertebral lumbar anesthesia, developed by Michael DeBakey in 1939, were all proposed and abandoned. The pathophysiological rationale for the 1940 lumbar sympathetic block was based on venographic series images, which suggested that DVT was accompanied by severe vasospasm.[8] Also in the early 1940s, Drs. Alton Ochsner and Michael DeBakey popularized IVC ligation as the best recurrent PE prophylactic method. However, the sudden interruption of caval venous flow was associated with profound hemodynamic changes, resulting in the post-phlebitic syndrome.[2]

1.2.13 The evolution of prophylactic treatment

Heparin became the thromboprophylactic treatment of choice for DVT in the 1950s, but surgery was still used, notably in cases of severe VTE.[8] In order to reduce surgery-related adverse outcomes, various devices were proposed from the mid-1950s onwards for temporary or partial interruption of the IVC. In the early 1960s, Adams-DeWeese and Miles developed partial IVC occlusion clips that successfully trapped potentially fatal clots without completely occluding blood flow. The clips were very popular throughout the 1960s; however, due to complications, including IVC thrombosis and narrowing, the devices failed to provide substantial clinical improvement. Intraluminal devices were then designed to act as filters.[2,8] DeWeese constructed the first intraluminal "harpgrip" filter in 1958, which could block the transit of emboli without significantly disturbing the function or dynamics of the venous system.[8,21] Although promising results were seen in preventing PE, filter placement required major surgery under general anesthesia. Finally, this problem was solved with the Mobin–Uddin umbrella, which was released for general clinical use in 1970. The device was simply installed via catheter under local anesthesia.[8] Unfortunately, the Mobin-Uddin umbrella also had a high complication rate. In 1969, a new generation of intraluminal filters was introduced by Dr. Lazar Greenfield and Mr. Garman Kimmel, an oil drilling engineer. Modifications of their prototype known as the "Greenfield filter" were widely used for over 25 years.[2] The next phase of development involved retrievable filters, which became available for clinical use only 20 years ago and are still the objects of therapeutic trials.[8]

Without doubt, the best protection against DVT and PE continues to be the identification of high-risk patients and the subsequent implementation of adequate medical anticoagulant prophylactic measures.

1.2.14 The modern era: Ambulatory management of DVT (since 1950)

Diagnostic progress radically modified DVT management. Venography was not consistently used to diagnose DVT until it was standardized in the 1970s. This allowed physicians to treat objectively confirmed DVT. Venography expedited treatment tremendously, even in clinically asymptomatic patients.[8,24,25] Heparin significantly decreased PE mortality, with both its anti-inflammatory and analgesic properties allowing for shorter bed rest recommendations.[8]

Fear of thrombus migration made most physicians reluctant to recommend immediate patient mobilization. Until the early 1990s, ambulation was not recommended and bed rest, often lasting 5–7 days, was still included in DVT treatment.[8,26] The introduction of low-molecular-weight heparin (LMWH) in the 1980s enabled simplification of anticoagulant treatment.[8,27] In 1996, it was demonstrated that LMWH given at home was as safe and effective as hospital-administered unfractionated heparin.[8,26] That same year, a small, randomized trial provided evidence that early ambulation with compression stockings improved pain and counteracted edema without increasing the risk of PE.[8,28] This evidence resulted in the recommendation for early ambulation with compression stockings as a part of standard management.[8] In 1997, compression stockings were shown to be efficacious for preventing post-thrombotic syndrome.[8]

Compared with the conventionally established VTE medications, new oral anticoagulants (factor Xa inhibitors) have shown equivalent or superior clinical benefit with comparable safety. They also have the potential to improve compliance, as they do not need routine monitoring.[8,29–32]

1.2.15 Conclusion: Modern economic implications of VTE treatment and prophylaxis

In spite of diagnostic and therapeutic progress, VTE is still a common and serious medical condition that affects approximately two million people in the United States yearly.[32,33] In 2011, the estimated annual cost of initial and recurrent VTE events was $13.5–$69.3 billion, of which $4.5–$39.3 billion is entirely preventable. VTE prevention recently became a priority of The Joint Commission (TJC), the Centers for Medicare and Medicaid Services (CMS), and the National Quality Forum in 2006.[31,34,35] The direct health care costs and indirect societal costs related to VTE and its complications are tremendous, and optimizing VTE treatment and prevention is critical to providing the best possible patient outcomes and minimizing costs related to treatment and future complications.[32,36] Thus, the field of venous thrombosis has the unique opportunity of changing the conversation, from VTE management via diagnosis and treatment, to prophylaxis, in order to improve the quality of health care and simultaneously reduce the burdensome morbidity, mortality, and costs associated with preventable VTE.

1.3 THE LYMPHATIC SYSTEM AND LYMPHEDEMA

1.3.1 Ancient understanding of the lymphatic system

The first recorded lymphatic system descriptions are attributed to the ancient Greeks. Many of the same scientists who made significant contributions to the discovery of varicose veins and chronic venous insufficiency also advanced our understanding of the lymphatic system. In the fourth century BCE, Aristotle described "fibers which take a position between blood vessels and nerves and which contain a colorless liquid." Later in 400 BCE, Hippocrates discovered axillary lymph nodes as "vessels containing white blood."[37] Galen (129–199 CE) and Paul of Aegina (607–690 CE) continued the observations of lymphatics. Hundreds of years

then passed before there was any notable progress in the study of the lymphatic system.

1.3.2 Fifteenth to seventeenth centuries

Nicola Massa (1499–1569), an Italian human anatomist, described the renal lymphatic vessels and pondered their function.[37] Eustachius found a white structure while dissecting a horse in 1552, and subsequently named it the "vena alba thoracis."[37] In the seventeenth century, the founder of microanatomy and the first histologist Marcello Malpighi (1628–1689) identified capillaries that linked the arteries and veins in the lungs. He also noted conglobate glands (nodes) positioned beside the course of lymphatics. Later, Henri Francois LeDran (1685–1770) was the first to note the spread of cancer throughout the lymphatic system.[37] The discovery of mesenteric lymphatics was made in 1622 by Gasparo Aselli (1581–1626), a professor of anatomy and surgery. Aselli coincidentally noticed what he later named "lacteal vessels" ("*venae albae aut lacteae*") while dissecting alive dogs in both fed and unfed states.[37] Initially, he believed that the network of fine, lightly colored cords were nerves; however, some started leaking a milky, white fluid, prompting his further attention and investigation.[37] He also noted valves within the lacteal vessels.[37] Johann Vesling (1598–1694), a German anatomist, published in 1634 some of the earliest human lymphatic system illustrations, including of the thoracic duct.[37,38] Other subsequent investigators demonstrated that lymphatic vessels were widely distributed throughout the body.

The term "lymphatics" was first used by Thomas Bartholin (1616–1680). Interest in the anatomy and function of the newly discovered lymphatic system continued to increase among scientists and anatomists, and the lymphatic system was proposed as having an important role in the development of ascites and edema.[37]

1.3.3 Eighteenth- to nineteenth-century discoveries

William Hunter (1718–1783) and his younger brother John Hunter, the infamous "father of modern surgery" (1728–1793), both researched and defined the course of the lymphatic system from their dissections of animals and human cadavers.[37] An atlas of the human lymphatic system published in 1787 by an anatomy professor from Italy, Paolo Mascagni, was more complete, emphasizing the lymphatic origins as completely separate entities from blood vessels in the tissue.[37]

1.3.4 Nineteenth and twentieth centuries

The lymphatic system was recognized as central to the immune system of the body. Lymphography was first introduced in 1931 by Hernani Monteiro in order to study the lymphatic system *in vivo*. Servelle in Paris was already using direct contrast lymphangiography in 1943. Kinmonth in 1952 used blue dye to stain the lymphatics and then directly injected radio-opaque contrast in order to investigate lymphatic diseases. Today, contrast magnetic resonance lymphangiography is the most commonly performed test (although it is still used only rarely).[39] In our era of digitalized technology and new contrast agents, the field of lymphatic imaging continues to evolve and progress as a powerful tool for future diagnostic and therapeutic advancements.[40]

1.3.5 Treatment options for lymphedema

Patients can develop debilitating lymphedema of the upper or lower extremities due to congenital or acquired causes. Surgical options have been slow to develop and have not been widely adopted because of their mixed results. Lymphatic reconstruction via microsurgery, lymph node transplant, and excisional surgery (the Charles procedure) have been the mainstays of therapeutic modalities. These options will be discussed in a later chapter.

1.4 CONCLUSIONS

The history of venous disease is rich, fascinating, and far-reaching. The discoveries in past centuries were tremendous. The explosion of recent developments is adding to the intriguing and interesting stories that should be recorded for future generations.

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2

Development and anatomy of the venous system

PETER GLOVICZKI

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In the last two decades, progress in modern imaging studies, such as with duplex scanning, three-dimensional computed tomography, and magnetic resonance imaging, has provided improved insight into our understanding of the anatomy of the venous system.[1–3] Increasing use of minimally invasive catheter-based therapies has furthermore required a more thorough knowledge of the venous anatomy in order to optimize outcome and minimize thromboembolic complications. Since the current *Terminologia Anatomica*[4] suggests terms that are frequently different from those used in clinical practice, a new international anatomic terminology has been developed in order to avoid confusion for those clinicians who treat patients with acute deep vein thrombosis and chronic venous disease.[5–7] International efforts have also resulted in a consensus document on the duplex anatomy of the venous system of the lower limbs.[2]

This chapter includes a review of the development of the venous system, followed by a description of the anatomy of the veins of the lower limb and pelvis. We also discuss relevant venous anatomy of the trunk and the upper limbs. The goal of the American Venous Forum is to entice venous specialists around the world to adopt the new terminology of leg veins in order to improve the safety and outcomes of treatments for venous disease and to permit international collaboration and communication among scientists who are interested in clinical venous research.

2.1 DEVELOPMENT OF THE VENOUS SYSTEM

Primitive vascular channels in the limb first appear in the third week of gestation. During development, the vascular system undergoes differentiation through multiple stages, first described by Woolard in 1922.[8] Stage 1 is the undifferentiated stage, with only a capillary network being present. Stage 2 is the retiform stage when large plexiform structures can be seen. Stage 3, the maturation stage, includes the development of large channels, arteries, and veins. Vascular endothelial growth factor (VEGF) secreted by keratinocytes has been found to induce the penetration of capillary vessels into the avascular epidermis.[9]

The venous system first appears in the trunk as bilaterally symmetrical vessels, with the left vessels regressing and the right vessels dominating as the superior and inferior vena cavae.[10] These patterns of development lend themselves to the anatomic variants found among individuals.

2.1.1 Veins of the trunk

2.1.1.1 SUPERIOR VENA CAVA AND TRIBUTARIES

Blood is initially returned to the heart tube via the paired sinus venosus.[11] The portion of the body that is cranial to the developing heart drains through the bilateral anterior cardinal veins, and the caudal portion of the body drains forward through the bilateral posterior cardinal veins (Figure 2.1). The anterior and posterior cardinal veins join to form the common cardinal veins, with the right and left common cardinal veins draining centrally into the sinus venosus. The common cardinal veins also receive the vitelline and umbilical veins; the vitelline veins later form into the hepatic portal system.

The anterior cardinal veins connect the left anterior cardinal vein with the right anterior cardinal vein. This left to right channel becomes the left brachiocephalic vein. The portion of the left anterior cardinal vein that is caudal to this anastomosis regresses but does not disappear; it forms the oblique vein of the left atrium (vein

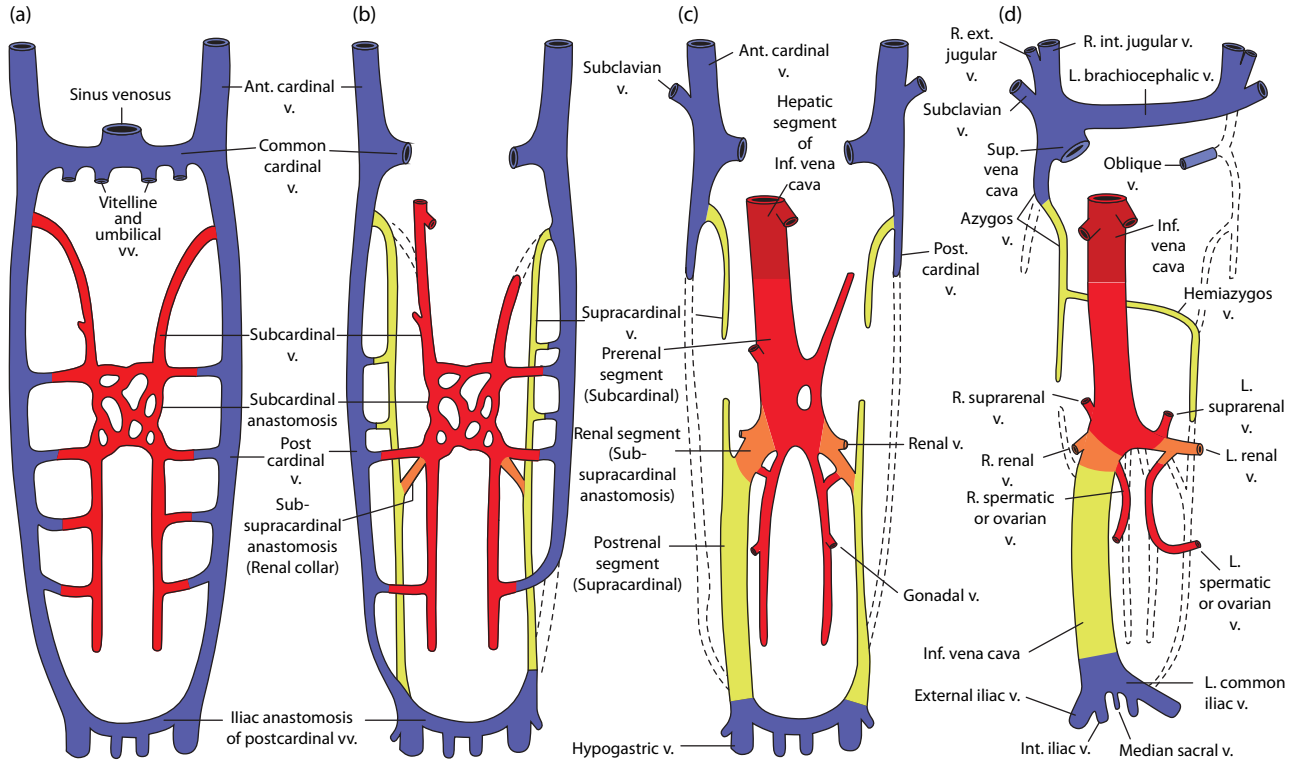

Figure 2.1 (a–d) Stages in development of the major veins. (Redrawn from Avery LB. *Developmental Anatomy*, revised 7th Edition. Philadelphia, PA: W.B. Saunders Co., 1974.)

of Marshall) and the coronary sinus. The persistence of the left caudal anterior cardinal vein results in a double superior vena cava (Figure 2.2a).[3] In the absence of the right proximal superior vena cava, the blood from the right upper body is drained into a left superior vena cava (Figure 2.2b).

2.1.1.2 INFERIOR VENA CAVA AND TRIBUTARIES

The inferior vena cava develops from multiple segments.[12] The paired posterior cardinal veins originally extend into the region that will become the pelvis, and are joined together at the iliac anastomosis (Figure 2.1). Most of the posterior cardinal veins disappear; the most cranial portion on the right persists as the arch of the azygos. The very caudal portion of the posterior cardinal veins and iliac anastomosis form the common, external, and internal iliac veins and the median sacral vein. The posterior cardinal veins are mostly replaced by the ventral subcardinal and the dorsal supracardinal veins. Drainage of the more cranial region of the abdomen goes mostly into the subcardinal veins, and that of the more caudal portion goes into the supracardinal veins. Most of the azygos system develops from the supracardinal veins. Lastly, the veins of the left side generally regress, resulting in a right-sided inferior vena cava.

The most inferior portion of the inferior vena cava—the postrenal segment—develops from the right supracardinal vein; therefore, it is relatively posterior in position. This is demonstrated by the confluence of the common iliac veins forming behind the common iliac arteries. At the level of the kidneys, the inferior vena cava is formed from the right sub-supracardinal anastomosis (renal segment), thereby becoming more anterior in position. Above the kidneys, the inferior vena cava is formed from the right subcardinal vein (prerenal segment), which is still more anterior, as it demonstrated by the inferior vena cava diverging anterior to the aorta. The hepatic segment of the inferior vena cava is formed directly by hepatic sinusoids.

Since the inferior vena cava develops from bilateral veins, with the right veins usually persisting, variations are to be expected, although they are unusual. If the right subcardinal vein fails to make connection with the liver, absence of the suprarenal inferior vena cava occurs, such that the inferior vena cava drains into the arch of the azygos and the hepatic veins drain independently through the diaphragm to the right atrium.[3] Double inferior vena cavae (0.2%–3%) usually occur in the infra-renal portion due to bilateral persistence of both the right and left supracardinal veins (Figure 2.2c).[13] A left inferior vena cava (0.2%–0.5%) results from caudal regression of the right supracardinal vein with persistence of the left supracardinal vein (Figure 2.2d). Renal vein anomalies include the persistent (circumaortic) renal collar (1.6%–14%)[14,15] and the posterior (retroaortic) left renal vein (3.2%)[14] (Figure 2.3).

Congenital absence of the inferior vena cava is a rare but important anomaly, since it is a cause of deep vein thrombosis in young patients, especially in those without risk factors for thrombosis.[12] Aneurysmal changes of retroperitoneal

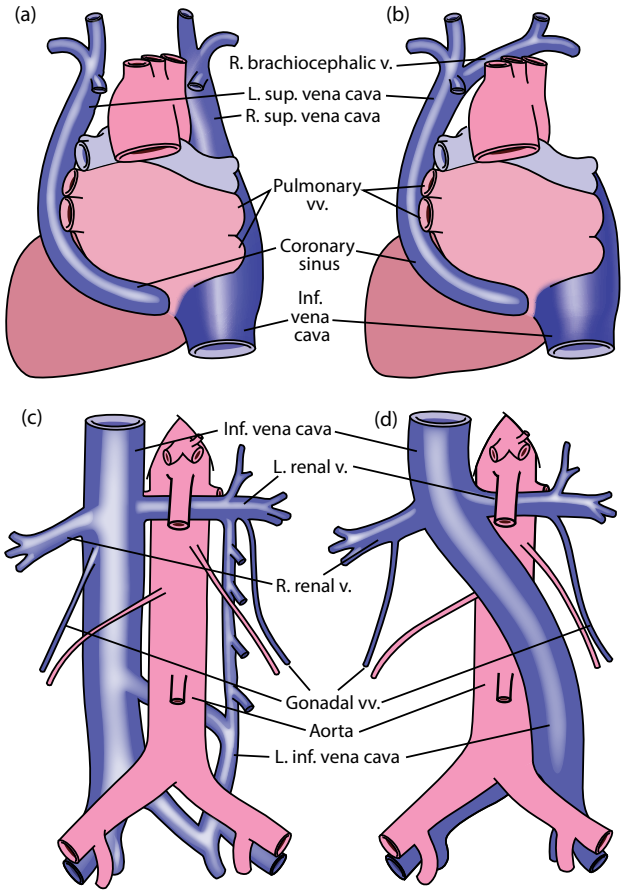

Figure 2.2 Anomalies of the vena cava. **(a)** Double superior vena cava. **(b)** Left superior vena cava. **(c)** Double inferior vena cava. **(d)** Left inferior vena cava (a and b: posterior views; c and d: anterior views).

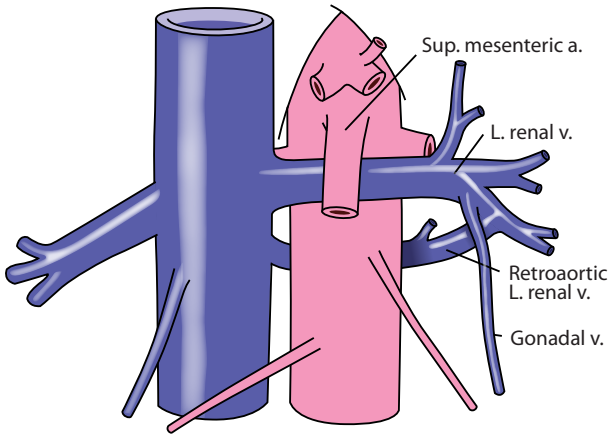

Figure 2.3 Circumaortic renal collar.

collaterals have been observed, rupture has been reported,[16] and some patients have presented with severe back ache due to venous congestion.[17] Previous deep vein thrombosis or retroperitoneal fibrosis should be considered in the differential diagnosis.[18]

2.1.2 Veins of the limbs

The general pattern for the development of the vasculature of the limbs begins as a fine capillary network arising from several segmental branches of the aorta. As the limb begins to extend from the body, a channel from within this network predominates as the axial or central artery. The blood returning to the body from capillary networks is first collected in a marginal sinus that extends around the apex of the limb bud, just deep enough to reach the apical ectodermal ridge. The capillary networks and the marginal sinus itself send out new vascular sprouts in response to growth of the limbs. Early on, blood drains from the marginal sinuses of the limbs into the superficial venous plexuses of the body, but the blood is progressively shunted into deeper channels as development progresses and deep veins—frequently paired—develop along major arteries. Valves form in the veins relatively early. It is thought that the definitive number of valves is reached by the sixth month of fetal life.

The development of the veins of the limb is likely preceded by the development of major nerves. Gillot proposed that venous development is induced by major nerves; in the embryo, these angioguiding nerves are the femoral, the sciatic, and the posterior femoral cutaneous nerves.[3,19] Many of the embryonic veins regress during development; their persistence (of the sciatic vein, lateral marginal vein, etc.) is, however, frequently seen in patients with venous malformations.[20–23]

The axial artery of the upper limb forms the brachial artery in the arm and the interosseous artery in the forearm, with the ulnar and radial arteries forming later. As the digits are forming, the apical marginal sinus regresses, but the proximal marginal channels persist as the cephalic and basilic veins.

2.2 ANATOMY

2.2.1 Veins of the lower extremity

The veins of the lower extremity are composed of the superficial, the deep, and the perforating veins (PVs). PVs connect the superficial to the deep venous system. They pass through the deep fascia which separates the superficial compartment from the deep. Communicating veins connect veins within the same system. The recent development of the evaluation of the veins with duplex scanning resulted in the recognition of the saphenous sub-compartment and the saphenous fascia.[1,2,7] The saphenous fascia covers the saphenous sub-compartment and separates the great saphenous vein (GSV) from other veins in the superficial compartment. Bicuspid valves are important structures in the leg veins, assisting unidirectional flow in the normal venous system.

2.2.2 Cutaneous microcirculation

The cutaneous branches of arteries reach the skin either directly or following the penetration of skeletal muscles. In the skin, the arterioles form a reticular and a more

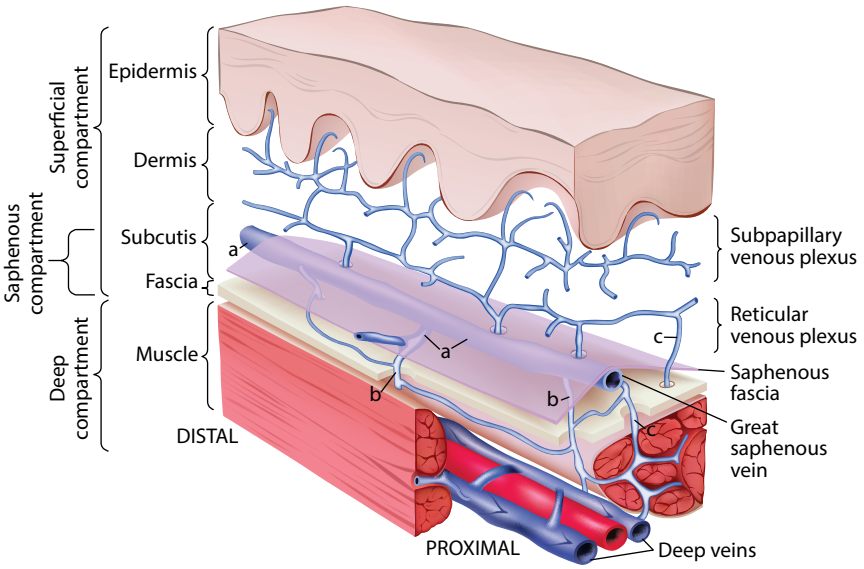

Figure 2.4 Venous networks in the lower extremity. Capillaries of dermal papillae are drained by the subpapillary venous plexus, which in turn joins to the reticular venous plexus. Superficial veins **(a)** drain dermal veins and empty into the deep axial veins through direct perforating veins **(b)**. Perforating veins communicate with each other through small branches. Muscular venous sinuses fill from the superficial veins or from the reticular venous plexus through indirect perforating veins **(c)** and they are drained into the deep axial veins.

superficial subpapillary dermal plexus.[24] Capillary loops of the dermal papillae emerge from the latter plexus and drain through venules into the subpapillary venous plexus, which again drains into the deeper reticular venous plexus at the dermal–subcutaneous junction (Figure 2.4). Vertically oriented, small-valved veins connect the reticular venous plexus to the superficial veins.

2.2.3 Superficial veins of the leg

Few veins of the human body have more variability in their gross anatomy than the superficial veins of the leg. Superficial veins—the GSV and the small saphenous vein (SSV) and their tributaries—course in the subcutaneous fat outside the deep fascia and drain blood from the skin and subcutaneous tissues (Figures 2.5 and 2.6, Table 2.1).[24–27]

The superficial venous system of the foot is divided into the dorsal and plantar subcutaneous venous networks (Figure 2.5). Superficial vein tributaries drain blood into the dorsal venous arch on the dorsum of the foot at the level of the proximal head of the metatarsal bones. The medial and lateral end of this arch continues through the medial and lateral marginal vein into the GSV and SSV, respectively.

The GSV begins just anterior to the medial ankle, crosses in front of the tibia and ascends medially to the knee (Figure 2.6). Proximal to the knee, the GSV ascends on the medial side of the thigh and enters the fossa ovalis at 3 cm inferior and 3 cm lateral to the pubic tubercle. The GSV is doubled in the calf in 25% of the population and in the thigh in 8%.[25] The saphenous nerve runs in close proximity to the GSV in the distal two-thirds of the calf. The accessory GSVs are frequently present and run parallel to the GSV in both the thigh and the leg. The veins lie either anterior, posterior, or superficial to the main trunk. The posterior accessory GSV of the leg (Leonardo's vein or posterior arch vein) is a common tributary, which begins posterior to the medial malleolus and ascends on the posteromedial aspect of the calf to join the GSV distally to the knee (Figure 2.6). The anterior accessory GSV of the leg drains the anterior aspect of the leg below the knee. The posterior accessory GSV of the thigh, if present, drains the medial and posterior thigh.[28] The anterior accessory GSV of the thigh collects blood from the anterior and lateral side of the thigh (Figure 2.6). The anterior and posterior accessory GSVs join the GSV just before it ends at the confluence of superficial inguinal veins

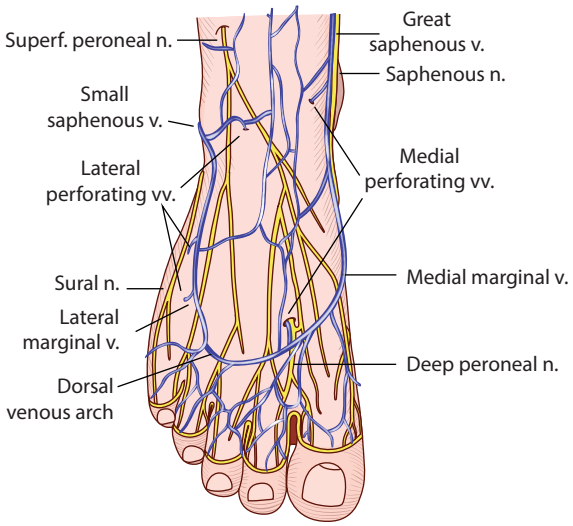

Figure 2.5 Superficial and perforating veins of the foot.

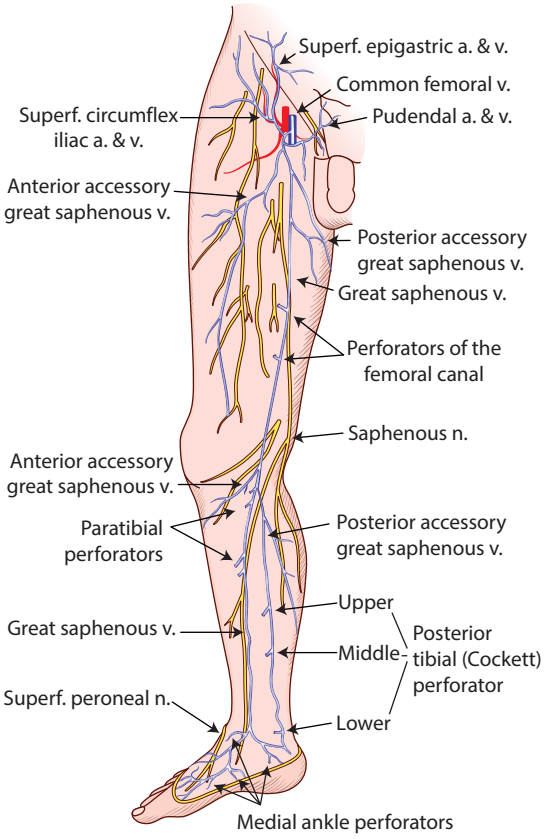

Figure 2.6 Medial superficial and perforating veins of the leg.

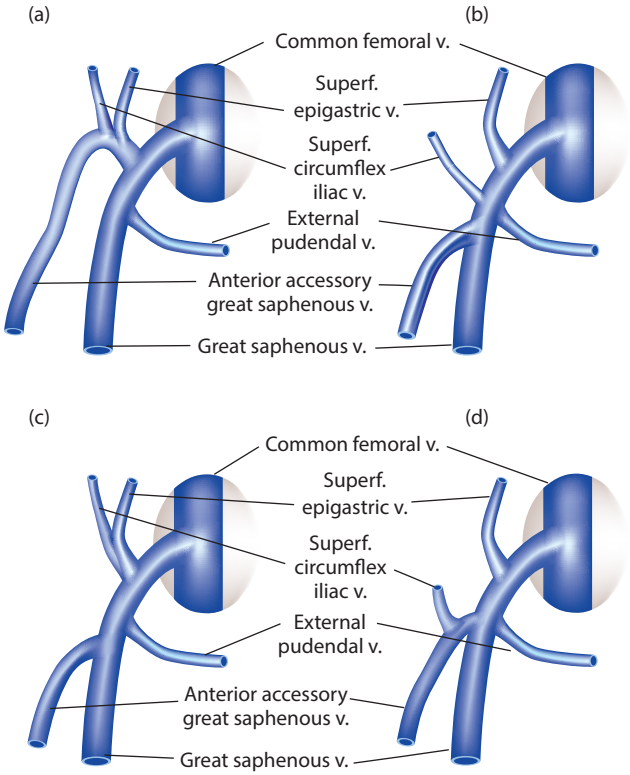

Figure 2.7 Most common anatomic variations of the confluence of superficial inguinal veins (a: 33%; b: 15%; c: 15%; d: 13%).

Table 2.1 New terminology of lower extremity veins

Old, historic terms or eponyms	"New" terms
Superficial femoral vein	Femoral vein
Greater or long saphenous vein	Great saphenous vein
Lesser or short saphenous vein	Small saphenous vein
Saphenofemoral junction	Confluence of the superficial inguinal veins
Giacomini's vein	Intersaphenous vein
Posterior arch vein or Leonardo's vein	Posterior accessory great saphenous vein of the leg
Cockett perforators (I, II, and III)	Posterior tibial perforators (lower, middle, and upper)
Boyd's perforator	Paratibial perforator (proximal)
Sherman's perforators	Paratibial perforators
"24-cm" perforators	Paratibial perforators
Hunter's and Dodd's perforators	Perforators of the femoral canal
May's or Kuster's perforators	Ankle perforators

(saphenofemoral junction) (Figure 2.7). The superficial circumflex iliac, superficial epigastric, and external pudendal veins join each other and the distal GSV in order to form the confluence of superficial inguinal veins (saphenofemoral junction) (Figure 2.8). Rarely, the GSV terminates high on the lower abdomen or joins the femoral vein very low, and the superficial inguinal veins empty individually into the femoral vein. Other occasional tributaries of the GSV in the groin include the posterior and anterior thigh circumflex veins.

The SSV lies lateral to the Achilles tendon in the distal calf (Figures 2.9 and 2.10). In the lower two-thirds of the calf, the SSV runs in the subcutaneous fat and then pierces the fascia to run between the two heads of the gastrocnemius muscle.[27] In the popliteal fossa at about 5 cm proximal to the knee crease, the main trunk of the SSV drains into the popliteal vein. A smaller vein—the cranial extension of the SSV—frequently continues in a cephalad direction (Figure 2.9). Uncommonly, the main trunk of the SSV continues without draining into the popliteal vein and eventually empties into the femoral vein or GSV. The intersaphenous vein (vein of Giacomini) is a communicating vein connecting the SSV to the GSV in the posterior–medial thigh; this vein, which is present in two-thirds of limbs with venous disease, usually ascends subfascially and perforates the fascia to join the superficial system.[29]

The sural nerve courses along the SSV in the distal calf. Superficial veins of the lateral leg and thigh form the

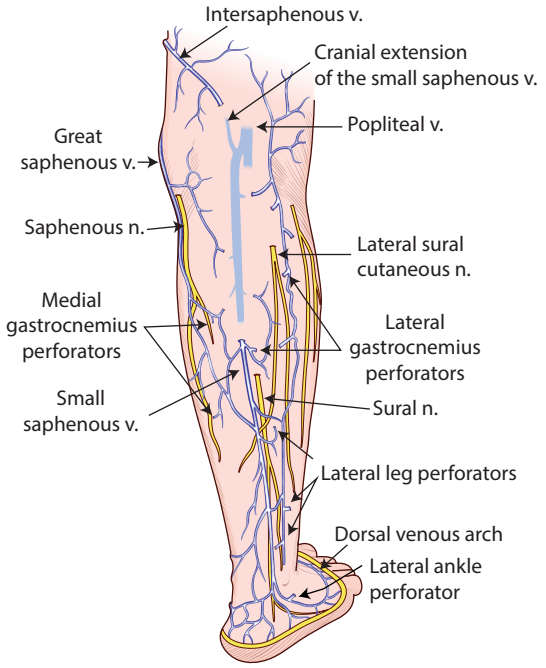

Figure 2.8 Posterior superficial and perforating veins of the leg.

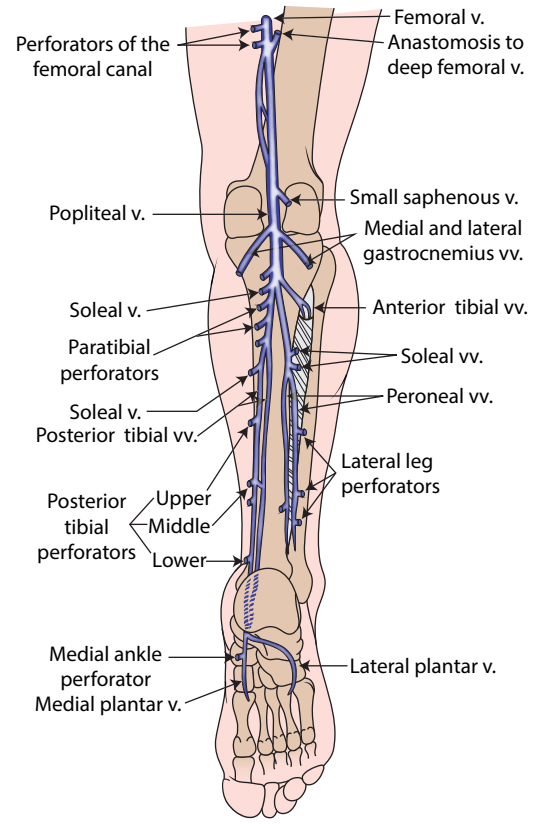

Figure 2.9 Deep veins of the lower extremities.

lateral venous system. The lateral venous system is drained through multiple small tributaries into the GSV and SSV or through PVs into the deep system.

In the superficial veins, bicuspid valves secure unidirectional venous blood flow towards the heart. There are more constant valves, which are usually located at the termination of the major venous trunks. These valves have strong, white cusps and marked sinusoid dilatation of the venous wall at the origin of the valves. Other valves are delicate, almost transparent structures. In the GSV, there are usually at least six valves (maximum: 14–25). A constant valve is present in the GSV within 2–3 cm of the saphenofemoral junction in about 85% of veins.[30] The frequency of valves is greater below than above the knee. In the SSV, valves are numerous (median: 7–10, range: 4–13) and more closely spaced. The highest valve is usually situated close to the termination of the SSV. Valves in communicating tributaries between the two saphenous veins are always oriented in order to direct blood from the SSV to the GSV.

Small superficial veins and venules, even those with a diameter of <2 mm, may contain valves.[31,32] These valves likely play an important role in the development of the skin changes in chronic venous insufficiency.[9]

2.2.4 Deep veins of the leg

Deep veins accompany their corresponding arteries, frequently in a paired fashion. On the sole, the richly anastomosing deep plantar venous arch collects blood from the toes and the metatarsals. The deep plantar venous arch continues into the medial and lateral plantar veins, which become the posterior tibial veins behind the medial ankle (Figure 2.9). On the dorsum of the foot, the major deep veins—the dorsalis pedis veins—continue into the anterior tibial veins.

In the calf, the paired posterior tibial veins run between the edges of the flexor digitorum longus and tibialis posterior muscles and under the fascia of the deep posterior compartment (Figure 2.10). They drain the muscles of the deep and superficial posterior compartments and are connected to the GSV and posterior accessory saphenous vein by perforators. The posterior tibial veins pierce the soleus muscle close to its bony adherence (soleal arcade) and continue into the popliteal vein. The anterior tibial veins ascend in the anterior compartment. Distally, there is a constant connection between the anterior tibial and the peroneal veins. The peroneal veins originate in the distal third of the calf and ascend deep to the flexor hallucis longus muscle. They receive the peroneal perforators and several large veins from the soleus muscle. The anterior tibial and peroneal veins form the short tibio-peroneal trunk, which joins the posterior tibial veins to form the popliteal vein.

The popliteal and femoral veins are usually duplicated in segments of various lengths and form a plexus around the corresponding arteries similarly to the deep veins of the calf (Figure 2.9). The gastrocnemius vein and the SSV are

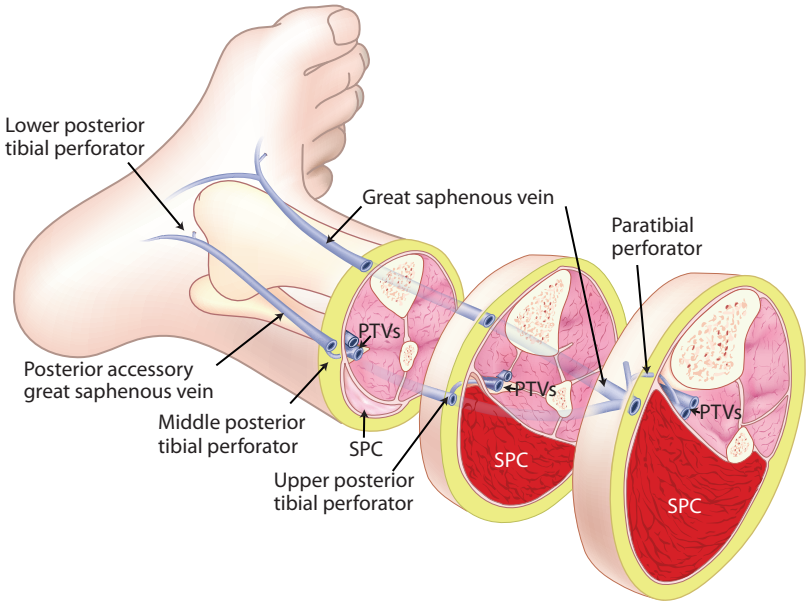

Figure 2.10 Relationship of the medial direct perforating veins to the deep and superficial posterior fascial compartments. PTV: posterior tibial veins; SPC: superficial posterior fascial compartment.

the main tributaries of the popliteal vein. In the adductor canal, the popliteal vein becomes the femoral vein and runs initially lateral and then medial to the femoral artery. The femoral vein unites with the profunda femoris (deep femoral) vein at about 9 cm below the inguinal ligament. In the adductor canal or sometimes more distally, there is a consistent (~84%) anastomosis between the profunda femoris and the femoral or popliteal veins that provides an important collateral channel in case of deep venous thrombosis. The common femoral vein is the continuation of the femoral vein after it joins the deep femoral vein. The GSV empties into the common femoral vein at the saphenofemoral junction. Further tributaries of the common femoral vein are the lateral and medial circumflex femoral veins, which can anastomose with the internal iliac vein. The common femoral vein is medial to the corresponding artery and ends at the inguinal ligament, where it continues as the external iliac vein.

The frequency of valves in deep veins increases in the proximal to distal direction. Deep veins of the foot, the posterior and anterior tibial, and the peroneal veins are profusely valved, containing valves at about 2-cm intervals. The popliteal vein and the most distal part of the femoral vein usually have one or two valves. There are three or more additional valves in the femoral vein, up to the junction with the profunda femoris vein. One of these valves is consistently (~90%) found just distal to this junction.[33] In the common femoral vein, there is usually only one valve. It is important to emphasize that in the external iliac and common femoral veins proximal to the saphenofemoral junction, there is only one valve or, in 37% of cases, there is no valve at all. The common iliac and cava veins are valveless.

2.2.5 Perforating veins

There are more than 150 PVs in the lower extremities; however, the medial PVs are most significant and have been the center of debate for decades.[34–42] Their role in the development of chronic venous insufficiency and venous ulcers is still not well defined. Significant variation exists in the location of leg perforators; however, the distribution of clusters of PVs follows a predictable pattern (Table 2.2). Dorsal, plantar, medial, and lateral foot perforators are the main groups of PVs in the foot. A large PV runs between the first and second metatarsal bones and connects the superficial dorsal venous arch to the pedal vein. The clusters of PVs at the ankle are the anterior, medial, and lateral ankle perforators. The medial calf perforators exist in two groups: posterior tibial and paratibial PVs. Three groups (lower, middle, and upper) posterior tibial PVs (Cockett I–III perforators) connect the posterior accessory GSV to the posterior tibial veins (Figure 2.10). The paratibial perforators drain the GSV into the posterior tibial veins. Other perforators of the leg below the knee are the anterior, lateral, medial, and lateral gastrocnemius, intergemellar, and Achillean PVs. Infra- and supra-patellar and popliteal fossa PVs are located around the knee. Perforators of the femoral canal connect tributaries of the GSV to the femoral vein (Figure 2.8). Inguinal perforators drain into the femoral vein in the proximal thigh.

2.2.6 Venous sinuses of calf muscles

Venous sinuses are thin-walled, large veins in the calf muscles, which have a capacity to hold great volumes of

Table 2.2 Studies on the location of direct medial perforating veins in the leg

First author (year)	Number of legs		Location of medial perforating veins[a]		
	Anatomic dissections	Surgical findings	Cockett II	Cockett III	Proximal paratibial PVs
Linton (1938)	10	50	Distal third of the leg	Middle third of the leg	Proximal third of the leg
Sherman (1948)	92	901	13.5 cm	18.5 cm	24 cm, 30 cm, 35 cm, 40 cm
Cockett (1953)	21	201	13–14 cm	16–17 cm	At the knee
O'Donnell (1977)	–	39	Half of the incompetent PVs are between 10 and 15 cm[b] (15–20 cm[a])		Few incompetent PVs
Fischer (1992)	–	194	Random distribution of incompetent PVs		
Mózes (1996)	40	–	7–9 cm[b] (12–14 cm[a])	10–12 cm[b] (15–17 cm[a])	18–22 cm[b], 23–27 cm[b], 28–32 cm[b] (23–27 cm[a]), (28–32 cm[a]), (33–37 cm[a])

Note: PV: perforating vein.
[a] Distances measured from the sole.
[b] Distances measured from the lower tip of the medial malleolus.

venous blood. They are embedded in skeletal muscles, which contract rhythmically during ambulation; therefore, they serve as "chambers" of the "peripheral heart," the calf muscle pump. The soleus muscle is particularly rich in venous sinuses; it may contain one to 18 of such sinuses. They are less developed in the gastrocnemius muscle. Venus sinuses are filled from the superficial veins and from the reticular venous plexus through indirect, muscular perforators and from the muscles through postcapillary venules and small muscular veins. Venous sinuses of the soleus muscle are drained into the posterior tibial and peroneal veins by the soleus veins (Figure 2.9). The soleus veins are large, short, and tortuous in order to accommodate the considerable range of muscular movements. In the lower third of the leg, the soleus veins frequently join directly into PVs before entering the deep veins. Bilateral gastrocnemius veins draining the two heads of the gastrocnemius muscle usually empty into the popliteal vein, distal to the confluence of the SSV with the popliteal trunk (Figure 2.9). The venous sinuses themselves are valveless; however, the small intramuscular veins linking them and the muscular veins draining venous sinuses into the deep veins contain numerous valves. Indirect PVs feeding venous sinuses are also valved. Valvular competence plays a critical role in the efficient functioning of the calf muscle pump.

2.2.7 Veins of the abdomen and pelvis

The external iliac vein begins at the inguinal ligament, courses along the pelvic brim, and ends anterior to the sacroiliac joint by joining the internal iliac to form the common iliac vein.[43] Its tributaries are the (deep) inferior epigastric, the deep circumflex iliac, and the pubic veins, which freely anastomose with the corresponding superficial veins and with the obturator vein. The internal iliac vein is a short trunk that is formed by the union of its extra- and intra-pelvic tributaries. The extrapelvic tributaries are the gluteal (superior and inferior), the internal pudendal, and the obturator veins. The gluteal veins anastomose with the medial circumflex femoral vein and receive numerous PVs from the corresponding superficial veins (Figure 2.11). The intrapelvic tributaries of the internal iliac vein, such as the lateral sacral and several visceral (middle rectal, vesical, uterine, and vaginal) veins, drain the presacral venous plexus and the pelvic visceral plexuses (rectal, vesical, prostatic, uterine, and vaginal). These plexuses and the additional superficial (pudendal) plexus provide free communication for venous flow between the two sides of the pelvis.[44]

The common iliac veins begin at the sacroiliac joints and form a confluence at the right side of the fifth lumbar vertebra to form the inferior vena cava. The only tributary of the right common iliac vein is the right ascending lumbar vein, whereas the left drains the median sacral vein as well. The ascending lumbar vein runs vertically along the vertebral column, collects blood from lumbar veins, and proximally anastomoses with the azygos system.

The inferior vena cava ascends on the right side of the vertebral column and terminates in the right atrium very shortly after passing through the diaphragm (Figure 2.11). Its tributaries are the lumbar veins, the right gonadal vein, the renal veins, and the right suprarenal, the right inferior phrenic, and the hepatic veins. The left gonadal and suprarenal veins join the left renal vein, and the left inferior phrenic vein opens into the left suprarenal vein. In case of inferior vena cava obstruction, anastomoses between the veins of the chest and abdominal wall (thoraco-epigastric, internal thoracic, and epigastric veins), the lumbar–azygos connections, and the vertebral plexuses can provide important collateral avenues.

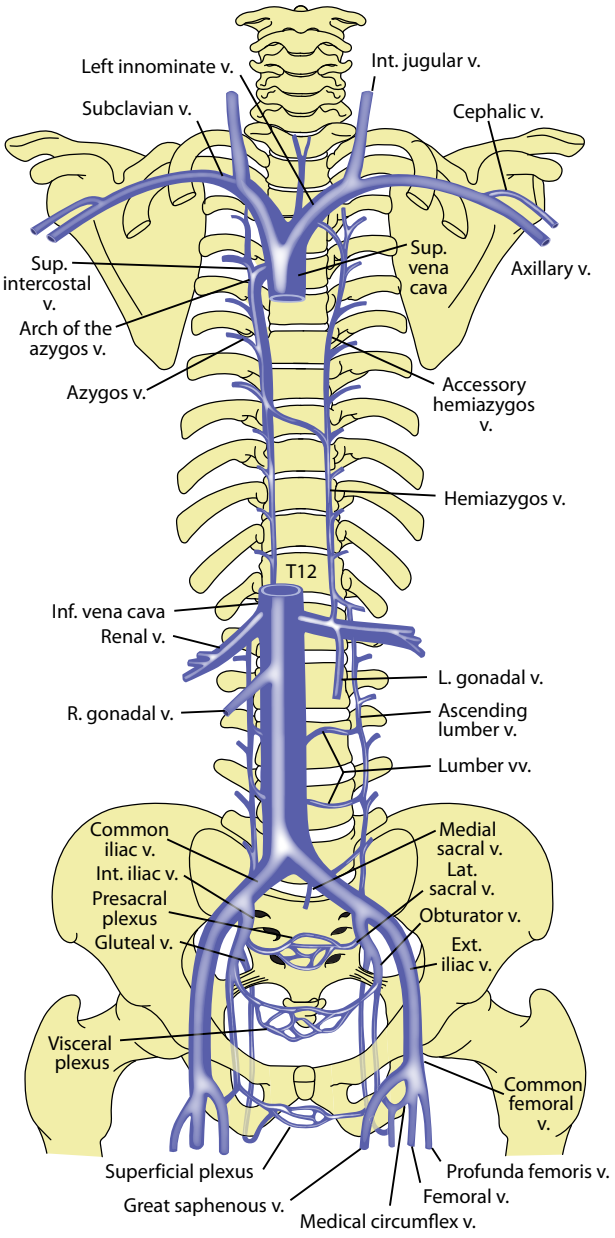

Figure 2.11 Major veins of the pelvis, abdomen, and thorax.

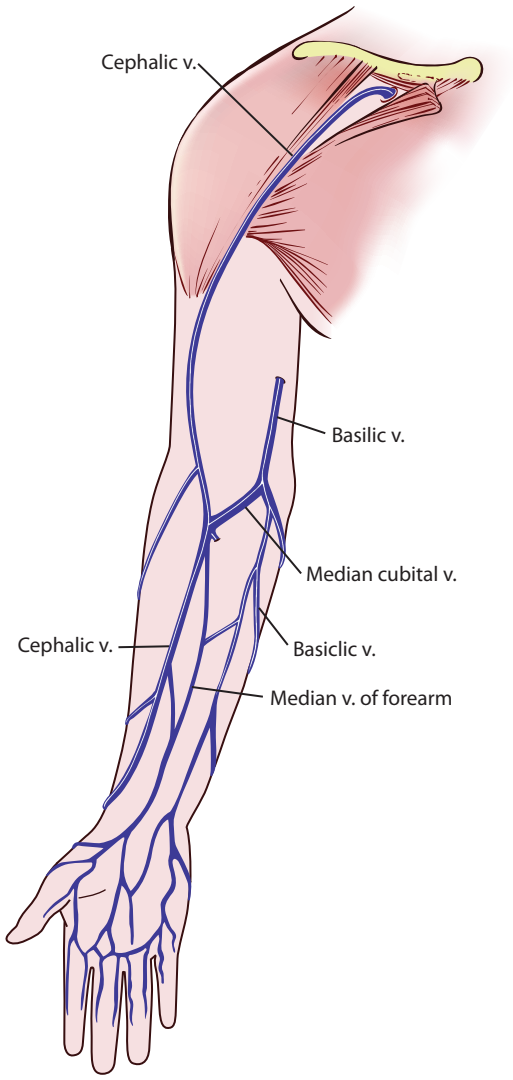

Figure 2.12 Superficial veins of the upper extremity.

2.2.8 Veins of the upper extremity and the thorax

2.2.8.1 UPPER EXTREMITY VEINS

Venous return from the arm is mostly maintained by the functioning of the heart. Valves do not play an important role in this venous circulation. The deep veins of the arm are paired and follow their corresponding arteries. Perforators between the deep and superficial veins are less numerous in the arm than in the leg.

The superficial veins of the upper limb are the cephalic and basilic veins and their tributaries (Figure 2.12). The dorsal venous plexus of the hand continues into the cephalic vein on the radial and into the basilica vein on the ulnar side. The cephalic vein begins at the "anatomical snuff box," courses over the distal radius to the ventral aspect of the forearm, and ascends on the lateral side of the arm and in the deltopectoral groove. It enters the infraclavicular fossa, pierces the clavipectoral fascia, and empties into the axillary vein. The basilic vein ascends on the ulnar side of the forearm, perforates the deep fascia about midway in the arm, and, after receiving the deep brachial vein, it continues into the axillary vein. The median cubital vein connects the cephalic and basilic veins in front of the elbow. Variations are common, including the presence of additional major venous trunks, such as the accessory cephalic or antebrachial veins. The deep veins (radial, ulnar, brachial, and axillary veins) are usually paired and follow the course of the main arteries of the arm.

The axillary vein begins at the lower border of the teres major, which corresponds with the lateral border of the scapula on an anteroposterior chest roentgenogram. At the outer border of the first rib, it becomes *the* subclavian,

which ends at the medial border of the scalenus anterior muscle, where it joins the internal jugular vein to form the brachiocephalic vein. The brachiocephalic (innominate) vein begins behind the sterno-clavicular joint. The left brachiocephalic vein descends obliquely to join the right one. Constant tributaries of the brachiocephalic vein are the vertebral, internal thoracic, and inferior thyroid veins. The superior intercostal vein drains the upper intercostal veins and opens into the brachiocephalic vein on the left, whereas on the opposite side it joins the azygos vein.

The superior vena cava is formed behind the first right costal cartilage by the union of the brachiocephalic veins. It descends right of the ascending aorta and opens into the right atrium at the level of the third right costal cartilage. Halfway along its length, before it enters the pericardium, it receives the azygos vein from behind.

2.2.8.2 AZYGOS VEINS

The origin of the azygos vein is not constant. It may arise from the back of the inferior vena cava at the level of the renal veins or it may be the continuation of the right ascending lumbar vein (Figure 2.11). The azygos vein ascends on the right side of the body until the fourth thoracic vertebra and then passes anteriorly to join the superior vena cava. Major tributaries of the azygos vein are the right superior intercostal, the hemiazygos, and the accessory hemiazygos veins. The hemiazygos vein courses on the left side of the vertebral column and its origin is similar to that of the azygos vein. At the level of the eighth thoracic vertebra, it crosses the column and joins the azygos vein. Often, the left renal vein communicates with the hemiazygos vein. The accessory hemiazygos vein descends left to the vertebral column and parallel with the azygos vein. Proximally, it anastomoses with the left brachiocephalic vein and ends distally when it joins to the azygos or the hemiazygos veins at the level of the seventh thoracic vertebra. The azygos veins drain the intercostal veins on both sides, receive several visceral tributaries, and freely anastomose with the vertebral venous plexuses. The azygos veins and their tributaries provide important collateral circulation in the face of superior or inferior vena cava obstruction.

2.3 HISTOLOGY

The venous wall is three layered: intima, media, and adventitia.[45,46] The intima uniformly consists of a single layer of endothelial cells resting on scant connective tissue. The internal elastic lamina, a layer of thick elastic fibers at the base of the intima, is frequently incomplete in medium-sized veins and absent in smaller ones. Venous valves are bicuspid infoldings of the intima covered by endothelium on both sides, with an intervening connective tissue skeleton (Figures 2.13a,b and 2.14). At the origin of valves, the veins may be focally distended, forming small sinusoid dilation, probably in response to the hemodynamic consequences of focally reversed flow.

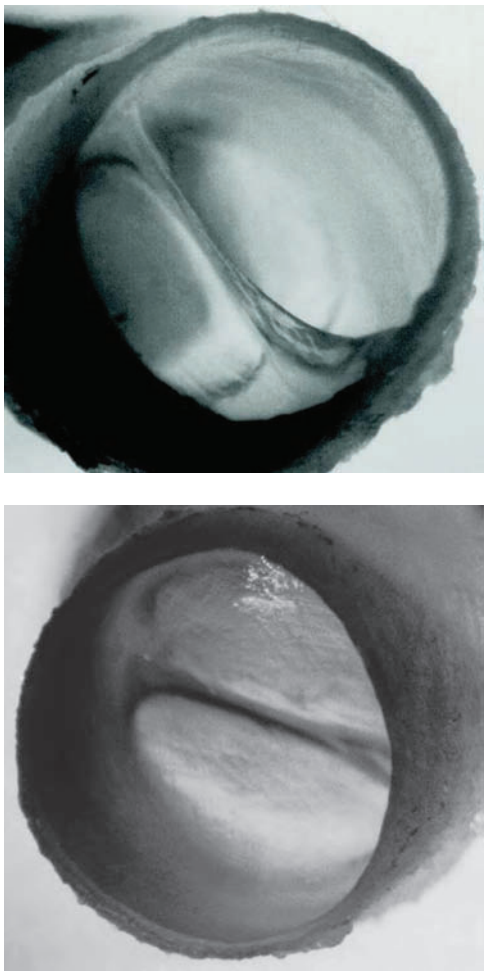

Figure 2.13 Proximal **(a)** and distal **(b)** aspects of a venous valve (stereo microscopy, magnification: ×14).

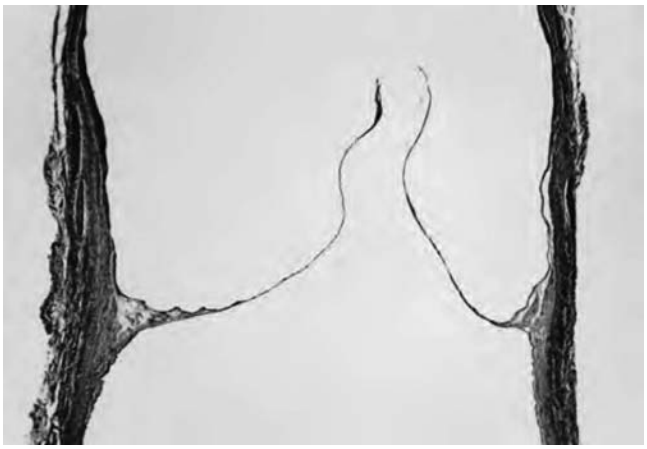

Figure 2.14 Histology of a venous valve (orcein, magnification: ×2.5).

The media is composed of layers of smooth muscle cells and connective tissue. The relative thickness of the media and the proportions of the two major components vary considerably with different sizes and functions. The major superficial veins, such as the greater and lesser

saphenous, have thick muscular media, providing the ability to contract and to resist the development of varicosities. Tributaries of the saphenous veins have thinner media and can become more easily varicosed. The media of the deep veins of the calf contain as much smooth muscle as saphenous veins; however, their collagen content is higher, resulting in a more rigid wall. The larger deep veins (femoral, iliac, axillary, subclavian, and innominate) contain less smooth muscle cell mass, and the almost complete lack of these cells in the media of the caval veins is remarkable.[20]

The adventitia is poorly demarcated and contains loose connective tissue with lymphatics, vessels (vasa vasorum), and adrenergic nerve fibers. The GSV is ensheathed in further layers of fibrous tissue associated with the deep fascia, which makes this vein even more resistant to the development of varicosities.[47]

ACKNOWLEDGMENT

The author would like to acknowledge the major contribution of the late Dr. Geza Mozes to this chapter.

Guidelines 1.1.0 of the American Venous Forum on the development and anatomy of the venous system

No.	Guideline	Grade of recommendation (1: strong; 2: weak)
1.1.1	The main deep vein of the thigh between the popliteal and the common femoral vein is the femoral vein. The old term "superficial femoral vein" should be abandoned.	1
1.1.2	The main superficial veins of the lower limbs are the great saphenous vein and the small saphenous vein.	1
1.1.3	The old terms "Cockett" and "Giacomini" veins should be replaced by the new terms "posterior tibial perforating vein" and "intersaphenous vein," respectively. The use of eponyms is discouraged.	1

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● = Key primary paper
★ = Major review article

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3

The physiology and hemodynamics of the normal venous circulation

FRANK T. PADBERG JR.

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3.1 INTRODUCTION

Venous disorders have been recognized since antiquity, and advances in physiology and diagnosis have led to improved understanding and therapy over the past 150 years. Anatomy and function are better appreciated now from the perspective of twentieth-century testing modalities. Studies from the middle of the twentieth century assessed useful and unique physiological concepts. Although somewhat limited by the available diagnostic modalities of the time, small sample sizes, and minimal descriptive statistics, these studies continue to offer valuable physiologic and hemodynamic data on normal individuals. Ambulatory pressure manometry, dynamic phlebography, plethysmographic evaluations, color flow duplex ultrasound, intravenous ultrasound, computed tomography, and magnetic resonance venography have contributed substantially to the advancement of current knowledge. Detailed discussions of the major pathological conditions affecting the venous circulation—obstruction and reflux—will be found in later chapters.

The primary purpose of the venous circulation is to return blood to the heart for reoxygenation and recirculation. Understanding volume and pressure relationships is essential for understanding normal and abnormal venous function. The enormous capacity of the venous reservoir plays a major role in the maintenance of cardiovascular homeostasis by accommodating volume shifts. Regulation of venous tone is an important aspect of volume accommodation and works in concert with arterial control mechanisms that effect changes in the distribution of cardiac output. Sympathetic-mediated adjustments of smooth muscle tone are most pronounced in the splanchnic and cutaneous distributions, which are also the most densely innervated. In the upright posture, the physiological effects of gravity and hydrostatic pressure would appear to oppose return flow, but these effects are largely offset by competent valvular function and an efficient peripheral pump mechanism.

3.2 VENOUS RETURN

Venous return is defined as the rate of blood flow toward the heart, which in homeostatic circumstances must equal cardiac output. It is expressed as volume per unit time and varies with age, gender, and physical conditioning. Mean human resting cardiac output (5040 mL/minute) is the product of stroke volume (70 mL) and heart rate (72 bpm).[1] Increasing fiber length (volume) or heart rate will increase cardiac output.

Active venoconstriction of capacitance vessels was once thought to have been a major contributor to changes in cardiac output. The accumulated evidence has now demonstrated that reflex-mediated control of the resistance (precapillary) vessels is the major determinant of the distribution of the circulation.[2–4] However, depending on activity and posture, 60%–80% of human resting blood volume (70 mL/kg in men and 65 mL/kg in women) resides in the venous system. A total of 25%–50% of this volume resides in the smaller post-capillary venules and their collecting systems. Approximately 25% (18 mL/kg) resides in the splanchnic network.[1–3]

The interaction of multiple components is required for effective venous return, involving a central pump, a pressure gradient, a peripheral venous pump, and venous valves.

3.2.1 Central

Blood moves through both arteries and veins because of the pumping action of the heart. Venous flow follows a dynamic pressure gradient toward the entry port of the central pump—the right atrium. In the normal individual, atrial pressures of 4–7 mmHg are relatively constant, regardless of position. When supine, pressures at the venular end of the capillary bed are estimated to be 12–18 mmHg, which is consistent with the venous pressure measured in ankle veins.[5–8] Thus, flow moves toward the lower pressures of the right atrium. Pressures in the upper extremity in the upright posture are increased by approximately 6 mmHg at the level of the first rib.[1,6] In an upright posture, with a raised arm, gravitational or hydrostatic forces propel upper extremity and cerebral blood toward the heart. The pliable venous wall collapses above the height of the central venous pressure, a fact that is utilized clinically during bedside estimation of the height of distention in the external jugular vein. Whether standing or sitting, gravity is additive to both arterial and venous pressures in the lower extremity. However, since the force of gravity is equilibrated between the arterial and venous circulation, it is not a significant factor when considering the pressure gradients influencing venous return in the normal lower extremity.

Venous return is enhanced by negative and neutral (usually 0 mmHg) intra-abdominal and intrathoracic pressures. Nevertheless, during inspiration, the increase in intra-abdominal pressure causes a transient reduction in flow from the lower extremities to the right atrium by acting as an external compressive force on flow through a collapsible tube such as the inferior vena cava (IVC).[9] Chronic, sustained elevation of intra-abdominal pressure occurs with clinical conditions such as ascites and morbid obesity; venous pressure in the lower extremities must rise above this chronically elevated pressure to effect flow through an IVC that has collapsed because of external pressure.

In normal circumstances, a pressure gradient begins at 12–18 mmHg at the venous end of the capillary, and falls steadily to 5.5 mmHg in the extrathoracic great veins.[10] When blood reaches the right atrium, it is actively pulled into the pump, oxygenated in the pulmonary circuit, and recirculated. Since there are no valves in the large venous conduits, the pathophysiologic consequences are generally those of obstruction to venous flow. The consequences of elevated central venous pressures are characterized by congestive heart failure, ascites, Budd–Chiari syndrome, morbid obesity, and superior vena cava syndrome.

3.2.2 Peripheral

Venous return from the dependent lower extremity is achieved by active pumping of the calf muscle assisted by competent venous valves. Normal valve closure effectively prevents retrograde flow of blood. In the normal lower extremity, venous return is primarily a function of the deep veins. Valves are distributed throughout upper and lower extremity veins, and are more numerous in the more distal segments. The anatomic distribution and extent of valvular incompetence that are necessary to produce clinical symptoms remain incompletely understood. As might be anticipated, the greater the valvular dysfunction or reflux, the greater the likelihood of symptoms from peripheral venous insufficiency arising.[11–15]

The plantar venous plexus probably serves to fill or prime the calf pump. Since most investigators have focused on the calf pump, the role of the foot and thigh components are less well defined. The calf pump is very efficient in the normal limb; however, it is unknown whether or how it might compensate for deficiencies such as outflow obstruction, proximal valvular failure, distal valvular failure, or muscle weakness.

3.3 PHYSIOLOGIC COMPONENTS OF THE RETURN CIRCULATION

The prominent roles of hydrostatic pressure and capacitance are unique to the venous circulation. Both interact with other physiologic and hemodynamic factors to exert a variable influence relative to circumstances such as posture, volume depletion, physical exercise, and ambient temperature. Adrenergic-mediated reflexes largely control the splanchnic circulation. Responding to local, hormonal, and reflex stimuli, blood flow to the skin and skeletal muscle fluctuates over a wide range.[2–4,16,17]

3.3.1 Hydrostatic and dynamic pressure relationships

Although local venous pressure varies with the recumbent, sitting, and standing positions, venous flow still follows a pressure gradient. The peripheral calf muscle pump is effective at returning venous blood, but it only functions when there are active muscle contractions. When active movement is artificially constrained, capacitance increases and pressure slowly rises to that produced by gravity—the hydrostatic pressure. Sustained exposure to elevated hydrostatic pressures is transmitted to the capillary bed, where the balance of filtration favors transudation into the extracellular fluid. Transient inactivity of the calf muscle pump may lead to edema in otherwise normal individuals when the extremity is immobilized for an extended period of time, such as an "economy" intercontinental flight or immobilization in a long leg cast. Likewise, most individuals will experience fatigue of the return system by an increasingly snug fit of their footwear near the end of the day.

The static or hydrostatic pressure represents the weight of the column of blood from the point where active recirculation begins—usually the right atrium. Topographically, this is assigned to the level of the fourth costosternal junction. The hydrostatic pressure at a given anatomic point is determined by measuring the vertical distance below this landmark.[5,18] The effect of gravity increases by 0.77 mmHg/cm of height below the atria, with this constant being derived from the product of the density of blood (1.056 g/cm^3) times

the acceleration of gravity (980 cm/second^2) divided by 13.33 mN/cm^2.[1,10] As demonstrated in Figure 3.1, the hydrostatic pressure at the distal calf in the average 174-cm tall American male is 94 mmHg when standing still.[6]

Chronic, sustained venous pressure elevation, or venous hypertension, is associated with pathologic consequences. In the peripheral venous circulation, the major outcomes are reflected in the skin and subcutaneous tissues, and include the typical changes described in CEAP clinical classifications 3–6: edema, pigmentation, fibrosis, and ulceration. The frequency of cutaneous ulceration increases with increasing end-exercise venous pressures above 30 mmHg[14]; this condition, termed venous hypertension, is not the only abnormality producing these symptoms, but remains a major focus for surgical correction.[6,11,15] Reflux, the most common pathophysiological effect associated with venous hypertension, may result from valvular insufficiency of either the deep or the superficial system.

3.3.2 Capacitance and pressure relationships

The total body venous reservoir has an enormous capacity for fluid volume. The healthy individual can accommodate as much as 20%–30% additional volume.[1,2] The normal blood volume is approximately 65 mL/kg in women and 70 mL/kg in men, of which 60%–80% resides in the venous circulation. Assumption of an upright posture alone is responsible for a 10% volume shift (7 mL/kg or 250–500 mL) into the lower extremity.[2,3]

The shape of the venous wall varies greatly depending upon pressure, volume, and flow as demonstrated in Figure 3.2.[9] When empty or flaccid, the walls are coapted and the pressure low. As the cross-sectional profile changes to that of a dumbbell or ellipse, large shifts in flow (or volume) are accommodated, with minimal changes in pressure. Until the vein becomes circular in shape, the pressures remain low. The enormous flow carried by an incompletely distended vein can be deceiving; just ask any surgeon who has nicked a flaccid iliac vein or the vena cava!

Once a vein achieves a circular geometry, further distention is accompanied by a sharp increase in pressure per unit volume (Figure 3.2). Over the normal pressure range of 5–25 mmHg, capacitance volume may change by large amounts without affecting flow or pressure.[2,9] As a result, within the range of normal pressures, the venous hydrostatic pressure becomes an inactive factor in the mechanics of venous return. The higher pressure needed to produce circular distention of the vein approximates that defined as "abnormal" by ambulatory venous pressure (AVP) studies (30 mmHg).[14] This biological pressure threshold is similar to that associated with pulmonary dysfunction from chronic obstructive or regurgitant valvular disease, as well as to the threshold for tissue dysfunction resulting from acute, sustained abdominal and extremity compartmental pressure syndromes.[19,20]

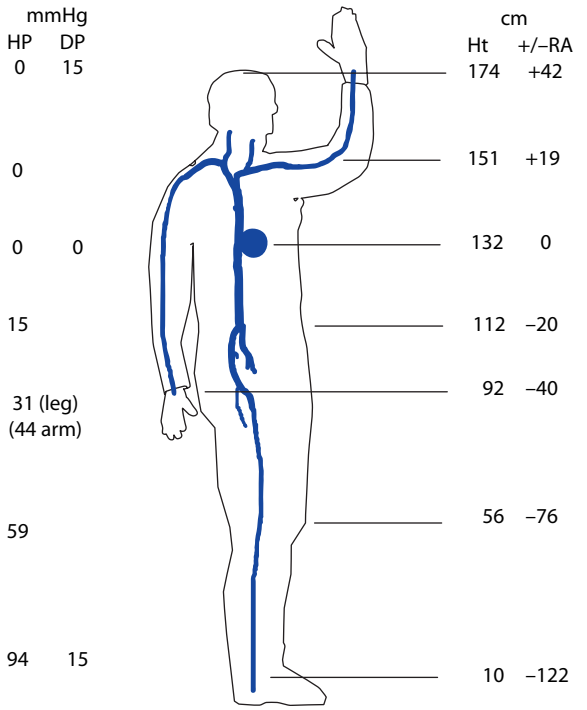


Figure 3.1 The relative pressures generated by dynamic (cardiac pump) and hydrostatic (positional) influences are illustrated in this schematic. The figure has been standing motionless with the dependent veins filling by gravity. Upper extremity pressures vary with position of the arm. DP: dynamic pressure; Ht: height; HP: hydrostatic pressure; RA: right atrium. (From Meissner MH et al. *J Vasc Surg* 2007;46(Suppl.):4S–24S.)

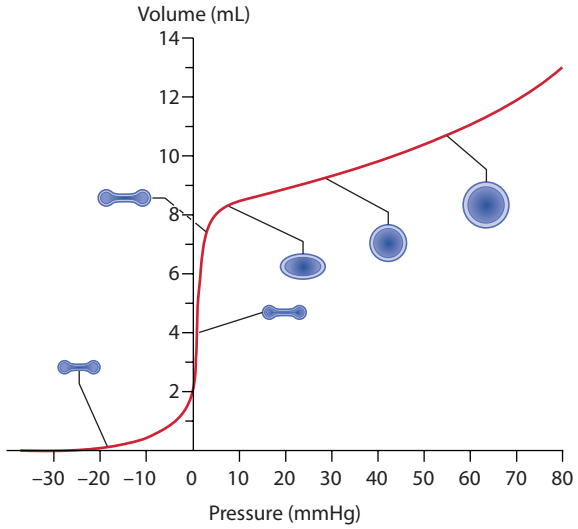


Figure 3.2 Pressure/volume relationships in the distensible venous lumen are reflected in this diagram. Considerable volume is introduced before pressure rises; pressures begin to rise as the vein becomes elliptical and increase further as a circular configuration is reached. (From Katz AI, Chen Y, Moreno AH. *Biophys J* 1969;9:1261–79.)

The venous wall is considerably thinner than the arterial wall, but consists of the same elements—intima, media, and adventitia. The walls of the subfascial deep veins have a relatively uniform thickness. In comparison to superficial tributary veins, the walls of the major superficial venous trunks—the saphenous, basilic, and cephalic veins—are relatively thick. Pliability is a key feature of venous or capacitance vessels. However, when fully distended at high pressures, a vein loses this pliability and becomes as stiff as an artery.[10] Another key feature related to capacitance function is the ability to constrict or dilate over a wide range of diameters. For example, venoconstriction often follows failed venipuncture or exposure for harvest in the operating room, and venodilation often follows increased ambient temperature, warmed acoustic gel, and general anesthesia.

3.3.3 Physiological control: Reflex, hormonal and local mechanisms

Volume flow through splanchnic, muscle, and cutaneous veins can change enormously in response to various stimuli. Reflex impulses are transmitted through sympathetic nerves, which predominantly exert their effects as arterial constriction. Baroreceptor- and chemoreceptor-mediated effects are the most effective acute adjustments to the distribution of blood flows.[1] Fluid shifts and hormonal mechanisms become more important with chronic adjustments to volume status. Although flow is largely controlled by the small resistance arterial beds, capacity is largely adjusted by dilation or constriction of the venous network.

Adrenergic innervation is distributed to both arteries and veins. Furness and Marshall,[21] in an elegant physiologic/anatomic study, demonstrated that the relative densities of these adrenergic endings in the microcirculatory bed are far greater in the arterial (resistance) circulation (Figure 3.3). The splanchnic and cutaneous distributions receive the greatest venous concentration of adrenergic fibers. These distributions also have the largest complement of smooth muscle.[1] Marked arteriolar smooth muscle hypertrophy facilitating precapillary vasoconstriction is one of many adjustment in the extremity skin of the giraffe, which helps in the animal's adaptation to extreme vertical physiologic stress.[22]

The splanchnic circulation normally contains approximately 18 mL/kg or about 25% of the total blood volume and accounts for approximately 27% of the total blood flow. Although normal splanchnic demand is determined from local regulatory mechanisms, acute control of splanchnic volume may be mediated by baroreceptors via adrenergic fibers.[2,4] In severe hypotension, circulating vasopressin and catecholamines may exert a substantial additive effect on the splanchnic adjustments. These redistributions account for approximately 50% of the acute volume compensation following a hemorrhage. Although a small proportion of this volume shift may result from active venoconstriction, the majority results from passive elastic recoil and redistribution of arterial flow.

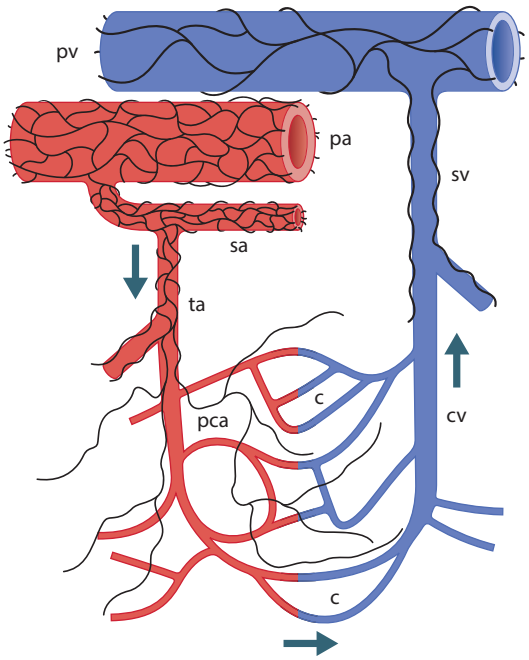


Figure 3.3 Diagrammatic representation of the relationship between adrenergic nerves and the mesenteric blood vessels. The adrenergic nerves are represented by the heavy lines. Arrows indicate the direction of blood flow. Note that the precapillary arterioles and the collecting venules are not innervated. pa: principal artery; pv: principal vein; sa: small artery of the microvasculature; ta: terminal arteriole; pca: precapillary arteriole; c: capillary; cv: collecting venule; sv: small vein. (Reproduced with permission from Furness JB, Marshall JM. *J Physiol* 1974;239:75–88.)

The blood flow to inactive skeletal muscle is only 3 mL/minute/100 g of tissue, but because of its large mass, this accounts for approximately 15% of the total blood volume. Adrenergic stimulation has little influence on skeletal muscle flow, which is primarily controlled by locally mediated stimuli.[1,2] Skeletal muscle flow may increase manyfold to 80 mL/minute/100 g tissue with sustained exercise. Venoconstriction occurs in response to exercise, although local heating abolishes this response in active muscle.[3] The increased volume of flow with exercise, along with the heat generated, secondarily recruits dilation of the cutaneous venous network.

Core temperature is maintained at a constant 36–37.5°C, whereas skin temperature varies markedly with the ambient temperature. Overall, temperature control is maintained by the hypothalamus, whereas cutaneous circulation responds to both reflex innervation and direct local stimuli. Cutaneous blood flow is approximately 3 mL/minute/100 g of tissue in cool weather, which accounts for approximately 6% of the total blood flow,[16] and may vary by as much as 30-fold. Conservation of body heat is achieved by constriction of the cutaneous network, which lowers flow even further. The deep veins are unaffected by cold.[17] Thus, extreme cold also concentrates venous flow in the deep system, where a countercurrent heat exchange efficiently preserves thermal

energy. A reduction in body temperature markedly enhances venoconstriction in response to local cooling through potentiation of the threshold of the adrenergic receptors of cutaneous veins.[17] In a warm environment, heat loss is facilitated in order to maintain homeostatic body temperature. Skin blood flow increases with reduced adrenergic impulses, leading to both arterial and venous dilation.[16] In severe heat stress, the skin blood flow may reach 2–3 L/minute.

Local injury leads to the release of histamine and bradykinin, which produce localized vasodilation. There is mounting evidence to suggest that the vasodilatory actions of progesterone seem to increase venodilation and even the incidence of varicose veins.[4] Despite having been evaluated by a number of investigators, only a limited role has been identified for nitric oxide in venous regulation.[23,24]

3.4 THE PERIPHERAL MUSCLE PUMP MECHANISM

Flow against gravity is maintained by a system of muscle pumps to eject the blood combined with internal valves to prevent retrograde flow (Figure 3.4). In normal individuals, this mechanism is remarkably efficient. The complex relationship between pressure and volume is integral to the comprehension of venous function.

3.4.1 Valvular function

Duplex surveys have defined normal valvular function as a duration of retrograde flow that is <0.5 seconds for all deep and superficial veins of the lower extremities, except for the femoral and popliteal veins (<1.0 seconds).[15,25,26] Soleal sinuses have no valves and a relatively fixed volume.[27] The paired gastrocnemius muscles also have sinuses, but apparently of reduced volume and number. Although the role of valves in the prevention of reflux flow is obvious, the importance of dysfunction (incompetence) of a single or even several valves is not clear. Incompetence of a single valve produces no known physiological consequences.[25]

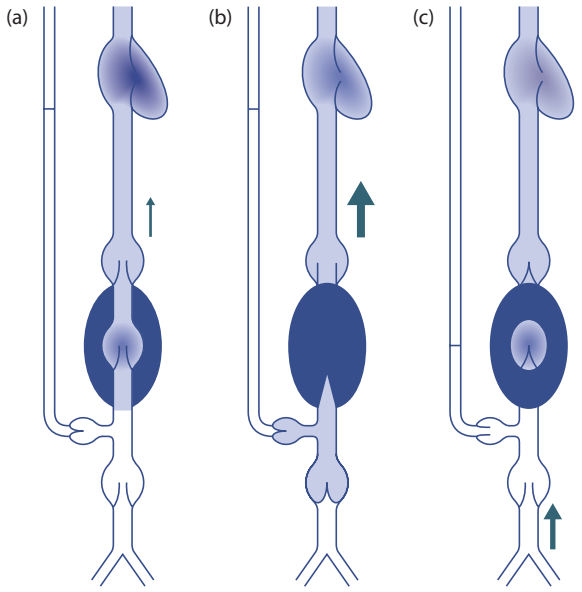


Figure 3.4 Drawing illustrating "operation of the muscle pump": **(a)** resting, **(b)** muscle contraction, and **(c)** muscle relaxation. Venous pressure in the distal leg is indicated by the length of the hydrostatic column. (From Sumner DS, Zierler E. Vascular physiology: Essential hemodynamic principles. In: Rutherford RB, ed. *Vascular Surgery*, 6th Ed. Philadelphia, PA: Saunders-Elsevier, 2005.)

The importance of various anatomic sites of valvular dysfunction is incompletely resolved. Some have ascribed great pathophysiological significance to the femoral and popliteal valves, while others have emphasized abnormalities of the distal valves.[25,28–30] In an analysis of 155 patients from a series of randomized trials, incompetence of the popliteal vein valve was the only significant risk factor for delayed healing.[28] Rosfors et al.[30] determined that distal valvular dysfunction was of greater significance than popliteal valvular dysfunction, but combined disease categories were most likely to be associated with severe chronic venous insufficiency (CVI).[13] The increased number of valves in the infrapopliteal segments suggests that their functional importance is greater in that location.

Perforating vein valves prevent outward flow when functioning properly.[27,31] This concept is consistent with the pressure/flow relationships of the calf pump. Cockett[27] colorfully captured the image of perforating vein malfunction with his description of the "ankle-blow-out" syndrome.

3.4.2 The calf pump

Contraction of the gastrocnemius and soleus muscles expels blood into the large-capacity popliteal vein. The normal limb has a calf volume ranging from 1500 to 3000 mL, a venous volume of 100–150 mL, and ejects over 60% of the venous volume with a single contraction.[12,32,33] Christopoulos et al.[32] normalized the reporting of air plethysmographic volumes in order to facilitate comparison of clinical groups and eliminate such effects as edema and variance in calf size. An ejection volume of 2.5–3.7 mL/100 mL of calf tissue volume was described for normal limbs. Expressing the ejection fraction as a ratio serves the same comparative function.

From a high resting hydrostatic pressure, venous pressure is substantially reduced within several contractions (Figure 3.5).[5] The end-exercise pressure, referred to as the AVP, is maintained at a relatively low value with continued calf contractions. When active contraction ceases, 31 seconds are required to restore hydrostatic pressure in the normal limb. Measurements of changes in venous pressure and volume during repetitive contractions of the normal calf transcribe similar curves (Figure 3.6a–c).[5,6,32,33] Separation of venous pressure relationships from musculofascial pressures is accomplished by simultaneous measurement of compartmental and venous pressures.[33,34] Restoration of >90% of volume requires over 70 seconds to refill the calf.[32]

In the normal resting state, the veins of the calf are filled at a rate of 1–2 mL/second by both active and passive

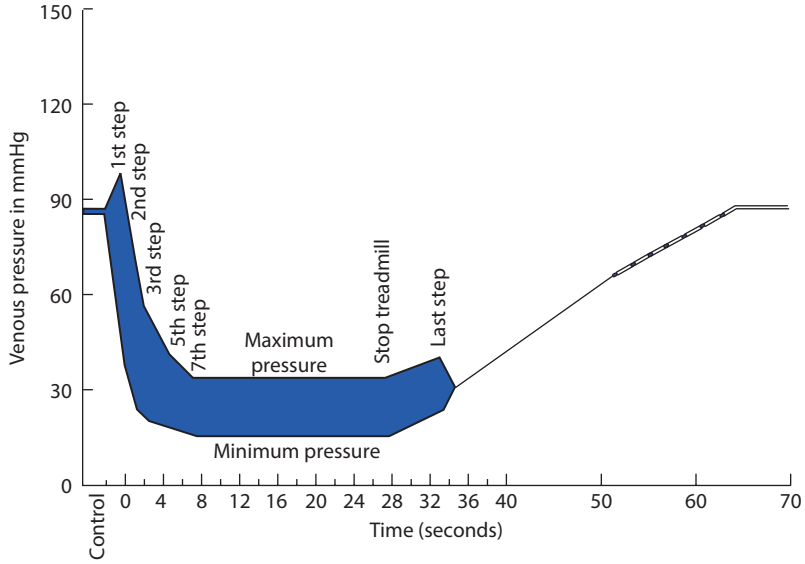


Figure 3.5 Mean pressure changes in the dorsal foot vein during standing, calf exercise, and the subsequent resting state. (From Pollack AA, Wood EH. *J Appl Physiol* 1949;1:649–62.)

mechanisms. The calf pump is actively primed by compression of the plantar venous plexus. Passive filling occurs during muscle relaxation when blood flows into the recently emptied deep veins from the muscle itself, the distal deep veins, and the superficial veins. Venous blood flows through perforating veins following the pressure gradient from elevated hydrostatic pressures in the superficial veins to the rhythmically decreased mean pressure in the deep veins of the calf. Not all perforating veins have valves, but those that do are oriented to prevent flow from the deep to the superficial system.[27] Abnormal function of either the deep or superficial venous system will commonly result in an increased venous pressure, an increased venous volume, and a shortened refill time.[5,14,32] Notably, external compression would benefit this flow pattern by actively encouraging flow into the deep system and reducing calf volume, thus effectively priming the peripheral pump.

Radiographic visualization of contrast movement during active calf contraction was described by Almén and Nylander.[31] The intramuscular soleal and gastrocnemial sinuses fill from the deep muscle compartment and empty completely with a single calf contraction. The intermuscular, paired, deep tibial veins, which lie between the muscle bundles, are substantially compressed, but are never completely empty. The proximal valves open during active calf contraction. The distal deep vein valves close during active calf contraction, along with those in the perforating veins, thus preventing retrograde or outward flow during the contraction cycle.[31] In addition, phlebography of the foot suggests a major role for the plantar venous plexus in filling the deep tibial veins.[35]

The use of direct pressure measurements in the tibial, popliteal, and saphenous veins has provided invaluable evaluations of hydrostatic pressure, pressure reduction with single and multiple calf contractions, and time for recovery of resting pressure. However, despite innovative and extensive experimental observations, the invasive aspects of these investigations have precluded repetitive examination. Plethysmography, whether by foot volume, air, or strain gauge, is well accepted, such that longitudinal data with these non-invasive methods are now appearing. Various authors have described the volume changes associated with elastic compression, surgical intervention, CEAP clinical class, late-day deterioration of venous function, and diminished joint function.[11,12,15,32,36,37]

3.4.3 Thigh and foot contributions to the peripheral venous pump

Although the thigh veins are surrounded by muscle, the contribution of the active contraction of thigh muscle to venous return is thought to be minimal. Ludbrook[33] was surprised by his data demonstrating that it required fewer than 10 seconds for normal venous filling in the thigh compared with over a minute for the calf. The virtually instantaneous refill of this segment is consistent with end-exercise pressure measurements in the popliteal vein.[18,38] A thigh segment ejection fraction of 20% was measured with a 15-cm air plethysmographic cuff.[33] Considerably less efficient venous return from the thigh segment was attributed to the observed rapid refill and less compressible intermuscular location of the deep veins in the thigh.

Compression of the plantar venous plexus actively pumps blood proximally.[35] Although the medial and lateral plantar veins are also intermuscular in location, intrinsic muscle contraction coincides with the timing of maximal weight bearing on the foot; compression then forces blood out of the foot. Blood flow from the plantar venous plexus is primarily directed into the paired, deep tibial veins; however, there is disagreement about whether it is all retained in the

deep system. Several investigators describe findings which suggest that flow passes from these and other deep foot veins into both the deep and the superficial venous networks.[39,40] Kuster et al.[40] studied the veins communicating between the deep and suprafascial systems of the foot in 10 unembalmed limbs and identified 6–12 communicating veins per foot. Approximately 50% of these veins had valves that, unlike the perforating veins of the calf and thigh, only allowed flow from the deep veins toward the superficial veins. Even with intraosseus tarsal phlebography, an ankle tourniquet was still needed to direct flow into the deep veins.[39]

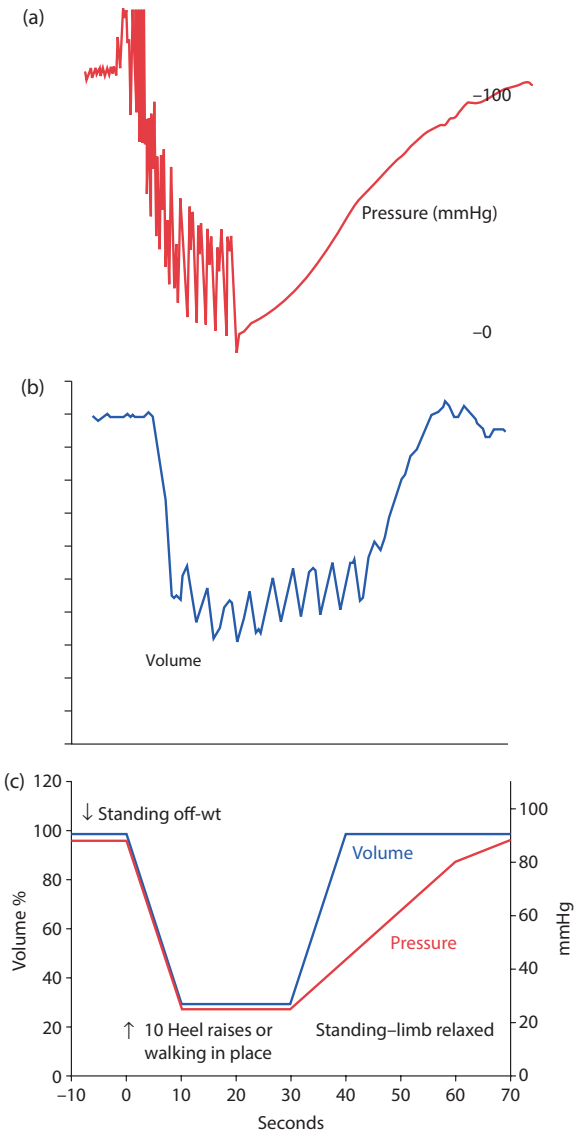
Although the interactions between the various leg pumps are not fully understood, they all work together with competent valve function to return the venous blood from one segment of the extremity to another.

3.4.4 Stroke volume and calf pump output

Like many biological systems, the provision for normal venous return from the peripheral muscle pump greatly exceeds the minimum required for normal function. If we postulate a conservative normal walking cadence of 100 steps/minute and a median ejection volume of 3.0 mL/100 mL in a 2.0-L calf, the calf pump output (CPO) would be 6.0 L/minute. The CPO per limb would be half of this, or 3.0 L/minute. Even by employing these conservative assumptions, the estimated CPO exceeds the resting cardiac output. Logically, if the proportion ejected was reduced, the result would be a less efficient pump and a decreased CPO. For example, in deep venous insufficiency, if the median ejection volume was decreased to 1.7 mL/100 mL, the CPO would still be 3.4 L/minute.

3.4.5 Pressure relationships in the lower extremity

In the normal limb, the pressure is reduced from the resting hydrostatic pressure (~90 mmHg) to a mean of 22 mmHg with ambulatory calf contractions, a value that is reached within 7–12 steps.[5] Similar pressure changes were observed with standing ankle plantar flexion or heel raising, which transfers weight to the forefoot (the tip-toe maneuver).[5,6,14] When resuming a static standing position, the hydrostatic pressure is restored in a mean of 31 seconds (Figure 3.6a–c). As a practical matter, venous pressure studies have generally been obtained from the dorsal foot veins, assuming that the pressure accurately reflects pressure determined from direct cannulation of the deep veins of the calf (posterior tibial). Several authors have compared simultaneous pressures from deep and superficial vein catheters placed at the same anatomic height.[8,18,38,40] These investigations demonstrated that pressures measured in the superficial veins at the ankle closely reflected those in the deep system. However, pressures measured in the skin and subcutaneous (superficial) venous network are most likely to be associated with dermal pathophysiologic changes. The incidence of cutaneous ulceration has a linear relationship with increases in AVPs above



Figures 3.6 The pressure and volume changes with activation of the calf muscle pump are demonstrated. Beginning in the standing posture, the hydrostatic pressure baseline is demonstrated in a dependent, but non-weight-bearing limb. The subject then performs 10 tip-toe (heel raising) maneuvers and resumes the non-weight-bearing posture. **(a)** Pressure changes during these maneuvers are illustrated in this recording from cannulation of a dorsal foot vein, reported in mmHg. **(b)** Volume changes during these maneuvers are illustrated in this air plethysmographic examination. The volume remaining in the limb after exercise divided by the venous volume standing still is reported as the residual volume fraction (RVF, %). **(c)** This schematic compares the pressure and volume changes along a concomitant timeline. Note the efficiency of the calf pump in terms of rapidly reducing either volume or pressure upon the commencement of muscle activity. Although volume filling begins within 5–7 seconds, pressure does not rise substantially for 30–40 seconds. Alterations in these relationships can generate chronic, sustained venous pressure elevations, the end products of which are the symptoms and findings of chronic venous insufficiency.

30 mmHg. Ulceration and an increased AVP was also associated with a 90% refill time of <20 seconds.[14] In addition, rapid reflux (i.e., venous filling of greater than 7 mL/second) is also associated with a high incidence of ulceration.[32]

Contracting muscle and an intact limb fascia are integral components of the peripheral musculovenous pump. During maximal contraction, intramuscular pressures of 250 mmHg are generated in the soleus muscle, and 215 mmHg in the gastrocnemius.[33] More recent studies have suggested that pressures measured within the fascial envelope of the leg ranged from 80 to 90 mmHg in various postural positions.[34] Intravenous pressures taken from the proximal posterior tibial vein rose to >200 mmHg during initial calf contraction, with subsequent peak pressures of >150 mmHg on repetitive contractions. These deep calf pressures fell to 30 mmHg on relaxation.[18] Saphenous vein measurements at the same anatomic height had a lesser initial peak pressure and also demonstrated declining peak pressures with each contraction. The pressure gradient thus favors superficial to deep flow only during the post-contraction relaxation phase of the calf muscle cycle. Pressures in the popliteal vein demonstrate a short rise during the initial calf contraction, which corresponds to expulsion of blood from the calf, but popliteal pressures do not decrease following relaxation; thus, the baseline, resting popliteal vein pressure remains close to the hydrostatic pressure for the greater proportion of the walking cycle.[18,38] The fixed, non-elastic investing fascia of the lower leg provides an unyielding envelope that permits the generation of these high pressures, but also prevents dilation of the capacitance chamber, eliminating an increase in stroke volume as a potential compensatory mechanism for calf pump failure.

Unlike the fascia, normal skin is elastic and can stretch in response to a sustained increase in subcutaneous pressure. The combination of stretched skin, edema, venous hypertension, and minor injury may predispose to ulceration. In contrast to humans, the giraffe exhibits several physical adaptations to its exaggerated physiological demands; these include an elevated interstitial fluid pressure (mean 40–50 mmHg) and a skin structure that is characteristic of a tight and unyielding fascia.[22] Clinically, these considerations are incorporated into therapeutic devices, such as the adjustable Velcro wrap and Unna's boot, which also provide an unyielding external envelope. The gradient compression stocking utilizes elastic in order to provide convenient, flexible, external support.

3.5 PHYSIOLOGIC COMPENSATIONS

3.5.1 Compensation for upright posture

In humans, the primary peripheral circulatory adaptation to the assumption of an upright posture is made by changes in arterial resistance and not by adjustments in venous tone or capacitance.[3,41] Circulatory homeostasis with this switch in position is largely achieved by immediate changes in heart rate and then adjustment in arterial resistance.[2,5,41] When the dependent capacitance vessels (veins) are allowed to continue to fill passively without emptying, the redistribution of blood volume may result in syncope. This is a common problem in fresh military recruits who are learning to stand in formation. Normal individuals who are standing in a static position fidget and shift weight from one leg to another at least once per minute; this frequency is not diminished by extreme heat or cold.[38,42]

3.5.2 Volume depletion: Hemorrhage (acute) and dehydration (chronic)

Compensation for an acute reduction in blood volume and the resulting decrease in venous return is mediated by baroreceptor stimulation and increased sympathetic output. Loss of approximately 10% of the circulating volume may be accommodated without changes in cardiac output or systemic pressure by sympathetic-mediated arteriolar constriction, venoconstriction, and increases in heart rate. Acute loss of approximately 30%–40% of the volume can be tolerated without death, but requires maximal utilization of compensatory mechanisms. Reflex vasoconstriction, which is most prominent in the splanchnic and cutaneous distributions, is accompanied by increased circulating catecholamines in severe acute blood loss. Canine studies suggest that acute volume depletion of approximately 29% (20 mL/kg) can be compensated for by the combination of vasoconstriction and transcapillary fluid reabsorption (6 mL/kg). Thus, 10–15 mL/kg is compensable by active venoconstriction and passive elastic recoil resulting from both reduced arterial pressure and vasoconstriction.[1,2]

Over a prolonged time interval, an individual can compensate for loss of almost 50% of the blood volume (35 mL/kg). The transfer of extracellular fluid volume to the circulating volume and the hormonal effects of aldosterone and the renin–angiotensin system are both involved in the accommodation of chronic volume loss of this degree.[1,2] Both acute and chronic adjustments to volume depletion are primarily achieved through the control of arterial resistance, with veins playing a passive, but essential role.

3.5.3 Musculoskeletal activity

To supply the enormous blood flow required by exercising muscle, three major circulatory accommodations take place.[1] First, cardiac output may increase by five to seven times relative to the normal resting values. Second, the mean arterial pressure rises by 20–80 mmHg. Third, the mass sympathetic discharge produces diffuse arteriolar constriction and venoconstriction. Local effects produce vasodilation of the muscle arterioles because local metabolic effects override the sympathetic signals to vasoconstriction.

Deterioration of calf pump function at the end of the day was observed using both photo and air plethysmography.[36,37] Although the variance was relatively limited, these findings suggest that venous return from the limb deteriorates with prolonged upright activity. The explanation for these findings may be related to stress relaxation of venous smooth muscle.

It is probable that the calf pump mechanism normally compensates for venous insufficiency, whether refluxive or obstructive in nature. However, calf pump function and ankle range of motion are progressively diminished with increasing severity of CVI.[6,7,11,12] The potential role of the calf pump in venous insufficiency has been known for some time, but little has been done in a direct attempt to effect a therapeutic intervention. The hypothesis that physical conditioning that is directed to improve calf pump function could be of therapeutic value was addressed in a small, randomized controlled trial; both improved calf pump function and muscle strengthening were observed.[43]

3.5.4 Temperature adjustment

Regulation of heat loss from the body is a major determinant of skin blood flow. A decrease in temperature produces cutaneous arterial vasoconstriction as well as subcutaneous venoconstriction. The combination of local and central effects can reduce skin blood flow to less than 3 mL/minute/100 g.[16] Additional physiologic compensations for cold include shivering, hunger, and catecholamine secretion.

Compensatory mechanisms to achieve heat loss include increased cutaneous arterial flow and increased subcutaneous venous capacitance. Maximal skin blood flow may increase by over 10-fold to 30 mL/minute/100 g with flows of 2–3 L/minute.[16] Additional physiologic compensations for heat include sweating, increased respiration, and decreased activity. At the extremes of ambient temperature (0–55°C), venous pressure measurements in normal individuals exhibit pathological findings.[42] By gradually adjusting ambient temperatures between 0°C and 55°C, toe temperatures of 23°C and 39°C, respectively, were recorded when subjects were stressed to the clinical end-points of shivering or sweating (Figure 3.7).[42] A cold extremity never achieved a full hydrostatic pressure head and required prolonged filling to reach even a reduced hydrostatic pressure. A warm extremity achieved a full hydrostatic pressure almost immediately, making assessment of post-exercise pressures difficult.[42] Although specifically determined in relatively extreme temperatures, these findings for AVP determinations have implications for other methods of venous testing as well. Therefore, the rooms used for these examinations should be maintained within a reasonable range of comfortable ambient temperatures.

3.5.5 Other

Active venoconstriction occurs with hyperventilation, cold showers, strong emotion, and muscular exercise; it is mediated by the adrenergic (sympathetic) nervous system.[3] Ongoing research continues to seek effective pharmacological solutions for venotonic therapy.[4]

Although a specific neural pathway for venodilation has not been identified in humans, the paracrine mechanism of the endothelial-derived relaxing factor has been an important focus of recent research. Now recognized as nitric oxide,

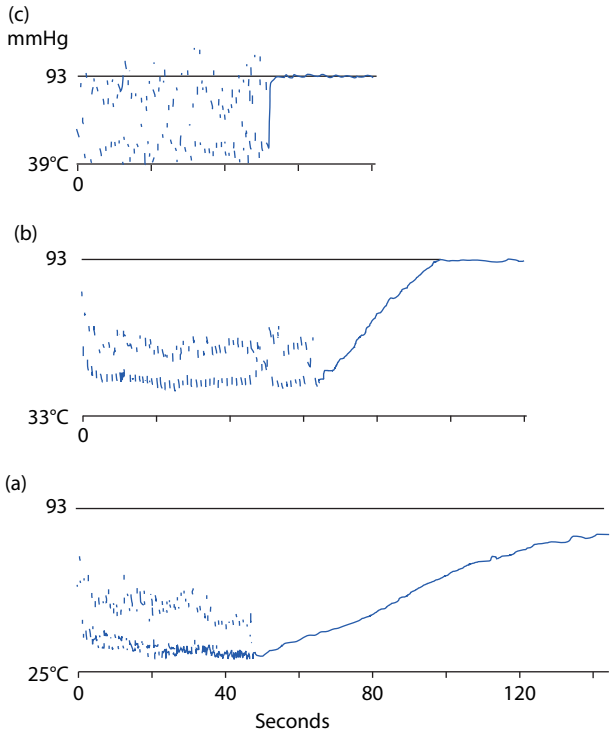


Figure 3.7 Changes in an ambulatory venous pressure tracing at extremes of ambient temperature (the temperature markings indicate toe temperatures). At a toe temperature of 33°C **(b)**, ambulatory venous pressure returns to the baseline hydrostatic pressure at 40 seconds, which is considered normal. Note the absence of a return to the baseline hydrostatic pressure (93 mmHg) in **(a)** cold conditions, and the immediate return to baseline hydrostatic pressure in **(c)** hot conditions. (From Henry JP, Gauer OH. *J Clin Invest* 1950;29:855–61.)

its vasodilator effect in the venous circulation is minimal compared with its effects in the arterial circulation. A clinical correlate was described by Lüscher et al.,[24] who studied internal mammary arteries, internal mammary veins, and saphenous veins harvested for coronary arterial bypass grafts. The relaxation response of the veins was markedly reduced compared with the artery (Figure 3.8). The authors postulated that these physiological characteristics influenced the patency of arterial and venous bypass conduits.

3.6 SUMMARY

Understanding the normal venous circulation requires mastery of complex hemodynamic and physiologic concepts. Gravity-induced hydrostatic pressure encourages flow into the dependent capacitance network. The distensibility of the venous wall permits the system to accept (or contribute) large-volume adjustments with a minimal rise (or fall) in pressure.

Venous return flows along a pressure gradient, just as the arterial and microcirculation flows do. The return of venous blood against gravity is accomplished by breaking the system into multiple pumped segments with internal

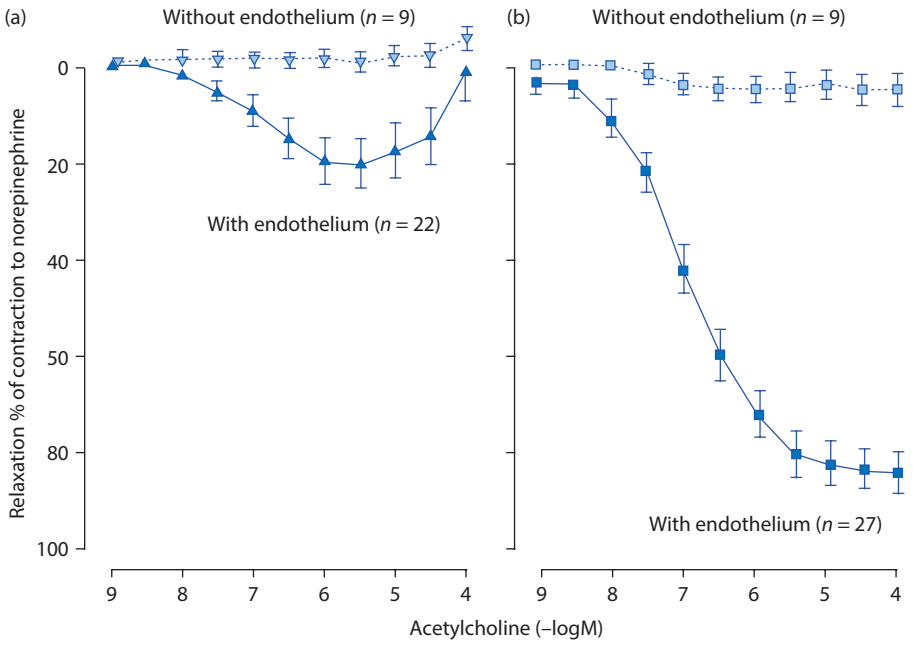


Figure 3.8 Endothelium-dependent relaxation responses to acetylcholine (ACH) in (a) human saphenous vein and (b) human internal mammary artery. (From Lüscher TF et al. *N Engl J Med* 1988;319:462–7.)

valves preventing the return of ejected blood. The calf muscle pumping mechanism is very efficient and empties into a capacious, valved, popliteal vein. Acute circulatory adaptation associated with standing, volume deficiencies, or changes in temperature are largely compensated for by reflex alterations in resistance vessels, in conjunction with adjustments of venous tone. The complex physiologic interactions of the return circulation provide a homeostatic milieu that supports varied human demands for function in a wide variety of circumstances.

Guidelines 1.2.0 of the American Venous Forum on the physiology and hemodynamics of the normal venous circulation

No.	Guideline	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.2.1	Venous return follows a continued dynamic pressure gradient. The majority of the energy imparted by the pumping action of the heart is dissipated in distribution to the arterial circulation.	A
1.2.2	The hydrostatic pressure in the venous system is directly related to the height of the column of blood in relation to the zero point of the right atrium.	A
1.2.3	Venous return against gravity is accomplished by the combined action of an active extremity muscle pump and one-way venous valves.	A
1.2.4	The plantar venous pump acts to prime the calf muscle pump.	C
1.2.5	The thigh muscle pump contributes little to venous return.	B
1.2.6	The anatomic structure of a vein allows for great variation in its diameter. This facilitates the capacitance function of the venous system for adjustment to volume and temperature changes.	A
1.2.7	External pressure on collapsible proximal veins increases distal venous pressure.	B

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● = Key primary paper
★ = Major review article

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4

Classification and etiology of chronic venous disease

ROBERT L. KISTNER AND BO EKLÖF

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The need for an accurate classification system in venous disease is fundamental to understanding the clinical disease processes and to inter-institutional communication about the separate entities. The imprecise diagnoses that were the norm in venous disease throughout the ages have been replaced by accurate imaging studies since the introduction of noninvasive ultrasound scans in the 1980s. Once presented with the ability to make accurate diagnoses of the cause and mechanism of chronic disease in the individual segments of the lower extremity veins, it was necessary to devise a classification system that was capable of organizing the data in a meaningful way.

In 1994, the American Venous Forum convened a subcommittee of world experts in chronic venous disease (CVD) to address this challenge. Recognizing that a modern classification of CVD must now embrace more than just the clinical state of the patient, this committee created the "CEAP" classification, which provides a system where the multiple variations of CVD can be communicated in a clinically and scientifically meaningful manner, enabling analysis and comparison of treatment modalities for similar conditions.[1]

Because identical clinical presentations of CVD arise from different etiologies and the distribution of specific pathologic processes have different implications for treatment and long-term prognosis, the CEAP classification organizes these elements into its methodology. In the CEAP system, the clinical state (C) is amended by the etiologic basis (E) for the disease in each case, and this is described in terms of the anatomic distribution (A) of the pathophysiologic process (P) throughout the axial venous drainage from the calf to the diaphragm. This organization of information has been successfully promulgated around the world by the international representation that devised it. Its wide acceptance has become fundamental to inter-institutional communication and to the description of chronic venous disorders.

4.1 DEVELOPMENT OF THE CEAP CLASSIFICATION

The CEAP classification that was introduced in 1994[1] provides a framework around which the clinical manifestations found in CVD are paired with key pathologic elements of causation and physiologic mechanisms in specific anatomic locations of the lower extremity. Specifically, for each clinical condition, it distinguishes:

- Primary from secondary and from congenital causes of the problem
- Reflux from obstructive pathophysiology
- The precise anatomic segments affected by reflux or obstruction through 18 named segments of the lower extremity venous tree

In this way, clinical manifestations are coupled with the precise pathological entity from which the natural history of the pathologic processes and the effects of management alternatives for similar clinical states can be identified and studied. The classification describes the status of the disease process at a point in time; these details can change over time with the introduction of interval treatments and with the

natural history of the disease process. By interval CEAP examination, the longitudinal changes that occur over time or after interventions can be documented.

This classification addressed the considerations imposed by modern diagnostic and treatment capabilities. It was incorporated into the updated Reporting Standards for Venous Disease in 1995[2] and became known as the CEAP classification. Its acceptance has been promulgated by venous authorities around the world, and it has been published in most native languages. This worldwide dissemination addresses the need for a universal classification system that enables accurate communication between institutions and countries regarding the details of CVD and the results of different forms of treatment.

The CEAP classification was originally intended to be a dynamic document that could be amended in the future in light of experience with its usage. Several evaluations of the clinical categories[3] and of the appended scoring systems[4] based upon CEAP have been published,[5–7] and provide both validity to and critique of their content. After the first 10 years of clinical usage, CEAP's validity and usefulness underwent its first critical review in 2004 in order to make needed revisions by a new international subcommittee of the American Venous Forum, chaired by Professor Bo Eklöf. In this revision,[8] the fundamental structure of the CEAP categories was affirmed and retained; additions to the classification included specific definitions of terms, clarification of details within the C class, and improvements in the methods of recording the findings in order to render the classification more complete in its long form and more user friendly in its short form. This chapter will present the approved revised format of CEAP, and will examine the fundamental importance of defining the etiologic basis of the clinical problem.

4.2 "REVISED" CEAP DOCUMENT[8]

The CEAP classification divides CVD into its component parts of clinical manifestations, etiologic basis for the disease, anatomic distribution of the disease, and pathophysiologic mechanism operating in the venous segments affected by the disease. Each of these elements of CVD is specifically defined within the classification in order to achieve uniform reporting wherever the classification is used, and thereby enable inter-institutional communication regarding similar problems throughout the world. It is important to understand that the classification is a time-specific qualitative assessment of the disease process, which requires interval updating for follow-up assessment of the individual case or for longitudinal studies that track the natural history of a disease entity.

The contents of the revised tables follow:

C (Table 4.1): the clinical classification is divided into seven classes of progressive severity ranging from C0, representing no diagnosable venous disease, through to telangiectasias/reticular veins, varicose veins, venous edema, mild and severe skin changes, and venous ulcer, divided into healed ulcer and active ulcer categories. The clinical category is amended by a notation to indicate whether the diagnosed abnormalities were accompanied by symptoms (s) or were asymptomatic (a). This ordering of the severity of the clinical manifestations was proposed in the initial report of the CEAP classification, and has been retained in validity studies of disease severity scoring.[4,5]

E (Table 4.2): the etiologic classification is divided into three classes of congenital, primary, and secondary categories, and a new designation to indicate instances in which no etiologic basis could be determined (En). Congenital disease refers to named, recognized problems, where the vessels themselves are deformed from birth, such as the Klippel–Trenaunay deformity. Primary disease refers to cases with degeneration of elements of the normally formed vein wall with valvular reflux, typified by varicose veins. Secondary disease refers to acquired deformities of the veins in which elements of obstruction and reflux often coexist, as in post-thrombotic veins.

A (Table 4.3): the anatomic classification is divided into three categories to denote superficial, perforator, and deep vein involvement, and a new category to indicate that no anatomical category could be determined (An). This simple anatomical classification is supplemented by 18 named segments (Table 4.4) of the veins from the infra-diaphragmatic inferior vena cava to the crural

Table 4.1 Clinical classification

Classification	Description
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation and/or eczema
C4b	Lipodermatosclerosis and/or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer
S	Symptoms including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, as well as other complaints attributable to venous dysfunction
A	Asymptomatic

Table 4.2 Etiologic classification

Classification	Description
Ec	Congenital
Ep	Primary
Es	Secondary (post-thrombotic)
En	No venous etiology identified

Table 4.3 Anatomic classification

Classification	Description
As	Superficial veins
Ap	Perforating veins
Ad	Deep veins
An	No venous location identified

veins, which are used in the following section to locate the segments of reflux and obstruction.

P (Table 4.5): the pathophysiologic classification is divided into two categories of reflux and obstruction, and a third category when elements of both reflux and obstruction coexist. A new category (Pn) is added in the revised format to indicate that no determination was made for reflux and obstruction.

When reflux and/or obstruction are found, the anatomic segments afflicted with each problem are identified by using the 18 designated segments described under anatomic classification (Table 4.4).

It is recognized that post-thrombotic disease is a dynamic process in which elements of obstruction become altered by the process of recanalization and maturation of the thrombus to yield a variable mix of reflux and obstruction in the later stages. This evolution of post-thrombotic changes may present as reflux, obstruction, or a mixture of both; the CEAP system allows for segment-by-segment classification of these findings at the time of the examination. Serial examinations can be used to catalogue the dynamic changes of reflux and obstruction that occur in the specific case over time.

Table 4.4 Venous anatomic segment classification

Classification	Description
Superficial veins	
1	Telangiectasias/reticular veins
2	Greater saphenous vein above knee
3	Greater saphenous vein below knee
4	Small saphenous vein
5	Non-saphenous veins
Deep veins	
6	Inferior vena cava
7	Common iliac vein
8	Internal iliac vein
9	External iliac vein
10	Pelvic: gonadal, broad ligament veins, other
11	Common femoral vein
12	Deep femoral vein
13	Femoral vein
14	Popliteal vein
15	Crural veins: anterior tibial, posterior tibial, peroneal veins (all paired)
16	Muscular veins: gastrocnemius, soleal, other
Perforating veins	
17	Thigh perforator veins
18	Calf perforator veins

Table 4.5 Pathophysiologic classification

Classification	Description
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

4.3 TERMINOLOGY AND NEW DEFINITIONS

The CEAP classification deals with all forms of chronic venous disorders. The term "chronic venous disorder" includes the full spectrum of morphological and functional abnormalities of the venous system, from telangiectasias to venous ulcers. Some of these, like telangiectasias, are highly prevalent in the normal adult population, and in many cases the use of the term "disease" is not appropriate. After the revision of CEAP in 2004, the VEIN-TERM transatlantic consensus was organized in 2007 in order to update the terminology of chronic venous disorders under the auspices of the American Venous Forum, the European Venous Forum (EVF), the International Union of Phlebology, the American College of Phlebology, and the International Union of Angiology. The VEIN-TERM consensus was established to complement terms previously defined in the revision of CEAP.

4.3.1 Definitions in the revision of CEAP of 2004[8]

Telangiectasia: A confluence of dilated intradermal venules of less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins.

Reticular veins: Dilated bluish subdermal veins usually from 1 mm to less than 3 mm in diameter. They are usually tortuous. This excludes normal visible veins in people with thin, transparent skin. Synonyms include blue veins, subdermal varices, and venulectasias.

Varicose veins: Subcutaneous dilated veins equal to or more than 3 mm in diameter measured in the upright position. These may involve saphenous veins, saphenous tributaries, or non-saphenous superficial leg veins. Varicose veins are usually tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose veins. Synonyms include varix, varices, and varicosities.

Corona phlebectatica: A fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot. This is commonly thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare.

Edema: A perceptible increase in the volume of fluid in the skin and subcutaneous tissue, which characteristically indents with manual pressure. Venous edema refers to edema in the leg, ankle, or foot associated with identifiable reflux or obstruction in the veins appropriate to the site of swelling. It usually occurs in the ankle region, but it may extend to the leg and foot.

Pigmentation: A brownish darkening of the skin resulting from extravasated blood, which usually occurs in the ankle region, but may extend to the leg and foot.

Eczema: An erythematous dermatitis, which may progress to a blistering, weeping, or scaling eruption of the skin of the leg. It is most often located near varicose veins, but may be located anywhere in the leg. Eczema is usually seen in uncontrolled CVD, but may reflect sensitization to local therapy.

Lipodermatosclerosis (LDS): Localized chronic inflammation and fibrosis of the skin and subcutaneous tissues of the lower leg, sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin that may be painful and is often referred to as hypodermitis. This condition must be distinguished from lymphangitis, erysipelas, or cellulitis by its characteristically different local signs and systemic features. LDS is a sign of severe CVD.

Atrophie blanche or white atrophy: Localized, often circular whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. This finding is a sign of severe CVD and not to be confused with healed ulcer scars. Scars of healed ulceration may also have atrophic skin with pigmentary changes, but are distinguishable by history of ulceration and appearance from atrophie blanche and are excluded from this definition.

Venous ulcer: Full-thickness defect of the skin, most frequently in the ankle region, which fails to heal spontaneously and is sustained by CVD. Defined by Guidelines for Management of Venous Leg Ulcers as "an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension."[9]

4.3.2 Added definitions in the VEIN-TERM consensus of 2007[10]

4.3.2.1 CLINICAL VENOUS TERMS

Chronic venous disease: Morphological and functional abnormalities of the venous system of long duration manifested either by symptoms and/or signs indicating the need for investigation and/or care.

Chronic venous insufficiency (C3–C6): A term reserved for advanced CVD, which is applied to functional abnormalities of the venous system producing edema, skin changes, or venous ulcers.

Venous symptoms: Complaints related to venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness, and/or fatigue. Although not pathognomonic, these may be suggestive of CVD, particularly if they are exacerbated by heat or dependency in the day's course, and may be relieved with leg rest and/or elevation. Existing venous signs and/or laboratory evidence are crucial in associating these symptoms with CVD. However, symptoms without signs (C0s) are common problems. A consensus committee on venous symptoms has been organized by the EVF, and the report should be available in 2016.

Venous signs: Visible manifestations of venous disorders, which include dilated veins (telangiectasias, reticular veins, and varicose veins), leg edema, skin changes, and ulcers, as included in the CEAP classification.

Recurrent varices: Reappearance of varicose veins in an area previously treated successfully.

Residual varices: Varicose veins remaining after treatment.

PREVAIT: This acronym stands for presence of varices (residual or recurrent) after intervention.

Post-thrombotic syndrome: Chronic venous symptoms and/or signs secondary to deep vein thrombosis (DVT) and its sequelae.

Pelvic congestion syndrome: Chronic symptoms which may include pelvic pain, perineal heaviness, urgency of micturition, and post-coital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower leg varices.

Varicocele: Presence of scrotal varicose veins.

Venous aneurysm: Localized saccular or fusiform dilatation of a venous segment with a caliber of at least 50% greater than the normal trunk.

4.3.2.2 PHYSIOLOGICAL VENOUS TERMS

Venous valvular incompetence: Venous valve dysfunction resulting in the retrograde venous flow of an abnormal duration.

Venous reflux: Retrograde venous flow of abnormal duration in any venous segment.

- *Primary:* Caused by idiopathic venous valve dysfunction
- *Secondary:* Caused by thrombosis, trauma, or mechanical, thermal, or chemical etiologies
- *Congenital:* Caused by the absence or abnormal development of venous valves

Axial reflux: Uninterrupted retrograde venous flow from the groin to the calf.

- *Superficial:* Confined to the superficial venous system
- *Deep:* Confined to the deep venous system
- *Combined:* Involving any combination of the three venous systems (superficial, deep, and perforating)

Segmental reflux: Localized retrograde flow in venous segments of any of the three venous systems (superficial, deep, and perforating) in any combination in the thigh and/or calf, but *not* in continuity from the groin to the calf. Explanation: the now-recognized significance of axial reflux in the pathophysiology of venous ulcers[11] justified the distinctions made in order to clarify the definitions of different types of lower extremity venous reflux with axial reflux, defined as uninterrupted retrograde

venous flow from the groin to the calf in continuity. It was accepted that axial reflux might be confined to the superficial or deep systems, but could also involve any combination of the superficial, deep, and perforator systems. This is in contrast to "segmental reflux," defined as localized retrograde flow in any of the three venous systems, but without continuity from the groin to the calf.

Perforator incompetence: Perforating veins with outward flow of abnormal duration.

Neovascularization: Presence of multiple new small, tortuous veins in anatomic proximity to a previous venous intervention.

Venous occlusion: Total obliteration of the venous lumen.

Venous obstruction: Partial or total blockage to venous flow.

Venous compression: Narrowing or occlusion of the venous lumen as a result of extra-luminal pressure.

Recanalization: Development of a new lumen in a previously obstructed vein.

Iliac vein obstruction syndrome: Venous symptoms and signs caused by narrowing or occlusion of the common or external iliac vein.

May–Thurner syndrome: Venous symptoms and signs caused by obstruction of the left common iliac vein due to external compression at its crossing posterior to the right common iliac artery.

4.4 WRITING OF THE CEAP

The method of recording the CEAP classification is important. When this was addressed in the 2004 revised CEAP, a simplified "basic CEAP" was added to the original "full CEAP" method of recording. The revised format[8] includes three basic elements to be included in the CEAP recording:

1. The CEAP findings
2. Date of the examination
3. Diagnostic "level" of the examination:
   a. *Level 1:* History, physical, and Doppler examination (hand-held)
   b. *Level 2:* Noninvasive: duplex scan and plethysmography
   c. *Level 3:* Invasive: venography, venous pressure, intravascular ultrasound (IVUS), spiral computed tomography (CT), and magnetic resonance venography (MRV)

4.4.1 Full CEAP

The full (advanced) CEAP classification system is essential for standardized reporting in scientific journals and for the researcher. It enables grouping of patients so that similar types of patients can be analyzed together for the study of both group and sub-group elements of C, E, A, and P. This complete classification, for example, enables any of the 18 named venous segments to be identified as the location of venous pathology. Consider a patient with pain, varicose veins, and LDS, where duplex scan confirms primary reflux of the greater saphenous vein (GSV) and incompetent perforators in the calf. The classification here would be:

$$\mathrm{C2,4b-S;\ Ep;\ As,p;\ Pr2,3,18.}$$

4.4.2 Basic CEAP

This format provides simplifications of the full format for more informal usage. It is meant to replace the habit of simply using the highest clinical class to denote the venous problem, a practice discouraged as being too incomplete.

Basic CEAP applies two simplifications:

1. The single highest descriptor can be used for clinical classification. For example, a patient with varicose veins, swelling, and LDS would be C4b (as opposed to the full CEAP format of C2,3,4b).
2. The anatomic segments are deleted. For example, the full CEAP format of:

$$\mathrm{C2,4b-S;\ Ep;\ As,p;\ Pr2,3,18.}$$

would be simplified to:

$$\mathrm{C4b-S;\ Ep;\ As,p;\ Pr.}$$

Venous disease is often considered to be a simple problem undeserving of a multi-categorized classification format. The truth is that venous disease is not so simple, and it demands well-defined categorical descriptions in order to be understood. In modern phlebological practice, the majority of patients should have a duplex scan of the leg veins in order to diagnose the E, A, and P categories of the CEAP classification. This examination is in contrast to an ultrasound survey of the limb for DVT and superficial venous thrombosis (SVT).

4.4.3 Identifying the date and method of examination

CEAP is not a static classification; it can be altered by factors such as a corrective treatment or a more definitive test, or simply the effect of the passage of time on the natural evolution of the disease process. For this reason, the date and the method of testing (Doppler, duplex scan, venography, etc.) used for a particular classification should be recorded.

Method of investigation: the accuracy of the diagnosis increases with the addition of imaging and invasive testing in CVD. Three "levels" of testing are outlined:

Level 1: The office visit with history and clinical examination, which may include use of a hand-held Doppler.

Level 2: The noninvasive vascular laboratory, which includes duplex color scanning and plethysmography.

Level 3: Tnvasive investigations or more complex imaging studies, including varicography, ascending and descending venography, venous pressure measurements, IVUS, spiral CT scan, or MRV.

4.4.4 Recording of the date and method used can be added in parentheses after the CEAP recording as follows

Basic form: C4b–S; Ep; As,p; Pr (Level 2; 8/21/2015)
Full form: C2,4b–S; Ep; As,p; Pr2,3,18. (Level 2; 8/21/2015)

4.5 CLINICAL APPLICATION OF CEAP

Example I (Figure 4.1 and Table 4.6): a patient presents with painful swelling of the leg and varicose veins, LDS, and active ulceration. Duplex scanning on May 17, 2015, showed axial reflux of the GSV above and below the knee, incompetent calf perforators, and axial reflux in the femoral and popliteal veins. There were no signs of post-thrombotic obstruction.

This entire paragraph is presented in CEAP as follows:

- Classification according to full CEAP:

C2,3,4b,6 – S; Ep; As,p,d; Pr2,3,18,13,14 (L2; 5 / 20 / 2015).

- Classification according to basic CEAP:

C6 – S; Ep; As,p,d; Pr. (L2; 5 / 20 / 2015).

Example II (Figure 4.1 and Table 4.6): six patients present with severe skin changes typical of advanced C4–C6 changes. From inspection alone, the clinical class of C4–C6 venous disease would be diagnosed, and many physicians would assume that all of these are due to post-thrombotic

Figure 4.1 Six cases of ulceration. **(a)** Isolated perforator reflux, (b) GSV and perforator reflux, (c) GSV reflux, (d) no venous disease, (e) post-thrombotic reflux: deep and superficial, and (f) primary reflux: deep, perforator, and GSV.

Table 4.6 CEAP classification and diagnosis of six patients with leg ulcers (Figure 4.1)

Case	CEAP
1 Isolated perforator reflux	C2,3,4b,6,-s; Ep; As,p; Pr18
2 Greater and perforator reflux	C2,3,4b,6,-s; Ep; As,p; Pr2,3,18
3 GSV reflux	C2,3,4b,6,-s; Ep; As,p; Pr2,3
4 No venous disease	C3,4b,6,-s;En; An; Pn
5 Post-thrombotic reflux: deep and perforating	C2,3,4b,6,-s; Es; As,p,d; Pr2,3,11,13,14,15,18
6 Primary reflux: deep, perforating, and GSV	C2,3,4b,6,-s; Ep; As,p,d; Pr2,3,11,13,14,15,18

disease. After full investigation, six different diagnoses emerged (Table 4.6).

These cases illustrate that the full CEAP classification is needed to identify the actual entity behind similar-appearing clinical conditions. The clinical class is C4–C6 in all six cases, but the details of E, A, and P vary widely. Treatment of these cases could range from simple ablation of the GSV or perforator veins for cases 1, 2, and 3, through to the potential for extensive deep vein reconstruction in cases 5 and 6, to no venous treatment at all for case 4.

4.6 IMPORTANCE OF DEFINING ETIOLOGY

Knowledge of the etiologic basis of the CVD process is fundamental to understanding the clinical progress and treatment of the disease. The three categories within etiology are entirely different in that the congenital cases represent malformation of the blood vessels, the primary cases represent a degenerative process in the normally formed vessel walls and valves, and the secondary cases represent an acquired inflammatory destructive process which incorporates destructive and reparative elements in its disease progression. Congenital cases are distinctive and relatively rare and are not further detailed in this discussion.

4.7 COMPARISON OF PRIMARY AND SECONDARY CVD

In primary and secondary CVD, the natural history and the treatment alternatives have major differences, but the clinical manifestations can be similar to the point of being indistinguishable (Figure 4.1). For too long, it has been accepted that the difference between primary venous insufficiency (PVI) and post-thrombotic secondary venous insufficiency (SVI) disease is of little relevance, since practical treatment of the two conditions is largely limited to providing external support for the duration of active life. An early report of the striking clinical similarities and the marked pathological differences between primary and secondary disease was beautifully described by Bauer in 1948 when he recognized, using descending venography for diagnosis, that 58% of his cases of advanced venous insufficiency were due to non-post-thrombotic disease.[12] With the later development of noninvasive imaging through ultrasound to correctly diagnose reflux and its apparent etiologic basis, the current standard of practice should be accuracy in diagnosis and specificity in treatment for chronic venous conditions. Knowledge of the natural history of the clinical problem provides a guide to preventive therapies, such as anticoagulation, or targeted sites for corrective surgery, and is essential if progress is to be made in the interventional management of chronic venous disorders. Consideration of the differences between PVI and SVI follows (Tables 4.6 and 4.7).

4.7.1 Primary venous insufficiency

PVI is a degenerative condition of the venous walls and valves. It usually begins as mild reflux in the superficial veins of the lower extremity.[13] In early stages, veins retain their fundamental elements of valves and intima. The superficial and perforator veins that are affected early are expendable because of their location and function. The sole pathophysiologic process in PVI is reflux. The condition is widespread in the population (20%–30% of the adult population[14,15]) and significantly more prevalent than post-thrombotic disease. The distribution of the affected veins in PVI begins in superficial veins of the lower extremity and progresses to involve perforator and ultimately deep veins in more advanced cases. Progression of PVI in the superficial veins can be tracked by using the anatomic elements of the full CEAP classification, which detail the patency and competence of all of the venous segments. Consecutive recording of these details over time details the progression of reflux and obstruction in additional segments of the leg veins. Reflux advances longitudinally up and down the extremity with the passage of time until it becomes axial. At this stage,

Table 4.7 Comparative features of primary versus post-thrombotic disease

Primary venous insufficiency	Secondary venous insufficiency
Degenerative	Acquired (inflammatory)
Reflux only	Obstruction–reflux
Intima retained	Intima destroyed
Valves stretched and atrophied	Valves scarred and destroyed
Primarily superficial veins	Primarily deep veins
Widespread occurrence	Limited occurrence
Slow progress to C4–C6 of decades	Faster to C4–C6 of years
Treatment: support and superficial surgery	Treatment: anticoagulant and support
Early surgery for quality of life	Late surgery for C4–C6 complications

continuous reflux may develop from the groin or upper thigh level to the lower calf or ankle level. Investigators have long been impressed with the importance of axial reflux in cases of PVI that have progressed to the advanced stages of CVI.[11,14,16,17]

Deep vein reflux is a late development in PVI; it is seen in fewer than 10% of early C1–C2 cases compared to about 70% of advanced (ulcerative) PVI cases in some series.[18] Large demographic studies of CVI demonstrate a preponderance of PVI over SVI as the etiology of the venous stasis syndrome and venous leg ulcers.[14,17] Smaller studies of venous ulcers have reported variable percentages of PVI versus SVI, reflecting the fact that either can cause ulceration.[18,19]

In its milder forms (CEAP C2), PVI affects >20% of the total adult population from 18 to 80 years of age, but the incidence rises to 50% of those from 50 to 70 years of age.[20–23] With the advent of large-scale imaging studies to track the natural history of PVI, there is clear evidence that it is a slowly progressive disorder which may advance to C4–C6 manifestations over time.[23,24–26] The frequency of its progression from clinical class 2 through to 6 remains under investigation,[24] although evidence is accumulating that the occurrence of progression is predictable in a high percentage of PVI cases. For those afflicted with early-stage PVI, the risk of advancing to ulceration rises as the individual progresses from C2 through to C4. This risk appears to rise to the range of 20%–40% for those with progressive changes.[14,16,17] In its far-advanced presentation, when it affects the deep veins, primary disease can be as devastating as late post-thrombotic disease, but the medical and surgical treatment considerations are distinctly different.[27–29]

Medical management of primary disease is limited to external support or limitation of activity. Drug treatment of symptomatic venous disorders is popular in Europe, but not recommended in the United States. Surgical management in primary disease varies from ablation of the offending segments of the superficial and perforator veins in the early stages to definitive repair of deep valve reflux in late stages. The results of definitive surgical treatment have been found to be long-lasting in 70%–90% of superficial and perforator cases[30–32] and 70% of deep vein valve repairs.[28,29,33,34] The very-long-term question relates to how many of these cases are permanently rescued from progression to ulceration, and how long the favorable course after surgical repair remains effective.

4.7.2 Secondary venous insufficiency

In contrast to primary disease, post-thrombotic secondary disease is an acquired inflammatory venous problem that begins as a purely obstructive phenomenon and evolves into a mixture of reflux and obstruction in the deep veins. It begins in superficial veins infrequently compared to its occurrence in deep veins.[35,36] Its effect is to interrupt the vessel linings and contained valve structures in at least half of the cases of proximal DVT in the lower extremity. In the majority of cases, the obstructive process undergoes recanalization of the obstructed lumina during the first 6–12 months,[37] and this process leads to a combination of partial obstruction and variable degrees of reflux in the diseased lumen due to synechiae, septae, and multi-channeled lumina in the deep veins. The ultimate result is variable destruction of venous valves, the development of collateral pathways around persistent obstructions, and tendencies to recurrent episodes of venous thrombosis.[35–37] None of these events are seen in primary disease.

The differences in pathologic development between primary and secondary post-thrombotic disease are outlined in Table 4.7. Since a competent saphenous system can provide compensating venous outflow in cases where the deep system has a significant obstructive element, the pre-existing status of the saphenous veins is of importance in the future course of DVT. When major DVT occurs in an individual who has pre-existing primary reflux of the saphenous veins, the venous return from the extremity is exposed to the double jeopardy of both reflux and obstruction, and the clinical condition may deteriorate more rapidly.

For advanced stages of post-thrombotic reflux and obstruction, there are highly individualized surgical techniques for providing substitute valves,[28,29,38] or for disobliterating the iliac vein[39,40] or shorter distal segments.[41] Bypass procedures are useful in secondary disease on a highly selective basis (e.g., short segment bypass with endophlebectomy),[41] while they have no role in primary disease, since there is no obstructive component except in the iliac vein syndrome, where angioplasty and stenting is now the treatment of choice. Various forms of valve substitution[33] or autogenous valve reconstruction[38] have been successful, although they require major surgery and can be attended by a significant rate of recurrent disease. Repair of valves that were not deformed by the thrombotic process can be very successful.[28,33,34] Recent experience with endovenous stenting[39,40] has been highly successful in the iliac veins for both PVI (iliac vein syndrome) and SVI (post-thrombotic webs or obstruction).

4.7.3 Influence of knowledge of etiology on the management in CVD

Clinical similarities between primary and secondary disease lead to confusion regarding the natural history and proper treatment of the clinical problem. These similarities include:

1. Both etiologies affect the veins in the beginning and cause similar complications in the skin in their later stages.
2. Both etiologies are attended by swelling and aching in the legs.
3. The clinical sequelae that cause late suffering and disability in CVD are largely due to similar skin and subcutaneous tissue complications in both entities. This

explains why the estimation of disease etiology based upon clinical examination of the skin is unreliable.
4. External support leads to clinical improvement in both etiologies, since it clearly helps to control swelling, and this is crucial to the health of the extremity. The support appears to act by improving the micro-circulation in the superficial tissues, but it is yet to be demonstrated whether it materially improves venous flow.[42,43]

Given the great differences in the disease process between primary and post-thrombotic etiologies, important advantages in case management accrue from classification systems that differentiate these two entities in terms of:

1. The ability to define the natural history of the disease process in terms of complications and length of time to development of complications (i.e., 2–10 years in secondary disease and 5 years to lifetime in primary disease).
2. The realization that the major involvement is of superficial veins in primary cases versus deep veins in secondary post-thrombotic cases.
3. The appreciation that early proximal thrombus removal and anticoagulation are key to the successful prevention of post-thrombotic secondary disease and have no role in primary disease.
4. The usefulness of specific surgical treatment alternatives:
   a. Saphenous vein ablation is essential to the management of primary disease and usually not needed or advisable in secondary disease.
   b. The results of direct deep vein valve repair are superior in primary disease. In post-thrombotic disease, newer techniques of neo-valve reconstruction are favorably reported and undergoing validation studies. Attempts to create neo-valves and valve substitutes are underway. At present, there are cases of post-thrombotic disease where valve reconstruction is not yet feasible.
   c. Other forms of deep vein reconstruction are selectively useful in secondary disease and play no or little role in primary disease below the iliac level, since PVI has no obstructive component.

4.7.4 Influence of knowledge of anatomical and pathophysiologic classifications on the management of CVD

Knowledge of the anatomic and physiologic details is fundamental to understanding the clinical progress and management options in both PVI and SVI. It is within these details that opportunities for the surgical correction of all disease components (reflux and obstruction) can be developed. In addition, the natural course of progressive venous reflux and obstructive phenomena is played out in the segments of the venous tree. For instance, there are no valves in the inferior vena cava and the common iliac veins, so reflux does not play a role in these segments. Likewise, obstructions are not of clinical relevance in pelvic veins other than the iliac veins or in distal tibial veins, since there are many opportunities for collateral circulation in these areas.

The progressive involvement of the superficial veins of the leg is important in PVI. The development of axial reflux in the superficial veins is a key pathway leading to progression in the severity of disease reflected by clinical classes, and the progression of PVI from the involvement of the superficial to the perforator veins and ultimately to the deep veins, appears to be important in the development of venous leg ulcers. These changes are readily identified by segmental recording of the reflux and obstruction within the full CEAP classification. Longitudinal studies of these pathways leads to a better understanding of the progression of PVI. Such studies can identify anatomic segments in the superficial, perforator, and deep veins that constitute the course of axial reflux from the upper thigh to the ankle, as well as determine the segments to be addressed by the surgeon during ablation procedures in order to treat or prevent venous ulcers.

These are some of the reasons that the determination of overall etiology with segmental anatomy and pathophysiology is fundamental to the management of CVD and needs to be an integral part of classification. To make progress possible in CVD management, clinical diagnosis has to be complete and accurate, and the many variations of pathologic processes have to be organized in a manner that enables the analysis of variables. The full CEAP system is the current best approach for this ideal. In clinical practice, the basic CEAP may be chosen as a simpler but adequate compromise.

4.8 CONCLUSIONS

- The CEAP classification and its scoring systems have been validated and critiqued by an international audience (3[1-B], 5[1-B], 6[1-B], 7[1-B]).
- The principle weakness of the original CEAP classification was identified as being inadequate for the differentiation of clinical class C1 (telangiectasia and reticular disease) (3[1-B]).
- The revised CEAP classification retains the basic format and contains important revisions; it replaces the original format (8[1-B]).
- It is necessary that the full CEAP presentation be followed in chronic venous publications in order to adequately describe the venous state (2[1-A], 3[1-B], 8[1-B]).
- Primary disease is a slowly progressive degenerative vein disorder that results in vein wall weakness, producing pure valve reflux, usually beginning in superficial veins (22[1-B], 13[1-B], 12[1-B], 19[1-C]).
- Post-thrombotic secondary disease is a more rapidly progressive inflammatory disease that results in vein valve and wall distortion, producing combinations of obstruction and reflux, usually beginning in deep veins (12[1-B], 35[1-B], 33[1-B]).

Guidelines 1.3.0 of the American Venous Forum on the classification and etiology of chronic venous disease

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.3.1	We recommend using the CEAP (clinical class, etiology, anatomy, and pathophysiology) classification to describe chronic venous disorders. The system has been validated.	1	B
1.3.2	We recommend using the basic CEAP classification to aid clinical practice and the full CEAP classification for clinical research.	1	B
1.3.3	We recommend distinguishing between primary and secondary venous insufficiency, because the two conditions distinctly differ in pathophysiology and management.	1	B

- Primary and secondary post-thrombotic diseases require identification in classification because of the manifold differences in their morphologic and physiologic effects and their clinical management (12[1-B], 35[1-B], 27[1-B], 28[1-B], 30[1-B] 32[1-B]).

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● = Seminal primary article
★ = Key review paper
◆ = First formal publication of a management guideline

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The pathophysiology and hemodynamics of chronic venous insufficiency of the lower limb

JOHN BLEBEA

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5.1 INTRODUCTION

The term chronic venous insufficiency (CVI) is used rather broadly by many physicians in reference to the entire spectrum of non-acute venous disorders. The development and revision of the CEAP classification and the Venous Clinical Severity Scores (VCSS) provided a methodology for describing specific venous disorders and clarified that CVI implies a functional abnormality of the venous system. Both CEAP and VCSS are recommended for use by clinical practice guidelines.[1–3] CVI should be reserved for the description of more advanced disease, beginning with venous edema (C3), but more commonly in conditions with skin changes (C4) or ulceration (C5–C6). In this chapter, we will discuss the pathophysiology and hemodynamics impairing normal function of the superficial and deep venous system. A clear distinction will be made between the roles of obstruction and valvular incompetence.

5.2 SUPERFICIAL VENOUS INCOMPETENCE

In the superficial venous system, the obstruction that occurs with thrombophlebitis is not a major consideration from a hemodynamic perspective. This can be explained by the multitude of superficial venous tributaries available to divert flow through perforating veins into the deep venous system. In addition, the main venous outflow of the leg occurs through deep veins. The mechanism of valvular incompetence and reflux in the superficial system, however, is of great importance because of both its hemodynamic effects and associated clinical sequelae. Currently used ultrasound technology provides reliable and quantitative diagnoses of superficial incompetence, and therapeutic interventions to a large extent are focused on the ablation of these incompetent venous segments. The duplex-derived valve closure time for the diagnosis of superficial reflux is 0.5 seconds.

The etiology of primary superficial valvular reflux is still disputed by some, although the majority of opinion favors a weakness of the vein wall inducing venous dilation and valve ring enlargement. The valve leaflets are no longer able to co-apt completely and valvular incompetence develops. This concept was originally proposed by Cotton more than 50 years ago when he demonstrated, using anatomical casts, that venous dilation developed below rather than above the valves in patients with varicose veins.[4] The previously prevailing descending valvular incompetence theory had been popular since the nineteenth century when Trendelenburg first ligated the saphenofemoral junction. In support of this hypothesis, numerous biochemical abnormalities have been reported within the venous wall, which have an impact on its distensibility. Varicose veins have abnormal elastic properties, with increased collagen content, elastin fiber fragmentation, and degradation and accumulation of extracellular matrix.[5,6] These abnormalities have supported either an initial deficiency in wall integrity or an induction of structural degradation. An early study by Ackroyd et al.[7] showed that the valve ring and its leaflets had far greater tensile strength than the vein wall itself, favoring the theory that valvular incompetence is secondary to a defect in the vein wall.

Secondary valvular dysfunction following episodes of thrombophlebitis undoubtedly occurs in the superficial system, although with less important effects than within

the deep system. After the initial thrombotic event, intrinsic thrombolysis and recanalization allows for blood flow to resume within the previously occluded vein. However, the inflammatory and fibrotic processes in the valve cusp restrict the movement of the leaflets, resulting in only a partially mobile leaflet or a completely "frozen valve" (Figure 5.1). The end result is valvular incompetence and reflux. In addition, inflammation of the non-valvular segments of the vein can lead to thickening and calcification in the wall (Figure 5.2). It is unclear to what degree this loss of elasticity and distensibility affects venous flow hemodynamics but, at a minimum, it must decrease volume flow in those segments because of the diminished luminal diameter.

An additional component to be considered is the gravitational pressure effect on superficial venous flow. The additional hydrostatic pressure upon standing undoubtedly increases the outward wall tension and thus the distension of the vessel. Superimposed on a structurally weakened wall, this supplementary force can increase vein diameter and separate the valve leaflets even further, leading to an exacerbation of reflux. The clinical finding that, over time, reflux progresses from a more distal, higher-pressure location to more proximal, lower-pressure segments supports the idea of gravitational pressure's contribution to superficial venous reflux.[8] The increased venous pressure on standing cannot be relieved by walking or exercise in patients with superficial reflux. When exercising, the measured superficial venous pressure in the dorsum of the foot decreased from an average of 87 mmHg to 22 mmHg in normal limbs. In those with varicose veins, it reached only 44 mmHg with a recovery or refilling time of only 3 seconds in the presence

Figure 5.1 Longitudinal ultrasound image of a thickened and immobile venous valve.

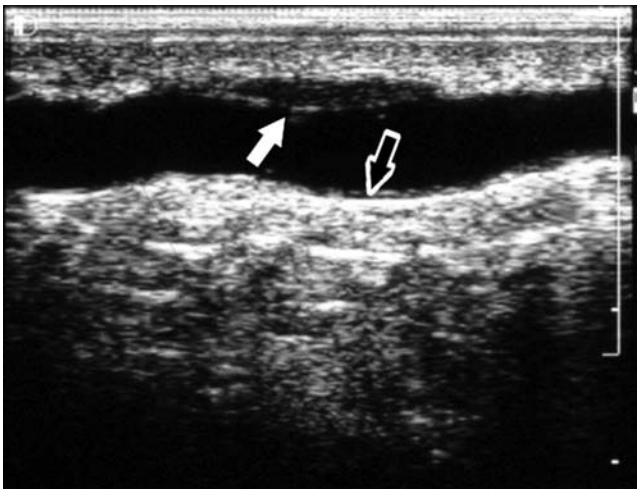

Figure 5.2 Post-phlebitic vein demonstrating an irregular luminal contour, thickening of the wall (filled arrow), and calcification (open arrow).

of great saphenous reflux, as compared to 31 seconds in controls.[9] This illustrates the reflux and increased pressure transmitted through the in-line column of fluid without the protective pressure separation of closed valves. In terms of leg blood volume rather than pressure, the ejection fraction is less than 65% and the residual volume fraction is greater than 30% as measured by air plethysmography.[10]

An understanding of these hemodynamic and pressure changes with superficial venous incompetence has formed the physiological basis of our treatment recommendations. Both the original proximal saphenofemoral ligation and complete great saphenous vein stripping sought to eliminate the entire axial pathways of reflux and venous hypertension. More recently, limited endovenous ablation, either by laser or radiofrequency sources, demonstrated that equivalent clinical improvement can be achieved with the limited closure of only proximal incompetent segments. To the surprise of many surgeons, the doctrine that all of the multiple branches at the saphenofemoral region needed to be ligated in order to achieve clinical improvement has been contradicted by satisfactory clinical outcomes after ablative procedures leaving those branches intact. A further recent challenge to our classical understanding has been the successful relief of superficial incompetence symptoms following the CHIVA (Cure Conservatrice et Hemodynamique de l'Insufficience Veineuse en Ambulatoire) procedure, in which the great saphenous vein is spared and only refluxing collateral branches are disrupted.[11] Finally, an improvement of venous edema (C3) can be achieved through the use of compression stockings. Class II (20–30 mmHg) and class III (30–40 mmHg) stockings not only reduce the volume of the leg in which interstitial fluid increases, but are able to compress the superficial subcutaneous veins and thereby help control reflux and venous hypertension. This latter conclusion, however, has been challenged by the magnetic resonance imaging finding that, in some positions in less diseased

legs, the deep veins are compressed more than the superficial by low-compression stockings.[12]

5.3 THE DEEP VEINS

Occlusion of the deep veins due to acute deep vein thrombosis (DVT) is a more serious event because of the mortality risk from pulmonary embolization and also because of the significant hemodynamic impact of venous outflow obstruction. Acute proximal vein thrombosis of the femoral, common femoral, or iliac veins can limit blood outflow to such an extent that arterial inflow to the leg is diminished. The resultant leg ischemia due to venous obstruction—phlegmasia cerulea dolens—is so severe that, if not urgently relieved, it leads to limb loss. Fortunately, a variety of thrombolytic, mechanical, and interventional procedures are available to treat such extensive acute venous occlusions. This is of major importance, as rapid thrombus resolution has been found to be associated with a higher incidence of valve competency.[13] The ultimate scientific evidence of thrombolysis effectiveness in the prevention of the post-thrombotic syndrome, awaits the outcome from a large prospective clinical trial.[14] In addition to the ischemic effects of acute occlusion, significant leg edema will occur if the thrombus is above the confluence of the deep femoral or great saphenous veins, which act as collateral channels for occlusions involving the femoral and more distal veins.

In circumstances involving less extensive or partial thrombosis of these proximal veins, or complete DVT in more distal vessels, treatment historically included acute heparin anticoagulation therapy in order to prevent thrombus extension, followed by conversion and long-term treatment with oral anticoagulants. The expectation was that intrinsic thrombolysis would subsequently take place if the systemic thrombotic balance was favorably tilted toward a lytic state. Indeed, with such treatment, approximately half of venous thrombi resolve completely within six months of presentation when assessed using Doppler ultrasound, through the process of lysis and reorganization.[15] The anatomical location of the thrombus is predictive of outcome to some degree. The femoral vein is likely to remain occluded, whereas partial to full recanalization is more commonly found in the external iliac, common femoral, and popliteal veins. This may be a result of higher flow rates, as well as the presence of collateral channels. Recanalization alone, however, is always hemodynamically incomplete and often results in relative obstruction and reflux.[16]

When early thrombus resolution does not occur, the remaining occlusive clot is remodeled, replaced by fibrous tissue, and even covered by neo-endothelium, preventing further lysis. Thrombi filling the lumen and adhering to the vein wall cause complete venous obstruction, which becomes permanent after it has been reorganized. This permanent occlusion has important hemodynamic obstructive effects, and induces a progressive increase in venous outflow through collateral vessels, which can be protected from thrombosis by the systemic anticoagulation maintained in the initial 3–6 months or longer. The extent of the obstruction and the amount of collateral pathways developed determine the venous outflow out of the leg, the severity of the hemodynamic changes, and therefore the severity of the post-thrombotic symptoms (Figure 5.3). With potentially fewer or less robust valves, collateral vessels themselves may become channels for reflux into the extremity. When the popliteal vein has been occluded, the calf perforating veins become important collaterals that flow retrograde to the superficial venous system. Popliteal obstruction, either in isolation or in combination with calf vein and iliofemoral damage, is usually associated with more severe symptoms and subsequent leg ulcer development.

Even non-occlusive thrombus in the deep venous system can be associated with significant hemodynamic dysfunction. Clots located in a valve pocket or in direct contact with valve cusps can irreparably damage their function.[17] Acutely, the valves cannot move when encased by thrombi. Lysis is more problematic and limited in the valve cusps due to the low vortex flow in this region as compared to the central lumen.[18] The fibrotic process is most damaging in the areas of the valve, as it causes retraction and shortening of the leaflets and further limits their mobility. This is not just a simple mechanical effect. There is evidence to suggest local neuro-hormonal sympathetic activity that controls venous wall tone and the base of the annulus.[19] Occlusion of the draining vasa venorum at the base of the valve would change the local norepinephrine concentrations and further limit both valve closure and vein dilation.

In this manner, permanent valvular incompetence develops and reflux occurs, defined for the deep system as being greater than 1 second.[20] In the portion of the veins in which there are no valves, synechiae can develop. Synechiae are permanent endothelialized strands of residual organized thrombus, often crisscrossing the lumen of the vein and producing a cribriform meshwork which limits blood

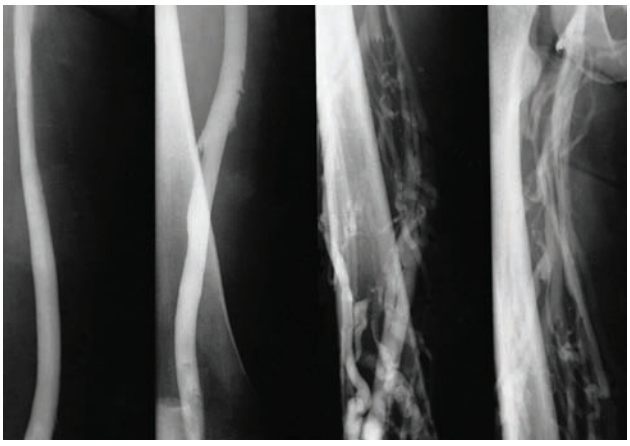

Figure 5.3 The left-hand two panels show a normal set of deep veins. The right-hand two panels show post-thrombotic femoral veins with synechiae and collateral pathways.

outflow (Figure 5.3). If extending to areas with valves, they can entrap the valve leaflets and bind them to the vein wall. Furthermore, in many patients, the perivenous inflammatory fibrosis that follows intra-luminal thrombosis prevents venous distension and may also act as a functional obstruction limiting total blood flow, even though no thrombus remains in the lumen.

Post-thrombotic damage within the deep veins is the most important cause of CVI within C5 and C6 CEAP classes. However, a third of patients with advanced CVI may have primary deep valvular incompetence with no history or evidence of an inciting thrombotic etiology. This could be secondary to primary dilation of the wall of the deep veins, or a flow phenomenon associated with superficial vein incompetence that resolved upon ablation of the latter system. Incompetence may also be a consequence of abnormal valves (the floppy valves of Kistner) or true congenital valvular agenesis. In some patients (e.g., in the case of Klippel–Trenaunay syndrome), the deep veins are completely absent and are functionally replaced by a primitive axial vein.[21] In addition, deep vein obstruction or internal damage may occur as a consequence of extrinsic compression, direct or indirect traumatic injury, interventional complications, or vascular tumors such as leiomyomas and leiomyosarcomas.[22,23]

The deep veins are more important hemodynamically because they are responsible for a greater portion of the blood flow out of the leg. However, because until recently we had been much more limited in terms of interventional therapeutic options, much less attention has been paid to the deep system. With deep venous obstruction, diversion of flow around the occluding segment remains a viable surgical option. The Palma procedure is a well-established and successful method, providing venous outflow when the iliac veins are occluded on one side but are open in the contralateral limb (Figure 5.4). This procedure usually requires a patent femoral vein and a non-diseased great saphenous vein of sufficient diameter to be used as a conduit, which is a circumstance that is not routinely present. When the iliac veins or the vena cava are involved with tumor and there are no prior phlebitic changes of the inflow veins, a bypass with a prosthetic graft can be successful with high venous flows.[24] A more frequent clinical condition is found consisting of acute or even chronic occlusion of the iliac veins or the vena cava in the presence of previously inserted filters. On these occasions, excellent and enduring relief has been attained through the use of percutaneous pharmaco-mechanical lysis and the insertion of venous stents. A greater appreciation has recently been attained regarding the possibility of relieving partial proximal venous obstruction in patients with May–Thurner syndrome when the extrinsic compression by the right common iliac artery has produced a clinically significant hemodynamic obstruction that is not complicated by a prior thrombotic episode.[22,23,25] Intravascular ultrasound has provided us with the tools to better define the presence of this stenosis and to evaluate

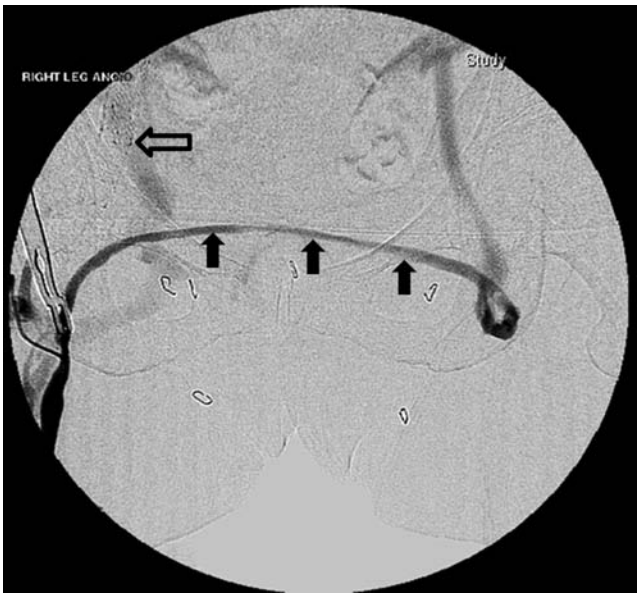

Figure 5.4 Venogram of a right-to-left femoral–femoral venous bypass (Palma procedure) utilizing the left great saphenous vein (arrows) in a patient with a thrombosed right iliac system following previous iliac stenting (open arrow).

the efficacy of interventions. Further significant progress is expected in the near future, with the development of venous-specific stents which will be larger, longer, and with more flexibility, but of sufficient radial strength and durability to cross the hip area of flexion underneath the inguinal ligament. Unfortunately, venous stents have not achieved clinical success when used in the femoral and popliteal veins. Although thrombolysis is commonly employed with reasonable results, venous stent patency and durability has not reached acceptable levels in these areas, probably because of the veins' small diameter and lower flows.

Advancements in the treatment of deep venous occlusive disease have not been mirrored in the treatment of valvular reflux and insufficiency.[26] The concept of repairing or replacing non-functioning valves promised to immediately and directly restore their hemodynamic performance. However, earlier historical experience with both valve repair and transplantation to the femoral and popliteal regions did not meet clinical expectations and were associated with early thrombosis, not justifying such interventions. Prior attempts at artificial valves have also been limited due to a lack of durable patency.[27] Early thrombosis of these valves and the technically demanding nature of valve transplantation or repair procedures precluded their widespread clinical use, although, while patent, they appeared to be associated with excellent clinical results, supporting their important value to deep system hemodynamics. On the other hand, the idea of immediately restoring valve function through the placement of a new valve, particularly at the femoral level, continues to induce investigations. It is hoped that in the future, with further progress in the

technology of stent and percutaneous techniques, such a valve will become available for patients with severe venous insufficiency and non-healing ulcers. In the meantime, surgical endophlebectomy in the common femoral region is available for a small subset of patients in order to extend the efficacy of iliac interventions.[28]

5.4 THE PERFORATING VEINS OF THE CALF

It has now been well demonstrated that in normal individuals blood does not flow from the deep to the superficial venous system via the perforating veins of the calf.[15] On the other hand, venous hypertension and reflux in the superficial system can be transmitted to the communicating veins and induce their dilatation and lead to valvular incompetence with retrograde flow from the deep to the superficial system. Perforating veins can also act as re-entry veins, allowing blood to reflux down the saphenous system in order to flow back into the deep system. In many patients, after ablation of the saphenous veins, postoperative duplex ultrasound shows that perforator valve competence has been restored.[29]

Incompetent calf perforating veins are also often associated with primary deep vein obstruction or incompetence.[16] Clinically relevant flow from the deep system to the superficial system is most frequently present with incompetence of valves in the axial and deep veins adjacent to the perforating veins. Under these circumstances, the perforating veins act as safety valves or collateral pathways, allowing blood under high pressure in the deep veins to escape to the superficial veins. During calf muscle contraction, the increased blood pressures in the deep veins are directly transmitted via the connecting perforating veins to the superficial venous system of the calf.[30] This in turn leads to venous hypertension extending into the microcirculation, with increased hydrostatic pressure in the capillaries. There is secondary enlargement of the dermal capillary bed and excessive transcapillary filtration, causing interstitial edema formation with the exudation of fibrinogen and proteins into the interstitial space, producing the characteristic changes of lipodermatosclerosis.[31]

Incompetence of one venous system in isolation is usually associated with minimal signs of CVI. Incompetence of all three, however, is much more likely to be associated with active ulceration and higher residual venous volumes following calf muscle pump contraction.

5.5 FOOT AND CALF PUMP FUNCTION

The hemodynamics in the venous system are more complex than on the arterial side because flow is intermittent and the veins are collapsible. Flow within them is also dependent on both the effects of gravity/hydrostatic pressure and extrinsic muscle compression. Let us first review their function in the normal condition without obstruction or valvular incompetence.

The calf muscles and, to a lesser extent, the foot and thigh musculature act as physiologic pumps and play critical roles in the standing position for returning venous blood against gravity from the lower limbs to the heart. The calf pump is the most important because it contains the largest venous capacitance within the soleal and gastrocnemious sinusoids and generates the highest pressures. Muscle contraction within the fascial compartments drives blood up the deep axial veins of the leg. The intramuscular pressures generated in the gastrocnemius and soleus muscles can increase up to 250 mmHg from 9–15 mmHg in their relaxed state.[32] With muscle contraction, the large pressure gradients induced in the deep calf veins and the popliteal vein induce rapid efflux of blood from the calf to the thigh. When muscles relax, venous pressure decreases within the calf compartments, and to the greatest degree in the deep veins, which, via the competent valves, allows the perforating veins to direct blood flow from the superficial to the deep system.[33] This subsequently dilates the deep veins and reduces the pressure in the superficial veins. The effect is incremental until the arterial inflow equals the venous outflow capacity of the venous pumps. After muscle activity ceases, capillary inflow slowly fills the superficial veins, which causes a slow increase in venous pressure over the next 20–35 seconds as the veins refill back to their original resting pressure.[34]

The efficiency of the calf pump in normal subjects is around 70%. The resting venous pressure is approximately 100 mmHg, depending on the patient's height, and is reduced to about 30 mmHg after 10 or more repetitive calf contractions (Figure 5.5).[35] Additional contractions fail to further decrease the venous pressure once a steady state has been reached.

The importance of the foot pump has become better understood and appreciated despite its obviously smaller size and venous capacitance as compared to the calf. Venous pressure at the ankle increases from 10 mmHg to over 90 mmHg in the upright position, which provides sufficient hydraulic pressure at rest to return blood back to the heart. Ambulatory venous pressure measured in the foot is considered normal at 10–30 mmHg, representing intermediate venous hypertension at 31–45 mmHg and severe venous hypertension when greater than 45 mmHg.[36] At rest, the foot pump is neither needed nor functional. Of greater interest is the role of the foot during exercise. The foot venous pump is mainly deep and intermuscular and is principally composed of the lateral plantar veins directly draining into the posterior tibial veins, as has been well documented by the injection studies of Uhl and Gillot.[37] It also communicates via the inframalleolar perforators into the medial marginal vein at the origin of the great saphenous vein below the ankle. Interestingly, this demonstrates reversed blood flow from the deep to the superficial system, rather than in the opposite direction that is seen everywhere else in the leg. Finally, there are the anterior communicating veins linking the plantar reservoir directly to the anterior

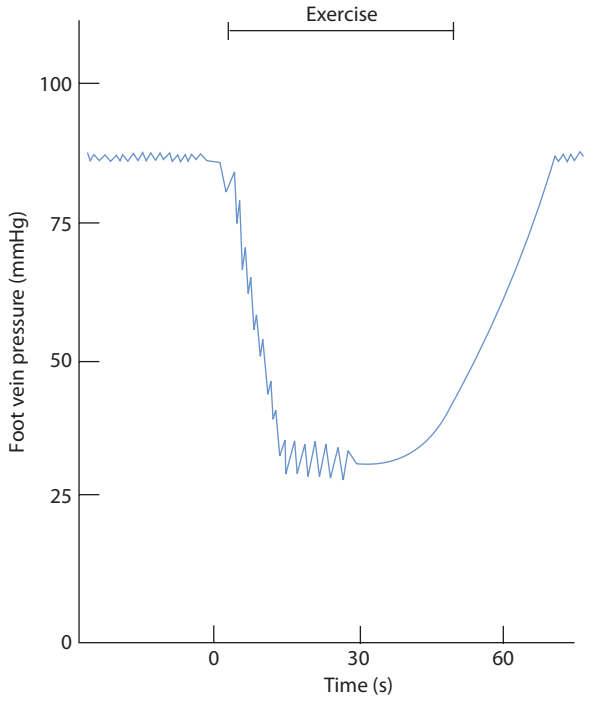

Figure 5.5 Changes in foot vein pressure during a heel-raising exercise in a normal limb. The pressure drops by 80%–90% from baseline and requires 20–35 seconds to return to resting levels. (From Browse NL, Burnand KG, and Irvine A. *Diseases of the Veins*, London: Arnold, 1999. With permission.)

tibial veins. Normal efflux takes place from the foot through both the deep and superficial venous systems. Scurr and Smith estimated by plethysmography the volume of blood ejected from the sole of the foot during contraction as being between 20 and 30 mL.[38] This pump is literally the first step in the venous return from the lower extremity to the heart. The normal foot venous pressure during exercise is shown in Figure 5.6.

The physiologic importance of the foot pump has also been used for the prevention of DVT in immobile post-operative patients who could not undergo calf intermittent compression because of trauma or orthopedic procedures. Extrinsic mechanical compression of the plantar venous plexus produces a peak velocity of 123 ± 71 cm/second in the posterior tibial veins, which is four-times greater than the induced velocity in the peroneal veins and anterior tibial veins.[39]

A final consideration is that of the foot architecture, where weight-bearing normally takes place almost entirely on the heel, the distal metatarsals, and the lateral part of the plantar surface. The instep is non-pressure bearing. The plantar veins are therefore protected, except in the case of people with flat feet. In such cases, insoles should be recommended both to offload the foot and also to potentially improve foot venous pump activity.

Air plethysmography enables quantitative measurements of volume changes in the whole leg, specifically of venous volume, ejected volume, and residual venous volume, from which ejection fraction and residual venous fraction can be calculated.[33] This makes possible objective and reproducible

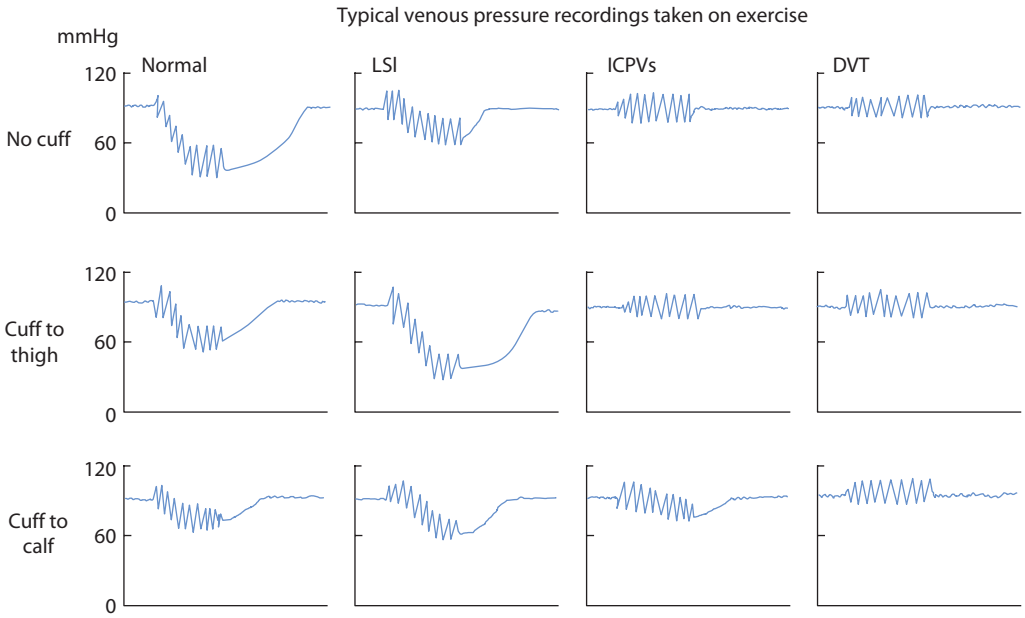

Figure 5.6 Changes in foot pressure with cuff applications at the thigh and calf in a normal patient, great saphenous incompetence or with great saphenous incompetence (LSI), incompetent perforating veins (ICPVs), and following deep venous thrombosis (DVT). (From Browse NL, Burnand KG, and Irvine A. *Diseases of the Veins*, London: Arnold, 1999. With permission.)

evaluation of hemodynamic dysfunction and amelioration following intervention.[40]

Under the pathological conditions of luminal obstruction and valvular dysfunction, the hemodynamic flow patterns are severely disturbed. Incompetence of the deep valves enables retrograde flow within the deep system, which both increases the overall calf volume and disturbs efficient blood return to the right heart. Deep venous valvular incompetence without coexisting cephalad obstruction can be compensated for by the presence of a powerful calf pump and competent perforating veins. If there is sufficient deep venous outflow obstruction or functional obstruction due to a fibrotic decrease in the lumen of the deep veins, and the perforating veins are primarily or secondarily incompetent, the muscle pump becomes even more inefficient at pushing blood out of the leg. By contrast, the calf pump exacerbates blood efflux through retrograde flow via the connecting perforating veins and induces superficial venous hypertension. In deep venous outflow obstruction or severe valvular insufficiency, the inability to induce sufficient venous outflow results in persistent ambulatory venous hypertension. These abnormalities are further exacerbated when there is concomitant pre-existing reflux in the superficial venous system. Similar but less severe effects are seen in the absence of deep venous pathology but with perforating and superficial system incompetence. Persistently elevated ambulatory pressure in the leg leads to raised pressure at the venous end of the capillaries. Increased capillary hydrostatic pressure induces both transudation and exudation with high protein content of interstitial fluid and the secondary skin changes associated with CVI.

With exercise and muscle contraction, the venous refill time or recovery time is shorter if there is incompetence of the valves in the superficial or communicating veins (Figures 5.6–5.8). In the presence of deep venous occlusion, obstruction, or agenesis (Figure 5.9), there is little reduction in superficial venous pressure, and the pressure during calf contraction may actually rise above the resting pressure,

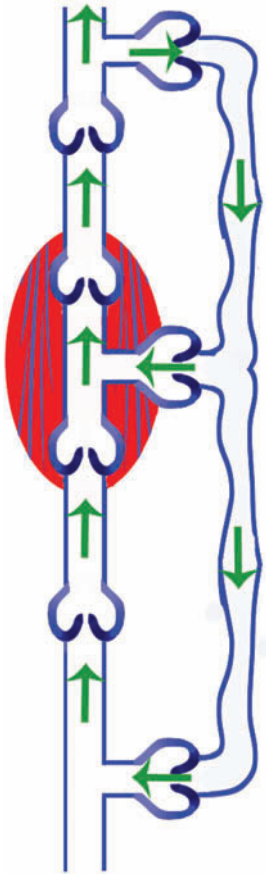

Figure 5.7 Superficial vein incompetence allows blood to reflux down the superficial veins but, provided that the communicating veins are competent, the calf pump can usually cope with the additional load and reduce the foot vein pressure during exercise. This is why simple superficial varicose veins alone are an uncommon cause of venous ulceration.

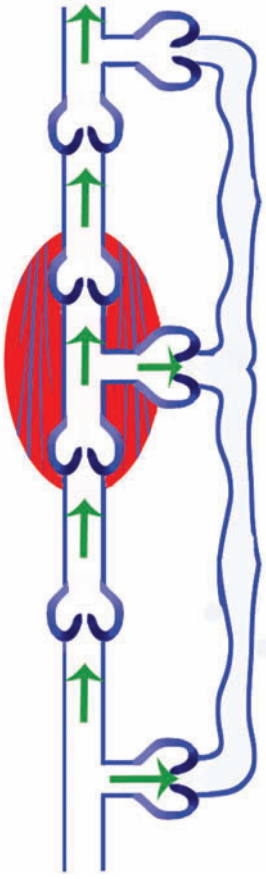

Figure 5.8 Perforating vein incompetence alone, as may develop after deep vein thrombosis, leads to dilatation and reflux of blood into the superficial compartment, which is exacerbated during calf muscle contraction. Communicating vein dilatation and valvular incompetence may also occur as part of the varicose vein diathesis. The arrows indicate the direction of blood flow.

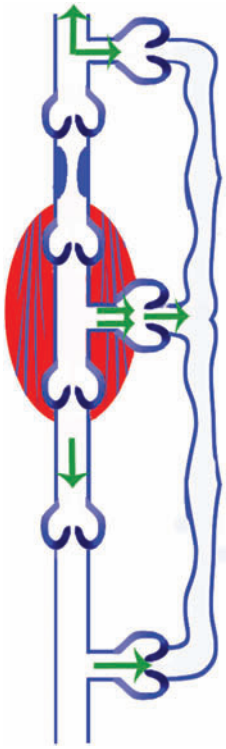

Figure 5.9 Deep venous obstruction causes upstream dilatation of the veins and secondary incompetence of the communicating veins because these veins become part of the collateral outflow tract. During exercise, the foot vein pressure will fall slightly.

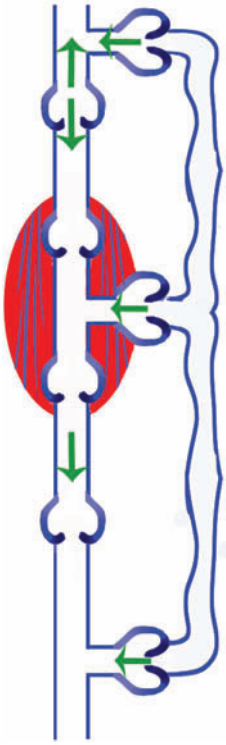

Figure 5.10 With deep venous reflux and perforator competence, the calf pump can compensate by increasing its output.

although persistent venous hypertension is rare. Deep valvular incompetence, with or without associated incompetence of the calf communicating veins, is responsible for blood travelling up and down the deep veins (Figures 5.10 and 5.11), with accompanying reflux through any associated incompetent perforating veins. This produces limited venous pressure reductions on calf contraction and a rapid return to a high resting pressure (Figure 5.6).

5.6 CONCLUSIONS

The importance of persistent ambulatory venous hypertension in the development of lower limb symptoms and ulceration is not disputed. The underlying pathophysiology and hemodynamics are more complex than most clinicians would acknowledge and not much progress has been made in the past several decades. Most efforts have focused on technological advances for the treatment of superficial venous disease and, more recently, interventions within the deep venous system. These interventions, while clearly needed, are however only a first step in treatment. In the future, we will need to use modern technology to more precisely investigate the hemodynamic abnormalities of CVI in order to understand in greater detail the mechanisms that cause leg ulceration. This should lead us to better methods of the prevention and treatment of venous ulcers.

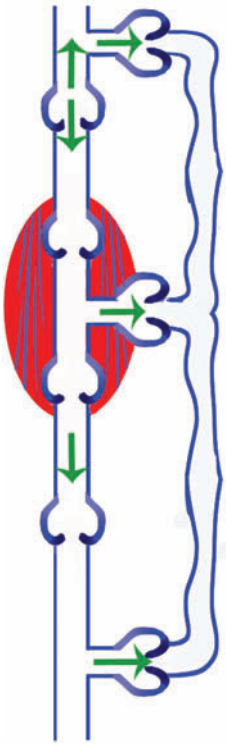

Figure 5.11 In the setting of both deep reflux and perforator incompetence, pump efficiency fails during exercise and ambulatory hypertension is not relieved.

Guidelines for the Management of Venous Leg Ulcers of the Society for Vascular Surgery and the American Venous Forum[3]

No.	Guideline		
3.12	Venous Disease Classification		
We recommend that all patients with venous leg ulcer be classified on the basis of venous disease classification assessment, including clinical CEAP, revised Venous Clinical Severity Score, and venous disease specific quality of life assessment. [BEST PRACTICE]			

Clinical Practice Guidelines of the European Society for Vascular Surgery—Management of Chronic Venous Disease[2]

2.2.2	Venous Clinical Severity, Segmental Disease and Disability Scores		
Recommendation 1		**Class**	**Level**
Use of the Clinical Etiological Anatomical Pathophysiological (CEAP) classification is recommended as a standardized, descriptive classification tool to assess disease severity in patients with chronic venous disease for research and audit.		I	B
Recommendation 2			
Use of one or more of the following scoring systems should be considered for chronic venous disease: Venous Clinical Severity Score to assess clinical severity, Venous Segmental Disease Score for pathophysiological and anatomical evaluation, Venous Disability Score for functional evaluation, and the Villalta-Prandoni Scale to assess severity of post-thrombotic syndrome.		IIa	B

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● = Key primary paper
★ = Published guideline

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6

Pathogenesis of varicose veins and cellular pathophysiology of chronic venous insufficiency

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6.1 INTRODUCTION

Chronic venous insufficiency (CVI) is the seventh leading cause of chronic debilitating disease in the United States. In total, 10%–35% of adults in the United States have some form of CVI, with venous ulcers affecting 4% of people over the age of 65 years.[1,2] An estimated 25 million people in the United States have varicose veins. Two to six million have more advanced forms of CVI (swelling and skin changes), and nearly 500,000 have active venous ulcers. The population-based cost to the U.S. government for CVI treatment and venous ulcer care has been estimated at over $1 billion a year. In addition, 4.6 million work days per year are lost to venous-related illnesses.[3,4] The chronicity of CVI and lack of effective treatment modalities place a heavy burden on the healthcare system, underscoring the need for more extensive CVI-related research. Over the past decade, researchers have made strides in defining the roles of genetics and leukocyte-mediated injury, and have elucidated the role of inflammatory cytokines in lower extremity dermal pathology. In addition, several investigations have been performed to highlight the pathologic alterations in cellular function and the molecular regulation of the processes observed in patients with CVI. This chapter will discuss the pathogenesis and pathophysiology of varicose vein formation and the molecular regulation of inflammatory damage to the lower extremity dermis caused by persistent ambulatory venous hypertension.

6.2 VARICOSE VEIN FORMATION (MACROSCOPIC ALTERATIONS)

6.2.1 Genetics and the role of deep venous thrombosis

Unlike arteries, veins are thin-walled, low-pressure conduits whose function is to return blood from the periphery to the heart. Muscular contractions in the upper and lower extremities propel blood towards the heart and a series of intraluminal valves prevent retrograde flow or reflux. Venous reflux is observed when valvular destruction or dysfunction occurs in association with varicose vein formation. Valvular reflux causes an increase in ambulatory venous pressure and a cascade of pathologic events that manifest themselves clinically as lower extremity edema, pain, itching, skin discoloration, varicose veins, venous ulceration, and, in its severest form, limb loss. These clinical symptoms collectively refer to the disorder known as CVI.[5] Age, gender, pregnancy, weight, height, race, diet, bowel habits, occupation, posture, previous deep venous thrombosis (DVT), and genetics have all been proposed as predisposing factors for the formation of varicose veins. However, except for a history of previous DVT and genetics, there is poor evidence to suggest a causal relationship between these predisposing factors and varicose vein formation.

There are a few reported epidemiologic investigations that suggest a relationship between varicose vein formation

and a genetic predisposition.[6,7] Historically, it was thought that axial destruction of venous valves led to the transmission of ambulatory venous hypertension, causing reflux and varix formation.[6] However, a publication by Labropoulos et al.[8] indicated that the most frequent location for initial varicose vein formation was in the below-knee great saphenous vein (GSV) and its tributaries, followed by the above-knee GSV and the saphenofemoral junction, respectively. The results of this study suggest that reflux appears to be a local or multifocal process. Vein wall degeneration with subsequent varix formation can occur in any segment of the superficial and deep systems, suggesting a genetic component to the disease.

In 1969, Gunderson and Hauge[9] reported on the epidemiology of varicose veins observed in a vein clinic in Malmo, Sweden. In this investigation, 154 female and 24 male patients provided complete survey information on their parents and siblings. Although biased by the predominance of women and dependence on survey data, this report suggested that patients with varicose veins had a higher likelihood of developing varicosities if their father had varicose veins. Furthermore, the risk of developing varicose veins increases if both parents had varicosities. To further support the genetic predisposition theory, Cornu-Thenard et al.[7] prospectively examined 67 patients and their parents. The non-affected spouses and parents of patients were used as controls, giving a total of 402 subjects. These investigators reported that the risk of developing varicose veins was 90% when both parents were affected, 25% for males and 62% for females if one parent was affected, and 20% when neither parent was affected. These data suggest an autosomal dominant mode of transmission with variable penetrance. The decreased incidence in males with an affected parent and the spontaneous development in patients without affected parents suggest that males are more resistant to varix formation and that other multifactorial etiologies, such as environmental factors and hormones, in patients with predispositions to the disease must exist.

Ng et al.[10] demonstrated that varicose veins in the normal population were linked to the candidate marker D16S520 on chromosome 16q24. A likely candidate gene within close proximity to the marker *D16S520* is the forkhead box C2 (*FOXC2*). *FOXC2* encodes a regulatory forkhead transcription factor and is expressed in the paraxial mesoderm and somites of the early vertebrate embryo. In later stages, its expression is noted in the heart and blood vessels.[11] *FOXC2* is noted to play an important part in the development of the lymphatic system, demonstrating its importance in the development of lymphedema distichiasis.[12] Since venous reflux is associated with valve abnormalities, *FOXC2* may play a role in the development of both venous and lymphatic valvular dysfunction.[13]

Serra et al.[14] reported that in nine families with varicose veins, the gene *D16S520* on chromosome 16q24, which is located near the gene *FOXC2*, was associated with varix formation. The authors determined that in families with affected members carrying the *D16S520* marker, there was evidence of saphenofemoral junction reflux. Linkage to the candidate marker for the *FOXC2* gene suggests that there is a functional variant within, or in the vicinity of, the *FOXC2* gene, which predisposes to varicose vein development.

An injury to the venous endothelium or local procoagulant environmental factors leads to thrombus formation in the venous system. It is currently well accepted that a venous thrombus initiates a cascade of inflammatory events that contributes to or causes vein wall fibrosis.[15] Thrombus formation at venous confluences and valve pockets leads to activation of neutrophils and platelets. Activation of these cells leads to the formation of inflammatory cytokines, pro-coagulants and chemokines, causing thrombin activation and further clot formation. Production of inflammatory mediators creates a cytokine/chemokine gradient, leading to leukocyte invasion of the vein wall at the thrombus wall interface and from the surrounding adventitia. Upregulation of adhesion molecules perpetuates this process, eventually leading to vein wall fibrosis, valvular destruction, and alteration of the vein wall architecture.[15,16] Although the mechanisms associated with vein wall damage secondary to venous thrombosis are beginning to be unraveled, the majority of varicose veins occur in patients with no prior history of DVT.

6.2.2 Vein wall anatomy, histopathology, and functional alterations

Whatever the initiating event, several unique anatomic and biochemical abnormalities have been observed in patients with varicose veins. Normal and varicose GSVs are characterized by three distinct muscle layers within their walls. The inner layer is referred to as the intima. It is one cell layer thick and is composed of endothelial cells. The media contains an inner longitudinal and an outer circular layer, and the adventitia contains a loosely organized extracellular matrix (ECM) in the outer longitudinal layer.[17–19] In normal GSVs, muscular layers in the media are composed of smooth muscle cells (SMCs) that appear spindle shaped (contractile phenotype) when examined with electron microscopy (Figure 6.1).[20] These cells lie in close proximity to each other, are in parallel arrays, and are surrounded by bundles of regularly arranged collagen fibers. In varicose veins, the orderly appearance of the muscle layers of the media is replaced by an intense and disorganized deposition of collagen.[20–22] Collagen deposits separate the normally closely opposed SMCs, and are particularly striking in the media. SMCs appear elliptical rather than spindle shaped, and demonstrate numerous collagen-containing vacuoles, imparting a secretory phenotype (Figure 6.2).[15] What causes SMCs to dedifferentiate from a contractile to a secretory phenotype is currently unknown. Ascher et al.[23,24] theorized that SMC dedifferentiation may be related to dysregulation of apoptosis. These investigators

Figure 6.1 Electron micrograph of a normal vein demonstrating a contractile smooth muscle phenotype.

reported a decrease in the pro-apoptotic mediators bax and poly-ADP-ribose polymerase in the adventitia of varicose veins compared with normal veins. Although no difference in these mediators was observed in the media or intima of varicose veins, a decrease in SMC turnover was postulated as a possible cause of the increase in the secretory phenotype. Increased phosphorylation of the retinoblastoma protein, an intracellular regulator of cellular proliferation and differentiation, has been observed in varicose veins, and may similarly contribute to this process.[18]

Vein wall remodeling has been consistently observed in histologic varicose vein specimens.[17,19–22,25] Gandhi et al.[25] quantitatively demonstrated an increase in collagen content and a decrease in elastin content compared to normal GSVs. The net increase in the collagen/elastin ratio suggested an imbalance in connective tissue matrix regulation.

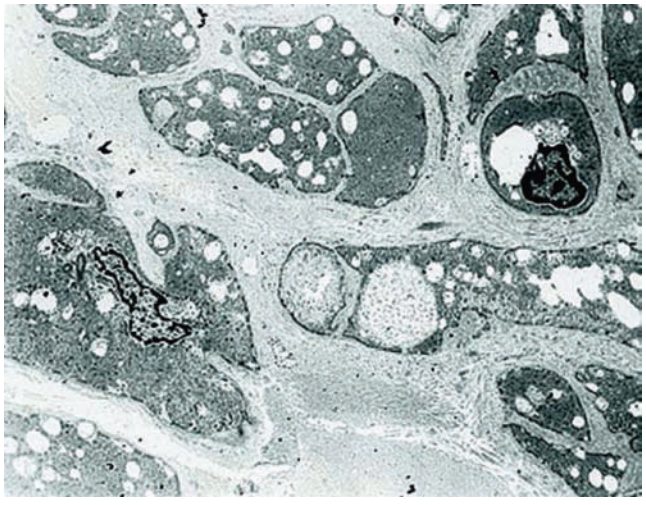

Figure 6.2 Electron micrograph of a varicose vein wall demonstrating a secretory phenotype of smooth muscle cells.

As a result, several investigators have observed alterations in matrix metalloproteinase (MMP) and fibrinolytic activity in varicose veins. TIMP-1 and MMP-1 protein levels are increased at the saphenofemoral junction compared with normal controls, whereas MMP-2 levels are decreased.[26] No overall differences in MMP-9 protein or activity levels have been identified; however, the number of cells expressing MMP-9 by immunohistochemistry has been reported to be elevated in varicose veins compared with normal veins.[27,28] There are conflicting reports regarding the role of plasmin activators and their inhibitors. Shireman et al.[29] reported that urokinase plasminogen activator (uPA) levels are increased by three to five times compared with normal controls in the media of vein specimens cultured in an organ bath system. No differences were noted in tissue plasminogen activator (tPA) or plasmin activator inhibitor 1 levels. However, other investigations have reported a decrease in uPA and tPA activity as assessed by enzyme zymography in varicose veins.[27,30] These data suggest that the plasminogen activators may play a role in MMP activation, leading to vein wall fibrosis and varix formation; however, further research into the mechanisms regulating vein wall fibrosis are clearly needed.

What effect vein wall fibrosis has on venous function needs further elucidation. The contractile responses of varicose and normal GSV rings to noradrenaline, potassium chloride, endothelin, calcium ionophore A23187, angiotensin II, and nitric oxide have been evaluated by several investigators.[31,32] These studies have demonstrated decreased contractility of varicose veins when stimulated by noradrenaline, endothelin, and potassium chloride. Similarly, endothelium-dependent and -independent relaxations after A23187 or nitric oxide administration, respectively, were diminished compared with normal GSVs. The mechanisms responsible for decreased varicose vein contractility appear to be receptor mediated.[32,33] By utilizing sarafotoxin S6c (a selective pharmacologic inhibitor of endothelin B) and competitive inhibition receptor assays with [^{131}I]-endothelin-1, a decrease in endothelin B receptors has been observed in varicose veins compared with normal GSVs.[33] Feedback inhibition of receptor production secondary to increased endothelin-1 is postulated to mediate the decreased receptor content in varicose vein walls. Other possible mechanisms of decreased contractility appear to be related to cyclic adenosine monophosphate (cAMP) levels and the ratio of prostacyclin to thromboxane-A2.[34] cAMP is increased in varicose vein specimens compared with normal GSVs. In addition, the ratio of prostacyclin to throboxane-A2 is increased, even though absolute protein levels do not differ between normal veins and varicosities. Whether venodilation of varicosities is caused by diminished endothelin receptor levels and responsiveness to cAMP or is a secondary effect of varix formation is not known. However, it is clear that with the development of vein wall fibrosis, varicose veins demonstrate decreased contractile properties that probably exacerbate the development of ambulatory venous hypertension.

6.3 MICROCIRULATION

6.3.1 Leukocyte activation

Dissatisfaction with the fibrin cuff theory and subsequent observations of decreased circulating leukocytes in blood samples obtained from the GSVs in patients with CVI led Coleridge Smith and colleagues[35] to propose the leukocyte-trapping theory. This theory proposes that circulating neutrophils are trapped in the venous microcirculation secondary to venous hypertension. The subsequent sluggish capillary blood flow leads to hypoxia and neutrophil activation. Neutrophil activation leads to degranulation of toxic metabolites with subsequent endothelial cell damage. The ensuing heterogeneous capillary perfusion causes alterations in skin blood flow and eventual skin damage. The problem with the leukocyte-trapping theory is that neutrophils have never been directly observed to obstruct capillary flow, therefore casting doubt on its validity. However, there is significant evidence that leukocyte activation plays a major role in the pathophysiology of CVI.

6.3.2 Role of leukocyte activation and functional status in CVI

In 1988, Thomas et al.[36] reported that 24% fewer white cells left the venous circulation after a period of recumbence in patients with CVI compared with normal patients. They studied three groups of ten patients each. Group 1 consisted of patients with no signs of venous disease. Group 2 were patients with uncomplicated primary varicose veins and group 3 were patients with long-standing CVI as determined by Doppler ultrasonography, strain gauge plethysmography, and foot volumetry. The GSV was cannulated just above the medial malleolus. Venous samples were obtained at various time points with patients in the sitting and supine positions. Samples were then placed in an automated cell counter and the numbers of leukocytes and erythrocytes determined. The ratios of white cells to red cells at the various time points were then compared. It was reported that with leg dependency, the packed cell volume significantly increased in patients with CVI compared with normal control subjects, whereas patients with primary varicose veins showed no difference from control subjects. It was also noted that the relative number of white cells was significantly decreased compared with control and primary varicose vein patients (28% vs. 5%, $P < 0.01$). It was concluded that the decrease in white cell number was due to leukocyte trapping in the venous microcirculation secondary to venous hypertension. It was further speculated that, while trapped, leukocytes may be activated and release toxic metabolites, causing damage to the microcirculation and the overlying skin. These important observations were the first to implicate abnormal leukocyte activity in the pathophysiology of CVI.

The importance of leukocytes in the development of dermal skin alterations was emphasized by Scott et al.[37] These authors obtained punch biopsies from patients with primary varicose veins, patients with lipodermatosclerosis, and patients with lipodermatosclerosis and healed ulcers, and they determined the median number of white blood cells (WBCs) per high-power field (40× magnification) in each group. No patients with active ulcers were included and no attempt to identify the type of leukocytes was made. It was reported that in patients with primary varicose veins, lipodermatosclerosis, and healed ulceration, there were medians of 6, 45, and 217 WBCs per mm^2, respectively. This study demonstrated that with clinical disease progression and increasing severity of CVI, there was a progressive increase in the number of leukocytes in the dermis of CVI patients.

The types of leukocytes involved in dermal venous stasis skin changes are controversial. In a study performed by Wilkinson et al.,[38] skin biopsies were obtained from 23 patients who required surgical ligation, stripping, and/or avulsion for their varicose veins. The condition of the skin was recorded as liposclerotic, eczematous, or normal. Lipodermatosclerosis was defined clinically as palpable induration of the skin and subcutaneous tissues and eczema as visible erythema with scaling of the skin. Immunohistochemical staining for leukocyte-specific cell surface markers was carried out, and it was reported that macrophages and lymphocytes were the predominant leukocytes observed in this patient population. Neutrophils and B-lymphocytes were rarely observed. T-lymphocytes and macrophages were predominantly observed perivascularly and in the epidermis. However, Pappas et al.[39] performed a quantitative morphometric assessment of the dermal microcirculation using electron microscopy and reported that macrophages and mast cells were the predominant cells observed in patients with CVI dermal skin changes. Furthermore, lymphocytes were never observed. This discrepancy may reflect the types of patients that were studied. Wilkinson et al.[38] biopsied patients with erythematous and eczematous skin changes, whereas Pappas et al.[39] predominantly evaluated older patients with dermal fibrosis. Patients with eczematous skin changes may have an autoimmune component to their CVI, whereas patients with dermal fibrosis may reflect changes that are consistent with chronic inflammation and altered tissue remodeling.

6.3.3 The venous microcirculation

Numerous investigations have attempted to evaluate the microcirculation of patients with CVI.[39–43] The majority of these investigations were qualitative descriptions of vascular abnormalities that lacked uniformity of biopsy sites and patient stratification. Prior to 1997, it was widely accepted that endothelial cells from the dermal microcirculation appeared abnormal, contained Weibel–Palade bodies, were edematous, and demonstrated widened inter-endothelial gap junctions.[42] Based on these descriptive observations, it was assumed that the dermal microcirculation of CVI patients had functional derangements related to permeability and

ulcer formation. It was not until 1997 that a quantitative morphometric analysis of the dermal microcirculation was reported.[39] The objectives of this investigation were to quantify differences in endothelial cell structure and local cell type, with an emphasis on leukocyte cell types and their relationship to arterioles, capillaries, and post-capillary venules (PCVs). The variables assessed were the numbers and types of leukocytes, endothelial cell thickness, endothelial vesicle density, inter-endothelial junctional width, cuff thickness, and ribosome density. Thirty-five patients had two 4-mm punch biopsies obtained from the lower calf (gaiter region) and lower thigh. Patients were separated into one of four groups according to the 1995 International Society for Cardiovascular Surgery/Society for Vascular Surgery (ISCVS/SVS) CEAP classification.[5] Group 1 consisted of five patients with no evidence of venous disease. Skin biopsies from these patients served as normal controls. Groups 2–4 consisted of patients with CEAP class 4 ($n = 11$), class 5 ($n = 9$), and class 6 ($n = 10$) CVI.

6.3.4 Endothelial cell characteristics

No significant differences were observed in the endothelial cell thickness of arterioles, capillaries, and PCVs from either gaiter or thigh biopsies.[39] Qualitatively, the endothelial cells appeared metabolically active. Many nuclei exhibited a euchromatic appearance, implying active mRNA transcription. In most instances, ribosome numbers were so abundant that they exceeded the resolution capacity of the image analysis system and were unable to be quantified. The prominence in the ribosome content and the euchromatic appearance of the endothelial cell nucleus strongly suggested active protein production. No significant differences in vesicle density were observed in gaiter biopsies between groups. Class 6 patients exhibited an increased number of vesicles in arterioles and PCV endothelia from thigh biopsies, but did not differ compared to gaiter biopsies. Mean inter-endothelial junctional width varied within a normal range of 20–50 nm. Significantly widened inter-endothelial gap junctions were not observed and thus conflicted with the reports of Wenner et al.[42] Mean basal lamina thickness differed significantly at the capillary level in both gaiter and thigh biopsies. Differences were most pronounced in patients with class 4 disease. These data indicated that endothelial cells from the dermal microcirculation of CVI patients were far from abnormal. They demonstrated increased metabolic activity, suggestive of active cellular transcription and protein production. Most surprising was the observation of uniformly tight gap junctions. Previously, these gap junctions were reported to be as wide as 180 nm, and it was assumed that these widened junctions were responsible for macromolecule extravasation and edema formation.[42,44] Pappas et al.[39] suggested that alternative causes of tissue edema, such as increased trans-endothelial vesicle transport, the formation of trans-endothelial channels, and alterations in the glycocalyx lining the junctional cleft, may be involved in CVI edema and macromolecule transport.

6.3.5 Types and distributions of leukocytes

The most striking differences in cell type and distribution were observed with mast cells and macrophages (Figure 6.3). In both gaiter and thigh biopsies, mast cell numbers were two- to four-times greater than those of controls in class 4 and 5 patients around arterioles and PCVs ($P < 0.05$). Class 6 patients demonstrated no difference in mast cell number compared to controls. Mast cell numbers around capillaries did not differ across groups in either gaiter or thigh biopsies. Macrophages demonstrated increased numbers in class 5 and 6 patients around arterioles and PCVs, respectively ($P < 0.05$). Differences in macrophage numbers around capillaries were observed primarily in class 4 patients in both gaiter and thigh biopsies. Surprisingly, lymphocytes, plasma cells and neutrophils were not present in the immediate perivascular space. Fibroblasts were the most common cells observed in both gaiter and thigh biopsies.

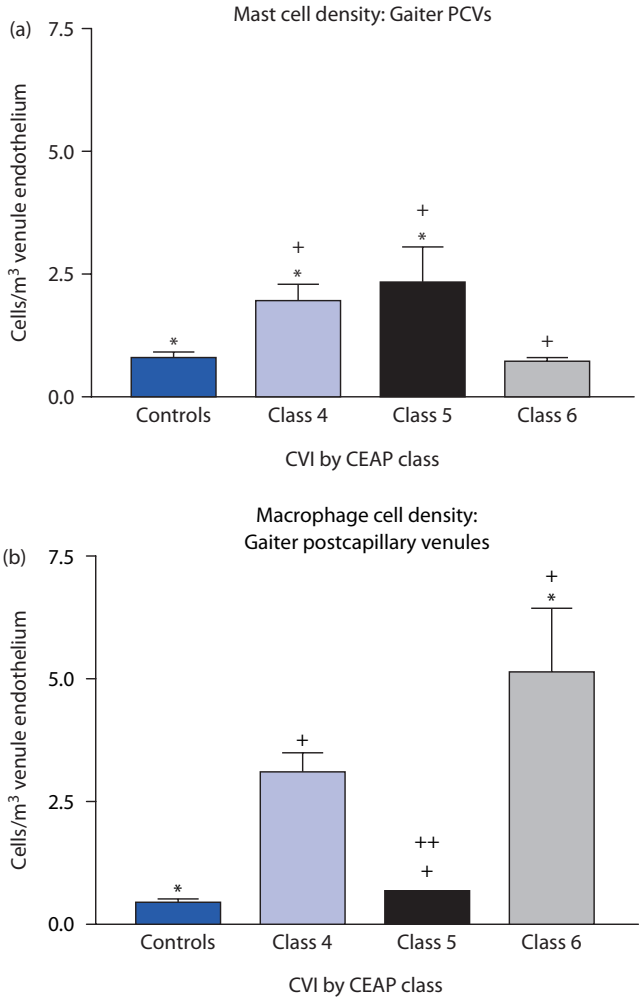

Figure 6.3 Histograms demonstrating mast cell densities **(a)** and macrophage cell densities **(b)** according to CEAP disease classification and their proximity to post-capillary venules (PCVs). Class 4: venous dermatitis only; class 5: venous dermatitis and a history of healed ulceration; class 6: active venous stasis ulcer. CVI: chronic venous insufficiency.

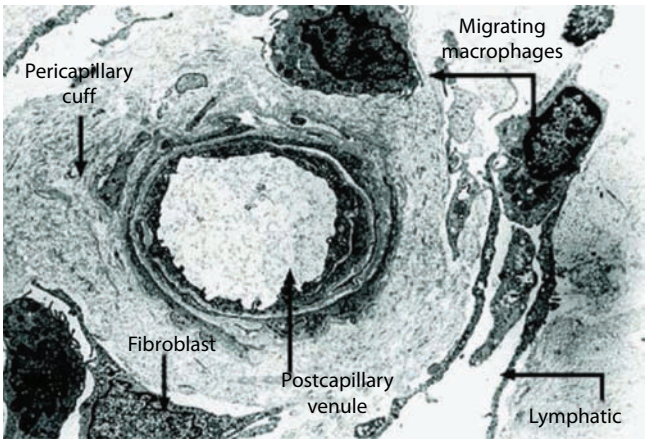

Figure 6.4 Photomicrograph (4300×) of chronic venous insufficiency dermal microcirculation demonstrating extracellular matrix changes (pericapillary cuff), migrating macrophages, a lymphatic vessel, and a fibroblast.

It was speculated that mast cells and macrophages may function to regulate tissue remodeling, resulting in dermal fibrosis.[39,45] The mast cell enzyme chymase is a potent activator of MMP-1 and -3 (collagenase and stromelysin).[46–48] In an *in vitro* model using the human mast cell line HMC-1, these cells were reported to spontaneously adhere to fibronectin, laminin, and collagen type I and III, all of which are components of the perivascular cuff (see Figure 6.4).[48] Chymase also causes the release of latent transforming growth factor-β1 (TGF-β1), which is secreted by activated endothelial cells, fibroblasts, and platelets from extracellular matrices.[49] Release and activation of TGF-β1 initiates a cascade of events in which macrophages and fibroblasts are recruited to wound healing sites and are stimulated to produce fibroblast mitogens and connective tissue proteins, respectively.[50] Mast cell degranulation leading to TGF-β1 activation and macrophage recruitment may explain why decreased mast cell and increased macrophage numbers were observed in class 6 patients. Macrophage migration, as evidenced by the frequent appearance of cytoplasmic tails in perivascular macrophages, further substantiates the concept of inflammatory cytokine recruitment.

6.4 ECM ALTERATIONS

Once leukocytes have migrated to the extracellular space, they localize around capillaries and PCVs. The perivascular space is surrounded by ECM proteins and forms a perivascular "cuff."[51,52] Adjacent to these perivascular cuffs and throughout the dermal interstitium is an intense and disorganized collagen deposition.[39,44] Perivascular cuffs and the accompanying collagen deposition are the *sine qua non* of the dermal microcirculation in CVI patients (Figure 6.4). The perivascular cuff was originally thought to be the result of fibrinogen extravasation and was erroneously referred to as a "fibrin cuff."[5] It is now known that the cuff is a ring of ECM proteins consisting of collagen types I and III, fibronectin, vitronectin, laminin, tenascin, and fibrin.[53] The role of the cuff and its cell of origin is not completely understood. The investigation by Pappas et al. suggested that the endothelial cells of the dermal microcirculation were responsible for cuff formation.[39] The cuff was once thought to be a barrier to oxygen and nutrient diffusion. However, recent evidence suggests that cuff formation is an attempt to maintain vascular architecture in response to increased mechanical load.[54] Although perivascular cuffs may function to preserve microcirculatory architecture, several pathologic processes may be related to cuff formation. Immunohistochemical analyses have demonstrated TGF-β1 and α2-macroglobulin in the interstices of perivascular cuffs.[55] It has been suggested that these "trapped" molecules are abnormally distributed in the dermis, leading to altered tissue remodeling and fibrosis. Cuffs may also serve as a lattice for capillary angiogenesis, explaining the capillary tortuosity and increased capillary density observed in the dermis of CVI patients.

6.5 PATHOPHYSIOLOGY OF STASIS DERMATITIS AND DERMAL FIBROSIS

The mechanisms modulating leukocyte activation, fibroblast function, and dermal ECM alterations were focuses of investigation in the 1990s. CVI is a disease of chronic inflammation due to a persistent and sustained injury secondary to venous hypertension. It is hypothesized that the primary injury is extravasation of macromolecules (i.e., fibrinogen and α2-macroglobulin) and red blood cells (RBCs) into the dermal interstitium.[41,42,44,55,56] RBC degradation products and interstitial protein extravasation are potent chemoattractants and, presumably, represent the initial underlying chronic inflammatory signal responsible for leukocyte recruitment. It has been assumed that these cytochemical events are responsible for the increased expression of intercellular adhesion molecule 1 (ICAM-1) on the endothelial cells of the microcirculatory exchange vessels observed in CVI dermal biopsies.[38,56] ICAM-1 is the activation-dependent adhesion molecule that is utilized by macrophages, lymphocytes, and mast cells for diapedesis. As stated above, all of these cells have been observed by immunohistochemistry and electron microscopy in the interstitium of dermal biopsies.[38,39]

6.6 CYTOKINE REGULATION AND TISSUE FIBROSIS

Leukocyte recruitment, ECM alterations, and tissue fibrosis are characteristic of chronic inflammatory diseases caused by alterations in TGF-β1 gene expression and protein production. To determine the role of TGF-β1 in CVI, Pappas and colleagues took dermal biopsies from normal patients and CEAP class 4, 5, and 6 CVI patients and analyzed them for TGF-β1 gene expression, protein production, and cellular location. TGF-β1 gene expression in class 4 patients was significantly elevated compared to controls

and class 5 and 6 patients (Figure 6.5; $P < 0.05$).[57] The data demonstrated that in areas of clinically active CVI, increased amounts of active TGF-β1 are present compared with normal skin. Furthermore, the active TGF-β1 protein concentrations in biopsies from the lower thigh did not differ from normal skin, demonstrating a regionalized response to injury.[57]

Immunohistochemistry and immunogold labeling experiments demonstrated intense TGF-β1 staining in perivascular cuffs, perivascular leukocytes, and fibroblasts. Many perivascular leukocytes demonstrated positive staining of intracellular granules and appeared morphologically similar to previously reported mast cells (Figures 6.3 and 6.6).[57] Preliminary TGF-β1 bioactivity assays, however, demonstrated increased active TGF-β1 protein production in all class 4, 5, and 6 CVI patients compared to normal patients and skin from ipsilateral thigh biopsies of CVI patients. Increased bioactive TGF-β1 in areas of stasis dermatitis alone signifies a regional response to venous hypertension. The increase in protein production with normal gene expression demonstrates either stabilization of the mRNA message or post-translational modification of the protein.

In 2008, a prospective observational study looked at 80 patients (43 men and 37 women) with chronic leg ulcers and

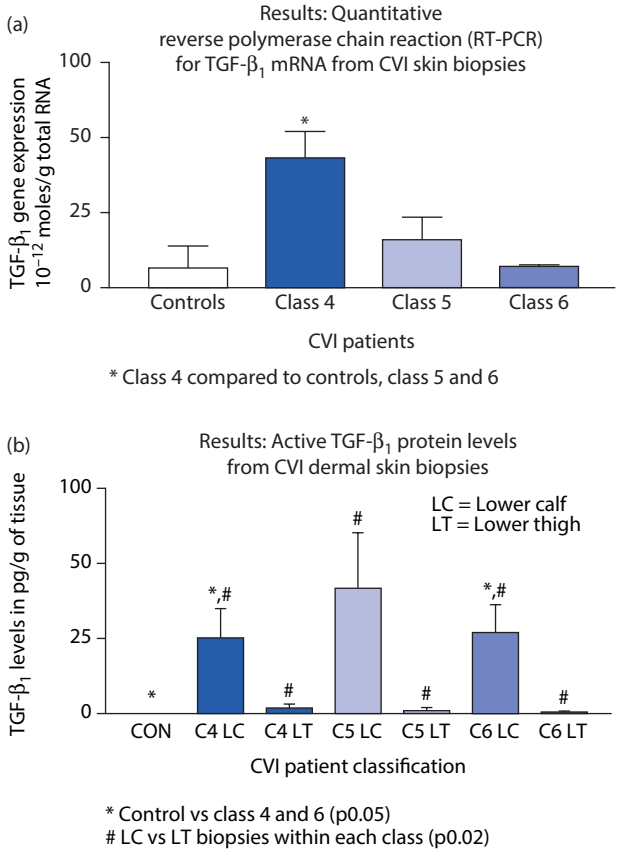

Figure 6.5 Increased transforming growth factor-β1 (TGF-β1) mRNA transcripts in class 4 patients only **(a)**; active TGF-β1 protein is observed in class 4, 5, and 6 patients in areas of clinically active disease **(b)**. CVI: chronic venous insufficiency.

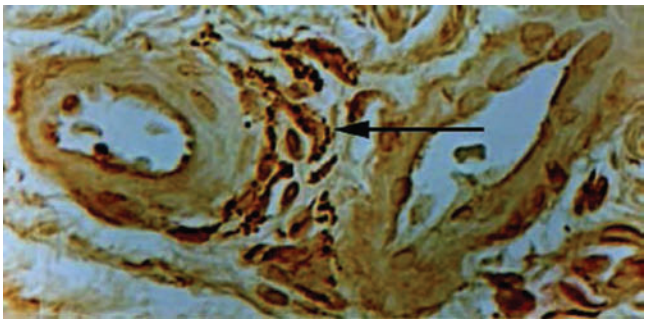

Figure 6.6 Perivascular cuff demonstrating transforming growth factor-β1-positive leukocytes. Horizontal arrow indicates a leukocyte morphologically similar to a mast cell (575×).

Ankle–Brachial Index scores of greater than 0.85. Gohel et al.[58] established an inverse relationship between TGF-β1 concentrations and changes in ulcer size, as well as a direct relationship between basic fibroblast growth factor (bFGF) concentrations and ulcer size. Although paired fluid analysis could not be performed in 43% of patients in this study, the results suggested the presence of greater fibrogenesis, matrix deposition, and proliferation in the healing ulcer.

A prospective study of 30 non-healing lower extremity ulcers with edema (CEAP class 6) by Beidler et al.[59] investigated the levels of pro-inflammatory and anti-inflammatory cytokines in chronic venous ulcers before and after four weeks of compressive therapy. The authors demonstrated that ulcers with higher levels of the pro-inflammatory cytokines interleukin-1α (IL-1α), IL-1β, interferon-γ (IFN-γ), IL-12p40, and granulocyte–macrophage colony stimulating factor were more likely to be rapid healers. The rapid-healing ulcers had very high pre-compression levels of IFN-γ and were noted to have a significant reduction of IFN-γ following compression therapy. IFN-γ is a glycoprotein with numerous immunologic functions. IFN-γ has been shown to suppress the cell cycle, DNA replication, and RNA metabolism of keratinocytes. It is the key mediator in keratinocyte apoptosis, and it acts synergistically with IL-1α to produce tumor necrosis factor-α. The data suggest that the expression of IFN-γ is important during the inflammatory phase of acute wound healing, but its down-regulation is necessary for wound healing to occur. In addition, this study indicates that the mechanism of action of compression therapy is the inhibition of the pro-inflammatory signals that prohibit ulcer healing.

The distribution and location of several other growth factors in the skin of CVI patients has also been investigated. Peschen et al.[60] investigated the role of platelet-derived growth factor receptor-α (PDGFR-α) and PDGFR-β and vascular endothelial growth factor (VEGF) using skin biopsies from 30 patients with symptoms of reticular veins, venous eczema, skin pigmentation, lipodermatosclerosis, and active leg ulcers. The data suggested that PDGFR-α and -β and VEGF expression was strongly increased in the stroma of CVI patients with eczema and

active ulcers compared with patients with reticular veins and pigmentation changes only. To a lesser degree, patients with lipodermatosclerosis also demonstrated immunoreactivity to PDGFR-α and -β and VEGF. PDGFR-α and -β expression was considerably elevated in the capillaries and surrounding fibroblasts and inflammatory cells of venous eczema patients. In addition, immunoreactivity was increased in dermal fibroblasts, SMCs, and vascular cells of lipodermatosclerosis patients compared with patients with reticular veins only. The greatest expression of PDGFR-α and -β was observed in the mesenchymal cells and vascular endothelial cells of patients with active venous ulcers. VEGF immunoreactivity correlated with disease severity. VEGF-positive capillary endothelial cells and pericapillary cells were increased in patients with venous eczema, lipodermatosclerosis, and active venous ulceration, respectively. Subsequently, these authors reported that with progression of CVI dermal pathology, there is increased expression of the endothelial cell adhesion molecules ICAM-1 and vascular adhesion molecule-1 and their corresponding leukocyte ligands LFA-1 and VLA-4.[56] These data suggest that leukocyte recruitment, capillary proliferation, and interstitial edema in CVI patients may be regulated through PDGF and VEGF by the up-regulation of adhesion molecules, leading to leukocyte recruitment, diapedesis, and the release of chemical mediators.[58]

6.7 DERMAL FIBROBLAST FUNCTION

Several studies have reported aberrant phenotypic behavior of fibroblasts isolated from venous ulcer edges when compared with fibroblasts obtained from ipsilateral thigh biopsies of normal skin in the same patients. Hasan et al.[61] compared the ability of venous ulcer fibroblasts to produce aI procollagen mRNA and collagen after stimulation with TGF-β1. These authors were not able to demonstrate differences in aI procollagen mRNA levels after stimulation with TGF-β1 between venous ulcer fibroblasts and normal fibroblasts (control) from ipsilateral thigh biopsies. However, collagen production was increased by 60% in a dose-dependent manner in control subjects, whereas venous ulcer fibroblasts were unresponsive. This unresponsiveness was associated with a four-fold decrease in TGF-β1 type II receptors. In a follow-up report, Kim et al.[62] indicated that the decrease in TGF-β1 type II receptors was associated with a decrease in phosphorylation of the TGF-β1 receptor substrates SMAD2 and SMAD3, as well as p42/44 mitogen-activated protein (MAP) kinases. A similar investigation reported a decrease in collagen production from venous ulcer fibroblasts, and similar amounts of fibronectin production when compared with normal control subjects.[63]

Fibroblast responsiveness to growth factors was further delineated by Stanley et al.[64] These investigators characterized the proliferative responses of venous ulcer fibroblasts when stimulated with bFGF, epidermal growth factor (EGF), and IL-1β. In their initial study, they reported that venous ulcer fibroblast growth rates were markedly suppressed when stimulated with bFGF, EGF, and IL-1β. In a follow-up investigation, these authors noted that the previously observed growth inhibition could be reversed with bFGF.[65] Lal et al.[66] reported that the proliferative responses of CVI fibroblasts to TGF-β1 correlated with disease severity. Fibroblasts from patients with CEAP class 2–3 disease retain their agonist-induced proliferative capacity. Class 4 and 5 fibroblasts demonstrated diminished agonist-induced proliferation, whereas class 6 (venous ulcer) fibroblasts did not proliferate after TGF-β1 stimulation, confirming the observations made by the previous investigators. Phenotypically, venous ulcer fibroblasts appeared large and polygonal and exhibited varied nuclear morphologic features, whereas normal fibroblasts appeared compact and tapered, with well-defined nuclear morphologic features. Venous ulcer fibroblasts appeared morphologically similar to fibroblasts undergoing cellular senescence. Therefore, the blunted growth response of CVI venous ulcer fibroblasts appears to be related to the development of cellular senescence.[65,66]

Other characteristics of senescent cells are an overexpression of matrix proteins such as fibronectin (cFN) and enhanced activity of β-galactosidase (SA-β-Gal). In an evaluation of seven patients with venous stasis ulcers, it was noted that there was a higher percentage of SA-β-Gal-positive cells in patients with venous ulcers than in normal control subjects (6.3% vs. 0.21%, $P \leq 0.0.6$).[65] It was also reported that patients with venous ulcer fibroblasts produced one- to four-times more cFN by western blot analysis than control subjects.[67] These data support the hypothesis that venous ulcer fibroblasts phenotypically behave like senescent cells. However, senescence is probably the end manifestation of a wide spectrum of events that leads to proliferative resistance and cellular dysfunction. Telomeres and telomerase activity are the *sine qua non* of truly senescent cells. To date, there are no reported studies indicating an abnormality in CVI fibroblast telomere or telomerase activity. Despite these investigations, the true role of senescence in CVI remains ill defined.

6.8 REGULATION OF VENOUS ULCER FORMATION AND HEALING

The primary method of normal wound healing is dependent on fibroblast-mediated matrix contraction, in association with keratinocyte epithelialization. The progression of CVI appears to be associated with a concomitant increase in fibroblast-mediated contractile properties and the potential for accelerated wound healing. Pappas and colleagues investigated the effect of TGF-β1 and MAP kinases on fibroblast-mediated matrix contraction in a prospective study using biopsies from patients with varying degrees of CVI.[68,69] It was found that treatment with TGF-β1 and inhibition of MAP kinase promoted gel contraction in a dose-dependent fashion, and a graded response to treatment was observed with increasing clinical disease severity using the CEAP

classification. This suggests that MAP kinases regulate TGF-β1-induced intracellular contractile proteins and the development of a myofibroblast phenotype.

Conversely, Ras activation of extracellular signal-regulated kinase (ERK)-1/2 was shown to irreversibly inhibit TGF-β1-induced gel contraction, suggesting that ERK-1/2 modulates TGF-β1-induced contraction. The molecular cross-talk between ERK-1/2 and TGF-β1 was altered according to the severity of CVI. There is an increase in stored kinetic energy and tension in the dermis of CVI that increases with TGF-β1 and/or ERK inhibition in adaptive wound healing. While increased fibroblast contractility is beneficial in the process of wound healing, injury to the CVI dermal architecture releases stored kinetic energy in the dermis. This release of energy clinically manifests as wound separation.

Bacterial contamination and persistent venous hypertension are thought to secondarily affect poor wound healing in the presence of increased matrix contraction. It is thought that hypertension influences ulcer wound healing through a mechanism known as mechanotransduction. Mechanotransduction is the process of converting physical forces into biochemical signals and integrating these signals into a cellular response. It is thought that mechanotransduction of pressure to the CVI dermal fibroblasts activates cellular senescence processes and stimulates signaling cascades that inhibit TGF-β1-mediated matrix contraction, resulting in prolonged wound healing.

Several studies have reported a loss of growth factor responsiveness in fibroblasts isolated from patients with venous ulcers. Senescent fibroblasts, although they do not proliferate, remain synthetically active. Increased synthesis and secretion of proteins by these fibroblasts cause an alteration in the tissue microenvironment, affecting tissue structure and function. Campisi has reported that the overexpression of oncogenic Ras stimulates ERK MAP kinase signaling and the induction of a senescence response in other fibroblast strains. Ras signaling might therefore affect CVI ulcer healing.[70]

6.9 ROLE OF MMPS AND THEIR INHIBITORS IN CVI

Wound healing is an orderly process that involves inflammation, re-epithelization, matrix deposition, and tissue remodeling. MMPs and tissue inhibitors of metalloproteinases (TIMPs) are known for their tissue remodeling properties and their involvement in inflammation and wound repair. They are often implicated in the pathogenesis of CVI. In general, MMPs and TIMPs are not constitutively expressed. They are induced temporarily in response to exogenous signals such as various cytokines or growth factors, cell–matrix interactions, and altered cell–cell contacts. Fluid from chronic venous ulcers shows a ten-fold increase in levels of MMP-2 and MMP-9 (gelatinases) and a 116-fold increase in MMP-1 (collagenase) levels when compared to fluid from acute wounds. TGF-β1 is a potent inducer of TIMP-1 and an inhibitor of MMP-1. Alterations in MMP and TIMP production may help modulate the tissue fibrosis of the lower extremity in CVI patients.[71,72] In patients with active ulcers, increases in TIMP-1 in keratinocytes from venous ulcers have been reported. For wound healing to occur, there is a delicate balance between MMPs and TIMPs, which must be maintained in order to prevent the uncontrolled ECM degradation by MMPs that is observed in non-healing ulcers.[73–77]

6.10 SUMMARY

CVI results from venous hypertension caused by venous incompetence and/or outflow obstruction. Prolonged exposure to venous hypertension in turn causes macromolecule and RBC extravasation, resulting in the activation of multiple biological processes, such as endothelial activation,

Guidelines 1.5.0 of the American Venous Forum on the pathogenesis of varicose veins and the cellular pathophysiology of chronic venous insufficiency

No.	Guideline	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.5.1	Genetics and deep venous thrombosis are predisposing factors for varicose veins.	A
1.5.2	Age, female gender, pregnancy, weight, height, race, diet, bowel habits, occupation, and posture are predisposing factors for varicose veins.	C
1.5.3	Vein wall remodeling and fibrosis, affected by hemodynamic factors, matrix metalloproteinases, and plasminogen activators, lead to varicose vein formation.	C
1.5.4	In chronic venous insufficiency, the transmission of high venous pressures to the dermal microcirculation causes extravasation of macromolecules and red blood cells that serve as the underlying stimulus for inflammatory injury.	A
1.5.5	Transforming growth factor-β1 and matrix metalloproteinases play key roles in the inflammatory injury that leads to lipodermatosclerosis and chronic skin changes.	B

leukocyte diapedesis, ECM alterations, and collagen deposition. TGF-β1 causes increased ECM and collagen production and altered tissue remodeling by affecting MMP and TIMP production. Wound healing is affected by increased TGF-β1 and/or inhibition of MAP kinase by mediating the differentiation of fibroblasts into contractile cells through the increased expression of α-SMA. This conversion is associated with enhanced matrix contraction that correlates with increasing CEAP disease severity. An unfortunate consequence of this increased contractility is the resultant tension on the dermis of the CVI, which often results in wound separation after an injury. The injury to the dermal architecture releases the kinetic energy stored in the matrix, resulting in wound separation. Venous hypertension might stimulate Ras production through pressure-mediated mechanotransduction. Ras stimulation of the ERK MAP kinases would inhibit TGF-β1-mediated matrix contraction, providing a possible mechanism for poor venous ulcer healing.

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● = Key primary paper
★ = Major review article
◆ = First formal publication of a management guideline

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7

Venous ulcer formation and healing at cellular levels

JOSEPH D. RAFFETTO

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7.1 INTRODUCTION

Venous leg ulcers (VLUs) occur in approximately 1% of the population. Risk factors for chronic venous disease (CVD) include genetics, age, female sex, and obesity. Although not restricted to the elderly, the prevalence of CVD, especially leg ulcers, increases with age.[1] CVD has a considerable impact on healthcare resources. It has been estimated that venous ulcers cause the loss of approximately two million working days and incur treatment costs of approximately $3 billion per year in the United States.[2] Overall, CVD has been estimated to account for 1%–3% of total healthcare budgets in countries with developed healthcare systems.[1] The pathophysiology of dermal abnormalities in VLU is reflective of a complex interplay that involves sustained venous genetic and environmental influences, alterations in shear stress and venous hypertension, injury to the glycocalyx glycosaminoglycan coating on endothelial cells, inflammatory cell activation and infiltration, changes in the microcirculation, overexpression of cytokines, and matrix metalloproteinase (MMP) activation (Figure 7.1), resulting in altered cellular function, the destruction of tissue integrity, and delayed wound healing.[3–6] Collectively, these abnormal wound states lead to chronic and recurrent bouts of venous ulceration. The mechanisms involved in the formation and recurrence of venous ulcers are unknown, but the current state of our understanding is the essence of this chapter review. The role of leukocytes cannot be overlooked, and their importance in venous ulcer pathogenesis is paramount. Chronic inflammation is a known component of venous ulcer formation, and is also presented in Chapter 6, and important information on leukocyte activation and activity and their roles in VLU are discussed.

7.2 THEORETICAL PERSPECTIVES ON VENOUS ULCER FORMATION

Pathological conditions involving venous disease, known as chronic venous insufficiency (CVI), result in venous hypertension from either valvular insufficiency or obstruction, or both.[7] CVD has been a challenging problem and was noted by Hippocrates more than 2500 years ago.[8] Hippocrates discussed the treatment of venous disorders and observed that "it was better not to stand in the case of an ulcer on the leg." Despite the passage of many millennia since Hippocrates' observation, the pathogenesis of venous ulcers remains elusive.

The mechanisms for dermal fibrosis and venous ulcer formation are not known. Based upon scientific observation, a number of investigators have proposed potential etiologies for the advanced forms of dermal pathology and ulceration observed in patients afflicted with CVI. In a study consisting of 41 patients with venous ulcers, tissue biopsies were stained for fibrin. Lipodermatosclerotic skin biopsies were found to have layers of fibrin around dermal capillaries, but no fibrin was found in the normal skin of control subjects. The pericapillary fibrin cuff observed in skin with lipodermatosclerosis was thought to cause the tissue

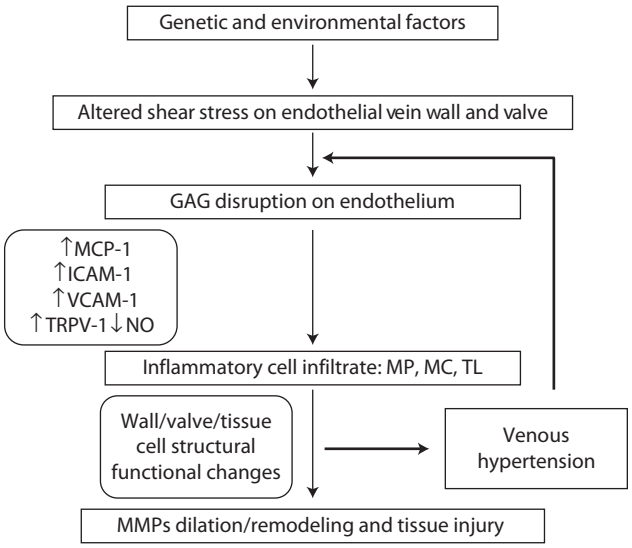

Figure 7.1 Schematic diagram of venous leg ulcer pathophysiology. Genetic and environmental influences predispose patients to developing chronic venous disease and venous leg ulcers. Alteration of shear stress on the endothelium of the venous wall and valve lead to disruption of the glycocalyx and activation of the endothelium with expression of adhesion molecules, recruitment of leukocytes, and transmigration into the vein wall, interstitium, and perivascular region of the microcirculation. Structural changes take place in the venous wall, with valvular insufficiency resulting in venous hypertension. The resulting increased venous pressure induces further destructive changes in the endothelium and glycocalyx, perpetuating the inflammatory response. The production and activation of cytokines and matrix metalloproteinases lead to continued inflammation, venous wall dilation, extracellular matrix degradation, and tissue destruction, with eventual venous leg ulcer formation.

fibrosis and hypoxia that led to ulcer formation.[9] A series of investigations conducted in patients with CVI determined that there were 24% fewer leukocytes leaving the dependent lower limb, but this reverted to normal with leg elevation.[10] This led to the hypothesis that leukocytes trapped in the microcirculation (dermal capillaries) resulted in tissue ischemia and venous ulceration.[11] Growth factors are considered to be important mediators for wound healing. A possible mechanism of venous ulcer formation proposed that growth factors became bound or "trapped" by macromolecules such as α-2 macroglobulin and fibrinogen present in wounds.[12] These proposed theories drove the current research aimed at defining the role of pericapillary changes, leukocyte function, cytokine and growth factor effects, and the effects of soluble compounds on the tissue fibrosis and venous ulcer formation connected with CVI.

7.3 ENVIRONMENTAL AND GENETIC INFLUENCES

The pathophysiology of CVD is a complex, multifaceted, and interconnected set of events leading to dilated, tortuous, valve-insufficient varicose veins, venous hypertension, and the associated clinical manifestations seen in CVD, including venous edema, hyperpigmentation, lipodermatosclerosis, and venous ulceration. Several epidemiologic studies have assessed the associated risk factors. Certainly, genetic and environmental factors influence the predisposition for, and perpetuation of, developing CVD. Some important observations are a family history, prolonged standing and sitting postures, obesity, female gender, pregnancy, and estrogen, the latter three being clinically associated with varicose veins.[13,14] There are several genes that predispose patients to VLUs. Studies have focused on genetic polymorphisms in populations with CVD in terms of the development and healing potential of VLUs.[15] The hemochromatosis C282Y (*HFE*) gene mutation, certain factor XIII (FXIII) *V34L* gene variants, the ferroportin (*FPNI*) gene, and the matrix metalloproteinase 12 (*MMP12*) gene have been investigated as potential genetic risk factors for VLUs, and may have long-term implications for an increased risk of developing VLUs, the onset of VLUs, their healing potential, and the size of VLUs.[16,17] In particular, the *HFE* gene mutation was demonstrated to increase the risk of VLUs in patients with primary CVD.[18] FXIII is an important crosslinking protein that plays a key role during ulcer healing.[19] *HFE* and FXIII genes have also been evaluated in predicting VLU healing following superficial venous surgery in patients with CVD. Specific FXIII genotypes have favorable ulcer healing rates, while the *HFE* gene mutation, despite its importance in venous ulcer risk, has no influence on healing time.[20] Several other genes have been identified as being associated with poor healing and/or progression of VLUs. These include the methylenetetrahydrofolate reductase (*MTFR*) gene mutation leading to reductions in the enzyme, the *SLC40A1* gene which encodes for ferroportin and abnormalities in the export of iron, and the fibroblast growth factor receptor-2 (*FGFR-2*) gene mutation and abnormalities in wound healing processes.[21]

7.4 SHEAR STRESS, GLYCOCALYX, AND ENDOTHELIAL ACTIVATION

The endothelium is a key regulator of vascular tone, hemostasis, and coagulation. Injury, infection, immune diseases, diabetes, genetic predisposition, environmental factors, smoking, and atherosclerosis all have adverse effects on the endothelium, which in turn must compensate in order to prevent further injury and maintain the integrity of the vascular wall. In CVD, the *sine qua non* condition is persistent elevated ambulatory venous pressure. The effect on the microcirculation begins with altered shear stress on the endothelial cells, causing endothelial cells to release vasoactive agents and express E-selectin, inflammatory molecules, chemokines, and pro-thrombotic precursors.[1,22] Mechanical forces, low shear stress, and stretch are sensed by the endothelial cells via intercellular adhesion molecule-1 (ICAM-1, CD54) and the mechanosensitive transient receptor potential vanilloid channels that are present in the

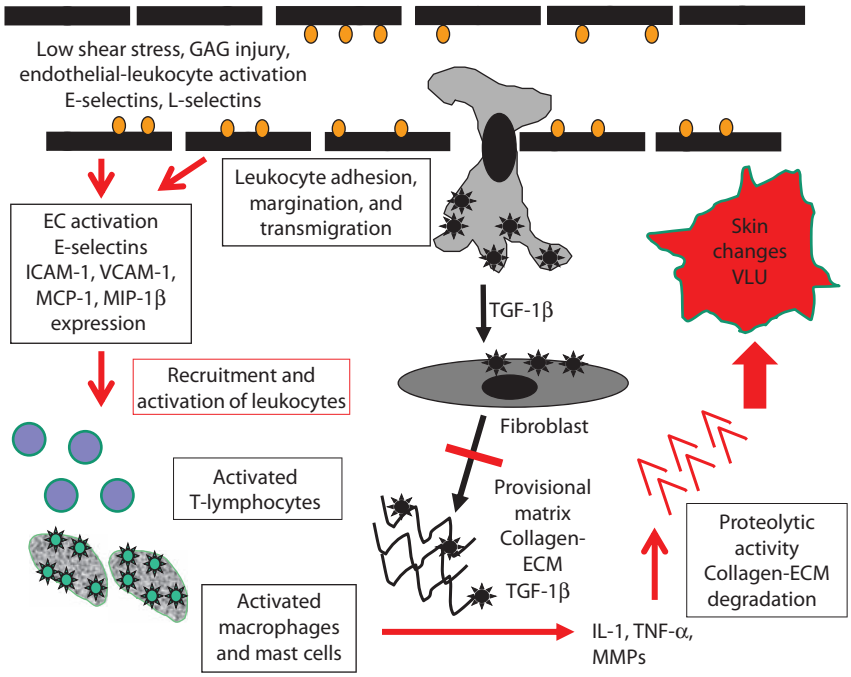

Figure 7.2 Schematic diagram of the inflammatory process in the venous circulation, leading to venous leg ulcers. Alterations in shear stress lead to glycocalyx injury, endothelial activation, the expression of adhesion molecules (selectins and ICAM-1) and the expression of chemokines (MCP-1 and MIP-1β). Leukocytes migrate to the endothelium and are activated. The injury response tries to compensate for leukocytes releasing TGF-β in order to stimulate fibroblasts and deposit provisional matrix (black arrows). However, the persistent venous hypertension and inflammatory response overwhelms the regenerative process, which is blocked (red bar across black arrow), and instead cytokine production, stimulation of MMPs, and degradation of the tissues predominates, leading to a compromised dermis and venous leg ulcer development (red arrows).

endothelium.[1,23] It is well known that patients with CVD have increased expression of ICAM-1, which is expressed on endothelial cells and activates the recruitment of leukocytes and initiates endothelial attachment, diapedesis, and transmigration, which initiate an inflammatory cascade.[24–26] Initiating events likely involve altered shear stress and mechanical stress forces on the endothelium and its glycocalyx (a glycosaminoglycan layer on the endoluminal surface of endothelial cells), with perturbations of nitric oxide production, vasoactive substance release, extravasation of macromolecules, and erythrocyte degradation into fibrin and hemosiderin, which activate leukocytes, the expression of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), and vascular cell adhesion molecule-1 (VCAM-1, CD-106), the expression and shedding of L-selectins, E-selectins, and ICAM-1, along with recruitment of leukocytes. Leukocytes transmigrate into the vein wall and valve, and eventually the surrounding tissues and perivascular microcirculation, setting up an inflammatory cascade, the production of several cytokines (transforming growth factor-β1 [TGF-β1], tumor necrosis factor-α [TNF-α], and interleukin-1 [IL-1]) and increased expression of MMPs, which lead to tissue degradation and eventual VLU formation (Figure 7.2).[1,27,28] In response to inflammation and injury, TGF-β1, which is provided by leukocytes, is released in order to activate fibroblasts and begin the reparative process. For unknown reasons, VLUs have abnormal TGF-β1 receptors and downstream signaling, leading to dysregulation and an inability to develop the provisional matrix. The destructive effects of inflammation, cytokines, and MMPs dominate and cause VLU formation.[5,27,28] In addition, the endothelial glycocalyx is an important structure that prevents leukocyte adhesion, inflammation, and thrombosis. However, altered shear stress and mechanical forces on the vein wall cause leukocyte adhesion, and inflammation leads to injury and loss of the glycocalyx.[29,30]

7.5 INFLAMMATORY CELLS AND CVI

7.5.1 Leukocytes in the CVI limb

In patients with CVI, biopsies of dermal tissue demonstrate an increased presence of leukocytes in lipodermatosclerotic and healed ulcerated skin.[10] Further work in this area has focused on defining the cell type and function responsible for the formation of skin fibrosis and ulceration. In a study evaluating the number of white blood cells in tissue biopsies of patients with CVI, it was determined that the number of leukocytes was highest in the dermis of patients with a history of ulceration, followed by tissues with

lipodermatosclerosis, and lowest in CVI patients with no evidence of skin changes.[31] In a careful histological study using immunohistochemistry in patients with severe lipodermatosclerotic skin changes, the predominant cell types were found to be T lymphocytes and macrophages, and only rarely were neutrophils observed. The expression of ICAM-1-activating leukocytes was elevated, but not endothelial leukocyte adhesion molecule-1 or VCAM-1. The authors concluded that the accumulation and adhesion of macrophages and T lymphocytes in the perivascular and dermal matrix was associated with CVI skin changes and ulceration.[32]

7.5.2 Activity and location of leukocytes in CVI

To further evaluate the activity of these leukocytes and confirm the observed dermal histological findings, an elegant study evaluated surface activation markers on leukocytes by comparing blood from normal control subjects with that of patients with CVI. Patients with CVI had decreased $CD3^+/CD38^+$ expression on T lymphocytes and increased expression of $CD14^+/CD38^+$ markers on monocytes, but no evidence of neutrophil activation was observed, consistent with the histologic leukocyte findings noted above.[33] The function of the mononuclear cells was evaluated by proliferation response assays in the presence of a staphylococcal enterotoxin antigen challenge. The study concluded that mononuclear cell function deteriorated with CVI, and that diminished proliferative responses were correlated with greater severity of disease (lipodermatosclerosis and VLUs), suggesting that decreased mononuclear cell proliferation may be involved in poor wound healing.[34] The role of leukocytes was studied by morphometric analysis in a quantitative study utilizing electron microscopy. Differences in endothelial cell structure and leukocyte cell type and their relationships with the microcirculation were investigated in dermal biopsies of patients with advanced CVI. The authors determined that tissues with severe lipodermatosclerosis and healed ulcers contained significant numbers of mast cells around arterioles and postcapillary venules, and in active ulcers, macrophages were predominantly located in the postcapillary venules. As might be expected in scarred tissue, fibroblasts were the most abundant cell type in all of the biopsies evaluated, but there was no association with the severity of disease and no difference in interendothelial junction width.[35] The significance of this study lies in its defining of the location of the inflammatory cells with respect to the microcirculation, and its demonstration of the predominance of macrophages in active ulcers.

7.5.3 Leukocytes and signaling markers

The involvement of leukocytes in CVI pathology requires interaction with endothelial cells (leukocyte/endothelial signaling) to allow the leukocytes to reach the dermal tissue. An immunohistochemistry study of biopsies obtained adjacent to ulcerated skin evaluated changes in adhesion molecules in patients with severe lipodermatosclerosis and active ulceration, demonstrating that increased expression of VCAM-1 and ICAM-1 (expressed on macrophages) and the endothelial and dendritic cell surface marker antigen CD54 (which activates T cells via lymphocyte function-associated antigen 1 [LFA-1]) were present. In addition, the expression levels of LFA-1 and very late-activated antigen 4 were dramatically increased on perivascular leukocytes compared with healthy skin, indicating that the upregulation of adhesion molecules in CVI patients is an important mediator that can facilitate leukocyte endothelial adhesion, activation, and transendothelial migration.[36]

7.5.4 The role of neutrophils in CVI

Although current evidence suggests that neutrophils are rarely found in the dermis of patients with severe CVI, and that activation has not been detected, several studies have identified a role for neutrophils in this disease process. Investigators evaluating patients with varicose veins with and without skin changes took blood samples from the foot in dependent legs and then again while in the supine position. Leukocyte surface marker CD11b and L-selectin expression levels were analyzed by flow cytometry, and plasma-soluble L-selectin was measured by enzyme-linked immunosorbent assay. In dependent legs with skin changes, both the median neutrophil and monocyte CD11b and the L-selectin levels decreased and remained low even after venous hypertension was reversed in the supine position. This was also noted in patients with uncomplicated varicose veins. The soluble L-selectin increased in the plasma of both patient groups with varicose veins during dependence, indicating that leukocytes were adhering to the endothelium. The authors concluded that venous hypertension resulted in a sequestration of activated neutrophils and monocytes in the microcirculation that persists, despite the removal of venous hypertension.[37] The systemic activation of leukocytes has also been studied in patients with lipodermatosclerosis and VLUs. Blood samples were analyzed for granulocyte activation with Nitroblue tetrazolium reduction. Neutrophil activation was observed in the patients' plasma, but not the whole blood. This finding was more pronounced in patients with lipodermatosclerosis and ulcers than in those with varicose veins and edema. The authors concluded that CVI patients' plasma may contain activating factors for granulocytes. Since neutrophils were fewer in CVI patients' whole blood than in healthy control subjects, it was suggested that activated neutrophils in CVI patients become trapped in the peripheral circulation, and that this phenomenon may be important in the development of CVI and dermal skin changes.[38]

7.6 ALTERATIONS IN VENOUS ULCER FIBROBLAST FUNCTION, SENESCENT PHENOTYPE, AND REGULATION

7.6.1 Venous ulcer fibroblasts and reduced proliferation

Fibroblasts are important in the healing of acute and chronic wounds and, in microscopic analysis, they have been determined to be a major cell type in dermal biopsies from venous ulcers and lipodermatosclerotic skin.[35] Alterations in fibroblast growth and growth factor responses from patients with VLUs were evaluated by biopsies taken from the ulcer margin and compared with normal ipsilateral thigh biopsy fibroblasts from the same patient. The authors found a significant reduction in proliferation, and the fibroblasts were morphologically larger and polygonal in shape, with less uniform nuclear features. However, the responses to growth factors (basic fibroblast growth factor [bFGF] and epidermal growth factor [EGF]) were maintained in venous ulcer fibroblasts, albeit not to the same magnitude as that observed for control fibroblasts. These results indicated the presence of a functional abnormality in dermal fibroblasts obtained from VLUs, suggesting that cellular senescence may be a factor in the pathophysiology of venous ulcer formation.[39]

7.6.2 Venous ulcer fibroblasts and senescence

The *sine qua non* of cellular senescence is an irreversible arrest of DNA synthesis that is otherwise required for replication (multiple transcription nuclear factors that are inactive and/or blocked), and such cells cannot initiate cellular proliferation by normal physiological means, including growth factor stimulation. However, the cell maintains normal biological functioning and remains viable. An interesting observation is that fibroblasts cultured from VLUs have senescent-like characteristics, yet have an ability to respond to growth factor (FGF and EGF) stimulation, although not to the same magnitude as that in normal control fibroblasts.[39,40] Other studies have determined that venous ulcer fibroblasts show a significant decrease in proliferative response to platelet-derived growth factor (PDGF).[41] The fibroblasts from patients with ulcers that were unhealed for more than three years grew significantly slower than those from ulcers of a lesser duration.[42] This could help explain why chronic VLUs are so difficult to heal. The environment of these ulcers may represent a state of exhausted cellular replication and arrested growth, leading to the inability of the ulcer wound to heal. This idea is supported by a study that evaluated patients with active VLUs of various durations. Biopsies were obtained from the ulcer border and the ipsilateral thigh, and fibroblasts from each site were cultured. The percentage of senescent cells was quantified *in vitro* by evaluating the number of fibroblasts expressing senescent-associated β-galactosidase, a specific senescence marker. The authors determined that there was a direct clinical relationship with time to ulcer healing in patients with greater than 15% fibroblast staining for the senescence marker.[43] Although this study is important for identifying an *in vitro* marker that is associated with prolonged ulcer healing, these findings should be interpreted with caution, since *in vitro* results may not reflect exactly what occurs *in vivo*. When compared with the defined setting of a tissue culture dish, in an active venous ulcer bed, there are many uncontrolled factors such as bandaging, infection, the continuous bathing of wound fluid, postural changes, medical comorbidities, and systemic pathologies. In addition, other cells such as keratinocytes are important in ulcer healing.

Certain characteristics of cellular senescence were elucidated in subsequent experiments. Venous ulcer fibroblasts contain more cells that stain positive for senescence-associated β-galactosidase, and have an increased expression of protein and mRNA products for cellular fibronectin. Mendez et al. speculated that the increased accumulation of senescent cells in VLUs led to the observed impaired healing.[40] Furthermore, when these investigators subjected the ulcer fibroblasts to progressive cell culture passage, the cells reacted differently than normal fibroblasts or fibroblasts cultured from patients with varicose veins only. Not only did the ulcer fibroblasts compared with controls have an increased mean number of senescence-associated β-galactosidase-expressing cells over six passages ($63.8\% \pm 8.9\%$ vs. $11.2\% \pm 3.1\%$, $P < 0.05$), but after these six passages, nearly all the ulcer fibroblasts were senescent (>95%). These data indicate that ulcer fibroblasts were significantly advanced in cellular age and closer to replicative exhaustion. The accumulation of such senescent cells in venous ulcer wounds may lead to recalcitrant healing.[44] Although demonstrated *in vitro*, definitive proof of fibroblast cellular senescence in venous ulcers or lipodermatosclerotic skin *in vivo* has yet to be provided. Fibroblasts from venous ulcer and CVI patients, when compared with normal control subjects, were found to have increased expression of fibronectin and MMP-2 when stimulated by bFGF. This may not necessarily signify that they possesses more of a senescent-like phenotype, but rather that they have been subjected to more mitogenic stimuli as a result of their slow growth or location in the ulcer environment.[45] The upregulation of fibronectin and MMP-2 may be a normal, transient, and inducible response to bFGF.

7.6.3 Venous ulcer fibroblasts: Myofibroblast differentiation, cell motility, receptors, and collagen synthesis

Myofibroblast differentiation is a normal process that occurs during wound healing, but in conditions of chronic inflammation, persistent myofibroblast expression has been known

to lead to tissue fibrosis.[46,47] Functional studies evaluating fibroblast motility by time-lapse digital photoimaging were performed for both venous ulcer fibroblasts and fibroblasts cultured from the medial malleolar skin of patients with varicose veins. The findings demonstrated a significant reduction in venous ulcer fibroblast motility compared with the ipsilateral normal thigh fibroblasts and fibroblasts from control subjects without any CVI. Interestingly, fibroblasts from varicose vein patients also had significantly lower motility. The decreased motility was associated with the expression of α-smooth muscle actin, a marker for myofibroblast differentiation. In the same study, it was demonstrated that, compared with bovine serum albumin (control), chronic wound fluid collected from venous ulcers dramatically decreased the motility of neonatal fibroblasts, and led to myofibroblast differentiation.[48] The data showing altered motility in CVI fibroblast and myofibroblast differentiation provide further evidence in support of the concept that fibroblast dysfunction is an important aspect in impaired VLU healing. In addition, the wound fluid from the ulcer causes significant alterations to the function and structure of fibroblasts.

The attenuated response to PDGF by venous ulcer fibroblasts was previously demonstrated.[42] Although the authors were unable to show any differences in PDGF receptors, they stated that venous ulcer fibroblasts had no growth response to PDGF-AB, and the basal levels of PDGF-α and PDGF-β receptors were decreased.[41] A possible explanation for these differences is that cultured fibroblasts were provided by biopsies taken from the ulcer margin[41] and from the central portion of granulation tissue and lipodermatosclerotic skin.[42] Certainly, there are biological, environmental, and biochemical differences that affect tissues in VLUs, and these are reflected in the findings from *in vitro* studies, and should always be taken into consideration when evaluating results and reaching conclusions. In the venous ulcer wound, there is variability in cellular function that is influenced by local environmental stimuli, cytokines, growth factors, proteinases, and inhibitors. This can account for the differences in results noted in tissue culture studies.[49]

In addition to PDGF receptors, the TGF-β type II receptors have also been studied. TGF-β is very important in fibroblasts' regulation of extracellular proteins, proliferation, and differentiation during wound healing.[50] In a study evaluating venous ulcer fibroblasts versus control fibroblasts, the investigators found that there was no difference in incorporation of proline into procollagen, the synthesis of total TGF, or mRNA levels of procollagen or TGF-β. However, when the fibroblasts were stimulated with exogenous TGF-β and collagen synthesis was measured, the venous ulcer fibroblasts failed to respond, whereas the normal cells showed a more than 60% increase in collagen production ($P = 0.0001$). Venous ulcer fibroblasts showed a fourfold reduction in TGF-β type II receptors, which could partly explain the absence of TGF-β-induced synthesis of collagen. It is unclear why the receptors are downregulated, but it has an effect on the response to TGF-β. This finding could explain the lack of appropriate extracellular matrix (ECM) deposition needed for re-epithelialization and wound healing in VLUs.[51] In a recent study, the TGF-β signaling pathway was examined in patients with VLUs. The critical findings of this study were suppression of TGF-β RI, TGF-β RII, and TGF-β RIII receptors, and complete absence of phosphorylated Smad2, which is important in TGF-β signal transduction. Transcriptional factors for cell proliferation and function (GADD45β, ATF3, and ZFP36L1), which are usually stimulated by TGF-β, were suppressed in VLUs, while genes suppressed by TGF-β (*FABP5*, *CSTA*, and *S100A8*) were induced in VLUs. These data indicate that TGF-β signaling is functionally blocked in VLUs by the downregulation of TGF-β receptors and the attenuation of Smad signaling, with deregulation of TGF-β target genes. Furthermore, application of exogenous TGF-β would likely not benefit ulcer healing.[52]

7.6.4 Alterations in venous ulcer fibroblast regulation

The regulatory mechanisms for explaining why fibroblasts from venous ulcers show reduced growth and an attenuated response to growth factors remain unknown. TGF-β has many cellular functions, including cell regulation and tissue remodeling and fibrosis. In an elegant study of CVI patients as well as VLUs, tissue biopsies in the vicinity of active skin disease demonstrated significant elevations of active TGF-β, which were not present in the same patient's thigh biopsies or control subjects. The authors concluded that changes in tissue remodeling occur in patients with CVI, and that dermal tissue fibrosis and probably VLU pathogenesis are regulated by TGF-β.[49] Cell proliferation and the senescent state are regulated by the activation or deactivation of key regulatory proteins and transcriptional factors[53,54] and, in addition to cell growth and differentiation, metabolic functions requiring activation of nuclear transcription, and subsequent protein synthesis, are tightly regulated by the mitogen-activated protein kinase (MAPK) cascade.[55] There are two very important regulatory proteins in this process. The first is p21 (also known as senescent cell-derived inhibitors, sdi1, cip1, waf1, or p21), which inhibits the cyclin-dependent protein kinases as well as the E2F transcription factor (E2F is a key regulatory gene product that activates necessary enzymes to allow the cell to proceed from the G1 to the S phase of cell cycle progression) and hence blocks DNA replication. The other is the tumor suppression protein retinoblastoma (pRb), which, when phosphorylated (ppRb), enables activation of the E2F transcriptional regulator and DNA synthesis. In senescent fibroblasts, there is overexpression of p21 and constitutive underphosphorylation of pRb, leading to growth arrest.[56–58] In venous ulcer-cultured fibroblasts compared with control fibroblast at basal levels, there is significant overexpression of p21 ($P = 0.016$) and underphosphorylation of pRb ($P = 0.069$). Importantly, treatment of the ulcer fibroblasts with bFGF caused significant downregulation of p21 ($P = 0.008$) and increased ppRb

($P = 0.03$) compared with basal (untreated) ulcer fibroblasts.[59] This study indicated the importance of alterations in cell cycle regulatory proteins in venous ulcer fibroblasts consistent with a senescent phenotype, but unlike senescent cells, ulcer fibroblasts responded to growth factors with a reversal of the inhibitory effects of p21 and a positive influence on ppRb. These alterations in cellular regulation could explain some of the findings of decreased proliferation and recalcitrant healing rates observed clinically in patients with VLUs.

As mentioned earlier, MAPK functions as an important signaling pathway for regulating cell proliferation, migration, and differentiation in all eukaryotic cells. The MAPK family is composed of three signaling pathways—ERK1/2 (p44/p42), p38, and JNK/SAPK—which all have upstream kinases (MKKK and MKK) that require phosphorylation for activation. ERK1/2 (p44/p42) is stimulated by mitogens (PDGF and FGF) and is responsible for transducing the signals to the cell nucleus, leading to proliferation and cell growth. The two other MAPKs (p38 and JNK/SAPK) are stimulated by stress states (ultraviolet light, oxidation, and inflammation) and cytokines, and are responsible for transducing signals to the nucleus, causing cell differentiation, growth arrest, and apoptosis.[55,60] The p38 pathway has been found to cause cell cycle arrest at the G1/S transition, and may force cells out of the cell cycle toward a postmitotic differentiated phenotype.[61] In an interesting study, the MAPKs ERK1 and ERK2 were studied in venous ulcer fibroblasts treated with PDGF-AB. The ulcer fibroblasts were found to activate MAPK. Inhibition (PD 98059) of the upstream kinase MEK1 (MKK) significantly reduced fibroblast proliferation, which was reversible by PDGF. In addition, venous ulcer wound fluid inhibited the MAPKs ERK1 and ERK2 directly. These data provide evidence that the MAPK ERK pathway is important in regulating venous ulcer fibroblast proliferation, and confirmed the inhibitory effects of wound fluid on the MAPK ERK pathway.[62] Moreover, VLU wound fluid has important inhibitory properties that affect the regulation of MAPK and proliferation. The MAPK pathway involving p38 is activated by stress responses (the venous ulcer microenvironment, cytokines, and inflammation) and is involved in regulating cell proliferation by inducing growth arrest at the G1/S phase of the cell cycle. In several experiments, it was demonstrated that venous ulcer fibroblasts have increased expression of phosphorylated p38 when compared with normal fibroblasts. Inhibition of p38 with SB203580 increased the growth of venous ulcer fibroblasts compared to untreated fibroblasts. When venous ulcer fibroblasts were treated with bFGF 10 ng/mL, there was a temporal reduction in the expression of p38 over 48 hours (i.e., bFGF can reverse p38, thereby leading to cell proliferation). Alternatively, treatment with the cytokines TNF-α and IL-1β upregulated p38.[63] The kinase p38 appears to be a key kinase in the growth attenuation of venous ulcer fibroblasts, but its effects are reversed with a potent mitogen such as bFGF. These data would suggest potential targets for treatment in patients with VLUs; however, clinical trials are necessary to determine the effectiveness of modulating the MAPK pathways and VLU healing. Recent studies have demonstrated the upregulation of dermal N-cadherin, zonula occludens-1, and the gap junction protein connexin 43 (Cx43) in venous ulcer fibroblasts compared to intact skin. Inhibition of Cx43 and N-cadherin accelerated cell migration and demonstrated that these proteins are important regulators in the function of cellular adhesion, migration, proliferation, and cytoskeletal dynamics, and may be potential therapeutic targets in the promotion of healing of VLUs.[64]

Figure 7.3 summarizes the regulation and alterations of venous ulcer fibroblasts and senescent cells in general.

7.7 KERATINOCYTES AND EPITHELIALIZATION IN VENOUS ULCERS

The importance of wound coverage by keratinocytes leading eventually to re-epithelialization and the impact of the granulating wound bed are emphasized in several studies. Cell cycle regulatory proteins for proliferation and apoptosis specifically involved with epithelialization have been examined. In biopsies of venous ulcers, diabetic ulcers, and control subjects, no major differences in keratinocyte immunohistochemical staining were observed for cell cycle regulatory proteins or apoptosis-related proteins.[65] In a follow-up study, these investigators compared the edges of venous ulcers to those of central granulation tissue for growth factor and cytokine expression levels of keratinocytes and endothelial cells by immunohistochemistry and phenotype characterization. Keratinocytes and endothelial cells on the ulcer margin retained their secretory potential for growth factors and cytokines. The ulcer bed was composed mainly of macrophages and very few fibroblasts were noted.[66] The authors speculated that the wound bed was altered by chronic infections and that the impaired nutrition inhibited keratinocyte migration. It is well known that fibronectin is an important protein of the ECM that is involved in keratinocyte re-epithelialization. A study evaluating biopsies from venous ulcer wound margins, acute wounds, and normal skin determined that the transcription product of fibronectin was significantly increased in venous ulcers. However, α5β1 integrin, the cell surface receptor for fibronectin, was undetectable via immunostaining in venous ulcer biopsies. Therefore, although fibronectin mRNA was expressed, the lack of an integrin receptor may have prevented keratinocyte migration and wound closure.[67] A study evaluating differentiation markers of keratinocytes found that the keratins K1/K10 and a subset of small proline-rich proteins, along with the late differentiation marker filaggrin, were suppressed in VLUs, while the late differentiation markers involucrin, transgultaminase 1, and another subset of small, proline-rich proteins were induced in VLUs compared to healthy skin. This study concluded that keratinocytes at the nonhealing edges of VLUs do not execute either activation or

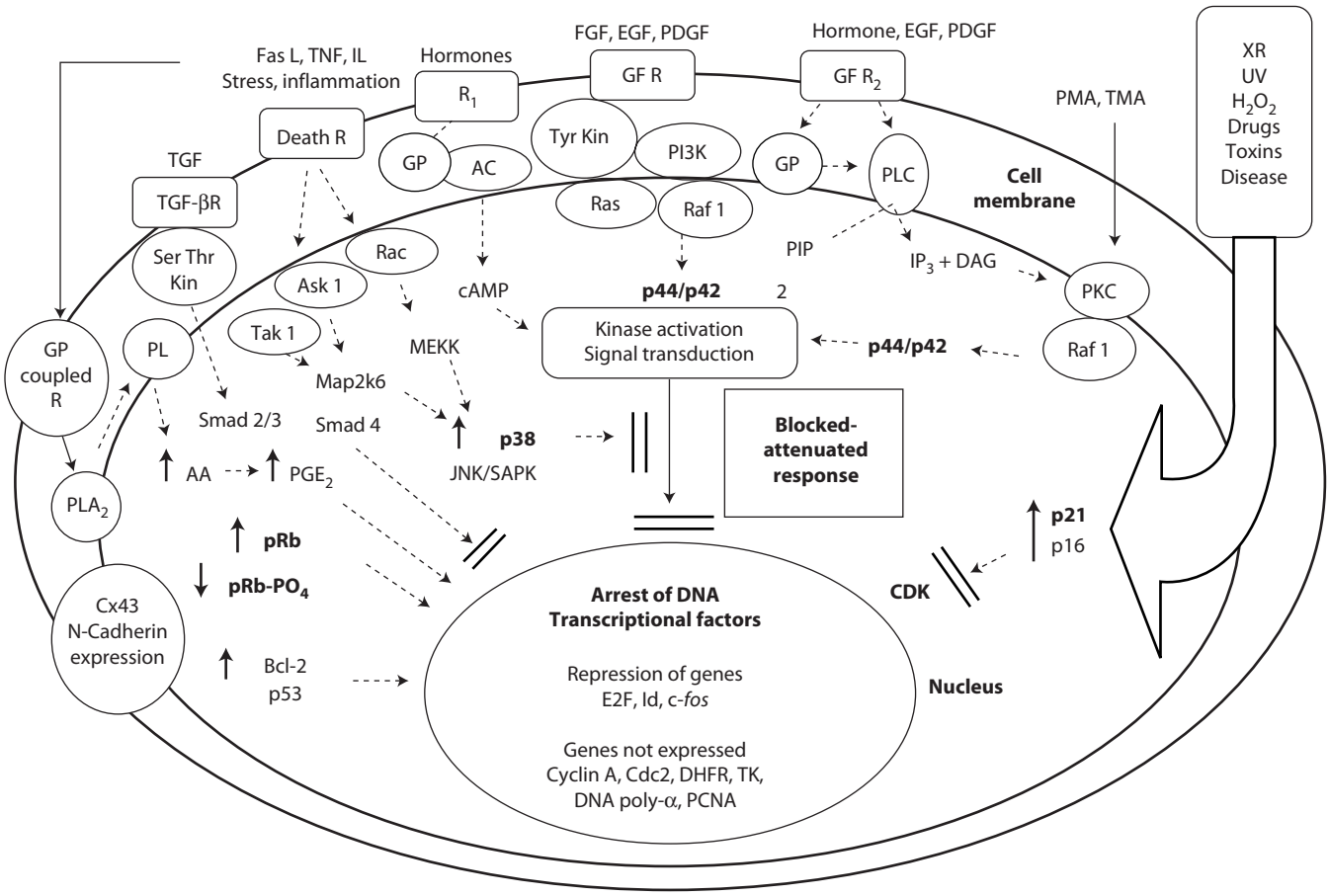

Figure 7.3 Signaling pathways leading to inhibition of DNA transcription and cell proliferation: senescence phenotype in venous ulcer fibroblasts. Schematic of the venous ulcer fibroblast signaling pathways for the regulation of cell proliferation and the pathways leading to growth attenuation and DNA inhibition rendering these cells with a senescent phenotype. Growth factors, hormones, and cytokines bind to cell surface receptors (TGF, death, Hormone R1, and growth factors), and various noxious stimuli (inflammation, radiation, and stress) and phorbol esters (phorbol-12-myristate 13-acetate [PMA] and 12-tetradecanoate phorbol 13-acetate [TPA]) have direct or indirect effects on receptors. Following receptor activation, signal pathways lead to protein phosphorylation and the production of secondary messengers involving various membrane-associated proteins: tyrosine kinase (Tyr Kin), serine threonine kinase (Ser Thr Kin), G-protein (GP), adenylyl cyclase (AC), Ras, Rac, phosphatidylinositol 3-kinase (PI3K), phospholipase C (PLC), and protein kinase C (PKC). The Ras (a GDP/GTP-activated protein)-dependent pathway activates the kinase cascade, activating Raf, MEK, and MAPK (ERK1/2 and p44/p42), and the Ras-independent pathway leads to the activation of PKC, Raf, and MAPK for the activation of transcription factors (Elk-1, c-Myc, CREB, and Sap-1) and DNA transcription and proliferation. Phosphoinositol 4,5-biphosphate (PIP_2) is the substrate in which PLC forms the secondary messengers inositol 1,4,5-triphosphate (IP_3) and 1,2-diacylglycerol (DAG). In turn, DAG is important in activating PKC by membrane translocation. The ligand-stimulated TGF-βR receptor complex causes phosphorylation of the Smad complex (Smad 2/3–Smad 4) and translocates to the nucleus, binding to transcription factors and leading to gene activation. Stimulation of the death receptors by cytokines and stress activates the Rac, Ask, and Tak pathways, leading to kinase activity (MEKK and Map2k6) and phosphorylation of p38 and JNK/SAPK kinase, leading to transcription factor activation (c-Jun, ATF-2, Elk-1, Sap-1, and CHOP), which brings about growth arrest and apoptosis. Note that active Ras can also activate p38 and JNK (not shown in the diagram). Senescent cells and venous ulcer fibroblasts (senescent-like phenotype) have attenuated responses to signal transduction (=), leading to inhibition of DNA synthesis. Arrest of DNA synthesis is also a result of increased metabolites of phospholipids (PLs) by the action of phospholipase A2 (PLA_2), producing elevated levels of arachidonic acid (AA) and prostaglandin E_2 (PGE_2), and by the inhibition of cyclin-dependent protein kinases (CDKs) by the overexpression of p21 and p16, causing underphosphorylation of pRb (i.e., decreased pRb-PO_4) and consequently inhibition of the gene expression that is necessary for DNA replication. Unlike senescent cells, venous ulcer fibroblasts, despite having fewer mitogenic receptors, utilize the MAPK pathway (elevated ERK 1/2 and p44/p42) and are able to respond to growth factors (bFGF) and downregulate negative proliferative proteins and kinases (p21 and p38) in order to increase proliferation. Dihydrofolate reductase (DHFR), thymidine kinase (TK), DNA polymerase-α (DNA polyα), and the cofactor proliferating cell nuclear antigen (PCNA). Dashed arrows indicate a pathway; solid up or down arrows indicate whether that compound is overexpressed or underexpressed, respectively; and double solid bars indicate a blocked/attenuated response.

differentiation pathways, and may in part be responsible for impaired VLU healing.[68]

7.8 WOUND FLUID ENVIRONMENT AND MMPs

7.8.1 Venous ulcer wound fluid

The venous ulcer microenvironment consists of dermal fibroblasts, keratinocytes, inflammatory cells, ECM, growth factors, cytokines, bacteria, and the microcirculation. An interesting aspect of the venous ulcer milieu is the presence of chronic venous ulcer wound fluid. The wound fluid is known to have important properties that affect cellular function, with many of the identified components being proteases, proteinases, ECM proteins, inhibitors, MMPs, chemokines, cytokines, and growth factors.[69] A significant number of chemokines (IL-8, MCP-1, MIP-1α, and RANTES) and cytokines (TNF-α, IL, interferon-γ [IFN-γ], growth-regulated protein α [GROα], and eotaxin-2) have been determined to be present in VLU wound fluid. Many of these chemokines and cytokines are produced and secreted in the ECM and tissue interstitium and in the wound fluid by inflammatory cells. These compounds are important for the recruitment of leukocytes, the activation of MMPs, tissue destruction, and a persistent inflammatory state in the VLU.[69] Because MMPs are involved in the pathogenesis of VLUs, it is essential to examine data that have evaluated proteinases in the VLU wound fluid. The collagenase activity of venous ulcer fluid is 116-fold more than that found in normal acute wound fluid. The collagenase activity decreases in VLUs, demonstrating healing at 2 weeks.[70,71] The venous ulcer fluid causes inhibition of fibroblast proliferation and induces changes that are consistent with cellular senescence.[48,72] It also inhibits the growth of neonatal fibroblasts, causing the majority of cells to remain in the G1 or G2 phases of the cell cycle (i.e., unable to enter the S phase, thereby blocking DNA synthesis). When compared with fibroblasts treated with bovine serum albumin, the wound fluid demonstrated dose-dependent inhibition at a concentration of 500 mg/plate and was not toxic (by trypan blue exclusion assay). The normal proliferation of neonatal fibroblasts treated with VLU wound fluid can be reversed by heat inactivation of the wound fluid or by the removal and placement of the cells in 10% serum.[73] In addition to fibroblasts, VLU wound fluid inhibits the proliferation of endothelial cells and keratinocytes in part by inhibiting DNA synthesis. Although the specific inhibitory components in VLU wound fluid are not known, there is evidence to suggest that this active inhibitory substance resides in the less than 30 kDa fraction, and has two to three times the inhibitory effect on cells than the fraction that is greater than 30 kDa.[74] The inhibitory effect of wound fluid can be reversed by heating to 100°C, and at concentrations of 2% and 4%, wound fluid causes cell death. Venous ulcer fluid was demonstrated to inhibit the expression of MAPK, specifically ERK1 and ERK2, with a simultaneous decrease in the proliferation of neonatal fibroblasts.[62] The mechanism of cell inhibition by wound fluid involves, in part, downregulation of the phosphorylated pRb tumor suppression gene and cyclin D1 via inhibition of the Ras-dependent MAPK pathway.[75] The compound(s) in VLU fluid that cause(s) changes in cellular function will be a focus of future investigations. Identifying the inhibitory substances in wound fluid will be important for understanding its molecular effects on cell behavior, regulation, transcriptional, and pre- and post-translational alternations, as well as phenotypic alterations, and will advance our knowledge for the better treatment of venous ulcers. Biomarkers found in VLU fluid may be useful for determining healing potential, as well as therapeutic targets in the treatment of VLUs.[69]

7.8.2 The ECM and MMPs

The ECM is an important structural and functional scaffolding that is made up of proteins that are necessary for cell function, wound repair, epithelialization, blood vessel support, cell differentiation and signaling, and cellular migration. The ECM is composed of many proteins and glycoproteins, including collagen, elastin, fibronectin, vitronectin, aggrecan, entactin, proteoglycans, glycosaminoglycans, growth factors, integrins, tenascin, fibrin, and laminin.[69,76,77] The ECM is particularly important for providing a substrate in which keratinocytes can migrate in order to ultimately establish skin coverage in both acute and chronic wounds.[67] Abnormal ECM metabolism in wounds has been an area of interest and investigation. The MMPs are proteases that are involved in both healthy and disease states involving ECM turnover. MMPs are highly homologous, zinc-dependent endopeptidases that belong to a large group of proteases called the metzincins, and they are able to cleave most of the constituents of the ECM. At least 26 identified and characterized MMPs are classified according to their substrate specificity and structural similarities. Their four major subgroups are interstitial collagenases, gelatinases, stromelysins, and membrane-type MMPs. Other MMPs are in different subgroups, such as the matrilysins.[78,79] The naturally occurring inhibitors of MMPs are the tissue inhibitors of MMP (TIMPs). Molecules such as trocade (Ro 32-3555), marimastat (BB-25160 and BB-94), and Ro 28-2653 are also known to inhibit MMPs, and are useful in studying the kinetics and mechanisms of MMPs in biological systems.[79] In an early report evaluating VLU wound fluid compared with fluid from acute wounds, it was found that the chronic wound fluid contained up to a 10-fold increase in the levels of MMP-2 and MMP-9 (gelatinases), as well as showing increased activity of these enzymes, suggesting a high tissue turnover.[80] Increased levels of MMP-1 and gelatinase activity from the exudates of chronic VLUs have been confirmed by other investigators, and doxycycline inhibition studies suggested that the protease activity was such that the cell source was from fibroblasts, mononuclear cells, keratinocytes, or endothelial cells, but not neutrophils.[81]

It was essential to determine the source of collagenase activity, since bacteria also produce collagenase and are abundant in venous ulcers. An important distinguishing feature of human collagenase is that it degrades collagen in specific 3/4 and 1/4 fragments, whereas bacterial collagenase degrades collagen randomly in a non-specific manner. It was determined that the collagenase from VLU fluid degraded collagen in the specific 3/4 and 1/4 fragments that are indicative of human collagenase.[81] The changes noted in the MMP levels and activity in venous ulcers are not specific to just venous disease, and similar alterations are found in other inflammatory wounds, including burns and pressure ulcers.[82] Other investigators have also demonstrated increased levels of MMP-1 and decreased levels of TIMP-1 in VLU fluid. Importantly, VLU fluid leads to the significant overexpression of MMP-1 and MMP-3 in newborn fibroblasts compared to fibroblasts treated with acute wound fluid or fetal calf serum.[83] In another interesting study, VLU fluid was compared to acute wound fluid and assessed for MMP-9 and neutrophil gelatinase-associated lipocalin (NGAL). NGAL binds covalently to MMP 9, inhibiting the deactivation of MMP-9 and increasing its activity. As expected, MMP-9 and NGAL were significantly elevated in VLU fluid compared to controls. The levels of MMP-9 and NGAL in VLU fluid decreased at 4 and 8 weeks in VLUs that healed.[84] The production of TIMPs can have a significant influence on MMP expression. In an *in vitro* study, fibroblasts cultured from venous ulcers demonstrated a marked reduction in MMP-1 and MMP-2 level and activity and a significant increase in TIMP-1 and TIMP-2 production. The authors concluded that the inhibition of fibroblast proteinase activity by TIMPs causes impaired reorganization of the ECM in chronic wounds, leading to delays in healing.[85] This study indicated that although there is elevated proteinase activity in the venous ulcer wound and wound fluid, cellular components studied *in vitro* (in this case, fibroblasts) compensate by altering their expression of MMPs and TIMPs.

The abnormalities in the structure and the healing process seen in lipodermatosclerotic skin have also been attributed to the MMP pathway. In one study, dermal biopsies were obtained from lipodermatosclerotic skin, compared with healthy skin, and analyzed by immunohistochemistry, reverse transcriptase polymerase chain reaction, immunoblot, and zymography analysis. The study found that lipodermatosclerotic skin had increased expression of mRNA and protein for MMP-1, MMP-2, and TIMP-1, and increased levels of active MMP-2. In addition, there was an increase in the proMMP-1–TIMP1 complex, indicating that the overexpression of proteinase was bound to TIMP.[86] As assessed by immunohistochemistry, both MMP-1 and MMP-2 were predominantly localized in the basal and suprabasal layers of the epidermis, the perivascular region, and the reticular dermis, and significantly reduced expression of TIMP-2 was found in the basement membrane of the diseased skin.[86] This demonstrates that in lipodermatosclerotic skin—a precursor to venous ulcer formation—excessive and unrestrained MMP activity and ECM turnover occurs, especially in the areas of the dermis, the epidermis, and the perivascular region. A consistent finding is the presence of MMPs in the perivascular region (see below in Section 7.7.3). A consideration is that MMPs may cause abnormalities in tissue perfusion, or affect angiogenesis and the microvasculature. In an elegant study, investigators compared VLU fluid with control acute wound fluid (donor skin graft sites) and tested both fluids in an *in vitro* angiogenesis model by measuring tubule length. The venous ulcer fluid caused a significant reduction in the formation of tubules and their length (490 ± 130 mm) compared with the control fluid (1740 ± 320 mm, $P < 0.05$). When a synthetic inhibitor of MMP-2 and MMP-9 was added to chronic venous ulcer fluid, angiogenesis increased significantly (870 ± 220 mm, $P < 0.05$).[87] The proteolytic activity of MMP-9 can generate angiostatin from plasminogen, which inhibits the proliferation of human microvascular endothelial cells. Endostatin is also antiangiogenic and can be activated by MMPs. These data raise the possibility that MMPs in venous ulcer wound fluid may have significant antiangiogenic effects and may disrupt the microcirculation in the perivascular regions, thereby inhibiting wound healing.

7.8.3 Modulation and activation of MMPs

MMPs are synthesized in a pro-enzyme form. The pro-enzymes have a cysteine domain called the cysteine switch that interacts with the zinc active binding site, preventing activation and substrate degradation. The cysteine switch is cleaved prior to the pro-enzyme becoming active.[78] The excess proteolytic activity in VLUs has been found to degrade essential plasminogen, activating proMMP to MMP, which is necessary for fibrinolysis and cell migration. MMPs also inhibit plasmin production by keratinocytes, which may lead to reduced cell migration.[88] Important to the healing wound is FXIII, which impacts collagen cross-linking. FXIII has the ability to modulate the detrimental effects of MMPs. In an *in vitro* study, the investigators evaluated the effects of increasing concentrations of collagenase and FXIII on fibroblast survival, as assayed by the MTT colorimetric test. At high concentrations of collagenase (2 mg/mL), 95% of fibroblasts were killed, and FXIII (5 U/mL) was unable to mitigate the effect. However, at lower collagenase concentrations (0.5–1 mg/mL), the addition of FXIII was able to abrogate the effects of collagenase and increase fibroblast survival. These data were consistent with clinical findings that the topical application of FXIII has the ability to improve venous ulcer healing.[19] In addition to FXIII, iron overload has been found in the serum and dermis of the limbs of patients with venous ulcer, compared with control subjects. A concomitant elevation in MMP-9 activity was also present in patients with VLUs. The importance of iron overload in venous ulcer tissue is that it can cause oxidative stress and the production of free radicals or reactive oxygen

species. The authors suggest that elevated iron deposits in the limbs are released into the serum with the activation of MMPs and reactive oxygen species, impairing ulcer healing.[89] Other investigators have also found increased ferritin and overall oxidative stress as measured by 8-isoprostane and total antioxidant status in VLU fluid. Importantly, the levels of ferritin and oxidative stress were significantly lower in patients with healing VLUs versus those that had non-healing VLUs.[90]

As mentioned previously, plasminogen is essential in MMP regulation.[88] Urokinase-type plasminogen activator (uPA) functions as a fibrin-independent plasminogen activator in a cell-bound fashion, and when uPA is bound to its receptor uPAR, the activity of uPA is potentiated. Comparing venous ulcers with normal dermis, one study found that both the transcriptional products and the proteins of uPA and uPAR were overexpressed in venous ulcers. Localization of uPA and uPAR by immunohistochemistry determined that these proteins were present in the dermis and in the pericapillary regions.[91] One could hypothesize that uPA is crucial for maintaining proteolytic activity and likely has a role in the activation of MMPs via plasmin in the pathogenesis of venous ulcers.

Two important molecules in the activation of MMPs are MT1-MMP and the extracellular MMP inducer (EMMPRIN; CD147).[78,92] Utilizing an immunohistochemistry assay, MMP-2, MT1-MMP, MT2-MMP, and EMMPRIN were found to be significantly elevated in the venous ulcer dermis, and only EMMPRIN and MMP-2 were overexpressed in the perivascular regions in venous ulcer biopsies. These data indicate the presence of MMP activators in venous ulcer tissue that favor extracellular turnover and unrestrained MMP activation.[92] In another study evaluating healing versus non-healing VLUs, the investigators determined that in healing ulcer tissue there were increased levels of PDGF-AA, but no difference in MMP or EMMPRIN levels. In the same study, the venous ulcer fluid of healing ulcers versus non-healing ulcers demonstrated elevated levels of PDGF-AA and TIMP-2 and low levels of MMP-2. These findings are significant as they help to define the factors that are important for ulcer healing and support the theory that elevated proteinase activity (MMP-2 and MMP-9) favors a non-healing environment. In addition, the growth factor PDGF-AA appears to be essential to promoting healing.[93] The activation of MMPs and their potential involvement in ulcer formation is summarized in Figure 7.4.

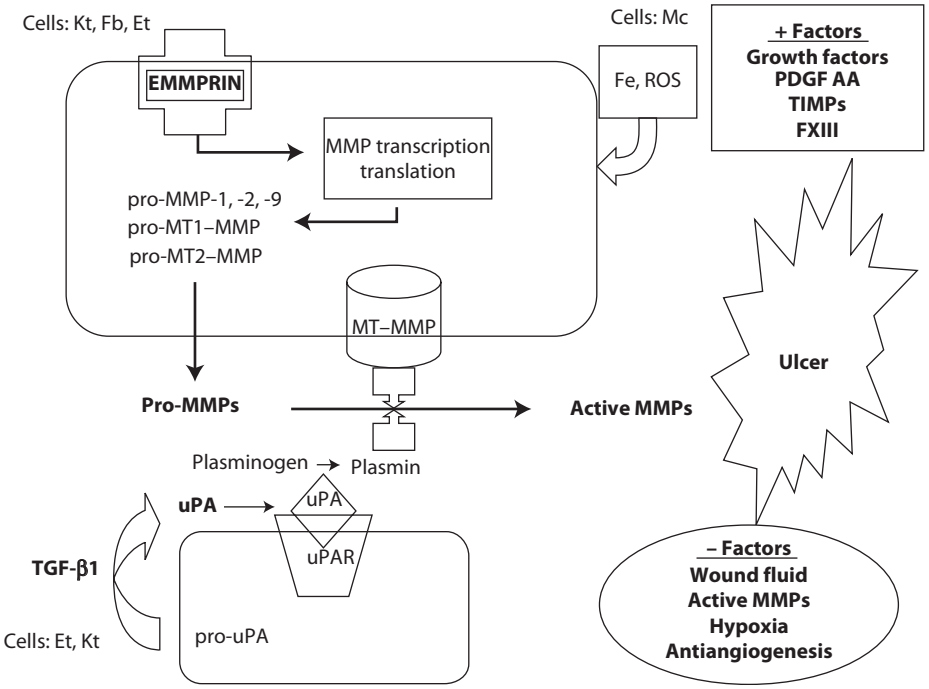

Figure 7.4 Matrix metalloproteinase activation and unbalanced proteinase activity leading to venous ulcer formation. Schematic diagram of the activation of MMPs. EMMPRIN activation leads to the synthesis of proMMPs. In addition, iron overload and reactive oxygen species lead to the expression of MMPs. Furthermore, pro-uPA is synthesized and converted to uPA by TGF and binds to its receptor, uPAR, which potentiates the conversion of plasminogen to plasmin. The proMMPs are secreted in their inactive forms and are activated by both plasmin and membrane-type MMPs (MT1-MMP and MT2-MMP). Active MMPs in the wound fluid cause tissue degradation, anti-angiogenesis, and fibroblast and keratinocyte inhibition, promoting non-healing venous ulcers (negative factors). Factors promoting the healing of venous ulcers are the presence of tissue inhibitors of MMP (TIMP), growth factors such as platelet-derived growth factor AA (PDGF-AA), and factor XIII (FXIII) (positive factors). Cells involved are keratinocytes (Kt), fibroblasts (Fb), endothelial (Et) cells, macrophages (Mc), and leukocytes.

7.8.4 Regulation of MMPs

The regulation of MMP production in venous ulcers and lipodermatosclerotic tissue is complex. Post-translational modifications of MMPs are essential for activity, and are likely regulated by TGF-β1. Dermal fibroblasts and leukocytes are major sources of MMPs, especially MMP-2.[94] The interplay of MAPK and MMP activation has also been investigated in fibroblasts. The cytokine TNF-α has been demonstrated to induce MMP-19 expression, which is inhibited by blocking the MAPK pathways ERK1 and ERK2 with PD98059 and p38 with SB203580. In addition, adenovirus-mediated induction of ERK1 and ERK2 in combination with p38 resulted in potent MMP-19 expression in fibroblasts, and the activation of c-JNK also produced abundant proMMP-19.[95] These data, as well as findings of MAPK alterations in venous ulcer fibroblasts due to the effects of wound fluid,[62,63,75] indicate the important regulatory functions of MAPK and proteolytic activity in dermal fibroblasts and their implications in venous ulcer pathogenesis.[95]

7.9 IMPORTANT MARKERS FOR VLU HEALING

VLU healing reaches between 60% and 70% at 12–24 weeks, and the principle treatment applied is compression.[96,97] It is essential to understand the pathophysiology of VLUs so that biomarkers that are predictive of VLU healing and potential therapeutic targets can be developed.[69] Several works have already indicated that VLU healing is associated with a decrease in MMP-9 and NGAL,[84] as well as a reduction in oxidative stress.[90] In a study of 40 patients with healing versus non-healing VLUs of greater than 8 weeks' duration, patients underwent tissue biopsy at the VLU edge and wound fluid evaluation at the initial visit. Evaluation of VLU healing occurred after 8 weeks. In healing VLUs, there were significantly higher ($P < 0.001$) levels of PDGF-AA in the perivascular region, and in the wound fluid there were significantly increased levels of PDGF-AA and a decreased ratio of MMP-2:TIMP-2 ($P = 0.0001$).[93] Collagen turnover and remodeling is an important function of healing VLUs. In a study evaluating VLU biopsies in healed patients ($n = 12$) and non-healed patients ($n = 15$), as well as controls ($n = 15$), after applying compression bandaging for 12 months, the degradation products of collagen and collagen turnover were determined. Healed VLUs had significantly ($P < 0.001$) elevated levels of degraded collagen and type III collagen ($P = 0.005$, as measured by collagen III N-terminal propeptide), and elevated levels of MMP-1 ($P < 0.001$; MMP-1 is important in tissue remodeling during healing).[98] The role of TGF-β1 in VLU healing was investigated in a study of 80 patients treated with multilayer compression bandaging. In the wound fluid and serum, cytokines and factors reflecting the processes of inflammation (IL-1 and TNF-α), proteolysis (proMMP-2 and proMMP-9), angiogenesis (bFGF and VEGF), and matrix deposition/proliferation/fibrosis (TGF-β1) were measured. Interestingly, ulcer healing at 5 weeks only correlated significantly with increased concentrations of TGF-β1 in the VLU fluid.[99] An elegant analysis of cytokine levels and venous ulcer healing determined that untreated ulcers typically display high levels of pro-inflammatory cytokines, including several interleukins, TNF-α, and IFN-γ. After 4 weeks of compression therapy, the levels of pro-inflammatory cytokines decreased significantly and the wounds began to heal. The levels of TGF-β1 increased significantly as the ulcers improved. When specific cytokine levels were related to the percentage of healing, it was found that those with higher levels of pro-inflammatory cytokines, including IL-1 and IFN-γ, healed significantly better than those with lower levels prior to compression. Treatment with compression therapy resulted in healing that was coupled with reduced pro-inflammatory cytokine levels and higher levels of the anti-inflammatory cytokine IL-1 receptor antagonist.[100] In another study evaluating patients with VLUs, tissue biopsies were obtained at the initial visit and after 4 weeks of compression therapy. At 4 weeks, significant decreases in both mRNA and protein were seen for MMP-3 (stromelysin-1) and MMP-9 (gelatinase-B). In addition, in those patients who had greater than 40% healing of the VLU versus those that had less than 40% healing, significant decreases in MMP-1, MMP-2, and MMP-3 were identified.[101] These studies indicate the complex interplay of collagen turnover, MMPs, pro-inflammatory and anti-inflammatory cytokines, and TGF-β1. The importance of balanced and temporal MMP and cytokine function, and the key role of TGF-β1 in promoting VLU healing, were also demonstrated.

7.10 CONCLUSION

VLU pathophysiology is a complex process that involves the many changes discussed in this chapter, including genetic and environmental influences, alterations in shear stress and injury to the glycocalyx with endothelial activation, the inflammatory response due to leukocytes acting on the venous endothelium and microcirculation, alterations in cellular functions, with dysregulation of important cellular elements (fibroblasts and keratinocytes), the overexpression of chemokines, cytokines, dysregulation of signaling pathways such as TGF-β and MAPK, and MMPs and their impact on the ECM. Another component that perpetuates an inflammatory and non-healing state is the inhibitory environment of VLU fluid, causing a significant negative influence on cellular growth and healing, in addition to some regulatory pathways. From this review and the research examined, several observations and conclusions can be summarized, as listed in the Guidelines. Venous ulcer pathophysiology involves systemic and local processes. It is likely that targeting only one system may not cause a clinical change in ulcer healing. It is likely that several systems need to be intervened in so as to achieve

clinical response and decrease recurrence. Our current understanding of VLU development is just the tip of an iceberg. However, as monumental as it may seem, the task of acquiring knowledge through careful scientific investigation must progress. As specialists in venous diseases, we must better understand the complexities of venous ulcer pathology and focus our resources on several issues, such as the regulation of shear stress and the glycocalyx, leukocytes in the microcirculation, the regulation of the cells involved in healing, wound fluid and its effect on the ulcer environment, and the effects and regulation of chemokines, cytokines, and MMPs.

Guidelines 1.6.0 of the American Venous Forum on venous ulcer formation and healing at cellular levels

No.	Guideline	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.6.1	We recommend a basic practical knowledge of venous physiology and venous leg ulcer pathophysiology for all practitioners caring for venous leg ulcers.	Best practice
1.6.2	Age, genetic, and environmental factors predispose to venous ulcers.	B
1.6.3	Shear stress, glycocalyx injury, and expression of adhesions molecules with venous endothelial activation allow attachment of leukocytes and are key steps in the progression of chronic venous insufficiency.	B
1.6.4	Leukocyte activity and interaction with endothelial cells initiate a cascade of inflammatory events.	B
1.6.5	Macrophages play a major role in ulcer formation.	C
1.6.6	Dysfunctional leukocytes, senescent fibroblasts, and keratinocytes contribute to delayed ulcer healing.	B
1.6.7	Key regulatory cell cycle proteins (p21 and pRb) affect fibroblast proliferation and delay wound healing.	B
1.6.8	Venous ulcer fluid has elevated inhibitory cytokines and matrix metalloproteinases (MMPs). MMPs play an integral role in venous ulcer formation.	A
1.6.9	Factor XIII, plasminogen, and extracellular MMP inducer (EMMPRIN) modulate MMP activity and contribute to venous ulcers.	C

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● = Key primary paper
★ = Major review article

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Acute and chronic venous thrombosis: Pathogenesis and new insights

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8.1 INTRODUCTION

Deep vein thrombosis (VT) refers to the formation of one or more thrombi within the deep veins, most commonly in the lower limbs. The thrombus may cause partial or complete blockage of the circulation in the vein, which may lead to characteristic symptoms such as pain, swelling, tenderness, discoloration, or redness of the affected area, as well as skin ulcers. In 2008, the Surgeon General's Call to Action to prevent VT and pulmonary embolism (PE) states, "the disease disproportionately affects older Americans, and we can expect more suffering and more deaths in the future as the population ages, unless we do something about it," inviting multiple stakeholders to come together in a coordinated effort to reverse this dramatic projected trend.[1]

8.2 VT: EPIDEMIOLOGY

VT remains a serious health care problems in the United States, with over 250,000 patients affected yearly and at least 200,000 diagnosed yearly with PE, although some suggest that these figures are conservative.[2–4] However, VT occur worldwide, affecting all socioeconomic populations. The incidence of VT has been increasing with the aging of the population. In those aged 85–89 years, the incidence is reported to be as high as 310/100,000 of the population.[5] Additionally, treatment costs are in the billions of dollars per year.[6] The late VT consequence of post-thrombotic syndrome (PTS) affects between 400,000 and 500,000 patients with skin ulcerations, and 6–7 million patients with severe manifestations, including stasis pigmentation and stasis dermatitis. It has been reported that up to 28% of the patients evaluated after having an iliofemoral VT develop marked edema and skin changes, and 28% of cases develop venous stasis syndrome within a period of 20 years.[5] Even asymptomatic VT has been associated with PTS.[7]

Treatment for VT is not perfect; even with the best therapies, there remains a significant risk of recurrence and extension. Recurrence rates of 29%–47% are observed with iliofemoral VT without anticoagulation, 5%–7% with full heparin anticoagulation, 4%–5% with low-molecular-weight heparin (LMWH) anticoagulation, and 3%–9% with direct thrombin inhibitors.[8–10] Bleeding complications include minor bleeding and major bleeding episodes, which can lead to death. The incidence of chronic venous insufficiency was approximately 29% after 8 years in treated patients, with the development of ipsilateral recurrent VT being strongly associated with an increased risk of this syndrome.[11,12] Thus, anticoagulant treatment for VT, although effective in preventing fatal PE after VT,[13] often does not result in optimal outcomes. Even thrombolytic therapy, which is designed to remove the thrombus, although demonstrating promise in early studies, is not the therapy that is chosen by most clinicians because of the bleeding risk associated with its use and the inability to predict who will benefit most from this aggressive therapy.[14]

8.3 ENDOTHELIUM

The endothelium forms the inner cell lining of all blood vessels in the body and is a spatially distributed organ. In an average individual, the endothelium weighs approximately 1 kg and covers a total surface area of 4000–7000 m^2.[15] The endothelium has been described as a primary determinant of pathophysiology or as a target for collateral damage in most, if not all, disease processes.[15,16] Endothelial cells play a

critical role in the balance between pro-coagulant and anti-coagulant mechanisms in healthy individuals. The endothelium is integrally involved in mediating hemostasis.[17] Despite this, the endothelial cells are considered mainly anti-thrombotic and pro-fibrinolytic; they are "mini-factories" for the production of many regulatory molecules that are pro-coagulants and anti-coagulants.[17,18] In contrast, a pro-coagulant effect is observed during states of endothelial cell activation and disturbance, either physical (vascular trauma) or functional (sepsis).[19] It is widely known that, under normal conditions, cellular blood components interact with the vessel wall, promoting vascular repair. Activated or dysfunctional endothelial cells trigger a mechanism of rapid deposition of platelets, erythrocytes, leukocytes, and insoluble fibrin, which establishes a thrombus.[15]

8.4 ACUTE VT

8.4.1 Advances in inflammation and VT

The link between inflammation and VT was first demonstrated by Stewart et al. back in 1974 using a dog model of VT.[20] It is known that the vascular inflammatory response is initially protective by nature due to its role in promoting the recruitment of inflammatory cells for the removal of microorganisms and endotoxins. However, local and systemic inflammation can produce a pro-thrombotic environment driven by tissue factor (TF), adhesion molecules, and pro-inflammatory cytokines, and pro-thrombotic cell-derived microparticles, membrane phospholipids, platelet reactivity, fibrinogen, and inflammation decrease thrombomodulin, the receptor for protein C, the half-lives of activated protein C and protein S, vascular heparins, and fibrinolysis (by increasing plasminogen activator inhibitor-1 [PAI-1]).[21] Inflammation and VT are inter-related and have mechanisms in common (Figure 8.1). After VT, an acute to chronic inflammatory response occurs in the vein wall and thrombus. The acute phase or thrombogenesis is led by neutrophils and the chronic phase or thrombus resolution is led by monocytes, progressively increasing fibrin deposition (Figure 8.2). This response leads to thrombus amplification, organization, and recanalization, and occurs at the expense of the vein wall and vein valve damage. Leukocytes, cytokines, chemokines, and inflammatory factors such as

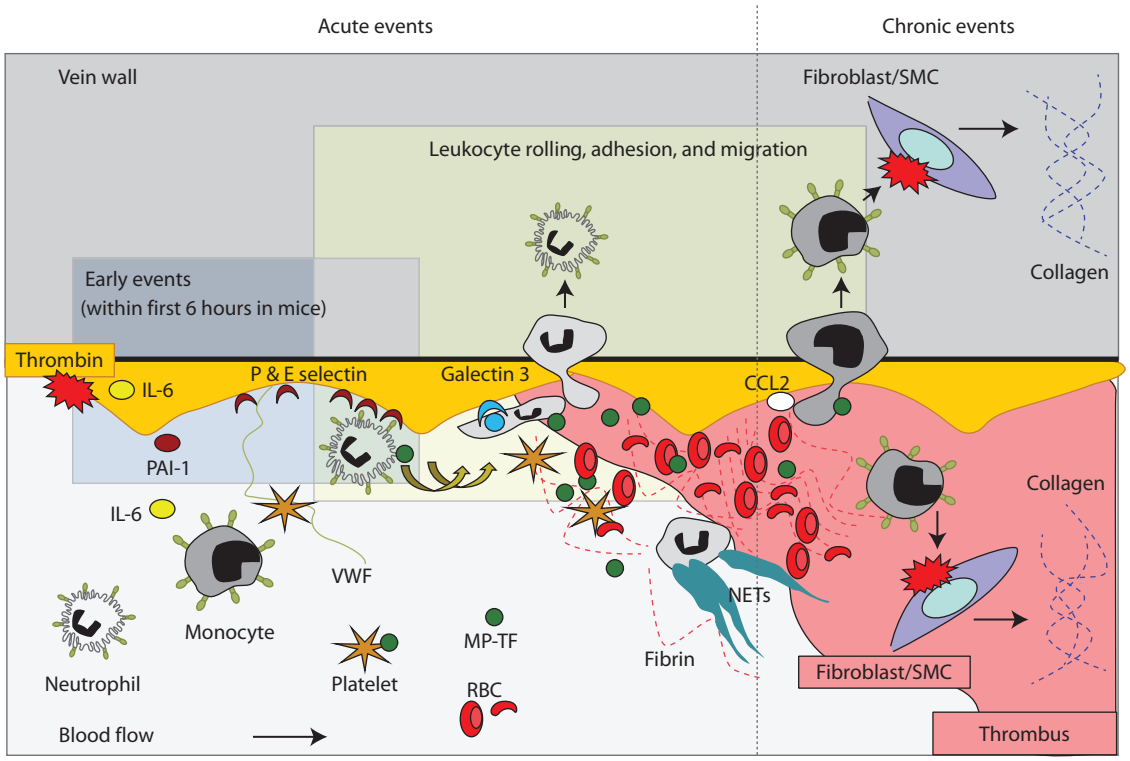

Figure 8.1 Mechanisms involved during acute and chronic venous thrombosis (VT). Acute VT: thrombus formation: inflammation appears to be closely involved in thrombus formation. Endothelial cells, platelets, MPs, and leukocytes (neutrophils and monocytes) are the main elements involved in VT. TF, VWF, and inflammatory cytokines, including IL-6, have been demonstrated to participate in this process. Thrombus resolution: vein wall and thrombus remodeling is a complex process that varies as the thrombus ages. The main inflammatory cell that participates in this stage is the monocyte. Pro-fibrotic mediators play an important role in this phase, leading to fibrosis. The severity of this fibrosis will determine the outcome after an episode of deep vein thrombosis (i.e., post-thrombotic syndrome or thrombus recanalization with or without valve insufficiency). IL-6: interleukin-6; PAI-1: plasminogen activator inhibitor-1; VWF: von Willebrand Factor; MP: microparticle; TF: tissue factor; CCL2: chemokine (C–C motif) ligand 2; NET: neutrophil extracellular trap; SMC: smooth muscle cell; RBC: red blood cell.

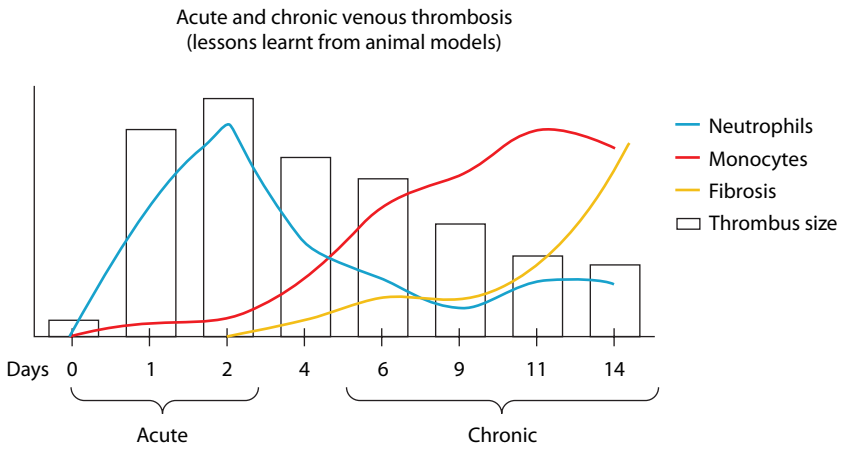

Figure 8.2 Venous thrombosis (VT) is a complex and dynamic process that in humans and experimental animals involves at least two phases: acute and chronic VT. This figure represents how VT occurs in mice. Thrombus size (bars) increase up to day 2 after thrombus initiation (thrombus burden) coincidentally with the increase of neutrophil influx to the vein wall (blue line). These data, together with histology, determine the acute-phase characterization in our mouse models of VT (first 2 days). The natural history of the thrombotic process shows that the thrombi decrease progressively in size from day 4. During this phase, monocytes (red line) are the dominant cells and a progressive increase in fibrosis occurs (yellow line). These data, together with histology, determine the chronic-phase characterization in our mouse models of VT (beyond 4 days after thrombosis was initiated).

interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) facilitate the inflammatory response.

8.4.1.1 SELECTINS AND VENOUS THROMBOSIS

Pro-inflammatory and anti-inflammatory mediators are involved in the ultimate vein wall and thrombus response. We have also found selectins (P- and E-selectin) to be integrally involved in this process (Figure 8.3a). These are cell adhesion molecules that modulate leukocyte–endothelial cell interactions (Figure 8.3b). In a rodent model of stasis VT that includes the interruption of all vein branches,[22] P-selectin is upregulated by as early as 6 hours after thrombus induction, whereas E-selectin is upregulated at day 6 after thrombosis, with increases in gene expression preceding the protein elevations. The anti-inflammatory cytokine IL-10 gene expression is upregulated at day 2, and remains so up to day 9 after thrombosis, suggesting a counterbalance to the inflammatory response. Additionally, IL-10 protein levels are elevated before mRNA upregulation, suggesting an initial increase from preformed IL-10 followed by IL-10 synthesis.[23]

P-selectin is a critical adhesion molecule involved in the interactions between inflammatory cells and vessels, and has been linked with cardiovascular events in both the arterial and the venous circulations.[24] This molecule is present in the α-granules of platelets and the Weibel–Palade bodies of endothelial cells. It is first translocated to the plasma membrane of these cells, mediating the initial inflammatory response.[25] Recombinant soluble P-selectin glycoprotein ligand-Ig (rPSGL-Ig) binds and inhibits cell-associated P-selectin. Thrombin-activated platelets expressing P-selectin bind to neutrophils, and rPSGL-Ig blocks this effect by approximately 90%.[26] Recently, a synergism between leukocytes and platelets has been identified,[27] such that TF can be transferred from leukocytes to platelets in a P-selectin-mediated fashion, and even platelets have been demonstrated to express functional PSGL-1, allowing for a P-selectin mechanism for platelet rolling (Figure 8.3c).[28,29]

In order to further define the importance of the selectins to the thromboinflammatory response, genetically modified knockout (KO) mice have been studied in which either P-selectin or E-selectin or both P- and E-selectin have been gene deleted. In these studies, deletion of E-selectin and combined P-selectin/E-selectin deletion were associated with decreased thrombosis, whereas the vein wall inflammatory response was most inhibited in the combined P-selectin/E-selectin and P-selectin KO groups.[23] We have also confirmed the importance of P-selectin and its receptor PSGL-1 in VT using a primate model of stasis-induced inferior vena cava (IVC) thrombosis, induced by a temporary 6-hour balloon occlusion. In this model, we have found that an antibody to P-selectin or a receptor antagonist (termed rPSGL-Ig) inhibits inflammation and thrombosis when given prophylactically.[30,31] Further study has demonstrated a significant dose–response relationship between rPSGL-Ig and thrombosis and rPSGL-Ig and spontaneous recanalization.[32] The peri-thrombotic vein wall had decreased gadolinium enhancement (a marker of inflammation) in all rPSGL-Ig groups compared with controls, despite no significant differences in inflammatory cell extravasation being observed. In fact, the highest dosage produced the best inhibition of thrombosis, but was associated with the greatest inflammatory cell influx, suggesting that the prevention of thrombosis does not depend on inhibiting vein wall leukocyte influx. Importantly, these effects that were observed with rPSGL-1g occurred with no systemic

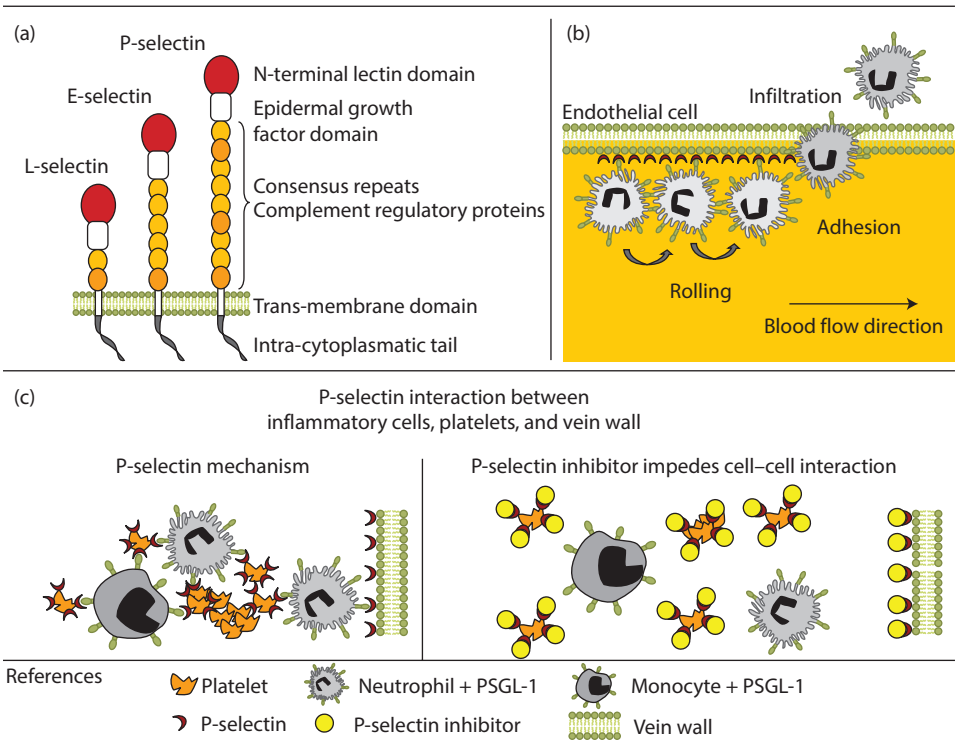

Figure 8.3 Selectins are critical for venous thrombosis (VT). **(a)** Schematic representation of the selectin structure. Note that the difference between selectins is due to the number of consensus repeats. **(b)** P-selectin participates in the rolling, adhesion, and infiltration of leukocytes during VT. **(c)** P-selectin and its receptor P-selectin glycoprotein ligand (PSGL-1 enable the interactions between leukocytes, platelets, and endothelial cells. However, if a P-selectin inhibitor is added, this decreases the interaction between the cells and directly impacts thombogenesis.

anticoagulation, bleeding time prolongation, thrombocytopenia, or wound-healing complications.

Direct selectin inhibition also effectively treats established VT in a primate model of iliofemoral VT formation. Two days after thrombus development, baboons were treated with rPSGL-Ig 4 mg/kg, LMWH, or saline, and treatment continued once weekly (rPSGL-Ig) or daily (LMWH and saline) based on drug half-life assessment.[33] The animals were examined and sacrificed 14 or 90 days after treatment initiation. The percentage spontaneous vein reopening was increased significantly in the proximal iliac vein in rPSGL-Ig- and LMWH-treated animals compared with controls. There were no differences in inflammation between groups. At 90 days after thrombosis, recanalization with iliac vein valve competence was found in the rPSGL-Ig- and LMWH-treated animals. Thus, rPSGL-Ig successfully treated established VT, as did LMWH; however, in this case, it enhanced spontaneous vein reopening without anticoagulation.

Thus, P-selectin blockade inhibits leukocyte–platelet, leukocyte–endothelial cell, leukocyte–leukocyte, and even platelet–endothelial cell interactions (Figure 8.3c), all actions that potentially would decrease thrombus amplification after its initiation. The finding of an improvement in spontaneous thrombolysis in animals in which P-selectin is inhibited by rPSGL-Ig is similar to results found in primate, porcine, and rat models of arterial and venous thrombolysis using P-selectin inhibition.[29,34,35] This finding is likely due to reductions in leukocyte–platelet interactions that lead to TF release and fibrin deposition, as these are P-selectin dependent.[36] Thrombi in P-selectin-null mice have decreased TF and fibrin accumulation compared with thrombi generated in wild-type (WT) mice, suggesting a decrease in fibrin formation.[37]

8.4.1.2 IL-6 AND OTHER MEDIATORS IN VT

Recently, a pathway linking IL-6, a well-studied inflammatory cytokine, and fibrosis was found in the context of cardiovascular diseases[38] and, importantly, in VT, using a mouse model of VT (Figure 8.1).[39] The biological effect of neutralizing IL-6 was demonstrated to occur via chemokine ligand 2 at both the gene expression and protein level at early time points during VT. These early events led to significantly decreased fibrosis at later time points in VT.[39] Another mechanism includes the activation of platelets that can cause the expression of CD40 ligand, which in turn has pro-inflammatory activities and augments the thrombogenic response.[40] There are specific mediators that have demonstrated anti-inflammatory effects during thrombosis. A study by Henke et al. established that IL-10 can modulate the inflammatory response in a rat ligation model of VT.[41] The rats that received viral IL-10 gene transfer had fewer leukocytes in their vein walls, and most notably affected was the number of polymorphonuclear neutrophils (PMNs). Thus, these data further support the link between

inflammation and VT during experimental VT. Moreover, a recent review of the literature highlighted that inflammation and VT are linked clinically.[42] In addition, there is a parallelism between inflammation and VT that further supports their link: "inflammation has an acute and chronic phase as does VT,"[43] and neutrophils are the cells that have been associated with both acute inflammation and acute VT, whereas monocytes have been characterized as the main cells in both chronic inflammation and chronic VT (Figure 8.1).

8.4.1.3 MICROPARTICLES AND VT

Circulating cell-derived microparticles contribute to the coagulation and amplification of thrombosis. They are present in the blood of healthy individuals and are increased in various diseases. Microparticles are small vesicles (<1 μm) that consist of a plasma membrane surrounding a small amount of cytoplasm with cell-specific surface molecules.[44] Endothelial cells, leukocytes, and platelets have a very well-structured plasma membrane characterized by a controlled transverse lipid distribution termed "rafts" (Figure 8.4). The activation of these cells promotes a general membrane content redistribution during which rafts concentrate in areas of the cell that the microparticles will ultimately be derived from. Therefore, the microparticle membranes are rich in lipid rafts.[45] Recent investigations suggest that microparticles that are considered pro-thrombotic, in part due to their content of TF,[27,46] are extremely important in early venous thrombogenesis. Platelet-derived microparticles are involved in VT in the syndrome of heparin-induced thrombocytopenia.[47] Ramacciotti et al. showed that microparticles are pro-thrombotic in a mouse IVC ligation model.[48] In this study, a group of microparticles was obtained from C57BL/6 mice at 2 hours and another group was collected 2 days after thrombosis was initiated. When re-injected into WT C57BL/6J mice, in which the IVC was then ligated for 48 hours, there was a trend towards higher thrombus weights in the mice that received the 2-day post-ligation microparticles compared to those that received re-injections of the 2-hour post-ligation microparticles. Furthermore, TF associated with microparticles showed a significant correlation to total microparticle concentrations ($R = 0.99$).[48] Although the importance of microparticles has been shown, they are difficult to measure and there are many different protocols available. Thus, a consensus in order to standardize both the identification and quantification of circulating cell-derived microparticles is needed.[45,49,50]

8.4.2 Advances in coagulation and VT

8.4.2.1 VON WILLEBRAND FACTOR AND VT

There is evidence that von Willebrand factor (VWF) participates in VT (Figure 8.1).[51] VWF is a multimeric protein held together by disulfide bonds that mediates platelet adhesion and stabilizes pro-coagulant factor VIII in order to promote the initiation and formation of a stable thrombus at the site of vascular injury.[52] VWF is found on endothelial cells (stored in Weibel–Palade bodies), platelets (synthesized in megakaryocytes and stored in platelets α-granules) and in sub-endothelial connective tissue.[53] Defects in VWF have been linked to von Willebrand disease.[54] In plasma, multimers of VWF ranging from 500 to 200,000 kDa are regulated and cleaved under shear stress into less active multimers by the protease ADAMS13.[55–58] VWF is a ligand for glycoprotein Ibα (GPIbα) within the GPIb–IX–V complex and integrin αIIbβ3, which mediates platelet adhesion and thrombus formation.[55,59] Using a ferric chloride venous injury model, Chauhan et al. reported that occlusive thrombus formation is dependent upon VWF and not GPIbα, indicating that VWF uses other adhesion molecules under venous flow conditions.[56] A recent *in vitro* study, evaluating the role of platelets in microscopic fibrin formation under pro-coagulant conditions and low shear rates, demonstrated that fibrin formation was reduced and delayed either when binding of VWF to GP1b–V–IX was blocked or if mouse plasma that was deficient in VWF was tested.[60] The results of these studies are promising, and provide evidence that future pharmacologic therapies aimed at modulating VWF activity may be useful for the treatment or prevention of VT. In a recent work using the bi-balloon model in non-human primates, an inhibitor of VWF was used as treatment (administrations after thrombus formation) and prophylaxis (on board at the time of thrombus initiation).[61] No impact on thrombus recanalization was observed in

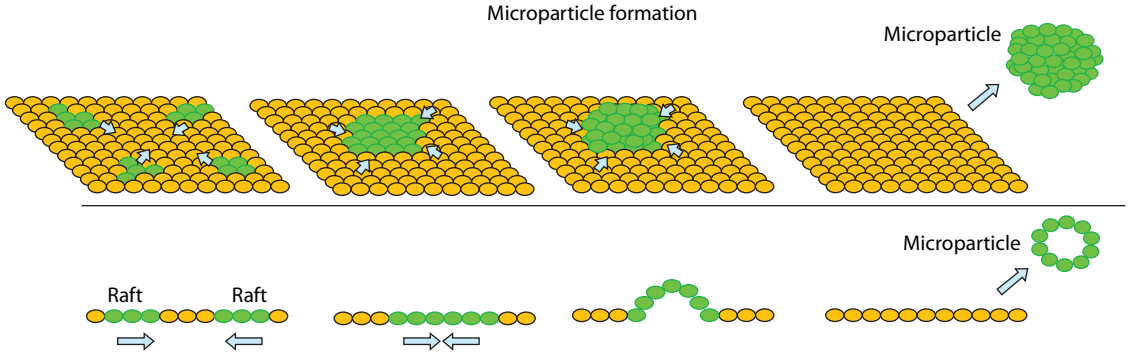

Figure 8.4 Schematic representation of microparticle formation. Microparticles are very small elements that are known to increase during venous thrombosis in both humans and experimental animals. Upper figure: 3D; lower figure: 2D.

animals receiving VWF inhibitor as treatment.[61] However, those animals that received VWF inhibitor as prophylaxis demonstrated improved vein recanalization by magnetic resonance venography versus controls. These data bring new insights into the participation of platelets in the VT initiation process.[61] As VWF inhibition was effective only in the prophylactic application, this suggests that VWF has greater participation in the early stages of thrombogenesis and plays a less important role in the later events of VT.

8.4.2.2 TF AND VT

TF is a three-domain (intracellular, transmembrane, and extracellular) glycoprotein (47 kDa) that triggers thrombin generation by forming a complex with factor VIIa, which activates factor X.[62,63] TF's organ distribution is non-uniform. Thus, high levels are found in the lung, brain, and placenta, intermediate levels are found in the heart, kidney, intestines, testes, and uterus, and low levels are found in the spleen, thymus, and liver.[64] TF cell distribution is also non-uniform. Several cell types express TF constitutively, such as astrocytes in the brain, epithelial cells enveloping organs, adventitial fibroblasts and pericytes, and cardiomyocytes in the heart. Other cells substantially enhance the production of TF upon exogenous or endogenous stimulation, such as smooth muscle cells, endothelial cells, and monocytes that contain small amounts of TF.[64,65] TF expression on monocyte surfaces promotes monocyte interactions with activated platelets and endothelial cells, leading to fibrin formation and deposition into the developing thrombus. Using cell culture techniques, monocytes and endothelial cells can be stimulated by TNF, IL-1, or monocyte chemoattractant protein (MCP)-1 to express TF on their cell surfaces.[66,67] Mouse models of stasis-induced VT using gene targeting and bone marrow transplantation technology found that TF in the vessel wall and not TF from leukocytes was most important for thrombus formation.[68] This result is perhaps due to the nature of the model: total IVC ligation. The participation of TF in the context of VT has been linked to circulating pro-coagulant microparticles (Figure 8.1).[69] It is well known that cancer, particularly gastrointestinal cancer, is associated with VT. In this setting, TF expression has been described in both colorectal and pancreatic cancers.[70–72] In addition, TF activity is increased in cells treated with chemotherapeutic agents, which increases the risk of VT.[73] Furthermore, cancer patients with venous thromboembolism (VTE) were found to have elevated levels of microparticle TF compared to cancer patients without VTE.[74,75]

8.4.3 Advances in fibrinolysis and VT

Fibrinolysis is produced by the fibrinolytic system, which is critical for regulating hemostasis, and comprises an inactive proenzyme, plasminogen, which can be converted to the active enzyme, plasmin (Figure 8.5). Fibrinolysis is a well-known mechanism, and we will focus on the new insight that links fibrinolysis with VT.

8.4.3.1 PAI-1 AND VT

Under normal conditions, the fibrinolytic system acts as a balance to the coagulation system in order to prevent vascular thrombosis in a process known as fibrinolysis. PAI-1 is responsible for regulating fibrinolysis by inhibiting both urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator, which activate plasminogen to form plasmin (Figure 8.5a).[16] Plasmin, a serine protease inhibitor, is the primary enzyme responsible for cleaving fibrin and fibrinogen during fibrinolysis.[16] The end result of this process is the formation of fragment E and two molecules of fragment D, which exist as a covalently linked dimer (D-dimer) (Figure 8.5a).[16,76] The size of the thrombus within a vein results from the balance between the coagulation cascade (forming the thrombus) and the fibrinolytic system (dissolving the thrombus). Increases in coagulation activity and/or decreases in

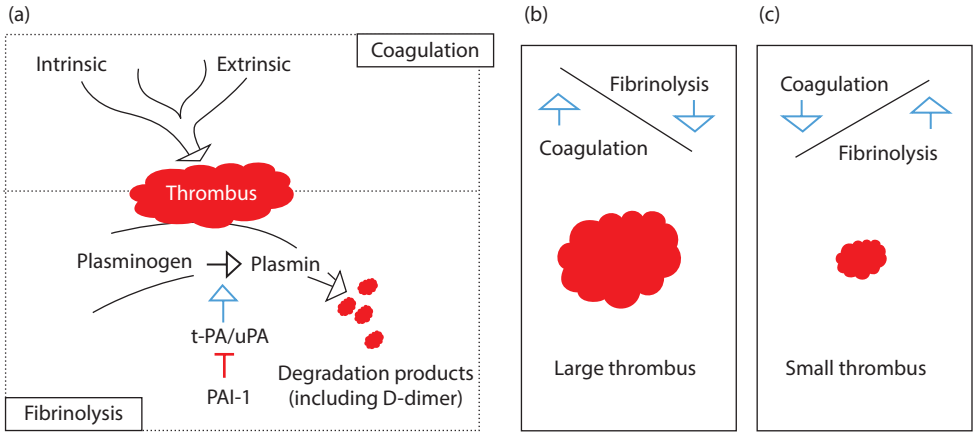

Figure 8.5 Coagulation, fibrinolysis, and venous thrombosis (VT). The coagulation cascade results in the formation of the thrombus, and its size will depend of several mechanisms, including fibrinolysis **(a)** (schematic representation). Considering these two variables, increases in coagulation or decreases in fibrinolysis will result in large thrombi **(b)** and decreases in coagulation or increases in fibrinolysis will result in small thrombi **(c)**. t-PA: tissue plasminogen activator; uPA: urokinase-type plasminogen activator; PAI-1: plasminogen activator inhibitor-1.

fibrinolytic activity result in large thrombus (Figure 8.5b). Decreases in coagulation activity and/or increases in fibrinolytic activity result in small thrombus (Figure 8.5c).

The effect of PAI-1 inhibition has been studied by Baxi et al. in a rat stenosis model, demonstrating that its inhibition significantly reduced thrombus weight compared to controls.[77] Although in this work enoxaparin-treated animals showed similar thrombus weight reductions to the PAI-1 inhibitor group, the coagulation parameters were significantly altered in the enoxaparin group compared to the PAI-1 inhibitor-treated group.[77] These results suggest that PAI-1 inhibition may be a useful therapy for the treatment of VT, with minimal direct effects on coagulation, and also suggest a role of PAI-1 in VT.[77] Recently, the role of PAI-1 in VT has been studied in the context of hyperlipidemia using apolipoprotein E gene-deleted mice ($ApoE^{-/-}$).[78] In this setting, the $ApoE^{-/-}$ mice had significantly larger thrombi after IVC ligation, secondary to an impaired fibrinolytic system. This impairment was found to be due to a significant increase of PAI-1 levels with a significant decrease of plasmin activity in $ApoE^{-/-}$ mice.[78] These results suggest that PAI-1 plays a role in VT in the context of hyperlipidemia.

8.5 CHRONIC VT

8.5.1 Advances in inflammation and vein wall damage

For many years, the endothelial lining of the vasculature was assumed to play little or no role in homeostasis, a tenet that was ultimately proven very wrong. In an analogous fashion, the *in vivo* thrombus is not inert, but biologically active, with specific cellular types and matrix components orchestrated in a temporal fashion. Thus, therapies to manipulate and accelerate its resolution are possible. The normal thrombus (even without anticoagulation treatment) does lyse over time, presumably through the plasmin system, activated by uPA.[79,80] It is likely that uPA is produced from leukocytes that have influxed into the thrombus as well as resident vein wall cells. At the current time it is not known what specific cellular signals modulate this process, but these probably include the natural anti-coagulant factors of antithrombin, proteins C, protein S, and thrombin.

VT resolution resembles wound healing and involves pro-fibrotic growth factors, collagen deposition, and matrix metalloproteinase (MMP) expression and activation.[81–84] In the rodent models of IVC stasis-induced VT and the electrolytic IVC model, we have found an acute to chronic inflammatory response in the vein wall and thrombus in response to IVC insult and thrombosis induction.[85–89] In the vein wall, PMNs are significantly elevated above sham control animals at day 2 after thrombosis, and monocytes are significantly elevated above sham controls at day 6 after thrombosis. Total inflammatory cell counts are significantly elevated at both time points.

Although PMNs may cause vein wall injury, they are essential for early thrombus resolution by promoting both fibrinolysis and collagenolysis.[86,90,91] We have found that neutropenia in a rat model of stasis VT is associated with larger thrombi at 2 and 7 days, increased thrombus fibrosis (larger and fewer cellular thrombi), and significantly lower thrombus levels of both uPA and MMP-9.[86,90] Counterintuitively, PMNs are not entirely detrimental to early vein wall remodeling via some of these same mechanisms.[86] It seems that a lack of intrathrombus PMNs when the thrombus forms may directly impair thrombus resolution, rather than by secondary cellular signaling. As a clinical correlate, patients with malignancy and neutropenia are significantly more likely to have a VTE recurrence than those that are not neutropenic, when other risk factors are controlled for.[92] An important unanswered question is whether patients with transient neutropenia have impaired thrombus resolution, and whether this manifests clinically as a higher long-term risk of PTS.

Stimulating the pro-inflammatory PMN response with exogenous administration of the chemotactic peptide IL-8 can accelerate experimental VT resolution.[93] It is speculated that IL-8 increases intrathrombus PMN activation and release of plasminogen activators. To further investigate the role of the chemokines involved in PMN influx into the resolving VT, we utilized mice with targeted gene deletion of the CXC receptor (CXCR2 KO) whose ligands include KC and MIP-2, analogs of human IL-8.[85] The CXCR2 KO mice had larger, less organized early thrombi, fewer intrathrombus PMNs, and fewer monocytes (over the first 8 days). Decreased late (day 12 and 21) thrombus neovascularization was also observed, as well as impaired fibrinolysis. Taken together, PMNs play a role in early thrombus resolution, whereas monocytes predominate later; both are mediated by CXC chemokine activity.

The monocyte is probably the most important cell for VT resolution as it is multifunctional and directs resident cell activation through multiple signals. Monocyte influx into the thrombus peaks at 8 days after thrombogenesis and correlates with elevated MCP-1 levels. This is one of the primary CC chemokines that directs monocyte chemotaxis and activation,[84,94] and has also been associated with VT resolution.[95] Targeted deletion of CC receptor-2 (CCR-2 KO) in the mouse model of stasis thrombosis was associated with early and late impairment of thrombus resolution, probably via impaired early interferon-γ (IFN-γ)-mediated MMP-2 and -9 activity. Indeed, CCR-2 KO mice with stasis thrombosis supplemented with exogenous IFN-γ had full restoration of thrombus resolution, in part due to recovery of MMP-2 and -9 activities, without an increase in thrombus monocytes or fibrinolytic activity.[96] These experiments suggest a broader and intriguing role of early Th1 lymphokine activity (e.g., IFN-γ) in thrombus resolution, probably mediated by $CCR2^{+}$ monocytes. Others have also shown a similar dependence of VT resolution on CCR2 cellular signaling activity.[97]

Healing tissue depends on physiologic neovascularization, and a thrombus is similar to a wound-healing milieu. The aforementioned experiments with chemokine receptor-deleted

mice have also confirmed a strong association between thrombus resolution and neovascularization. However, neovascularization may reflect thrombus organization and not impact thrombolysis. For example, we have administered exogenous pro-angiogenic agents in the rat model of stasis VT and, despite documenting increased thrombus microvascular blood flow, no significant decrease in thrombus size was found.[98] However, other investigators have found a potential role of vascular endothelial growth factor in accelerating thrombus resolution when administered exogenously.[99]

8.5.1.1 ADVANCES IN THROMBUS RESOLUTION AND VEIN WALL DAMAGE

As the thrombus resolves, numerous pro-inflammatory factors are released in the local thrombovenous environment. These include IL-1, TNF-α, and transforming growth factor-β (TGF-β), which are present in the thrombus at differing times and may have direct effects on the vein wall.[85,100] Associated with this biomechanical injury from the VT is an elevation of pro-fibrotic mediators, including TGF-β, RANTES (regulated on activation, normal T cell expressed and secreted), and MCP-1. Late fibrosis has been observed in the mouse model of VT, with a significant increase in total vein wall collagen after stasis thrombosis.[101] This factor may be one local mechanism promoting vein wall fibrosis. However, early vein wall collagenolysis (rather than collagen production) seems to occur within the first 7 days in stasis VT in the rat model, representing an acute response to injury. Interestingly, P-selectin inhibition has been found to be associated with a decrease in thrombus collagen content and vein wall fibrotic injury in our mice, rat, and baboon models,[61,102,103] suggesting that such inhibition may be protective of late vein wall damage. To eliminate the role of stasis but assess the contribution of the thrombus to the injury, a transvenous chemical injury was induced with a 3-minute application of 10% $FeCL_3$ on the exposed IVC.[83,104] This consistently produces a thrombus in the IVC for ≥24 hours. Preliminary studies with these models suggest that non-stasis thrombosis causes lesser injury than stasis VT (e.g., decreased vein wall stiffness and no alteration in collagen levels, with less activation of MMP-9), and it seems that the longer a stasis thrombus is in contact with the vein wall, the greater the injury (Figure 8.6).

Recently, Toll like receptor 9 (TLR9) signaling on thrombus resolution was investigated using the IVC stasis mouse model of VT. The thrombi were significantly larger in $TLR9^{-/-}$ mice compared with WT mice, whereas thrombus collagen and neovascularization were 55% and 37% less, respectively, at 8 days after thrombosis was initiated.[105] Coincidently, decreased fibrinogen and increased thrombin–antithrombin complex were observed in $TLR9^{-/-}$ mouse thrombi.[105] In addition, vein wall IFN-α, IL-1α, and IL-2 were significantly reduced in $TLR9^{-/-}$ mice compared with WT. MyD88 confers TLR9 intracellular signaling, but $MyD88^{-/-}$ mice had VT resolution rates similar to those of WT mice. However, inhibition of the Notch ligand δ-like 4 was associated with larger VT.[105] Finally, stimulation with a TLR9 agonist was associated with smaller VT.[105]

Using the mouse IVC ligation model in $uPA^{-/-}$ or $PAI\text{-}1^{-/-}$ mice and their genetic WT counterparts, the authors created stasis thrombi, with tissue harvested at chronic time points (either 8 or 21 days). Thrombi were significantly

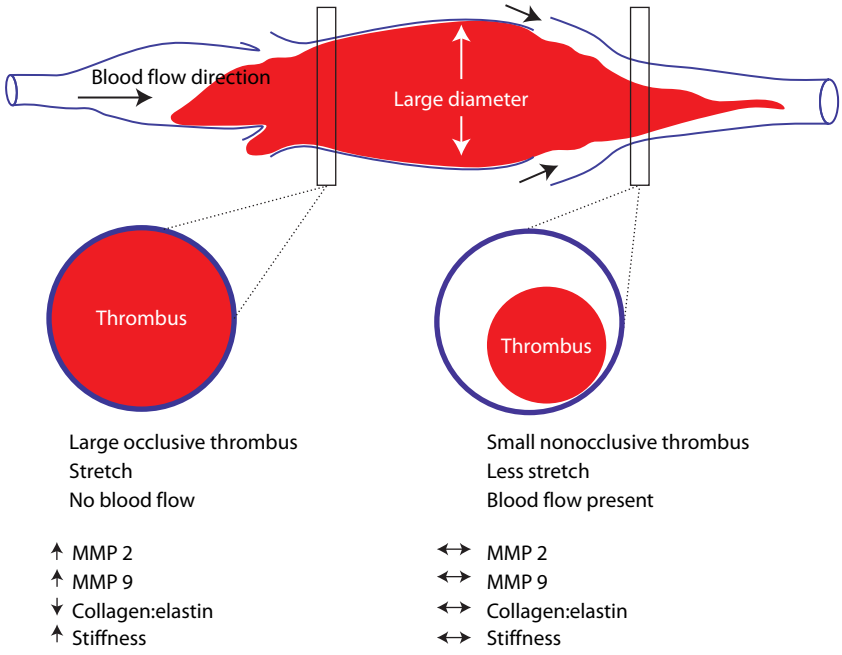

Figure 8.6 Advances in thrombus resolution and vein wall damage. The distribution of the thrombus is not homogeneous and there are areas of total occlusion combined with areas of partial occlusion. The main parameters for tissue remodeling that have been explored are presented for conditions with and without the presence of blood flow. Note that enlarged vein diameters occur in order to host the thrombus. MMP: matrix metalloproteinase.

larger in both 8-day and 21-day uPA$^{-/-}$ mice as compared with WT mice, and were significantly smaller in both 8-day and 21-day PAI-1$^{-/-}$ mice as compared with WT mice.[106] Correspondingly, 8-day plasmin levels were reduced by half in uPA$^{-/-}$ mice and increased three-fold in PAI-1$^{-/-}$ mice when compared with respective WT thrombi. The endothelial cell marker CD31 was elevated two-fold in PAI-1$^{-/-}$ mice at 8 days, but reduced 2.5-fold at 21 days in uPA$^{-/-}$ mice, as compared with WT mice, suggesting less endothelial preservation.[106] Vein wall vascular smooth muscle cell gene expression showed that 8-day and 21-day PAI-1$^{-/-}$ mice had 2.3- and 3.8-fold more SM22 and 1.8- and 2.3-fold more alpha smooth muscle actin (αSMA) expression than respective WT mice, as well as 1.8-fold increased αSMA^{+} cells ($P \leq 0.05$; $n = 3–5$). Lastly, collagen was two-fold greater at 8 days in PAI-1$^{-/-}$ mice IVC as compared with WT mice, with no differences observed in uPA$^{-/-}$ mice.[106] This work supports the notion that in stasis VT, plasmin activity is critical for thrombus resolution.[106] In another recent study focused on thrombus resolution and vein wall remodeling, deletion of MMP-2 was associated with less mid-term vein wall fibrosis and inflammation, despite an increase in monocytes. Consideration that VT resolution was impaired with MMP-2 (and MMP-2/9) deletion suggests that direct inhibition will likely also require anticoagulant therapy.[107]

Two recent studies explored the link between PAI-1 and vein wall damage.[108,109] In the first one, the authors observed that the absence of vitronectin increases circulating PAI-1, which positively modulates vein wall fibrosis in a dose-dependent manner.[109] PAI-1 elevation decrease vein wall damage after VT by decreasing macrophage-mediated activities.[109] This occurred despite the fact that in animals with elevations in PAI-1, the thrombus was larger. Another work evaluated the effect of PAI-1 and LMWH on vein wall injury after thrombosis.[108] The authors showed that LMWH is protective against vein wall fibrosis, but that this is abrogated in PAI-1-deleted mice and correlated with monocyte vein wall influx.[108] These data support the clinical observation that LMWH may be protective against post-thrombotic vein wall injury in a PAI-1-dependent manner.[108]

Over the last several years, in human and experimental studies, circulating bone marrow endothelial progenitor cells have been shown to be important in the repair of arterial injury. Intriguing work from Modarai and colleagues[110] has shown these cells also play a significant role in VT resolution. We have found evidence of these circulating cells in the resolving thrombus, and also in the expression of CCR7. This chemokine receptor is involved in lymphocyte hemostasis and also confers fibrogenesis in models of pulmonary inflammation.[111] Interestingly, post-thrombotic vein wall remodeling is impaired in CCR7$^{-/-}$ mice with a pro-fibrotic phenotype, is dependent on the thrombotic mechanism, and is mediated by circulating CCR7^{+} cells. Unlike other post-injury fibrotic responses, CCR7^{+} cell signaling may be important for positive vein wall remodeling, as VT antibody blockade of CCR7 was associated with less vein wall fibrotic injury.[112]

8.6 CURRENT DEBATES AND NEW DISCOVERIES IN VT

8.6.1 Statins, hyperlipidemia, and VT

Recently, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial examined a large group of patients with high levels of C-reactive protein treated with rosuvastatin or placebo.[113] This trial focused on the effects of rosuvastatin on major cardiovascular events; however, the patients receiving rosuvastatin were found to have significantly decreased rates of VT. Statin therapy is usually initiated in patients with hyperlipidemia. Although hyperlipidemia is currently not considered to be a risk factor for VT, this concept may change in the future. Most clinical trials investigating hyperlipidemia involve patients on statins, which may be masking the link between hyperlipidemia and VT. Following this direction, we previously investigated VT in the context of hyperlipidemia using ApoE$^{-/-}$ mice. We found that the fibrinolytic system was impaired in ApoE$^{-/-}$ mice due to increased levels of PAI-1, the main regulator of this system, leading to an increase in VT.[77] In a second study, our laboratory used ApoE$^{-/-}$ mice on a normal diet and the IVC ligation model to be consistent with our previous work.[114] We demonstrated for the first time that rosuvastatin lessens VT due to: (1) significantly decreased soluble P-selectin at all time points compared to controls. It is known that activated endothelial cells and platelets are the main source of soluble P-selectin in VT initiation. (2) Significant decreases in circulating active and total PAI-1 were found 6 hours after thrombosis in the rosuvastatin group. In addition, gene expression of PAI-1 was decreased in the IVC and significantly decreased in the liver in the rosuvastatin group at the same time point. These results suggest that rosuvastatin decreased PAI-1 and ultimately improved the fibrinolytic system in hyperlipidemic mice. (3) The gene expression of inflammatory markers was significantly decreased in the liver in the rosuvastatin group 3 hours after thrombosis compared to controls, and was decreased, but not significantly, in the vein wall. This is the first work that explores the JUPITER trial's results using an animal model of VT.[114] This was further supported by anther work demonstrating that statins improve VT resolution via pro-fibrinolytic, anti-coagulant, anti-platelet, and anti-vein wall scarring effects.[115] Statins may offer a new pharmacotherapeutic approach to improving VT resolution and reducing vein wall injury post-VT.[115]

8.6.2 Extracellular DNA and VT

Extracellular DNA in the form of neutrophil extracellular traps has been shown to kill bacteria, fungi, and parasites,

while forming a microbial containment barrier,[116,117] and it has also been reported in the vasculature during sepsis and in inflammatory non-infectious disease states, such as small-vessel vasculitis.[118,119] It has recently been shown that extracellular DNA contributes to thrombosis in experimental animal models.[120] In addition to their phagocytic and bactericidal functions, neutrophils and other leukocytes are known to release DNA fibers to form extracellular traps,[121–124] and neutrophils are one of the main inflammatory cells that participate in acute VT.[20] In thrombi obtained from experimental VT in baboons[125] and mice,[126,127] extracellular traps are a structural part of the thrombi, and co-localize with VWF.[120] Based on these studies, extracellular DNA has recently been studied as a potential biomarker of VT. The results of this study showed a significant increase in circulating extracellular DNA in VT-positive patients compared to healthy and VT-negative controls.[128] Extracellular DNA linked to VT is one of the most promising discoveries in thrombogenesis, and we believe this will lead to a new era in VT research.

8.6.2.1 GALECTINS AND VT

Galectin 3 (gal3) and gal3 binding protein (gal3 bp) play important roles in a number of pathologies, such as cancer, infections, diabetes, atherosclerosis, wound healing, and in inflammatory disorders such as asthma and rheumatoid arthritis, but their role in VT has not been defined.[129–137] gal3 bp was found to be upregulated in microparticles collected from human patients diagnosed with deep VT.[138] gal3 bp is a member of the lectin family and is associated with integrin-mediated cell adhesion.[139] Recently, a detailed review of galectins and their potential role in venous thrombogenesis, inflammation, and fibrosis was published.[78] The results of these studies provide evidence that microparticles are associated with VT; however, their role in thrombogenesis and also their potential role as biomarkers of VT were recently studied.[140] Our laboratory recently discovered that gal3 and gal3 bp are associated with murine thrombogenesis and co-localization, and that thrombogenesis is in part gal3 dependent. We also showed that gal3 could be a potential biomarker in patients with acute VT.[140] gal3 bp and gal3 were found in all tissue and blood elements pertinent to the thrombi that were examined (microparticles, red blood cells, platelets, vein wall, and thrombus), with the exception of leukocytes. In addition, increased levels of gal3 bp and gal3 were observed during VT conditions in both mice and humans in our recent work, showing parallelism between these two species. However, despite the fact that the concentration levels of gal3 bp exceeded gal3 levels, our data showed that the increased levels of gal3 were higher in VT compared to the non-VT condition. Biomarkers of VT are being intensively explored due to the absence of any that are capable at present of ruling in VT, and herein we present two clear biomarker candidates to be evaluated in future studies.[140]

8.7 CONCLUSION

It is an exciting time to study venous thrombogenesis and the pathophysiology of the resulting vein wall damage, in part because it has been relatively neglected compared with arterial disease. Fortunately, the National Institutes of Health has put forth two requests for funding applications in the last several years to better study the clinical and basic pathobiology of venous disease, and the Surgeon General has approved a call to action against VTE. Adjuncts to or replacement therapies for anticoagulants hold tremendous promise, and will hopefully decrease the early risk of PE and the late complications of PTS for the benefit of the patient.

Guidelines 1.7.0 of the American Venous Forum on Acute and Chronic Venous Thrombosis: Pathogenesis and New Insights

No.	Guideline	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.7.1	Acute venous thrombosis causes an acute to chronic inflammatory response in both the vein wall and the thrombus. This leads to thrombus amplification, organization, and recanalization and damage to the vein wall and the valves	A
1.7.2	D-dimer, endothelium, platelet derived microparticles and soluble P-selectin are markers of thrombosis and they are increased in patients with acute venous thromboembolism.	A
1.7.3	Resolution of the thrombus is modulated by natural anticoagulants such as antithrombin III, protein C and S, and thrombin.	B
1.7.4	Polymorphonuclear cells promote both fibrinolysis and collagenolysis and they play key role in thrombus resolution. Monocytes are essential in late thrombus resolution.	A

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Epidemiology and risk factors of acute venous thrombosis

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9.1 INTRODUCTION

Deep venous thrombosis (DVT) and pulmonary embolism (PE) share many risk factors and pathophysiological features and are usually considered manifestations of the same disease: venous thromboembolism (VTE). A total of 25%–40% of patients with DVT have asymptomatic PE.[1,2] VTE is the third most common cardiovascular disorder in Western populations, following only myocardial infarction and stroke.[3]

The incidence of DVT is approximately twice that of PE,[2] so that among patients presenting with VTE, approximately a third manifest PE while two-thirds manifest DVT. The deep veins of the lower extremity are most commonly involved, although with more frequent instrumentation and improved diagnostic tests, thrombosis of the upper extremity veins is increasingly being recognized. Thrombosis only rarely involves unusual sites such as the cerebral sinuses, retina, and mesenteric veins. The prevention and management of VTE requires some understanding of its epidemiology and associated risk factors, particularly in recognizing populations warranting prophylaxis, counseling patients regarding high-risk situations such as pregnancy, contraception, and hormone-replacement therapy, and determining the duration of anticoagulation required to minimize recurrent thrombosis.

9.2 THE EPIDEMIOLOGY OF LOWER EXTREMITY DVT

The incidence of lower extremity DVT is highly dependent on the population studied, their underlying risk factors, and the means by which DVT is documented. Autopsy studies are biased by the inclusion of the very sick and very old, while clinical trials are often directed towards specific inpatient groups, such as post-operative patients. True estimates of the incidence of DVT are limited by the few population-based studies, the clinically silent nature of most thromboses, and the need for objective documentation of the diagnosis. Even the interpretation of methodologically sound studies is complicated by the inconsistent inclusion of DVT and/or PE, differing exclusion or inclusion of recurrent DVT, and variable age ranges. It is generally believed that incidence rates from autopsy studies are overestimates, while those from epidemiological studies are underestimates.[4]

Although likely an underestimate due to the outpatient treatment of VTE, recent estimates suggest an average of 547,596 hospitalizations with a diagnosis of VTE per year in the United States.[5] A systematic review of nine methodologically sound epidemiological studies suggests a weighted mean age-adjusted incidence of a first episode of DVT alone of 50.4 per 100,000 person-years.[6] Considering both DVT and PE, the age- and sex-adjusted incidence of first-time symptomatic VTE (DVT + PE) in the United States is estimated to be between 71 and 117 cases per 100,000 population.[4] A substantial increase in the incidence of VTE has been noted since 2001, largely due to an increased incidence of PE but not DVT.[7] Among people of European descent, more recent reviews report an incidence of 104–183 per 100,000 for VTE, 45–117 per 100,000 for isolated DVT, and 29–78 per 100,000 for PE alone.[7] It has been suggested that the rising incidence of PE is related to the increased availability and diagnostic accuracy of computed tomography pulmonary angiography and magnetic resonance imaging. Despite this observation, the age-adjusted PE mortality rate in France has been noted to decline by 3% per year between 2000 and 2010.[8]

DVT is a multi-causal disease resulting from the interaction of genetic and environmental risk factors. Thrombosis occurring in the absence of recognized thrombotic risk factors is designated primary, idiopathic, or unprovoked DVT, while that developing in their presence is designated secondary or provoked DVT. The proportion of patients with idiopathic DVT ranges between 26% and 49%.[1,3,4,9,10] Risk factors for secondary or provoked DVT may be either transient or permanent and may be either genetic or acquired (environmental). Permanent risk factors may be considered to be those that raise an individual's baseline thrombotic potential, while transient risk factors are often those that trigger an acute thrombotic event. Temporary, reversible risk factors are present in 42.4% of patients, most commonly immobility (15%), surgery (14.4%), and severe medical illness (8.2%).[10]

Most risk factors for DVT can be related to the components of Virchow's triad—stasis, abnormalities of the vessel wall, and abnormalities of blood—and many are associated with some component of hypercoagulability on a genetic, acquired, or situational basis (Table 9.1). Well-established risk factors for thrombosis are shown in Table 9.2.[11–27] There are substantial differences between the risk factors associated with inpatient and outpatient DVT. Although malignancy, surgery, and trauma within the previous 3 months remain significant risk factors for outpatient thrombosis, the frequencies of surgery and malignancy are higher among inpatients with DVT.[28,29] Furthermore, although usually considered to be manifestations of the same disease, some of these factors do appear to have a differential effect on the risk of DVT and PE.[2] Black ethnicity and some inflammatory pulmonary diseases (chronic obstructive pulmonary disease, sickle cell trait, and pneumonia) appear to be stronger risk factors for PE, while minor leg injuries, obesity, reproductive factors (oral contraceptives [OCs] and pregnancy) and the factor V Leiden mutation are stronger risk factors for DVT.[2] Many of the risk factors more strongly associated with DVT arise from activated protein C resistance, and it has been postulated that this may be due to associated impaired fibrinolysis and decreased embolic risk in these patients.

The degree of risk associated with each of these factors has been established to a variable extent (Table 9.2), but the importance of any individual factor is a function of both its relative risk in comparison to normal controls and its prevalence in the population. For example, although deficiencies of the natural anticoagulants (antithrombin, protein C, and protein S) are associated with an approximately 10-fold increased risk of thrombosis, they are rare defects. In contrast, the factor V Leiden mutation is associated with a much lower relative risk, but with a prevalence of 5% in Caucasians, it is far more important from a population-based perspective.

Perhaps most importantly, the development of clinically manifest thrombosis usually occurs with the convergence of multiple genetic and acquired risk factors. The simultaneous presence of multiple risk factors is in fact often a prerequisite for thrombosis. In symptomatic outpatients, the odds ratio for an objectively documented DVT increases from 1.26 for one risk factor to 3.88 for three or more risk factors.[28] However, many gene–gene and gene–environment interactions are synergistic, dramatically increasing risk above the sum of individual risk factors.[17] For example, air travel in a patient with factor V Leiden and high factor VIII levels increases thrombotic risk by approximately 50-fold.[30]

Finally, it is clear that VTE is the acute manifestation of a chronic disease. Approximately 30% of patients will sustain a recurrent event within 10 years of a first episode of VTE.[7] Although the 10-year risk of recurrence is as high as 50% in patients with idiopathic DVT, even among those with secondary VTE it may be as high as 22.5%.[31] Risk factors for recurrence include unprovoked DVT, thrombophilia, age, obesity, male gender, active cancer, and neurological diseases associated with lower extremity paresis.[7,31] Persistently elevated D-dimer levels, as an indicator of ongoing activation of coagulation, are also predictive

Table 9.1 Congenital, acquired, and situational thrombophilias

Congenital	Acquired	Situational	Congenital or acquired
Factor V Leiden	Age	Surgery	Hyperhomocysteinemia
Prothrombin G20210A	Malignancy	Trauma	Factor VIII, IX, and XI excess
AT deficiency	Antiphospholipid antibodies	Pregnancy	
Protein C deficiency	HIV infection	Oral contraceptives	
Protein S deficiency	Polycythemia vera	Hormone-replacement therapy	
Elevated plasma factor VIII	Paroxysmal nocturnal hemoglobinuria		
Elevated plasma factor XI	Heparin-induced thrombocytopenia		
Non-type O blood	Behcet disease		
	Nephrotic syndrome		
	Inflammatory bowel disease		
	Hyperthyroidism		

Note: AT, antithrombin.

Table 9.2 Thromboembolic risk factors

Risk factor	Prevalence[a]	Risk	References
Age		1.9× per 10-year increase	11
Surgery	18%–39%	4–5.9× (general surgery: 25%; retropubic prostatectomy: 32%; gynecology (benign disease): 14%; neurosurgery: 22%; hip/knee arthroplasty: 51%/47%)	12,13
Trauma	3%–12%	20.5×	14
Malignancy	18%–51%	Without chemotherapy: 4.4–6.9× With chemotherapy: 6.5–9.9×	14,15
Hospital/nursing home		18.4×	14
History of venous thromboembolism		15.6×	16
Primary hypercoagulable states			
AT, protein C&S deficiency	5.5%–9.5%	10×	
Factor V Leiden	20%		
Heterozygous		3–8×	2,13,15,17,18
Homozygous		50–80×	
Prothrombin 20210A	4%–7%	2–4×	
Increased factor VIII	25%	6×	
Increased factor IX	10%	2×	
Increased factor XI		2.2×	
Hyperhomocysteinemia		2–3×	
Non-O blood type		1.6–2.3×	
Family history		2.9×	19
Oral contraceptives	16%[b]	2.9× (30–50× with factor V Leiden)	20
Estrogen replacement		2–4×	21
Immobilization	10%–17%	2× (pre-operative) to 5.6× (medical patients)	16,22
Long-distance travel	13.3%	2.4–4×	13,16,23,24
Pregnancy and puerperium	25%–30%[b]	4.3×	25
Central venous catheter		11.8×	14
Antiphospholipid antibodies	3.1%	Lupus anticoagulant: 6× Anticardiolipin antibody: 2×	26
Inflammatory bowel disease	1.2%–7.1%	1.5–3.6×	2,27
Hyperthyroidism		2×	2
Obesity		Variable	
Varicose veins		Variable	
Myocardial Infarction/CHF	11%	Variable	

Note: AT, antithrombin; CHF, congestive heart failure.
[a] Prevalence of risk factor among patients with deep venous thrombosis or venous thromboembolism (population-attributable risk).
[b] Among women <45 years of age.

of recurrence.[32] There is also a significant relationship between the incident event—whether DVT or PE—and the type of recurrent event. Those with a PE as the index event are more likely to present with recurrent PE than those with primary DVT.

9.3 RISK FACTORS FOR DVT

9.3.1 Demographic risk factors

Age, gender, and race may influence the incidence of DVT. Among these, age has been most consistently associated with an increased risk of DVT. The incidence of DVT increases exponentially with age,[3] rising by a factor of 200 between 20 and 80 years of age, with a relative risk of 1.9 for each 10-year increment.[11] Rosendaal[33] similarly noted an incidence of 0.006 per 1000 children under 14 years of age increasing to 0.7 among adults of 40–54 years of age, while Hansson et al.[34] found the prevalence of objectively documented thromboembolic events among men to increase from 0.5% at 50 years of age to 3.8% at 80 years of age. Several age-associated factors, including decreased mobility, an increased number of major thrombotic risk factors, age-related hypercoagulability, and changes in the venous

system, are likely to be responsible for this risk. Three or more risk factors are present in 30% of hospitalized patients over 40 years of age, in comparison to only 3% of those less than 40 years of age.[35] Increased levels of thrombin activation markers also suggest an acquired pro-thrombotic state, while anatomic changes in the soleal veins, as well as increased stasis in the valve pockets, have also been noted with advanced age.[36,37]

Gender differences in the incidence of DVT have been variable, and may be related to other risk factors. Some have noted no significant differences in incidence between men and women,[28,38] while others have noted a slightly increased risk (relative risk: 1.4) in males.[11] As >100 million women use OCs, >85% have at least one pregnancy, and 10%–20% use hormone replacement at some point, there are clear differences in reproductive risk factors. Although there are no gender differences in the common genetically determined thrombophilias, there do appear to be some X-linked single-nucleotide polymorphisms that predispose men to thrombosis.[39]

Incidence rates are higher in women during the childbearing years and may be higher in men over 45–60 years of age.[3,9,39,40] Half of thromboembolic events in women less than 40 years of age are associated with pregnancy.[41] On entering middle age, the unadjusted risk of DVT becomes twice as high in men (risk ratio: 2.0, 95% CI: 1.61–2.49), while the risk of PE is similar.[1] However, when adjusted for height, body mass index, smoking, and physical activity, DVT rates in men and women are identical, while men are at significantly lower risk for PE (risk ratio: 0.6, 95% CI: 0.41–0.87). The increased unadjusted risk of DVT in men has been attributed to differences in height, while the higher incidence of PE in women is independent of underlying provoking factors. It has been postulated that increased venous stasis in tall individuals may predispose them to thrombosis.[39] In contrast to the variable influence of sex on a first episode of VTE, men have consistently been reported to be at higher risk for recurrent VTE.[39]

Geographic differences in the incidence of DVT do exist. In the United States, the incidence of VTE is higher in the interior than on either coast.[42] However, regional variations in medical and surgical diseases, prophylactic measures, and methods of diagnosis make conclusions regarding ethnic differences difficult. Autopsy series[43] and coded hospital discharge data[44,45] suggest an identical prevalence of thromboembolism among American black and white patients. However, other data suggest that in comparison to white patients, black patients tend to develop PE more often than DVT.[2,42] Although there is suggestive evidence that the incidence of post-operative DVT may be lower in Asian, Arab, and African populations than among Europeans,[46] the incidence of post-operative DVT is similar among South African European and non-European patients,[47] Hispanics, and Asians. The incidence of VTE in Asian populations is particularly low, with the rate ratio being only 0.21 in comparison to whites in the United States.[45] A variety of observations suggest that such differences are more likely due to genetic factors than to acquired thrombotic risk factors.[48] Racial and ethnic differences in genetic determinants such as blood group and the factor V Leiden mutation are well recognized. The prevalence of the factor V Leiden mutation in Asians (0.5%) is only a tenth of that of Caucasian populations (5%).[4]

9.3.2 Surgery

The thromboembolic risk associated with surgery is multifactorially related to peri-operative immobilization, activated coagulation, and transient depression of fibrinolysis. Increases in thrombin activation as well as elevated levels of plasminogen activator inhibitor-1 (PAI-1) have been well documented peri-operatively. The degree of risk further varies with both patient-specific factors, such as age and prior VTE, and procedure-specific factors, such as duration and degree of immobilization. The impact of comorbid conditions on post-operative thrombosis is somewhat unclear, with some[49] reporting relatively little effect of OC use, myocardial infarction or heart failure, inflammatory bowel disease, respiratory failure, stroke, or varicose veins. Although lower than after inpatient surgery, the risk of VTE after outpatient surgery is also substantially elevated.[49]

Without appropriate prophylaxis, the incidence of DVT is approximately 25% in patients undergoing general surgical operations, 32% for retropubic prostatectomy, 22% and 14% for gynecological procedures with and without malignancy, 22% for elective neurosurgical procedures, and 45%, 51%, and 47% among those undergoing surgery for hip fracture, hip arthroplasty, and knee arthroplasty, respectively.[12] Models such as the Caprini and Rogers scores have been developed to assist in the identification of patients at very low, low, moderate, or high risk for thromboembolic complications.[50] Of 7.7 million patients older than 18 years of age and hospitalized for longer than 2 days in the United States, only 40% were at low risk for VTE, while 41% were at high or very high risk.[51]

Approximately half of post-operative DVTs develop in the operating room, with most of the remainder occurring during the first 3–5 post-operative days.[52] However, the risk of developing a DVT does not uniformly end at the time of hospital discharge. Among gynecology patients, 51% of thromboembolic events occurred after initial discharge.[53] Similarly, up to 25% of patients undergoing abdominal surgery have been noted to develop DVT within 6 weeks of discharge.[54] The Million Women Study[49] followed 947,454 women recruited from a National Health Service breast cancer screening study. Among the 5689 first venous thromboembolic events during 5.84 million person-years of follow-up, a third occurred in the 25% of women undergoing surgery, with a peak incidence during the third post-operative week. In comparison to women without surgery, those undergoing inpatient surgery were 69.1 times (95% CI: 63.1–75.6) more likely to sustain a VTE event during the first 6 weeks after surgery. This risk remained elevated at 7–12 weeks (relative risk 19.6, 95% CI: 16.6–23.1) and

at 1 year (relative risk 3.7, 95% CI: 2.8–4.9). The period of increased risk after surgery thus extends well beyond the early post-operative period. This is particularly true for cancer surgery, in which the risk of VTE extends beyond 1 year (relative risk after 12 months: 6.1, 95% CI: 4.9–7.6).

9.3.3 Trauma

The trauma patient perhaps best represents the convergence of all components of Virchow's triad. Direct venous injury, multiple coagulation and fibrinolytic derangements, and immobilization due to skeletal injuries, paralysis, and critical illness may all contribute to the high incidence of DVT in the injured patient. The prevalence of DVT among autopsied trauma casualties has been reported to be 62%–65%,[55,56] comparable to the 58% incidence among injured patients in modern venographic series.[57] The incidence in series employing only duplex ultrasonography has generally been substantially lower. Factors identified as important determinants of DVT in this population have included advanced age, blood transfusion, surgery, fractures of the pelvis, femur, or tibia, spinal cord injury, Injury Severity Score, Trauma Injury Severity Score, major venous injury, and femoral venous catheters.[58]

9.3.4 Medical illness

Approximately 60% of VTE events are related to confinement in a hospital or nursing home, and coded discharge data suggest that approximately 1% of hospitalized patients are diagnosed with DVT.[45] Medical (22%) and surgical (24%) illnesses account for approximately equal proportions of these events.[7,40] Among medical patients with DVT, 85% have at least one risk factor, and over 50% have at least two risk factors.[16] Data from clinical trials suggest that age greater than 75 years, cancer, previous VTE, and acute infectious disease are independent predictors of VTE.[59] The American College of Chest Physicians considers high-risk medical patients to be those who have been hospitalized with congestive heart failure, severe respiratory illness, or having risk factors including previous VTE, cancer, acute neurological disease, sepsis, and inflammatory bowel disease.[60]

9.3.5 Malignancy

Active cancer is associated with an approximately sevenfold increased risk of VTE, and accounts for approximately 20% of all thromboembolic events.[40,15,13,61] DVT may complicate 19%–30% of malignancies, may be present at the time of diagnosis in 3%–23% of patients with idiopathic thrombosis, and may develop 1–2 years after presentation in another 5%–11% of patients. Aggressive cancers, particularly hematologic malignancies and those of the pancreas, brain, stomach, and ovary, are associated with the highest incidence of VTE, while those of the prostate, breast, and melanoma have a much lower incidence.[61,62] Localized malignancies are associated with a much lower incidence of VTE than metastatic disease. Thromboembolic risk is highest early after diagnosis. A 54-fold increased risk of VTE over the first 3 months after diagnosis decreases to a 13.4-fold increase over the first year.[63] The risk of recurrence is also quite high—two- to three-fold higher than in non-cancer patients with VTE.[61] Complications of VTE are the second leading cause of death among cancer patients,[61,64] likely related to an association between cancer progression and pro-coagulant activity. This relationship may also explain the survival advantage seen among patients treated with low-molecular-weight heparins.

VTE may also be a harbinger of undiagnosed cancer. The incidence of occult malignancy diagnosed within 6–12 months of an idiopathic DVT is 2.2–5.3-times higher than that expected in the general population.[65,66] Preclinical malignancy may be even more common among those presenting with upper extremity thrombosis. Patients discovered to have a malignancy after an initial VTE have a higher mortality rate than those without VTE.

The thrombogenic potential of various cancers is linked to underlying tumor biology. Mechanisms associated with cancer-related thrombosis include tissue factor expression, platelet activation, microparticle shedding by circulating tumor cells, and the generation of neutrophil extracellular traps (NETs).[64] Abnormalities of the coagulation system are present in up to 90% of patients with cancer. Membrane-bound and circulating tissue factors are upregulated in many cancers, with high levels being particularly associated with cancers of the brain, pancreas, stomach, and ovaries.[64] Tumor cells may also elaborate tissue factor-expressing microparticles. High levels of circulating tumor cells may serve as a source of cell-free DNA that, in turn, promotes the formation of NETs as a scaffold for platelet adhesion and thrombus formation. Patients with metastatic malignancies may also demonstrate enhanced platelet reactivity. Finally, associated macrophages may produce pro-coagulants and inflammatory cytokines.

In addition to the tumor-related factors, cancer-associated VTE is related to a number of patient- and treatment-related risk factors. Comorbid medical conditions and underlying thrombophilias, such as factor V Leiden and prothrombin 20210A, increase the risk of cancer-related VTE. Scoring systems for predicting the risk of VTE have been developed and include the five clinical risk factors of cancer site, platelet count $\geq 350 \times 10^9$/L, hemoglobin <10 g/dL or the use of erythropoiesis-stimulating agents, leukocyte count $>11 \times 10^9$/L, and body mass index ≥ 35 kg/m^2, as well as the biomarkers P-selectin (≥53.1 ng/mL) and D-dimer (≥1.44 μg/mL).[62] Among 819 prospectively followed cancer patients, the cumulative probability of VTE at 6 months was only 1.0% among those with a score of 0 in comparison to 35.0% in those with a score ≥5. Cancer treatment may further add to the risk of VTE. In addition to the risks of surgery and central venous catheters, the treatment of some malignancies may be associated with direct endothelial toxicity, induction of a hypercoagulable state, a reduction in fibrinolytic activity, and tumor cell lysis.[64,67,68]

9.3.6 Immobilization

A relationship between bed rest and DVT has long been recognized. Prior to the use of DVT prophylaxis, the autopsy incidence of lower extremity thrombosis was noted to rapidly rise from 15% to 77% and 94% after 1, 2, and 4 weeks of confinement, respectively.[37] The importance of immobilization is further emphasized by observations that thrombosis following bed rest is frequently bilateral, while that associated with stroke is often confined to the paralyzed limb.

PE is estimated to occur with an incidence of 0.39 per 1 million passengers after long-haul air flights,[23] and is the second leading cause of travel-related mortality.[69] This corresponds to an attributable risk of over 150,000 additional cases of VTE per year.[30] Four case–control studies have demonstrated a recent travel history in 13.3% of VTE patients in comparison to 6.9% of controls.[23] Prospective trials have further demonstrated ultrasound-documented DVT to have an overall incidence of 3.9% after long-distance air travel. Such thrombi are usually asymptomatic, confined to the calf veins, and largely prevented by the use of knee-high elastic compression stockings.[70]

Although sometimes termed the "economy class syndrome." At least some data suggest that travel-related thrombosis can occur with modes other than air travel.[13] Putative mechanisms of travel-related thrombosis include hypobaric hypoxia-induced activation of coagulation, stasis, and dehydration.[71] Older age, tall stature, obesity, a previous history of VTE, the use of OCs, and underlying thrombophilia significantly increase the risk of travel-related thrombosis.[13,23,30]

9.3.7 History of venous thromboembolism

As many as 15%–26% of DVT patients will have a history of a previous thromboembolic event. The incidence of recurrent DVT is higher among those having irreversible thrombotic risk factors and those with idiopathic DVT. Some[72] have also noted a significantly higher incidence in patients less than 65 years of age.

Although other factors may also play a role, many recurrences are associated with primary hypercoagulability. The cumulative incidence of recurrent thrombosis among patients who are heterozygous for the factor V Leiden mutation is 40% at 8 years of follow-up, which is 2.4-fold higher than in those without the mutation.[73] Others[74] have estimated that 17% of recurrent thromboembolic events may be due to hyperhomocysteinemia. A relationship between impaired fibrinolysis and recurrent DVT has been suggested, although the methodological validity of these findings has been questioned.[75]

9.3.8 Primary hypercoagulable states

The primary hypercoagulable states include those thrombophilic conditions that have a genetic basis. Primary thrombophilia accounts for approximately 25% of confirmed thromboses occurring in the absence of surgery or malignancy.[15] Although occasionally associated with thrombosis in unusual sites, hypercoagulable states appear to be less important as risk factors for upper extremity thrombosis.[76] Those thrombophilias leading to a loss of function (antithrombin, protein C, and protein S) tend to be more severe than those causing a gain of function (factor V Leiden and prothrombin 20210A). In general, the more common thrombophilias are associated with less risk, although because of their frequency, they are responsible for more thrombotic events (Table 9.2). The phenotypic expression of these abnormalities varies both within and between families, but the risk is higher and the age at first thrombosis earlier among those with a family history of thrombosis. Thrombophilic families appear to have a significant incidence of combined, multigenic defects. Guidelines for thrombophilia screening are shown in Table 9.3.

Classical deficiencies of the naturally occurring anticoagulants—antithrombin, protein C, and protein S—are present in approximately 0.5% of healthy subjects[77] and 5%–10% of patients with DVT. A variety of nonsense (type I deficiencies characterized by the absence of a protective protein) and missense (type II deficiencies characterized by the presence of an abnormal protein) mutations have been described in association with these congenital deficiencies. Heterozygous deficiencies are associated with an approximately 10-fold increased risk of thrombosis.[13]

Resistance to activated protein C is characterized by the failure of exogenous-activated protein C to prolong the activated partial thromboplastin time. A single point mutation in the factor V gene, resulting in replacement of arginine 506 with glutamine (factor V Leiden; FV:R506Q), is present in 94% of individuals with activated protein C resistance,[78–80] and renders factor V less sensitive to degradation by activated

Table 9.3 Guidelines for thrombophilia screening

A first episode of idiopathic VTE
VTE occurring at <50 years of age, even in the presence of transient risk factors
VTE occurring during pregnancy or oral contraceptive/hormone-replacement therapy
Children with VTE
Recurrent VTE
Recurrent superficial thrombophlebitis in the absence of cancer or varicose veins
VTE at unusual sites (cerebral sinus or mesenteric/hepatic veins)
Warfarin-induced skin necrosis and infants with purpura fulminans in the absence of sepsis
Females of childbearing age with documented symptomatic thrombophilia in a first-degree relative
Two consecutive/three non-consecutive abortions at any gestational age; one fetal death after the 20th week
Severe pre-eclampsia

Source: Adapted from Nicolaides AN et al. *Int Angiol* 2005; 24:1–26.

Note: VTE, venous thromboembolism.

protein C. The factor V Leiden mutation is inherited in an autosomal dominant pattern, and is the most common heritable thrombophilic disorder. The mutation shows significant geographic variability, but, depending on ethnicity, may be present in 0%–15% of the normal population and up to 20% of patients with DVT. Limited data suggest that the mutation is also present in up to 37% of patients with post-thrombotic syndrome.[15] Allele frequency is highest in Scandinavian, Northern European, and Eastern Mediterranean populations, lower in Asians and South Americans, and almost nonexistent in Oriental populations.[15]

A variety of other genetic conditions have also been associated with an increased risk of VTE. A mutation in the 3′ region of the prothrombin gene, prothrombin 20210A, is associated with increased plasma levels of prothrombin and is present in approximately 6% of those with venous thrombosis. Although there is significant regional variation, the mutation is present in 2%–3% of Caucasians. Increased plasma levels of other coagulation proteins, including factors VIII, IX, and XI, have also been associated with a two- to three-fold increased risk of VTE.[13,15,18] Elevated factor VIII levels may be present in as many as 25% of those with VTE. Levels of both von Willebrand's factor (vWF) and factor VIII are increased in those with non-type O blood, and blood type has been consistently associated with a two-fold increased risk of VTE.[81] It has been postulated that the A and B antigens protect vWF, a carrier of factor VIII, from cleavage, causing elevated levels of both.[82] High levels of homocysteine have a number of pro-coagulant effects, including direct endothelial toxicity, impairment of nitric oxide and prostacyclin generation, tissue factor induction, activation of factor V, increased platelet adhesion, and tissue plasminogen activator (t-PA) inhibition, which are associated with a two- to three-fold increased risk of VTE.[18,74,83] However, polymorphisms of the methylenetetrahydrofolate gene, which regulates the re-methylation of homocysteine to methionine, do not appear to substantially elevate the risk of VTE.

Although several fibrinolytic disorders have been described, including qualitative and quantitative plasminogen defects, as well as increased circulating levels of PAI-1, thrombin-activatable fibrinolysis inhibitor, factor XIII, and lipoprotein(a), the data supporting an increased risk of VTE remain weak.[18]

9.3.9 OCs and hormonal therapy

Approximately a quarter of thromboembolic events among women of childbearing age have been attributed to OCs.[84] The risk of hospital admission for a thromboembolic event, including cerebral thrombosis, has been estimated to be 0.4–0.6 per 1000 for OC users in comparison to 0.03–0.06 per 1000 for non-users.[85–88] Two meta-analyses suggest an overall summary relative risk for VTE in OC users of 2.9–3.5 in comparison to non-users.[20,88] In comparison to subsequent years, the relative risk of VTE is about 50% higher during the first year of use.[89]

Thrombotic risk is correlated with estrogen dose as well as the type of progestin. Pharmacologic doses of estrogen are associated with a number of alterations in the coagulation system. PAI-1[90] is decreased, while blood viscosity, fibrinogen, plasma levels of factors VII and X, and platelet adhesion and aggregation may be increased.[85,91,92] The type of progestogen further influences levels of sex hormone binding globulin.[88]

Preparations containing more than 50 μg or less than 20 μg of estrogen are associated with the highest and lowest risks of VTE, respectively. First-generation OCs contain lynestrenol or norethisterone as protogestins; second-generation OCs contain levonorgestrel or norgestrel; third-generation products contain desogestrel, gestodene, or norgestimate; and fourth-generation products contain a heterogeneous group of non-testosterone-derived progestins, including drospirenone, dienogest, and nomegestrol. The progestin components in third- and fourth-generation contraceptive formulations have been associated with an approximately two-fold increased thrombotic risk in comparison to other formulations.[13,81,89]

Risk factors for contraceptive-associated thrombosis include age, the congenital thrombophilias, non-type O blood group, smoking, obesity, and immobilization.[81,89] Resistance to activated protein C is present in 30% of patients with contraceptive-associated VTE.[93] Factor V heterozygotes using combined OCs are at 25- to 35-fold increased risk of VTE, while those who are heterozygous for the prothrombin 20210A mutation or with elevated factor VIII levels are at 16-fold and 10-fold increased risk, respectively.[15] However, in the absence of a family history of VTE, routine thrombophilia screening is not recommended prior to the use of OCs.[81] Women with significant risk factors should consider progestin-only contraception, including levonorgestrel intrauterine systems and progestin-only pills.[89] It has been estimated that conformance to current guidelines regarding the use of OCs could prevent approximately a quarter of contraceptive-associated VTEs.[81]

Non-oral hormonal contraceptives, including transdermal combined contraceptive patches (relative risk: 7.9, 95% CI: 3.5–17.7) and vaginal rings (relative risk: 6.5, 95% CI: 4.7–8.9) have also been associated with an increased risk of VTE. Injectable depot medroxyprogesterone acetate increases the risk of VTE three-fold,[7] while subcutaneous progestogen implants confer a non-significant 40% increased risk.[89] The levonorgestrel intrauterine system may lower (relative risk: 0.6, 95% CI: 0.4–0.8) the risk of VTE in comparison with non-hormonal contraceptive users. Pharmacologic doses of estrogen, such as those used for the suppression of lactation, have similarly been associated with an increased risk of thromboembolism. Although the estrogen doses used for postmenopausal replacement therapy are approximately a sixth of those in OCs, there is a two- to four-fold increased risk of thromboembolism. The risk appears higher for estrogen–progestin combinations than for estrogen-only preparations.[94,95] However, the risk of replacement therapy must be kept in perspective, as it contributes only about two new

cases of VTE per 10,000 women per year.[21] As with OCs, the presence of congenital thrombophilic defects, particularly the factor V Leiden mutation, protein S deficiency, and high factor XI levels, increase the thrombotic risk associated with estrogen replacement. The estrogen receptor antagonist tamoxifen, which is used in the treatment of estrogen receptor-positive breast cancer, also significantly increases thrombotic risk.[15] Finally, very limited data suggest that testosterone therapy could be associated with VTE in patients with underlying thrombophilia.[96] It has been postulated that this increased risk is related to aromatization of testosterone to estradiol.

9.3.10 Pregnancy

Maternal mortality per 100,000 live births varies from 12.1 (95% CI: 10.4–13.7) in developed countries to 232.8 (95% CI: 207.3–260.6) in developing countries.[97] Although abortion and hemorrhage continue to be the most important causes of maternal death worldwide, VTE is the leading cause in the United States, accounting for 20% of such deaths.[98] Although rates of pregnancy-associated VTE have varied from 0.08% to 7.13%, a pooled analysis of 27 studies suggests an overall rate of 1.4% (95% CI: 1.0%–1.8%) for VTE, 1.1% (95% CI: 1.0%–1.3%) for DVT, and 0.3% (0.2%–0.4%) for PE.[99] Data regarding the timing of DVT during pregnancy are conflicting. Although some data suggest that risk is equally distributed over all trimesters, more recent data[7] suggest a lower incidence of DVT during the first trimester. In contrast, the risk of postpartum DVT is two to four-fold higher than that during pregnancy. This is consistent with meta-analyses suggesting that 57.5% of VTE events occur postpartum, and that, among antepartum events, 55.95% occur in the third trimester.[99] The overall incidence is 351.4 per 100,000 women-years for DVT occurring within 3 months of delivery in comparison to 85.2 per 100,000 women-years during pregnancy.[25] Recurrent thromboembolism may complicate 4%–15% of subsequent pregnancies.[100]

The thrombotic risk during pregnancy has been attributed to impaired venous outflow due to uterine compression in combination with an acquired pro-thrombotic state. DVT involves the left leg in 72.1% of pregnancy-related cases.[99] Pregnancy is associated with a variety of changes in the coagulation system, including increases in fibrinogen and factors II, VII, VIII, and X, decreases in protein S levels, and diminished fibrinolytic activity. Other concurrent risk factors, notably documented hypercoagulable states, suppression of lactation, increased maternal age, and assisted delivery, are associated with an increased risk. Among women with thrombophilia, those with antithrombin deficiency are at very high risk for pregnancy-associated thrombosis; those with protein C or S deficiency or homozygous or combined factor V and prothrombin mutations are at high risk; and those with heterozygous factor V or prothrombin mutations are at moderate risk.[15] However, due to its high prevalence, the factor V Leiden mutation has been associated with up to 59% of cases of pregnancy-associated VTE.[93,101]

9.3.11 Antiphospholipid antibodies

Antiphospholipid antibodies may be present in 4%–20% of patients with VTE. Lupus anticoagulant (LA) and anticardiolipin antibodies (ACAs) may be seen in association with systemic lupus erythematosus, other autoimmune disorders, non-autoimmune disorders such as syphilis and acute infections, drugs, including chlorpromazine, procainamide, and hydralazine, and in the elderly.[102] They are present in 34% and 44% of patients with systemic lupus erythematosus in comparison to 2% and 0%–7.5% of the general population, respectively.[102] Among patients with systemic lupus erythematosus, those with LA are at a six-fold increased risk for VTE, while those with ACAs are at a two-fold greater risk.[26] LA activity is also associated with a 3.6-fold increased risk of thrombosis in otherwise healthy patients, a risk further increased by the presence of anti-β_2-glycoprotein I or anti-prothrombin antibodies.[103] Although the data are conflicting, there are at least suggestions that VTE and ACAs may be unrelated in patients without autoimmune disorders.[104]

The antiphospholipid antibody syndrome is characterized by at least one episode of arterial or venous thrombosis and/or a history of at least three spontaneous abortions prior to the 10th week, one fetal death after 10 weeks, or one premature delivery before 24 weeks. Laboratory confirmation requires the presence of LA or moderate to high titers of IgG or IgM ACAs on at least two occasions at least 6 weeks apart.[15] Approximately 80% of those with antiphospholipid antibody syndrome are women.[103]

9.3.12 Other risk factors

Although lacking the strong epidemiologic support discussed above, a number of other circumstances have been consistently associated with an increased incidence of DVT. These include central venous instrumentation and inflammatory bowel disease. Other risk factors, such as obesity, smoking, varicose veins, myocardial infarction, congestive heart failure, and microalbuminuria, have been inconsistently identified as independent risk factors for acute DVT.

Obesity has been associated with an increased thrombotic risk by some,[21,52,105] but not others.[106] It has been associated with an increased incidence of DVT in trauma patients,[107] but not in medically ill patients.[59]

Varicose veins have also been included as a risk factor for acute DVT, presumably as a marker of either previous DVT or venous stasis. The evidence supporting such an association has been equivocal and has often been complicated by the presence of other risk factors. The few studies evaluating outpatients have suggested that varicose veins are either not a risk factor for DVT[29] or are an independent risk factor only among women and those greater than 65 years of age.[28] The importance of varicose veins in the general population is questionable, although their role in some high-risk groups cannot be entirely excluded.

Systemic hypercoagulability, congestive heart failure, and enforced bed rest could theoretically predispose patients who are hospitalized for acute myocardial infarction to DVT. The incidence of DVT in this population has been reported to be 20%–40%, with an overall average of 24%.[108–110] Although Kotilainen et al.[108] found the incidence of DVT to be similar among those in whom myocardial infarction was confirmed (21%) and excluded (25%), a substantially higher incidence was noted among those over 60 years of age with congestive heart failure (54%). This finding has been confirmed by some,[111] but not others.[22] Heit et al.[14] found that congestive heart failure was not a risk factor for VTE manifesting either before death or as a cause of death, although it was a risk factor for post-mortem VTE, as an incidental finding. The balance of evidence suggests that severely ill medical patients are at significant risk for VTE,[112] although it is difficult to precisely define the additional risk associated with cardiac disease in these patients.

9.4 CONCLUSIONS

The appropriate management of VTE requires a thorough knowledge of diagnostic and treatment modalities. However, an understanding of the underlying epidemiology and associated risk factors is equally essential. Risk stratification is obviously important in determining which patients require prophylaxis in high-risk situations. Schemes for risk stratification in these situations,[113] such as patients undergoing surgery or who are hospitalized for medical illness, as well as appropriate evidence-based prophylactic measures, have been well described.[50] However, an understanding of the risk factors leading to VTE is also important in terms of: counseling patients regarding their risk associated with contraception, pregnancy, and hormone replacement; understanding who requires further consideration of an underlying malignancy or hypercoagulable state; determining the risk of recurrent VTE; and defining the duration of therapy after an episode of VTE. These considerations require knowledge of thrombotic risk factors, their relative importance in thrombogenesis, and their synergistic interaction. The latter is particularly important, as VTE almost always develops in the setting of multiple genetic and environmental risk factors. The synergistic effects of gene–gene and gene–environment interactions are the bases for venous thrombosis, and the relative risks of these interactions are becoming better understood.

Guidelines 1.8.0 of the American Venous Forum on the epidemiology and risk factors of acute venous thrombosis

No.	Guideline	Strength of recommendation	Grade of evidence
1.8.1	The prevention and management of venous thromboembolism (VTE) requires an understanding of the interactions of underlying risk factors. All episodes of VTE should be characterized as primary (unprovoked and idiopathic) or secondary (provoked).	1	A
1.8.2	All hospitalized patients should have a thorough assessment of thromboembolic risk factors at the time of admission.	1	A
1.8.3	Recognized models, such as the Rogers or Caprini scores, should be used to assess thromboembolic risk in surgical patients.	1	B
1.8.4	Established evidence-based guidelines should be followed for deep venous thrombosis prophylaxis in high-risk patients.	1	A
1.8.5	Thrombophilia screening should be limited to patients included in established guidelines.	1	A

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● = Key primary paper
★ = Major review article
◆ = First formal publication of a management guideline

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Epidemiology of chronic venous disorders

EBERHARD RABE AND FELIZITAS PANNIER

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10.1 INTRODUCTION

In recent decades, epidemiological studies of chronic venous disorders (CVDs) were performed in many countries worldwide. Most of these were focused on the prevalence of varicose veins.[1–8] By reviewing these data, some principal problems were noted. Different definitions for CVDs or for chronic venous insufficiency (CVI) and different age groups were used in the various studies. In very few cases, the investigated population was based on a random sample of the general population.[9] In many studies, only information gathered from questionnaires was used. Clinical and duplex evaluation were incorporated into the protocols only rarely, and a few recent studies incorporated the CEAP classification into the study design.[9–15] Recently, longitudinal data on the incidence of CVDs have been published.[16–19]

10.2 EARLY EPIDEMIOLOGICAL STUDIES

Early studies reported the prevalence of varicose veins as being from 1% to 73% in females and from 2% to 56% in males, and of CVI being from 1% to 40% in females and from 1% to 17% in males.[1] The results varied by geographic region and also by the methods used for evaluation. In Western countries, varicose veins are reported to be present in 25%–33% of female adults and 10%–20% of male adults.[1,2,5,8] The incidence of varicose veins per year in the Framingham study was 2.6% in women and 1.9% in men.[20] The prevalence of skin changes varied between 3% and 13%, and active and healed ulcers varied between 1% and 2.7% in the investigated populations. Established risk factors for varicose veins were older age, a positive family history, female gender, multiple pregnancies, a standing occupation, and obesity in females.[1,2,5,20]

10.3 EPIDEMIOLOGIC STUDIES BASED ON THE CEAP CLASSIFICATION

In the revised CEAP classification, precise venous definitions have been given.[21] Telangiectasia is the confluence of dilated intradermal venules of less than 1 mm in caliber. Reticular vein is a dilated bluish subdermal vein, usually 1 mm to less than 3 mm in diameter. Varicose vein is a subcutaneous dilated vein 3 mm in diameter or larger, measured in the upright position. Edema is the perceptible increase in volume of fluid in skin and subcutaneous tissue, characteristically becoming indented with pressure. The term "chronic venous insufficiency" implies a functional abnormality of the venous system, and is usually reserved for more advanced disease, including edema (C3), skin changes (C4), or venous ulcers (C5–C6).[21] In recent years, several studies have been published using the CEAP classification (Table 10.1).[9–15]

10.4 PREVALENCE OF CVD

10.4.1 The San Diego Population Study[13]

Between 1994 and 1996, 2211 men and women between 40 and 79 years of age in San Diego, CA, were evaluated by visual inspection and duplex ultrasound for manifestations of CVD: telangiectasias, varicose veins, trophic changes, and edema. A modified CEAP classification was applied using the most severe clinical findings and excluding C3.

Table 10.1 Prevalence of chronic venous disorders C0–C6 (CEAP) in Western countries

First author (year)	Country	M/F proportion (%)	Age (years)	Sample size	C0			C1			C2			C3			C4			C5			C6		
					All (%)	M (%)	F (%)	All (%)	M (%)	F (%)	All (%)	M (%)	F (%)	All (%)	M (%)	F (%)	All (%)	M (%)	F (%)	All (%)	M (%)	F (%)	All (%)	M (%)	F (%)
Criqui (2003)[13a]	USA	35.3/64.7	40–79	2211	19.0	33.6	11.0	51.6	43.6	55.9	23.3	15.0	27.7	5.8	7.4	4.9[b]	6.2	7.8[f]	5.3						
Jawien (2003)[14a]	Poland	16.0/84.0	16–97	40,095	51.5			16.5			21.8			4.5			4.6			1.0			0.5		
Rabe (2003)[9a]	Germany	43.9/56.1	18–79	3072	9.6	13.6	6.4	59.1	58.4	59.5	14.3	12.4	15.8	13.4	11.6	14.9	2.9	3.1	2.7	0.6	0.6	0.6	0.1	0.1	0.1
Carpentier (2004)[10c]	France	67.7/32.3	Over 18	409		48.7[g]						23.7	46.3		1.1	2.2		4.0	2.1		1.4	0.7		0.0	0.0
Chiesa (2005)[12c]	Italy	14.1/85.9	18–90	5187	22.7	36.0	20.6	64.8	33.4	69.9	29.4	29.3	29.4[d]	13.6	11.4	13.9	3.4	5.2	3.1	8.6	11.6	8.1			
											13.6	11.4	13.9[e]					[h]			[i]				
Rabe (2012)[15a]	Worldwide	31.6/68.4	50.6 ± 16.9	91,545	36.1			21.7			17.9			14.7			7.5			1.4			0.7		

Note: m: male; f: female.

[a] Highest assigned clinical category.
[b] Edema in the whole population.
[c] All clinical categories listed.
[d] Non-saphenous varicose veins.
[e] Saphenous varicose veins.
[f] Including C4–C6.
[g] Including C0 + C1.
[h] Including C4a only.
[i] Including C4b–C6.

A total of 19% were classified C0, 51.6% C1, 23.3% C2, and 6.2% C4–C6. Out of the whole population, 5.8% presented with edema, 7.4% among men and 4.9% among women. Prevalence of venous disease increased with age and in the non-Hispanic white subpopulation. C1 and C2 were more common in women than in men, but C4–C6 were more common in men.

10.4.2 24-Cities Cohort Study, Italy[11,12]

In this cross-sectional population study, 5247 participants from 24 cities in the north, center, and south of Italy were recruited during spring and summer 2003 by advertising on television, in newspapers, and by leaflets. The majority of the participants were women (85.9%). All answered a standardized questionnaire and were investigated clinically and by duplex sonography. All clinical findings were used to define the CEAP classes: 22.7% of the population was in class C0, 64.8% C1, 43.0% C2, 13.6% C3, 3.4% C4a, and 8.6% C4b–C6. CVI was defined as C1–C6. Risk factors for varicose veins were older age, living in southern Italy, number of pregnancies, and positive family history.

10.4.3 Bonn Vein Study, Germany[9]

Between November 2000 and March 2002, the German Society of Phlebology performed the Bonn Vein Study in the city of Bonn and two rural townships. The participants were chosen from a random sample of the population registers. A total of 3072 participants (1722 women and 1350 men) between 18 and 79 years of age were investigated. All participants answered a standardized questionnaire and were investigated clinically and by duplex sonography by four physicians trained in phlebology. The complete CEAP classification was used. Within the clinical stages, the participants were classified according to the most severe clinical findings.

Leg complaints consistent with symptoms of venous diseases, such as heaviness and a feeling of swelling, etc., were present in 49.1% of the male population and 62.1% of the female population. The prevalence increased with age. In the 4 weeks preceding the investigation, 14.8% of the population experienced leg swelling: 7.9% of the men and 20.2% of the women. Concerning the CEAP classification, only 9.6% of the population (13.6% men and 6.4% women) had no signs of venous disorders (C0), while 59.1% (58.4% men and 59.5% women) demonstrated telangiectasia or reticular veins (C1) (Table 10.1).

Varicose veins without edema or skin changes (C2) were present in 14.3% (12.4% men and 15.8% women) of the population. At the time of investigation, 13.4% (11.6% men and 14.9% women) had pretibial pitting edema (C3). Only 2.9% (3.1% men and 2.7% women) showed a C4 classification with skin changes such as eczema, pigmentation, or lipodermatosclerosis. Only 0.6% had healed venous ulceration (C5), and 0.1% were afflicted with active venous ulcers (C6). Stages C2 and C3 had a significantly higher prevalence in the female population. The urban population showed a higher frequency of CVI (C3–C6). The prevalence of stages C2–C6 increased with age.

In a multivariate analysis adjusted for age and region of living, risk factors for varicose veins were older age, female gender, and number of pregnancies. Risk factors for CVI were older age, obesity, and urban inhabitance.

10.4.4 The Polish Study[14]

This cross-sectional, multicenter study involved 803 Polish primary care physicians (general practitioners, internists, and gynecologists). Fifty consecutive patients were selected from their outpatient clinics. A total of 40,095 adults between 16 and 97 years of age (mean age: 44.8 years) were interviewed and clinically investigated. The majority were women (84%). The clinical classification of CEAP (highest level) was used. CVI was diagnosed when any of the stages C1–C6 was present. Leg complaints were reported in up to 81% in the varicose vein group and up to 35% in the varicose-free participants. A total of 10% of the population presented with edema, 34.3% had varicose veins, and 1.5% had active or healed venous ulcers. C0 was found in 51.1% of the population, C1 in 16.5%, C2 in 21.8%, C3 in 4.5%, C4 in 4.6%, C5 in 1.0%, and C6 in 0.5%. Risk factors for varicose veins were older age, number of pregnancies, positive family history, and obesity. Female gender was not shown to be a risk factor for varicose veins.

10.4.5 The French Study[10]

In this cross-sectional study, a sub-population of a survey concerning Raynaud's phenomenon was used. A total of 409 participants (277 males and 132 females) were investigated using a standardized questionnaire and clinical examination by trained vascular medicine professionals; 48.7% were classified as C0 or C1. C2 was present in 23.7% of the males and 46.3% of the females. C3 was found in 1.1% and 2.2%, respectively. A total of 4% of the men and 2.1% of the women had skin changes (C4). Healed ulcers were found in 1.4% of the males and 0.7% of the females. No active ulcers were reported.

Positive family history, advanced age, pregnancies and height in women, and exercise frequency of less than once a week in men were the main risk factors for varicose veins.

10.4.6 The Vein Consult Program[15]

The most recent data derive from the Vein Consult Program, a large, international observational prospective survey that has been carried out on the initiative of the Union Internationale de Phlébologie. A total of 6232 general practitioners in Western, Central and Eastern Europe, Latin America, and the Middle East screened 91,545 consecutive patients clinically for the presence of CVDs. The mean age was 50.6 years. A total of 16.4% of all participants showed an asymptomatic C0 level and 19.7% had venous symptoms but

no clinical signs of CVD (C0S). A total of 21.7% had reticular veins or telangiectasias, A total of 17.9% were on level C2, 14.7% C3, 7.5% C4, 1.4% C5, and 0.7% C6.

Even in the recent study protocols, there are still differences concerning recruitment of the study population, the age and sex distributions, and the definition of CVI (Table 10.1). Only in three studies were the participants investigated by duplex ultrasonography.[9,12,13] The method of pitting edema assessment was mentioned only in the Bonn Vein Study. This could explain the differences in the reported prevalence of C3, which varied between 1.1% and 14.9% (Table 10.1).

In the CEAP-based epidemiological studies, the reported prevalence is similar for most of the classes (Table 10.1). C0 and C1 together are present in more than 60% of the population (48.7%–70.6%). The prevalence of C2 is over 20% (17.9%–29.4%), with a higher number in women. Skin changes due to venous diseases, including venous ulcers, are reported in less than 10% of investigated individuals (3.6%–8.6%). The range of prevalence is from 0.6% to 1.4% for healed ulcers and from 0% to 0.7% for active ulcers.[9,10,12–15]

10.5 PREVALENCE OF VENOUS REFLUX

In the pathogenesis of CVD, valve dysfunction and wall dilation are followed by venous reflux. In the Bonn Vein Study, reflux longer than 0.5 seconds was present in 21% of the adult population (17.7% in men and 23.5% in women).[22] A total of 20% of the adult population showed deep venous reflux (23.1% in men and 17.6% in women).[22] Evans et al. found similar results in the Edinburgh Vein Study.[23]

10.6 PREVALENCE OF VENOUS SYMPTOMS

The CEAP classification distinguishes symptomatic and asymptomatic cases, with the symptoms being aching, pain, tightness, sensation of skin irritation, heaviness, muscle cramps, and others. Symptoms are typically exacerbated by heat or at the end of the day and relieved with leg rest or elevation.[21] Recent epidemiologic studies showed a high prevalence of these symptoms in the general population being associated with, but not specific for, CVD.[24–29] In the Bonn Vein Study, 56.4% of the participants claimed leg symptoms assignable to CVD in the 4 weeks preceding the investigation.[30] Venous symptoms were more frequent in the female population (62.1%) compared to the male population (49.1%). The prevalence of symptoms increased with age and with the clinical classes according to the CEAP classification.[30] For participants in the San Diego Study, the prevalence of leg symptoms was higher when CVI trophic skin changes were present. [24] In the varicose vein group, feeling of heaviness was reported in 11.8% compared to 16.0% in the trophic changes group. Similar differences occurred for sensation of swelling (19.1% vs. 35.7%), tired legs (18.3% vs. 21.1%), aching (25.5% vs. 29.1%), itching (8.7% vs. 13.1%), and cramps (17.7% vs. 19.7%). Symptoms were more common in the female compared to the male population.[24]

10.7 INCIDENCE OF CVD AND VENOUS REFLUX

The incidence of CVD was assessed only in a few studies.[16,18,20] In the Framingham study, the incidence of varicose veins was 2.6% per year in women and 1.9% per year in men.[20] The incidence was comparable in all age groups. In the Bonn Vein Study, we found an incidence for varicose veins of 13.7% and for CVI of 13.0% after a follow-up of 6.6 years.[16] The incidence increased with age. In a follow-up study of the Edinburgh Vein Study, Robertson et al. found a 13-year incidence of venous reflux in the legs of 12.7% (95% CI: 9.2%–17.2%) or 0.9% per year.[18] The 13-year incidence of reflux was higher in the superficial veins at 8.8% compared to the deep veins at 2.6%. No age and sex differences were found, but there was a higher incidence in obese participants and after DVT.[18]

10.8 PROGRESSION OF CVD

Recently, Lee et al. published the progression results of the Edinburgh Vein Study.[19] After a follow-up of 13.4 years, 57.8% of the participants (or 4.3% per year) showed a progression of venous disorders. A total of 31.9% of the participants who showed only varicose veins at baseline progressed to CVI. Risk factors were family history of varicose veins (odds ratio [OR]: 1.85, 95% CI: 1.14–1.30) and history of DVT (OR: 4.10, 95% CI: 1.07–15.71). Overweight varicose vein patients had a higher risk of developing CVI (OR: 1.85, 95% CI: 1.10–3.12).[19] Participants of the Bonn Vein Study with varicose veins from a symptomatic or asymptomatic C2 class at baseline progressed to higher clinical classes in up to 30% after a follow-up of 6.6 years.[17] These data confirm the results from follow-up studies with patients on the waiting list for varicose vein surgery. Brewster et al. reported the follow-up results of 304 patients on a waiting list for varicose vein surgery.[31] After a mean waiting time of 4 years, 64% reported a progression of the disease. A total of 5.2% developed a superficial vein thrombosis while waiting for the operation, 22% developed skin changes, and 12% developed venous leg ulcers. In a study of 116 limbs in 190 patients waiting for varicose vein surgery, Labropoulos et al. reported 11.2% progression of the clinical stage after a median follow-up of 19 months.[32] Seven limbs progressed from C2 to C3, four limbs from C3 to C4, and two limbs from C4 to C6.[32]

10.9 RISK FACTORS ASSOCIATED WITH VARICOSE VEINS AND CHRONIC VENOUS INSUFFICIENCY

The main risk factors associated with varicose veins are advanced age, female gender, pregnancies, and positive family history (Table 10.2).

Table 10.2 Association of risk factors with varicose veins and chronic venous insufficiency

Risk factor	VV	CVI
Older age	+	+
Family history	+	+
Female gender	+	±
Pregnancies	+	±
Obesity	±	+
Oral contraceptives or hormone-replacement therapy	–	–

Note: +: established; ±: uncertain; –: no association; CVI: chronic venous insufficiency; VV: varicose vein.

10.9.1 Age

Older or advanced age was the most important risk factor for varicose veins and CVI in all studies.[1,5,8–11,13–15] The mean 2-year incidence rate for varicose veins in the Framingham study was 5.2% for women and 3.9% for men, resulting in a steady increase in prevalence for varicose veins with age.[20] In the San Diego Study, older or advanced age as a risk factor showed a significant OR of up to 2.42 for varicose veins and up to 4.85 for CVI.[13] In the Bonn Vein Study, older age was the most important risk factor for varicose veins and CVI. The ORs in the subgroup of age 70–79 years were 15.9 for varicose veins and 23.3 for CVI.[9]

10.9.2 Positive family history

A positive family history for varicose veins or venous diseases is associated with a higher risk for varicose veins in several studies.[1,8–10,14] In the Bonn Vein Study, the ORs for varicose veins were 2.1 in men and 2.3 in women, and for CVI were 1.4 (95% CI: 1.01–2.02) in men and 1.3 (95% CI: 0.92–1.74) in women. This effect diminishes with age.[33] Although heredity seems to be a risk factor for varicose veins, no responsible genetic defects have been identified to date.

10.9.3 Gender, pregnancies, and hormones

The prevalence of varicose veins is higher in women than in men.[1] In the San Diego Study, the OR for female gender as a risk factor for varicose veins was 2.18, and in the Bonn Vein Study, it was 1.5.[9,13] Similar results could be shown in many studies.[2,5,8] In contrast, there is no obvious gender difference for the prevalence of CVI. Chiesa et al.[12] found a higher prevalence rate of edema (13.9% vs. 11.4%) but lower prevalence rates of C4a (3.1% vs. 5.2%) and C4b–C6 (8.1% vs. 11.6%) in women. Similar results were found in the Bonn Vein Study.[9] In the San Diego Study, the OR for female gender and trophic changes was 0.65.[13] The main cause of the gender differences in varicose veins could be the number of pregnancies. Chiesa et al.[12] found a higher OR for non-saphenous varicose veins in women with previous pregnancies (OR: 1.11) than that noted in nulliparous women (OR: 0.75). Jukkola et al.[34] confirmed parity as an independent risk factor for varicose veins (OR: 2.0). In the Bonn Vein Study, the OR increased with the number of pregnancies from 1.3 to 2.2. Never-pregnant women and men had similar prevalence rates for varicose veins.[35] Hormone-replacement therapy or oral contraceptives seem not to be risk factors for varicose veins or CVI. In the Bonn Vein Study, we did not see a consistent effect of hormone intake on varicose veins (OR: 0.9), but there was a negative association with CVI (OR: 0.6).[35] In a 5-year follow-up study, Jukkola et al.[34] also demonstrated that hormone-replacement therapy and oral contraceptives did not increase the risk of varicose veins. Bérard et al.[36] found a protective effect of hormone-replacement therapy on the development of venous ulcers.

10.9.4 Obesity

The role of obesity in varicose veins is controversial. In the Framingham study, obesity with a body mass index (BMI) greater than 27 kg/m^2 increased the risk of varicose veins in women but not in men.[20] In the Bonn Vein Study, a BMI greater than 30 kg/m^2 increased the risk of varicose veins for women (OR: 1.9), but not significantly so. However, the risk for CVI was increased significantly for men and women (OR: 6.5 and 3.1, respectively).[9] Iannuzzi and colleagues[37] demonstrated a positive association of BMI greater than 30 kg/m^2 with varicose veins in postmenopausal women (OR: 5.8). Carpentier et al.[10] did not find an elevated risk for varicose veins with obesity, but found a correlation with height in women. In the Polish Study, obesity was a risk factor for venous disease compared with participants without CVD.[14]

10.9.5 Other risk factors

For other risk factors, such as smoking, hypertension, physical activity, or constipation, the data are inconsistent. If positive, the risk seems to be low.[1,2,4,5,38,39]

10.10 SUMMARY

CVDs are among the most prevalent conditions in the Western population, and venous symptoms such as heaviness of the legs, feeling of swelling, and pain during standing are frequent complaints in the general population. The prevalence of more severe chronic venous signs such as eczema, pigmentation, and lipodermatosclerosis or venous ulceration reaches around 5% in men and women. Varicose veins can be found in more than 20% of the general population. Established risk factors for varicose veins are older age, family history, female gender, and pregnancies. In CVI, obesity plays an important additional role.

10.11 CLINICAL RECOMMENDATIONS

1. The prevalence of C0/C1 together is over 60% (48.7%–70.6%), with varicose veins (C2) present in more than 20% of the population (21.8%–29.4%). Skin changes resulting

from venous disease, including venous ulcers, are present in less than 10% of the population (3.6%–8.6%), with a prevalence of between 0.6% and 1.4% for healed ulcers and between 0% and 0.5% for active ulcers.[9,10,12–14]

2. Relevant risk factors for varicose veins are:
   a. Advanced age[9,13,20]
   b. Positive family history[9,10,14]
   c. Female gender[9,13]
   d. Multiparity[12,34]
   e. Obesity[20]
3. Relevant risk factors for CVI are:
   a. Advanced age[9,13]
   b. Positive family history[9]
   c. Obesity.[9,14]

Guidelines 1.9.0 of the American Venous Forum on the epidemiology of chronic venous disorders

No.	Guideline	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.9.1	The prevalence of varicose veins in the adult population is more than 20% (21.8%–29.4%).	A
1.9.2	About 5% (3.6%–9.6%) of the adult population has skin changes or ulcers due to chronic venous insufficiency.	A
1.9.3	Active venous ulcers are present in 0.1%–0.7% of the adult population; 0.6%–1.4% have healed ulcers.	B
1.9.4	Advanced age is a risk factor for varicose veins and chronic venous insufficiency.	A
1.9.5	Positive family history, female gender, and multiparity are risk factors for varicose veins.	A
1.9.6	Age and obesity are risk factors for chronic venous insufficiency.	A

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PART 2

Diagnostic Evaluations and Venous Imaging Studies

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11

Evaluation of hypercoagulable states and molecular markers of acute venous thrombosis

DIANE M. NITZKI-GEORGE AND JOSEPH A. CAPRINI

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11.1 INTRODUCTION

Normal hemostasis provides a balance between clot formation and dissolution. Vessel injury, venous stasis, and thrombophilias favor thrombosis. These three factors, described as Virchow's triad, represent a disruption in the normal hemostatic processes.[1] The risk of venous thromboembolism (VTE) increases in proportion to the presence of these predisposing risk factors.[2,3] (See Chapter 9 for a more detailed discussion on the epidemiology and risk factors for VTE.)

Hypercoagulable states can be categorized as inherited, acquired, or mixed.[4] Thrombophilic patients most commonly present with characteristic features such as thrombosis at a young age, recurrent thrombosis, resistance to heparin, warfarin-induced skin necrosis, purpura fulminans, family history of thrombosis, or thrombosis that develops at an unusual site. The identification of an inherited or acquired thrombophilic defect is most essential when the information obtained would affect clinical management of the patient or of a family member.[5]

11.2 MARKERS OF THROMBOTIC RISK

11.2.1 β2-glycoprotein

β2-glycoprotein I (β2-GPI) is a major antigen found in patients who have circulating antiphospholipid antibodies.[6] β2-GPI removes microparticulates from the circulation, including anionic and lipopolysaccharide cellular remnants.[6] Repeated exposure and binding of β2-GPI to cellular phosphatidylserine has been theorized as a mechanism for the formation of anti-β2-GPI antibodies. These antibodies appear to be more specific for antiphospholipid antibody syndrome (APS) and can cause activation of the different cell types involved in the regulation of hemostasis.[6]

11.2.2 D-dimer

Elevated D-dimer is not necessarily a risk factor causing VTE, but it should be used and interpreted as a marker of hypercoagulability. D-dimer is formed when fibrin is proteolysed by plasmin.[7] The presence of elevated levels of D-dimer in the circulation signifies fibrinolysis.[8] The degree of D-dimer elevation with VTE may depend on the extent of disease, the duration of symptoms, and the use of anticoagulants, with lower D-dimer levels being associated with less extensive disease, longer duration of symptoms, and anticoagulant use.[7]

Elevated D-dimer levels can also result from recent major surgery, hemorrhage, trauma, pregnancy, cancer, or acute arterial thrombosis.[9] Different assays vary with respect to sensitivity and specificity, speed of testing, and the labor involved in performing the assay.[7] Moderately and highly sensitive assays range from about 85% to at least 95%, respectively, but specificity can be as low at 40% depending on the assay used.[9] Other issues with the D-dimer assays include differences in the specificity of the antibody to the various binding sites on the D-dimer molecule, lack of a definitive cut-off value between abnormal and normal results, lack of a reference standard assay, and lack of a standard unit of measurement.[7] One fibrinogen-equivalent unit is approximately half of a D-dimer unit. Because the D-dimer assay has a high negative predictive value, it is used to help "rule out" VTE.[9]

In patients with a normal D-dimer at 1 month after discontinuing anticoagulation, repeat D-dimer testing every few months for 1 year can be used to identify the risk for recurrence.[10–12] Repeat D-dimer tests have not only been used to identify people who are at risk for recurrent VTE, but have identified differences in recurrence rates based on gender, with men being at greater risk.[13] The Vienna Prediction Model uses a web-based calculator to stratify VTE recurrence risk based on gender, location of VTE, and D-dimer results 3 weeks after anticoagulation is stopped.[14] Other D-dimer-based rules to predict VTE recurrence include the age-adjusted D-dimer and DASH (D-dimer, Age, Sex, Hormonal) therapy.[15–17]

11.2.3 Factor VIII

Elevated plasma levels of factor VIII (FVIII), one of five cofactors that control the generation of thrombin, have been associated with an increased risk of recurrent VTE.[18] This risk was initially identified in patients who had a FVIII level in about the 90th percentile. A more recent study found an adjusted multivariate hazard ratio (HR) of 4.5 (95% CI: 1.7–12.2) in patients with a FVIII level above the 75th percentile compared with a normal D-dimer.[19] When compared with an abnormal D-dimer, the HR of an elevated FVIII (>75th percentile) was 7.1 (95% CI: 2.8–17.6).[19] However, since FVIII is activated during an acute phase, these results demand careful interpretation. In a follow-up study of people who presented with an initial VTE and FVIII levels >230 IU/dL, the probability of recurrent thrombosis at 2 years after discontinuing anticoagulation was 30% (95% CI: 13%–46%).[20]

11.2.4 Hyperhomocysteinemia

Hyperhomocysteinemia (HHC) refers to an elevation of the plasma homocysteine levels, a metabolic substrate derived from the amino acid methionine.[21,22] HHC may occur in certain medical conditions, such as renal insufficiency, hypothyroidism, or deficiencies in folate, vitamin B6, or vitamin B12, since these vitamins are important in the metabolism of homocysteine. Warfarin use has also been suggested to contribute to HHC, since patients often avoid green vegetables that supply these necessary vitamins.[23] HHC may also be suggestive of a mutation in the methylenetetrahydrafolate reductase (*MTHFR*) gene, an inherited thrombophilia.

HHC has been correlated with a greater occurrence of idiopathic deep vein thrombosis (DVT).[24] A 4.8-fold increase risk of VTE has been found in people with HHC.[25] Unlike other thrombotic conditions, except for antiphospholipid antibody syndrome, HHC is associated with both arterial and venous thrombosis. In fact, fasting homocysteine levels have been positively associated with myocardial infarction risk in women (relative risk [RR]: 3.37, 95% CI: 1.30–8.70, $P = 0.014$).[26] The mechanism of HHC-associated thrombosis is not fully elucidated, but may involve effects on the endothelium, factor V, thrombomodulin, and tissue factor.[21,22]

For arterial thrombosis, the authors of the randomized, double-blind Vitamin Intervention for Stroke Prevention (VISP) trial found that, despite reducing levels of homocysteine, high-dose vitamin therapy had no effect on stroke, coronary heart disease events, or death.[27] In addition, the Norwegian Vitamin (NORVIT) trial also demonstrated that folate plus vitamin B12 with or without vitamin B6 does not lower cardiovascular disease or death after acute myocardial infarction, and actually led to a non-statistically significant increase in events, despite a reduction in homocysteine.[28] Heart Outcomes Prevention Evaluation 2 (HOPE 2) also found that folic acid and vitamins B6 and B12 did not reduce cardiovascular events in 5522 patients.[29] Of note, the NORVIT and HOPE 2 trials included patients without regard to baseline homocysteine levels. Furthermore, the china stroke primary prevention trial (CSPPT) found that patients who took folic acid in combination with enalapril demonstrated a significant risk reduction in first stroke.[30]

11.2.5 P-selectin

P-selectin, an adhesion molecule expressed on the surfaces of activated platelets and endothelial cells, is increased in the presence of acute VTE, and is therefore used to aid in the diagnosis of DVT and pulmonary embolism.[31] P-selectin is a mediator of leukocyte recruitment that promotes the formation of pro-coagulant microparticles, and directly affects thrombus stabilization.[32] Evidence from basic and clinical studies has suggested that P-selectin can be used as a marker for reflecting a pro-thrombotic state, and has demonstrated value in cancer patients.[33,34]

11.3 THROMBOPHILIA

Most thrombophilias are inherited, with antiphospholipid syndrome representing an acquired thrombophilia.[35] Other disease states, conditions, and laboratory abnormalities that predispose patients to thrombosis[4,5,36] are not considered to be true thrombophilias, but are discussed elsewhere in this chapter.

Inherited thrombophilias may be classified into two or more groups (Table 11.1).[21] Group 1 disorders are defined as deficiencies of coagulation factor inhibitors, while group 2 disorders represent an increased level or function of coagulation factors.[21] Other inherited thrombophilias include rare disorders of the fibrinolytic system.[37]

In general, the group 1 disorders are less common, but more thrombogenic than the group 2 disorders. The group 2 disorders, although likely risk factors for single thrombotic events, may not be strong risk factors for subsequent thrombosis.[21] Patients with group 1 disorders usually present at a younger age with idiopathic or recurrent VTE, have a higher likelihood of recurrent VTE, and are more likely to have a family history of VTE.[36]

Table 11.1 Classification of inherited thrombophilias[28]

Group 1 inherited thrombophilia	Group 2 inherited thrombophilia
• Antithrombin deficiency	• Activated protein C resistance with or without factor V Leiden mutation
• Protein C deficiency	• Prothrombin G20210A mutation
• Protein S deficiency	• Factor elevation
	• Methylenetetrahydrafolate reductase (*MTHFR*) gene mutation

11.3.1 Activated protein C resistance with or without the factor V Leiden mutation

Activated protein C resistance (APC) refers to the resistance of factor V to cleavage by APC, slowing down factor V cleavage by about 10-fold and thus increasing thrombin production.[21,37,38]

Factor V Leiden (FVL) is the most common inherited thrombophilia, affecting approximately 5% of Caucasians, 1.2% of African–Americans, 2.2% of Hispanic–Americans, 1.2% of Native Americans, and 0.45% of Asian–Americans.[21,37–39] Compared with group 1 disorders (deficiencies of antithrombin, protein C, and protein S), APC resistance is a relatively weak risk factor for thrombosis.[21] The lifetime probability of symptomatic VTE in patients with a heterozygous FVL mutation is approximately 10%; thus, the vast majority of patients will not develop complications due to this mutation.[38] Adjusted HRs of 2.2 (95% CI: 2.0–2.5) for people with heterozygous mutations and 7.0 (95% CI: 4.8–10) for those with homozygous mutations have been reported.[40] The risk of recurrent VTE is higher in people with heterozygous FVL (odds ratio [OR]: 2.4, 95% CI: 1.6–3.6, $P < 0.01$).[41]

11.3.2 Antiphospholipid antibody syndrome

Antiphospholipid antibodies are a heterogeneous family of autoantibodies, including the lupus anticoagulants and anticardiolipin antibodies, and are directed against the phospholipid binding proteins that are important for coagulation.[42] APS is an antibody-mediated hypercoagulable state, defined by the combination of clinical and pathological characteristics as detailed by the Sydney classification.[43] The laboratory criteria are anchored on persistently positive antibodies: anticardiolipins, β2-glycoprotein, and lupus anticoagulant testing. Primary APS includes patients with the syndrome but without lupus or other autoimmune conditions, whereas secondary APS includes patients who also have systemic lupus erythematosus.[44] Catastrophic APS, the most severe form, is definitive in the presence of four clinical–pathological features: multi-organ involvement, the development of manifestations in less than a week, the presence of antiphospholipid antibodies (persistence of antibodies is not mandatory for the diagnosis), and small vessel occlusion.[43] The presence of antiphospholipid antibodies can also develop during treatment with certain medications and also during periods of infection, but their clinical significance in these scenarios is not known.[45,46]

Antiphospholipid antibodies are reported in up to 10% of healthy subjects and in 30%–50% of patients with systemic lupus erythematosus.[45] In patients with thrombotic events, the prevalence is higher, being in the range of 4%–21%, suggesting a potential association between antiphospholipid antibodies and thrombosis.[45,47]

When screening for lupus anticoagulants, current guidelines recommend using two or more phospholipid-dependent coagulation tests.[45,48] In patients taking anticoagulant therapy, particularly heparin, the accuracy of the test may be affected. Anticardiolipin antibodies—immunoglobulin (Ig) isotypes IgG, IgM, and IgA—are detected by using enzyme-linked immunosorbent assays, and are usually reported as a titer that is specific to each isotype. It is believed that the IgG isotype is most strongly linked with the development of thrombosis.

The incidence of recurrent VTE in patients with APS has been reported to be in the range of 52%–69%, appearing to be highest in the first few months of stopping anticoagulation.[44] Patients who are at higher risk for a thrombotic event are those who have triple positivity consisting of confirmed positive anticardiolipin, anti-β2-glycoprotein antibodies, and lupus anticoagulant.[49]

11.3.3 Antithrombin deficiency

Antithrombin (formerly termed "antithrombin III") is a natural anticoagulant that binds and inactivates factors IIa (thrombin), IXa, Xa, XIa, and XIIa in order to reduce clot formation.[21] More than 100 mutations may result in antithrombin deficiency, which is inherited as an autosomal dominant trait.[37] Antithrombin deficiency is classified into two types: type I indicates reduced levels of both functional (activity) and antigenic antithrombin, while type II indicates reduced functional but preserved antigenic levels.[21,37,50]

A deficiency in antithrombin is present in 0.07%–0.2% of the general population and 0.5%–8% of patients presenting with VTE.[21,37,50] Antithrombin levels can be decreased during an acute thrombotic event, so laboratory diagnosis should occur at least 3 months after the event. Diagnosis should also be deferred until at least 5 days after the cessation of heparin therapy, as antithrombin levels may be low during therapy.[37,50] The VTE risk in patients with heterozygous antithrombin deficiency is increased by 5–50 times. Most (>50%) patients with heterozygous mutations will develop VTE by 30 years of age.[50]

11.3.4 Factor elevations

The prevalence of elevated factor levels ranges from 10% to 20% for factors VIII and IX.[51] Elevated plasma concentrations of coagulation factors V, VII, VIII, IX, X, and XI are potentially induced by regulatory proteins or by unidentified mutations in the factor genes. Whether the elevated levels contribute to thrombosis or a reflection of another thrombophilic process is not known; however, persistent factor level elevations are more common in patients with a history of VTE.[21,51]

Factor levels can be measured using functional or antigenic tests. Levels of factors VII, IX, and X may be reduced in conditions that are associated with vitamin K deficiency, such as vitamin k antagonists (VKAs), malnutrition, and hepatic or biliary disease. Other conditions associated with changes in factor levels include oral contraceptive use, pregnancy, dyslipidemia, obesity, aging, acute stress, chronic inflammation, recent aerobic exercise, and blood type.[51]

11.3.5 Fibrinolytic system disorders

Emerging laboratory markers suggesting defects in the fibrinolytic system include heparin cofactor II deficiency and deficiencies in contact factors.[51–56] Intuitively, elevated fibrinogen, changes in fibrinogen structure, plasminogen deficiency, elevated plasminogen activator inhibitor-1 (PAI-1), and tissue plasminogen activator (tPA) deficiency could all increase the thrombotic risk.[21,51,55,57] Besides increasing fibrin levels, an elevated fibrinogen level may enhance platelet binding to the glycoprotein IIb/IIIa receptor and increase plasma viscosity. An acquired or inherited change in fibrinogen structure—dysfibrinogenemia—may result in abnormal fibrinogen function and either hemorrhagic or thrombotic complications. Testing for any of the fibrinolytic system defects is not routine, as the tests are not standardized, the thrombotic risk is not established, and it is unclear how treatment would change because of a positive result.[51,55]

11.3.6 *MTHFR* gene mutation

Inherited HHC can result from mutations in the genes coding enzymes involved in homocysteine metabolism: *MTHFR*, cystathione b synthase (*CBS*), or methionine synthase.[21,22] These mutations may or may not lead to HHC, depending on the homozygosity or heterozygosity of the mutations, co-inheritance with another mutation, or the presence of concurrent B vitamin deficiency.[37] The most common known mutations resulting in HHC are the *MTHFR* C677T ("thermolabile") and the *MTHFR* A1298C mutations. Although these mutations may result in HHC, they are not directly associated with thrombosis.[21,22]

The prevalence of the heterozygous *MTHFR* C677T mutation is 34%–50% and the prevalence of the homozygous mutation is 12%–15%, depending on the population. The *MTHFR* A1298C mutation is less common.[21,22,37] Since an elevated homocysteine level, not the underlying mutation, is associated with thrombosis, measuring the total plasma homocysteine level (tHcy) is more useful than testing for genetic mutations.[8,22] Reasonable definitions for moderate, intermediate, and severe elevations are tHcy 15–30 µmol/L, 31–100 µmol/L, and 100 µmol/L, respectively.[21] The relative risk for arterial thrombosis, according to a meta-analysis, was 1.3 (95% CI: 1.1–1.5); data showing an increased risk of recurrent VTE are more substantial than those for first VTE.[22]

11.3.7 Protein C deficiency

Similar to antithrombin deficiency, protein C deficiency is classified into two types: type I implies a reduction in both functional and antigenic levels, usually due to low protein C production, and type II implies a reduced functional level but a normal antigenic level. More than 160 mutations result in protein C deficiency, which makes genetic testing impractical.[21,37,50] Protein C deficiency is present in approximately 0.17%–0.4% of the general population, with the majority being type I deficiency. Heterozygous deficiency is present in 1.5%–11.5% (mean: 4%) of patients with VTE.[21,37,50]

Protein C deficiency should be diagnosed with a functional protein C level.[37,43] This level is not elevated during an acute VTE episode, which enables testing to be done at any time.[58] A finding of a normal protein C level during an acute event would rule out deficiency.[50] Warfarin and other vitamin K antagonists are the most common reasons for low protein C functional or antigenic levels; thus, waiting to test until 2–4 weeks after warfarin is discontinued is prudent.[37,50]

The OR of VTE in patients with protein C deficiency is 3.1. By 40 years of age, about 50% of patients with heterozygous protein C deficiency will have an episode of VTE, and the risk is increased by an additional concurrent inherited or acquired thrombophilia.[50]

11.3.8 Protein S deficiency

Like protein C, protein S is a vitamin K-dependent endogenous anticoagulant that is primarily produced in the liver.[37,59] Protein S is a cofactor for APC's inactivation of factors Va and VIIIa; therefore, protein S deficiency is phenotypically similar to protein C deficiency. Protein S deficiency differs from the other two deficiencies of natural anticoagulants in that 60%–70% of the total protein S is bound to the transport protein C4b-binding protein and is not available as a cofactor for APC. More than 131 mutations are associated with protein S deficiency.[21,37,59]

Protein S deficiency is classified into three types based on free, total, and functional tests. Type I deficiency denotes low levels of both free and total antigen, type II denotes low activity but normal free and total levels, and type III denotes low free but normal total levels. Type III deficiency usually results from abnormal binding of protein S to C4b-binding protein.[37,59]

Approximately 0.03%–0.2% of the general population have protein S deficiency, but the true prevalence is unknown due to the difficulty in making an accurate diagnosis. Diagnosing protein S deficiency is challenging due to multiple factors affecting the free protein S level. Total protein S level is not a clear predictor of VTE risk.[57]

The available tests for the diagnosis of protein S deficiency are free antigen level, total antigen level, and functional (APC cofactor activity) level. Routine testing of antigenic total protein S is not usually necessary. The functional test is influenced by factors other than protein S activity, and should be interpreted with caution. Fluctuations in protein S levels have been noted over time. Thus, the diagnosis should be confirmed with a second test.[37,59]

The rates of VTE being associated with protein S deficiency have been reported to range from zero to 11.5-fold.[37] A familial study showed that 50% of patients with protein S deficiency develop VTE by 45 years of age, but population-based studies show a weaker or no association, possibly due to the difficulty in reaching statistical significance with the low incidence of protein S deficiency.[59]

11.3.9 Prothrombin defects: Prothrombin gene 20210A mutation

The prothrombin G20210A (P20210) mutation is a G to A point mutation on the factor II gene at position 20210, which results in higher circulating levels of functionally normal prothrombin.[21,37,60] P20210 is the second most common inherited thrombophilia. The prevalence in the United States is 1%–2%. About 5%–10% of patients with VTE have P20210.[21,60] Since P20210 is a mutation, it is diagnosed with a genetic test, and can be tested without regard to a patient's current conditions.[37,60] The adjusted risk for VTE in people with homozygous prothrombin P20210 is higher (HR: 11, 95% CI: 2.8–44) than for those with a heterozygous mutation (HR: 1.5, 95% CI: 1.2–1.9).[40] The risk of recurrent VTE is less significant, with an OR of 1.72 (95% CI: 1.27–2.31) for recurrence after a first event in patients who are heterozygous for P20210, which is lower than the risk for first VTE, but higher than the risk for non-carriers.[61]

11.4 PREDISPOSING CONDITIONS

11.4.1 Blood groups

Patients who have type 0 blood appear to be at lower risk for developing DVT. High levels of factor VIII and von Willebrand factor are associated with certain genotypes, specifically the A1 and B alleles, of the ABO blood system. The O1 and O2 alleles impart a lower VTE risk.[62] Data on the VTE risk associated with the A2 allele are conflicting and require further investigation.[62–64] In a series of 712 consecutive patients who presented with DVT, the OR of having a non-O blood type was 2.21 (95% CI: 1.78–2.75). The combination of a non-O blood type plus thrombophilia is an even greater risk for DVT (OR: 7.06, 95% CI: 4.85–10.28).[40,64,65] This is especially true in patients with homozygous FVL.[66]

11.4.2 Cancer

VTE is a major cause of morbidity and mortality in cancer patients. Pulmonary embolism is the cause of death in one of every seven hospitalized cancer patients who dies.[67,68] The frequency of new and recurrent VTE is much higher in cancer patients than in non-cancer patients, and the majority of the events occur spontaneously without the presence of other triggering risk factors, as in the case of non-cancer patients. The reverse association is also true, as evidenced by the high rate of cancer development in patients with VTE, especially idiopathic thrombosis.[67] Some common risk factors that further heighten the risk of VTE in cancer patients include surgery, chemotherapy, the insertion of central venous catheters, and immobility. Treatment of VTE should be continued indefinitely until the cancer is in remission and the patient is no longer receiving chemotherapy. Treatment with low-molecular-weight heparin is more effective than warfarin, and it is the preferred treatment approach for the first 3–6 months after an acute event.[67,69]

11.4.3 Family history

Patients who have one first-degree relative with a history of VTE are at a two-fold greater risk of developing VTE (OR: 2.2, 95% CI: 1.9–2.6), and those who have more than one affected relative have up to a four-fold increased risk of VTE (OR: 3.9, 95% CI: 2.7–5.7).[70] These findings apply to siblings, parents, children, maternal and paternal half-siblings, nieces, nephews, cousins, and spouses of those diagnosed with VTE.[71]

11.4.4 Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a severe pathological adverse effect of heparin that involves an immunoglobulin-mediated response to the heparin molecule, leading to platelet activation and thrombin generation. Although heparin-induced antibody formation occurs in 10%–20% of patients treated with heparin, the vast majority of these patients never develop HIT. Antibodies to the heparin/PF-4 complex are transient and have been reported to disappear from the circulation within a median of 85 days.[72,73] Low-molecular-weight heparins are associated with a significantly lower risk of HIT than unfractionated heparin (UFH) (<1%).[72]

11.4.5 Pregnancy

In patients who are pregnant, the risk for arterial thrombosis is four-fold greater compared to non-pregnant women. The risk of VTE during pregnancy is four- to five-fold greater.[74] Pregnancy is normally associated with increases in factors VII, VIII, and X, as well as fibrinogen, von Willebrand factors, and PAI-1. These changes in hemostasis,

in addition to the physically decreased venous capacity and outflow imposed by the pregnancy, are implicated as contributing to the VTE risk, and are not expected to normalize until 8 weeks post-partum.[74]

Of the VTEs, about 80% present as a DVT, while 20% are pulmonary embolisms. Recurrent VTE accounts for 15%–25% of the events that occur during pregnancy, representing a three- to four-fold increase in risk (RR: 3.5, 95% CI: 1.6–7.8). The most important risk factor is the presence of a thrombophilia, which has been found in 30%–50% of women who have a VTE during pregnancy.

11.4.6 Surgery

In patients with past thrombosis or thrombophilic defects, the chance of recurrent thrombosis post-operatively may be well over 50%.[8] It is most important that patients with known thrombophilic defects or related positive family members are carefully screened and counseled pre-operatively.[75] This knowledge will enable proper selection, onset, dosage, and duration of thromboprophylaxis, as well as justifying the addition of physical methods of prophylaxis, despite their added costs.

11.5 BEST DEMONSTRATED PRACTICES

11.5.1 Testing

The combination of a genetic thrombophilic defect and one or more acquired risk factor(s), such as surgery or oral contraceptive use, lead to a higher risk of VTE than the separate effects of these single factors.[36] Universal testing for an inherited thrombophilia is inappropriate and not recommended. A negative test only rules out the presence of the thrombophilic defects for which the patient has been tested, and is not necessarily proof that an unidentifiable defect does not exist. Thus, in each case, evaluating and documenting a detailed initial clinical history are crucial.[4]

Currently, there are no consistent guidelines in the literature by which patients should be considered for thrombophilia work-up and for which specific tests should be included if patients are tested. Box 11.1 gives some practical recommendations regarding these issues. Many of the function and antigen assays for thrombophilias can be affected by a variety of external factors, such as medications, acute thrombosis, and other acquired conditions. Thus, these assays should be repeated after ruling out any external factors and before a final diagnosis of an inherited thrombophilia is made.[76]

11.5.2 Risk assessment using scoring systems

There are many scoring systems for evaluating the thromboembolic risk in surgical patients, and the most widely validated is the Caprini score.[77] This system consists of a number of common risk factors, each of which is assigned a numerical weight. This number reflects the likelihood of each factor causing a thrombotic event. In studies conducted to date, the total score was compared to the actual development of a thrombotic event within 30–60 days post-operatively. This system has been tested in over 25,000 patients worldwide in more than 15 trials of medical and surgical patients. The risk of a clinical event is <1.0% in those with a score of 4 or less. The clinically relevant VTE rate increases parallel to rising scores. Scores of 9 or more increase the VTE risk to 18% after some operations. The concept seems to hold true regardless of the specialty tested. Boston University has shown the best results using this score tied to a mandatory prophylaxis schema.[78] Patients with a score of 4 or less can receive prophylaxis at the discretion of the treating physician (low to moderate risk) during hospitalization. Many of these low-risk patients are not given anticoagulant prophylaxis, since the risk of a clinical bleeding event is greater than the chance of a clinically evident thrombosis. On the other hand, those with a score of 5–8 are considered to be in the high-risk group and need to be protected for the period of time shown in clinical trials in order to prevent post-operative thrombosis. This time period is 7–10 days regardless of their length of hospital stay. Finally, patients with a score of 9 or more (highest risk) are given prophylaxis for 30 days, since the incidence of real thrombotic events is 6%–18%. These rules are mandatory, but the physicians can opt out if they feel that there is a high bleeding risk. Physician compliance in high-risk patients was 89%, and it was 77% in the highest-risk group. The VTE rate in general surgery was 0.2%, and the pulmonary embolism rate approached zero during this time. This system at Boston University has recorded the lowest VTE event rates ever seen in the National Surgical Quality Improvement Project (NSQIP) database.[78]

BOX 11.1: Patients who may be considered for thrombophilia work-up[7,62]

- Unexplained or "idiopathic" thromboembolism (first event)
- Secondary, non-cancer-related first event and age <50 years (includes thrombosis on oral contraceptives and hormone-replacement therapy)
- Recurrent "idiopathic" or secondary non-cancer-related events
- Thrombosis at unusual sites (portal vein, sinus veins, etc.)
- Extensive thrombosis
- Strong family history of venous thromboembolism

11.5.3 The importance of scoring in patients with thrombophilia

Patients with a history of thrombosis receive a score of 3 points, with an additional 3 points for those with a thrombophilic defect. Family history of thrombosis increases the score to 9. This means that in some patients who are contemplating elective quality-of-life procedures, a high score may

cause them to rethink the advisability of going ahead with the planned surgery. The risk of major or fatal complications in this small subset of patients may be as high as 5%.

11.5.4 General recommendations

Informed consent should be obtained from patients, and especially asymptomatic family members, before thrombophilia testing is performed. Counseling should be provided to patients who test positive for one or more thrombophilias regarding their risk of thrombosis, the signs and symptoms of VTE, and the benefits of antithrombotic prophylaxis in high-risk situations such as elective surgery or pregnancy.[4,36,37,76]

Since more than one thrombophilic defect can be present in a given patient, testing for additional inherited or acquired thrombophilias should be considered, even after the identification of a single thrombophilic defect. Consider repeating function or antigen diagnostic assays after ruling out interfering factors such as medications and acquired conditions, and before a definite diagnosis of an inherited thrombophilia is made.[4,36,37,76]

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Guidelines 2.1.0 of the American Venous Forum on the evaluation of hypercoagulable states and molecular markers of acute venous thrombosis

No.	Guideline	Grade of recommendations (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
2.1.1	Patients with the following conditions are considered for evaluation for thrombophilia: 1. Unexplained or "idiopathic" thromboembolism (first event) 2. Secondary, non-cancer-related first event and age <50 years (includes thrombosis on oral contraceptives and hormone-replacement therapy) 3. Recurrent "idiopathic" or secondary non-cancer-related events 4. Thrombosis at unusual sites (portal vein, sinus veins, etc.) 5. Extensive thrombosis 6. Strong family history of venous thromboembolism	1	C
2.1.2	Testing for thrombophilia is recommended to most patients 2–4 weeks after completing the typical course (usually 6 months) of anticoagulant therapy.	1	C
2.1.3	Long-term, primary pharmacologic thromboprophylaxis of asymptomatic thrombophilic patients is not recommended.	2	B
2.1.4	Patients with thrombophilia should be considered for thromboprophylaxis at times of high thrombotic risk such as surgery, trauma, prolonged immobility, pregnancy, or acute illness.	1	A
2.1.5	Patients with thrombophilia should be considered for prolonged anticoagulation following acute deep vein thrombosis.	1	B

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● = Key primary paper
★ = Major review article

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12

Duplex ultrasound scanning for acute venous disease

TIMOTHY K. LIEM

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12.1 INTRODUCTION

The incidence of first-time venous thromboembolism (VTE) has been estimated to range between 70 and 113 per 100,000 population/year, with at least 350,000 cases of deep vein thrombosis (DVT) and pulmonary embolism occurring each year in the United States.[1,2] It is a frequent complication in patients who undergo major surgery and prolonged hospitalization, and the Surgeon General's 2008 Call to Action described VTE as the most common cause of preventable in-hospital mortality.[3]

Successful therapy requires prompt diagnosis and initiation of antithrombotic therapy within the first 24 hours of the onset of symptoms. Prior to the 1980s, patients were more commonly diagnosed via impedance plethysmography (IPG), I^{121}-labeled fibrinogen nuclear scanning, and contrast venography. However, the accuracy of IPG is limited, demonstrating decreased sensitivity in patients with non-occlusive proximal thrombosis, those with duplicate femoral or popliteal veins when only one channel is affected, and those with isolated calf DVT. Labeled fibrinogen scanning and contrast venography are more labor intensive, time consuming, and are not readily available at every medical facility. The use of B-mode and Doppler for the assessment of venous disease was first introduced in 1968, but did not become a validated diagnostic tool for another decade.[4–6] Since the 1980s, the venous duplex examination has been the mainstay of the diagnosis of acute DVT and superficial venous thrombosis. Although venous duplex imaging was initially utilized to detect thrombosis in the upper and lower extremity venous beds, duplex is now being utilized for the detection of thrombosis in the ilio-caval and mesenteric veins as well. This chapter will discuss indications for testing, examination techniques, the accuracy of the venous duplex examination in various anatomic beds, and controversies in the imaging of acute venous disease.

12.2 INDICATIONS FOR TESTING

Venous duplex ultrasound has become the imaging test of first choice to aid in the diagnosis of venous thrombosis. This is related to multiple factors, which include its relatively high accuracy in detecting upper and lower extremity DVT and very low risk for complications. Duplex imaging has also become widely adopted due to the capacity for portable bedside examinations and the greater availability of vascular laboratories and ultrasound services at more health care facilities. In fact, this mode of imaging is so widely available that it may have become a victim of its own success, with multiple reports suggesting that health care providers generally have a low threshold for ordering duplex scans in order to "rule out" DVT.[7,8] This contributes to an overutilization of venous ultrasound, with ultrasound testing demonstrating the absence of DVT in as many as 80%–90% of patients.

More recent criteria have been published to standardize the appropriate use of duplex scanning for acute venous disease.[9] Table 12.1 summarizes the recommendations from numerous professional societies, and categorizes various clinical indications as either appropriate or rarely appropriate, based on the anatomic region in question. Extremity

Table 12.1 Guidelines regarding the appropriate use of venous duplex scanning for patients with venous disease, categorized according to anatomic region

Anatomic region	Appropriate	Rarely appropriate
Upper extremity	• Limb edema • Non-articular upper extremity pain or palpable cord • New pain or edema in the presence of known upper extremity DVT	• Fever of unknown origin in the absence of an indwelling venous catheter • SOB in patient with known upper extremity DVT • Screening asymptomatic patients with prolonged ICU stay, prior to pacemaker/defibrillator, for monitoring of a functional venous catheter, patients with hypercoagulable state, or positive D-dimer testing
Lower extremity	• Limb edema • Non-articular lower extremity pain or palpable cord • Pulmonary embolism • New pain or edema in the presence of known lower extremity DVT • Surveillance of calf DVT for proximal extension when anticoagulation is contraindicated • Surveillance for GSV or SSV SVT when near a deep vein junction • Early follow-up after endovenous saphenous ablation • Patent foramen ovale with suspected paradoxical embolism • Evidence of lower extremity venous obstruction on plethysmography suggesting DVT	• Screening asymptomatic patients with prolonged ICU stay, after orthopedic surgery, with hypercoagulable state or positive D-dimer testing
Inferior vena cava and iliac veins	• Routinely or selectively in conjunction with lower extremity scanning if proximal DVT was identified or if abnormal flow pattern is found in one or both common femoral veins • May be appropriate for procedure planning prior to inferior vena cava filter placement	• Standalone testing without LE venous scanning • Abdominal pain • Abdominal bruit • Fever of unknown origin
Hepatoportal and renal veins	• Evaluation of cirrhosis without ascites/hematomegaly/splenomegaly/portal hypertension • Evaluation of abnormal LFTs and jaundice if no alternative diagnosis • Surveillance after TIPS	• Initial diagnostic test for jaundice

Source: Adapted from Gornik HL et al. *J Am Coll Cardiol* 2013;62:649–65.
Note: DVT: deep vein thrombosis; GSV: great saphenous vein; ICU: intensive care unit; LFT: liver function test; SOB: shortness of breath; SSV: small saphenous vein; SVT: superficial vein thrombosis; TIPS: transjugular intrahepatic portosystemic shunt.

pain and edema are common and appropriate indications for duplex imaging of the upper or lower extremity veins. Additional indications include follow-up surveillance for patients with isolated calf DVT who are unable to receive therapeutic anticoagulation, and patients with isolated superficial vein thrombosis when near a junction with the deep venous system. Although duplex surveillance after endothermal ablation are listed and widely practiced indications (Figure 12.1a and b), the utility and cost-effectiveness of routine venous imaging after radiofrequency or laser ablation have recently been called into question.[10]

Despite the use of standardized indications for venous duplex testing, the majority of patients will test negative for deep or superficial vein thrombosis. In patients with clinical suspicion for lower extremity DVT, clinical decision rules, in combination with qualitative or quantitative D-dimer assays, have been evaluated as means to "rule out" DVT without having to perform further diagnostic testing, such as venous duplex imaging.[8,11,12] The Wells rule is the most widely studied clinical decision scoring system and is shown in Table 12.2. Earlier descriptions of the Wells rule dichotomized patients into likely versus

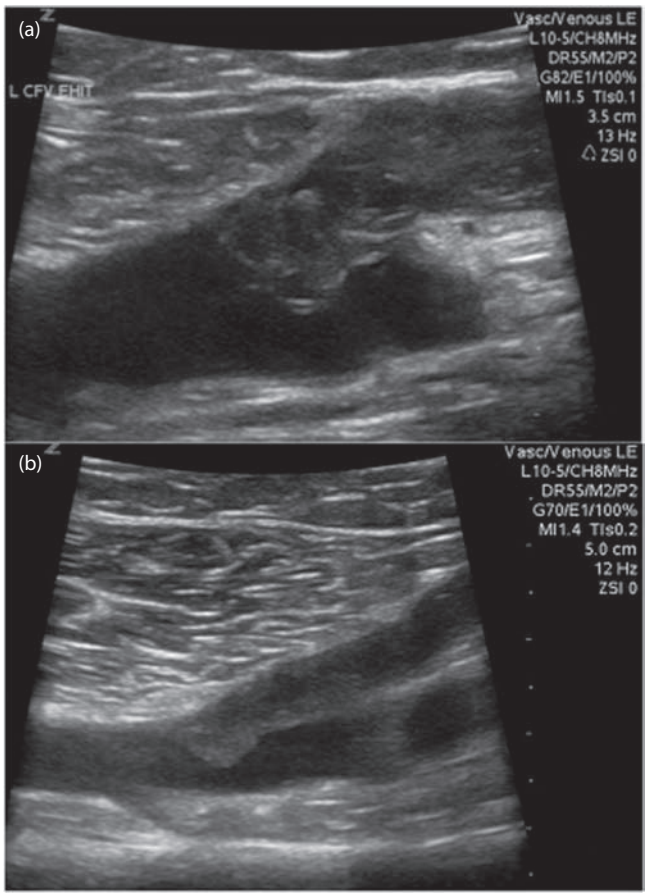

Figure 12.1 Grayscale images of patients who developed endothermal heat-induced thrombosis (EHIT) after endovenous ablation of the great saphenous vein **(a)** and small saphenous vein **(b)**.

Table 12.2 Clinical model for predicting pre-test probability of deep vein thrombosis

Clinical characteristic	Score
Active cancer (≤6 months)	1
Paralysis, paresis, or recent plaster immobilization of leg	1
Recently bedridden for >3 days or major surgery <4 weeks ago	1
Localized tenderness along the deep venous system	1
Entire leg swollen	1
Calf swelling >3 cm compared with asymptomatic side (10 cm below tibial tuberosity)	1
Pitting edema confined to symptomatic leg	1
Collateral superficial veins	1
Previous documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	− 2

Source: Adapted from Geersing GJ et al. *Br Med J* 2014;348:g1340.
Note: DVT unlikely if score ≤1 and likely if >1.

unlikely for DVT. An unlikely Wells rule score (≤1) combined with a negative D-dimer assay is associated with a very low probability of DVT (<2%), except in patients with active malignancy and those with recurrent VTE.[12] Patients with a likely Wells score (>1) should undergo further testing with venous duplex imaging. Use of such a clinical decision algorithm can potentially eliminate the need for venous duplex imaging in about a third of patients.[10] The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines suggest the use of a clinical assessment tool in combination with D-dimer assays and venous duplex scanning (grade 2B recommendation). However, the algorithms suggested by the ACCP Guidelines trichotomize the Wells rule into low (≤0), moderate (1–2), and high probabilities (≥3). The suggested diagnostic algorithms are significantly more complicated, potentially decreasing their utility and appeal to many health care providers.[13] Similar clinical decision rules have also been recently described for patients who are suspected of upper extremity DVT, but further confirmation is warranted before they can be applied.[14]

12.3 EXAMINATION TECHNIQUE

12.3.1 Lower extremity venous examination

The patient is placed supine and comfortable, with the bed in a slight reversed Trendelenburg position. Optimally, the room is warmed, but this is not always possible when portable venous examinations are performed in the emergency department, hospital ward, or intensive care unit. Examination for lower extremity venous thrombosis is usually performed with slight external rotation of the hip and flexion of the knee, the latter of which allows access to the popliteal vein from the posterior approach. A linear transducer with a broadband frequency in the range of 5–10 MHz is usually employed for the assessment of lower extremity and upper extremity veins. Some anatomic locations require the use of lower frequencies within this range, especially in patients with large body habitus.

Examination standardization is of paramount importance, not only to improve diagnostic accuracy, but also to enable comparison with prior imaging studies, whether or not they have been performed at the same institution. Standards and guidelines for the duplex assessment of acute venous disease may be found from the Intersocietal Accreditation Commission (IAC) for vascular testing.[15] Venous segments are examined for thrombosis or patency using the following criteria: (1) venous compressibility (or coaptation); (2) spectral Doppler waveform assessments of spontaneous venous flow, phasic flow, or flow with distal augmentation; and (3) thrombus visualization. Not all of these criteria are applicable to all venous segments.

Compressibility of the vein should be assessed with transverse grayscale imaging at the saphenofemoral junction, as well as the common femoral, femoral (proximal,

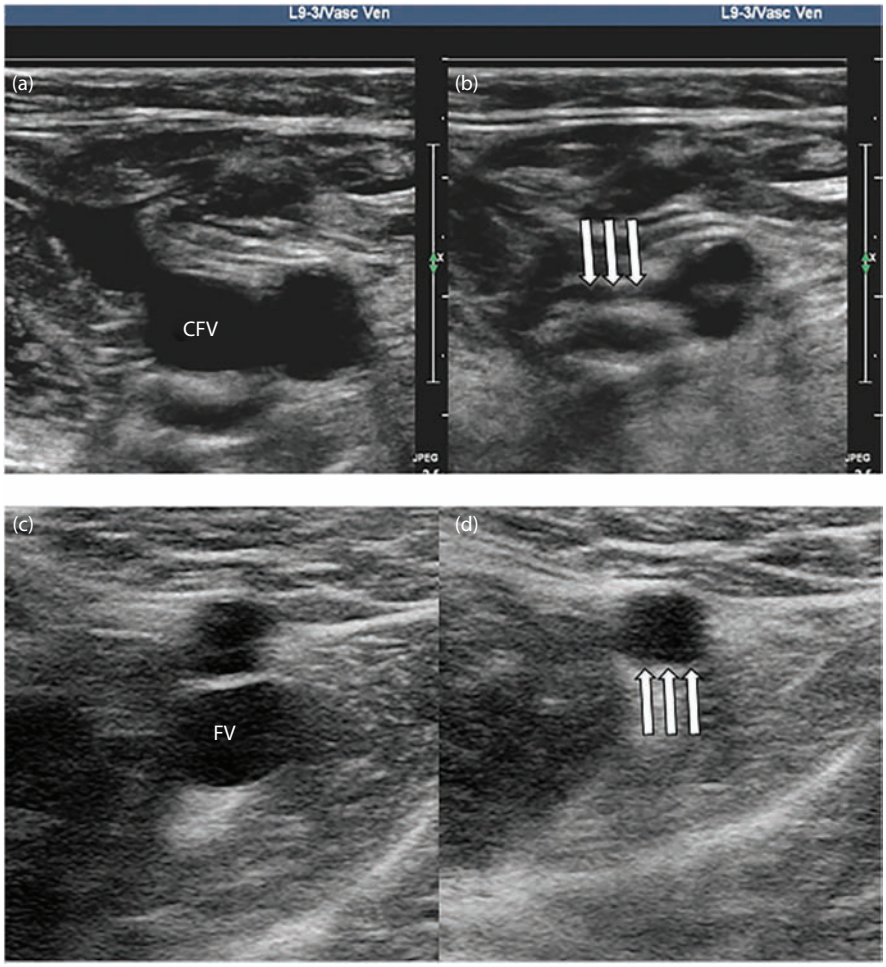

Figure 12.2 Transverse grayscale image of the left common femoral vein (CFV) at the saphenofemoral junction without compression **(a)** and with compression **(b)**. Similar grayscale image of the left femoral vein (FV) without compression **(c)** and with compression **(d)**. The white arrows indicate the locations of the compressed veins.

mid, and distal), popliteal, posterior tibial, and peroneal veins (Figure 12.2). The IAC Standards and Guidelines include Doppler waveform assessment of the common femoral and popliteal veins at a minimum. Our institutional protocol adds an evaluation of the great saphenous veins for compressibility, and Doppler assessment of deep femoral, femoral, posterior tibial, and peroneal veins for the evaluation of phasic flow or flow in response to distal augmentation (Figure 12.3). The superficial veins (varicose and small saphenous) and muscular veins of the calf (gastrocnemial and soleal) should also be imaged if the patient's symptoms warrant further examination. The anterior tibial veins are excluded from most routine venous duplex studies due to their small size and relatively low likelihood of anterior tibial DVT (1%).[16]

Thrombus visualization is accomplished with both B-mode and color flow imaging, allowing for direct visualization of occlusive and non-occlusive thrombus as well (Figure 12.4). B-mode imaging is useful when evaluating the degree of echogenicity within a visualized thrombus, the thickness of a vein wall, and the size of the vein (contracted versus dilated), with a hyperechoic thrombus, a thickened vein wall, and a contracted vein suggesting a more chronic process. Doppler and color flow assessment are typically performed with the probe oriented longitudinally, with color sensitivity set for low flow and proper Doppler angulation.

12.3.2 Iliac vein and inferior vena cava examination

Any suggestion of DVT extending above the inguinal ligament should warrant evaluation of the iliac veins and inferior vena cava (IVC). This includes direct evidence such as visible thrombus above the common femoral vein, and indirect evidence such as continuous flow in the common femoral vein with a lack of respiratory variation, suggesting proximal venous obstruction. Sonographic evaluation of these deeper structures usually requires lower-frequency abdominal probes, ranging from 2.0 to 5.0 MHz. Optimal visualization of the IVC and iliac veins may require positioning in the supine, semi-right lateral, or semi-left lateral decubitus positions, with the patient fasting for at least 6 hours prior to the duplex scan. Iliac veins and the IVC are

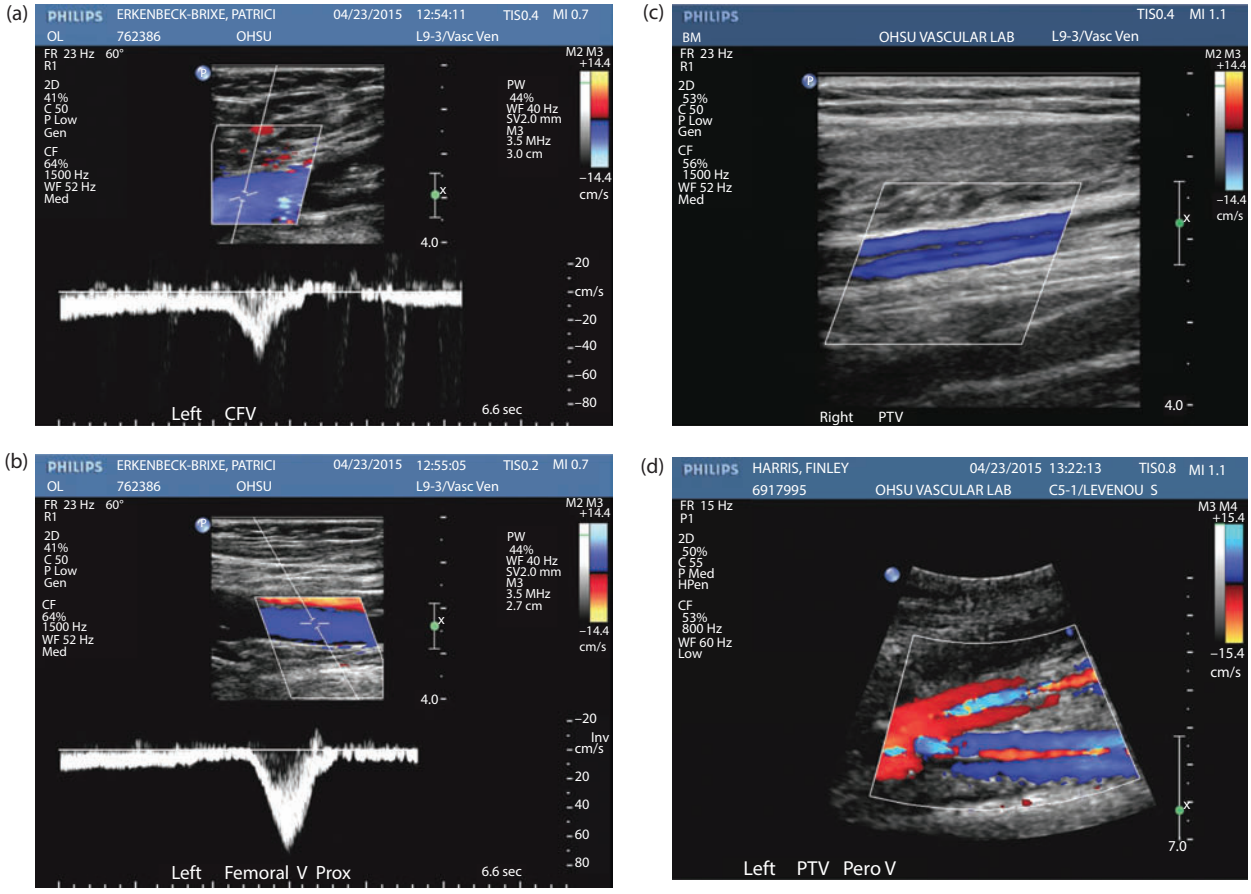

Figure 12.3 Doppler waveform assessment of the common femoral vein **(a)** and femoral vein **(b)** in response to distal augmentation. Tibial veins often are smaller and multiple, and assessment is usually made with B-mode imaging and color flow. Color flow at the posterior tibial vein **(c)** and at the confluence of the posterior tibial and peroneal veins **(d)**. In **(d)**, the paired peroneal veins demonstrate an opposite color flow signal (red) to the paired posterior tibial veins (blue) due to the angle of the veins in relation to the transducer.

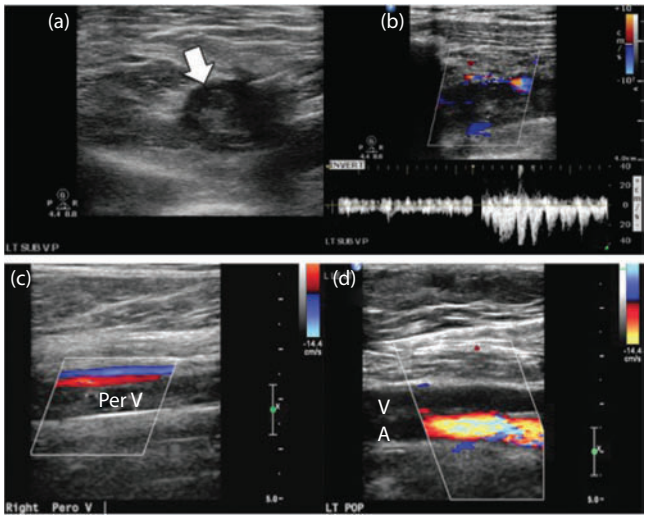

Figure 12.4 Representative images demonstrating thrombus visualization in the subclavian vein with B-mode imaging **(a)** and color flow **(b)**. Color flow of one of two paired peroneal veins demonstrates a sizable peroneal deep vein thrombosis **(c)**. Color flow imaging of the popliteal artery (A) and vein (V) show absent flow in the popliteal vein **(d)**.

too deep to compress, and the imaging evaluation is typically limited to the Doppler flow evaluation in combination with color flow imaging.

12.3.3 Upper extremity venous examination

Duplex examination of the upper extremity veins is more challenging than that of the lower extremity veins. The mid-portion of the subclavian vein is partially obscured by the overlying clavicle, and the innominate vein is obscured at the thoracic inlet. The examination is started with the patient in the supine position, with the examined arm abducted and externally rotated in order to facilitate access to the axillary and brachial veins. The head is rotated away to allow imaging of the ipsilateral internal jugular vein. A 5–10-MHz probe is utilized for the upper extremity veins, with curved probes being reserved for larger patients, especially in the region of the axilla.

Assessment for upper extremity venous thrombosis and patency is similar to that of the lower extremity. The IAC standards include transverse grayscale imaging for compressibility of the internal jugular, subclavian, axillary,

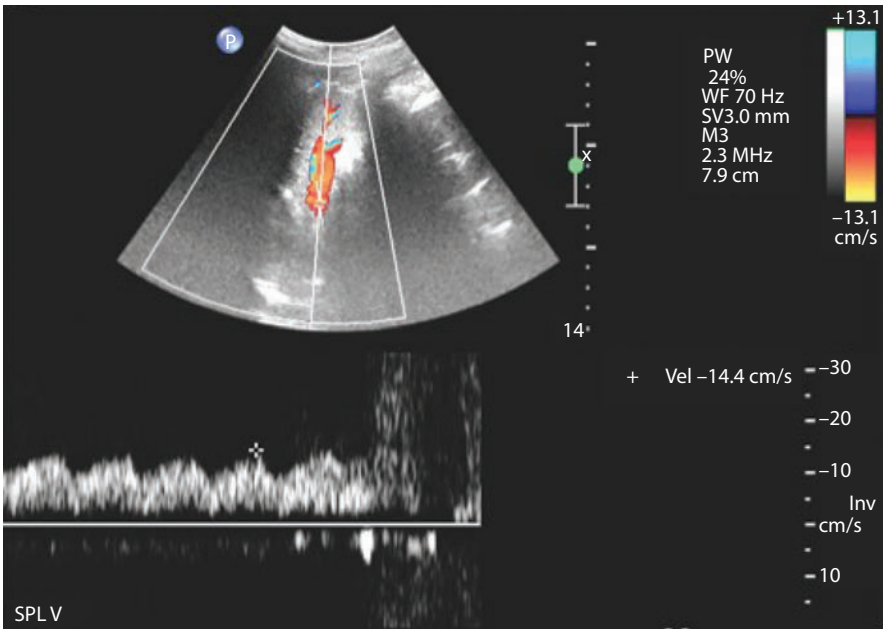

Figure 12.5 Doppler waveform of the portomesenteric venous circulation (splenic vein depicted), demonstrating continuous flow with a mildly pulsatile waveform.

brachial, basilic, and cephalic veins, with additional assessment of antecubital and forearm deep veins if symptoms suggest thrombosis.[14] Spectral Doppler waveform assessments for spontaneous and phasic flow, and/or flow with augmentation, are usually performed with longitudinal views of the ipsilateral internal jugular and axillary veins and bilateral subclavian veins (Figure 12.3). In contrast to the lower extremities, upper extremity venous phasic flow is more pronounced during inspiration.

12.3.4 Porto-mesenteric and hepatic venous examination

Ultrasound diagnosis of porto-mesenteric venous thrombosis was first reported in the late 1970s, and duplex assessment of the hepato-portal and mesenteric venous circulation is currently an important tool in the evaluation and follow-up of patients with liver disease.[17] Portal and mesenteric venous imaging is one component of a more comprehensive evaluation, which includes the intra- and extra-hepatic portal vein, superior mesenteric and splenic veins, hepatic veins, IVC, liver parenchyma, and any portosystemic shunts or collateral pathways.[15]

Scanning of the porto-mesenteric veins often requires the use of a curved abdominal transducer with a lower frequency range of 2–5 MHz for better tissue penetration, and visualization is improved when the patient has fasted for at least 6 hours. The sonographer should be familiar with the anatomic variations that occur, since they may be present in about 35% of patients. The most common variant is a trifurcation of the portal vein into right anterior, right posterior, and left portal branches.[18] Scanning often begins with the patient in the supine position, but may require left lateral decubitus positioning in order to obtain appropriate transabdominal, subcostal, and intercostal windows. The normal Doppler venous waveform in the portal venous circulation is described as a continuous flow with a mildly pulsatile waveform (Figure 12.5). Hepatic venous flow is multiphasic with an early retrograde component during atrial contraction and double peaked forward flow, which is affected by ventricular contraction and relaxation, tricuspid opening and closure, and respiration.[18]

12.4 ACCURACY AND OUTCOMES AFTER VENOUS DUPLEX SCANNING

The accuracy of venous duplex imaging for lower extremity DVT varies depending on the presence or absence of symptoms and the anatomic location of the thrombosis (Table 12.3).[19] In a large meta-analysis, duplex imaging for patients with symptomatic DVT was associated with a significantly higher sensitivity (89%) when compared to asymptomatic patients (47%). However, the specificities remained equivalent between the two groups (94%).[19] With regard to location, the duplex detection of isolated calf vein thrombosis was less sensitive than for proximal veins of the lower extremities.

The accuracy of ultrasound in other anatomic locations is not as well known, typically being based on data from the 1990s. Based on limited information, venous duplex scanning of the IVC and iliac veins is less sensitive than computed tomography (CT) or magnetic resonance imaging in

Table 12.3 The sensitivity and specificity of venous duplex diagnosis of deep vein thrombosis for symptomatic and asymptomatic patients, categorized according to anatomic venous beds

Venous bed	Sensitivity	Specificity
All lower extremity deep vein thrombosis[a]		
Symptomatic patients	89%	94%
Asymptomatic patients	47%	94%
Proximal lower extremity veins[a]		
Symptomatic patients	97%	
Asymptomatic patients	62%	
Isolated calf lower extremity deep vein thrombosis[a]		
Symptomatic patients	73%	
Asymptomatic patients	53%	
Inferior vena cava and iliac veins[b]	46%	100%
Portal veins[c]	89%	92%
Upper extremity veins[d]	78%–100%	82%–100%

[a] Kearon C et al. *Ann Intern Med* 1998;128:663–77.
[b] Laissy JP. *Am J Roentgenol* 1996;167:971–5.
[c] Tessler FN et al. *Am J Roentgenol* 1991;157:293–6.
[d] Sajid M et al. *Acta Haematol* 2007;118:10–18.

detecting proximal thrombosis.[20] Data regarding the accuracy of portal venous duplex imaging also come from single-institution studies, with results shown in Table 12.3.[21] More information is available regarding the duplex diagnosis of upper extremity DVT, since this modality has largely replaced venography and CT angiography for the majority of patients with suspected upper extremity venous thrombosis. The sensitivity of upper extremity venous duplex imaging ranges from 78% to 100%, and specificity ranges from 82% to 100%.[22–24]

These accuracy studies differ significantly from "management studies," in which patients who test negative for DVT and in whom anticoagulation is withheld are followed for the development of subsequent VTE. The previously mentioned meta-analysis demonstrated that patients who test negative on venous duplex imaging have a consistently low rate of developing confirmed VTE (2.0%) during an average of 6 months of follow-up.[19]

12.5 CONTROVERSIES IN DUPLEX SCANNING FOR ACUTE VENOUS DISEASE

12.5.1 Whole-leg versus proximal venous duplex

The arguments for performing a whole-leg venous duplex versus a more limited assessment of the proximal veins (femoral and popliteal) are related to numerous factors, which include not only the clinical decision regarding therapeutic anticoagulation for a patient with an isolated calf DVT, but also the sensitivity and specificity of calf venous duplex, the pre-test probability of DVT, and the D-dimer assay. In the past, patients with an isolated calf DVT did not routinely receive therapeutic anticoagulation. However, the more recent 2012 ACCP Guidelines suggest therapeutic anticoagulation for 3 months (versus shorter duration) in patients with isolated distal DVT provoked by surgery or a non-surgical transient risk factor. The Guidelines also recommend anticoagulation for at least 3 months in patients with an unprovoked DVT (including isolated distal DVT).[25] Therefore, whole-leg venous duplex imaging may significantly affect the decision regarding antithrombotic therapy.

Another argument in favor of performing a whole-leg venous duplex is the relative simplicity of the diagnostic algorithm: a technically adequate whole-leg ultrasound that is negative for DVT leads to no further treatment or testing, and a test that is positive for proximal DVT leads to anticoagulation therapy. In a whole-leg scan that is positive for isolated distal DVT, the clinician must decide between a follow-up duplex scan (in approximately 1 week) versus therapeutic anticoagulation.[13] In contrast, the ACCP diagnostic algorithm for patients who receive a limited proximal venous duplex is more complicated. A scan that is positive for proximal DVT would lead to anticoagulation, whereas the ACCP Guidelines suggest that a limited proximal venous duplex that is negative for DVT should be followed by one of the following: whole-leg venous duplex; repeat imaging in 1 week; D-dimer assay; or conventional venography. Based on the more efficient algorithm associated with a whole-leg venous duplex (as shown in Figure 12.6), we favor this study.[26]

12.5.2 Unilateral versus bilateral venous duplex imaging

Bilateral venous duplex scans are performed frequently, even when patients present with unilateral signs and symptoms. One rationale for routine bilateral scanning is the concern for silent contralateral DVT. Among patients who are diagnosed with an ipsilateral DVT, the reported rate at which a contralateral DVT is identified ranges from 3.6% to 29%.[27–30] However, a smaller number of patients are diagnosed with an asymptomatic contralateral DVT in the absence of an ipsilateral thrombosis (<1%).[24,26,27] Thrombi from a contralateral asymptomatic DVT are more likely to be chronic, more likely to occur in hospitalized patients, and are associated with active malignancy.[24,25]

Although unsuspected bilateral DVT is a fairly common finding in patients with unilateral symptoms, some authors have recommended that routine bilateral duplex scans should be avoided, since the vast majority of these patients would not have required any change in the management of

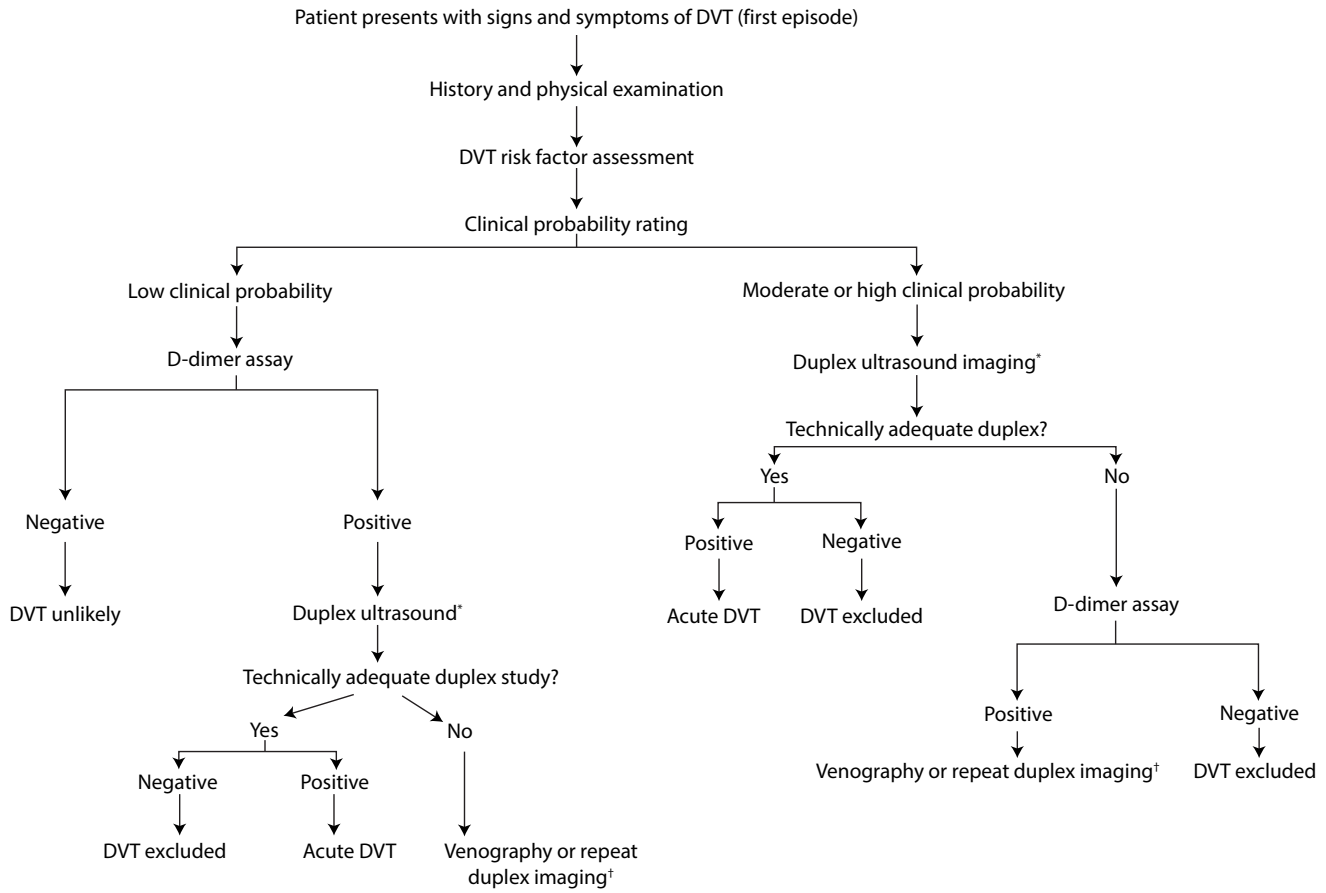

Figure 12.6 Diagnostic algorithm using clinical probability testing, D-dimer assay, and whole-leg venous duplex scanning. * Whole leg duplex imaging; † contrast venography or magnetic resonance venography. (From Zierler BK. *Circulation* 2004; 109(Suppl. I):I-9–I-14.)

their antithrombotic therapy.[24] Others have recommended bilateral scanning in patients with active malignancy[25–27] or in hospitalized patients,[26] since the rate of contralateral thrombosis in these patient subgroups is significantly higher than in the outpatient setting (34% versus 16%) or in patients without cancer (38.3% versus 12%). Of concern with this rationale is that the absence of these clinical risk factors (inpatient setting and malignancy) is still a relatively poor negative predictor for excluding contralateral DVT. Scanning the contralateral asymptomatic limb, at least at the initial duplex scan, does provide the clinician with useful baseline information, since the rate of recurrent VTE can be greater than 30%.[31]

12.5.3 Scanning for residual venous obstruction to guide antithrombotic therapy

The presence of residual venous obstruction (RVO) at the time of discontinuing anticoagulation has been shown by some authors to correlate with recurrent VTE, making it a potential tool to help optimize the duration of therapy.[32] However, the data regarding RVO are inconsistent, and significant disparities remain with regard to the definition of RVO.[33,34] A recent patient-level meta-analysis demonstrated a mild association between RVO and VTE recurrence (hazard ratio: 1.32), present only within the first 3 months following a diagnosis of DVT.[35] Without a more definitive relationship, most validated VTE recurrence prediction models exclude RVO as a factor.[36] That being said, a follow-up baseline venous duplex of the affected limb at the time of discontinuing anticoagulation does help clinicians interpret subsequent duplex scans regarding questions of recurrent VTE.[37]

12.6 CONCLUSIONS

Venous duplex scans play a critical role in the diagnosis of acute venous thrombosis. In general, they have a high rate of accuracy and a very low rate of complications. However, imaging should be performed for appropriate indications, and may be more useful when used in combination with pre-test probability scoring and D-dimer analysis. In patients with established DVT, follow-up duplex imaging at the time of discontinuing therapy is likely to be useful for subsequent comparisons, especially since the rate of recurrent VTE remains significant.

Guidelines 2.2.0 of the American Venous Forum on duplex ultrasound scanning for acute venous disease

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
2.2.1	Duplex ultrasound scanning is recommended to be the standard of care for diagnosing acute deep vein thrombosis (DVT) of the limbs.	1	A
2.2.2	We recommend that duplex examination for DVT includes three components in each vein segment studied: thrombus visualization, venous coaptability or compressibility, and detection of venous flow.	1	A
2.2.3	We recommend that duplex scanning has a sensitivity of ≥90% for the detection of symptomatic femoropopliteal thrombosis and a range of 50%–70% for calf vein thrombosis.	2	B
2.2.4	We recommend that duplex scanning for upper extremity DVT has a sensitivity of between 78% and 100% and a specificity of between 82% and 100%.	2	B

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● = Key primary paper
★ = Formal publication of a management guideline

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13

Duplex ultrasound scanning for chronic venous obstruction and valvular incompetence

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13.1 INTRODUCTION

Venous obstruction and reflux are the two pathologies that lead to venous hypertension, which causes the sequelae of chronic venous disease (CVD). Despite the high prevalence of CVD and the number of studies that have been performed in this area, the etiology of CVD is poorly understood. The challenge to the clinician is to find a method of reliably evaluating a patient for CVD. The physical examination is useful. Many of the signs and symptoms of CVD can be detected by physical examination, but physical examination alone is inadequate.

Phlebography, plethysmography, and duplex ultrasound (DUS) are the main methods for the evaluation of the venous system. Computed tomography and magnetic resonance imaging have also been utilized lately in CVD workups, especially in cases where iliocaval obstruction is suspected.[1] Plethysmography is used in the assessment of the amount of reflux, the efficiency of the calf muscle pump, and obstruction. Phlebography is used when there is a need for endovenous therapy and deep vein reconstruction. Plethysmography is also recommended in patients with advanced CVD if duplex scanning does not provide definitive information on pathophysiology.[1] DUS has become the test of choice for the evaluation of CVD in most patients as it is safe, noninvasive, cost-effective, and reliable. Although the evaluation of acute venous pathology has been discussed in Chapter 18, it must be mentioned that such pathology can recur in new or previously affected vein segments and can worsen the clinical severity of CVD.

The CEAP classification was developed by the American Venous Forum in 1994 and revised in 2004 to delineate the severity of CVD, improve standards of reporting, and develop treatment plans for the various stages of the disease.[2] It relies on the four components of clinical signs (C), etiology (E), anatomy (A), and pathophysiology (P). Recently, a more detailed venous score system, the Venous Clinical Severity Score (VCSS), has been utilized to grade the severity of CVD. The VCSS is composed of 10 categories which mainly consider the degree of pain, amount of varicose veins, skin damage, and the use of compression stockings. Both the physical examination and diagnostic tests are employed in order to report the patient's condition before and after treatment.

13.2 DUPLEX ULTRASOUND

The choice of the ultrasound probe is important. The pulse-wave Doppler of a 4–7-MHz linear array transducer is ideal for the examination of most veins. Other multi-frequency arrays can be used as well. The more superficial veins can be evaluated using higher-frequency probes that give better resolution. The deep veins and veins in obese patients are evaluated using a 3-MHz curvilinear probe that provides better depth of penetration. Lower-frequency probes are also used to evaluate the venous system in the pelvis and abdomen. Curvilinear lower-frequency transducers should also be utilized whenever the depth of imaging is >6 cm (large limbs).

During imaging, low flow settings are most commonly used. The pulse repetition frequency (PRF) is set at 1500 Hz or lower. In cases of vein stenosis or arteriovenous fistula, the PRF is set higher, since the flow velocity is significantly elevated in such situations. The focus is set with the posterior wall (far wall in relation to the skin) to enable better lateral resolution in the field of imaging. The vein lumen should be set to appear dark in the absence of stasis and thrombosis. The time gain compensation is set according to the echogenicity and depth of the relevant tissues in order to perfect the imaging of the pertinent pathology. When obtaining velocity waveforms, the gain is set to have a dark background in order to avoid overestimation. If the signal is weak because of depth, the gain is increased accordingly. The angle of insonation in the venous system is often set at 0°. However, because most veins run parallel to the skin, if a precise velocity is needed, then the angle has to be corrected to be parallel to the flow channel.

The examination room conditions should also be conducive to obtaining optimal results. The room should be warm and comfortable and a warm gel must be utilized on the skin in order to ensure that there is no spasm of veins at the time of examination and that the veins are at their natural size.

13.3 OBSTRUCTION

Obstruction in the venous system can occur due to extrinsic and intrinsic pathologies. Tumors, hematomas, cysts, aneurysms, and musculoskeletal structures can cause extrinsic vein compression. However, the most common cause of obstruction is venous thrombosis. Its diagnosis is critical, as deep vein thrombosis (DVT) is obviously a significant cause of long-term morbidity and premature mortality in those afflicted with the disease.

The long-term consequences of DVT are devastating in terms of numbers and cost of care. Post-thrombotic syndrome (PTS) is a term that is used to describe the sequelae of CVD. The typical findings are pain, a burning sensation, itching, varicose veins, chronic limb swelling, skin discoloration, and ulceration. After a single episode of DVT, the incidence of PTS has been reported to range from 23% to 79%. A large prospective study showed an incidence of about 25% at 5 years.[3] Ipsilateral recurrent DVT has been shown to increase the odds for developing PTS by six times.[3] The sensitivity and specificity of DUS for identifying thrombosis is >95% proximal to the knee, whereas the accuracy may decrease in the below-knee segment.[4] The evaluation of functional obstruction cannot be achieved with DUS, as it assesses a single vein segment at a time. Unfortunately, it is difficult to measure functional obstruction, since there are no validated tests to quantify functional obstruction.

Duplex techniques for the evaluation of CVD are similar to those used in the evaluation of acute venous thrombosis. In chronic disease states, the major veins might be chronically obstructed. Collateralization and recanalization may also occur. The major veins are seen in immediate proximity to the corresponding artery. If a vein is seen more than 1 cm away from the artery, one must consider the possibility of a dilated collateral vein. Normal venous Doppler signals are obtained in cases where full recanalization has occurred or in the presence of duplicated veins that were unaffected by the thrombotic process. The popliteal vein is duplicated in 35%–40% of people and occasionally is triplicated. The femoral vein in the thigh is duplicated in about 25%–30% of people, and this duplication may have different patterns along the course of the vein. The veins in the calf are often paired around the corresponding artery. A single calf vein or a triplication may also be found. Aplasia of the posterior tibial veins has also been reported. In cases of venous duplication or aplasia, direct visualization, attention to detail, and experience with the ultrasound techniques are invaluable for reducing erroneous results. In patients with previous DVT, the technician has to be vigilant when scanning the previously affected and the contralateral limb for recurrence of DVT. Risk factors for recurrent DVT are previous ipsilateral DVT, age >65 years, residual thrombus, or previous iliofemoral involvement.[3,5] Knowing these risk factors aids the operator when carefully seeking signs of recurrent DVT, such as thrombus found in a new location, thrombus extending >9 cm further in the vein, a previously recanalized segment that is not compressible, and thrombus thickness ≥2 mm for calf veins and ≥4 mm for proximal veins.[6]

Venous ultrasound studies are reasonably well standardized. In brief, the patient is placed on the examination table in the reverse Trendelenburg position. The knee is bent and externally rotated. The examination is started below the inguinal ligament at the common femoral vein and saphenofemoral junction (SFJ). The probe is placed in transverse direction to the vein and compression is applied. The probe is then turned longitudinally to evaluate flow and augmentation. The veins are examined in 3–5-cm intervals. In a similar manner, all of the deep veins of the leg, including the femoral, deep femoral, popliteal, peroneal, soleal, gastrocnemial, and posterior tibial veins, are examined for obstruction. An examination of the anterior tibial veins is not routinely performed due to their low incidence of thrombosis, unless local symptoms or trauma to the anterior leg compartment area are present. The superficial veins, including the great saphenous vein (GSV) and small saphenous vein (SSV), are then evaluated. Finally, in cases of obstruction, it is important to check the iliac veins and the inferior vena cava (IVC). In abdominal and pelvic veins, mainly flow is evaluated, since compression can be difficult and uncomfortable for the patient. A normal venous flow is phasic with respiration and is augmented with distal compression or is stopped with the Valsalva maneuver. Asymmetry in flow velocity and waveform patterns at rest and during flow augmentation in the common femoral veins indicate proximal obstruction. However, the absence of such asymmetry does not exclude obstruction. Therefore, when iliocaval obstruction is suspected, the full extent of these veins must be imaged.

The presence of stenosis, usually from extrinsic compression, is recognized by a mosaic color pattern that denotes

post-stenotic turbulence, abnormal Doppler waveform at the area of stenosis, slow flow, spontaneous contrast, and vein dilatation prior to the stenosis.[7] The vein diameter reduction can be measured by planimetry, comparing the smallest lumen to the normal lumen. Peak vein velocity ratios comparing intra-stenotic to pre-stenotic peak velocities or comparing post-stenotic to pre-stenotic peak velocities can be calculated. In patients with a pressure gradient across the stenosis ≥3 mmHg, the peak systolic velocity (PSV) ratio has been shown to be >2.5. This is particularly useful when investigating central vein stenosis.[7]

The four components that should be examined in all venous duplex examinations are visualization, compressibility, flow, and augmentation. There are ways to potentially distinguish acute obstruction from chronic obstruction (Table 13.1). The veins with acute thrombosis are echolucent, distended, and have smooth walls. In chronic thrombosis, the veins are echogenic, contracted, and have thick, irregular walls (Figure 13.1). Acute thrombus is "spongy" on compression examination, but will still keep the walls of the vein from coapting with probe compression. On the color flow examination, acute thrombus will have confluent flow channels. Chronic thrombus will either have multiple channels or collateralization. Intraluminal webs and wall thickening, with or without reflux, indicate a previous thrombosis in the absence of visible thrombus. The presence of dilated collateral veins indicates the presence of obstruction, but unfortunately, their absence cannot exclude it. It is also possible for the veins to be fully recanalized without any evidence of anatomic obstruction. However, the thickening and increased stiffness of the vein wall can still result in functional obstruction.

Signs and symptoms in both lower extremities are present when there is bilateral iliac vein obstruction or when the IVC is involved. The iliac veins and IVC may have extrinsic compression from masses (Figure 13.2). The extrinsic compression can lead to signs and symptoms of CVD. In such patients, thrombosis of the compressed vein is a common event.

13.4 REFLUX

Venous reflux is the reversal of flow in the veins of the lower extremity. The reversal of flow in the vein can be subdivided into physiologic and pathologic. Physiologic reversal of flow accounts for the fraction of the second it takes for the valve leaflets to appose. A prospective study has demonstrated that the acceptable physiologic reversal of flow is different for various venous systems in the lower limb.[6] The cut-off value for reflux, in the authors' experience, in the common femoral, femoral, and popliteal veins is >1000 ms. For the superficial, deep femoral, deep calf axial, and muscular veins, the value is 500 ms, and in the perforating veins (PVs) it is 350 ms. It is postulated that in the larger veins with fewer valves, the time it takes for the valve leaflets to come together is longer in comparison to smaller, shorter veins. A recent multicenter prospective study has determined that a reflux of ≥0.5 seconds is accepted as abnormal.[8] Different patterns of reflux are displayed in Figure 13.3.

It is important to differentiate between primary, secondary, and congenital reflux. This classification is based on the pathophysiology of the reflux. Congenital reflux exists at birth, but is rarely recognized early, since there is a lag in the presenting signs and symptoms. Secondary reflux is most often the result of thrombosis. The most common type of reflux is primary, where the cause has not been determined. A study that has used the CEAP classification to investigate the causes of CVD showed that congenital reflux accounts for 1%–3% of CVD, secondary reflux accounts for 18%–28% of CVD, and primary reflux accounts for 64%–79% of CVD.[9]

Table 13.1 Duplex ultrasound criteria used to differentiate acute versus chronic obstruction

Criterion	Acute (days to weeks)	Subacute (weeks to months)	Chronic (months to years)
Size	Distended	No longer distended due to lysis	Reduced; sometimes unable to be traced by duplex ultrasound
Echogenicity	Echolucent: acute thrombi	Moderate echogenecity	Echogenic: as the clot ages, dense material, increased cellular components, fibroblasts, and collagen deposits form.
Lumen characteristics	The lumen is not present or only partially present	Recanalization with adherence	Partial recanalization with compressible filling, often has residual thrombus or vein wall defects, and reflux may have a spongy feel on compression
Wall characteristics	Thin and smooth	Thickened	Thickening with luminal reduction due to inflammatory response to the thrombus
Flow characteristics	Absence of flow/ fillings defects	Partial recanalization	Partial recanalization with reflux. Enhanced flow in dilated collateral veins
Thrombus characteristic	–	Presence of tail	Decreased linear extension of thrombus
Collateral veins	Absent	May be present	Often found around the obstructed segments

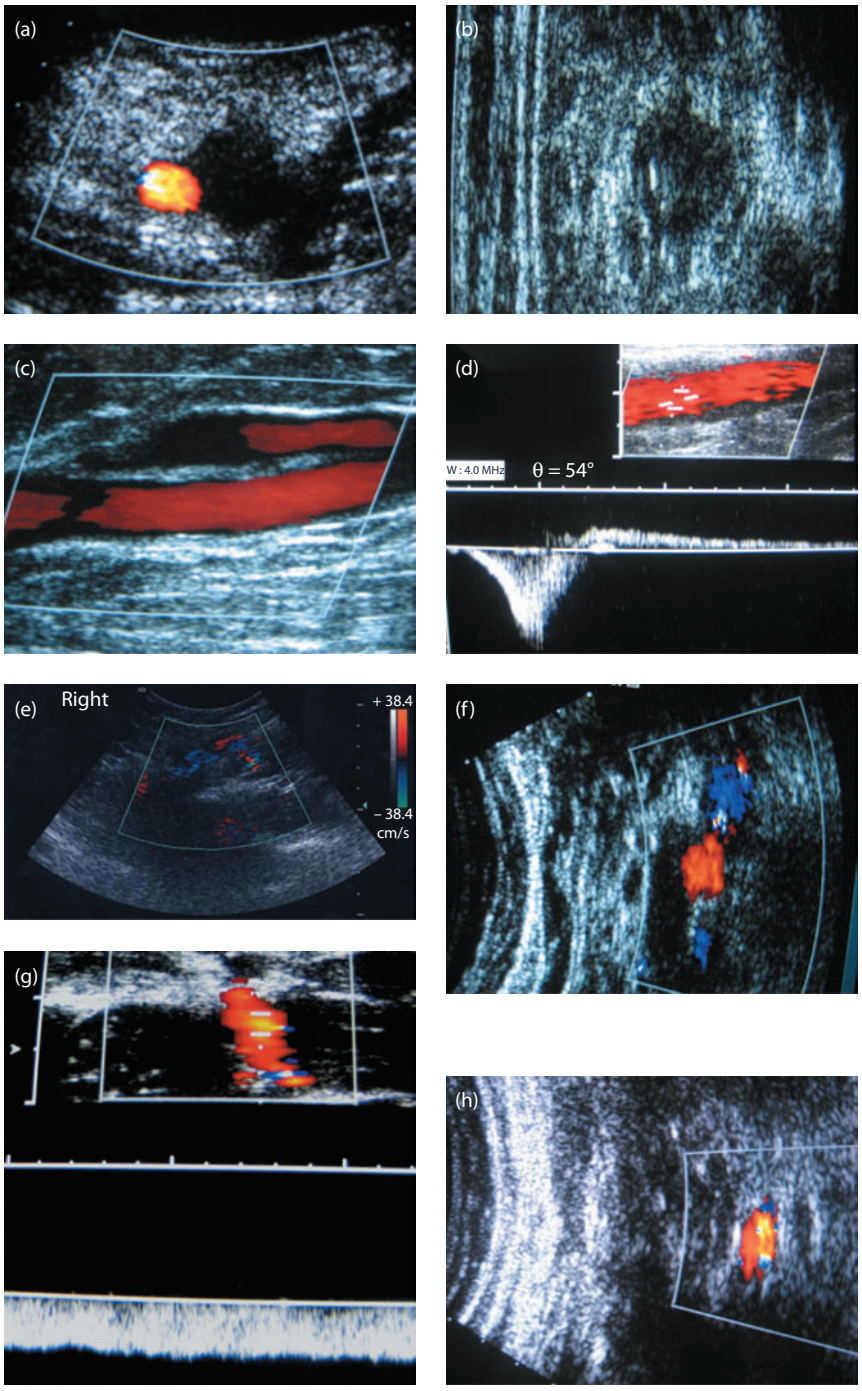

Figure 13.1 **(a)** Acute thrombosis in the common femoral vein. There is absence of color, the vein is dilated (twice the size of the adjacent common femoral artery in red) with a homogeneous echolucent texture. **(b)** Acute on chronic thrombosis in the soleal vein in a patient with recent calf pain. The vein is dilated and has echogenic material (old thrombus), and echolucent material (fresh thrombus). **(c)** Chronic thrombus with partial recanalization in the great saphenous vein. Flow channels with reflux are seen over the old thrombus that appears as an echogenic band in the lumen. **(d)** Complete recanalization with prolonged reflux in the popliteal vein. Thickening is seen in the far wall. **(e)** Chronic iliofemoral occlusion with collaterals from the inferior epigastric and internal iliac veins. **(f)** Chronic IVC obstruction with partial recanalization. The lumen of the IVC is smaller than the adjacent aorta. The azygos vein is dilated and larger than the aorta. **(g)** Nonphasic flow in a groin collateral in a patient with iliofemoral occlusion. **(h)** Chronic occlusion of the external iliac vein in a female patient who underwent stenting for previous thrombosis. Flow is seen in the adjacent artery. The vein has a small diameter and echogenic material in the lumen. The stent is seen in both the near and the far wall as an echogenic rim between the wall and the thrombus.

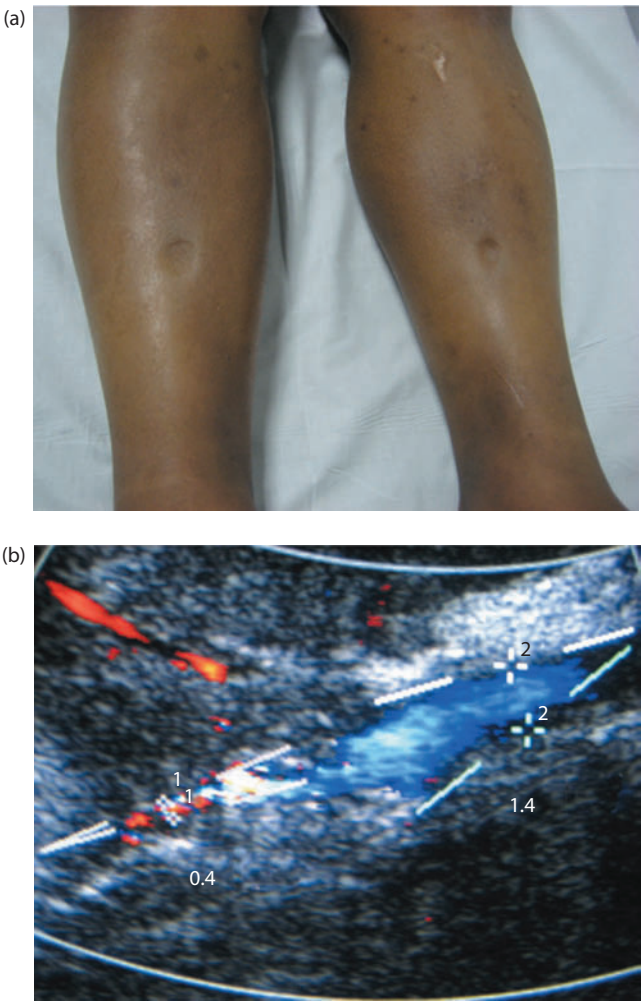

Figure 13.2 **(a)** Bilateral swelling in a patient with inferior vena cava (IVC) compression. Notice the pitting edema in both limbs after digital compression over the tibia. **(b)** Compression of the IVC by a tumor at the level of the liver. The lumen of the IVC at the site of compression measured 0.4 mm whereas the normal distal segment measured 1.4 mm. The color changes from blue in the normal portion of the IVC to white at the area of compression indicating significant vein stenosis.

13.5 TECHNIQUE

Reflux can be elicited in two ways. During the Valsalva maneuver, the intra-abdominal pressure is increased, and this can lead to reversal of flow if there is valvular incompetence. This technique is mainly useful in the evaluation of valves in the groin, as competent valves proximally will limit its usefulness.

Compression and release distal to the point of examination on the limb is a reliable method of evaluating reflux, and is referred to as augmentation. With compression there is an initial increased flow in the vein as the blood is pushed in the normal direction of flow from distal to proximal. Once the pressure is released, the blood flow reverses momentarily. If there are competent valves, there is minimal to no back flow. However, with incompetent valves, the blood continues to flow in the reverse direction. For the purposes of more precise measurement and standardization, the use of automated pneumatic cuffs with rapid inflation and deflation is essential. The cuff is placed around the leg 5 cm below the probe site. A 24-cm cuff is used around the thigh, a 12-cm cuff around the calf, and a 7-cm cuff around the foot. The inflation lasts for 3 seconds followed by rapid deflation in 0.3 seconds. To ensure complete venous emptying and to overcome the hydrostatic pressures from above, thigh cuffs are inflated to 80 mmHg, those on the calf to 100 mmHg, and 120 mmHg is required for foot cuffs. Occasionally in patients with significant edema, the above techniques are inadequate and dorsiflexion/plantar flexion is also used.

To obtain the best results, the examination should start with the patient in the standing position, with the weight of the patient on the contralateral limb. The limb of interest should be slightly flexed and externally rotated. If a patient is unable to stand for the time required, the veins from the mid-thigh and below can be assessed in the sitting position. If the test is performed on a bed, the torso should be elevated to >45°. A tilt-table with a leg rest to keep weight on the contralateral limb and reflected backwards into a 60° position is another technique that can be used for reflux measurements.

The routine examination of the veins of the lower extremity starts at the common femoral vein above the junction of the femoral and deep femoral veins. The SFJ at the terminal and pre-terminal valve and the associated tributaries are examined next. This is followed by the popliteal and the deep calf veins. The GSV, SSV, their tributaries, and non-saphenous veins are examined in detail, as these are the most common sites of reflux. Reflux in veins that are not part of the GSV or SSV system are found in about 10% of the patients. Veins of interest involved in non-saphenous vein reflux are the gluteal vein, postero-lateral thigh PV, vulvar vein, lower posterior thigh vein, popliteal fossa vein, knee perforator vein, and sciatic nerve vein.[10] The GSV can be identified and differentiated from other superficial veins because it is surrounded by two layers of fascia in the saphenous eye.[11] The SSV is found in the triangular fascia and is surrounded by the crural fascia and the medial and lateral heads of the gastrocnemius muscle.[12] The tributaries of the superficial veins that are often incompetent in the thigh are the anterior and medial accessory veins, and in the calf they are the posterior and anterior arch veins. These veins should be examined along their full length if they are incompetent.

Duplication of the saphenous veins is rare, reflecting <3% of patients with CVD.[12] The most common anatomic variations of the saphenous veins are segmental hypoplasia and aplasia.[13] Accessory veins ensuring good venous drainage are frequently found close to such segments.[13]

PVs are the last to be examined. They can be distinguished from the superficial and deep veins since they course perpendicular to these veins and pierce the deep fascia. The deep fascia is dense and echogenic and can

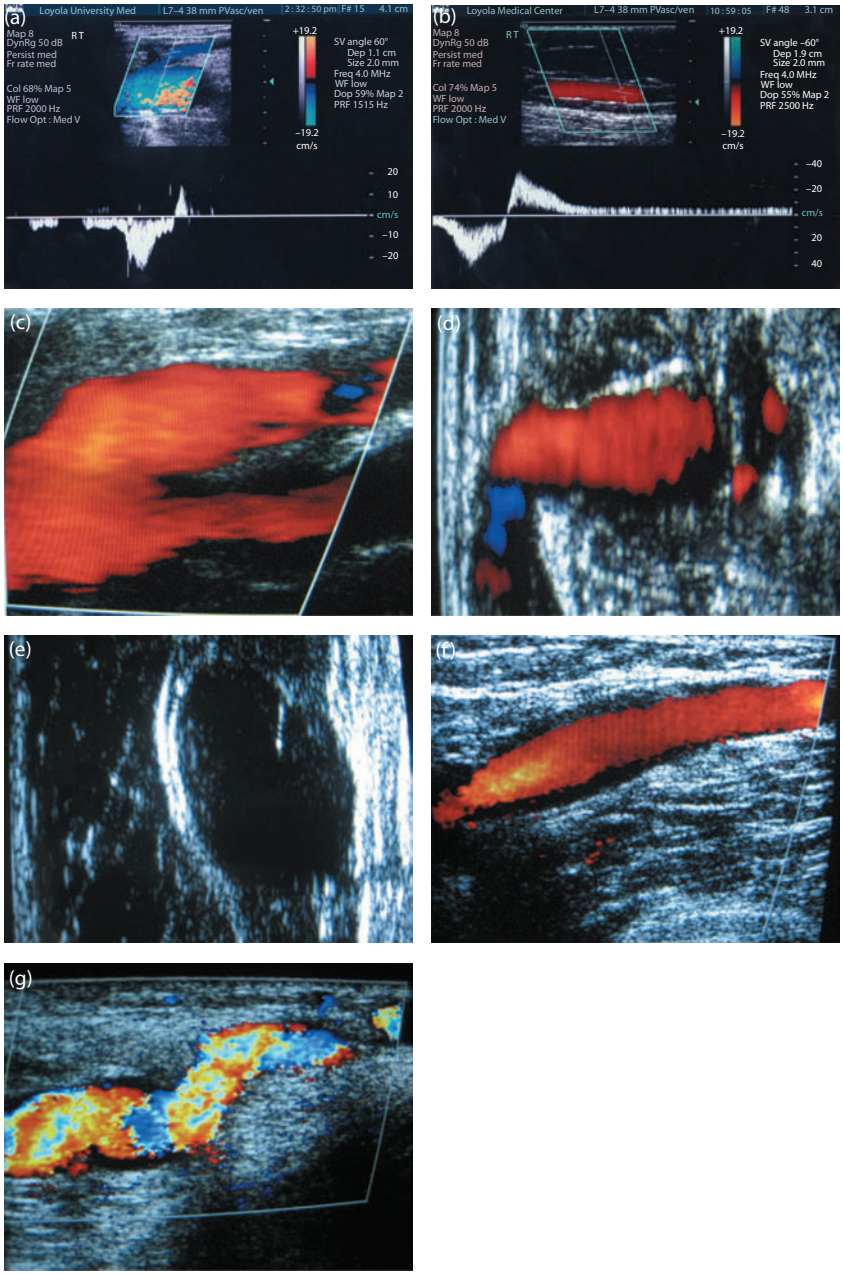

Figure 13.3 **(a)** Normal saphenofemoral junction. During distal augmentation there is flow towards the heart (negative deflection as blood traveling away from the transducer). After release of the compression there is a short duration of retrograde flow until the valve is closed. **(b)** Prolonged reflux in the great saphenous vein (GSV) below the knee. The vein has a normal diameter indicating that a vein does not have to be dilated when it is incompetent. This patient had asymptomatic CEAP class 2 disease. **(c)** Reflux in the popliteal, medial gastrocnemial, and small saphenous vein (SSV). This patient had a chronic thrombosis that was fully recanalized. He presented with CEAP class 4 and had pain and itching. **(d)** Reflux in a lower calf medial perforator in a patient with a healed ulcer (C5). The vein was dilated (>6 mm) and had prolonged outward flow. **(e)** Cross-sectional view of a focal dilation in the lower thigh GSV with a frozen valve seen at the 4 o'clock position. **(f)** Dilation of the SSV in the upper calf with wall thickening in a patient with skin changes, edema, and varicose veins in the posterior calf. The diameter of the SSV measured 8 mm and the reflux duration was longer than 5 seconds. **(g)** Prolonged reflux from the medial gastrocnemius vein (GV) to the SSV. The SSV was incompetent from its junction with the gastrocnemial vein at mid-calf to the lateral malleolus. The proximal SSV was normal.

be easily visualized on an ultrasound scan. There are approximately 150 PVs in the lower extremity, of which only 20 are of clinical significance in terms of reflux possibly leading to clinical pathology. The normal direction of flow is from the superficial to the deep veins through the PVs. These veins are examined using transverse and oblique scanning, since their long axes are seen in these planes. They are found by following the course of the GSV,

the SSV, and the tributaries. Outward flow in these veins is seen only in the presence of superficial and deep vein reflux. Based on the current Society for Vascular Surgery and American Venous Forum guidelines for the care of patients with CVD, duplex scanning of the PVs should be performed selectively.[1] PVs are deemed to be "pathologic" when an outward flow of duration of ≥500 ms, a diameter of ≥3.5 mm, and a location beneath healed or open venous ulcers (CEAP class C5–C6) are present.[1] These guidelines aid physicians in making their decisions on whether or not PVs need to be treated.[1]

The results of an ultrasound examination in patients with CVD are often depicted in drawings. An example of this is given in Figure 13.4. The left and right lower extremities have been drawn to scale and have skin, muscular, and bony landmarks such as the popliteal skin crease, sartorious muscle, knee, and medial malleolus. Such drawings enable better understanding and interpretation of the findings and therefore facilitate the planning of treatment in each limb.

13.6 ROLE OF DUS IN UNDERSTANDING THE PATHOPHYSIOLOGY OF CVD

The majority (70%–80%) of patients presenting with CVD are symptomatic. These symptoms include itching, ache, restless limb, heaviness, burning, and ulceration. Varicose veins and telangiectasias are present in 80% of patients. Skin changes of some sort are seen in 20%–25%, and active or healed ulcerations in 12%–14% of patients with CVD (Figure 13.5). Patients with C1 and C2 disease have reflux confined to the superficial system. As the clinical severity worsens (C3–C6), the prevalence of incompetence in the perforator and deep veins increases. In limbs with CVD, reflux alone exists in 80% of patients, reflux and obstruction are present in 17% of patients, and only 2% of patients have obstruction alone.[9] In addition, the combination of reflux and obstruction has a worse prognosis for the development of skin lesions.[3]

The most common location of reflux in patients with CVD is the saphenous vein trunks and their tributaries, irrespective of clinical class. These veins are affected in 90%

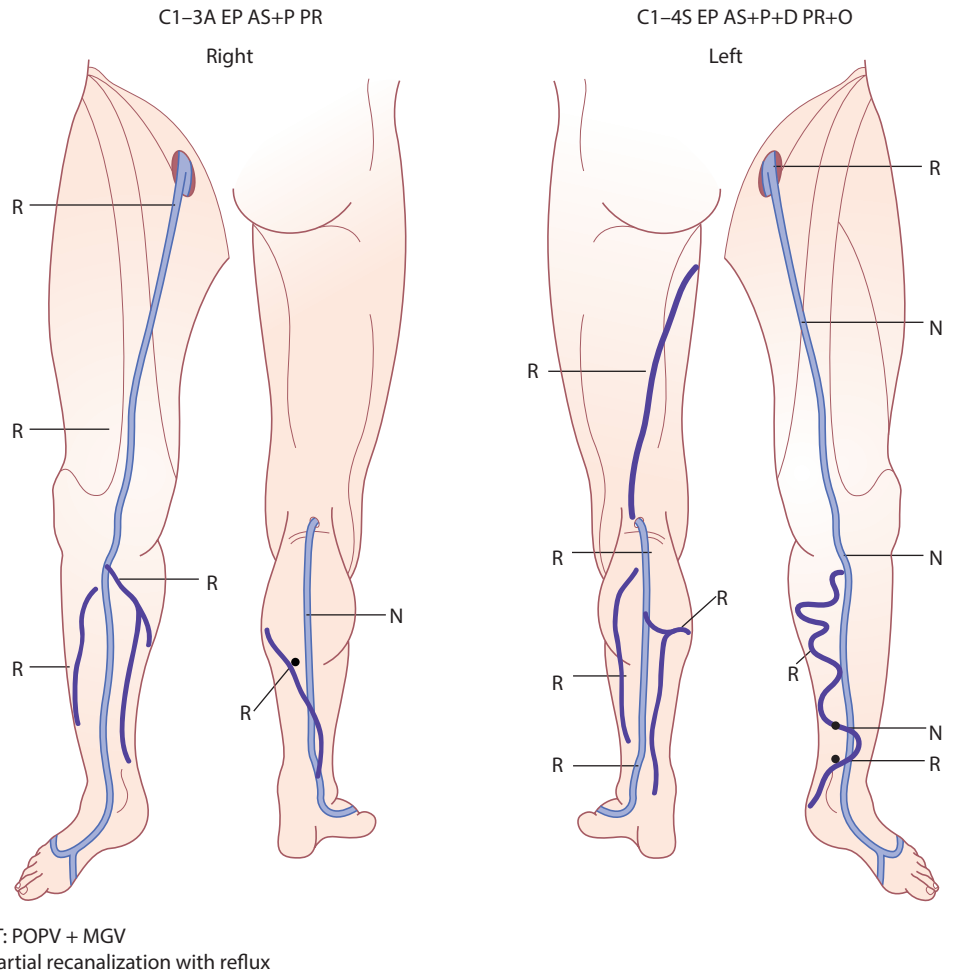

Figure 13.4 Report of a duplex ultrasound examination in a patient with bilateral chronic venous disease (CVD). She was a 53-year-old female with two pregnancies and a positive family history of CVD in both parents. She noticed signs and symptoms of CVD after her second pregnancy, first in the left lower extremity and 2 years later in the right lower extremity. She had also developed thrombosis in the left lower extremity 7 years previously. LT, left; MGV, medial gastrocnemius veins; N, no reflux; POPV, popliteal vein; and R, reflux.

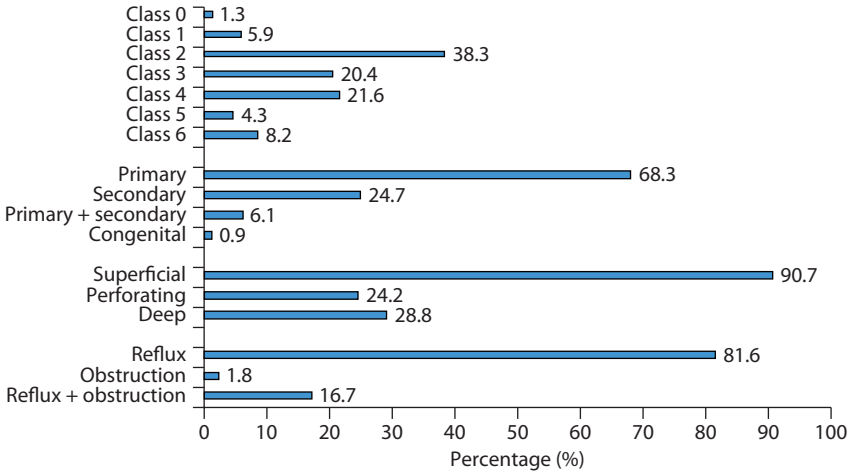

Figure 13.5 Presentation of 1000 consecutive limbs with chronic venous disease according to the CEAP classification.

of patients. Of the superficial veins, the GSV is involved in 70%–80% of cases, the SSV is involved in 15%–20%, and non-saphenous veins are involved in about 10%. The deep system is only affected in 30% of patients with CVD, and the PVs in 20%.[9] Complex patterns of reflux are present in patients with skin damage.[14] Several studies have demonstrated that reflux in the superficial system alone is the cause of 17%–54% of venous ulcerations. Of all limbs with venous ulceration, 74%–93% have reflux in the superficial system.[15–17] Superficial reflux, with or without perforator reflux, is present in more than 50% of patients with ulceration. This subclass of patients will benefit from intervention directed towards the superficial venous system.[18] Isolated deep vein reflux occurs in <10% of patients.[17–19] Among the deep veins, popliteal vein reflux has the strongest association with the severity of CVD. Two vein systems are involved in ulcerated limbs in 52%–70% of patients, and all three systems are involved in 16%–50% of patients.[17–19] The veins that are in the ulcer bed or within 2 cm of the ulcer have reflux in 86% of cases. However, perforator vein reflux is found only in a third of cases in this area.[17] Saphenous reflux can occur without SFJ and saphenopopliteal junction (SPJ) incompetence; therefore, ligation of these junctions may not be appropriate in such patients.[20,21] In 2.6%–4.0% of patients, no reflux or obstruction is found in any of the systems. In these patients, other causes of ulceration should be evaluated.[22]

It has been shown that saphenous hypoplasia occurs in varicose limbs more frequently than in healthy ones ($P < 0.001$). It greatly influences the path of the reflux and the anatomy of the varicose veins. GSV segmental hypoplasia can be detected pre-operatively by duplex ultrasonography. Its occurrence may influence surgical management for two main reasons: in about 68% of varicose limbs with segmental hypoplasia, the distal GSV is competent; if the distal GSV is incompetent, its size and flow direction are normalized by treating the accessory vein that bypasses the hypoplastic segment.[13]

Several patterns of reflux in the superficial veins are worthy of discussion, as treatment of the saphenous trunks may be avoided. In fact, there are occasions where both the GSV and SSV should be spared. An incompetent anterior accessory vein with or without involvement of the SFJ in the absence of GSV reflux is found in 9% of patients. After treating the anterior accessory vein, at 1-year follow-up, no patients had reflux in the GSV and 95% were satisfied with the treatment. In a large series of patients with reflux in the SSV system, 3.1% had incompetence in the thigh extension of the SSV only.[12] In another series where the thigh extension was studied, in the GSV and SSV system, reflux was found in 4.7%.[23] Reflux in the tributaries alone was detected in 9.7% of limbs with CVD. The most common site was the posterior arch vein.[24]

Reflux in non-saphenous veins, such as those of the vulvar, gluteal, posterolateral thigh, and other locations, is found in 10% of limbs with CVD.[10] These are mostly multiparous female patients with a mean of three pregnancies. On all of these occasions, treatment can be targeted by ultrasound and the saphenous veins spared. Reflux in non-saphenous veins is seen in Figure 13.6.

It has been suggested that in patients with primary reflux in the superficial and deep system, deep venous reflux may be directly linked to superficial reflux. The reflux circuit theory of venous overload states that reflux in the superficial system at the level of the perforators and major superficial to deep vein junctions will flow into the deep system and overload the deep system. This leads to dilatation and the development of reflux in the deep system. It has been demonstrated that, by surgically correcting the reflux in the superficial system, the deep system reflux is also eliminated in more than 90% of patients.[25] In a prospective study, deep reflux in patients with primary CVD was shown to occur near the SFJ, SPJ, and gastropopliteal junction.[26] It was more likely to occur when the reflux at these junctions had high peak velocity and long duration. The reflux in the deep veins was usually segmental and of shorter duration than post-thrombotic reflux. A recent study of 30 limbs has demonstrated that significant hemodynamic compromise is present when deep vein reflux is

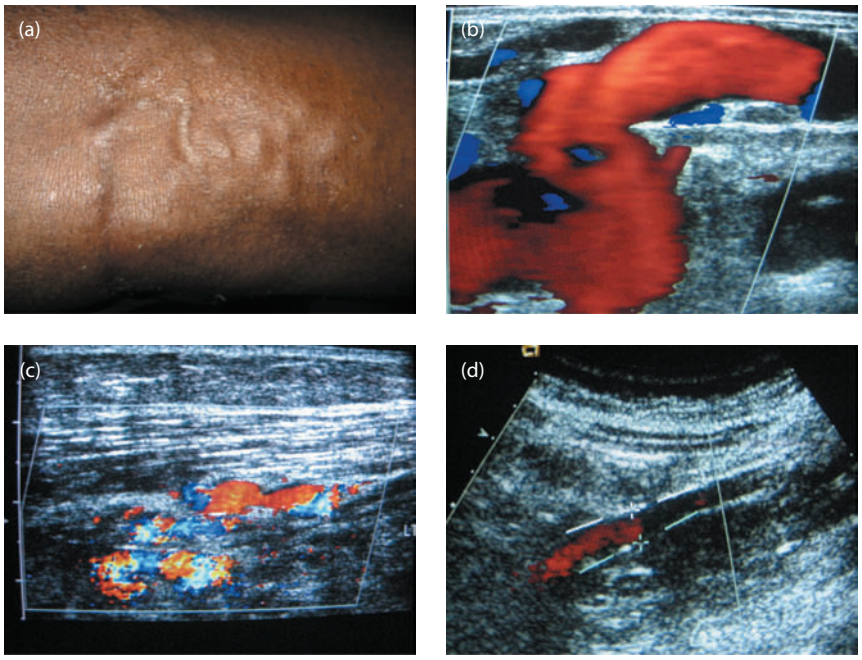

Figure 13.6 Examples of reflux in nonsaphenous veins. **(a)** Varicose tributaries are seen in the right popliteal fossa of a male patient who presented with pain and itching. The varicosities disappear above the popliteal skin crease as they dive deeper to join the popliteal vein. **(b)** Significant reflux in the vein of the popliteal fossa of the same patient. The vein is dilated and varicose and pierces the deep fascia just above the popliteal skin crease. It unites with the lateral aspect of the popliteal vein above the saphenopopliteal junction. **(c)** Reflux in the dilated and tortuous veins of vastus medialis muscle. These veins were connected with a perforating vein at the lower thigh that was in continuity with posteromedial varicose tributaries. **(d)** Left ovarian vein reflux in a 24-year-old woman with three pregnancies. She presented with left vulvar veins that were extending from the groin medial to the GSV to the posterolateral calf. The ovarian vein measured 8.8 mm in diameter.

caused by superficial vein reflux only when the popliteal vein valves are incompetent.[27]

Most PVs have at least one subfascial bicuspid valve that prevents reflux from the deep system to the superficial system. The role of PV incompetence in the development of the signs and symptoms of CVD remains unclear. However, there is evidence to suggest that the number of incompetent PVs and the sizes of competent and incompetent PVs increase with worsening CVD.[28,29] It has also been reported that patients with increasing numbers of incompetent PVs have a higher venous filling index. The venous filling index is known to correlate well with the severity of CVD.[29] PV incompetence occurs more in the calf than in the thigh.[16,28,29] There are more incompetent PVs found in the lower and middle thirds of the medial calf. Most PVs that are >3.5 mm in diameter will be incompetent.[28] However, the sensitivity of size alone determining incompetence is low, as about a third of the refluxing PVs have a diameter of <3.5 mm. The duration of outward flow and local hemodynamics worsen in PVs when both the superficial and deep veins connected to those PVs are incompetent.[28,30] The development of new PV reflux is closely related to reflux in the superficial system. In primary CVD, reflux in PVs develops in an ascending manner through the adjoining incompetent superficial vein, in a descending manner from the re-entry flow of a refluxing superficial vein, and in new locations where the superficial veins are also involved.

The correction of reflux in the superficial system has been shown to eliminate reflux in the PV. This is not the case when the deep system is incompetent.[31] In a prospective study where PVs were treated with surgical ligation using DUS guidance, it was shown that recurrence of PVs at 3 years was very common (76%).[32] The recurrent PVs were due to neovascularization or the development of incompetence in new sites, and not because of poor surgery.

DUS can also identify other uncommon pathologies in the veins, such as aneurysms, tumors, and phlebosclerosis (Figure 13.7). These pathologies are not usually associated with the signs and symptoms of CVD unless there is concomitant reflux or obstruction. However, their diagnosis is important, and can alter management.

13.7 PROGRESSION OF CVD

It was previously hypothesized that because of hydrostatic pressure, reflux must start at the level of the iliac or common femoral valves and develop in a retrograde manner. However, studies on the morphology, biochemistry, and function of the venous wall have demonstrated that changes can occur in any vein segment, irrespective of the site and function of the valves. With the use of DUS, it has been clearly shown that in the early stages of CVD, reflux develops in most people in the lower thigh, knee, and calf, without having a connection to the groin area.[26] Reflux, therefore, may have

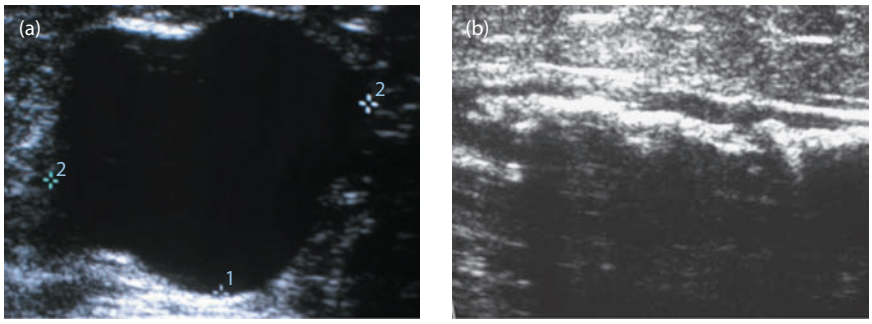

Figure 13.7 **(a)** Cross-sectional view of an anterior accessory saphenous vein aneurysm in the upper thigh measuring 23 mm. The adjacent vein segment that is partially seen at the 7 o'clock position measured 3.4 mm. The aneurysm is free of thrombus as seen from the echolucent lumen. This was also documented by its full compressibility. **(b)** Dense calcification of the great saphenous vein (GSV) near wall in the lower thigh. Acoustic shadowing is seen throughout the calcification. Phlebosclerosis occasionally is seen in the lower extremity veins and has no significant implications in contrast to calcification in intestinal veins that may lead to significant morbidity.

an ascending progression, descending progression, both, or may be multifocal. These findings are further supported by a recent study that examined patients below the age of 30 years with varicose veins and compared them with another group of patients over the age of 60 years.[33] It was shown that most often the saphenous and non-saphenous tributaries are diseased, and this was more common in younger patients. Junctional involvement was significantly less prevalent in the younger group (38% vs. 59%, $P = 0.0005$).

A prospective study of 126 limbs including three distinct groups of patients with primary, secondary, and no signs or symptoms of CVD showed that secondary CVD progresses faster than primary CVD. The authors demonstrated that at 5-year follow-up, skin damage was more prominent in patients with secondary CVD, and that those skin changes were seen earlier in the course of the disease in patients with secondary CVD compared to primary CVD.[34] Another study that followed 116 limbs in 90 patients studied the progression of reflux in CVD and its relation to physical findings.[35] These patients had two or more DUS examinations prior to operation since the procedure was delayed for various reasons. It was demonstrated that in 73.3% of patients, there was no change in the DUS examination and extent of reflux. In 13 limbs, there was advancement of CEAP staging, of which seven also had progression on DUS as well. Progression of reflux was seen in 26.7% of patients. These results indicated that physical examination or DUS alone were not reliable for predicting the progression of disease. Progression of reflux occurred mostly with anatomic extension in an ascending or descending manner and in both directions. Few patients developed reflux in a different area.

13.8 RECURRENT VARICOSE VEINS

In 1998, an international committee met in Paris to establish guidelines for recurrent varices after surgery (REVAS). Their findings and classification were to supplement the CEAP system, taking into account intervention. This system accounts for true recurrence, residual disease, and progression of existing disease. The prevalence of REVAS has been reported to be 20%–80%.[36] Perrin and colleagues performed a multicenter study in order to evaluate the etiology, pathophysiology, and progression of disease in REVAS.[37] They enrolled 170 patients with 199 affected limbs in 14 different institutions over a period of 1 year. The areas most affected by recurrent reflux in these patients were the SFJ in 47% of patients and the perforators in 55% of the limbs. Recurrent reflux resulted from technical failure to ligate the SFJ, neovascularization in cases of SFJ disease, and failure to recognize significantly diseased perforators in the pre-operative evaluation. More patients tended to have below-knee reflux after their procedures rather than thigh reflux. This is because the entire GSV is often obliterated or removed above the knee and the veins below the knee are simply ligated or stripped. Technical failure occurred in 19% of patients, and neovascularization occurred in 20%. A combination of the two was seen in 17% of the patients. In 35% of the recurrences, the cause was unknown. Recurrence developed in a new site in 32% of the limbs. Family history had the highest prevalence of recurrence (68%). This is not a surprising finding, since the strong relationship between hereditary and venous disease has been established.[38] Women tended to have more procedures to correct recurrence than men, even though the severity of recurrence was greater in men.

13.9 USE OF DUS BEFORE, DURING, AND AFTER TREATMENT

DUS can also be used as an adjunctive tool during therapy and for follow-up. The type of treatment is based on the baseline DUS. In the first examination, a map is made of the distribution and extent of reflux and obstruction. Additional tests may be necessary if deep vein reconstruction, endovenous or bypass operations to relieve obstruction, and pelvic vein reflux treatment are planned.[39] The effect of the procedure at a local level (i.e., improvement, elimination, or worsening of the reflux and obstruction) can

be documented. In addition, the effect of the procedure in veins that are proximal and distal to the site of the treatment can be assessed. However, DUS evaluates one short venous segment at a time. The overall effect of the treatment in the limb can be assessed better with physiological testing, such as plethysmography and pressure measurements.

Endovenous treatment of the superficial veins and PVs by ablation or sclerotherapy is now performed with DUS guidance. It is important to document the vein diameter, proximity to the skin, tortuosity, obstruction, and areas with hypoplasia and aplasia in order to have a good treatment plan.[40] Saphenous vein diameter is measured 3 cm below its respective femoral (SFJ) or popliteal (SPJ) junction, and at mid-thigh for GSV.[40]

During the procedure, DUS is used to obtain percutaneous venous access and to guide the wire and catheters. Accurate positioning at the treatment area of interest is easily achieved as the tip of the catheter is placed in the correct location safely. Before the ablation takes place, the tumescence fluid is injected around the vein. The goal is to create a halo sign over the entire length of the treated segment, with the vein being collapsed around the catheter. During the catheter pullback, the immediate effect on the vein can be observed. The vein is re-examined at the end of the procedure to ensure complete ablation and that the saphenous junctions and deep veins are free of thrombus. If adjunct procedures are performed, such as phlebectomies or sclerotherapy, DUS can also be used to guide that treatment as

Guidelines 2.3.0 of the American Venous Forum on duplex ultrasound scanning for chronic venous obstruction and valvular incompetence

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
2.3.1	Duplex scanning is recommended as the first diagnostic test for all patients with suspected chronic venous obstruction or valvular incompetence. The test is safe, noninvasive, cost-effective, and reliable.	1	A
2.3.2	We recommend that the four components included in duplex scanning examinations for chronic venous disease are visualization, compressibility, venous flow, and augmentation.	1	A
2.3.3	Duplex scanning is recommended to distinguish acute from chronic venous occlusion.	2	B
2.3.4	We suggest that reflux is elicited in two ways: increased intra-abdominal pressure using a Valsalva maneuver or manual or cuff compression and release of the limb distal to the point of examination.	2	B
2.3.5	We recommend that reflux is elicited in the upright position in one of two ways: either with increased intra-abdominal pressure using a Valsalva maneuver to assess the common femoral vein and the saphenofemoral junction or, for the more distal veins, the use of manual or cuff compression and release of the limb distal to the point of examination.	1	A
2.3.6	A cut-off value of 1 second is recommended to define abnormally reversed flow (reflux) in the femoral and popliteal veins and of 500 ms for the great saphenous vein, the small saphenous vein, and the tibial, deep femoral, and the perforating veins.	1	B
2.3.7	We recommend that in patients with chronic venous insufficiency, duplex scanning of the perforating veins is performed selectively. We recommend that the definition of "pathologic" perforating veins includes those with an outward flow of duration of 500 ms, with a diameter of 3.5 mm and a location beneath healed or open venous ulcers (CEAP class C5–C6).	1	B

well. In many centers, various forms of sclerotherapy are being performed as sole treatments, and this is also carried out under DUS guidance.[41,42]

Follow-up of endovenous therapy is important in order to monitor its success and to identify complications such as DVT. It is also recommended to perform a DUS study 1 year after endovenous thermal ablation in order to determine whether the GSV or SSV remain obliterated. If obliterated, it is likely that the vein will remain so for at least 3–5 years.[40] This 1-year follow-up study is also important in order to identify newly developed incompetent veins at the same treated site (due to neovascularization or dilation of pre-existent veins) or new sites. These findings will aid further treatment when deemed appropriate by the patient and the specialist.[40]

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14

Evaluation of venous function by indirect noninvasive testing (plethysmography)

FEDOR LURIE AND THOM W. ROOKE

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Venous disease is typically divided into two broad, distinct categories: acute (usually caused by thrombosis) and chronic (most often a combination of chronic venous obstruction, valvular incompetence, and/or muscle pump dysfunction). In acute venous thrombosis, it is important to not only diagnose the presence of thrombus, but also to identify its location, determine its age, and assess any ongoing changes (i.e., clot propagation, organization, recanalization, etc.). Duplex ultrasound has become the standard test for addressing these diagnostic needs.

The optimal approach for the assessment of chronic venous disease (CVD) is less clear, owing to the increased complexity required to evaluate the separate hemodynamic contributions of obstruction, reflux, and pump function. Despite this uncertainty, the need for detailed assessment is significant. Management of CVD has made significant advances in the past three decades, and new treatment modalities, ranging from surgical reconstruction of venous valves to office-based minimally invasive treatment of superficial veins to endovascular treatment of acute and chronic venous obstruction, are now available. In this environment, the demand for reliable testing techniques that are capable of answering key clinical questions is growing.

Venous testing (usually with duplex scanning) is a key component of the CEAP[1] classification approach, which provides a framework for characterizing patients with CVD. The diagnosis of disease and the definition of clinical class are based on clinical evaluation, while noninvasive testing is used to identify pathophysiological changes (reflux or obstruction) in individual anatomical segments of the venous system, and, in some cases, to define etiology. Designed as a descriptive classification, CEAP does not address the severity of the disease. Even clinical class "C" may not be directly related to clinical severity. For example, patients with venous ulcers who are successfully treated remain classified as C5 even when completely asymptomatic and free of signs of venous disease. In addition, the pathophysiologic part of the classification—the "P" of CEAP—is also purely descriptive. It includes the identification of reflux and obstruction, but does not quantify the severity of either reflux or obstruction. While assessment of the clinical severity of CVD is possible by using instruments such as Venous Clinical Severity Score,[2] the severity of reflux or obstruction cannot be defined by imaging modalities such as ultrasound and venography—not in individual segments, and definitely not for an entire extremity. Despite the fact that the goal of CVD treatment is to correct the hemodynamic abnormalities, the assessment of CVD severity over time and after treatment is especially challenging, because the relationships between clinical manifestations and underlying pathophysiology are complex and poorly defined.

These limitations dictate the need for testing modalities that can assess the global function of the venous system of the lower extremity. Venous pressure measurements can serve this purpose, but are invasive and unpractical. Indirect noninvasive tests, such as the various forms of plethysmography, are alternatives.

14.1 TECHNICAL PRINCIPLES

The indirect noninvasive tests most often used in the evaluation of patients with CVD are air plethysmography (APG) and strain-gauge plethysmography (SGP). Both of these techniques assess venous function by measuring changes in the size of the extremity in response to exercise, postural change, and the application and release of a venous

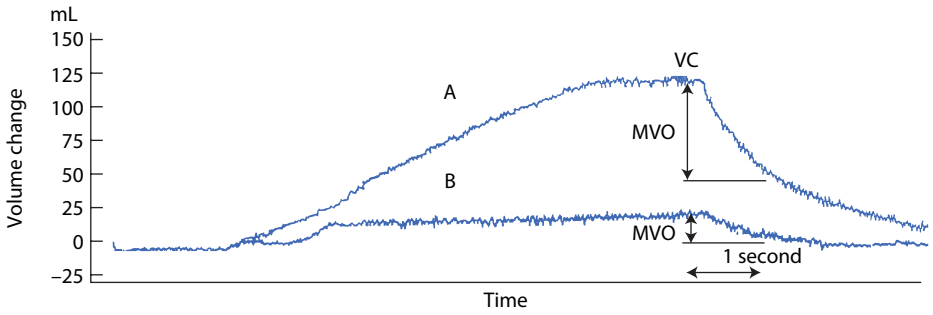

Figure 14.1 Air plethysmography tracings of a patient 3 years after femoropopliteal deep venous thrombosis. (A) Unaffected extremity; (B) extremity with venous obstruction has decreased venous capacitance (VC), and decreased maximum venous Pc is the pressure in the occlusion cuff. MVO: maximal venous outflow.

tourniquet. The main assumption of these examinations is that the arterial blood supply to the extremity and transcapillary fluid exchange do not change significantly in response to the utilized maneuvers. Changes in the extremity's volume are therefore attributed to filling and emptying of the veins (Figure 14.1).

APG and SGP use different models for the calculation of volume changes. APG measures changes in pressure in a measurement cuff calibrated to reflect volume changes. SGP calculates volume changes from changes in circumference. It assumes the extremity to have a cylindrical shape with an even distribution of volume changes in response to the testing maneuvers. The two methods give quantitatively different, but qualitatively identical information.[3]

Both APG and SGP require considerable patient cooperation. Consistency in performing exercise, maintaining position, and distributing weight between the legs can contribute significantly to variability in the results. External mechanical, thermal, and chemical (pharmacological) stimuli may also cause significant changes in the size of the venous lumen and in venous capacitance. All of these factors, along with changes in central venous hemodynamics and arterial supply, should be considered when the results of these indirect tests are analyzed.

Photoplethysmography and light reflection rheography calculate changes in tissue blood density by measuring the intensity of reflected light. Because of the inability of the light to penetrate deeper through the skin, difficulties in calibration, and poor specificity, these techniques currently have found little application in the evaluation of CVD.[4]

14.2 PRACTICAL APPLICATIONS

Although plethysmography studies can identify both obstruction and reflux, they are unable to allocate these changes to specific venous segments. Duplex ultrasound is the preferable and standard technique for the identification of reflux and, when feasible, obstruction. When venous obstruction is suspected, but not identified by duplex scan, plethysmography can help to overcome the low sensitivity of the ultrasound for the detection of venous obstruction.

An advantage of these indirect tests over ultrasound is their ability to provide a quantitative measure of the impact of obstruction and valvular insufficiency on the overall function of the venous system of the lower extremity. In addition, plethysmography can provide a quantitative assessment of muscle pump function (Figure 14.2). This

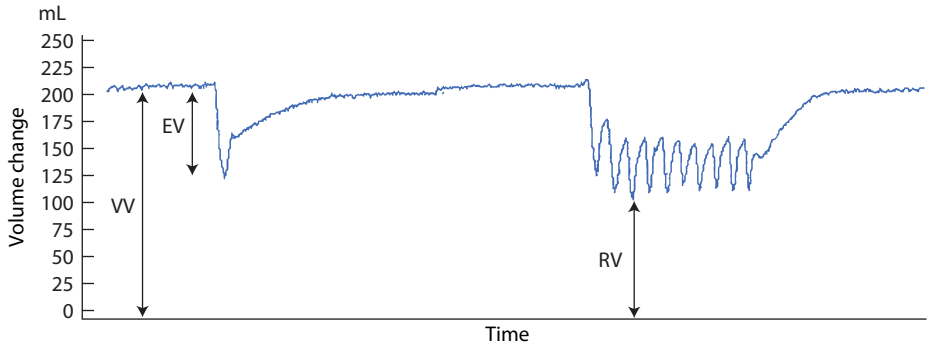

Figure 14.2 Assessment of muscle pump function by air plethysmography. The ejection fraction is calculated by dividing the EV by the VV and is expressed as a percentage by multiplying by 100. The residual volume fraction is calculated by dividing RV by the VV, and is also expressed as a percentage. VV: functional venous volume; EV: ejected volume (single tiptoe exercise); RV: residual volume after 10 consecutive tiptoe exercises.

information can also be used in the assessment of treatment outcomes and for follow-up.[5,6]

14.2.1 Identification and assessment of obstruction

The physiological roles of the venous system of the lower extremities include adjustments to changes in circulating blood volume and central hemodynamics by the accumulation and release of additional volumes of blood. To serve this need, under normal conditions, veins maintain a significant reserve capacity. Venous obstruction can measurably decrease this reserve. Increased resistance to outflow decreases the rate of emptying of more distal veins. Identification and assessment of venous obstruction by plethysmography is based on the estimation of the following two parameters: venous capacitance and venous resistance.

Measurements of the calf volume increase in response to venous occlusion by tourniquet, and the calf volume decreases after its rapid release; this constitutes the basis of venous occlusion plethysmography. Although venous pressure rises to equal the pressure of the tourniquet, blood accumulates in the veins of the studied extremity. Because veins easily increase their size under low pressure and become inextensible after the pressure exceeds 50–80 mmHg, they reach the level of maximal capacity, which is reflected in the maximally increased size of the calf.

Rapid release of the tourniquet creates a pressure gradient between extremity veins, where the pressure is equal to the pressure of the tourniquet and the central venous pressure, which is close to zero. Defining the pressure gradient makes possible the calculation of venous resistance by measuring the rate of decrease in the calf volume after the tourniquet is released. In extremities with venous obstruction, this resistance can exceed normal values by three-fold or more,[7] unless the developed collateral flow offsets the effects of axial vein obstruction.

14.2.2 Assessment of reflux severity

Leg elevation or exercise can be used to decrease the blood volume that has accumulated in the veins of an extremity. When an extremity is positioned vertically, refill of the veins can occur from relatively slow arterial inflow or, in the case of valvular incompetence, by rapid refluxing from a larger proximal segment. Measuring the rate of venous refill, usually indexed to 90% of the total volume, provides an estimate of overall valvular competence or the severity of reflux in extremities with no venous obstruction. When limited to patients with isolated superficial vein incompetence, venous refilling by plethysmography correlates well with great saphenous vein reflux as determined by duplex scan.[8]

14.2.3 Assessment of muscle pump function

Active evacuation of blood from the venous system of the lower extremity against hydrostatic pressure is a function of muscle pumps that integrate the effects of muscle contractions with the ability of the venous valves to provide unidirectional flow. Evaluation of muscle pump function in patients with CVD is important, because its impairment contributes significantly to the severity of CVD.[9] Improvement in muscle pump function through physical therapy[10] and/or elastic compression[11] can have beneficial therapeutic effects.

The decrease in calf volume following a single calf muscle contraction, and the amount of blood not expelled by repeated contractions, can be indexed to the functional venous volume (ejection fraction and residual volume fraction, respectively) in order to assess the calf muscle pump function. Plethysmographic findings correlate well with measurements of ambulatory venous pressure.[12] Its noninvasive nature makes this indirect test the only practicable option for the evaluation of the calf muscle pump.

14.2.4 Clinical correlations

Clinical correlations with the results of indirect noninvasive tests remain to be defined. Although potential for the prediction of ulceration has been demonstrated in early works,[13] more careful analysis revealed that deterioration of venous hemodynamics (as measured by plethysmography) parallels clinical severity only before skin changes develop[12] or during ulcer healing.[9]

14.2.5 Reliability

The reliability and repeatability of plethysmography have been demonstrated by Christopoulos and Nicolaides,[13] and were later confirmed by others.[14] The limits of reproducibility, however, differ significantly between the reports, and should be defined by systematic investigation.

14.3 SUMMARY

Plethysmography is currently the only practical noninvasive modality for global physiologic evaluation of the venous system of an extremity. It not only provides valuable information on the impact of reflux and obstruction on overall venous function, but also provides a way to assess the calf muscle pump. Plethysmography is a noninvasive modality that complements duplex ultrasound, and can be used to monitor venous hemodynamics over time and/or evaluate treatment outcomes.

Guidelines 2.4.0 of the American Venous Forum on the evaluation of venous function by indirect noninvasive testing (plethysmography)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
2.4.1	We suggest that venous plethysmography is used selectively for the noninvasive evaluation of the venous system in patients with simple varicose veins (CEAP class C2).	2	C
2.4.2	We suggest that venous plethysmography is used for the noninvasive evaluation of the venous system in patients with advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C3–C6).	2	B

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Direct contrast venography

HARALDUR BJARNASON

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15.1 INTRODUCTION

The introduction of X-rays by Dr. Wilhelm Konrad Roentgen in 1895 and the subsequent injection of contrast medium into vessels led to a better understanding of the anatomy and function of the vascular system. Venography became a significant part of the diagnostic armamentarium in the 1970s, and enabled clinicians to diagnose deep vein thrombosis (DVT) reliably, without the need to base the diagnosis entirely on clinical findings, since they are poor and imperfect ways of identifying often deadly conditions.[1]

Direct venography requires the infusion of contrast into a peripheral vein, and relies on preferential flow of the contrast medium towards the heart. The contrast medium will mix with the blood, making the blood opaque. The blood flow and, thereby, the inner lumen of the vessels, can then be followed with fluoroscopy, and still images (X-rays) can be taken and reviewed. This will not only give an image of the anatomy, but also of vascular pathology affecting the lumen of the vessel. As the blood flows along a gradient towards the heart, one can also get an impression of the hemodynamics in the vessels. The venous circulation can be altered or influenced, for example, by placing a tourniquet around a limb, forcing the contrast-mixed (enhanced) blood to flow into the deeper venous system. This technique is commonly used to evaluate DVT or to look for incompetent perforator veins. A tourniquet at the knee level can also be applied to slow down contrast flow into the central veins.

Because contrast is heavier than blood, contrast will layer in the dependent part of the vessel, and high-lying veins may not fill. As the contrast is layered at the dependent portions of the larger veins, one may not see the entire circumference of the vessel. This is a common pitfall of venography.

15.2 LOWER EXTREMITY ASCENDING VENOGRAPHY

Ascending venography, as the name implies, is based on contrast flow in the bloodstream that is upward or central in the direction of the heart along pressure gradients. This is the traditional venography, and was one of the most commonly performed radiologic procedures until ultrasound replaced it for the diagnosis of DVT.[2] Upper extremity venography is also technically an ascending venography, but the term is mainly used for lower extremity venograms. Ascending venography can be used to examine deep veins, superficial veins, and—as the connections between these two—the perforating veins. Introduced first in 1923 by Dr. Berberich and Dr. Hirsch,[3] contrast venography became the gold standard for diagnosing DVT when Dos Santos demonstrated its utility for imaging blood clots in 1938.[4]

15.2.1 Technique

Rabinov et al.[1] and others[5] described the technique of ascending venography in 1971 and 1972. The procedure is preferentially performed on a tilt-table, with the head end of the table raised 40–60°. At the foot end of the table, there should be a "footboard" with an elevation upon which the patient will rest the contralateral leg; the leg being examined should be non-weight bearing. An 18–20-gauge plastic catheter (Angiocath) is placed into a peripheral dorsal foot vein. The more peripheral the needle is placed, the better, because the contrast should be dispersed evenly into the venous bed. Distal directed puncture is recommended for that reason. One should avoid medial foot vein access, as the contrast will then preferably flow into the greater saphenous vein, rather than the deep venous system.

Figure 15.1 **(a)** Tourniquet is applied for the first part of the (arrow) study in order to direct the contrast mixed blood into the deep veins. Note that the anterior tibial vein is hardly filled. **(b)** The tourniquet has now been released. Superficial vein do now fill (arrow) and the anterior tibial veins are also filled (arrow heads).

Typically, a tourniquet is tightly placed around the ankle at the beginning of the examination (Figure 15.1). The purpose of the maneuver is to direct the contrast into the deep venous system. This enables examination of the deep veins of the calf. Because of how superficial the anterior tibial vein is at the ankle level, it may not fill with the tourniquet applied. When the deep veins have been evaluated, the tourniquet is released; the superficial veins will fill with further contrast injection, as will the anterior tibial vein and the muscular branches, if they have not filled already (Figure 15.1).

Typically, a second tourniquet is placed around the upper or lower part of the knee. The purpose of this is to delay the contrast flow to the thigh veins, allowing time to adequately evaluate the lower leg veins. This tourniquet is released, typically after the ankle tourniquet is released, and then a larger bolus of contrast-enhanced blood will enter the thigh veins and flow towards the pelvic veins (Figure 15.2). Up to this time, the table has been kept tilted with the head end at 40–60°. When the thigh veins have been evaluated, the head end of the table can be lowered to horizontal level or even to a head down (Trendelenburg) position, and the contrast-enhanced blood can be observed flowing into the pelvic veins and up to the inferior vena cava.

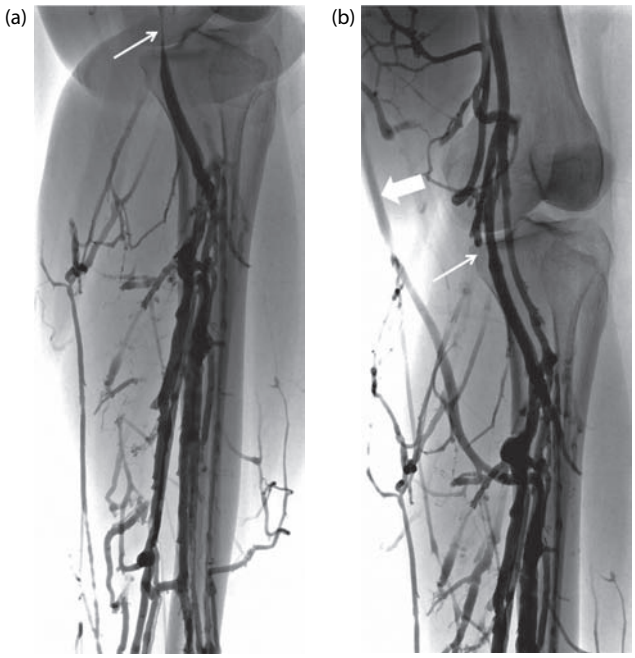

Figure 15.2 Before **(a)** and after **(b)** release of the tourniquet (arrow) at the knee. Note the normal looking duplicated popliteal vein. Also note the superficial vein filling after the release (arrow head). Contrast will now fill the thigh veins and by squeezing the calf contrast bolus can be pressed up into the thigh veins.

During the venogram, the examiner can turn the leg inwards and outwards and take X-rays in different obliquities in order to better understand the anatomy and any possible pathology.

By pressing on the sole of the foot, contrast filling the plantar venous plexus (Figure 15.3) can be ejected up into the calf, which will increase the visualization of the calf veins. A similar technique can be applied to the higher leg segment, when manual compression of the calf forces contrast into the thigh veins, increasing the opacification of these veins.

The contrast of choice is non-ionic contrast medium, typically with 300 mg/mL of iodine. For good filling of the venous system, 100–150 mL of contrast should be injected firmly. It is best to have an assistant injecting the contrast while the person performing the study rotates the leg medially and laterally under fluoroscopic visualization and takes images (X-rays) intermittently for review and documentation (Figure 15.4). Different positions of the limb help with three-dimensional understanding and clarify the anatomy and possible pathology.

Figure 15.3 The plantar veins are nicely filled (arrow). By compressing the sole, a bolus of contrast can be "squeezed" into the calf veins increasing the visibility of the calf veins.

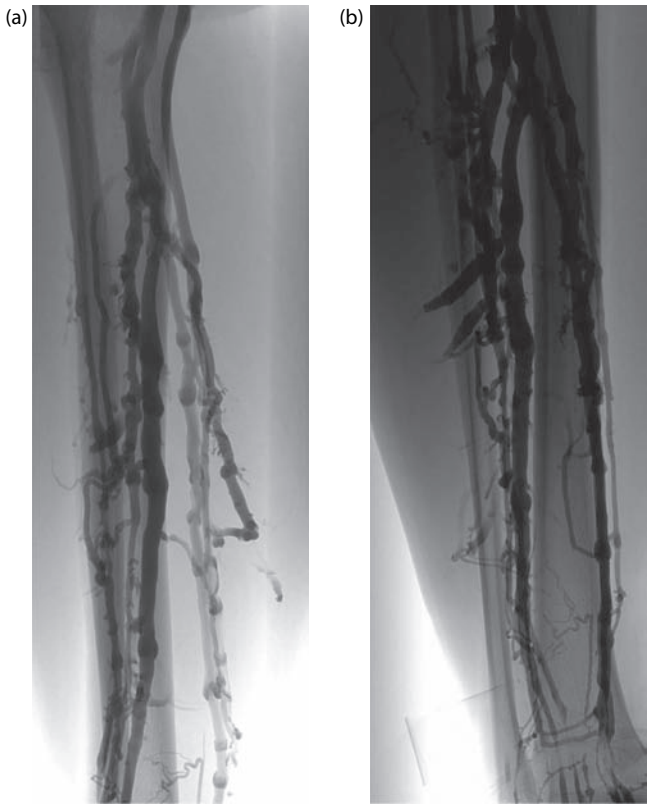

Figure 15.4 **(a)** Lateral view from a right lower extremity venogram. **(b)** Front view (PA). Comparing the two views clarifies the anatomy which is normal but the anterior tibial vein is not filled well, probably due to the tourniquet compressing the vein at the ankle.

15.2.2 Indications

Diagnosis of DVT was the main indication for ascending venography until ultrasound took its place. Ascending venography still has its place in a select group of patients where ultrasound has either been negative or inconclusive, but with high suspicion of DVT, as well as in instances where ultrasound cannot be relied upon or cannot be performed for some reasons (e.g., presence of a cast, severe swelling, scar tissue, etc.). The American College of Chest Physicians recommendations for the diagnosis of DVT published in 2012 stated that: "In patients with suspected first lower extremity DVT in whom [ultrasound] is impractical (e.g. when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest [computed tomography] scan venography or magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography."[6] They also add that: "In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (e.g. a short segment of venous no compressibility)." The new problem is related to the lack of experience of some physicians/institutions. Indeed, the performance of this study demands an understanding of the technical aspects, as well as extensive training in the practice and interpretation of the results/images.

In many cases, acute DVT causes occlusion of the vein, which will then be seen on the venography as an abrupt termination of the contrast-filled vein (Figure 15.5a). Frequently, there is slight flow around the thrombus—between the vein wall and the thrombus—giving an impression of lines up along the vein, referred to as the "tram track sign" (Figure 15.5b).[5,7,8] Abrupt occlusion and the tram track sign are often regarded as the diagnostic signs of acute DVT. The thrombus may not be occlusive, but rather firmly adherent to the wall of the vessel on one side, but allowing contrast to flow around the thrombus (the filling defect sign) (Figure 15.5c).

Chronic post-thrombotic changes are easily documented on an ascending venogram. Use of an ankle tourniquet is very important to direct the contrast into the deep vein system. If there are chronic thrombotic changes in the deep veins, the pressure in the deep veins is typically high and

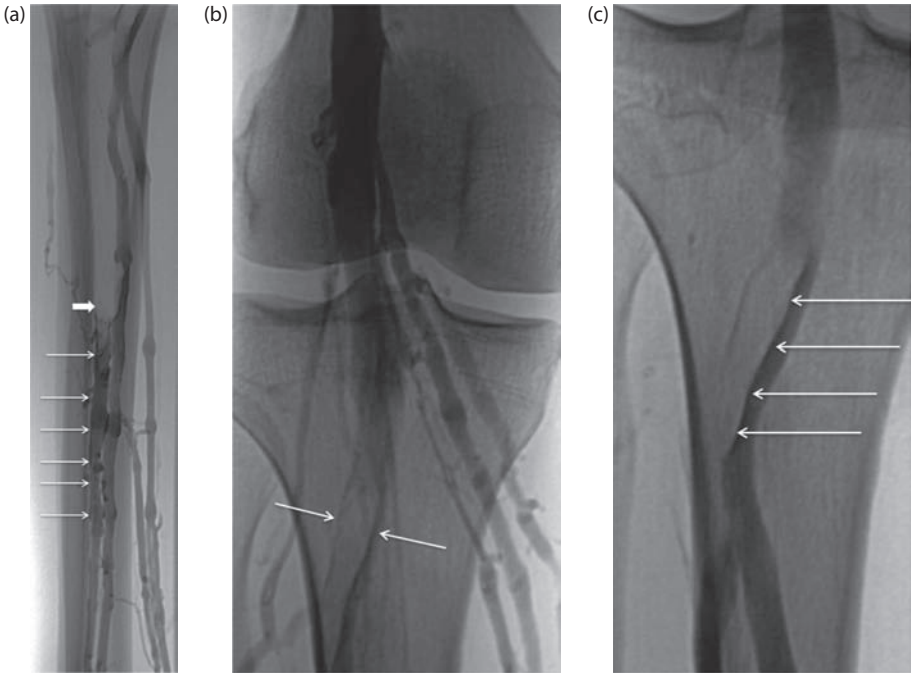

Figure 15.5 **(a)** Occlusion (arrow head) of one of the two peroneal vein branches with a filling defect (arrow). **(b)** Tram tracks are faintly seen as contrast is traveling between the thrombus and the vessel wall (arrows) and the density is most when seen "tangential." **(c)** Thrombus adherent to the vein on one side but allowing flow around it (arrows) on the opposite side. Sometimes it is only held in place by the thrombus caudal and then it is referred to as a free floating thrombus or thrombus tail.

flow is diverted into the superficial system. The degree of post-thrombotic changes varies from a patent vein with possible smaller-than-expected diameter and lack of valves (Figure 15.6a) to complete occlusion with no filling of the vein lumen. In-between findings, corresponding to septations or webs from the thrombus recanalization process, involve small strands of contrast tracking along the previously healthy veins, looking like a "water filter" (Figure 15.6b).

Venography of patients with Klippel–Trenaunay syndrome presents a logistical problem. The indication for a venogram in this case is to demonstrate the patency and size of the deep venous system, the extent of the superficial veins, and the communication from the superficial system to the deep system. The deep system can often be small (hypoplastic); therefore, it is important to have tight tourniquets around the ankle in order to divert the contrast into the deep system (Figure 15.7). In difficult cases, Alomari[9] recommended identifying the perforating veins initially using ultrasound. Tourniquets could then be placed at the level of the identified perforators, trying to prevent early filling of the perforators,[9] so that the deep system can be better evaluated. In other instances, it may be the marginal (lateral veins) and other congenital portions of the system that are of interest for pre-operative evaluation. In such cases, large volumes of contrast may be needed to fill the veins adequately[9]; therefore, Alomari[9] recommended using diluted contrast and subtractions imaging.

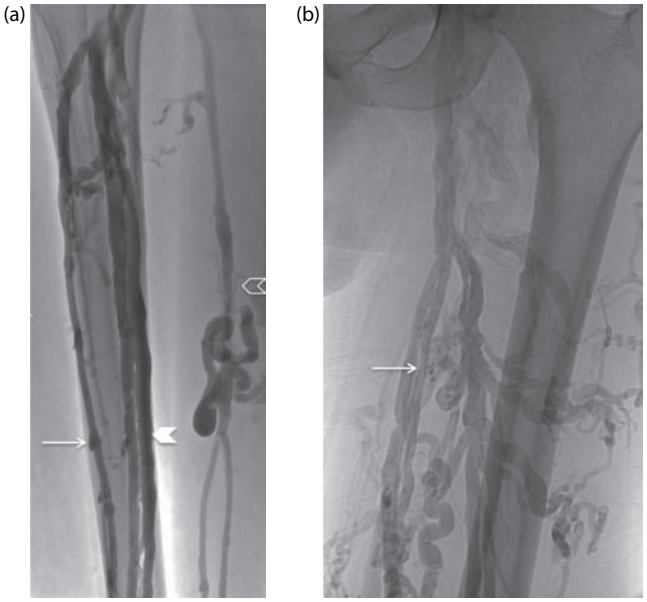

Figure 15.6 **(a)** Right lower leg ascending venogram. Note normal valve sinuses in the anterior tibial vein (arrow) indicative of normal vein. The peroneal vein is smooth with "wave" outlines and no valves, indicative of chronic postthrombotic changes (arrow head). Note varicosity of the small saphenous vein with filling of the vasa vasorum (hollow arrow head) possible indicating recent superficial thrombophlebitis. **(b)** Typical postthrombotic changes with a "water filter" appearance from the recanalization's process with webs (arrow).

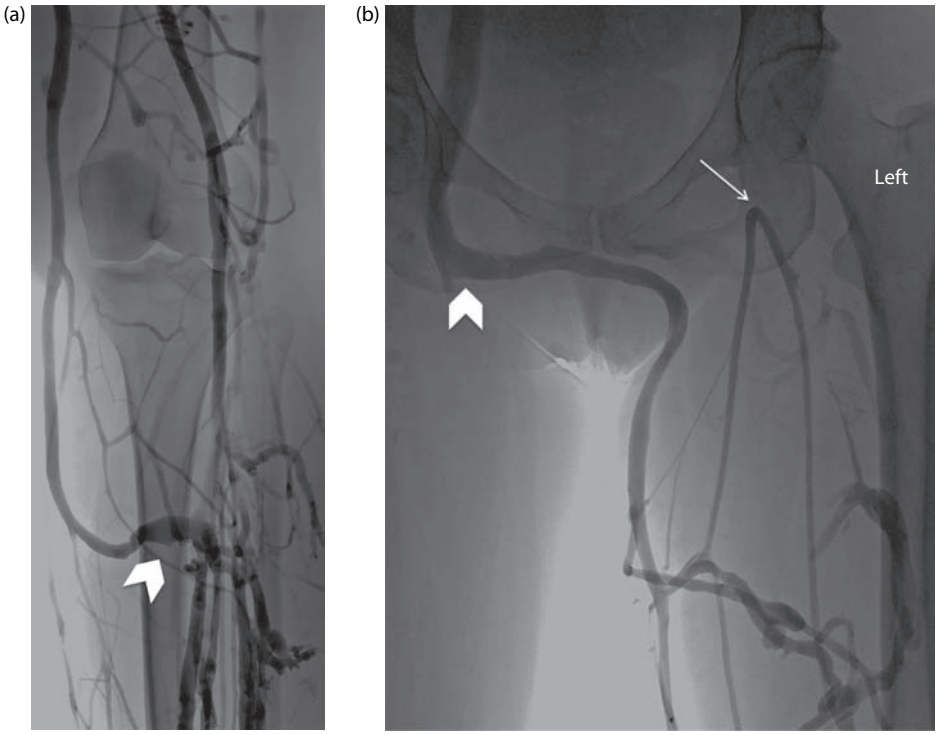

Figure 15.7 Klippel Trenaunay syndrome left side. **(a)** Prominent greater saphenous vein appearing to communicate with the deep vein (arrow head). **(b)** Small femoral vein (arrow). No filling of the common femoral vein (arrow) and the greater saphenous vein drains prepubic into the contralateral greater saphenous vein (arrow head).

Currently, perforators are localized and evaluated for incompetence using ultrasound and Doppler, but the technique of identifying and marking perforators with ascending venography can be helpful. When looking for an incompetent perforator, a tourniquet should be placed around the ankle to force the contrast into the deep venous system and prevent contrast flow directly into the superficial system. On ascending venogram, an incompetent perforating vein can be seen filling from the deep venous system towards the superficial system (Figure 15.8).[10] It helps to have a measuring device (radiopaque ruler) next to the examined leg at the same time, so that the perforators can be identified on the leg using bone landmarks such as the malleoli.[11]

How good is ascending venography at detecting acute DVT? Ascending venography served as the reference study (gold standard) when evaluating new technology for the diagnosis of DVT. Hull et al.[12] followed patients who had negative venography for DVT and found that two out of 160 (1.3%) patients who were not treated based on negative ascending venography presented within 8 days with verifiable DVT. This was felt to be a strong indication that patients with symptoms that are suggestive of DVT but with negative ascending venograms could safely forgo treatment.[12] Ascending venography requires expertise and training, and one study found that 10%–15% of ascending venography examinations were inadequate for diagnostic purposes due to insufficient contrast.[13]

15.3 LOWER EXTREMITY DESCENDING VENOGRAPHY

Ultrasound with Doppler can give accurate indications of the location of the venous valvular incompetence. In the 1980s, descending venography was popularized, mainly for evaluating valvular competence in the central lower extremity veins as workup for valvular surgery.[14]

15.3.1 Technique

Descending venography requires placement of a catheter at the common femoral vein level (junction of the external iliac and common femoral vein), or at the popliteal vein level in the case of competent common femoral and femoral valves but suspicion of popliteal and calf incompetence (this may require popliteal vein puncture).[15] Access can be gained from any accessible vein where a catheter can be advanced to the common femoral veins, such as the internal jugular veins, arm veins, contralateral common femoral vein, and even the ipsilateral common femoral vein.[14,16] The procedure is performed on a tilt-table with the head end elevated to approximately 60°. A footrest is in place and a block placed under the contralateral foot such that the studied leg is free. Contrast is then injected at 7 mL/second, with a total volume of 70 mL, and the patient is asked to perform the Valsalva maneuver during the injection. Care has to be taken that the X-ray equipment is positioned such that the contrast can be

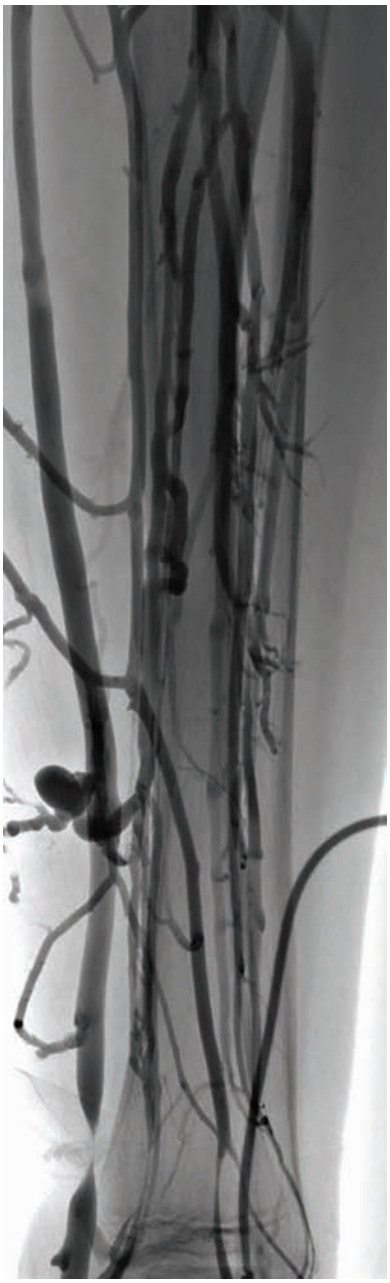

Figure 15.8 A perforating vein (arrow) from the posterior tibial vein to superficial varicosities. Note tourniquet around the ankle (arrow head).

followed below the knee and up to the inferior vena cava during and immediately following the injection.

Using fluoroscopy, the examiner observes contrast flow down the leg and images are taken, typically consisting of spot images, but the fluoroscopic evaluation can also be stored as a "video recording."[17] The reflux is then graded based on how far down the leg along the axial deep veins the contrast descends during the injection.[14,18] Grade 0 indicates no contrast beyond the common femoral vein confluence; grade 1 indicates reflux into the femoral vein down to, but not beyond, the mid-thigh (Figure 15.9); grade 2 indicates reflux beyond the mid-thigh but not into the popliteal vein; grade 3 indicates incompetence of the popliteal vein but not beyond that, not opacifying the deep veins of the calf; and finally, grade 4 reflux includes the deep veins of the calf down to the ankle level. This grading is for the deep veins only, but by positioning the catheter close to the ostium of the greater saphenous vein, reflux in that vein can also be evaluated in a similar manner. It is important to note that the test will not give any indication of the competency of the valve beyond the most cephalic competent valve unless a catheter is placed below that level, either with direct puncture or by advancing a catheter distal to that level.

15.3.2 Indications

This study is mostly used to map for valve surgery.[17]

Descending venography is invasive and ultrasound with Doppler has very much replaced it for patient workup. One of the challenges of the interpretation of the examination is that contrast may "leak" through the valves. It is often difficult to decide whether this is true reflux or clinically unimportant "leaky valves."

15.4 UPPER EXTREMITY VENOGRAPHY

Venography of the upper extremity is, in many regards, akin to what was described for the lower extremity.

Venography is rarely used for the diagnosis of DVT of the upper extremity, but occasionally ultrasound is not convincing or uncertain, and in those cases, venography provides the answer.

15.4.1 Technique

The venogram is carried out in a similar way to lower extremity venogram. An 18–20-gauge Angiocath is placed into a dorsal hand vein and 20–30 mL of non-ionic contrast with 300 mg/mL of iodine is injected. A tourniquet can be placed at the elbow level or just above in order to force the contrast into the deep vein system. The same criteria are used to diagnose thrombus as for lower extremity DVT.[8] Sometimes, the venogram is performed with injection into a dorsal hand vein. This is done for the purposes of delineating the venous anatomy, such as before the creation of a dialysis fistula. In such a case, it is best to place the access needle peripherally in order to achieve dispersal of the contrast into the superficial veins as well as the deep veins.

Venous thoracic outlet syndrome is caused by compression of the subclavian vein as it passes out of the chest in front of the anterior scalene muscle, behind the costoclavicular muscle and between the collarbone and the first rib. Venography was the most-used test for its diagnosis, but now computed tomography and MR imaging have replaced venography for the most part,[19,20] as venography only demonstrates whether there is occlusion or not, without identifying the structures around the vein.

Venography for thoracic outlet syndrome is typically done with the patient lying flat on the examination table.

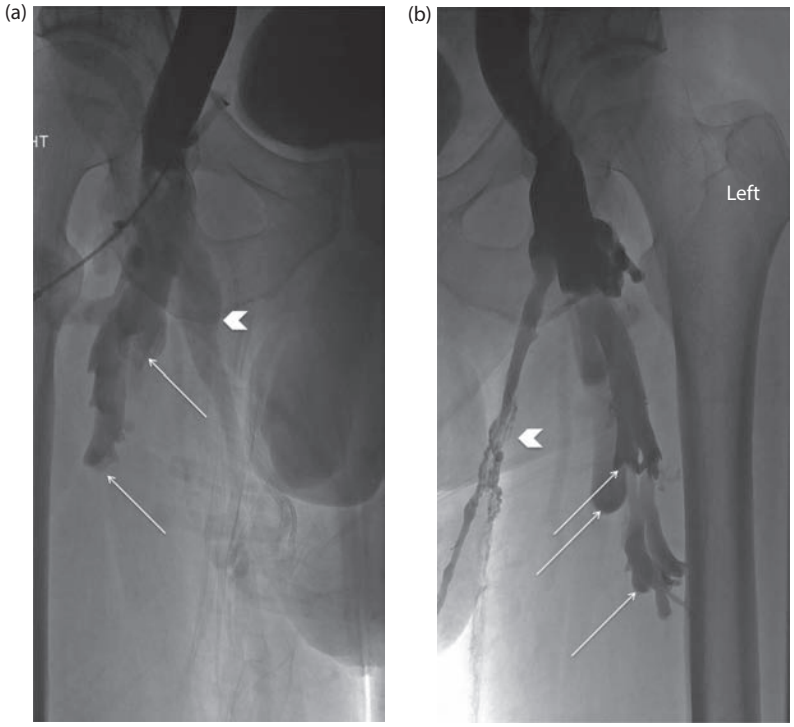

Figure 15.9 Bilateral lower extremity descending venogram. Puncture was made into the right common femoral vein and a catheter then advanced over the bifurcation into the left common femoral vein and the left extremity was examined. The catheter was then pulled back into the right external iliac vein just above the puncture and the right veins evaluated. **(a)** Right leg venogram demonstrates grade 1 reflux into the profunda femoral and femoral veins (arrows) with reflux into a large and incompetent greater saphenous vein (arrow head). **(b)** Left leg venogram shows Grade 1 reflux into the mid-thigh vessels. See competent valves (arrows). Also note postthrombotic changes in the greater saphenous vein which is incompetent (arrow head).

An 18–20-gauge Angiocath is placed in an antecubital vein and 20 mL of non-ionic contrast and 300 mg/mL of iodine are injected firmly. Three separate studies are typically done: the first one has the arm lying neutral by the patient's side; the second has the arm reaching out at 90° holding a weight, such as a 1 L saline bag, and the same injection is repeated; and the final injection is then performed with the arm stretched above the head. On the second injection, impression at the pectoralis minor muscle is visible, and on the third injection, one can usually see impression at the thoracic outlet in the case of compression. The diagnosis is made by the imaging of collaterals with an obstruction, typically at the inner border of the first rib (Figure 15.10).

15.4.2 Indication

Direct venography is a dying imaging technique, giving way to more advanced cross-sectional imaging, such as MR imaging,

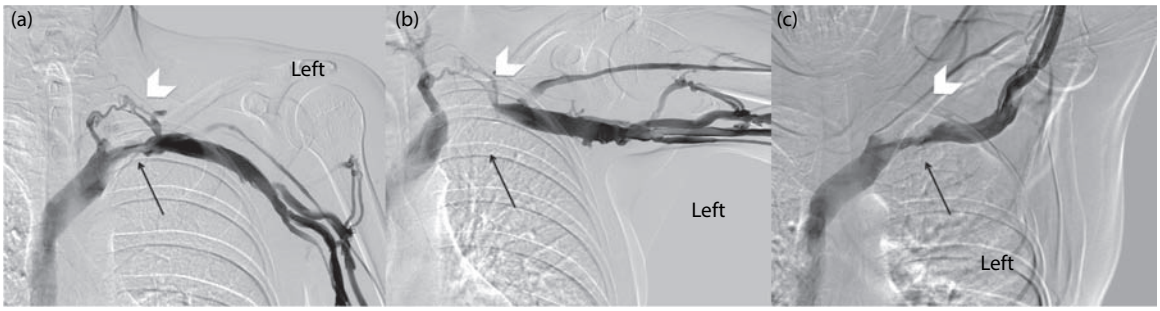

Figure 15.10 Left upper extremity venogram with maneuvers directed at the diagnosis of thoracic outlet syndrome. **(a)** Neutral position. The subclavian vein is narrow (arrow) at the medial vein and there are collaterals bridging (arrow head). **(b)** With the arm at 90° the central subclavian vein is obstructed (arrow) and the collaterals are still seen (arrow head). **(c)** With the arm stretched above the head the subclavian vein is narrowed (arrow) but the collaterals do not fill (arrow head) probably as they are compressed.

computed tomography, and, not least, ultrasound. The ability to visualize surrounding structures and obtain three-dimensional correlations make these studies very valuable. The addition of flow evaluation by ultrasound is significant. However, direct contrast venography still has a place in the evaluation of the patient with complex venous abnormalities.

Guidelines 2.5.0 of the American Venous Forum on direct contrast venography

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality C: low or very low quality
2.5.1	We recommend contrast venography before performing endovenous reconstructions for acute or chronic venous disease.	1	B
2.5.2	We suggest contrast venography for patients suspected of having acute deep vein thrombosis only if other imaging modalities are inconclusive.	2	B

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● = Key primary papers
★ = Major Review articles
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16

Computed tomography and magnetic resonance imaging in venous disease

TERRI J. VRTISKA AND JAMES F. GLOCKNER

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16.1 INTRODUCTION

Current diagnostic evaluation of disorders of the venous system have benefited from advances in state-of-the-art computed tomography (CT) and magnetic resonance imaging (MRI) applications. An understanding of the fundamentals and the appropriate utilization of each technology will provide useful information for medical management and decisions regarding surgical interventions for venous disease.

16.2 IMAGING TECHNOLOGIES: CT OF VENOUS DISEASE

During the past decade, CT has become a standard noninvasive imaging modality for the depiction of a wide variety of vascular anatomies and pathologies. Modern CT acquisitions have evolved from single-detector spiral scanners to multichannel helical CT examinations. More recently, 256-slice, 320-slice, and dual-energy CT systems have become available in many practices, and have replaced catheter-directed vascular imaging for many diagnostic studies. The proper application of modern CT techniques provides an extremely accurate, time-efficient, and cost-effective diagnostic evaluation prior to surgical intervention.

The two dominant advantages of CT are the speed and resolution of image acquisition. Modern CT acquisitions can be acquired in less than a minute during a single breath-hold. In addition, submillimeter resolution details are available for accurate depiction of the imaging details communicated to clinicians using advanced post-processing techniques and 3D displays (Figure 16.1). One additional distinct advantage of CT compared with MRI is the ability to demonstrate calcified densities such as calcified granulomatous lymph nodes as a cause of superior vena cava (SVC) obstruction on pre-contrast acquisitions.

The two primary disadvantages of CT imaging of the venous system include radiation exposure and the necessity for administration of iodinated contrast material. A typical abdominal and pelvic CT evaluation includes a radiation exposure of approximately 5–10 mSv. Ongoing efforts within the CT physics community are focused on optimizing the necessary radiation required for CT acquisitions by tailoring the dose to the individual patient size via modulation of the radiation beam.[1] Administration of iodinated contrast material is necessary for accurate evaluation of the venous system and, therefore, patients with a significant allergic reaction to iodinated contrast material or decreased renal function should be evaluated with alternative imaging techniques, including ultrasound or MRI.

16.2.1 Clinical applications

16.2.1.1 SVC AND BRACHIOCEPHALIC VEINS

CT evaluation of the SVC is most commonly performed for the evaluation of acute or chronic occlusive changes, and has been shown to be a useful noninvasive imaging technique for the diagnosis of SVC and central venous disorders.[2–5] Evaluation of post-procedural changes, including endovascular stent patency or post-operative changes of surgically placed bypass grafts, can also be performed. Regardless of the indication, CT acquisitions are optimally performed by the simultaneous injection of the antecubital veins using 90–100 mL of dilute contrast material in each extremity at an injection rate of 2–3 mL/second. The bilateral arm injections provide homogeneous opacification of the innominate veins and SVC, and avoid potential artifacts from unopacified blood within the central venous structures (Figure 16.2).

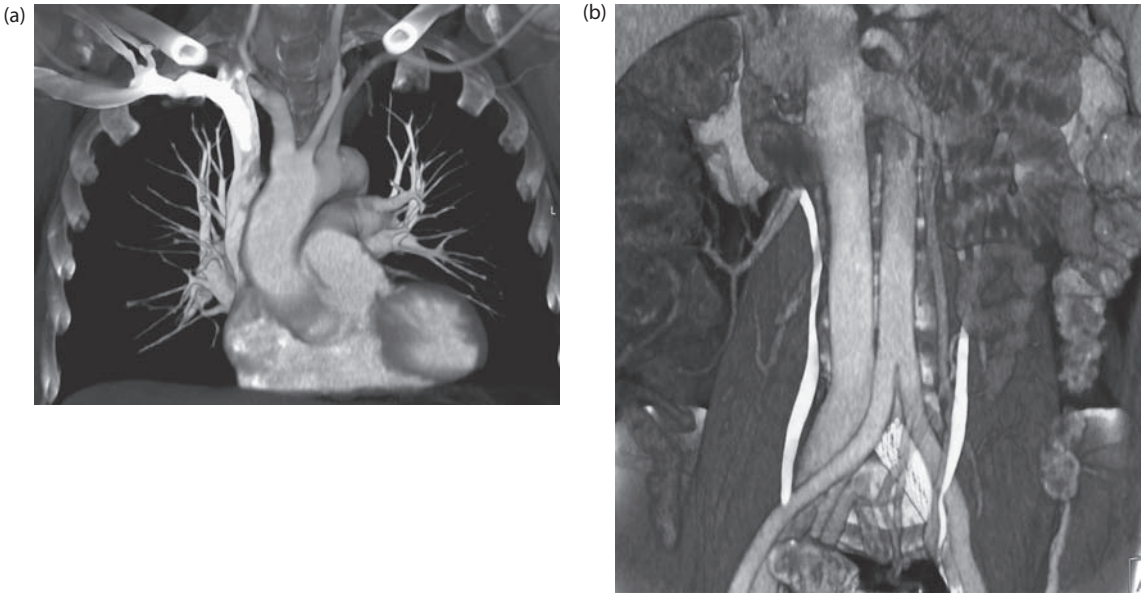

Figure 16.1 Current computed tomography technology combined with tailored acquisition techniques and post-processing applications provide accurate depiction of **(a)** the thoracic and **(b)** abdominal venous vasculature.

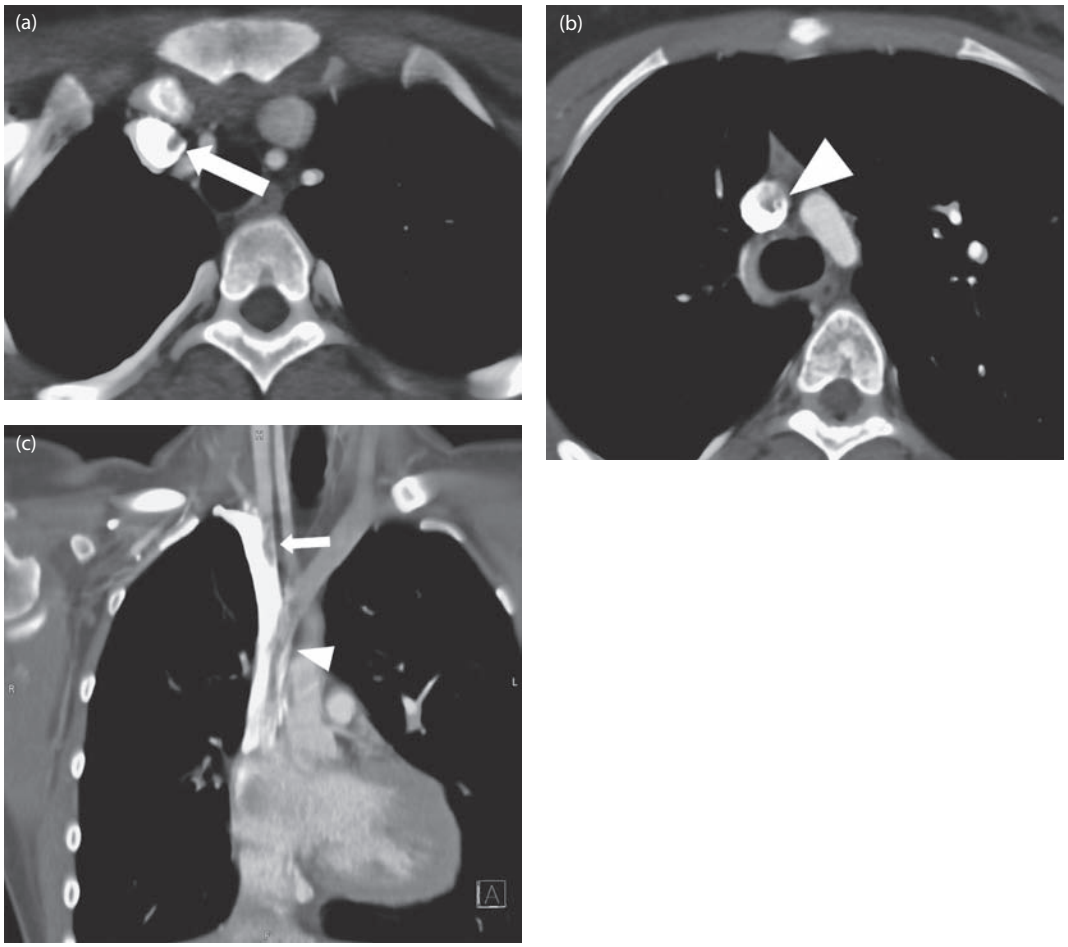

Figure 16.2 **(a, b)** Contrast-enhanced axial and **(c)** coronal computed tomography of the chest demonstrate artifactual low density filling defects because of unopacified blood flow from the right jugular vein and unopacified blood from the left brachiocephalic vein entering the opacified right brachiocephalic vein (**a** and **c**, arrows) and the superior vena cava (**b** and **c**, arrowheads).

Subsequent injection of 20–30 cm^3 of saline is helpful for flushing the contrast material from the brachial and axillary veins into the central venous system. CT acquisition using thin collimation (1–2 mm) is useful in order to provide both traditional axial images and appropriate reconstructions that can be analyzed in the coronal, sagittal, or tailored off-axis planes. Careful review of the axial images and dedicated reconstructions are useful for optimal visualization of venous patency, obstructed venous segments, intraluminal thrombus, and collateral venous pathways.

On contrast-enhanced (CE) CT images, acute thrombus within the SVC or central venous structures is characterized by a low-attenuation filling defect within the lumen of the vessel (Figure 16.3). The involved venous segment may be normal caliber or expanded. Chronic occlusive changes are most commonly visualized as small, non-opacified, fibrotic-appearing linear densities. Extensive upper chest wall and azygous collaterals can be precisely depicted by 3D images (Figure 16.4).

An advantage of evaluation of the SVC and central venous structures by CT rather than catheter venography is the ability of CT to accurately depict the pathology resulting from venous occlusive changes. The most common cause of obstruction of the SVC and upper venous structures is malignancy, most commonly pulmonary neoplasm. The obstruction may result from extrinsic compression due to primary or metastatic neoplasm, or from direct invasive changes. Other common causes of SVC obstruction include granulomatous disease and iatrogenic occlusive changes (transvenous cardiac pacers, central venous catheters, and post-radiation changes). Anatomic variants of the SVC can also be accurately visualized by CT evaluation, such as a left-sided SVC.

16.2.1.2 INFERIOR VENA CAVA

Accurate evaluation of the inferior vena cava (IVC) requires knowledge of potential flow artifacts that are especially prominent due to the rapid acquisitions provided by modern CT scanning (Figure 16.5). In addition, knowledge of anatomic variation of the IVC is important for determining the accurate evaluation of findings due to anatomic variation rather than pathology (Figures 16.6 and 16.7).[6–9] The flow artifacts visualized with the IVC are due to the unopacified blood from the lower extremities entering the infrarenal IVC, whereas the suprarenal IVC receives an admixture of opacified blood, due to the rapid transit of the

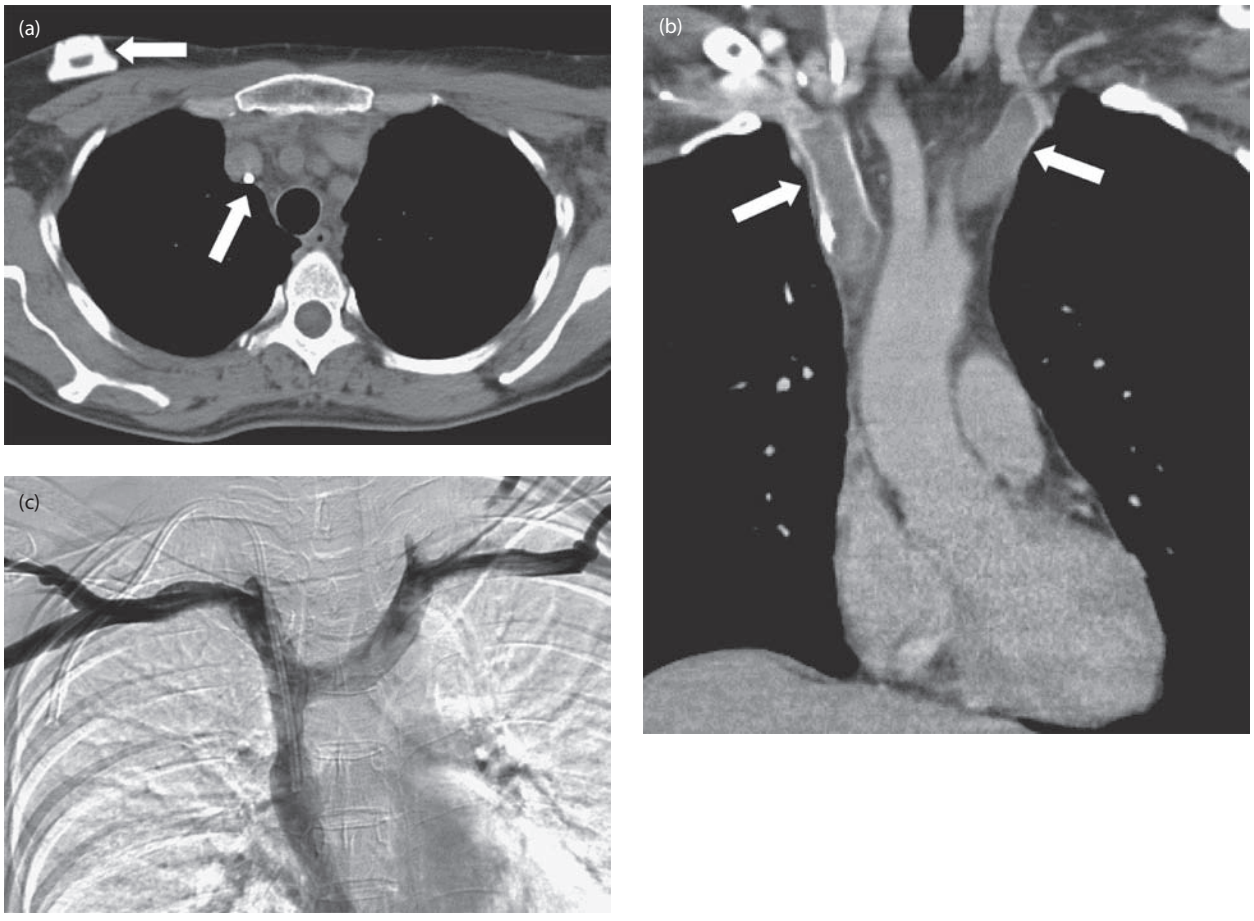

Figure 16.3 Thrombotic occlusion of the superior vena cava. **(a)** Unenhanced axial image of the chest demonstrates the location of a tunneled central venous catheter (arrows). **(b)** Coronal CT image acquired with iodinated contrast material injected simultaneously via bilateral antecubital iv access shows low attenuation thrombus in the right and left brachiocephalic veins (arrows). **(c)** Subsequent post-lysis catheter venogram with widely patent brachiocephalic veins.

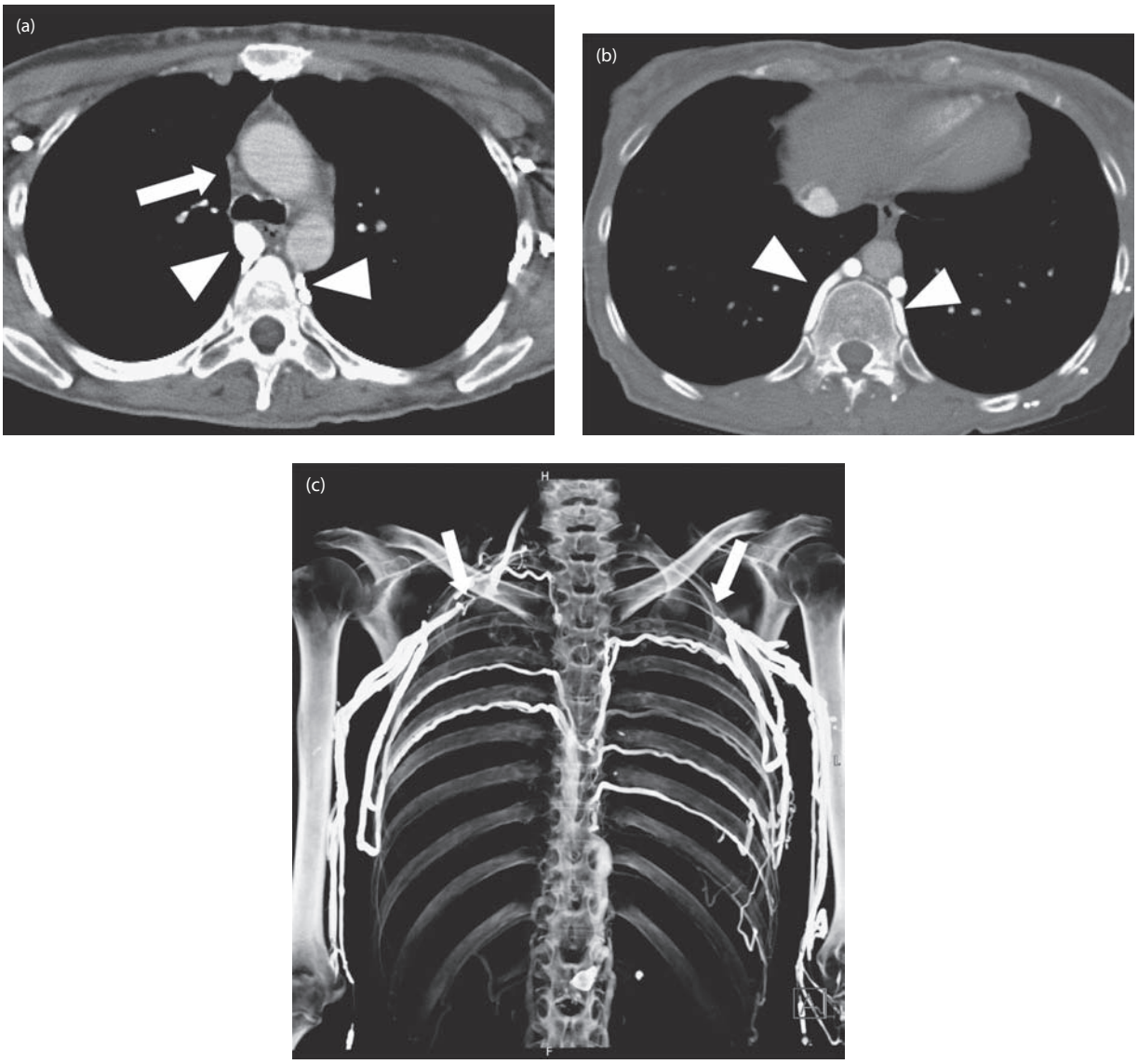

Figure 16.4 Contrast-enhanced axial computed tomography demonstrates **(a)** occlusion of the SVC (arrow) with **(b)** dilatation of the azygous and hemiazygous systems (arrowheads). **(c)** Volume-rendered 3D image of the chest demonstrates occlusion of the brachiocephalic veins bilaterally (arrows) with extensive chest wall collaterals.

contrast material through the kidneys. Anatomic variants of the IVC are due to persistent embryologic remnants. The prevalence of the most common anatomic variants include persistence of a solitary left-sided IVC (<1%) and duplication of the infrarenal IVC segment (1%–3%), retroaortic left renal vein (2%–3%), and circumaortic left renal vein (2%–9%).[7]

Optimal opacification of the IVC typically requires delayed CT imaging at 90–110 seconds following the administration of iodinated contrast material, to allow homogeneous opacification of the entire infrarenal cava. As with the SVC, current CT evaluation provides accurate off-axis display of the entire caval segment in any orientation; however, the coronal display most commonly provides the most complete depiction because of the longitudinal orientation of the IVC within the abdominal cavity. The most common pathology depicted within the IVC is bland thrombus due to thrombotic disease, and may be visualized within the central cava (Figure 16.8), or due to extension of thrombus from malignant occlusive changes (Figure 16.9). Thrombus may also be visualized within venous branches such as the renal veins or common femoral veins (Figure 16.10). Tumor thrombus within the IVC is most commonly due to local extension from adjacent organs such as the kidneys (renal cell carcinoma), liver (hepatocellular carcinoma), or adrenal glands (adrenal cortical carcinoma). An uncommon cause of a filling defect within the IVC is due to a primary tumor arising in the smooth muscle of the IVC, as seen with leiomyosarcoma.[10,11] Rarely, the IVC may be traumatically disrupted (Figure 16.11). The ability of the CT evaluation to display the orientation of an IVC filter can be helpful for depicting associated thrombus or migration (Figure 16.12).

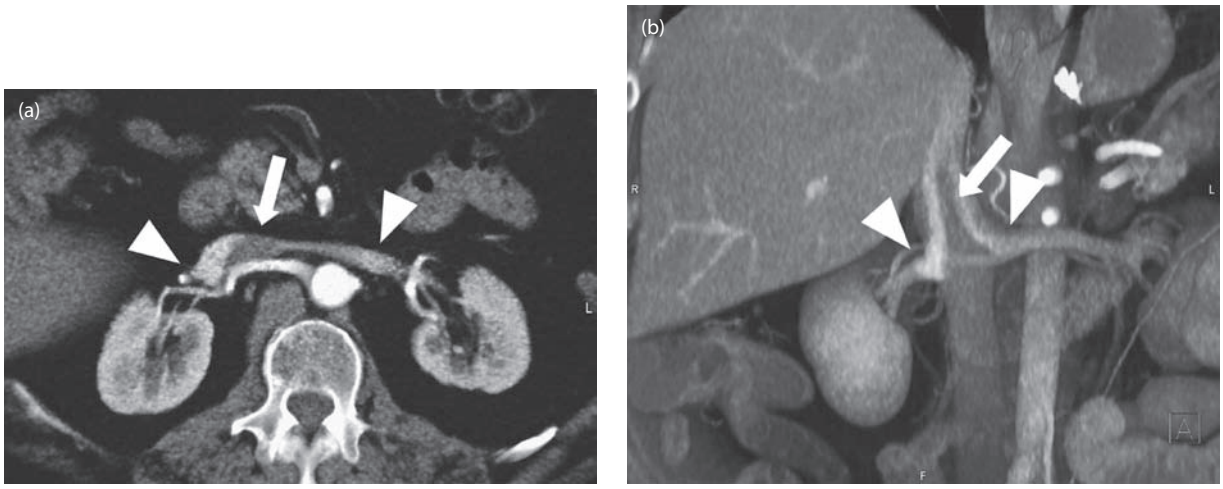

Figure 16.5 **(a, b)** Contrast-enhanced axial computed tomography demonstrates flow artifact (arrow) from unopacified blood from the infrarenal inferior vena cava streaming into the juxtrarenal (IVC) with admixture of opacified blood from the renal veins (arrowheads).

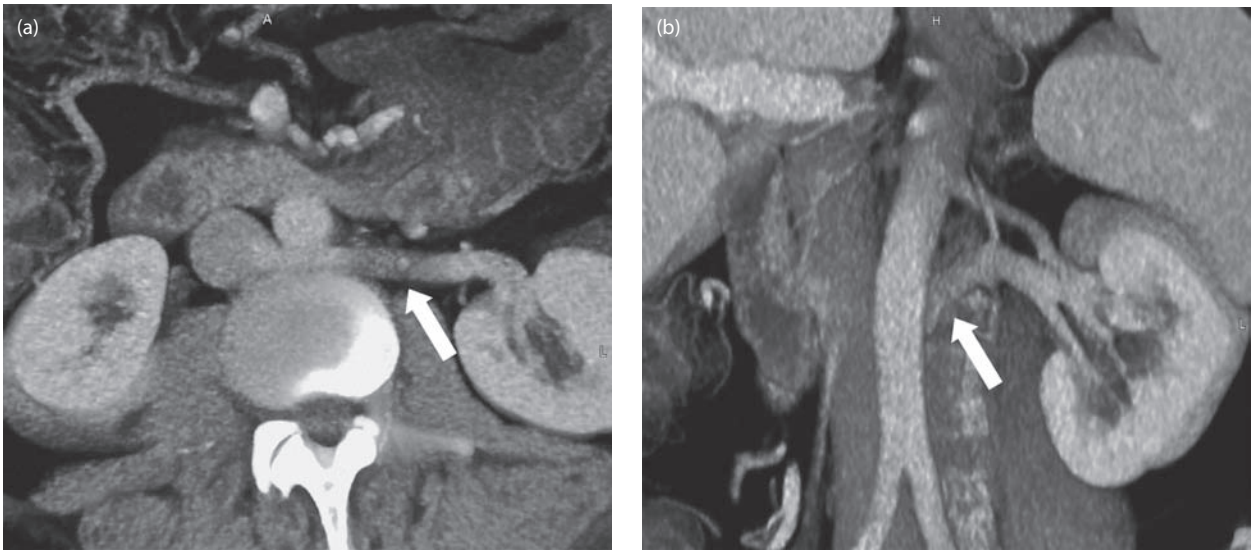

Figure 16.6 **(a, b)** Contrast-enhanced computed tomography with axial and coronal volume-rendered images demonstrates the anatomic relationships of a single retroaortic left renal vein (arrow).

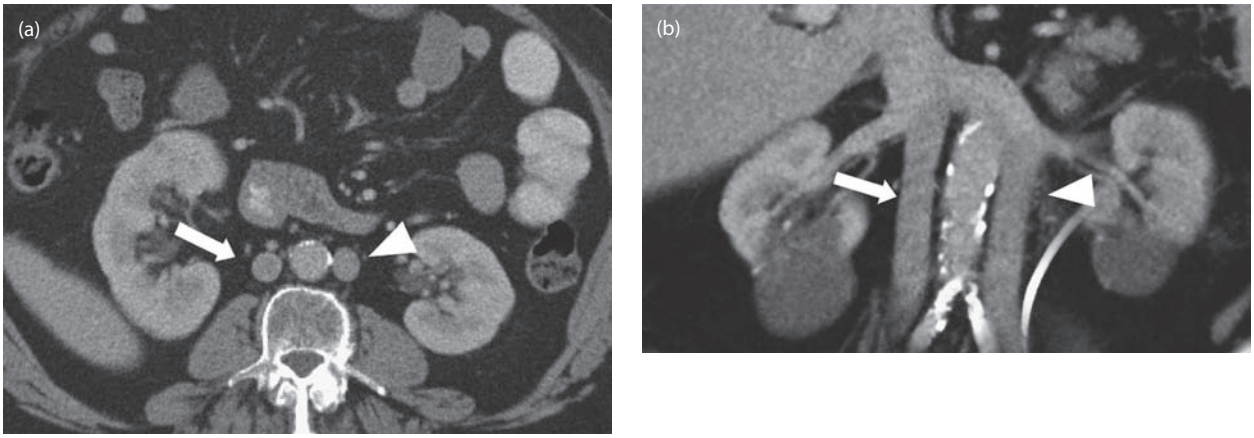

Figure 16.7 **(a, b)** Contrast-enhanced axial computed tomography demonstrates duplication of the infrarenal inferior vena cava (IVC) with a right-sided (arrows) and left-sided infrarenal IVC (arrowheads).

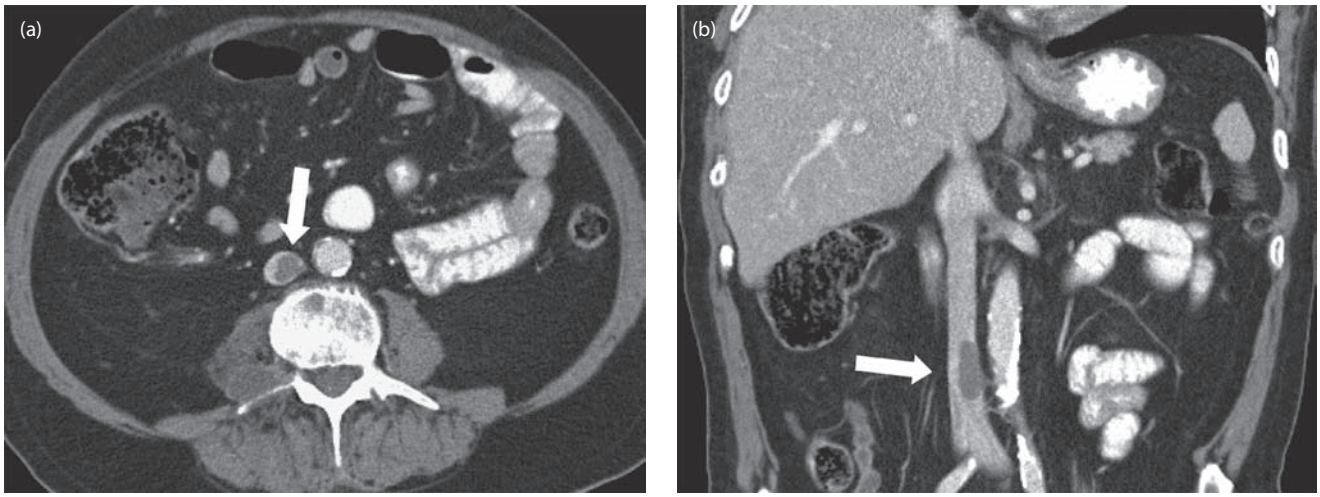

Figure 16.8 Inferior vena cava (IVC) bland thrombus. **(a)** Contrast-enhanced axial and **(b)** coronal computed tomography images with low attenuation thrombus in the infrarenal IVC consistent with bland thrombus (arrows).

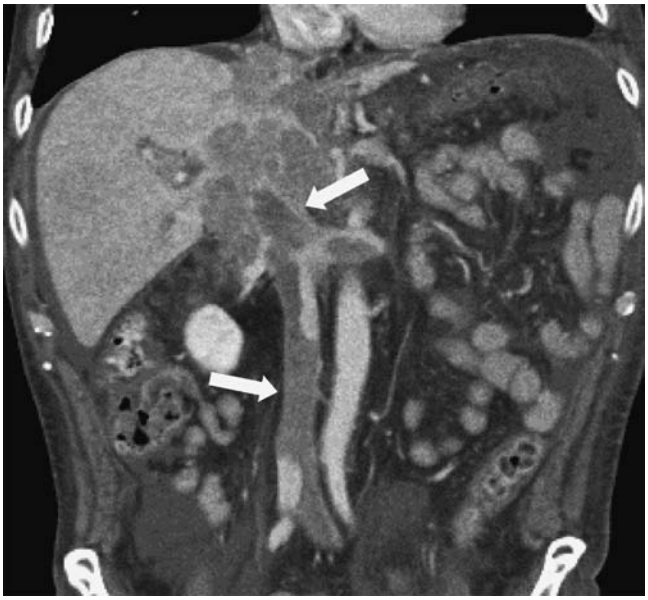

Figure 16.9 Inferior vena cava (IVC) malignant thrombus. Contrast-enhanced coronal CT image with mixed density tumor and bland thrombus filling the suprarenal and infrarenal IVC (arrows).

16.2.1.3 PULMONARY ARTERIES

CT of the pulmonary arteries has largely replaced catheter-directed pulmonary angiography and ventilation and perfusion scintigraphy (VQ scans) of the pulmonary arteries because of the rapidity of the scan's acquisition and the high sensitivity and specificity (approaching 100%) for central pulmonary emboli.[12,13] In other studies, the detection of small sub-segmental pulmonary emboli has been shown to be less accurate, with a sensitivity of 83% and a specificity of 96% for CT angiography.[14] However, further research using the latest CT technology may provide improved accuracy

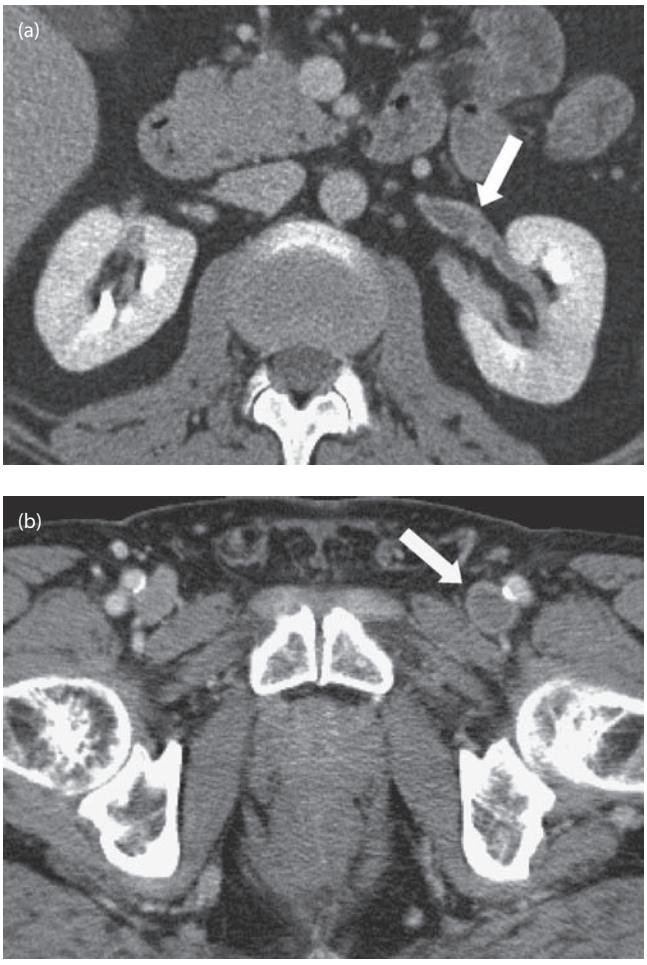

Figure 16.10 Venous branch thrombus. Contrast-enhanced axial CT images with **(a)** acute thrombus within the left renal vein (arrow) and **(b)** within the left common femoral vein (arrow).

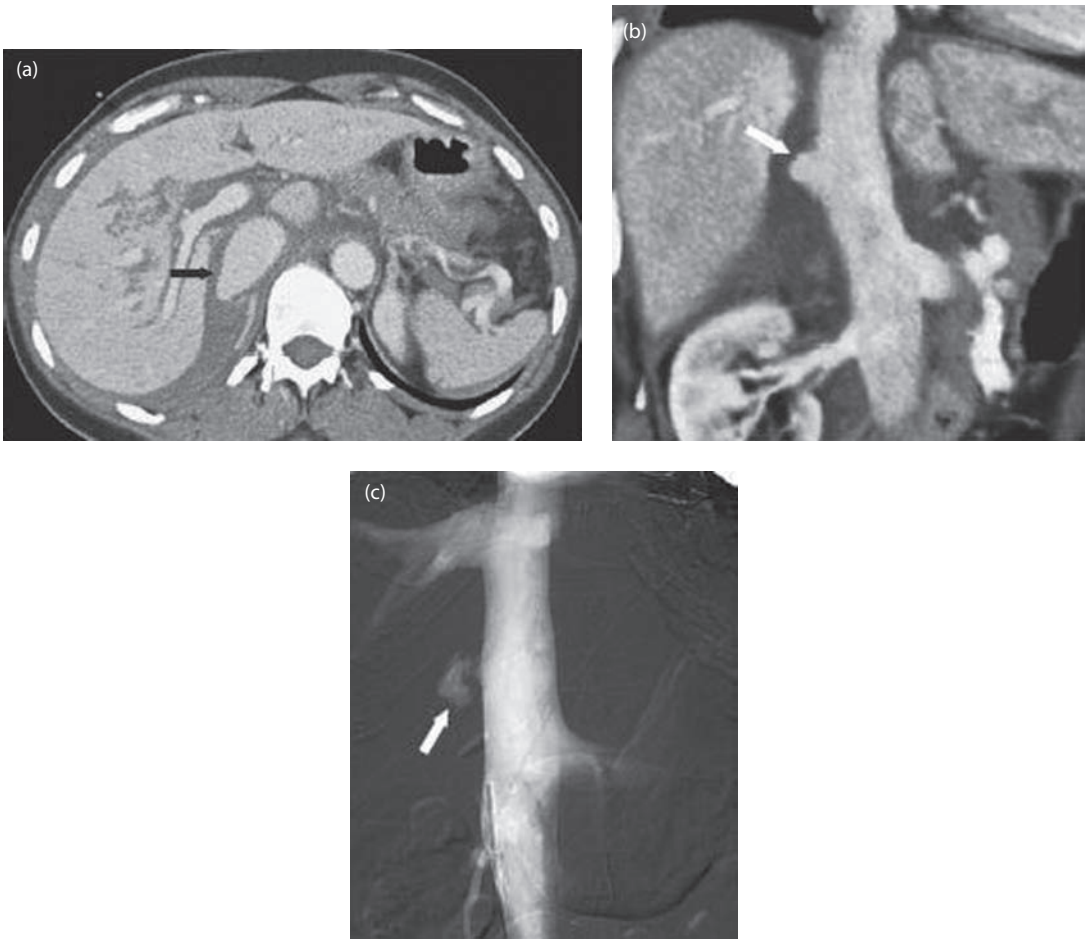

Figure 16.11 Traumatic disruption of the inferior vena cava (IVC). **(a, b)** Axial and coronal CT exams show extraluminal extravasation of contrast material (arrows) consistent with infrahepatic disruption of the IVC. This finding was confirmed on subsequent catheter directed cavagram (**c**, arrow).

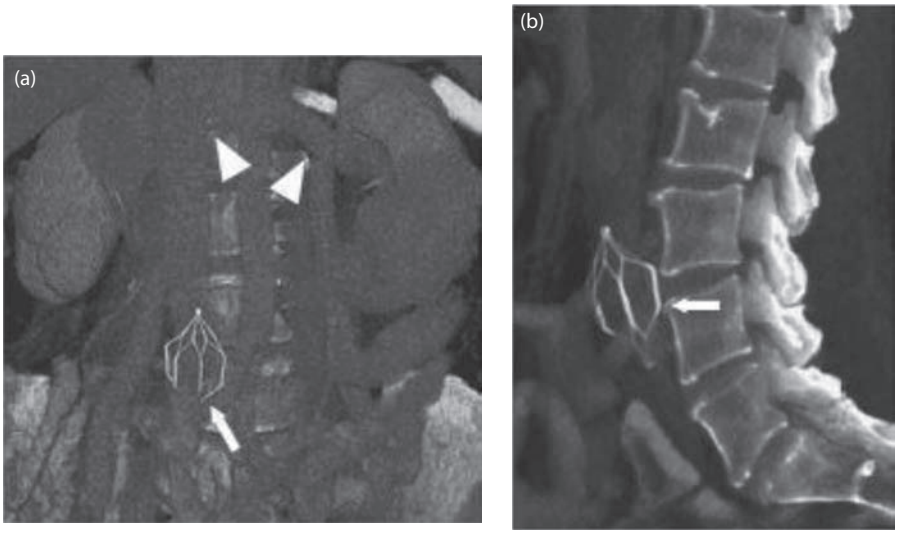

Figure 16.12 Inferior vena cava (IVC) filter migration. **(a)** Volume-rendered coronal and **(b)** sagittal computed tomography images demonstrate migration of an IVC filter caudally near the common iliac vein bifurcation (arrows) rather than at the level of the renal veins (arrowhead).

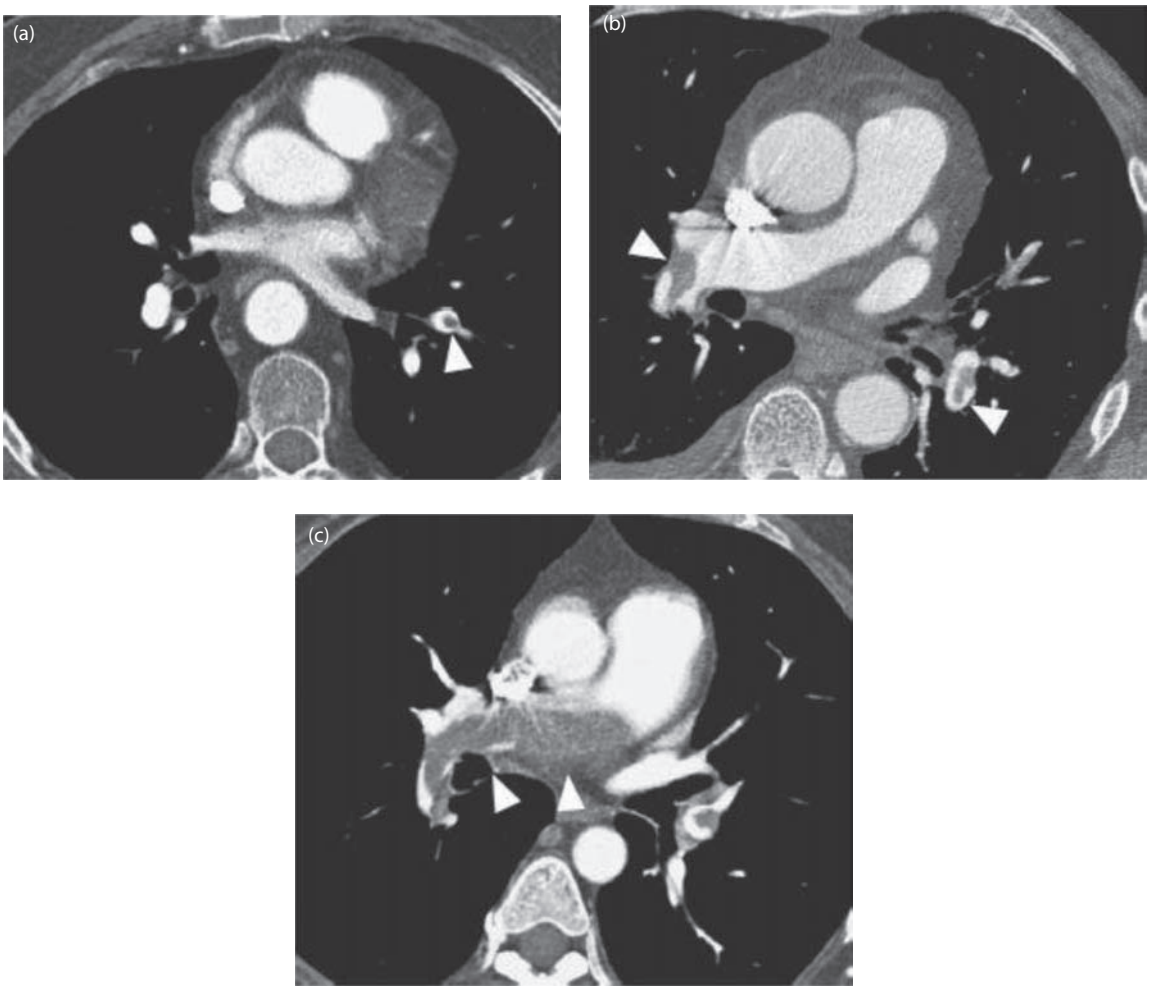

Figure 16.13 Acute pulmonary emboli in three patients. **(a)** Axial computed tomography imaging of pulmonary emboli in a small segmental pulmonary artery (arrowhead), **(b)** bilateral pulmonary emboli (arrowheads) and **(c)** a large central pulmonary embolus (arrowheads) in the main right pulmonary artery ("saddle" embolus).

in small peripheral pulmonary arteries, with accurate detection of pulmonary emboli of all sizes (Figure 16.13). In addition, the stratification of patients based on clinical assessment provides the optimal strategy for the diagnosis of pulmonary emboli.[15]

Acute pulmonary emboli are diagnosed by filling defects within the involved pulmonary arterial segments, which are often slightly enlarged. The optimum administration of the intravenous contrast material is the key factor in the acquisition of an accurate pulmonary arterial CT evaluation, and this may be acquired in a single breath-hold by using a fixed acquisition delay of approximately 20–25 seconds after initiating the contrast injection, or by using bolus tracking software that optimizes the CT acquisition based on the peak enhancement of the central pulmonary arterial vasculature. Chronic pulmonary emboli are often represented by recanalization of the thrombosed pulmonary arterial segment (Figure 16.14). Specific CT findings for chronic pulmonary emboli include peripheral eccentric thickening of the involved pulmonary arterial vasculature, represented by soft tissue rinds or linear webs. On reconstructed arterial segments, there may be abrupt caliber change of the involved pulmonary arterial segments.

16.2.1.4 MAY–THURNER SYNDROME

Obstruction of the common iliac and external veins may be due to bland tumor thrombus or malignancy, as has been described for the IVC. One unique diagnosis seen with the iliac veins is that of May–Thurner syndrome, which is defined as isolated left lower extremity swelling due to compression of the left iliac vein by the right common iliac artery. On axial CT evaluation, the maximum diameter of the left common iliac vein is decreased, measuring 3–4 mm in maximum diameter (Figure 16.15) versus a normal caliber iliac vein measuring 10–12 mm in average diameter.[16] Treatment for May–Thurner syndrome has historically involved anticoagulant therapy, but advances in interventional therapy have enabled relief of the associated mechanical compression by open surgical or endovascular repair (Figure 16.16). The success of primary and secondary endovascular techniques approaches 90%.[17,18]

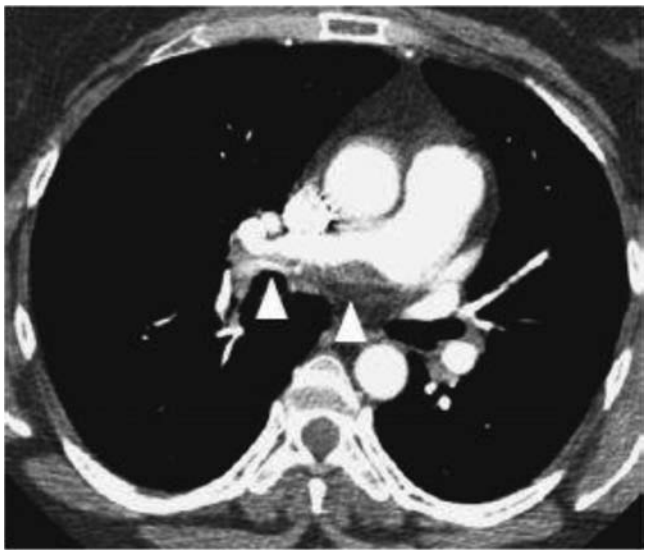

Figure 16.14 Chronic pulmonary emboli. Axial computed tomography imaging with chronic pulmonary emboli characterized by recanalization and irregular wall thickening (arrowheads).

16.2.1.5 TAILORED APPLICATIONS

State-of-the-art CT technology enables rapid acquisition of submillimeter high-resolution CT scans that can be interrogated and displayed in any imaging plane using 3D volumetric imaging analysis for accurate characterization of the sites of obstruction and for the patency of treated venous segments. Manipulation of the datasets allows exquisite display of complex anatomical and pathological relationships, including complex pulmonary arteriovenous malformations (Figure 16.17), complex intra-abdominal or pelvic venous malformations (Figure 16.18), or direct lower extremity venography (Figure 16.19).

16.3 IMAGING TECHNOLOGIES: MRI OF VENOUS DISEASE

16.3.1 Magnetic resonance venography

Magnetic resonance (MR) venography is usually not the first examination performed to evaluate the venous system, but it has a wide range of applications, and is often successful

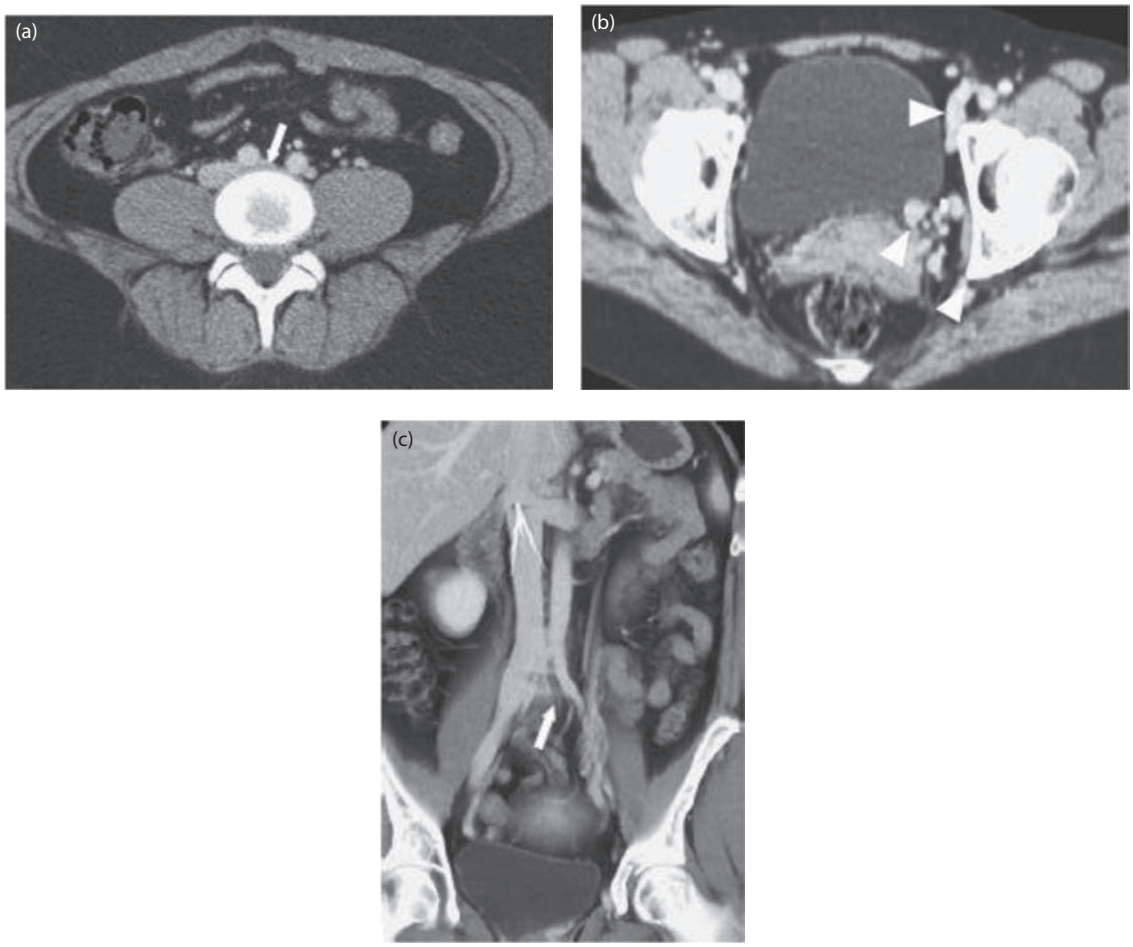

Figure 16.15 May–Thurner syndrome. Contrast-enhanced axial computed tomography shows marked compression of the left common iliac vein by the right common iliac artery (arrow in **a**, **c**) and associated prominent left pelvic venous collaterals (arrowheads in **b**).

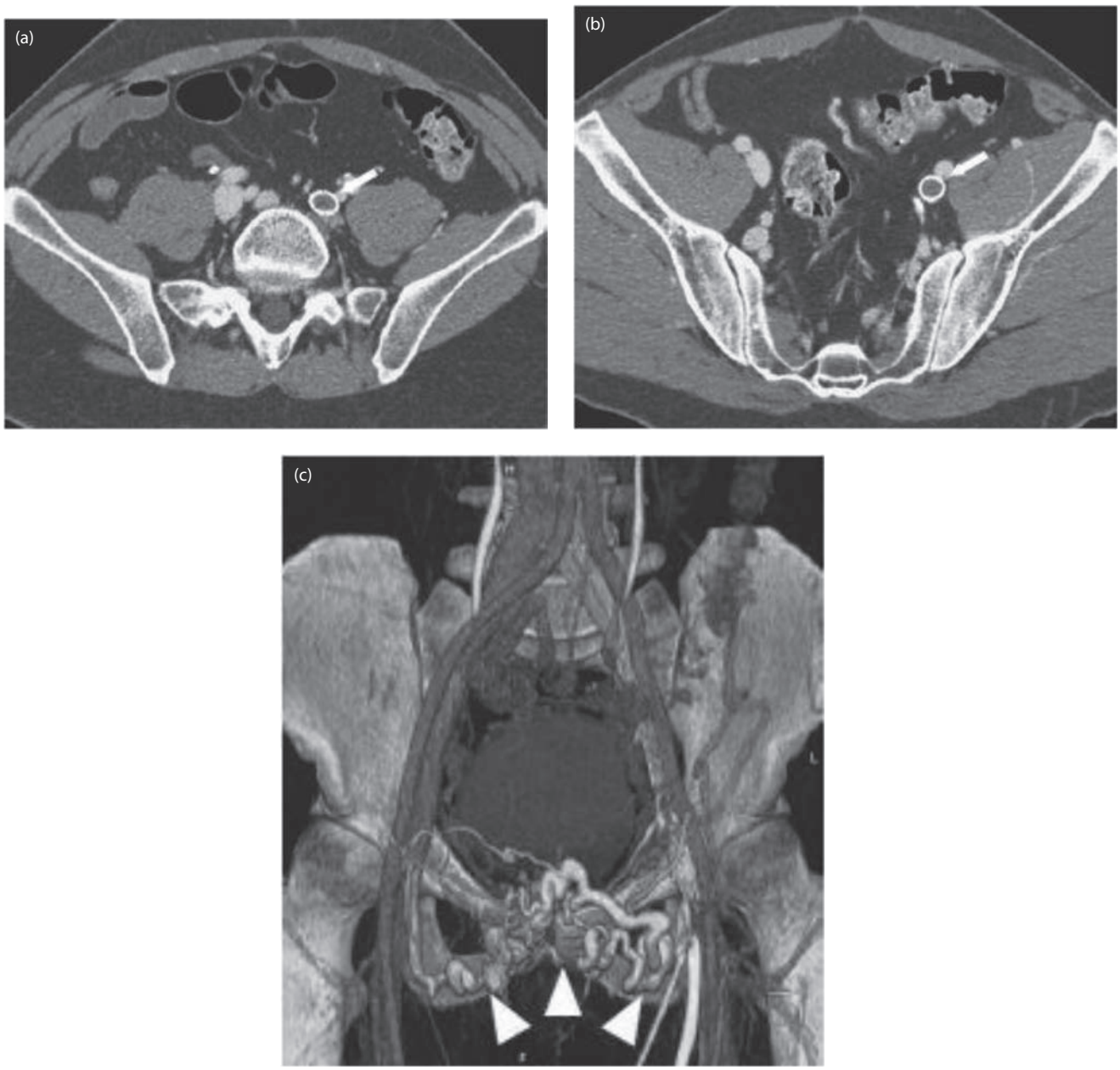

Figure 16.16 Post-procedural stent occlusion with venous collaterals. **(a, b)** Contrast-enhanced axial computed tomography demonstrates occlusion of the left iliac venous stent (arrows). **(c)** Volume-rendered 3D reconstructions demonstrate the extensive venous collaterals overlying the pubic symphysis (arrowheads).

where other techniques yield ambiguous results. MR venography comprises a number of different techniques, with different mechanisms of achieving vascular contrast. As such, flexibility is a major advantage of MR venography over most competing technologies: where one technique may not be particularly successful for a given application, it is usually possible to apply a different method and achieve satisfactory results. This flexibility can also be something of a limitation, however, since the range of choices can be somewhat daunting to those with limited experience.

Advantages of MR venography over CT venography include the ability to obtain diagnostic examinations without intravenous contrast, superior contrast-to-noise ratios of venous blood, and the ability to perform multiple acquisitions while waiting for contrast to appear in veins without incurring penalties in terms of additional radiation dose. In addition, a blood pool gadolinium-based MRI contrast agent (gadofosveset tridsodium) has recently been introduced, with an intravascular half-life of approximately 30 minutes. This agent provides a sustained high intravenous signal-to-noise ratio (SNR) in comparison to traditional extracellular gadolinium contrast agents, and enables improved flexibility in acquiring post-contrast MR venography data. MR venography is limited by generally lower spatial resolution in comparison to CT, by longer examination times, and by the exclusion of patients who are unstable

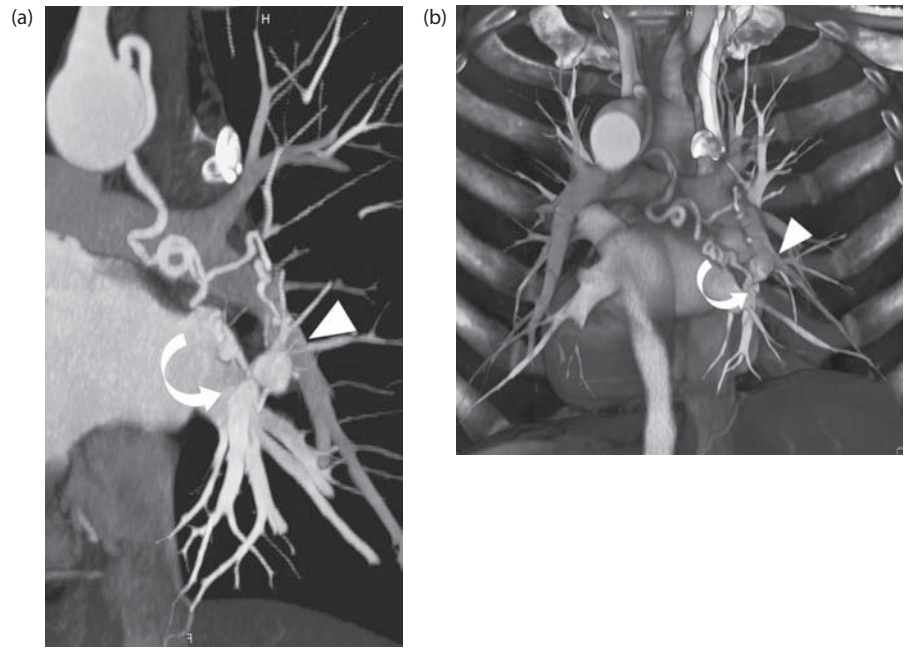

Figure 16.17 Computed tomography evaluation including **(a)** maximum intensity projection and **(b)** volume-rendered images with depiction of a complex pulmonary arteriovenous malformation communicating with the thoracic aorta (arrows) and pulmonary arteries (arrowheads) and pulmonary veins (curved arrows).

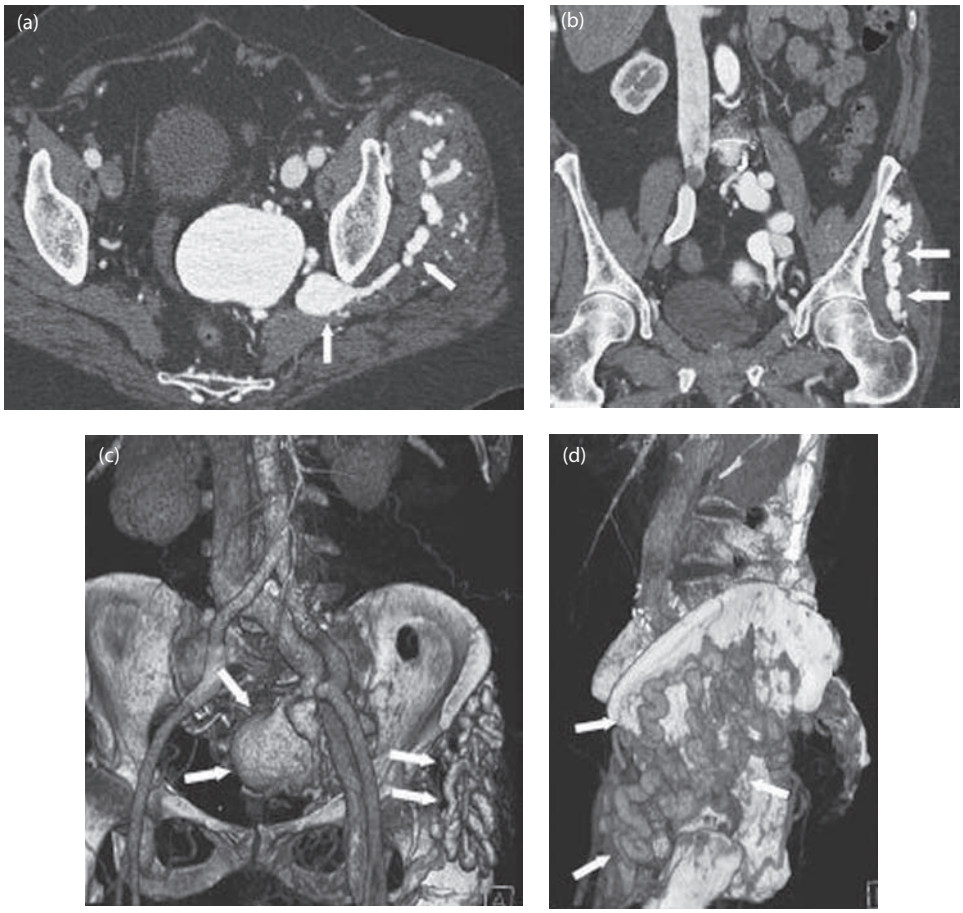

Figure 16.18 Contrast-enhanced computed tomography of the abdomen and pelvis demonstrates a large arteriovenous malformation surrounding the left hemipelvis on the **(a)** axial (arrows), **(b)** coronal (arrows), and **(c, d)** volume-rendered 3D reconstructions (arrows).

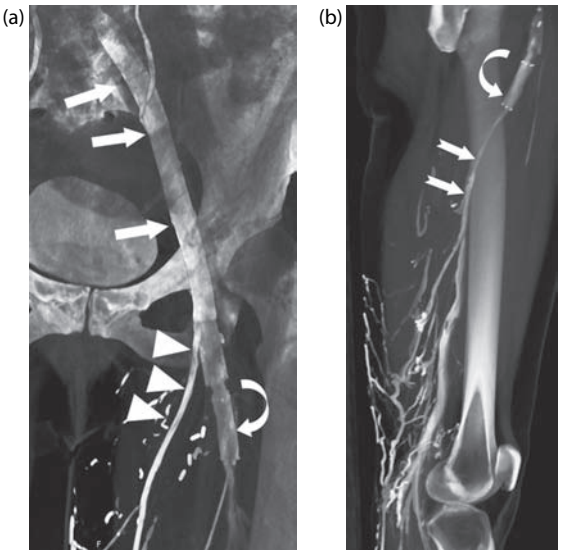

Figure 16.19 Lower extremity direct computed tomography (CT) venography. **(a)** Volume-rendered images acquired via direct CT venography with injection of contrast material into a dorsal vein of the foot demonstrates a patent covered stent in the left iliac vein (arrows) and a patent greater saphenous vein (arrowheads). **(b)** Patent stent in the proximal superficial femoral vein (curved arrows) with chronic changes due to deep venous thrombosis in the superficial femoral vein adjacent to the stent (notched arrow).

or have pacemakers or automatic implantable cardioverter defibrillators, and certain cerebral aneurysm clips.

16.3.2 Techniques

A large number of MR venography techniques are available. We have arbitrarily divided these into black blood, bright blood, and CE techniques.

Black blood MR venography pulse sequences are employed relatively infrequently as a dedicated venography technique; however, black blood effects are commonly seen in spin-echo and fast spin-echo sequences as a result of excited spins in blood flowing out of the imaging plane during acquisition (Figures 16.20 through 16.22). Spin-echo and fast spin-echo sequences employ a series of 90–180° radiofrequency (RF) pulses prior to data acquisition. Stationary spins experience both pulses and contribute to the resulting signal in the expected manner. Moving spins, on the other hand, may pass through the imaging slice between the initial 90° pulse and data acquisition, being replaced by non-excited spins that never experienced the initial pulse and therefore do not contribute signal to the image. This leads to a signal void, or black blood effect. More sophisticated black blood sequences employ electrocardiogram (ECG) gating as well as two inversion pulses in order to improve the reliability of this effect. Most black blood vascular sequences are designed for arterial imaging, but are also effective for venography, or can be optimized for venography by adjusting a few imaging parameters. Black blood venography sequences can clearly demonstrate filling defects in veins, and often provide high-quality anatomic images. It should be noted, however, that these techniques are notoriously artifact prone—slow-flowing blood, for example, often yields an incomplete signal void and can simulate venous thrombus. Likewise, in-plane rather than through-plane flow can lead to positive signals within veins that can be misinterpreted as thrombus. Diffusion-weighted imaging (DWI) (Figure 16.22) is an additional black blood technique that is rarely employed as a dedicated venography acquisition. DWI uses two or more gradient pulses applied in opposite directions, separated by a short time interval. The gradient pulses sensitize the acquisition to effects of microscopic diffusion, with signal loss occurring in proportion to small increments in microscopic diffusion. This technique is also exquisitely sensitive to bulk motion, such as blood flow, and generates a very reliable black blood effect in veins and arteries.

Most bright blood techniques rely on enhancing the signal of blood flowing into the imaging plane. These methods generally employ gradient echo or spoiled gradient echo sequences with sequential acquisition, in which all of the data for a single image are acquired before moving on to the next slice. In sequential imaging, stationary spins in a given slice are continually excited, and the magnetization does not have sufficient time to recover fully before the next excitation. This phenomenon of spin saturation results in a reduced signal in the stationary spins within the imaging slice. Moving spins, on the other hand, may enter the slice and contribute unsaturated signal to the image, leading to a higher signal intensity, or bright blood effect (Figure 16.20). Sequential gradient echo pulse sequences represent the most common form of bright blood venography—these are also known as time-of-flight techniques, and have been used in both MR angiography and venography.[19–21] Since blood flowing into the slice carries a bright signal from either direction, saturation pulses are applied either above or below the imaging slice to eliminate the inflow signal from arteries or veins. Time-of-flight MR venography is generally performed as a contiguous stack of thin 2D slices, ideally oriented perpendicular to the veins of interest. The 2D data can then be used to obtain 3D reconstructions, applying standard algorithms such as volume rendering or maximum intensity projection. Time-of-flight MR venography is a more robust technique than black blood methods, but remains prone to flow-related artifacts. Slow flow or in-plane flow may lead to pseudo-filling defects or poor vessel visualization.

A significant limitation of time-of-flight MR venography is the long acquisition times, typically in the order of 5–15 minutes, depending on the in-plane spatial resolution, slice thickness, and anatomic coverage. This is most problematic for imaging in the chest and abdomen, where motion artifacts from breathing can severely limit image quality. Images can be obtained during breath-holding—in this case, thicker slices are usually acquired with lower spatial resolution, so that breath-holds and total acquisition times are reasonable. This generally precludes 3D reconstructions of acceptable quality, however.

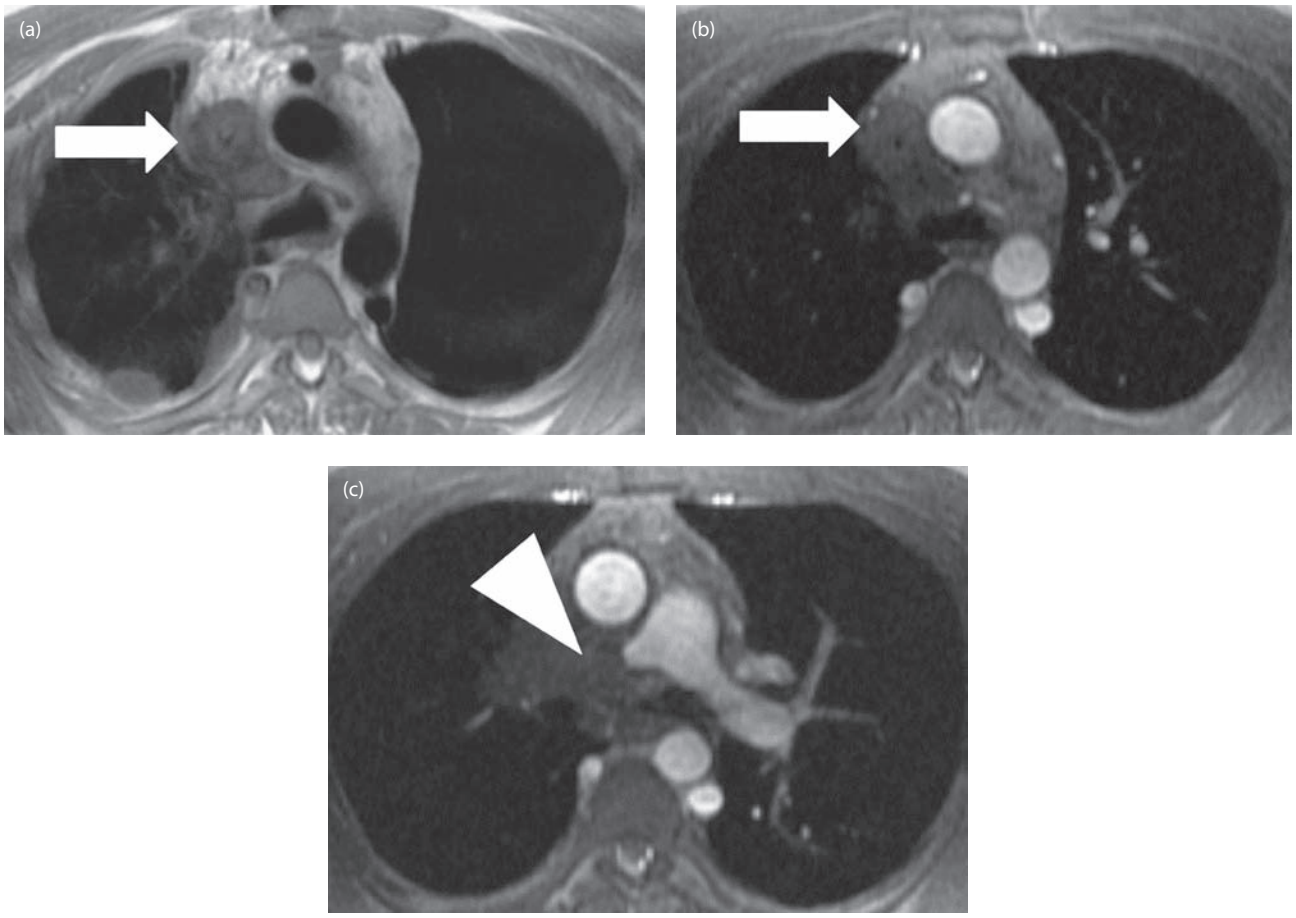

Figure 16.20 Black blood **(a)** and bright blood **(b, c)** non-contrast MR venography in a patient with fibrosing mediastinitis and superior vena cava (SVC) and right pulmonary artery occlusion. Occlusion of the SVC is demonstrated by the absence of flow void in the double inversion recovery fast spin echo image (arrow in **a**) and absence of bright blood signal in the fast gradient echo image (arrow in **b**). Note also the lack of bright blood signal in the right pulmonary artery (arrowhead in **c**), consistent with thrombosis.

Steady-state free precession (SSFP) pulse sequences represent another bright blood technique (Figures 16.21 and 16.22). These sequences maintain a steady state of both longitudinal and transverse magnetization by application of a series of balanced RF pulses. 2D SSFP sequences are generally faster than gradient echo or spoiled gradient echo acquisitions, and have higher SNRs. The most important difference, however, is that the bright blood appearance in SSFP images is primarily the result of the intrinsic magnetic relaxation properties of blood, rather than an inflow effect. This in turn means that there are fewer artifacts related to slow flow or in-plane flow. Acquisition times (particularly if used in conjunction with parallel imaging) are fast enough that two to four images can be obtained per second, and image quality is usually acceptable, even in patients who are unable to suspend respiration.[22,23] 3D SSFP pulse sequences can be acquired at a longer breath-held acquisition of 15–20 seconds, or can be obtained with respiratory triggering. Respiratory-triggered 3D SSFP magnetic resonance angiography (MRA) or magnetic resonance venography (MRV) pulse sequences often have additional modifications for improving background suppression and improving the SNR and contrast-to-noise ratio (CNR) of blood in order to enable 3D reconstructions—this generally involves a form of spin labeling, where a slab-shaped inversion pulse suppresses the signal of stationary spins within the imaging volume, while blood flowing into the slab is bright. These techniques are almost all designed with MR arteriography in mind, rather than venography, but can generally be modified fairly easily to accommodate venous imaging.

The limitations of SSFP sequences include fairly high background signals, even with fat suppression, so that 3D reconstructions are usually not practical. Banding artifacts near the edge of the field of view and adjacent to gas-containing structures are occasionally problematic. Optimal SSFP images with minimal artifacts require high-performance gradients, which are not universally available.

Phase-contrast pulse sequences are relatively uncommon in MR venography. In this technique, additional positive and negative gradient pulses are applied to a standard gradient recalled echo or spoiled gradient recalled echo (SPGR) sequence. Stationary spins experience no net accumulation of phase, whereas spins moving across the gradient accumulate a phase proportional to velocity. By

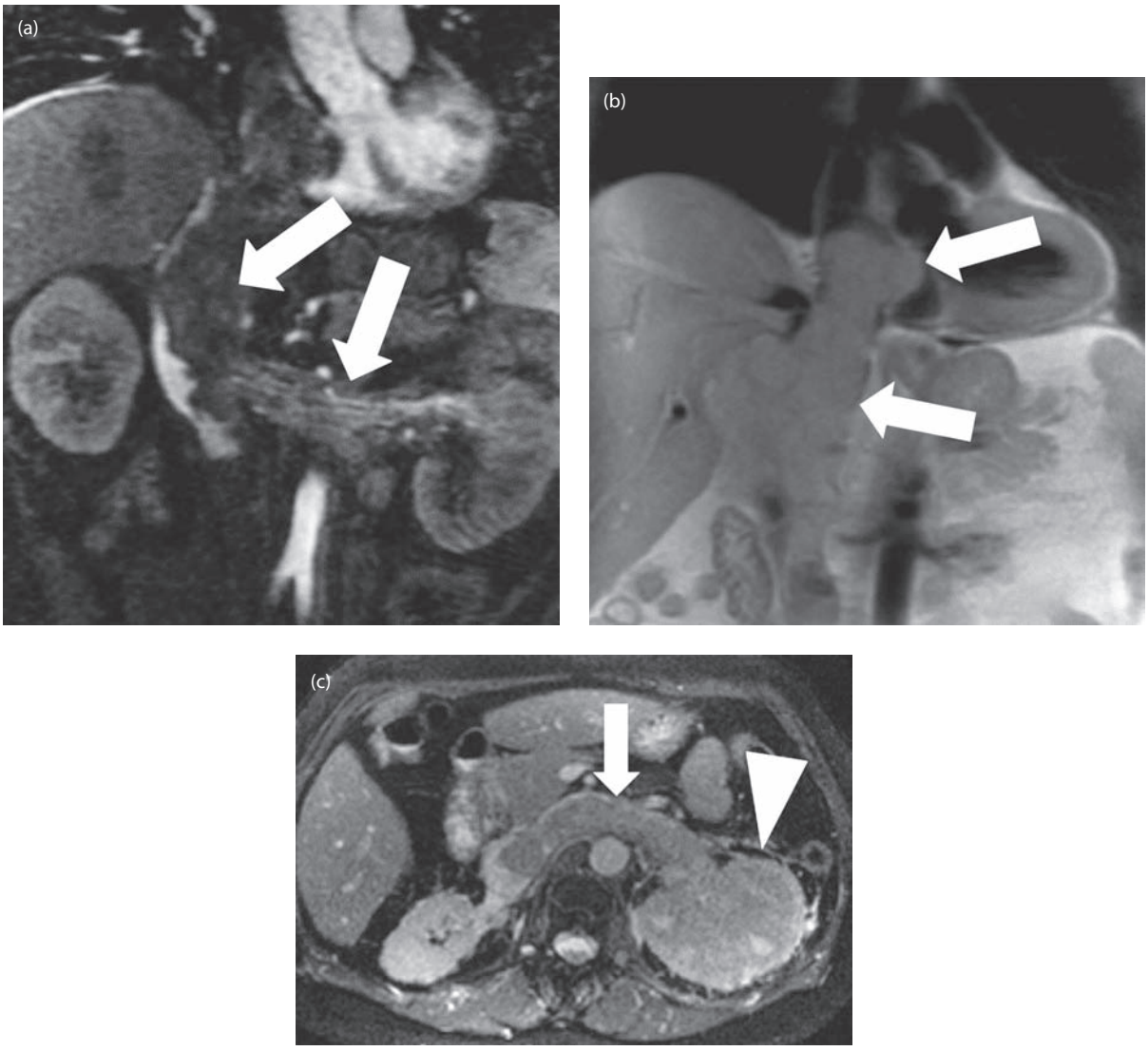

Figure 16.21 Renal cell carcinoma with renal vein and inferior vena cava (IVC) tumor thrombus. **(a)** Arterial phase 3D fat-saturated spoiled gradient echo image demonstrates extensive renal vein and IVC thrombus (arrows). Note linear enhancing thrombus in the left renal vein. **(b)** Black blood single shot fast spin echo image reveals large filling defect in IVC and right atrium (arrows) consistent with tumor thrombus. **(c)** Axial steady state free precession image reveals left renal mass (arrowhead) and renal vein tumor thrombus (arrow).

adjusting the strength of these velocity-encoding gradients, a range of velocities can be detected and measured. The major advantage of phase-contrast venography is that it generates images in which the velocity of each pixel can be determined. By incorporating ECG triggering, venous flow can be measured with high accuracy. This can be useful in the setting of chronic mesenteric ischemia and in evaluating the significance of a venous stenosis. The major limitation of phase-contrast techniques is that the acquisition times are longer than for time-of-flight and SSFP sequences.

CE MR venography is probably the most widely used technique currently. This technique is essentially identical to 3D CE MR angiography, employing a 3D spoiled gradient echo sequence, with or without fat saturation, in conjunction with a bolus of gadolinium-based contrast (Figures 16.21 and 16.23 through 16.25). Vascular contrast is the result of the T1-shortening effects of gadolinium on adjacent water protons and has relatively little dependence on inflow effects. The T1-weighted 3D SPGR sequence provides a moderate amount of background suppression.[24–26]

The simplest 3D CE MR venography techniques involve one or more additional acquisitions after performing MRA: the contrast bolus is injected and MRA is performed when the concentration of the gadolinium contrast agent is maximal in the arteries. Additional phases are then acquired until venous contrast is maximal. Alternatively, a test bolus or fluoroscopic triggering can be used to optimize the timing of the acquisition to maximize venous rather than arterial concentration: this reduces the total number of acquisitions, but does limit opportunities for subtraction of arterial phase data.

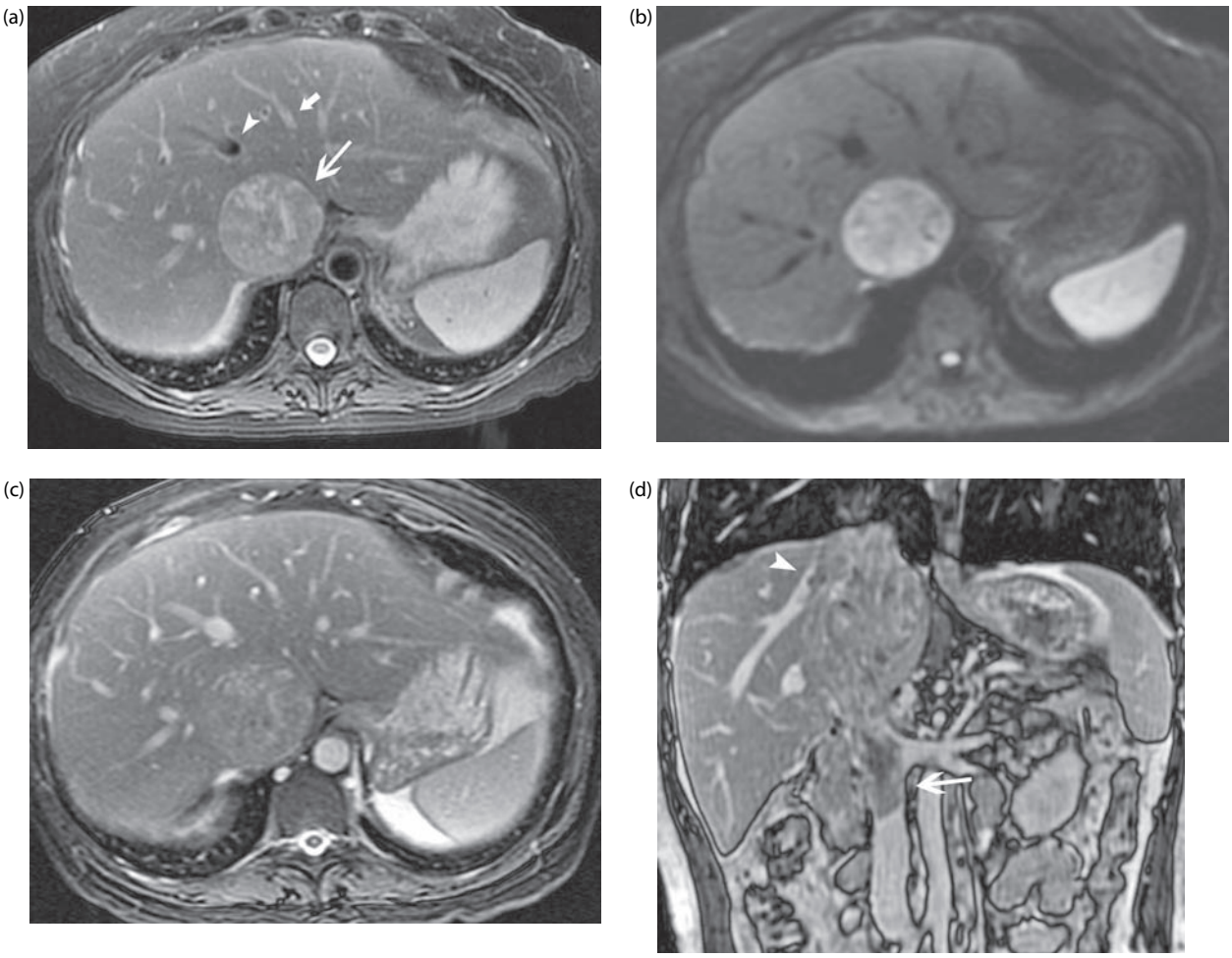

Figure 16.22 Inferior vena cava (IVC) sarcoma imaged with non-contrast black and bright blood techniques. Axial fast spin echo (FSE) black blood image **(a)** reveals a large heterogeneous mass expanding the intrahepatic IVC (large arrow). Note the absence of flow voids in the left (small arrow) and right hepatic veins due to the presence of slow in-plane flow. A flow void is present in the middle hepatic vein (arrowhead). Diffusion-weighted image **(b)** at a similar location again shows the IVC mass, with greater contrast in comparison to the FSE image. Diffusion-weighted images show a more robust black blood effect, with dark flow voids in all hepatic veins. Bright blood axial 2D steady-state free precession (SSFP) image **(c)** again demonstrates an IVC mass, with bright signal intensity in the hepatic veins. Coronal 3D SSFP image **(d)** reveals a small amount of tumor thrombus in the orifice of the middle hepatic vein (arrowhead). Note also bland thrombus with darker, more uniform signal intensity along the inferior margin of the IVC mass (arrow).

A significant advantage of 3D CE MR venography relative to time-of-flight MR venography techniques is that the acquisition times are generally short enough for acquisition in a single breath-hold. Since there is no reliance on vascular inflow effects, the plane of acquisition has no effect on the vascular signal. The 3D acquisition volume can therefore be optimized for maximum efficiency: oblique coronal for visualizing the IVC, pelvic veins, and extremity veins, for example, achieving maximal volumetric coverage within a breath-hold.

CE MR venography has some limitations compared with the more common MRA technique: the contrast bolus is less compact and more dilute by the time it reaches the venous system, and therefore the maximal contrast enhancement in veins is generally lower than that achieved in arteries. Nevertheless, it is usually more than adequate for diagnostic purposes. The addition of fat saturation (usually via chemical saturation pulses) is often helpful in reducing background signal and improving venous contrast, albeit at the cost of slightly longer acquisition times. Finally, the requirement for breath-hold imaging places fundamental constraints on achievable spatial resolution and SNR: increments in both spatial resolution and SNR generally require increased acquisition times, and increased spatial resolution results in reduced SNR. Breath-hold imaging is not a requirement in some anatomic regions, such as the pelvis and extremities; in these cases, multiple acquisitions can be performed with relatively high spatial resolution and high SNR.

The recent introduction of an intravascular—or blood pool—gadolinium-based contrast agent (gadofosveset tridsodium) has increased the flexibility of 3D CE MRV.[27]

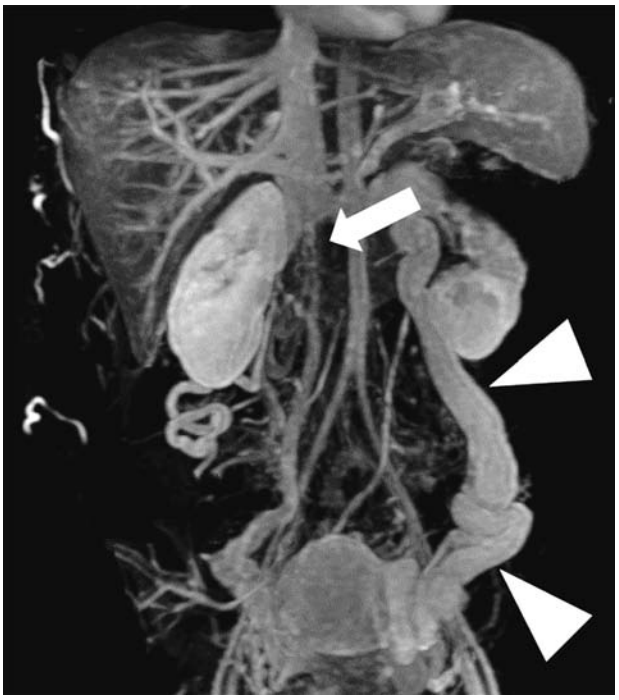

Figure 16.23 Chronic IVC occlusion with collateral formation. Maximum intensity projection image from contrast-enhanced 3D spoiled gradient echo acquisition demonstrates occlusion of the IVC below the renal veins (arrow) with massive dilatation of the left gonadal vein (arrowheads).

Figure 16.24 IVC thrombosis. Partial volume maximum intensity projection image from 3D spoiled gradient echo acquisition reveals extensive bland thrombus in the IVC and left renal vein (arrows).

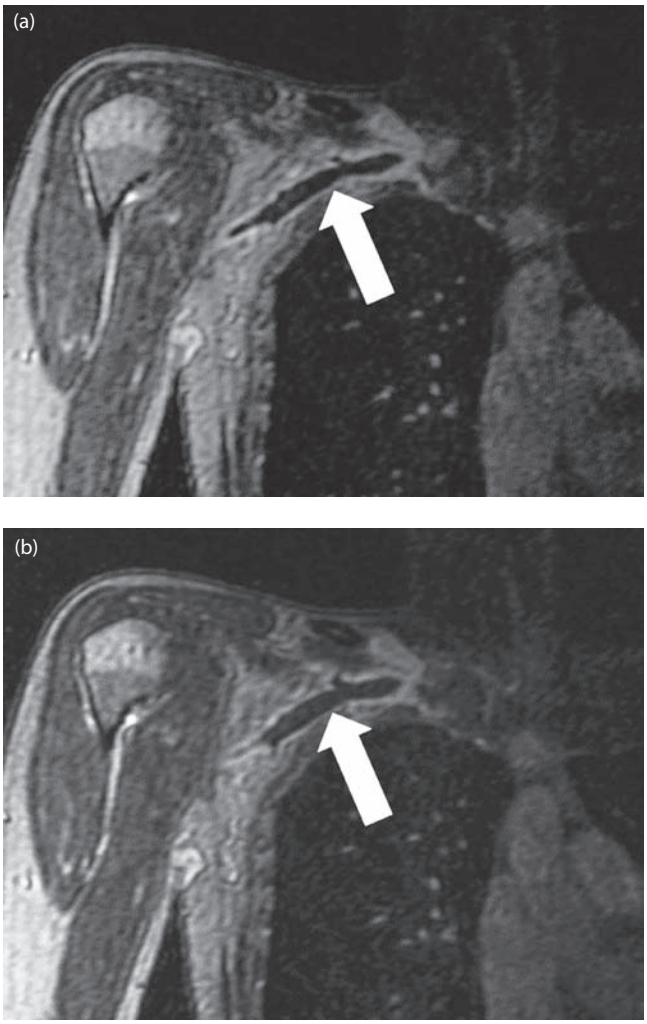

Figure 16.25 Axillary and subclavian vein thrombosis. Source images from 3D contrast-enhanced MR venography reveal occlusive thrombus (arrows).

Intravascular agents reversibly bind to albumin and have an intravascular half-life of approximately 30 minutes, which improves the intravascular SNR over a long temporal window and allows for multiple repeated acquisitions. Intravascular agents are particularly helpful for visualizing slow-filling structures such as complex venous malformations (Figure 16.26), and also allow extended field-of-view examinations, where previously excretion of contrast and loss of intravascular signal would be problematic by the end of the examination. The lengthened temporal window for vascular imaging also means that higher-spatial resolution images can be acquired, particularly in regions without underlying motion (extremities and pelvis).

3D MR venography data can be reconstructed using standard techniques, such as reformatting, maximum intensity projection, and volume rendering. Partial volume minimum intensity projection images may be useful for accentuating venous thrombosis. Subtraction techniques are sometimes useful for removing background signal or arterial signal. If pure arterial phase images are acquired,

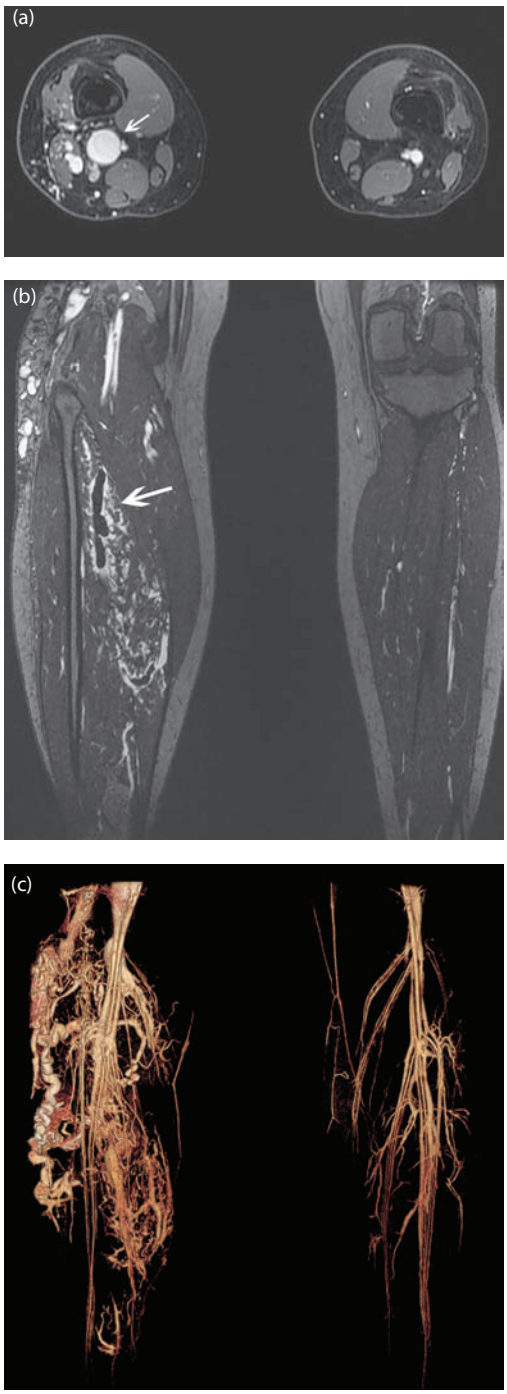

Figure 16.26 Klippel–Trenaunay syndrome in the right lower extremity demonstrated using an intravascular contrast agent. Axial fat-suppressed 3D spoiled gradient recalled echo (SPGR) image **(a)** obtained approximately 10 minutes after contrast injection demonstrates massive enlargement of the central right popliteal vein (arrow) in comparison with the normal left side, with multiple additional enhancing intramuscular and subcutaneous varicosities. Coronal 3D SPGR image **(b)** again demonstrates extensive right calf varicosities, as well as an expanded thrombosed intramuscular vein (arrow). Volume-rendered image **(c)** again demonstrates extensive deep and superficial varicosities in the right calf in comparison to the normal left-sided arteries and veins.

for example, these can be subtracted from venous phase images to generate a purely venous dataset (Figure 16.27b). Likewise, simply subtracting a pre-contrast mask acquisition from the optimal venous phase data will reduce the amount of background signal and may improve the quality of the 3D reconstructed images. Subtraction techniques rely on the assumption that there is no shift in position between the two acquisitions; this is not always the case, particularly in patients who are not consistent breath-holders.

Limitations of the CE MR venography techniques include the need for intravenous contrast: there is an association between gadolinium contrast administration and nephrogenic sclerosing fibrosis in patients with severe renal insufficiency,[28] and as a general rule, gadolinium-based contrast agents are not recommended in patients with an estimated glomerular filtration rate of <30 mL/minute/1.73 m^2. In addition, there is also a small risk of allergic reaction to gadolinium-based contrast agents, although this is probably somewhat lower than the risk associated with the iodinated contrast agents used in CT. Occasionally, the amount of contrast in the veins is not adequate for optimal visualization; this is probably most common in the lower extremities and pelvis in patients with very slow venous return. In these cases, an increased contrast dose or multi-excitation acquisitions may improve image quality. An important advantage of MR venography with respect to CT is that the exact timing of the venous phase acquisition is less important: there is no penalty in MRI for acquiring multiple acquisitions until the venous contrast is optimal, whereas the cumulative radiation dose is a significant consideration in CT.

Direct MR venography is a technique that is advocated by several authors in which a dilute bolus of gadolinium contrast is injected directly into the venous territory of interest

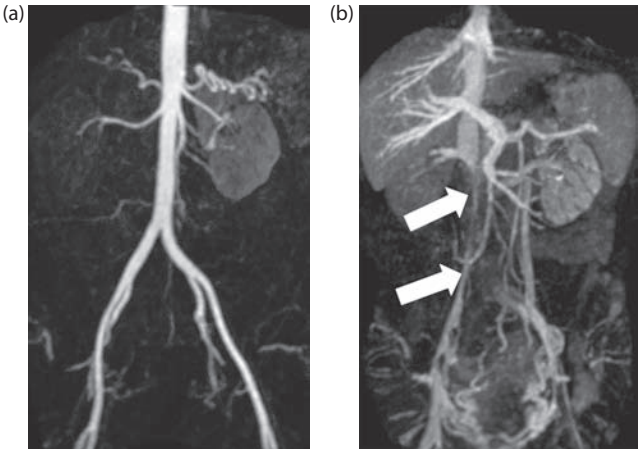

Figure 16.27 **(a)** Arterial and **(b)** venous phase maximum intensity projection images from contrast-enhanced MR angiography/venography in patient with severe IVC stenosis following radiation therapy to a lumbar vertebral metastasis. Note thread-like IVC (arrow) in **(b)**. Residual arterial contrast was removed from the venous phase image by subtracting the arterial phase source images from the venous phase source images.

Figure 16.28 Direct venogram in patient with subclavian vein thrombosis. Volume-rendered image from contrast-enhanced 3D spoiled gradient echo sequence obtained while injecting dilute gadolinium contrast into a peripheral right-sided vein reveals patent SVC (arrow), occluded distal right subclavian vein (arrowhead), and extensive collateral formation (asterisks).

while simultaneous scanning is performed (Figure 16.28). This avoids the problem of contrast dilution that occurs when the contrast bolus first passes through the arterial system. The two major limitations of this technique are that venous access needs to be established in a peripheral vein of interest (typically the hand or foot) and that unless both arms or legs are injected simultaneously, there will be only minimal visualization of contralateral veins.[28–30]

16.3.3 Clinical applications

MR venography generally plays a secondary role in venous imaging. Duplex Doppler sonography is generally the first test performed in assessing lower or upper extremity veins for thrombosis. Sonography is accurate, portable, and considerably less expensive than MR venography, but is occasionally limited. Sonography is less effective at visualizing the central veins of the thorax, the entire extent of the IVC, and the iliac veins.

16.3.3.1 UPPER EXTREMITY AND CENTRAL THORACIC VEINS

Deep and superficial veins of the upper extremity are generally well seen with sonography; however, visualization of more central thoracic veins is limited, and MRV can generally provide diagnostic images in patients with suspected SVC, brachiocephalic, subclavian, or jugular vein stenosis or occlusion (Figures 16.20, 16.25, and 16.28).[25,30] Both CE and non-contrast techniques[31,32] are effective, and MRV can be combined with anatomic imaging to characterize obstructing lesions in the mediastinum.

16.3.3.2 PULMONARY VEINS

Assessment of pulmonary veins with MRV is useful both before (to define anatomy) and after (to detect complications, such as pulmonary vein stenosis or occlusion) RF ablation of arrhythmogenic foci in the left atrium (Figure 16.29).[33] Pulmonary MRV can be combined with cardiac MRI; some authors have suggested that the presence of atrial late gadolinium enhancement may be helpful in planning therapeutic interventions.[34] Congenital anomalies of the pulmonary veins, such as anomalous pulmonary venous return, are also well seen with MRV (Figure 16.30),[35] and can be combined with functional assessment of the heart and quantification of shunt severity by measurement of the ratio of pulmonary artery to aortic blood flow (Q_p/Q_s).

16.3.3.3 IVC AND RENAL VEINS

The IVC can be accurately assessed with CE or non-contrast MRV. Venous extension is an important consideration in staging and treating renal cell carcinoma: the renal vein is invaded in as many as 20% of cases and the IVC in approximately 10%. MRI is an ideal technique for the evaluation of renal cell carcinoma. It is highly accurate at detecting and characterizing renal masses. Regional adenopathy, direct invasion of adjacent structures, and distant metastases are easily visualized. Vascular staging including MR venography reveals the presence or absence of bland or tumor thrombus in the renal veins and IVC, as well as the venous anatomy, and this information plays a role in choosing the most appropriate surgical approach and technique.[23,24,36–38] Tumor thrombus enhances after contrast administration and is generally heterogeneous in appearance, whereas bland thrombus is uniformly dark on all pre- and post-contrast sequences (Figures 16.21 and 16.31). Several recent studies have compared MRI with multi-detector CT for the vascular staging of renal cell carcinoma, and have generally found both techniques to be highly accurate.[37,38] Both MRI and CT are commonly used to screen potential living renal transplant donors: the number and location of renal arteries and veins is important in surgical planning. MR venography in conjunction with MRA can answer these questions effectively, without exposing patients to iodinated contrast and ionizing radiation.[39]

16.3.3.4 PORTAL, HEPATIC, AND MESENTERIC VEINS

The portal, hepatic, and mesenteric veins are well visualized during standard abdominal MRI; thrombosis can easily be detected, and often the underlying cause elucidated. MRI is an excellent technique for the detection and characterization of hepatic masses, and invasion of hepatic or portal veins is usually well seen (Figure 16.32). Varices in the setting of portal hypertension can be demonstrated,

and the direction of portal venous flow determined using phase-contrast techniques.[40] Sonography is the primary technique used to assess for vascular complications following hepatic transplantation. MRI is a useful secondary examination technique when sonography is limited or indeterminate. Portal vein and IVC anastomoses can be directly visualized and stenosis or thrombosis detected.

Figure 16.29 Pulmonary vein stenosis following left atrial radiofrequency ablation of the left atrium. Posterior volume-rendered image from 3D gadolinium-enhanced pulmonary venogram demonstrates severe stenosis of the left superior pulmonary vein (arrow) at its junction with the left atrium.

Computed tomographic angiography (CTA) is probably slightly more sensitive for the detection of arterial complications; however, MRI excels at the assessment of the biliary tree and hepatic parenchyma. Some authors have also advocated the use of phase-contrast techniques in patients with suspected chronic mesenteric ischemia, demonstrating a lack of normal increased flow in the superior mesenteric vein following a fatty meal.

16.3.3.5 ILIAC AND LOWER EXTREMITY VEINS

Deep vein thrombosis (DVT) is a fairly common problem, with approximately 260,000 cases diagnosed in the United States every year. The diagnosis is most often made with duplex sonography, which is usually highly accurate for the detection of femoral and popliteal DVT, but is somewhat limited in the evaluation of pelvic and calf veins, obese patients, and chronic asymptomatic thrombus.

Several studies have demonstrated the effectiveness of MR venography for detecting pelvic and lower extremity venous thrombosis.[19,20,27,41–43] Carpenter et al.[19] reported a sensitivity of 100% and specificity of 96% for the evaluation of DVT from the IVC to the popliteal vein compared with 2D time-of-flight MR venography and conventional venography. Evans et al.[20] found MR venography to be more sensitive than sonography, but of equivalent specificity for femoropopliteal DVT. More recently, Fraser et al.[41] employed a CE subtraction technique to evaluate femoral and iliac veins for DVT, finding sensitivity and specificity values of 100% in comparison to conventional venography. Ruehm et al.[42] achieved excellent image

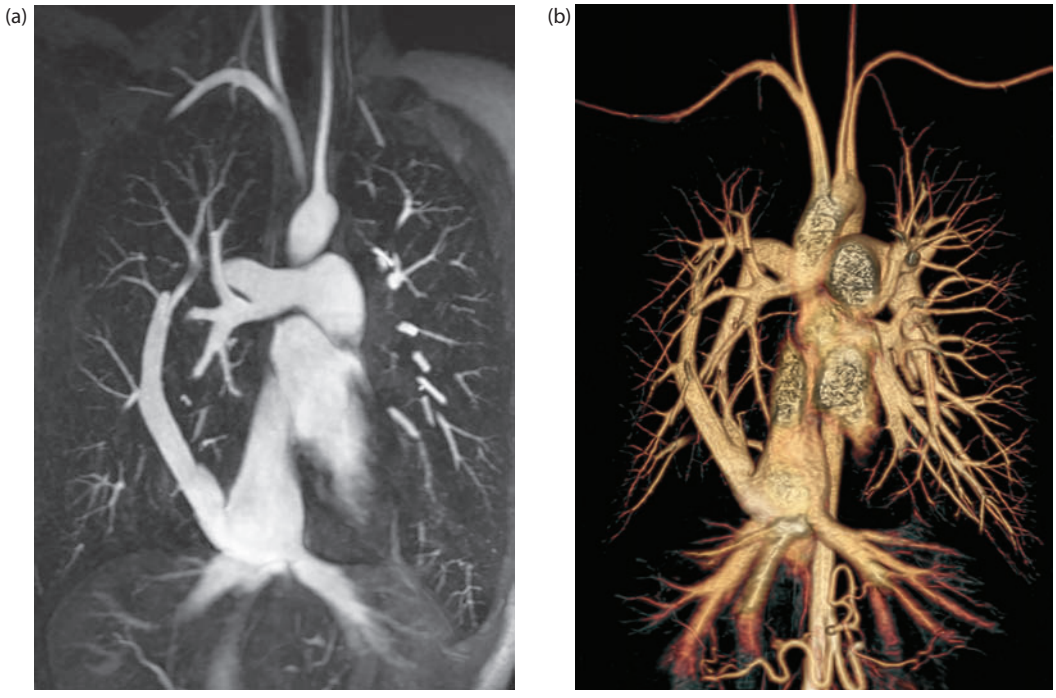

Figure 16.30 Scimitar syndrome. Partial maximum intensity projection (MIP) image **(a)** and volume-rendered image **(b)** from 3D gadolinium-enhanced pulmonary venogram reveal a large anomalous vein draining the right lung and entering the inferior vena cava just above the diaphragm.

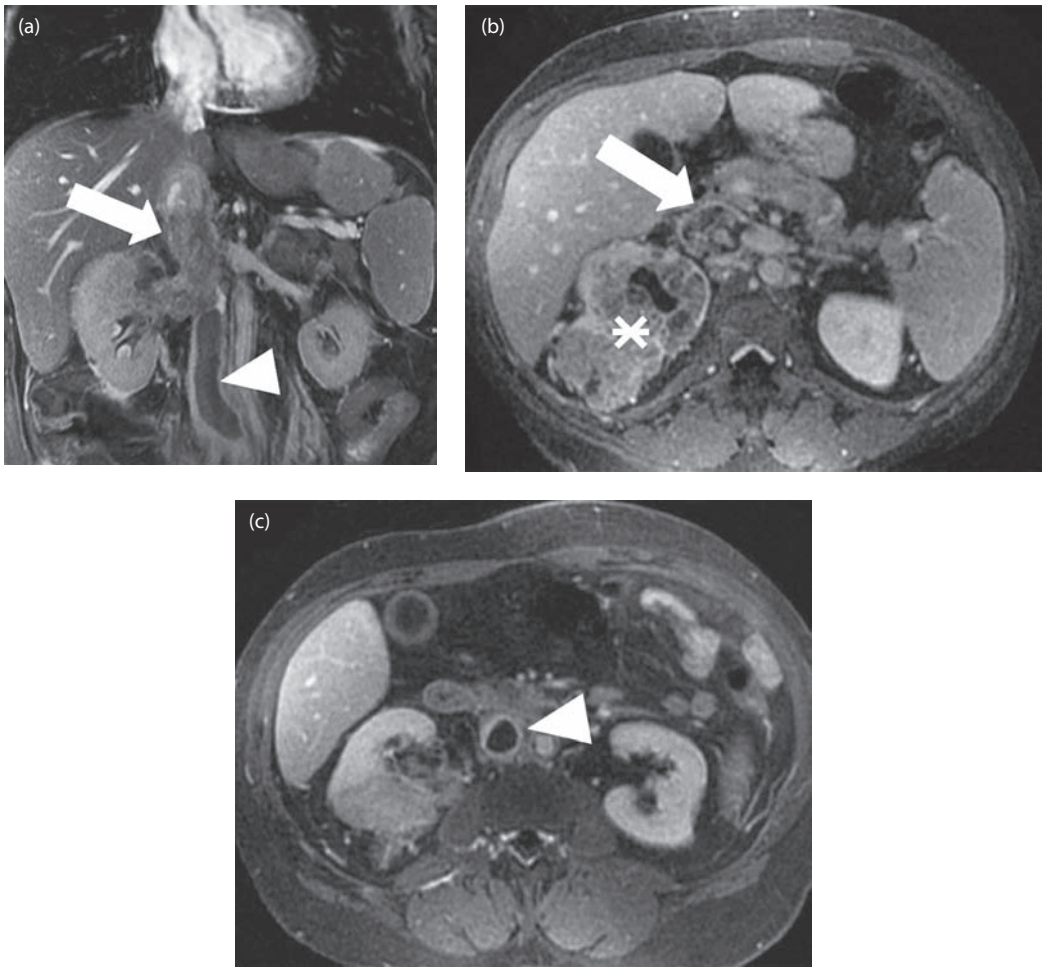

Figure 16.31 Renal cell carcinoma (asterisk) with tumor thrombus and bland thrombus. **(a)** Coronal fat-saturated steady-state free precession image reveals a right renal mass with expansion of the renal vein and IVC and absence of the normal bright-blood signal within these vessels. Note the difference between the more heterogeneous and higher signal intensity tumor thrombus extending superiorly (arrows) and the bland thrombus in the IVC below the level of the renal vein (arrowhead). **(b, c)** Axial contrast-enhanced fat-saturated 3D spoiled gradient echo images show similar findings, with enhancing, heterogeneous tumor thrombus at the level of the left renal vein (arrow in **b**), and uniform, non-enhancing bland thrombus more inferiorly (arrowhead).

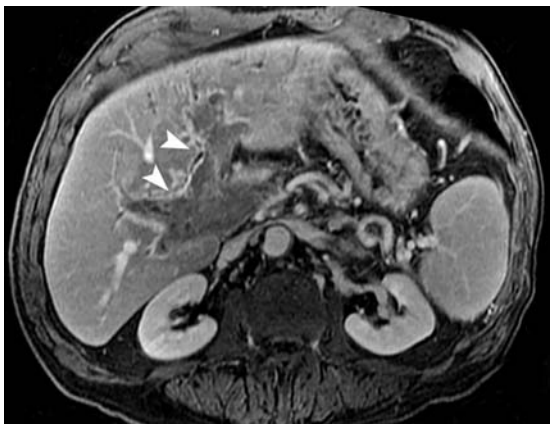

Figure 16.32 Infiltrative hepatocellular carcinoma (HCC) predominantly involving the portal vein. Axial venous phase post-gadolinium 3D spoiled gradient recalled echo image demonstrates expansion of the main and peripheral portal veins with heterogeneously enhancing tumor (arrowheads).

quality in a CE direct MR venography study of the lower extremity veins.

Although non-contrast techniques have proved sensitive and specific in several studies, their acquisition times can be quite long, potentially reducing patient cooperation and image quality—the major advantage of the CE methods is probably their the much shorter acquisition and reduced total examination times (Figures 16.26 and 16.33). An additional advantage of MR and CT venography compared with conventional venography in the evaluation of iliac and lower extremity veins is the excellent soft tissue detail inherent in these techniques, which can provide insight into the cause of venous thrombosis (Figure 16.34).

16.3.3.6 SPECIFIC SYNDROMES AND SPECIAL SITUATIONS

May–Thurner syndrome represents symptomatic stenosis or thrombosis of the left common iliac vein by the overlying

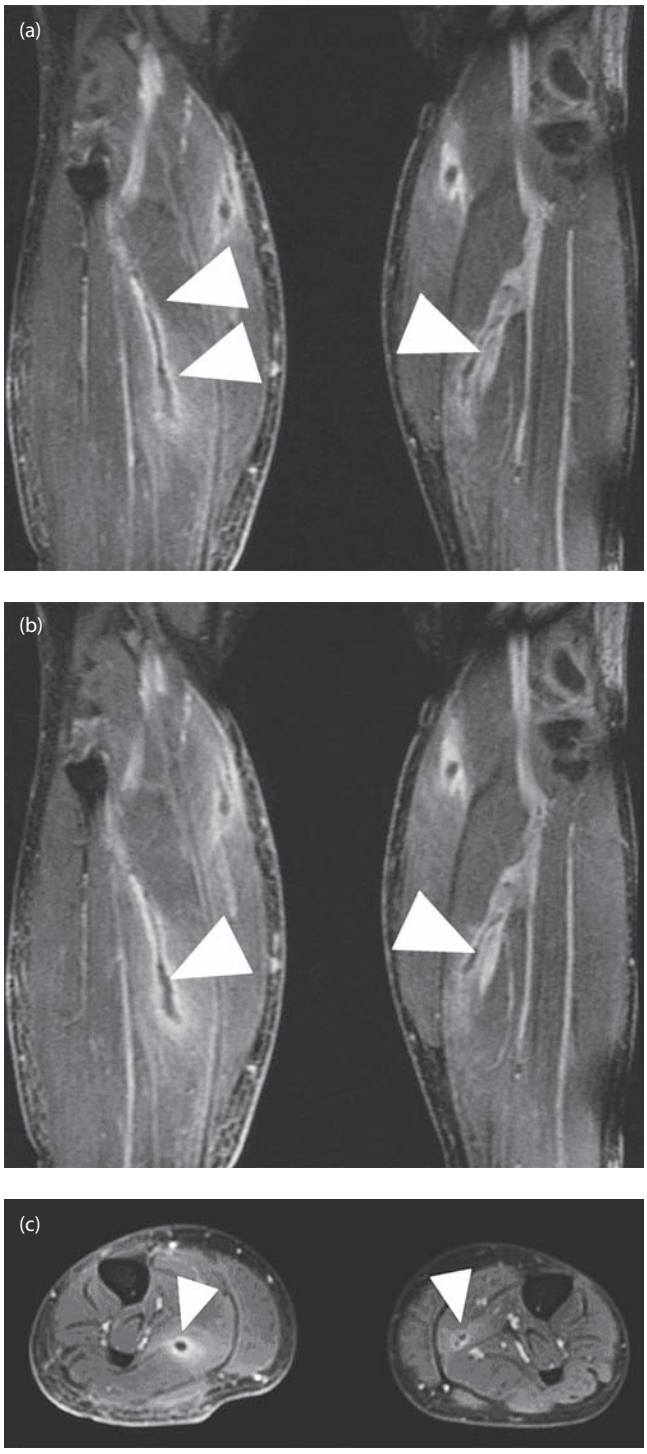

Figure 16.33 Superficial venous thrombosis in the calf. **(a, b)** Coronal and **(c)** axial contrast-enhanced fat-saturated 3D spoiled gradient echo images reveal filling defects in bilateral veins (arrowheads), surrounded by inflammatory enhancement of the vessel walls and adjacent muscle.

right common iliac artery. MRA/MRV can show the course of both the iliac arteries and veins (Figure 16.35), and the use of an intravascular contrast agent allows for additional maneuvers (prone imaging to demonstrate persistent iliac vein stenosis) without the need for additional contrast injection.

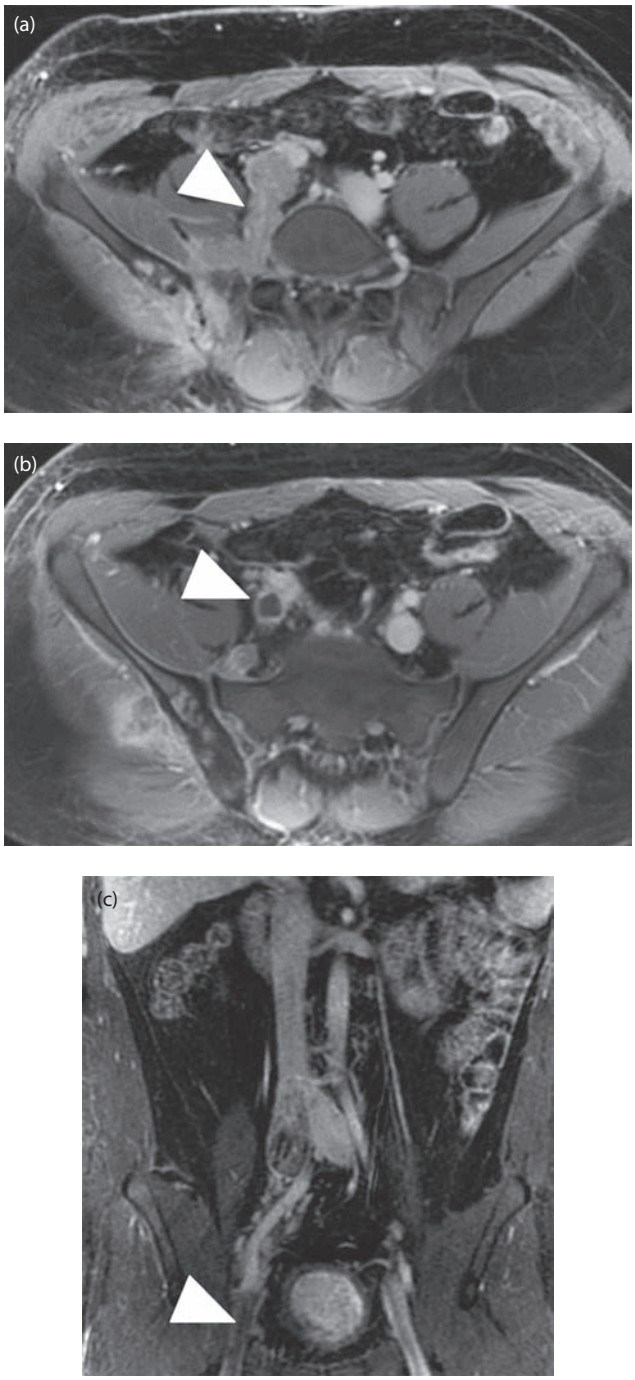

Figure 16.34 Ewing sarcoma with venous extension. **(a, b)** Axial contrast-enhanced fat-saturated spoiled gradient echo images reveal a mass in the right iliac bone with extension into the adjacent muscle. Note enlarged right internal iliac vein filled with tumor thrombus (arrowhead in **a**), and bland thrombus in the external iliac vein at a lower level (arrowhead in **b**). **(c)** Coronal 3D spoiled gradient echo image again demonstrates tumor thrombus in the right common iliac vein (arrowhead).

Nutcracker syndrome describes compression of the left renal vein between the abdominal aorta and superior mesenteric artery, with resultant development of venous varicosities adjacent to the left kidney and ureter and dilatation of

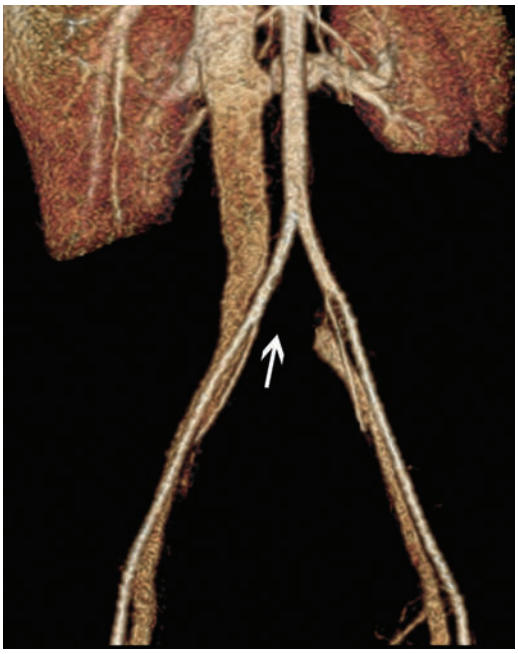

Figure 16.35 May–Thurner syndrome. Coronal volume-rendered image from 3D contrast-enhanced MRA/MRV demonstrates focal thrombosis of the left common iliac vein (arrow) distal to the overlying right common iliac artery.

the left gonadal vein (Figure 16.36). Demonstration of these findings is most easily accomplished with coronal CE MRA/MRV.

Pelvic congestion syndrome describes chronic pelvic pain associated with pelvic venous congestion and incompetent, dilated ovarian veins. Standard CE or non-contrast pulse sequences can demonstrate prominent parametrial pelvic veins, which is a relatively non-specific finding. Time-resolved MRA has been proposed as an additional technique, with demonstration of contrast reflux from the renal veins into the dilated, incompetent ovarian veins.[44]

Venous thoracic outlet syndrome occurs with chronic thrombotic (Paget–Schroetter syndrome) or non-thrombotic (McCleery syndrome) compression of the subclavian veins. Sonography is often adequate for diagnosis; however, MRV is useful in equivocal cases.[45] Images can be acquired with provocative maneuvers, and the use of an intravascular gadolinium contrast agent allows for multiple acquisitions following a single dose of contrast (Figure 16.37).

16.3.3.7 VENOUS AND ARTERIOVENOUS MALFORMATIONS

Arteriovenous malformations exhibit rapid filling from feeding arteries with immediate visualization of draining

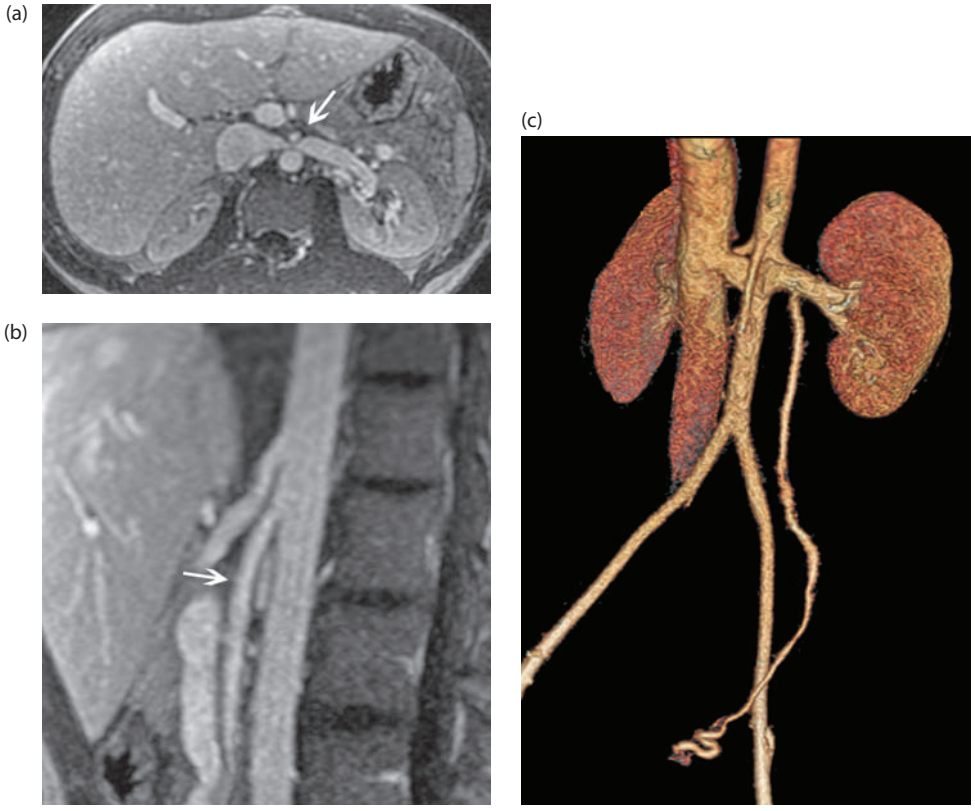

Figure 16.36 Nutcracker syndrome. Axial **(a)** and sagittal **(b)** reformatted images from 3D contrast-enhanced MRV demonstrate marked compression and narrowing of the left renal vein by the overlying superior mesenteric artery (arrows). Coronal oblique volume-rendered image **(c)** again shows focal compression of the left renal vein, as well as a dilated left gonadal vein and small varicocele.

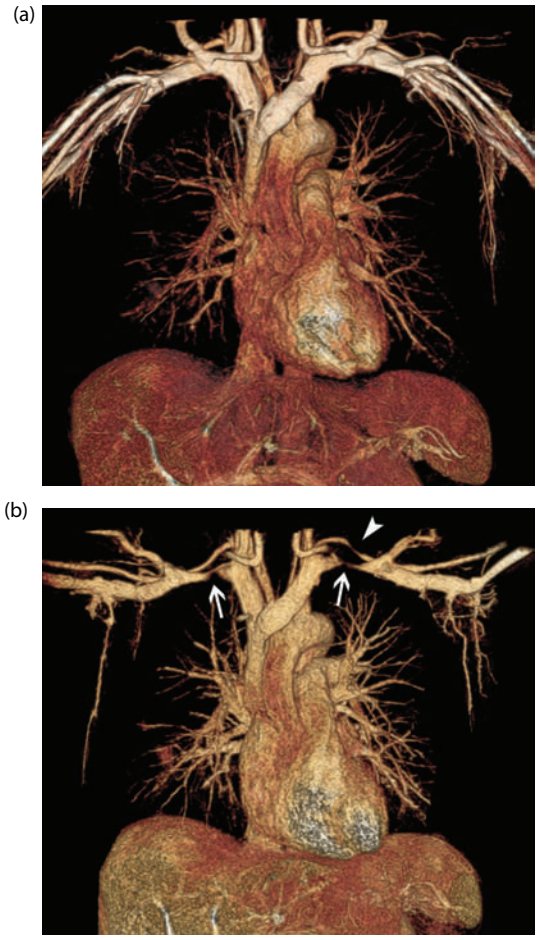

Figure 16.37 Venous thoracic outlet syndrome. Volume-rendered image from a thoracic venogram with the arms in a neutral position **(a)** obtained following a single injection of intravascular gadolinium contrast agent, demonstrating normal appearance of the thoracic veins. Volume-rendered image with the arms elevated **(b)** reveals severe stenosis of the subclavian veins bilaterally (arrows), as well as stenosis of the left subclavian artery (arrowhead).

veins. Time-resolved CE MRV acquisitions are helpful in order to fully depict the anatomy of these lesions. Venous malformations may fill slowly, and delayed acquisitions can be helpful for appreciating the extent of the lesions, particularly following injection of an intravascular contrast agent.

16.3.3.8 POST-OPERATIVE IMAGING

MRV can be very useful for assessing complications following venous surgery (Figure 16.38), although visualization of the vessel lumen may be limited following stent placement.

16.3.4 MR versus CT venography

The major advantages of CT with respect to MR are its speed and spatial resolution. Large volumes can be covered in only a few seconds with state-of-the-art, 64-row multidetector CT, with an isotropic spatial resolution of less than

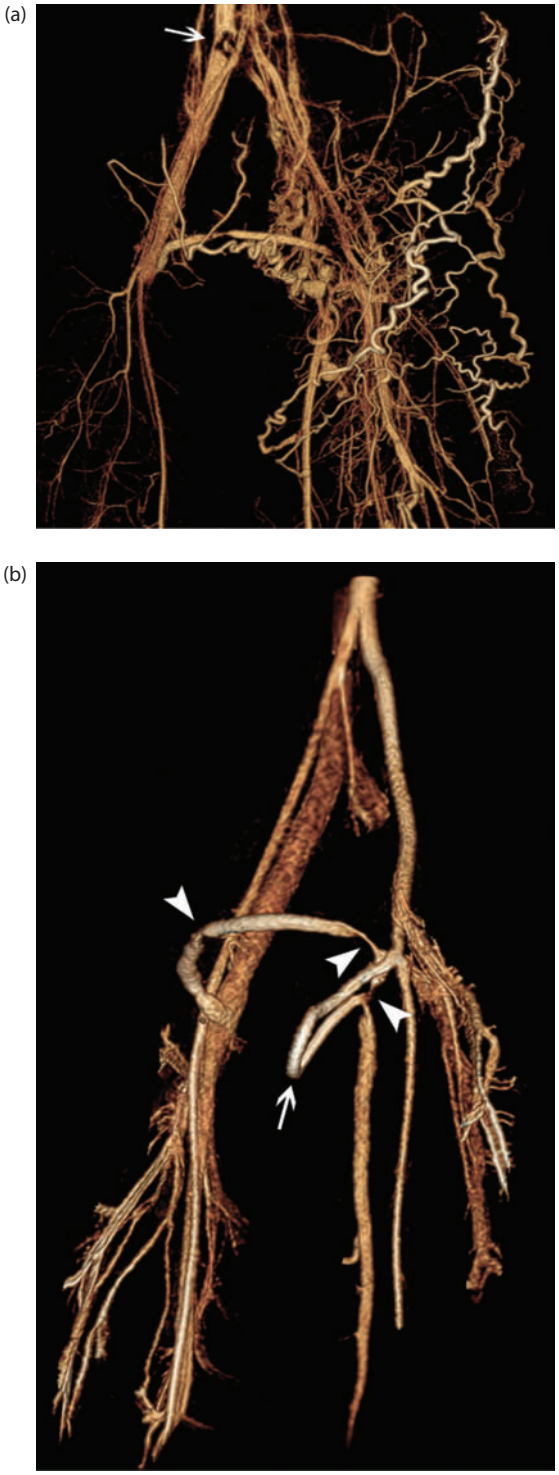

Figure 16.38 Stenosis of a femoral–femoral venous bypass graft in a patient with chronic left iliac vein thrombosis. Volume-rendered image from contrast-enhanced MRV **(a)** demonstrates extensive venous collateral vessels near the left-sided anastomosis. Filling defect in the inferior vena cava (arrow) represents an occluded left common iliac vein stent. Sub-volume volume-rendered image **(b)** with the collateral veins removed reveals multiple stenoses near the left-sided anastomosis and within the graft (arrowheads). A patent surgical arteriovenous fistula (arrow) has been placed in order to improve flow within the graft.

Table 16.1 Advantages and disadvantages of computed tomography and magnetic resonance imaging for the evaluation of venous disease

	Advantages	Disadvantages
Computed tomography	Speed	Iodinated contrast
	Superior spatial resolution	Radiation
	Calcifications	
Magnetic resonance imaging	No radiation exposure	Contraindications
	No iodinated contrast	Pacemaker
	Multiple acquisitions possible	Aneurysm clips
	Superior contrast resolution	Claustrophobia

1 mm. Standard acquisition times for 3D SPGR MR venography sequences are generally between 10 and 20 seconds, which is occasionally problematic for patients who are short of breath. The in-plane spatial resolution for typical MR venography acquisitions is ≤1 mm; however, slice thickness is generally in the range of 2–4 mm—significantly lower than CT, but generally adequate for most applications. CT is also preferable in patients with claustrophobia, pacemakers, or other contraindications to MR.

On the other hand, MR is a much more flexible technique, with numerous non-contrast and CE methods relying on different contrast mechanisms, so that more choices are available in difficult cases. In general, contrast-to-noise ratios of venous blood are significantly higher with MRI, although SNRs are occasionally lower. MR venography is preferred in patients with allergies to iodinated contrast or renal insufficiency. MR venography is also the test of choice in patients without venous access, since many non-contrast techniques are available with MRI and not with CT. Radiation dose is also a consideration, particularly in pediatric or pregnant patients or other radiation-sensitive populations (Table 16.1).

16.3.5 Future prospects

The recognition that gadolinium-based contrast agents could cause nephrogenic systemic fibrosis (NSF) when administered to patients with severe renal insufficiency has led to the development of several robust non-contrast MRA techniques, the most common of which employ 3D SSFP or 3D FSE pulse sequences.[31,46,47] These methods have

Guidelines 2.6.0 of the American Venous Forum on computed tomography and magnetic resonance imaging in venous disease

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
2.6.1	Computed tomography with intravenous contrast is recommended for the evaluation of obstruction of large veins in the chest, abdomen, and pelvis. Computed tomography accurately depicts the underlying pathology and confirms extrinsic compression, tumor invasion, traumatic disruption, anatomic variations, extent of thrombus, and position of a caval filter.	1	B
2.6.2	Computed tomography with intravenous contrast is recommended to diagnose pulmonary embolism. Sensitivity and specificity approaches 100% for central emboli, whereas for small, sub-segmental pulmonary emboli, sensitivity and specificity are 83% and 96%, respectively.	1	A
2.6.3	Magnetic resonance venography is recommended for the diagnosis of acute iliofemoral and caval deep vein thrombosis. A sensitivity of 100% and specificity of 96% was reported. The study is also recommended for the diagnosis of portal, splenic, or mesenteric venous thrombosis.	1	A
2.6.4	Magnetic resonance imaging and magnetic resonance venography are highly accurate for imaging inferior vena cava thrombus associated with renal, adrenal, retroperitoneal, primary caval, or metastatic malignancies. Magnetic resonance venography reveals the presence or absence of bland thrombus or tumor thrombus in the renal veins and inferior vena cava.	1	A

robust background suppression and enable 3D reconstructions that are very similar in appearance to those obtained from 3D CE MRA and have been shown to be as accurate or nearly as accurate as standard 3D CE MRA, in a variety of situations, such as assessment of renal artery stenosis. The same techniques can be applied to venography, and it is likely that similar success will be achieved in non-contrast venous imaging.

16.4 SUMMARY

CT and MR are both effective tools for answering a large number of clinical questions regarding the venous system. Each technique has unique advantages and disadvantages, as outlined above. Advances in each technology will continue to provide optimal imaging evaluation for a wide variety of venous disorders.

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● = Key primary paper
★ = Major review article

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17

The clinical presentation and natural history of acute deep venous thrombosis

MARK H. MEISSNER

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17.1 INTRODUCTION

The spectrum of venous thromboembolism (VTE) includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). Among 2119 patients enrolled in a prospective, multicenter registry, 72.7% had DVT, 9.7% had PE, and 17.5% had both DVT and PE.[1] First episodes of clinically recognized DVT occur with an age-adjusted incidence of 50.4 per 100,000 person-years.[2] However, many episodes are asymptomatic and the symptoms of acute DVT, including edema, pain, and erythema,[1] are non-specific. The formation of thrombi within the venous system depends in large measure on imbalances within the coagulation and fibrinolytic systems, and similar interactions continue to be important throughout the subsequent evolution of these thrombi. Over time, the processes of recanalization and organization compete with thrombus extension and re-thrombosis. Recurrent thrombosis and the post-thrombotic syndrome dominate the late natural history of acute DVT. The treatment of DVT is aimed at preventing its complications—PE, recurrent DVT, the post-thrombotic syndrome, and death. These complications are closely related to the natural history of DVT, an understanding of which is required for determining optimal management.

17.2 CLINICAL PRESENTATION OF ACUTE DVT

The clinical presentation of an acute DVT varies with the anatomic distribution, extent, and degree of occlusion of the thrombus. Symptoms may accordingly range from being absent to massive swelling and cyanosis with impending venous gangrene (phlegmasia cerulea dolens). Although DVT has historically been characterized as involving the proximal or distal veins, there are in fact three anatomic patterns—isolated calf vein (distal), femoropopliteal, and iliofemoral thrombosis—that have somewhat different natural histories. The Guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) accordingly recommend the use of precise anatomic terminology to characterize the most proximal extent of venous thrombosis as involving the iliofemoral veins, with or without extension to the inferior vena cava, the femoropopliteal veins, or isolated to the distal calf veins.[3]

Symptoms do tend to be more severe as thrombosis extends more proximally. When present, signs and symptoms of acute DVT may include pain, edema, erythema, tenderness, fever, prominent superficial veins, pain with passive dorsiflexion of the foot (Homan's sign), and peripheral cyanosis. Although potentially associated with concurrent DVT, a palpable cord is more suggestive of superficial venous thrombosis. However, up to 50% of patients with an acute DVT may lack specific signs and symptoms.[4,5] Post-operative patients are, in particular, more likely to have small, asymptomatic, distal, non-occlusive thrombi. Phlegmasia cerulea dolens, characterized by the triad of massive swelling, cyanosis, and pain,[6] is the most severe form of acute DVT and results from near-complete thrombosis of an extremity's venous outflow. In advanced cases, it is marked by severe venous hypertension with collateral and microvascular thrombosis, leading to venous gangrene. Venous gangrene has been particularly associated with warfarin-mediated protein C depletion in patients with cancer or heparin-induced thrombocytopenia.[7,8]

The diagnosis of acute DVT based upon clinical signs and symptoms alone is notoriously inaccurate. The signs and symptoms are non-specific and may be associated with other lower extremity disorders, including lymphedema, the post-thrombotic syndrome, superficial venous thrombosis, cellulitis, musculoskeletal trauma, and Baker's cysts. Among patients referred to the vascular laboratory for exclusion of DVT, only 12%–31% will have a positive ultrasound study.[9–11] However, 12.8% will have incidental lower extremity findings, 3.3% of which will be significant.[12]

The most common presenting symptoms have a wide range of reported sensitivities and specificities: calf pain, sensitivity 75%–91% and specificity 3%–87%; and calf swelling, sensitivity 35%–97% and specificity 8%–88%.[13–18] None of the signs or symptoms are sufficiently sensitive or specific, either alone or in combination, to accurately diagnose or exclude thrombosis.[19] For example, although Markel et al.[10] found a history of swelling in 83% of patients with a DVT, it was also present in 63% of those with a clinical suspicion but no documented DVT. Limb pain was similarly present in 51% and 41% of patients with and without DVT, respectively. The overall sensitivity and specificity of the clinical examination have ranged from 60% to 96% and from 20% to 72%, respectively.[20]

The accuracy of the clinical evaluation also differs between inpatients and outpatients. Inpatients are more likely to have undergone surgery or to be critically ill, while outpatients are less likely to have had recent surgery, trauma, or a prior DVT.[9] Additionally, the incidence of DVT is lower among outpatients, while specific leg symptoms are more common. The absence of certain risk factors, signs, or symptoms may thus have a higher negative predictive value in outpatients.[11]

As the clinical presentation of acute DVT is non-specific, the presence or absence of associated thrombotic risk factors may alter diagnostic suspicion. For example, in outpatients without cancer, a duration of symptoms of greater than 7 days and a differential thigh circumference of <3 cm has a negative predictive value of 95%.[11] Unfortunately, the positive predictive value is only 28.6%. Similarly, a difference in calf circumference of <2 cm demonstrated a negative predictive value of 85% among outpatients and 93% among inpatients.[9] However, when combined with the absence of risk factors, the negative predictive value of the absence of swelling increased to 97% in outpatients and 92% in inpatients. Despite these observations, withholding treatment based only on empirical clinical observations poses an unacceptable thromboembolic risk of up to 2%–4% in secondary referral outpatients, 8% in inpatients, and 12% in primary care patients.[9,11,21] Further diagnostic testing is therefore usually necessary, both to ensure appropriate treatment of those with confirmed DVT and to prevent the complications of inappropriate anticoagulation in those with other disorders.

Clinical assessment does, however, have a role in determining pre-test probability in algorithms incorporating further diagnostic modalities such as venous duplex ultrasonography and D-dimer measurements.[22] The probability model developed and validated by Wells et al.[23] has been used most widely. The model effectively stratifies patients into low, moderate, and high pre-test probability groups based on the presence of cancer; lower extremity immobilization by paralysis or plaster dressings; recent surgery or bed rest longer than 3 days; thigh and calf swelling; tenderness along the course of the deep veins; a >3-cm increase in calf circumference; pitting edema; collateral superficial vein; and the possibility of an alternative diagnosis. A valid alternative diagnosis, most often cellulitis or musculoskeletal disorders, is present in 56% of those without DVT, in comparison to only 17% of those with confirmed DVT.[24,25] Unfortunately, although such models are useful in guiding further diagnostic tests, the 3% prevalence of DVT in low-probability patients precludes diagnosis based on clinical strategies alone.[23] Fortunately, D-dimer has an excellent negative predictive value in low-probability outpatients, and algorithms combining clinical pre-test probability assessment, D-dimer measurement, and venous duplex ultrasound have been developed and validated.[22]

Delayed diagnosis of DVT is not uncommon. Among 2047 patients with symptomatic DVT, a diagnosis was established within 5 days of the onset of symptoms in only 47.1%, while it was delayed beyond 10 days in 22.6%.[1] Much of this time can be attributed to delays in presentation, with patients on average presenting for medical attention 4.4 days after the onset of symptoms.[26] Although diagnostic delays are often shorter,[26] many of these can be attributed to inadequate appreciation of a patient's underlying risk factors.[1]

17.3 COMPLICATIONS OF ACUTE DVT

17.3.1 Pulmonary embolism

The potentially life-threatening consequences of PE make it the most important short-term complication of acute DVT. Symptomatic PE accompanies approximately 10% of DVTs.[27] Recent reviews report an incidence of 29–78 per 100,000 for isolated PE.[28] The incidence of PE has substantially increased since 2001, likely related to the increased availability of computed tomography and magnetic resonance pulmonary angiography.[28] Despite this observation, the age-adjusted PE mortality rate in France declined by 3% per year between 2000 and 2010.[29]

However, respiratory symptoms correlate poorly with the presence or absence of objectively documented PE, and as many as 75% of pulmonary emboli may be asymptomatic.[30,31] Routine diagnostic testing suggests that PE accompanies acute DVT much more frequently than is currently appreciated. As many as 25%–52% of patients with documented DVT but no symptoms of PE will have high-probability lung scans at presentation.[30–33] Although regarded as an unusual source of symptomatic PE, high-probability scans have also been noted in 18%–29% of patients with isolated calf vein thrombosis.

The outcomes after PE vary with patient comorbidities and presenting features. The American Heart Association recommends stratifying patients into massive, sub-massive, and non-massive categories.[34] Massive PE is characterized by sustained hypotension (systolic blood pressure <90 mmHg), pulselessness, or persistent profound bradycardia; submassive PE by evidence of right ventricular dysfunction (echocardiography, computed tomography, brain natriuretic peptide [BNP or pro-BNP] or myocardial necrosis [troponin I or T]); and non-massive PE by normotension with normal right ventricular (RV) function and biomarkers. Mortality varies from 25% to 52.4% for massive PE to approximately 1% for non-massive PE.

17.3.2 The post-thrombotic syndrome

The post-thrombotic syndrome, with symptoms including pain, edema, skin changes, and ulceration, is the most important late complication of DVT. Older studies, many with methodological flaws, reported post-thrombotic manifestations in up to two-thirds of patients with an acute DVT. More recent studies suggest that, although the incidence of the post-thrombotic syndrome is still underappreciated, it occurs less commonly than in historical studies. Among 224 patients followed for 5 years after venographically confirmed DVT, the post-thrombotic syndrome developed in 29.6% of those with proximal thrombosis and 30% of those with isolated calf vein thrombosis.[35] Population-based studies have suggested that skin changes and ulceration are present in 6–7 million and 400,000–500,000 people in the United States, respectively.[36] In addition to the substantial economic costs, the physical limitations of patients with post-thrombotic symptoms are comparable to those of patients with other serious chronic medical conditions.[27]

17.3.3 Mortality after acute DVT

Mortality after an episode of acute DVT exceeds that expected in age-matched populations. Although the in-hospital case–fatality rate for DVT is only 5%, 1, 3, and 5-year mortality rates of 22%, 30%, and 39%, respectively, have been noted.[27,37,38] Early mortality is most frequently secondary to cancer, PE, and cardiac disease. Among patients ≥45 years of age, cancer is the most important predictor of early death,[39] with 28-day mortality rates among those with cancer being as high as 25.4%.[40] In comparison to the 12.6% rate in patients without cancer, 1-year mortality rates are as high as 63.4%.[37] Although deaths among cancer patients and those with idiopathic DVT remain high for at least 3 years beyond the index event, mortality rates for those with secondary VTE unrelated to cancer return to those of the general population after 6 months.[37]

DVT is also associated with an increased risk of cardiovascular morbidity and mortality.[41] The 10-year cumulative risk of a symptomatic vascular event among patients with idiopathic DVT is 25.4% in comparison to 12.9% in those with secondary VTE.[42] Patients with idiopathic DVT also have a higher prevalence of atherosclerotic risk factors (diabetes, hypertension, and hypercholesterolemia) and coronary artery calcium than controls without VTE.[43] The presence of residual thrombus at the time that anticoagulants are stopped may be a marker for subsequent cardiovascular events.[41,44] Patients with residual venous obstruction 3 months after a symptomatic DVT are 2.5-fold more likely to develop recurrent VTE, post-thrombotic syndrome, cancer, or have an arterial thrombotic event.[45] Although the reasons for this are not clear, it has been postulated that the presence of residual thrombus is associated with generalized hypercoagulability. Such a relationship is supported by the higher levels of activated coagulation seen in DVT patients with cardiac disease,[46] and the observation that delayed recanalization and myocardial infarction are both associated with increased levels of plasminogen activator inhibitor-1 (PAI-1).[47]

17.4 THE NATURAL HISTORY OF ACUTE DVT

17.4.1 Venous thrombogenesis

As initially proposed by Virchow, three factors are of primary importance in the development of venous thrombosis: abnormalities of blood flow, abnormalities of blood, and vessel wall injury. However, despite the accuracy of Virchow's postulates, it is now apparent that all three components are not equally important in individual patients. The role of structural injury to the venous wall is disputable; even in the presence of stasis, overt endothelial injury appears to be neither a necessary nor sufficient condition for thrombosis.[48] With the notable exceptions of direct venous trauma, hip arthroplasty, and central venous catheters, there is little evidence that gross venous injury plays a significant role in most thromboses. In contrast, data are accumulating that biological injury to the endothelium may have a very important role in venous thrombogenesis. The venous endothelium is normally antithrombotic, producing prostaglandin I_2, thrombomodulin, tissue-type plasminogen activator, and glycosaminoglycan cofactors of antithrombin. Under conditions favoring thrombosis, the endothelium may become pro-thrombotic, producing tissue factor, von Willebrand factor, and fibronectin. Leukocytes may be key mediators of both endothelial injury and hypercoagulability, with the early phases of thrombosis being marked by increases in permeability followed by leukocyte adhesion, migration, and endothelial disruption.[49,50] Associated cytokines may also be of importance, with factors such as interleukin-1 increasing tissue factor expression while diminishing protein C activation.[51]

Although most venous thrombi originate in areas of low blood flow, stasis alone is also an inadequate stimulus in the absence of low levels of activated coagulation factors.[52,53] Although stasis may facilitate endothelial leukocyte adhesion[49] and cause endothelial hypoxia, leading to a pro-coagulant state,[54] its most important role may be in permitting

the accumulation of activated coagulation factors in areas that are prone to thrombosis. Stasis may thus be a permissive factor for the other events required for thrombosis.

Imbalanced activation of the coagulation system appears to be the most important factor underlying many episodes of acute DVT. Although the hemostatic system is continuously active, thrombus formation is ordinarily confined to sites of local injury by a precise balance between activators and inhibitors of coagulation and fibrinolysis. A pre-thrombotic state may result either from imbalances in the regulatory and inhibitory systems or from activation exceeding antithrombotic capacity.[55] Some component of imbalanced coagulation appears to be associated with most thrombotic risk factors, including age, malignancy, surgery, trauma, primary hypercoagulable states, pregnancy, and oral contraceptive use.

Based on perceived differences in their natural histories, lower extremity venous thrombi are classified as involving the iliofemoral, femoropopliteal, or calf veins.[3] These thrombi originate in areas where imbalanced coagulation is localized by stasis: in the soleal sinuses, behind venous valve pockets, at venous confluences, and distal to areas of extrinsic compression. This is a very important and often misunderstood concept—DVT is fundamentally a disease of coagulation localized to regions of stasis, rather than a disease of the veins themselves. The calf veins are the most common sites of origin, although 40% of proximal thrombi arise primarily in the femoral or iliac veins. In the femoral veins, these are presumably in regions behind the valves,[56] while in the iliac veins, DVT is frequently associated with compression of the left common iliac vein by the overlying right common iliac artery (May–Thurner syndrome). In flow models, vortices produced beyond the valve cusps tend to trap red cells in a low-shear field near the apex of the cusp.[57] Such vortices have also been demonstrated *in vivo* using B-flow ultrasound.[58] Red cell aggregates forming within these eddies are likely to be the early niduses of thrombus formation.[59] However, such aggregates are probably transient until stabilized by fibrin in the setting of locally activated coagulation. After their formation, these early thrombi may become anchored to the endothelium near the apex of the valve cusp,[60,61] a process that is postulated to be mediated by adherent leukocytes.[50]

Propagation of thrombi beyond areas of stasis probably depends largely on the relative balance between activated coagulation and thrombolysis. If local conditions favor propagation, laminated appositional growth occurs outward from the apex as platelets are surrounded by a red cell, fibrin, and leukocyte network. In contrast to arterial thrombi, venous thrombi are composed largely of red cells and fibrin, with relatively few platelets. Once luminal flow is disturbed, prograde and retrograde propagation may also be promoted by hemodynamic factors. Conversely, such early thrombi may fail to propagate, with aborted thrombi appearing as endothelialized fibrin fragments within the valve pockets.

17.4.2 Recanalization

Once formed, the competing processes of recanalization and recurrent venous thrombosis characterize the natural history of acute DVT. The development of chronic sequelae is closely related to the balance between these two processes. The venous lumen is most often re-established after both experimental and clinical thrombosis.[62] The mechanisms of thrombus organization and recanalization have been extensively investigated in animal models of DVT. Both the vein wall and thrombus play important roles in these processes. In short, there is rapid regeneration of a fibrinolytically active neoendothelium soon after thrombosis, with an early neutrophilic infiltrate within the thrombus and vein wall, followed by a predominantly monocyte infiltrate.[63,64] Monocytes appear to play a particularly important role in thrombus organization and recanalization, functioning as a source of both fibrinolytic and cytokine mediators. Experimental thrombi show complete recanalization by 3 weeks, with the thrombus reduced to an endothelialized subintimal streak.

Although less extensively investigated, histologic studies suggest that clinical DVT follows a similar course. As in the animal models, recanalization appears to be a complex process involving intrinsic (arising within the thrombus) and extrinsic fibrinolysis, peripheral fragmentation, neovascularization, and retraction. Thrombus organization begins in the attachment zone with the migration of surfacing cells—presumably derived from the endothelium—over the thrombus.[60] Pockets formed between the thrombus and the vein walls then progressively enlarge through peripheral fragmentation and fibrinolysis. The thrombus simultaneously undergoes central softening as well as contraction. In the absence of propagation, the ultimate result is a restored venous lumen with a slightly raised fibro-elastic plaque at the site of initial thrombus adherence to the vein wall.

Serial noninvasive diagnostic tests permitting venous thrombi to be followed over time have confirmed the clinical importance of these processes. Among 21 patients prospectively followed with ultrasound, Killewich et al.[65] noted that some recanalization was present by 7 days in 44% of patients and by 90 days in 100% of patients. The percentage of initially involved segments that remained occluded decreased to means of 44% by 30 days and 14% by 90 days. van Ramshorst et al.[66] similarly noted an exponential decrease in thrombus load over the first 6 months after femoropopliteal thrombosis. Most recanalization occurred within the first 6 weeks, with flow re-established in 87% of 23 completely occluded segments during this interval. Approximately 55% of subjects will show complete recanalization within 6–9 months of thrombosis.[67,68] However, some reduction in thrombus load may continue, albeit at a slower rate, for months to years after the acute event (Figure 17.1). Notably, clinical studies assessing two-point compressibility in the common femoral and popliteal veins have demonstrated similar rates of incomplete recanalization (49.4%) at 3 months.[45]

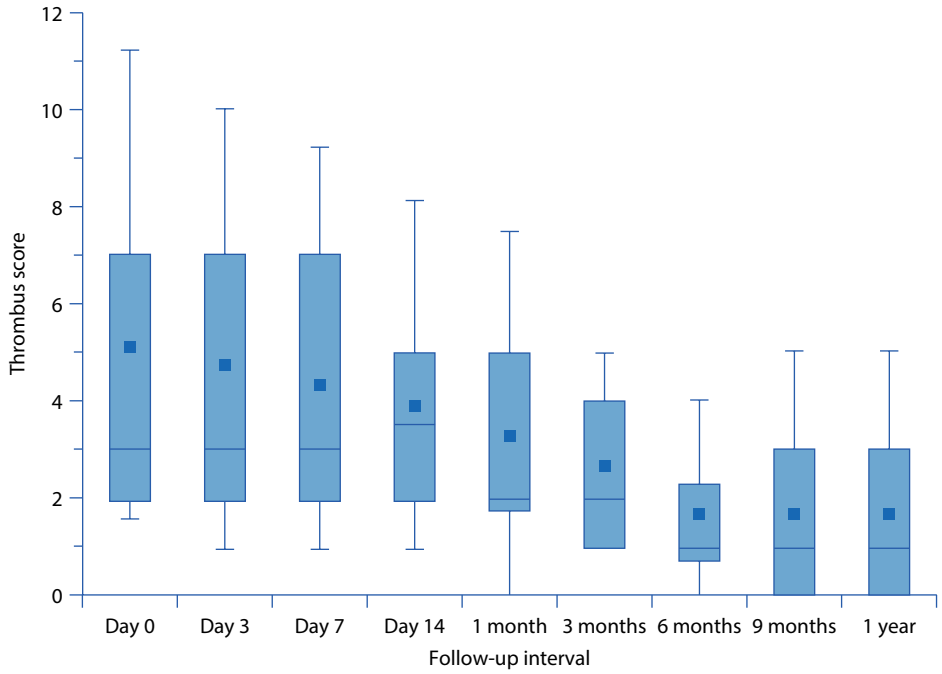

Figure 17.1 Boxplot showing reduction in thrombus score determined by serial ultrasound examinations over the first year after deep venous thrombosis. Top, middle, and bottom lines of boxes represent the 75th, 50th (median), and 25th percentiles, respectively. Closed squares show the means, with top and bottom error bars representing the 90th and 10th percentiles, respectively. Progressive recanalization occurs with a reduction in mean thrombus score from 5.1 at the time of presentation to 1.8 at 12 months. Mean percentage rates of recanalization were 52.4% at 6 months, 57.9% at 9 months, and 58.8% at 12 months. (From Meissner MH et al. *J Vasc Surg* 2002;35:278–85. Reprinted with permission.)

Although thrombus resolution proceeds at a similar rate in the femoropopliteal venous segments,[66] some[47,69] have found more rapid clearance from the tibial segments, perhaps reflecting the increased efficiency of thrombolysis in small veins. In contrast, recanalization of thrombosed iliac segments is slower and more often incomplete. Iliofemoral venous patency rates may be as low as 24%, 18%, and 18% at 1, 3, and 5 years after DVT.[70]

The degree of recanalization is related to both the degree of activated coagulation and fibrinolytic inhibition (Figure 17.2). Recanalization is negatively correlated with levels of thrombin activation products (prothrombin fragment 1 and 2) at the time of presentation.[47] Others[47,68] have found higher PAI-1 levels in patients with poor thrombus resolution. From a clinical perspective, more complete recanalization has been reported in older patients, those with asymptomatic post-operative thrombosis, and patients with involvement of only one venous segment.[71] Cancer is associated with less complete recanalization. The presence of a permanent risk factor has also been associated with an 11-fold higher risk of delayed recanalization.[72]

17.4.3 Recurrent venous thrombosis

Recurrent thrombotic events compete with recanalization early after an acute DVT. Most clinical studies have included both symptomatic recurrent DVT and PE, with rates depending on treatment, proximal or distal location of thrombus, and duration of follow-up. Fortunately, standard anticoagulation is very effective at preventing recurrent VTE while on treatment. Among patients with proximal DVT, recurrent thromboembolic events occurred in 5.2% of patients treated with standard anticoagulation measures for 3 months,[73] in comparison to 47% of patients inadequately treated with a 3-month course of low-dose subcutaneous heparin.[74] Others[75] have reported a 7% rate of recurrent VTE during 3 months of anticoagulant treatment. More recent randomized comparisons of the direct thrombin (dabigatran etexilate) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) to warfarin have demonstrated similar rates of recurrent VTE for the new anticoagulants (2.1%–3.2%) and warfarin (1.8%–3.5%) over the initial 3–12 months of treatment.[76]

As VTE is fundamentally a disease of disordered anticoagulation, either acute or chronic, it is not surprising that most symptomatic events occur after anticoagulation has been stopped. The risk of recurrence is at least as great in the contralateral as in the ipsilateral extremity.[77] Sarasin and Bounameaux[78] calculated a theoretical recurrence rate of 0.9% per month after discontinuing anticoagulant therapy for proximal DVT, similar to observed annual recurrence rates of 7.0%–12.9%.[39,44] The risk of recurrent VTE is highest over the first 6–12 months after the index event, although cumulative rates are as high as 24% at 5 years and

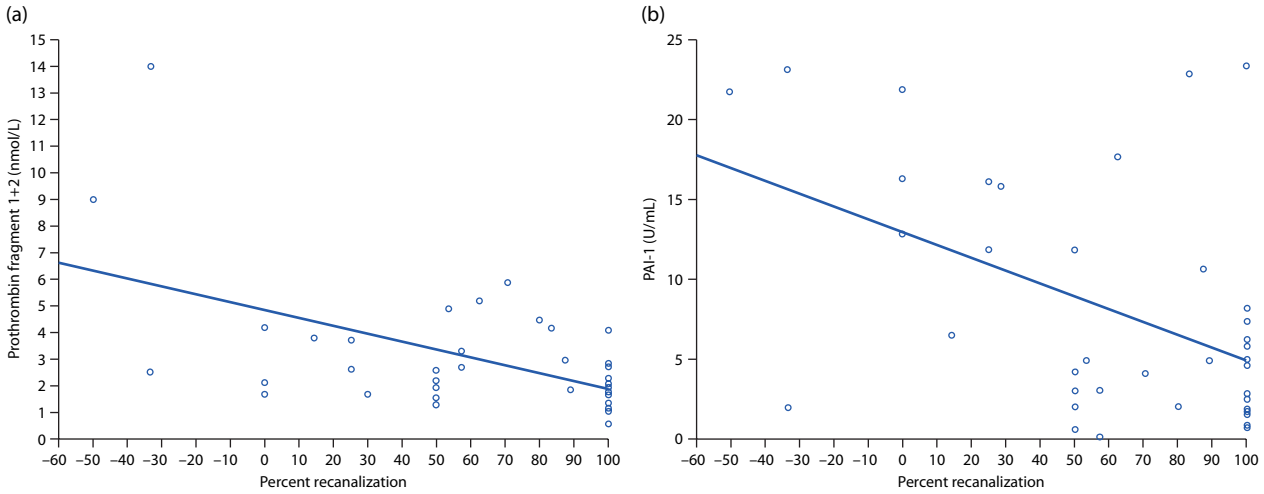

Figure 17.2 Scatterplots of percentage recanalization versus prothrombin fragment 1 and 2 **(a)** and plasminogen activator inhibitor (PAI-1) activity **(b)** at presentation among patients followed for at least 9 months ($n = 44$). Solid regression lines show correlations between recanalization and initial fragment 1 and 2 ($R = -0.53$, $P = 0.0004$) and PAI-1 ($R = -0.48$, $P = 0.002$) levels. Patients with negative percentage recanalization values had progression of thrombus during follow-up. (From Meissner MH et al. *J Vasc Surg* 2002;35:278–85. Reprinted with permission.)

30% at 8 years after initial presentation.[44,75,77] Among 1626 patients followed after a first episode of VTE, the cumulative incidence rates of recurrence after discontinuing anticoagulation were 11.0%, 19.6%, 29.1%, and 39.9% at 1, 3, 5, and 10 years, respectively.[79]

The risk of recurrence is highly related to underlying thrombotic risk factors. In comparison to those with provoked DVT, the risk of recurrence is two- to three-fold higher among those with idiopathic thrombosis.[44,75,79] However, even though the 10-year risk of recurrence may be as high as 52.6% in patients with idiopathic VTE, it is not inconsequential (22.5%) in patients with secondary, provoked thrombosis.[79] Specific risk factors for symptomatic recurrent DVT include advanced age, male gender, increased body mass index, lower extremity paresis, active malignancy, and a shorter duration of anticoagulation.[79,80] The role of the inherited thrombophilias as risk factors for recurrent VTE remains controversial. While some congenital thrombophilias—including antithrombin, protein C, and protein S deficiency, hyperhomocysteinemia, and increased levels of factors VIII and XI—appear to be associated with an increased risk of recurrence, the data supporting an increased risk associated with the common factor V Leiden and prothrombin G20210A mutations are conflicting.[81] Several clinical models for predicting the risk of recurrent thrombosis have been developed, but are awaiting prospective validation.[81] Finally, the risk of recurrence also appears to be related to thrombus location. Proximal venous thrombosis is associated with a three-fold higher risk of recurrence than isolated calf vein thrombosis, and iliofemoral thrombosis is associated with a 2.4-fold higher risk than femoropopliteal thrombosis.[82]

Recurrence after isolated calf vein thrombosis requires special consideration. Limited data suggest that isolated calf vein thrombosis is associated with less extensive activation of coagulation than proximal venous thrombosis, perhaps implying some difference in pathophysiology.[46] At least two types of calf vein thrombosis may be differentiated—those with involvement of the paired posterior tibial and peroneal venae comitantes (axial calf vein thrombosis) and those isolated to the veins draining the gastrocnemial and soleal muscles (muscular calf vein thrombosis)—and their natural history may be different. In patients with thrombosis isolated to the axial calf veins, proximal propagation occurred in 23% of untreated patients and 10% of patients treated with only intravenous heparin.[83] As ultrasound technology has improved, muscular calf vein thrombi are more often identified, and now account for approximately 40% of isolated calf vein thrombi. The natural history of these thrombi has only recently been described. Among 135 limbs followed after isolated muscular calf vein thrombosis, 16.3% propagated to the axial tibial veins or higher, the majority (90.9%) within 2 weeks of presentation, and only 2.9% propagated to the level of the popliteal vein.[84] Cancer was the only risk factor associated with propagation of these thrombi. Although such data suggest that thrombosis isolated to the muscular calf veins may be more benign than that involving the axial calf veins, there are conflicting reports[85] of associated PE in 7% of patients at the time of presentation, and long-term recurrence rates of 18.8%. More information is needed regarding the natural history and management of these thrombi.

Not surprisingly, noninvasive natural history studies have disclosed a much higher rate of asymptomatic recurrence than is suggested by clinical studies. Serial duplex studies have shown propagation of thrombus in 26%–38% of treated patients within the first few weeks of presentation (Figure 17.3).[86,87] In a larger series of 177 patients followed for a median of 9.3 months, ultrasound-documented recurrent thrombotic events were observed in 52% of patients.[88]

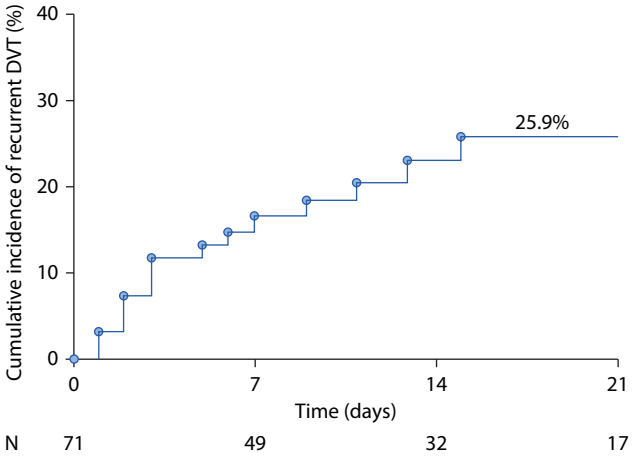

Figure 17.3 Cumulative incidence of ultrasound-documented recurrent thrombotic events during the first 3 weeks of therapy. DVT: deep venous thrombosis. (From Caps MT et al. *Vasc Med* 1999;4:9–14, 1999. Reprinted with permission.)

Among initially involved extremities, propagation to new segments occurred in 30% and re-thrombosis of a partially occluded or recanalized segment occurred in 31%. New thrombi were also observed in 6% of initially uninvolved contralateral extremities.

Although asymptomatic ultrasound-documented recurrences are not clearly associated with underlying risk factors,[88] they are related to the degree of activated coagulation and the adequacy of anticoagulation. Initial levels of thrombin activation products (prothrombin fragment 1 and 2) and D-dimer are significantly higher in patients with subsequent ultrasound-documented recurrence.[46] Elevated D-dimer levels after discontinuing anticoagulation have also been associated with a higher risk of symptomatic clinical recurrence.[89] In the case of isolated calf vein thrombosis, D-dimer levels of ≥2000 ng/mL at the time of presentation had sensitivity and specificity rates of 88.9% and 76.5%, respectively, in terms of predicting recurrent events. Asymptomatic recurrence is prevented by adequate anticoagulation, with the risk of new thrombotic events increasing 1.4-fold for each 20% reduction in the time that anticoagulation is adequate, according to standard laboratory measures.[87]

Recanalization and recurrent thrombosis may in fact be related. Among 313 patients followed for up to 6 years after a first episode of DVT, 41 of 58 episodes of recurrent VTE occurred in patients with residual thrombus present.[75] However, the importance of residual thrombus as a predictor of recurrent DVT remains controversial. While some have found a 2.2- to >5 fold increased risk of recurrent thrombosis among those with incomplete recanalization,[44,71] others have failed to demonstrate such a relationship.[90,91] A meta-analysis including 3531 patients from 13 studies suggested that residual venous obstruction after discontinuing anticoagulation was not associated with recurrent VTE in patients with idiopathic DVT (odds ratio: 1.35, 95% CI: 0.87–2.08), although a significant relationship was present in secondary VTE (odds ratio: 2.78, 95% CI: 1.41–5.50) that was attributable to an increase risk in patients with cancer.[92] As many recurrent events occur in the contralateral leg, or are episodes of PE, it is likely any risk of residual thrombus is related to underlying hypercoagulability rather than mechanical abnormalities of the venous system.[41,44] The presence of ongoing hypercoagulability is, in fact, perhaps a better predictor of the risk of recurrent VTE.[93] At least one study has found that, although residual thrombus was not an independent predictor, a D-dimer level of >500 ng/mL measured 1 month after discontinuing anticoagulants was associated with a 3.3-fold increased risk of recurrence.[90]

17.5 THE NATURAL HISTORY OF DVT AND THE POST-THROMBOTIC SYNDROME

17.5.1 Pathophysiology of the post-thrombotic syndrome

As discussed above, manifestations of the post-thrombotic syndrome include pain, edema, skin changes, and ultimately ulceration. At least three scoring systems—the Ginsberg criteria,[94] the Villalta scale,[95] and the Venous Clinical Severity score[96]—have been developed for classifying the clinical severity of the post-thrombotic syndrome, and the incidence varies widely with the system used. Although there are some concerns that the Villalta scale may be overly sensitive to mild post-thrombotic disease, it has been the most widely used in clinical studies. Among 355 patients evaluated with the Villalta instrument after a first episode of DVT, the cumulative incidence rates of any and severe post-thrombotic syndrome at 5 years were 28% and 9.3%, respectively.[35]

Ambulatory venous hypertension resulting from a combination of venous reflux and obstruction is responsible for the more severe post-thrombotic sequelae. Although experimentally produced thrombi frequently recanalize to produce a patent but valveless lumen, valvular destruction is not a universal consequence of clinical DVT. Many patients remain free of chronic symptoms after an episode of acute DVT, and only 69% of extremities have ultrasound-documented reflux at 1 year after thrombosis.[97] The incidence of reflux in individual venous segments is even lower, with only 33%–59% of involved segments becoming incompetent.

Histologic examination of post-thrombotic veins provides some explanation for the differential development of reflux after DVT. In extremities with established post-thrombotic syndrome, approximately 50% of popliteal valves will demonstrate thrombus formation on the valve leaflets, while others show endothelial erosion, with basement membrane thickening and atypical subintimal collagen fibers.[98] However, most episodes of acute DVT are not associated with such extensive histologic changes. In contrast to the observations in patients with established post-thrombotic syndrome, early fibrocellular organization after an acute DVT rarely involves the valve cusps.[60,99] Thrombus adherence to the valve cusp was noted in only four out of 44

specimens examined by Sevitt.[99] In the majority of cases, the thrombus was separated from the valve cusp by a cleft, postulated to arise from the local fibrinolytic activity of the valvular endothelium. These observations likely reflect the intense plasminogen activator activity of the venous valve cusps, which may act to preserve some valves during recanalization.

These histologic observations are consistent with the natural history of valvular reflux. Serial duplex studies have shown the development of reflux to coincide with or slightly precede complete recanalization of a segment.[69] As with recanalization, the rate at which reflux develops is highest during the first 6–12 months after DVT.[100] Reflux may be transient in up to 23% of involved segments, resolving during the course of follow-up.[100] This phenomenon conceivably occurs when valves protected by the lytic clefts described above remain partially encumbered by residual thrombus. Normal valvular function then presumably returns with complete recanalization.

Despite the importance of venous reflux, limbs developing edema, hyperpigmentation, or ulceration are more likely to have a combination of reflux and residual obstruction than either abnormality alone (Figure 17.4).[18] In addition to its direct effects on ambulatory venous pressure, obstruction may indirectly contribute to the development of reflux. As many as 30% of segments developing reflux during follow-up have not been previously thrombosed.[100] The precise mechanism by which reflux develops in initially uninvolved segments remains unclear, but may be related to persistent proximal obstruction. There may therefore be at least two different means by which reflux develops: a more common mechanism related to recanalization of a thrombosed segment, and a less common mechanism related to proximal obstruction of uninvolved segments. The risk of developing reflux in segments affected by thrombus is almost three-times that of uninvolved segments.[100]

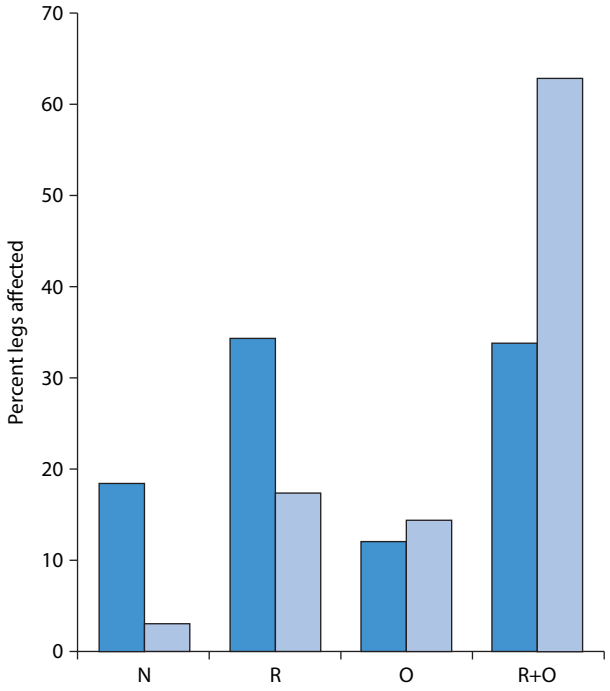

Figure 17.4 Proportion of limbs demonstrating no abnormality (N), reflux alone (R), obstruction alone (O), and reflux with obstruction (R+O) after deep venous thrombosis with respect to symptoms. Dark bars indicate asymptomatic legs; light bars indicate legs with post-thrombotic symptoms. (From Johnson BF et al. *J Vasc Surg* 1995;21:307–13, 1995. Reprinted with permission.)

17.5.2 Determinants of the post-thrombotic syndrome

Although our understanding remains incomplete, an appreciation of the factors involved in the development of the post-thrombotic syndrome is important for its prevention and management. Most investigators have not found a clear relationship between the initial extent of thrombus and ultimate outcome. However, other potential determinants of post-thrombotic manifestations include the rate of recanalization, recurrent thrombotic events, the global extent of reflux, and the anatomic distribution of reflux and obstruction.

Rapid recanalization of venous thrombi theoretically both relieves proximal venous obstruction and preserves valve function. In the long-term ultrasound follow-up of 113 patients with an acute DVT, the majority of whom were treated with standard anticoagulation measures, the time to complete recanalization was related to the ultimate development of reflux.[69] Depending upon the venous segment involved, complete recanalization required 2.3–7.3-times longer in segments developing reflux than in segments in which valve function was preserved (Figure 17.5). Limited data also suggested that thrombolytic therapy has a role in reducing the incidence of post-thrombotic syndrome after iliofemoral DVT. Unpublished data from a multicenter registry[101] demonstrated that, among 102 patients with iliofemoral DVT treated with catheter-directed thrombolysis, patients with complete thrombolysis were significantly more likely to be asymptomatic (84% without symptoms) at 1 year than were those with <50% lysis (36% without symptoms). A systematic review including four studies comparing catheter-directed thrombolysis with conventional anticoagulation has further shown significant reductions in the development of venous reflux, persistent venous obstruction, and the post-thrombotic syndrome among those treated with thrombolysis.[102] Finally, the CaVentT trial demonstrated a 14.4% absolute risk reduction in the incidence of post-thrombotic syndrome at 2 years among patients treated with catheter-directed thrombolysis in comparison to standard anticoagulation.[103]

Recurrent thrombotic events also have a detrimental effect on valvular competence and the development of the post-thrombotic syndrome. Extension of thrombus to initially uninvolved segments obviously places these segments at risk of valvular destruction. However, re-thrombosis of a

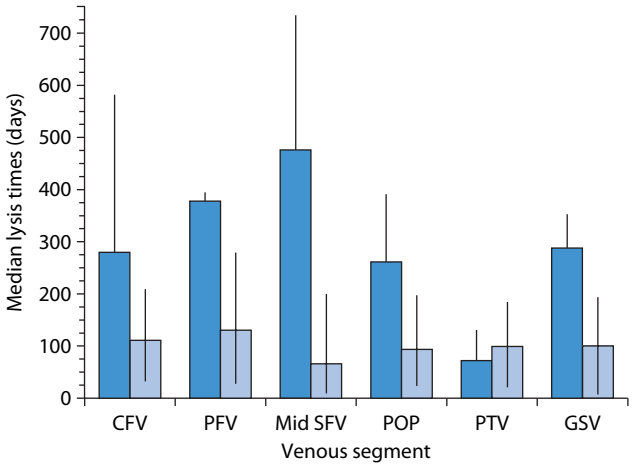

Figure 17.5 Median time from thrombosis to complete recanalization, grouped according to ultimate reflux status. Error bars denote interquartile range. Segments: common femoral vein (CFV), profunda femoris vein (PFV), mid-femoral vein (SFM), popliteal vein (PPV), posterior tibial vein (PTV), and great saphenous vein (GSV). (From Meissner MH et al. *J Vasc Surg* 1993;18:596–608. Reprinted with permission.)

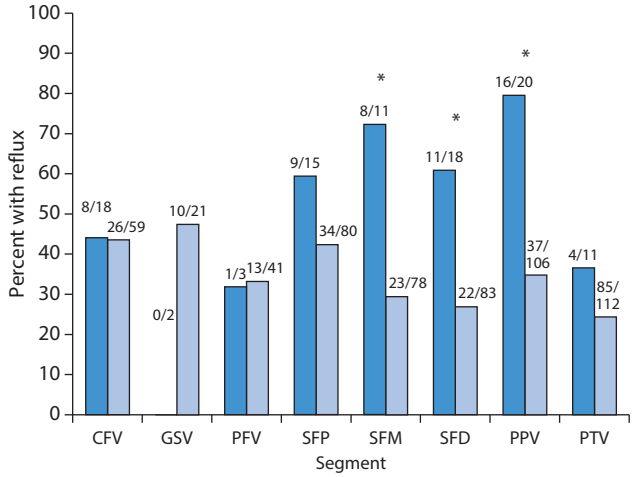

Figure 17.6 The development of reflux in initially involved venous segments with and without subsequent re-thrombosis. Segments: common femoral vein (CFV), great saphenous vein (GSV), profunda femoris vein (PFV), proximal, mid, and distal femoral vein (SFP, SFM, and SFD), popliteal vein (PPV), and posterior tibial vein (PTV). Numbers above bars indicate the numbers of segments in which reflux was observed over the numbers of segments in which reflux could be definitively assessed. Differences between segments with and without re-thrombosis are statistically significant (*$P < 0.005$) for the SFM, SFD, and PPV segments. (From Meissner MH et al. *J Vasc Surg* 1995;2:v558–67. Reprinted with permission.)

partially occluded or recanalized segment further increases the risk of reflux.[88] Reflux has been noted to develop in 36%–73% of such segments, which is considerably higher than the incidence in segments without re-thrombosis (Figure 17.6). Consistent with these observations, recurrent thrombotic events have been noted in 45% of patients with post-thrombotic symptoms, in comparison to only 17% of asymptomatic subjects.[27] The risk of post-thrombotic syndrome is six-times greater among patients with recurrent thrombosis.[35]

Finally, the development of clinical signs and symptoms is related to the global extent of reflux[104] and the anatomic distribution of reflux and obstruction. Reflux in the distal deep venous segments, particularly the popliteal and posterior tibial veins, is most significantly associated with post-thrombotic skin changes.[105–107] However, associated superficial reflux has been reported in 84%–94% of patients with chronic skin changes and 60%–100% of patients with venous ulceration. Although pressure transmission through incompetent perforating veins may play a role, direct thrombotic involvement of the superficial veins and thrombus-independent degenerative processes also appear to be important in the development of superficial venous incompetence.[108]

With respect to obstruction, the severity of post-thrombotic manifestations is most significantly related to persistent iliofemoral and popliteal obstruction.[104] Persistent iliofemoral venous thrombosis appears to be particularly important, with significantly worse post-thrombotic syndrome, as measured by the Villalta score, in comparison to femoropopliteal or isolated calf vein thrombosis, at 24 months. In contrast, femoral vein obstruction appears to be relatively well tolerated in many patients,[109] likely secondary to axial transformation of the profunda femoris vein.[110] Persistent popliteal obstruction does, however, appear to be associated with more advanced CEAP clinical classification.[104]

17.6 CLINICAL APPLICATIONS OF NATURAL HISTORY STUDIES

The natural history of acute DVT has management implications that afford some opportunity to modify outcome. When combined with the application of compression, early ambulation results in faster resolution of acute pain and edema, with no increased risk of PE.[111,112] The evidence supporting the long-term value of compression in preventing post-thrombotic sequelae is controversial. Early unblinded randomized trials suggested 30–40-mmHg compression stockings to be associated with a 50% reduction in the risk of the post-thrombotic syndrome.[113,114] Although a more recent placebo-controlled trial did not find a benefit with stockings,[115] low patient compliance (55.6%) has caused these results to be questioned. Furthermore, there may be some high-risk populations, such as those with persistent iliofemoral venous obstruction or with reflux involving the popliteal, posterior tibial, and superficial veins, that may warrant particular attention to the use of compression stockings.

Based on our current understanding, recurrent venous thrombosis is the most powerful predictor of the

post-thrombotic syndrome. Early ambulation, although not effecting recanalization,[116] may reduce risk of thrombus propagation. More importantly, ensuring an adequate duration and intensity of anticoagulation is critical to preventing recurrent thrombosis. The incidence of recurrent thromboembolic events is 15-times higher among patients with inadequate early anticoagulation,[73] and the low-molecular-weight heparins offer some theoretical advantages over unfractionated heparin in this regard (grade 1A).[117–119] The increased bioavailability and more predictable dose–response relationships of these agents are associated with more rapid inhibition of coagulation.[120] Although a difference in the incidence of symptomatic recurrent thromboembolism among those treated with low-molecular-weight and unfractionated heparin has not been consistently demonstrated in clinical trials,[121,122] at least some studies have suggested lower rates of asymptomatic extension among patients treated with low-molecular-weight heparins.[123] The predictability of the direct thrombin and Xa inhibitors may potentially also play some role in reducing the incidence of the post-thrombotic syndrome.

It is increasingly recognized that the risk of recurrent thromboembolism differs among patients, and that patients with idiopathic DVT or irreversible risk factors warrant a longer duration of treatment. It is therefore imperative that the risk of recurrent thrombosis be thoroughly assessed prior to discontinuing anticoagulation, particularly among those with idiopathic DVT. The risk of recurrent VTE is influenced by ongoing hypercoagulability, and management trials suggest that there is a role for D-dimer determination in guiding the duration of anticoagulation in patients with unprovoked VTE.[93]

With respect to recanalization, the degree and rate at which this proceeds are important determinants of both valve function and recurrent thrombosis. As for recurrent thrombosis, thrombus resolution is also related to the adequacy of anticoagulation. Use of the low-molecular-weight heparins during the maintenance phase of therapy may have some advantages over warfarin. In comparison to standard oral anticoagulation, 3–6 months of treatment with low-molecular-weight heparin have been associated with greater degrees of recanalization, variable improvements in short-term clinical outcome, and a non-significant trend towards less reflux.[119,124] The potential role of the direct thrombin and Xa inhibitors in reducing post-thrombotic manifestations awaits clinical trials. Thrombolytic therapy does appear to have a role in promoting rapid and complete recanalization in at least some patients, specifically good-risk patients with acute iliofemoral DVT of less than 14 days duration. Early trials do suggest a modest reduction in the post-thrombotic syndrome among patients with iliofemoral DVT treated with catheter-directed thrombolysis,[103] and trials further defining the role of pharmacomechanical thrombectomy in both iliofemoral and femoropopliteal DVT are forthcoming.[125] Finally, early application of compression hosiery may also play a role in promoting early recanalization. In a small

Guidelines 3.1.0 of the American Venous Forum on the clinical presentation and natural history of acute venous thrombosis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.1.1	Based on differences in natural history, we recommend that lower extremity deep venous thrombosis (DVT) be precisely characterized as involving the iliofemoral veins, the femoropopliteal veins, or isolated to the calf veins rather than being simply designated as involving the proximal or distal veins.	1	A
3.1.2	We recommend formal determination of the pre-test probability of DVT using a validated scoring system in all patients presenting with signs and symptoms of acute DVT.	1	A
3.1.3	We recommend that the risk of recurrent VTE be thoroughly assessed prior to discontinuing anticoagulation, particularly among those with idiopathic DVT.	1	A
3.1.4	We suggest a strategy of early thrombus removal in selected patients meeting the following criteria: (a) a first episode of acute iliofemoral deep venous thrombosis; (b) symptoms <14 days in duration; (c) a low risk of bleeding; and (d) ambulatory with good functional capacity and an acceptable life expectancy.	2	C
3.1.5	We recommend the use of 30–40-mmHg knee-high compression stockings to reduce the risk of post-thrombotic syndrome in compliant patients after an episode of acute DVT.	1	C

randomized trial comparing immediate versus delayed use of compression stockings, complete recanalization at 90 days was achieved in 82% of occluded segments in the early compression group in comparison to 60% of those in the delayed group.[126]

As most late deaths associated with DVT are due to cardiac and malignant disease, few interventions are likely to reduce mortality. Notably, the routine use of vena cava filters has not been shown to decrease either immediate or long-term mortality.[127,128] However, several studies have now suggested a survival advantage among cancer patients with early or limited disease treated with low-molecular-weight heparins.[129] No similar advantage has been noted for patients with advanced metastatic disease.

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● = Major primary paper
★ = Major review paper
◆ = Published guideline

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18

Diagnostic algorithms for acute deep venous thrombosis and pulmonary embolism

JOANN LOHR

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18.1 DEEP VENOUS THROMBOSIS

18.1.1 Introduction

Venous thromboembolism (VTE) encompasses a spectrum of disease, beginning with deep venous thrombosis (DVT) and commonly resulting in pulmonary embolism (PE) or post-thrombotic syndrome. Given the numerous diagnostic studies now available, the task of accurately and cost-effectively ruling VTE out can at times be daunting. The intent of this chapter is to provide a brief overview of the widely available diagnostic studies, as well as an algorithm, seen in Figure 18.1, to assist in the workup of patients with suspected VTE.

18.1.2 Signs and symptoms

The classic "textbook" patient is rarely encountered in medicine, and this is especially true with regard to the presentation of patients with possible DVT. The "textbook" patient is one who presents with pain, pitting edema, and blanching (phlegmasia alba dolens) or a painful blue leg (phlegmasia cerulean dolens). Much of the time, presenting complaints are vague and can be attributable to a host of other etiologies. Up to 70% of patients presenting with complaints compatible with DVT will not have the disease, and many patients with DVT will not have any symptoms.

In a study of patients presenting to their primary care physicians with symptoms of DVT, a multivariate regression analysis of 17 predictors led to the establishment of nine independent predictors of DVT.[1] Interestingly, despite identifying these independent risk factors, the authors noted that the predictive value of the variables was low. In fact, the patients who were categorized as low risk based on these variables had a 15% prevalence of DVT. A prevalence rate of 35% was found for the patients labeled as being at moderate risk, and the prevalence in the high-risk group was 100%, but consisted of only a few patients.

In the primary care setting, patient history and physical examination are insufficient to rule in or out the presence of DVT.[1,2] It is therefore the responsibility of the care provider to maintain a high clinical suspicion of DVT and to order the appropriate confirming studies.

18.1.3 Clinical decision/scale

With technological advances in medicine, the emphasis on proper diagnosis appears to have shifted from the clinician's skills of observation and examination to the clinician's ability to order the correct diagnostic study. As mentioned earlier, the classically taught methods of diagnosis may indeed be lacking in both sensitivity and specificity when compared to the diagnostic modalities available today.[1,2]

In 1997, Wells et al. developed a clinical model for predicting pre-test probability of DVT based upon nine variables that can be seen in Table 18.1.[3] By implementing these variables, symptomatic patients were stratified into high-, moderate-, and low-probability groups with overall prevalence rates of VTE at 75%, 17%, and 3%, respectively. A subsequent comparison of the Wells score and empirical assessment demonstrated poor agreement between the two.[4] The Wells score was better at categorizing the low-risk patients, and empirical assessment was better at identifying high-risk patients. Other studies comparing clinical intuition to validated scoring systems have been published, with similar results of poor correlation.[5] Close to 40% of patients evaluated were underestimated by physicians in one study, whereas the patients were overestimated by physicians in a different study.[4,5]

Although the Wells scoring system is the most widely used, its validity has been questioned. Oudega et al. studied

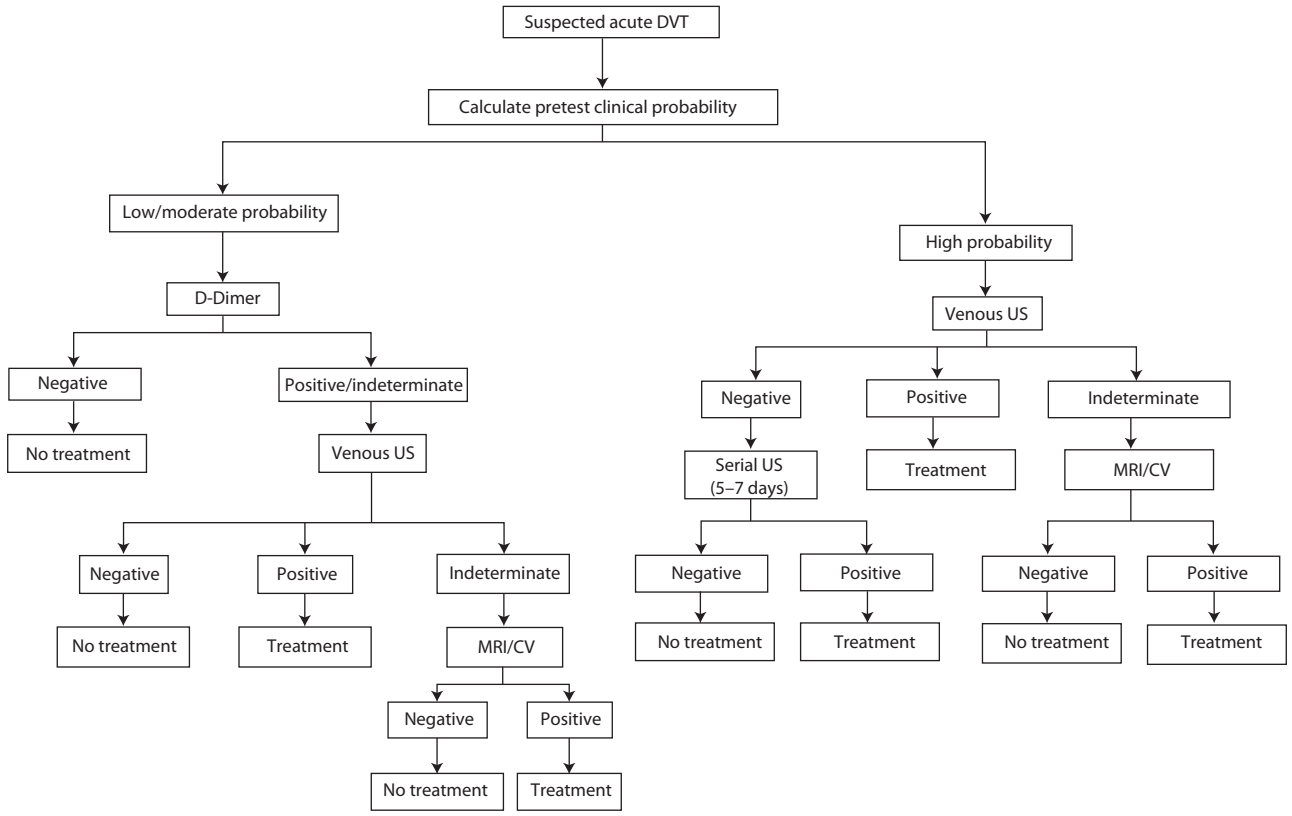

Figure 18.1 Algorithm for the diagnosis of deep venous thrombosis. CV: cardiovascular; DVT: deep vein thrombosis; MRI: magnetic resonance imaging; US: ultrasound.

patients with suspected DVT based upon the presence of a painful, swollen leg for less than 30 days.[2] Contrary to the previous study by Wells et al., Oudega et al.'s results demonstrated that, based on the Wells pre-test probability score, 15% of the patients in the lowest-risk group were diagnosed with DVT using compression ultrasound (US).[3] However, a more recent meta-analysis of 14 studies by Wells et al. supports their earlier findings, with pooled prevalence rates of DVT in the low-, moderate-, and high-risk groups of 5%, 17%, and 53%, respectively.[6]

No study suggested that clinical probability scoring alone was adequate to rule DVT in or out, as the utility of

Table 18.1 Clinical model for predicting the pre-test clinical probability of deep venous thrombosis

Clinical characteristic	Score[a]
Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep venous thrombosis	1
Alternative diagnosis at least as likely as deep venous thrombosis	–2

Source: From Wells PS et al. *N Engl J Med* 2003;349(13):1227–35. With permission.

[a] A score of 2 or higher indicates that the probability of deep venous thrombosis is likely; a score of less than 2 indicates that the probability of deep venous thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

the scoring system comes from combining a low/moderate-probability score with an additional study to rule out the presence of DVT. There is a large degree of variability with regard to clinical assessment, rendering its usefulness suspect at best.

18.1.4 Contrast venography

Contrast venography (CV), as detailed in Chapter 15, has, by default, long been hailed as the gold standard for the detection of symptomatic DVT. As of late, its current role in the diagnosis of DVT has been largely relegated to one of historical interest. The study is limited in its practicality by both the availability of highly sensitive, noninvasive studies; and by its own disadvantages, including risk of phlebitis, intravenous contrast load with associated risk of nephrotoxicity and allergic reactions, increased cost, and need for adequate intravenous access.

Of the available methods for performing CV, two techniques have emerged as being dominant. The first technique, described by Rabinov-Paulin, involves spot films, whereas the second technique involves long-leg films. Lensing et al. compared the two techniques and documented an inadequacy rate for interpretation of 20% for the Rabinov-Paulin technique versus an inadequacy rate of 2% for the long-leg films ($P < 0.001$).[7] There was also a much higher level of interobserver disagreement using the Rabinov-Paulin technique (21%) versus the long-leg technique (4%). If CV is to be performed, the long-leg technique is preferable.

Given CV's role as the gold standard for the detection of symptomatic DVT, subsequent studies have been compared to CV in order to establish their suitability. Terao et al. compared CV to US in the same group of patients and noted a sensitivity and specificity of 95.5% and 91.4% for CV and a sensitivity and specificity of 78.3% and 96.5% for US.[8] US sensitivity was inferior to CV especially in the calf, detecting only 73.6% of the DVTs noted on CV. An additional smaller study by Ozbudak et al. reported that 11.8% of the patients were discovered to have DVT by CV, which US did not demonstrate.[9] de Valois et al. echoed this opinion in a study that compared CV to duplex sonography and strain gauge plethysmography.[10] The authors admitted that duplex sonography was promising, but concluded that CV should be used as a "golden backup" in case of doubt.

In recent years, newer imaging modalities and technologies have emerged that may rival CV with regard to sensitivity and specificity. Additionally, the newer methods seek to address, in some part, the shortcomings or inconveniences of CV. A role for CV may still exist when noninvasive studies are unavailable, non-diagnostic, or in the presence of a clinical condition that is known to produce false results (e.g., D-dimer levels post-operatively or during pregnancy, compression of the iliac veins by the uterus in pregnant women, or recently post-partum women on a magnetic resonance venography [MRV] study). Rarely is CV a first-line study.

18.1.5 Impedance plethysmography

Impedance plethysmography (IPG), as discussed in Chapter 14, is based upon the physiological principle that the impedance between two points on the skin of an extremity will decrease as the volume of blood contained in the extremity increases. The technique examines the rate at which venous outflow occurs, thereby determining the presence or absence of venous outflow obstruction. The presence of DVT in the major vessels of the lower extremity, including the popliteal vein and proximally, should reduce the rate of venous outflow and subsequently affect the tracing. In the instance of non-flow-limiting thrombi, the study will be negative.

Contemporary studies examining IPG are increasingly difficult to find, as the clinical role of IPG continues to decrease. In a study by Anderson et al., testing outpatients with suspected DVT resulted in 15% of patients with abnormal IPG findings, and an additional 22% of patients with normal IPG findings but high clinical suspicion of DVT.[11] For proximal DVT, IPG had a positive predictive value of only 65% and a sensitivity of 66% when compared to CV or compression US (CUS). This low sensitivity is supported by another study, in which the sensitivity of IPG for proximal DVT was 65% and the specificity was 93%.[12] IPG detected only 23% of the DVTs that involved the popliteal but not the superficial femoral vein. In the inpatient setting, when IPG was compared to CV, IPG was noted to have 96% sensitivity and 83% specificity for proximal DVT.[13]

Kearon and Hirsh performed a literature review to identify the reasons for the large discrepancy in the sensitivity and specificity of IPG.[14] Several biases were found, including repeated IPG before CV and the inclusion of patients with known abnormal IPGs. Additionally, the conversion rate from a negative to a positive study for IPG is higher than for US. This difference may result from IPG missing smaller proximal DVTs, which propagate or become flow-limiting.

Given the inconsistent sensitivity and specificity demonstrated by IPG, especially in the outpatient setting, as well as the inability of IPG to detect DVT distal to the popliteal vein, there is little to recommend the use of IPG as a first-line study. Even in the setting of a negative IPG study, adjunctive studies are recommended for patients with high clinical suspicion of DVT.[14] Alternative imaging studies of higher sensitivity, specificity, and convenience are readily available at most institutions.

18.1.6 Duplex US

US, as detailed in Chapter 12, has almost completely replaced CV as the diagnostic test of choice for the detection of DVT. Its benefits over CV include lack of radiation, portability, noninvasiveness, and cost-effectiveness. In addition, US can also distinguish non-vascular pathologies such as inguinal adenopathy, Baker's cysts, abscesses, and hematomas. Duplex US (DUS) combines compression using

real-time B-mode US with Doppler venous flow detection. The main concern is whether or not US is comparable to CV in its diagnostic ability.

In a meta-analysis, Goodacre et al. compared US to CV. The overall sensitivity for proximal DVT was 94.2% and 63.5% for distal DVT. Specificity was 93.5%.[15] The combined color Doppler technique was noted to have a higher sensitivity, whereas CUS had optimal specificity. A similar study of CUS and CV measured a sensitivity of 97% with a specificity of 87% for CUS.[13]

The role of repeat US examinations in a patient with documented DVT was examined by Ascher et al.[16] Patients were retrospectively analyzed after an initial diagnosis of lower extremity DVT. Proximal extension of DVT was noted in 19% despite adequate heparin and warfarin therapy. In addition, those with proximal extension were noted to have an increased prevalence of PE ($P < 0.05$). Given the results of this study, repeat DUS may help to distinguish those high-risk patients who may benefit from placement of an inferior vena cava filter.

Debate continues regarding the role of repeat/serial US in the diagnosis of DVT. The sensitivity of CUS is high for proximal DVT and lower for non-occluding and isolated calf vein thrombosis. As a result, the missed thrombus may propagate and produce pulmonary emboli. After a single normal US examination with no additional testing, a VTE rate of 2.5% is noted.[17,18] With the addition of repeat US 7–14 days after an initial negative examination, the rate of thromboembolic complications is reduced to approximately 1% over 3 months of follow-up.[19] Based on similar studies, the general consensus has been to repeat US examinations when persistent clinical concern remains despite a negative initial examination, although this has not been clearly validated.[15,20] Additionally, the vast majority of repeat US examinations will be negative, proving this method both costly and time consuming.[3]

Further studies have examined the role of combining D-dimer and ultrasonography to reduce the number of repeat US examinations required. Those patients with a negative D-dimer assay and a negative initial US were noted to have a thromboembolic complication rate of 1.3% in 3 months of follow-up, a rate that is comparable to repeat sonography at a greatly reduced cost and time commitment.[19,21] In these situations, repeat US should still be employed, but only in those with positive D-dimer tests and negative initial US.[19,22]

Superficial venous reflux disease has been treated with endovenous ablation techniques for more than 15 years. Thrombi discovered in the post-operative period are referred to as endovenous heat-induced thrombi (EHIT). Very few studies have looked at the US differentiation between EHIT and spontaneous thrombosis.[23]

Radiofrequency ablation results in vein occlusion by inducing vein wall collagen contraction through heat-induced denaturation of the collagen matrix, followed by fibrosis, with sealing of the vessel lumen due to injury and inflammation of the vein wall.[24]

Secondary methods of vein closure include endothelial denudation, which is swelling of the vein wall components due to heat-induced inflammatory processes that occur as responses to temperature gradients created during the treatment from the intima to the adventitia.

The total injury to the vein wall collagen, and subsequently the total shrinkage of the vein wall, is determined by the intima to the adventitial temperature gradient and the duration of the time of heating. Laser venous-induced injury is caused by steam bubbles. With both techniques, the thrombus appears different on venous duplex and pathologically than with a spontaneous thrombosis.[23,25]

It is important to differentiate *de novo* thrombi from EHIT in the development of a treatment algorithm in patients who have undergone endovenous ablations. Thrombi that are associated with ablation techniques have a greater degree of hypercellular response, a fibroblastic reaction, and edema. *De novo* thrombi have a more prolific response to trichrome staining pathologically. In an experimental study by Santin et al.,[23] evidence of neovascularization was found in all EHIT specimens, but only in 33% of *de novo* thrombi. While it may be possible histologically to differentiate the source of thrombus on US, this can be difficult.[23]

The EHIT is more hyperechoic with less venous distention and less compressibility. It has more echogenicity than the *de novo* thrombus on US scanning.

Post-treatment duplex scans should report the extent of thrombus from the superficial vein into the deep vein, whether this is at the saphenofemoral or saphenopopliteal junction. The degree of extension must be reported, as this will be used in the determination of treatment. Those causing less than 50% occlusion may be treated conservatively with observation and sequential scanning, while those treated with greater than 50% occlusion can be managed expectantly with short-term anticoagulant therapy.[25–27] Totally occlusive thrombi are treated as a DVT (Figures 18.2 through 18.6).

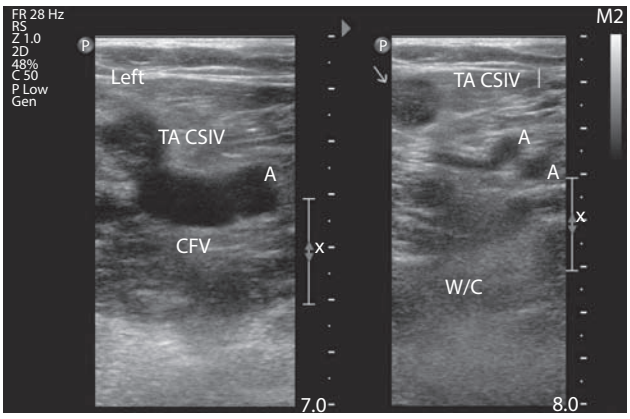

Figure 18.2 Ideal duplex image after radiofrequency ablation. Vein occluded without thrombus extension into the common femoral vein (CFV). A: artery; CSI: confluence of the superficial inguinal veins; TA: total occluding acute; W/C: with compression. (From Lohr J, Kulwicki A. *Semin Vasc Surg* 2010;23:90–100. With permission.)

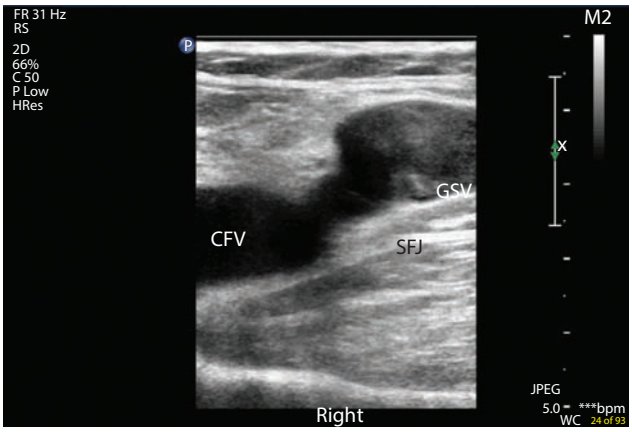

Figure 18.3 Compressed hyperechoic image.

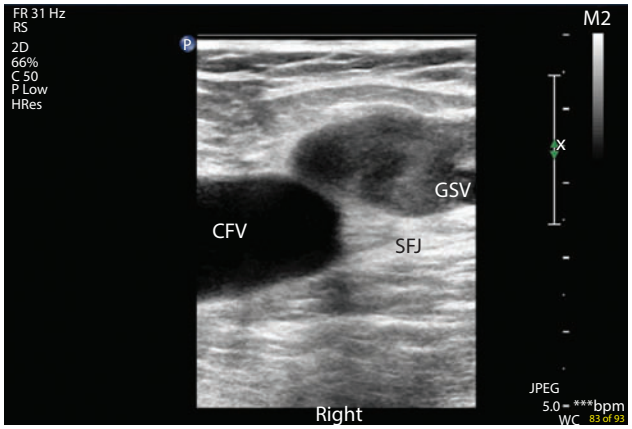

Figure 18.4 Flush occluded saphenofemoral junction endovenous heat-induced thrombus.

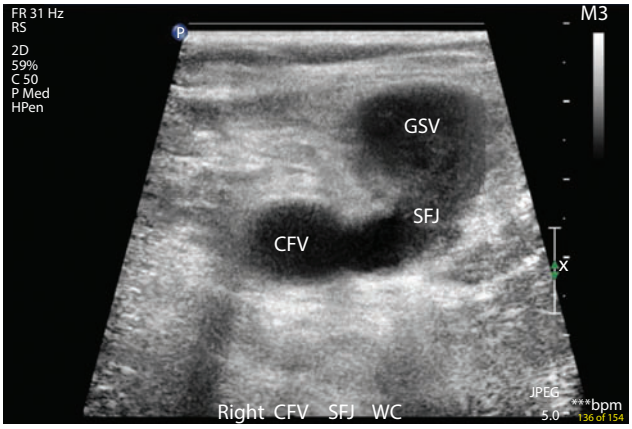

Figure 18.5 Protruding endovenous heat-induced thrombus.

Pitfalls in venous duplex imaging include misidentification of veins, duplicated vein systems, systemic illness or hypovolemia decreasing venous distention, suboptimal imaging in obese or edematous patients, or areas not amenable to compression, such as the iliac veins and adductor canal. As with most US-based imaging studies, the quality of the examination depends largely on the technician performing the examination.

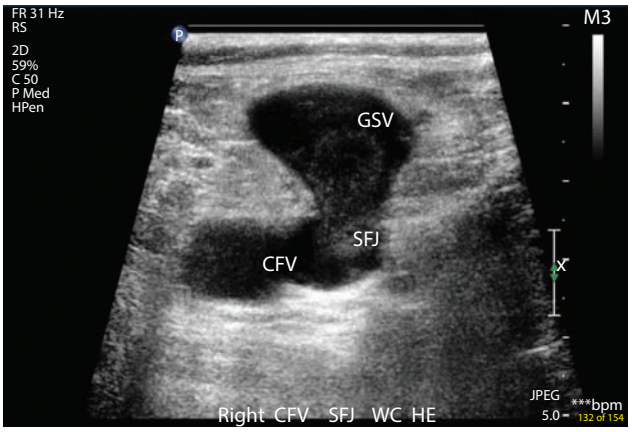

Figure 18.6 Free-floating endovenous heat-induced thrombus tip in common femoral vein.

18.1.7 Magnetic resonance imaging/MRV

Magnetic resonance imaging (MRI)/MRV, as discussed in detail in Chapter 16, has gained momentum in recent years for the detection of DVT. In addition to being less invasive than CV, MRV overcomes some of the limitations of CUS and IPG. Since MRV directly visualizes the thrombus, even non-flow-limiting thrombi should be detectable, in contrast to IPG. MRV should also be able to detect thrombi proximal to the inguinal ligament, an area which has been problematic for CUS in the past. Furthermore, MRV results are also independent of the technologist's experience and availability, in contrast to CUS.

When Carpenter et al. compared MRV to CV, the results were identical in 97% of the patients scanned.[28] In fact, the extent of the thrombus and whether it was partially or totally occlusive was in complete agreement between the two studies. MRV had a sensitivity and specificity of 100% and 96%, respectively. Similar results were noted by Laissy et al., with MRV demonstrating 100% sensitivity and specificity compared to CV.[29] MRV was, once again, noted to have a high sensitivity of 95% for detecting the extent of the DVT.

As with most studies involving DVT in the lower extremities, the sensitivity of MRV decreases the more peripherally a thrombus is located. In a prospective, blinded study, MRV direct thrombus imaging had sensitivity values of 94% or 96%, depending on the reader.[30] When isolated calf DVTs were examined, the sensitivity values of MRV were 83% and 92% for the two readers. For DVT involving the femoropopliteal segment, sensitivities were significantly higher at 97% for both readers. When the iliofemoral segment was examined, sensitivity rose to 100% for both readers.

An additional benefit that MRV may share with CUS is in the aging of thrombi. In a comparison study of venous-enhanced subtracted peak arterial MRV to CV,

100% sensitivity and specificity values for DVT in the iliac and femoral veins were noted.[31] Interestingly, vessel wall enhancement was noted for acute thrombosis and not for chronic thrombosis.

Tempering the enthusiasm for MRI/MRV are the time requirements and patient cooperation needed to perform the study. Using MRV to diagnose DVT might limit the availability of MRI for other uses due to scheduling difficulties. In addition, patients with certain implants may not be able to undergo testing. Lastly, the cost of MRV is significantly higher than most other DVT studies. In one study, MRV's cost was 1.4-times that of CV and 2.5-times that of duplex scanning.[28]

Recently, concerns have been raised regarding the safety of gadolinium in patients with renal insufficiency. There is evidence to suggest that gadolinium is associated with nephrogenic systemic fibrosis.[32–35]

18.1.8 D-dimer

Using D-dimer to preselect patients who are likely to have DVT has gained considerable interest in an effort to reduce costs and expedite patient workup. The D-dimer assays currently available include turbidimetry, enzyme-linked immunosorbent assay (ELISA), latex particle agglutination, fluorescence immunoassay, and immunofiltration tests. Each assay has a corresponding normal reference range, which is typically not interchangeable.

A combination of the Wells pre-test clinical probability (PCP) score and quantitative D-dimer testing was used by Yamaki et al. to reduce the number of venous duplex scans performed.[36] A 100% sensitivity and a 100% negative predictive value (NPV) were noted in the study. The authors recommended no further testing to rule out DVT in patients with low to moderate PCP and a negative D-dimer test. This recommendation reflects the findings of previous studies in which the NPV of D-dimer using the SimpliRED assay decreased from 94.1% in the moderate PCP group to 86.7% in the high-probability patients.[37] A systematic review by Fancher et al. and a meta-analysis by Wells et al. concluded that DVT could effectively be ruled out in patients with low to moderate clinical probability and a negative D-dimer assay.[6,38]

D-dimer levels in patients without a PCP score were measured by Diamond et al.[39] Compared to duplex imaging, the D-dimer results revealed 100% sensitivity and 100% NPV, but only 48.8% specificity due to the large number of false positives. It was estimated that 42% of the venous duplex studies could have been eliminated based on D-dimer assay alone. Five different quantitative D-dimer assays were compared by Stevens et al., and the NPV was uniformly high as long as the cut-off level for the D-dimer assays was set for high sensitivity.[40] The high sensitivity of the study is maintained even in the presence of cellulitis.[41]

In a review by Goodacre et al. of 97 studies, the sensitivity and specificity of the D-dimer assays were observed to vary widely.[15] The *post hoc* thresholds yielded higher sensitivity since levels that maximize sensitivity were probably chosen, and the use of D-dimer in patients with low clinical probability was likely to yield a higher specificity secondary to the lower number of false positives.

There are situations where the D-dimer assay may produce false positives. These situations include pregnancy, malignancy, recent post-operative state, and total bilirubin greater than 2 mg/dL. Further confounding factors may include the age of the clot (as significant declines in the D-dimer level may occur with time), position of the clot (isolated calf DVT reduces sensitivity), and heparin use (which may significantly reduce D-dimer levels).[42] Despite its limitations, D-dimer is a useful tool for ruling out DVT as long as the threshold is set low enough to keep the sensitivity high. If a higher specificity is desired, the D-dimer assay should be used in conjunction with a PCP score.

18.1.9 Additional studies

Studies examining other diagnostic modalities, including computed tomography (CT), liquid crystal contact thermography, C-reactive protein, rheography, and photoplethysmography, have been performed with varying degrees of success.[43–48] At this time, however, none of the alternative imaging modalities have achieved mainstream status, limiting their usefulness in the clinical setting.

18.1.10 DVT in pregnancy

The diagnosis of DVT during pregnancy adds another level of complexity. There are the obvious concerns for the well-being of the fetus, as well as questions regarding the diagnostic accuracy of DVT studies during this period.

The amount of ionizing radiation the fetus would be exposed to during VTE workup is only considered significant in the induction of malignancy.[49] Even then, the dose received during DVT workup would be less than the background radiation received during the 9 months of pregnancy. The contrast agent may pose a risk of anaphylaxis, in addition to crossing the placenta and possibly suppressing thyroid function in the fetus.[49]

US remains the front-line study for detection of DVT in pregnancy. If the quality of the US study is suboptimal, or there is suspicion of pelvic thrombus, MRI/MRV should be considered. D-dimer levels have been known to increase even during the course of a normal pregnancy and are of unproven usefulness.[42] In pregnant patients, repeat US is recommended if the initial scan is negative for DVT.

18.1.11 Intravenous drug users

This group poses special challenges for the diagnosis of DVT. These patients will frequently have a positive D-dimer assay secondary to infection. Furthermore, on duplex scanning, chronic vein wall changes may be present as well. A negative initial scan in this group should be followed up with a repeat study in 7–10 days, although compliance is frequently problematic.

18.1.12 Controversies

The role of unilateral venous scanning has been greatly debated. The Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) has acknowledged the need for unilateral or limited scans and published revised guidelines. However, the frequency and importance of finding thrombi in the asymptomatic limb are unresolved.[50–52] Ultimately, the diagnosis and treatment of DVT continues to evolve. Even the nomenclature of veins has evolved. Among the changes are the renaming of the superficial femoral vein as the femoral vein, the greater/long saphenous vein as the great saphenous vein, and the lesser saphenous vein as the small saphenous vein, in an effort to more accurately reflect their true anatomy.[53]

18.2 PULMONARY EMBOLISM

18.2.1 Background

As is the case with DVT, PE is a diagnosis that must be confirmed through objective testing. The non-specific signs and symptoms of PE in association with risk factors are insufficient to allow for a definitive diagnosis, and should prompt the clinician to further investigation.[54] The importance of correct diagnosis and timely treatment cannot be overstated, as the mortality after PE is much higher than with DVT alone.[55] Figure 18.7 displays the algorithm described in the following sections.

18.2.2 Signs and symptoms

The most common signs of PE are tachypnea and tachycardia. Less common signs including syncope, hypoxemia, and sudden hypotension are also associated with PE. However, all of these signs are non-specific and can be found in other illnesses or conditions as well. The symptoms of PE range widely and include anxiety, dyspnea, pleuritic chest pain, and lightheadedness.[56] Although it appears that the ability to accurately determine the pre-test probability of PE increases with experience, the difference is not sufficiently large, and almost a quarter of the patients with PE will have sudden death as the first clinical presentation.[55,57]

18.2.3 Clinical probability scoring

The use of a validated pre-test probability score is recommended as the first step in the workup of patients suspected of having PE.[58] Calculating the PCP is both a cost-effective and expedient way to stratify patients into low/intermediate/high-probability or unlikely/likely groups, depending on the assessment tool employed. Based upon the results,

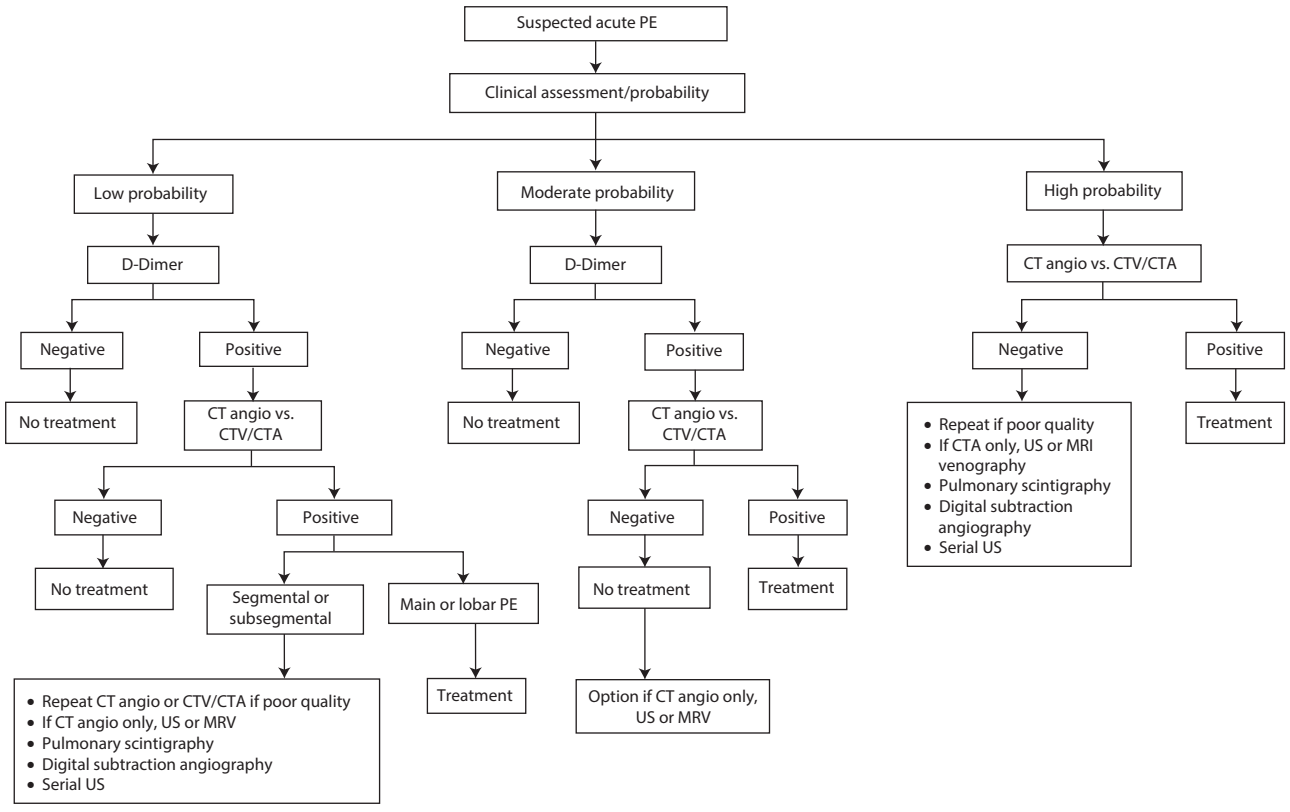

Figure 18.7 Algorithm for the diagnosis of pulmonary embolism. CT: computed tomography; CTA: computed tomographic angiography; CTV: computed tomographic venography; MRI: magnetic resonance imaging; MRV: magnetic resonance venography; PE: pulmonary embolism; US: ultrasound.

Table 18.2 Wells Short Clinical Score list for pulmonary embolism

Criteria	Score[a]
Clinical signs and symptoms of deep venous thrombosis: minimal swelling of the leg and pain on palpation of the deep leg veins	3.0
Pulmonary embolism more likely than an alternative diagnosis	3.0
Heart beat frequency >100 beats per minute	1.5
Recent immobilization or surgery within <4 weeks	1.5
Documented history of deep venous thrombosis and/or pulmonary embolism	1.5
Hemoptysis	1.0
Recent history of malignancy <6 months (treatment or palliative treatment)	1.0

Source: From Michiels JJ et al. *Semin Vasc Med* 2002;2(4): 345–51. With permission.

[a] Clinical score for pulmonary embolism: low = ≤2; moderate = 2.0–6.0; high = ≥6.

patients should then undergo additional testing to confirm/exclude the diagnosis of PE. Used appropriately, the scoring system can reduce the need for imaging studies and associated costs.

In a study which reviewed the Wells simplified score, Geneva score, and empirical assessment, the authors concluded that all three methods were clinically useful, although empirical assessment tended to classify fewer patients as having low probability.[58] It is the low/moderate-probability group that is of particular interest, since this group of patients can have a diagnosis of PE effectively ruled out with an adjunctive study.[59,60] Using the Wells clinical decision rule shown in Table 18.2,[61,62] a combination of unlikely probability and a normal D-dimer test resulted in a subsequent VTE rate of only 0.5% in untreated patients.[63]

Other validated scoring systems, like the one in Table 18.3, have proven similarly useful.[59]

18.2.4 Ventilation–perfusion scintigraphy

Prior to the widespread use of spiral CT (s-CT), ventilation-perfusion (VP) scintigraphy was often the first-line study. VP scintigraphy is less invasive than pulmonary angiography, and a normal study can effectively exclude PE. A positive study is also highly specific for PE, allowing for directed treatment.[64] However, one of the major shortcomings of VP scintigraphy is the high number of intermediate-probability scans. As noted in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, up to 70% of VP scans are non-diagnostic and require additional studies.[64] In addition, the sensitivity of VP scans is suboptimal. In patients with PE, the results of VP scans are of high probability in only about 40%. The majority of patients with PE will have intermediate- or low-probability results.[65]

Table 18.3 Antwerp Clinical Score list for pulmonary embolism

Criteria	Score[a]
Age >60 years	0.5
One or more risk factors for venous thromboembolism	1.5
One or more eliciting circumstances for venous thromboembolism	1.0
Respiratory signs and symptoms	
Dyspnea	1.5
Pleuritic pain	1.0
Non-retrosternal, non-pleural chest pain	1.0
PaO_2 <92% (<3 L O_2)	1.0
Hemoptysis	1.0
Pleural rub	1.0
Cardiac and other signs and symptoms	
Heart beat frequency >100 beats per minute	1.0
Temperature <37.5°C and >38.6°C	1.0
Chest X-ray: atelectasis and/or unilateral diaphragm elevation suspicious for pulmonary embolism and no other explanation	1.0
Leg symptoms suspicious of deep venous thrombosis (swelling, pain, etc.) (clinical score of Wells et al.[62] for deep venous thrombosis)	3.0
Signs of circulatory and/or of respiratory insufficiency: 1, 2, or 3	6.0
1. Hypotension (systolic BP < 90 mmHg and heart frequency >100 beats per minute)	
2. Respiratory insufficiency (artificial breathing >3 L O_2)	
3. Recent decompensation cordis right	

Source: From Michiels JJ et al. *Semin Vasc Med* 2002;2(4): 345–51. With permission.

Note: PaO_2: arterial partial pressure of oxygen.

[a] Clinical score for pulmonary embolism: low = <3; moderate = 3.0–6.0; high = >6.

There have been subsequent attempts to improve on the diagnostic capability of VP scans. In the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED), only perfusion scans were performed after patients were assigned a clinical probability.[66] Using the combined approach, a positive predictive value of 92%–99% and a NPV of 97% was obtained. Other studies have examined VP scans in conjunction with s-CT and noted improvements in the diagnostic performance.[67–69]

VP scintigraphy may still be the first-line study in patients with contraindications to iodinated contrast due to dye allergy or renal insufficiency. Furthermore, the higher radiation exposure with s-CT in young women may be of clinical significance.[70] In pregnant women, 69% of the PIOPED II investigators recommended pulmonary scintigraphy over CT angiography.[59]

18.2.5 Pulmonary angiography

Long considered the gold standard for diagnosing PE, pulmonary angiography is no longer routinely used. Considering the invasive nature of the procedure, the potential for higher radiation exposure, and the significantly higher cost, there is little evidence to support the use of pulmonary angiography as a first-line study.[59]

Based on the PIOPED patient population, an analysis of pulmonary angiography demonstrated 98% interobserver agreement for PE in the main or lobar pulmonary arteries, and 90% interobserver agreement for PE limited to the segmental or subsegmental pulmonary arteries. When PE limited to the subsegmental arteries was studied, there was only 66% interobserver agreement.[71]

In earlier studies, pulmonary angiography demonstrated considerably higher sensitivity than s-CT (67%).[72] Even with considerable improvement in multi-detector CT technology, pulmonary angiography continues to show higher sensitivity, although the gap is smaller and may be of limited clinical significance.[73] After a negative pulmonary angiogram, 0.6% of the patients followed were noted to have a PE.[74]

The complications associated with pulmonary angiography are limited but not insignificant. In a study based on the PIOPED patients, complications were noted to be death in 0.5%, major non-fatal complications in 1%, and less significant events in 5%.[74] A total of 1% of patients experienced renal dysfunction after the study.[74]

18.2.6 D-Dimer

The utility of D-dimer assays in the workup of PE and DVT is quite similar. Both conditions are a part of the same disease spectrum, and it stands to reason that the findings would show a high degree of congruity.

A systematic review of prospective studies on the diagnostic role of D-dimer concluded that the ELISA and quantitative rapid ELISA had the highest sensitivities (96%) and negative likelihood ratios (0.13) among the various assays.[75] Similar results of high sensitivity but moderate specificity were noted in other studies as well.[76–78] In one study, it was also suggested that D-dimer levels were of greater benefit in the outpatient setting, since conditions which could lead to false-positive results (e.g., inflammation, trauma, and surgery) were more often seen in the inpatient setting.[75] As for the diagnostic role of D-dimer in pregnant patients, there is as yet no clear consensus.[76]

With high sensitivity and only moderate specificity, the D-dimer assay is limited in its ability to accurately rule in PE. However, the combination of a low to moderate probability score using a clinical assessment scale and a normal D-dimer assay result can effectively rule out the presence of PE.[60,63,77] Unfortunately, negative D-dimer assay results in patients with high-probability clinical assessments are still associated with PE rates of more than 15%, and should not be relied upon. Further testing is indicated in the high-risk group.[77]

18.2.7 Spiral CT

s-CT has emerged as one of the predominant studies for the diagnosis of PE. Not only is the study less invasive than pulmonary angiography, it also has the ability to depict other conditions that may be confused with PE. Pneumonia, pneumothorax, pneumomediastinum, pleural/pericardial effusion, aortic dissections, and various other conditions can mimic the signs and symptoms of PE, and have been noted in 11%–70% of CT examinations performed for suspected PE.[65]

In the 1990s, studies comparing s-CT to VP scans and angiography were based on single-detector CT scanners. Despite technological limitations, s-CT was noted to be useful in the diagnosis of PE, especially in the scenario of intermediate-probability VP scans. In one prospective study comparing scintigraphy to s-CT with pulmonary angiography as the gold standard, s-CT was in concordance with angiography 80% of the time in patients noted to have intermediate-probability VP scans.[79] A separate study of patients with intermediate-probability VP scans demonstrated a PE rate of 24.4% using s-CT.[80] The superiority of s-CT over VP scanning is supported by other studies as well, but the reported sensitivity of s-CT has ranged widely, from 53% to 100%.[65,72,81,82]

With the single-detector CT scanners, subsegmental and peripheral pulmonary arteries were poorly visualized, and sensitivities for PE in these locations were especially low.[83] False-negative rates of single-detector CT scanning were as high as 30% when used alone.[84,85]

The current generation of multiple detector CT (MDCT) scanners is faster and able to visualize smaller pulmonary arteries.[86] As a result, higher sensitivities have been reported that rival even pulmonary angiography.[73] For subsegmental pulmonary arteries evaluated with single-detector, 4-MDCT, and 16-MDCT scanners, the arteries were well visualized in 36%, 75%, and 88% of the scans, respectively.[65] In recent years, the impetus has been to perform synchronous indirect CT venography and CT pulmonary angiography scans. By doing so, the presence of both PE and DVT can be evaluated with higher sensitivity and similar specificity.[59,65,87] These analyses, however, are biased regarding DVT sensitivity and/or specificity, as the samples are derived from PE patient groups, which have a higher incidence of DVT.

18.2.8 MRI/magnetic resonance angiography

The use of MRI/magnetic resonance angiography (MRA) for the diagnosis of PE has received greater attention in recent years. Even with this increased interest, most diagnostic algorithms and recommendations, including PIOPED II, only mention MRI briefly.[59]

The sensitivity of MRA, when compared to conventional angiography, ranges from 77% to 100%, depending on the study.[88,89] With the addition of magnetic resonance

perfusion imaging, there is a subsequent increase in sensitivity rivaling that of 16-MDCT angiography.[90] The current role for MRI/MRA is as a backup when conventional diagnostic methods are unavailable or contraindicated due to dye allergy, renal insufficiency, or concerns about radiation exposure.[59,88,89] MRI may also prove to be valuable in the follow-up of acute PE in order to determine thrombus age.[91]

Notably, recent studies have questioned the traditional thinking that gadolinium was less nephrotoxic than iodinated contrast. In fact, at angiographic concentrations, gadolinium has demonstrated equal or greater renal cell toxicity than iodinated contrast.[32] There is also mounting evidence that gadolinium administration may play a significant role in the development of nephrogenic systemic fibrosis.[33–35]

18.2.9 Other studies

Other modalities have been studied with the intention of using them for the diagnosis of PE, with varying levels of success. Although electrocardiogram (ECG) changes may be present, they are neither sensitive nor specific for PE.[92] The changes may, however, indicate a way of stratifying risk, since patients with acute major PE and ECG changes have worse outcomes than those without the changes.[93] Likewise, although arterial blood gas changes may be present, they are non-specific and therefore of limited diagnostic utility in the workup of PE.[94] Lastly, although chest radiographs are routinely ordered in those experiencing respiratory distress, the results are most often normal, even in the presence of PE. Chest radiographs may be useful for determining which patients should undergo s-CT versus VP scintigraphy, since abnormal chest radiographs increase the likelihood of indeterminate-probability VP scans.[95]

Once a PE has been confirmed, algorithms now exist to help risk-stratify patients into treatment groups, and/or testing groups for further evaluation. The process of patient risk stratification helps identify patients who will do well with standard therapy and who are likely to need more aggressive treatment. This also helps determine resource utilization. Some patients with small, incidental pulmonary emboli and some segmental pulmonary emboli are now being treated as outpatients, while other patients may require immediate interventional therapy, either operative or lytic. Two different scoring systems have been used to predict the severity of PE. These include the Pulmonary Embolism Severity Index (PESI) score and the Geneva score (Table 18.4).[96,97]

In validation studies, a PESI score of less than 66 predicts a 30-day mortality rate of less than 3%.[98] Studies have recently been completed of large multinational randomized trials comparing outcomes and costs for inpatient management versus immediate discharge from ambulatory centers when patients had a PE diagnosed and a PESI score of less than 66 (Figures 18.8 through 18.11).[98,99]

The use of ECG, biomarkers, echocardiography, and CT pulmonary angiogram findings can be combined to predict mortality in those with and without right ventricular

Table 18.4 Two scoring systems to predict the severity of pulmonary embolism

PESI score[96]	Points assigned
Age, per year	Number of years of life
Male gender	10
Cancer	30
Heart failure	10
Chronic lung disease	10
Pulse >110 beats/minute	20
Systolic blood pressure <100 mmHg	30
Respiratory rate >29 breaths/minute	20
Temperature <36°C	20
Altered mental status	60
SaO_2 <90%	20
Low-risk score	<66
High-risk score	>125
Geneva score[97]	
Cancer	2
Heart failure	1
Prior deep venous thrombosis	1
Systolic blood pressure <100 mmHg	2
PaO_2 <8 kPa	1
Concomitant deep venous thrombosis	1
Low-risk score	<3
High-risk score	>2

Source: From Kline JA, Miller DW. *J Natl Compr Canc Netw* 2011;9(7):800–10. With permission.

Note: PaO_2: arterial partial pressure of oxygen; PESI: Pulmonary Embolism Severity Index; SaO_2: percentage of oxygen saturation of arterial blood.

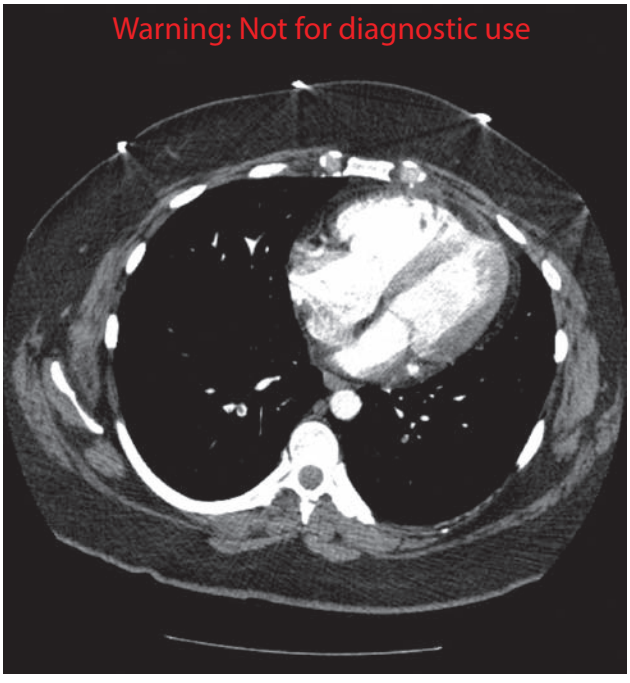

Figure 18.8 Right ventricular shift into the left ventricle.

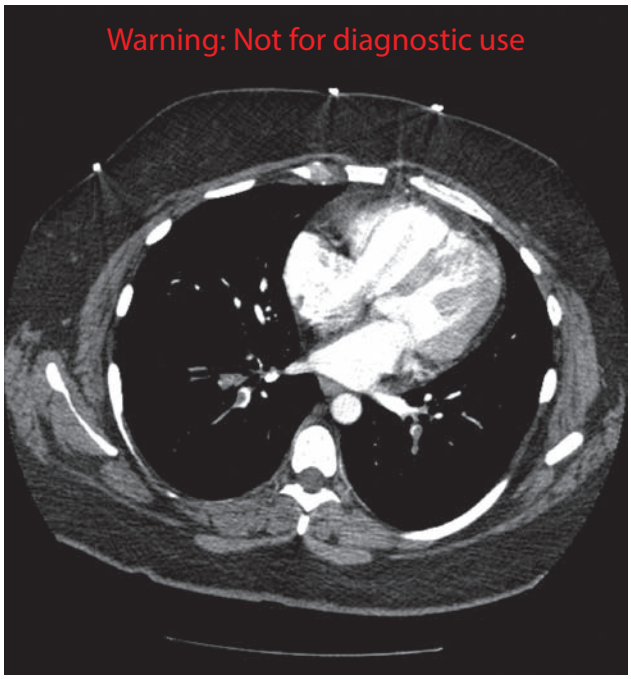

Figure 18.9 Bowing of septum into the left ventricle.

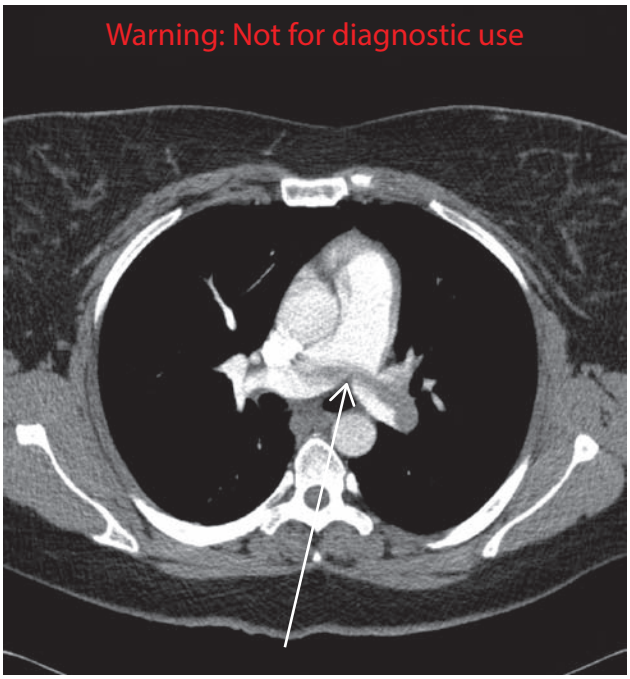

Figure 18.11 Central saddle embolus.

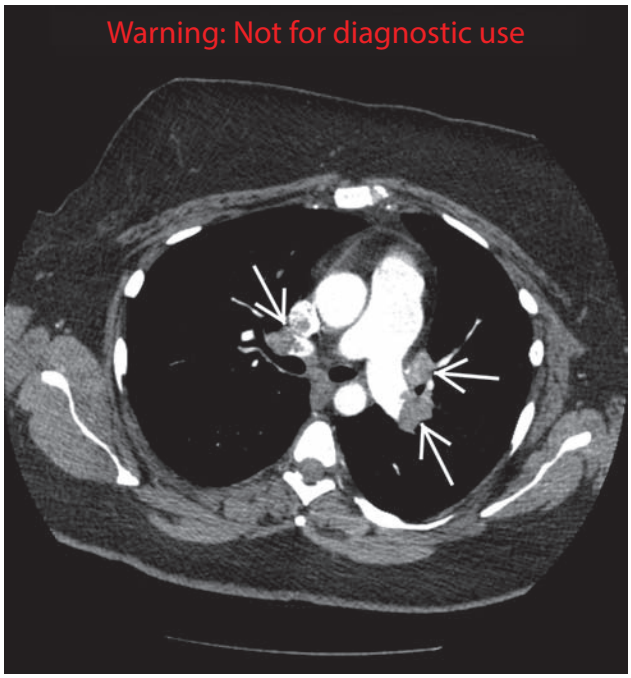

Figure 18.10 Proximal pulmonary emboli.

dysfunction. For patients with right ventricular dysfunction, mortality is 15%; for those without, mortality is 5%. If there is elevated troponin, the mortality rate is greater than 43%, while those without have less than 15% mortality. In those with an elevated brain natriuretic peptide (BNP), the mortality risk is 47%, but less than 13% in those who lack elevated BNP. For those with an elevated n-terminal prohormone of BNP (proBNP), mortality is 32%; if it is not elevated, mortality is less than 5%.[98]

Experts can then bundle this stratification data in order to categorize patients into risk categories and thus determine different treatment and monitoring needs (Table 18.5). Patients at low risk for PE may require heparin anticoagulation with either low-molecular-weight or unfractionated heparin. Patients at low risk for PE can be admitted to an unmonitored bed, and some of these patients may be discharged directly to home.[100–109]

Patients with moderate-risk PE should be hospitalized with telemetry monitoring and initial heparinization. Any patient with degradation or development of new or worsening signs should undergo repeat biomarker testing and echocardiography. The risk should be re-evaluated.

Patients with more severe and moderate pulmonary emboli or submassive pulmonary emboli may require more aggressive care and monitoring, with consideration of fibrinolytic therapy (Figure 18.12). The treatment of submassive embolism remains one of the most controversial subjects, and is currently the subject of much ongoing research.[110]

High-risk patients may also be reported as severe, and major pulmonary emboli may occur in association with hypotension, and may require heparin anticoagulation, intensive care unit monitoring, and treatment escalation.

The most common relative contraindications for fibrinolytic therapy include age over 80 years, advanced directives, a "do not resuscitate" order, trauma associated with syncope or seizure-like presentation, anemia or thrombocytopenia, current menstruation, recent childbirth, a remote or vague history of stroke, gastrointestinal bleeding, and metastatic carcinoma.

Table 18.5 Criteria for categorizing patients with acute pulmonary embolism and associated treatment options

Category	Definition	Recommended treatment options
Low risk	Systolic blood pressure >90 mmHg at all times and all of the following: • Shock index <1 • SaO_2 almost always >94% • Normal electrocardiogram (or Daniel score <3) • Normal troponin and BNP or proBNP • PESI score <66	• Begin low-molecular-weight heparin • Optional admission to unmonitored regular bed • Consider outpatient treatment if adequate compliance and follow-up can be assured
Moderate risk	Systolic blood pressure >90 mmHg at all times and any one of the following: • Shock index ≥1 at any time • SaO_2 persistently <94% • Electrocardiogram showing any signs of pulmonary hypertension (tachycardia, S1Q3T3, or incomplete RBBB) • Elevated troponin or BNP or proBNP • PESI score >65 • Echocardiography with any degree of right ventricular hypokinesis	• Begin heparin treatment • Fibrinolytics in the minority of cases • Admission to a telemetry bed
More severe (submassive) moderate risk	Appearance of at least moderate distress and: • Shock index >1 and severe right ventricular hypokinesis on echocardiography • Worsening electrocardiogram, such as S1Q3T3 and a new incomplete RBBB, or progression of incomplete to complete RBBB, or development of T-wave inversion in V1–V3	• Begin heparin treatment • Fibrinolytic treatment in most patients without contraindications in the emergency department • Admission to a step-down or intensive care unit
High risk (major)	Any systolic blood pressure <90 mmHg or <20 mmHg below documented baseline and appearance of distress Any persistent systolic blood pressure <90 mmHg regardless of appearance	• Begin heparin treatment • Fibrinolytic treatment in the emergency department in all patients without contraindications • Admission to intensive care unit

Note: BNP: brain natriuretic peptide; PESI: Pulmonary Embolism Severity Index; proBNP: prohormone of brain natriuretic peptide; RBBB: right bundle branch block; SaO_2: percentage of oxygen saturation of arterial blood.

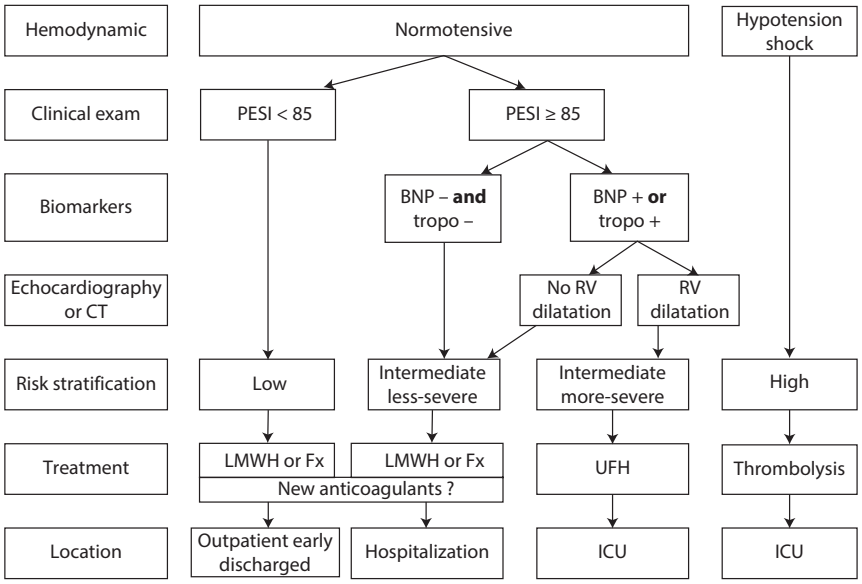

Figure 18.12 Algorithm management in risk stratification and treatment strategy for patients with acute pulmonary embolism. BNP: brain natriuretic peptide; Fx: fondaparinux; ICU: intensive care unit; LMWH: low molecular weight heparin; PESI: Pulmonary Embolism Severity Index; RV: right ventricle; tropo: troponin; UFH: unfractionated heparin. (From Penaloza A, Roy PM, Kline J. *Curr Opin Crit Care* 2012;18:318–25.)

18.2.10 Algorithm use for DVT and PE

The use of algorithms seeks to separate patients into risk groups for testing and evaluation while not missing any significant pathologies. The algorithms only apply to symptomatic outpatients, using exclusion criteria to increase sensitivity and specificity. They have not been validated for inpatients or asymptomatic patients. Algorithms perform differently in different populations and when used by different care providers. A standardized treatment management plan is also defined through the algorithms. These may be useful with inexperienced staff and decrease practice variation, and may provide some control over risk management. Algorithms do not include consideration of diagnostic uncertainty and patient anxiety while waiting for a definitive diagnosis. Clinician and patient acceptance are required to use an algorithm, and the algorithm should utilize tests that are widely available.

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Guidelines 3.2.0 of the American Venous Forum on diagnostic algorithms for acute deep venous thrombosis and pulmonary embolism

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.2.1	In symptomatic outpatients with suspected acute deep venous thrombosis (DVT), we recommend to obtain first a clinical score and D-dimer level to select patients for further diagnostic studies.	1	B
3.2.2	D-dimer levels are inaccurate for diagnosing DVT in several clinical conditions, including recent surgery, pregnancy, malignancy, infection, elevated bilirubin, trauma, and heparin use. In these situations, alternative diagnostic modalities are recommended.	1	B
3.2.3	We recommend to repeat duplex scan or alternative imaging modality in the follow-up of patients with negative duplex studies and high clinical suspicion of DVT.	1	B
3.2.4	We suggest that a combination of clinical probability score and D-dimer level has similar utility in the diagnosis of DVT to a computed tomography scan.	2	B
3.2.5	We suggest judicious use of Gadolinium in patients with renal insufficiency because of the risk of nephrogenic systemic fibrosis.	2	C

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● = Key primary papers
★ = Major reviews

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19

Medical treatment of acute deep venous thrombosis and pulmonary embolism

ANDREA T. OBI AND THOMAS W. WAKEFIELD

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19.1 INTRODUCTION

Despite recent advances in medical and interventional therapy for venous thromboembolism (VTE), it continues to be a major cause of in-hospital deaths and emergency room visits. Historically, VTE was treated with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), commonly as a bridge to anticoagulation with a vitamin K antagonist (VKA). In the last several years, the available therapies for the treatment of VTE have broadened to include new classes of oral and injectable anticoagulants, new thrombolysis devices, and new vena cava filters. Throughout this chapter, we provide an overview of the basic principles of the treatment of VTE, from initial presentation to determining optimal therapy and duration of anticoagulation to aggressive therapies and special circumstances.

19.2 PRINCIPLES OF THE TREATMENT OF VTE

The objectives of treatment in patients with VTE are to prevent death from pulmonary embolism (PE), to prevent recurrent VTE, and to prevent the post-thrombotic syndrome (PTS). Traditionally, anticoagulant drugs such as heparin, LMWH, and warfarin constitute the mainstay of the initial treatment of venous thrombosis, effectively decreasing thrombus extension and subsequent embolization. New oral factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and a thrombin inhibitor (dabigatran) have recently been approved for the treatment of VTE. For patients with iliofemoral thrombosis, catheter-directed thrombolysis has been shown to decrease the risk of PTS. In patients who cannot be anticoagulated, such as those with intracranial hemorrhage or major trauma, inferior vena cava (IVC) filters significantly reduce the risk of death from PE. The prevention of PTS remains a vexing problem, with no available medical therapy. Some data suggest that the use of LMWH, graduated compression stockings, and restoration of venous flow in massive obstructing iliofemoral thrombosis can decrease the risk of PTS, although none reliably prevent it.

19.3 STANDARD INITIAL THERAPY

Immediate anticoagulation is paramount in the initial treatment of the patient presenting with VTE (Figure 19.1). Systemic anticoagulation decreases thrombus extension, PE, and recurrence. Failure to achieve therapeutic anticoagulation within 24 hours increases the risk of recurrence. Therefore, it is often necessary to empirically anticoagulate the patient with presumed PE while waiting for diagnostic testing. This is infrequently indicated in the patient with suspected deep venous thrombosis (DVT), as bedside duplex ultrasound testing is rapid and nearly universally available. The risks, benefits, and costs of anticoagulation should be weighed carefully against the patient's clinical probability of having a VTE while waiting for testing. When using validated clinical prediction scores for estimating risk of DVT or PE,[1] it is acceptable to wait up to 24 hours for low-risk patients and up to 4 hours for intermediate-risk patients for objective imaging data prior to

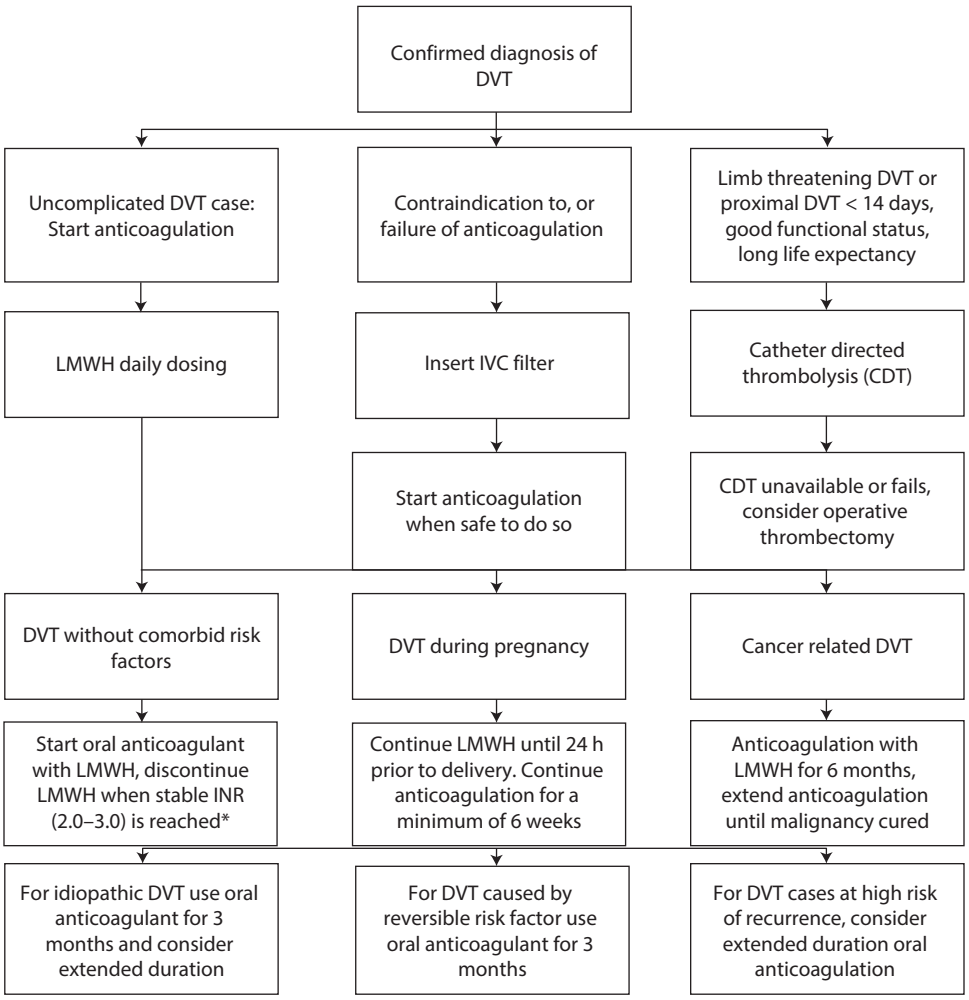

Figure 19.1 Treatment algorithm for acute deep venous thrombosis. *Some of the new oral anticoagulants do not require a LMWH bridge, and the new oral anticoagulants are not monitored with INRs. CDT: catheter-directed thrombolysis; DVT: deep venous thrombosis; INR: international normalized ratio; IVC: inferior vena cava; LMWH: low-molecular-weight heparin.

beginning anticoagulation.[2] High-risk patients are likely best served by immediate anticoagulation. Risk factors for major bleeding, such as a recent operation, may support a longer delay to initiation of anticoagulation, whereas patients with poor cardiopulmonary reserve may benefit from earlier initiation of anticoagulation. Even with appropriate anticoagulant therapy, however, recurrent DVT can still occur in up to a third of patients over an 8-year period of time.[2] Treatment agents that are available for immediate anticoagulation include UFH, LMWH, warfarin, and the new anticoagulants such as fondaparinux, rivaroxaban and apixaban. Additionally, dabigatran and edoxaban maybe used as monotherapy after initial treatment with a UFH or LMWH bridge (Table 19.1).[3]

19.3.1 LMWH/heparin

The current recommended therapy for the acute treatment of DVT is LMWH, derived from the lower molecular range of UFH (4–5 kDa compared to 10–16 kDa), which has the advantages of reliable weight-based dosing that does not require monitoring (except in morbid obesity, renal failure, or perhaps pregnancy) and ease of administration (subcutaneous route), allowing for home administration (Table 19.2) and lower bleeding risk. LMWH is at least as effective and safe as UFH, and in practical terms it allows achievement because therapeutic dosing is more rapid and dependable. A number of high-quality randomized controlled trials have compared LMWH to UFH in the treatment of DVT. LMWH confers a lower risk of major bleeding (absolute risk reduction of approximately 2 per 100 patients treated; relative risk [RR]: 0.6–0.7), a lower risk of recurrent thromboembolic disease (RR: 0.7–0.8), and a lower risk of death (RR: 0.7–0.8).[4] Several LMWHs are currently marketed. Each is dosed differently; some are administered intravenously or subcutaneously, and some subcutaneously only—however, in all cases, their dosage is fixed in total amount or by body weight. The two most commonly used LMWHs are enoxaparin (1 mg/kg subcutaneously every 12 hours or 1.5 mg/kg every 24 hours for VTE)

Table 19.1 Dosing of new oral anticoagulants for the initial treatment of venous thromboembolism

Medication	Mechanism of action	Initial dosing	Long-term dosing
Dabigatran[16] (Pradaxa, Boehringer Ingelheim)	Direct thrombin inhibitor	5–10 days standard anticoagulant (LMWH or UFH)	150 mg twice daily
Rivaroxaban[18,19] (Xarelto, Bayer)	Direct Xa inhibitor	15 mg twice daily for 3 weeks	20 mg every day
Apixaban[20] (Eliquis, Bristol Myers-Squibb)	Direct Xa inhibitor	10 mg twice daily for 1 week	5 mg every day
Edoxaban[22] (Savaysa, Daiichi Sankyo)	Direct Xa inhibitor	5–10 days standard anticoagulant (LMWH or UFH)	60 mg every day

Note: LMWH: low-molecular-weight heparin; UFH: unfractionated heparin.

and dalteparin (120 anti-Xa units/kg subcutaneously every 12 hours for VTE). Once-daily dosing is superior to twice-daily dosing due to improved patient compliance for non-pregnant patients (Table 19.2). Twice-daily dosing should be used in pregnancy, considering the increased glomerular filtration rate (GFR). Due to their pleotropic effects or more consistent anticoagulation, LMWH tinzaparin have been found to decrease indices of chronic venous insufficiency compared to standard therapy when used over an extended period. In 480 patients, tinzaparin for 12 weeks was superior to warfarin in this regard.[2,5]

Historically, most patients were treated with a heparin infusion, consisting of a weight-based bolus dose (80 units/kg) following by weight-based infusion with adjustments every 6 hours based on a nomogram. In recent years, a shift away from measuring partial thromboplastin time (PTT) towards using Xa levels for UFH monitoring has occurred due to an improvement in the time within the therapeutic range and the time to first therapeutic result (Table 19.2).[6] This treatment is still common, especially among post-operative patients in whom the short half-life and relatively straightforward reversal of anticoagulation is desirable should a bleeding complication or need for re-intervention be encountered. UFH also may still be elected for in the case of renal insufficiency (GFR < 30 mL/minute). A 5-day course has been shown to be as effective as longer courses at preventing recurrent thrombosis, provided that warfarin is started early (usually within 24 hours of diagnosis) and oral anticoagulation is therapeutic prior to discontinuing heparin.[7] LMWH has not been specifically tested, but is believed to behave similarly. Anticoagulation with heparin followed by warfarin reduces the incidence of recurrent thrombosis and PE in patients with lower extremity DVT, and also reduces mortality due to PE. In a study of 4221 patients with DVT and 1302 patients with PE, the rates of fatal PE during and after therapy for DVT were only 0.4% and 0.3%, respectively, while the rates of fatal PE during and after therapy for PE were only 1.5% and 0%, respectively.[7]

UFH or LMWH are given for 5 days. During the time of heparin bridging, oral anticoagulation is begun, traditionally with a VKA, although current guidelines support the use of NOACs over VKAs (grade 2B, Table 19.2). Edoxaban and dabigatran require a bridge, whereas rivaroxaban, apixaban and fondaparinux do not.[8] Warfarin alone without a heparin or LMWH "bridge" is inadequate. Certain patients may use LMWH as the sole antithrombotic agent throughout their course. For patients with malignancies and acute DVT, this strategy appears to roughly halve the risk of recurrence without an increase in adverse events, and avoids difficult warfarin management resulting from variable food intake. The recommended treatment duration is indefinite in both patients at low risk of bleeding and high risk of bleeding (Figure 19.1, Table 19.2).

19.3.2 Warfarin

Warfarin and other VKAs reduce the incidence of the recurrence of thrombosis in patients with DVT and PE by 30 or more per 100 patients treated. Warfarin (Coumadin) should be started after anticoagulation is therapeutic (heparin bridging) to prevent paradoxical thrombosis—so-called warfarin-induced skin necrosis. The reason for this is that warfarin causes inhibition of protein C and protein S before factors II, IX, and X, leading to potential hypercoagulability when the drug is started. For standard UFH, this requires measuring a therapeutic activated PTT or anti-factor Xa level (Figure 19.2), while for LMWH, an appropriate weight-based dose of LMWH being administered and allowed to circulate is adequate.

Transition from heparin to VKAs (warfarin) involves an overlap between heparin and warfarin therapy. Clinical trials suggest that heparin can be discontinued safely once the INR enters the therapeutic range (2.0–3.0) if the patient has received ≥5 days of heparin therapy. Some recommend that heparin be continued until the INR has been in the therapeutic range for at least 24 hours (essentially two measurements over 2 days), since the antithrombotic effect of warfarin may be delayed relative to its effect on the prothrombin time. However, clinical trials have not tested whether this approach offers greater protection against thrombosis than discontinuation of heparin as soon as the INR is therapeutic.

The goal of warfarin dosing is an INR between 2.0 and 3.0. The use of loading doses of warfarin is not recommended, as the coagulation factors are not reduced symmetrically, and the INR may not accurately reflect the antithrombotic effect of warfarin during the initiation phase of therapy. The initial warfarin dosing is 5 mg daily, with doses usually given in the evenings. Lower doses are often considered for

Table 19.2 Summary of key recommendations to the American Venous Forum on the medical therapy of acute deep vein thrombosis and pulmonary embolism

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.3.1[a]	If home circumstances are adequate, we recommend that initial treatment of acute deep venous thrombosis (DVT) take place at home rather than in the hospital.	1	B
3.3.2[a]	We suggest low-molecular-weight heparin (LMWH) over unfractionated heparin for the treatment of acute DVT.	2	B
3.3.3[a]	We suggest once- over twice-daily administration of LMWH for the treatment of acute DVT.	2	C
3.3.4[b]	We suggest LMWH over NOACs or VKAs for patients with cancer and acute DVT.	2	C
3.3.5[b]	In patients with acute DVT and no cancer, as a long-term anticoagulant therapy we susggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K agonist (VKA) therapy.	2	B
3.3.6[b]	We suggest that patients with an unprovoked proximal DVT who are stopping anticoagulant therapy should take an aspirin to prevent recurrent VTE.	2	B
3.3.7[b]	We recommend 3 months of treatment for acute proximal DVT provoked by transient risk factors (surgical or non-surgical).	1	B
3.3.8[b]	We suggest monitoring over 2 weeks with serial imaging over anticoagulation for the treatment of acute isolated distal DVT without severe symptoms or risk factors.	2	C
3.3.9[b]	We suggest anticoagulation for acute isolated distal DVT with severe symptoms and risk factors.	2	C
3.3.10[b]	We suggest extended anticoagulation therapy in patients with an acute unprovoked proximal DVT who have low or moderate bleeding risk.	2	B
3.3.11[b]	We recommend 3 months of anticoagulant therapy rather than extended therapy in patients with an acute unprovoked proximal DVT who have high bleeding risk.	1	B
3.3.12[b]	We recommend extended anticoagulation beyond 3 months for acute DVT of the leg in the setting of active cancer if the risk of bleeding is not high.	1	B
3.3.13[b]	We suggest that anticoagulation be preferred over catheter directed thrombolysis for acute proximal DVT.	2	C
3.3.14[b]	We suggest systemic thrombolysis for pulmonary embolism associated with hypotension or when hypotension is likely without a high bleeding risk.	2	C

[a] Based on the recommendations of Kearon C et al. *Chest* 2012;142:1698–704.
[b] Kearon C et al. *Chest* 2016;149(2):315–52; Meissner MH et al. *J Vasc Surg* 2012;55:1449–62.

elderly, debilitated, liver disease, or heart failure patients. Subsequent dosing depends on the results of laboratory monitoring of the PTT/INR, which should be performed at least twice during the first week of therapy. A target INR of 2.0–3.0 is effective at preventing thrombus extension or recurrence, and is associated with a relatively low risk of bleeding.[7] Despite careful monitoring, patients with VTE treated with warfarin have a major bleeding risk of 5%–6% per year, even within the target INR range.[9] Long-term anticoagulation with lower-dose warfarin (INR: 1.5–2.0) does not reduce the risk of thrombus recurrence/extension and carries the same bleeding risk as a higher INR (2.0–3.0).[10,11] Another difficulty with warfarin is the effect of both diet and drug interactions on the effectiveness of the agent.

Anti-Xa (units/mL)	Repeat heparin bolus dose	Hold infusion (minutes)	Rate change	Repeat anti-Xa level
Less than 0.2*	80 units/kg	0	Increase 1.5 units/kg/hour	6 hours
0.2–0.29	40 units/kg	0	Increase 1units/kg/hour	6 hours
0.3–0.7	None	0	No change	6 hours
0.71–0.8	None	0	Decrease 1 units/kg/hour	6 hours
0.81–0.99	None	30	Decrease 1.5 units/kg/hour	6 hours
≥1*	None	60	Decrease 3 units/kg/hour	6 hours

Figure 19.2 Weight-adjusted heparin nomogram. Table created by Anticoagulation Committee (subcommittee of Pharmacy & Therapeutics Committee) © University of Michigan Health Systems, used with permission. *Notify physician if two consecutive anti-Xa values are in this range. **When two consecutive anti-Xa values are in therapeutic range (0.3–0.7 units/mL), obtain anti-Xa assay the next morning and every 24 hours thereafter.

Patients should receive information on dietary vitamin K, which can reduce the effectiveness of warfarin, as well as warnings about over-the-counter vitamins and information on dietary interactions.

19.3.3 Location of treatment

Outpatient treatment has become preferred due to its advantages of lower cost and greater patient comfort. Patients must be able to clearly understand and effectively adhere to the detailed instructions. Proper patient (or caregiver) education is critical to safe outpatient management. Patients who may have difficulty understanding or adhering to therapy, who have high-risk comorbid conditions, or who have severe symptoms, should be hospitalized, at least initially. Inpatient treatment provides closer monitoring and quicker responses to clinical changes. LMWH is less costly in terms of overall treatment expense, although its acquisition cost is higher. Shorter, (or even no), hospital stay(s) account for some of that advantage. However, even in the inpatient setting, the costs of intravenous administration and monitoring make UFH more expensive than LMWH.

Many patients with DVT may be safely treated as outpatients, and a smaller number of patients with PE also have sufficiently low risk to justify an outpatient treatment recommendation. These patients should be hemodynamically stable and normoxemic before outpatient treatment is considered, without signs of right ventricular dysfunction by echocardiography. Absolute contraindications to outpatient management of DVT would also apply to PE patients, and include massive thrombosis, presence of active bleeding, high risk for hemorrhage, history of heparin sensitivity, underlying liver disease, clinical instability, and extensive thrombus burden leading to severe swelling, cyanosis, and/or severe shortness of breath. Biomarkers can help predict outcome but are not definitive, with a normal brain natriuretic peptide being highly predictive of good outcome, and elevated troponin being predictive of patients who are at higher risk of adverse outcome.

19.3.4 New anticoagulants (factor Xa and factor IIa inhibitors)

There are many agents in development for anticoagulation, aiming to replace either LMWH or warfarin. Fondaparinux (Arixtra®, GlaxoSmithKline), a synthetic pentasaccharide that has an antithrombin sequence identical to heparin, targets factor Xa. Fondaparinux has been approved for the treatment of DVT and PE when administered in conjunction with warfarin, for thrombosis prophylaxis in patients with total hip replacement, total knee replacement, and hip fracture, and in patients undergoing abdominal surgery. Fondaparinux, administered subcutaneously, has a 17-hour half-life and dosage is based on body weight. It exhibits no endothelial or protein binding, and importantly does not produce thrombocytopenia. No antidote is readily available for this agent. In VTE prophylaxis, a meta-analysis involving more than 7000 patients demonstrated a greater than 50% risk reduction in VTE using fondaparinux begun 6 hours after surgery compared to LMWH begun 12–24 hours after surgery.[12] Although major bleeding was increased, critical bleeding was not increased. Fondaparinux has also been found to be effective in the prophylaxis of other groups of patients, including general medical patients.[13] For the treatment of VTE, fondaparinux was found to be equal to standard heparin and LMWH for DVT and for PE.[13,14] Fondaparinux has also been found to be effective for the treatment of superficial thrombophlebitis over a 45-day course of treatment at a prophylactic dose (level of evidence: 2B).[2,15]

More recently, several novel oral anticoagulants (NOACs) have gained Food and Drug Administration (FDA) approval to replace warfarin (Tables 19.1 and 19.2). Dabigatran targets active factor II (factor IIa), whereas rivaroxaban, apixaban, and edoxaban target activated factor X (factor Xa). Similar to warfarin, dabigatran and edoxaban require the use of a LMWH or UFH "bridge" during initiation of therapy, whereas rivaroxaban and apixaban can be instituted as immediate monotherapies. All agents are

currently FDA approved in the United States for the treatment of acute DVT, although differences amongst the particular pharmacokinetics may lead a practitioner to choose one over another (Table 19.2).

19.3.4.1 DABIGATRAN

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim Pharmaceuticals) is FDA approved for stroke and systemic embolization prevention in patients with atrial fibrillation, and for the treatment and prevention of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days.[16] Dabigatran has the longest half-life of all of the NOACs at 12–17 hours, which is prolonged with age and decreased renal function. It is the only one which can be at least partially reversed with dialysis.[17] It is also the only NOACs which has a commercially available reversal agent.

19.3.4.2 RIVAROXABAN

Rivaroxaban (Xarelto®, Bayer) is FDA approved for VTE prophylaxis in patients undergoing hip or knee replacements, for stroke and systemic embolization prevention in patients with atrial fibrillation, and for VTE treatment. This is the first monotherapy agent to be approved of the NOACs. The EINSTEIN trial evaluated rivaroxaban compared to standard anticoagulation in the treatment of acute DVT.[18] Rivaroxaban was found to be statistically noninferior to standard therapy, without increased bleeding. Additionally, the EINSTEIN group added a continued treatment group compared to placebo for an additional 6–12 months after the completion of 6–12 months of therapy. Extended rivaroxaban showed a significant decrease in recurrent VTE without an increase in major bleeding compared to placebo, although it was not directly compared to VKAs or LMWHs. A similar finding with PE has been noted (EINSTEIN-PE).[19] Rivaroxaban has the benefit of once-daily dosing and immediate monotherapy, making it a convenient choice for patients.

19.3.4.3 APIXABAN

Apixaban (Eliquis®, Bristol Myers-Squibb) is currently FDA approved for the prevention of complications of atrial fibrillation, for the prophylaxis of DVT following hip or knee replacement surgery, for the treatment of DVT/PE, and for reduction in the risk of recurrence of DVT/PE. This is the only new oral agent that has shown superiority to standard therapy without an increase in bleeding. Recently, apixaban as an extended treatment of VTE was investigated compared to placebo. The study revealed a significant decrease in the rate of VTE without an increase in bleeding risk.[20] Apixaban is the only agent among the NOACs to demonstrate a slight decrease in gastrointestinal bleeding compared to warfarin.[21]

19.3.4.4 EDOXABAN

Edoxaban (Savaysa®, Daiichi Sankyo) is the most recently approved agent for treatment of DVT.[22] It is currently FDA approved for the prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation, as well as for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5–10 days. Edoxaban carries a boxed warning stating that the novel anticoagulant is less effective in atrial fibrillation patients with a creatinine clearance of >95 mL/minute, and that kidney function should be assessed prior to starting treatment. According to the FDA, patients with a creatinine clearance of >95 mL/minute have a greater risk of stroke compared with similar patients treated with warfarin. Edoxaban is the only agent specifically tested at a lower dose in patients at high risk of bleeding complications (low body weight and/or decreased creatinine clearance).[22]

19.3.4.5 COMPLICATIONS WITH NOACS

Problems with these new agents include the inability at the present time to reliably follow their levels, reverse their anticoagulant effects, and the lack of data available on the bridging of these agents when interventions need to be performed. Situations in which it might be useful to monitor drug levels have been published by the International Society of Thrombosis and Hemostasis (ISTH) and include: (1) bleeding; (2) before surgery or an invasive procedure when the patient has taken the drug in the previous 24 hour, or longer if creatinine clearance is <50 mL/minute; (3) the identification of subtherapeutic or supratherapeutic levels in patients taking other drugs that are known to significantly affect pharmacokinetics; (4) the identification of subtherapeutic or supratherapeutic levels in patients at the extremes of body weight; (5) patients with deteriorating renal function; (6) peri-operative management; (7) reversal of anticoagulation; (8) suspicion of overdose; and (9) assessment of compliance in patients suffering from thrombotic events while on treatment (this application may be limited by the short half-life of the oral agents).[23]

Currently, the only FDA reversal agent is approved for dabigatran. Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran and sequesters both thrombin-bound and free dabigatran. The REVERSE AD phase III trial demonstrated that 5 g of antibody administered to patients requiring emergent reversal normalized thrombin time at a median of 11.4 hours. It was well tolerated without any major side effects. Until the time that specific reversal agents exist for the remaining NOACs, supportive care is the mainstay of therapy. In cases of trauma or severe/life-threatening bleeding, administration of concentrated clotting factors (prothrombin complex concentrate) or dialysis (dabigatran only) can be utilized, although data from large clinical trials are lacking (Figure 19.3).

19.3.5 Aspirin

Although aspirin (ASA) is not a new agent, the use of ASA for the extended treatment of VTE after a standard course of therapy has gained renewed interest. Two trials have evaluated ASA versus placebo in idiopathic DVT in patients who had completed initial treatment with heparin followed by warfarin for a minimum of 6 weeks (most 3 months); ASA was used at a dose of 100 mg every day for 2–4 years. In the

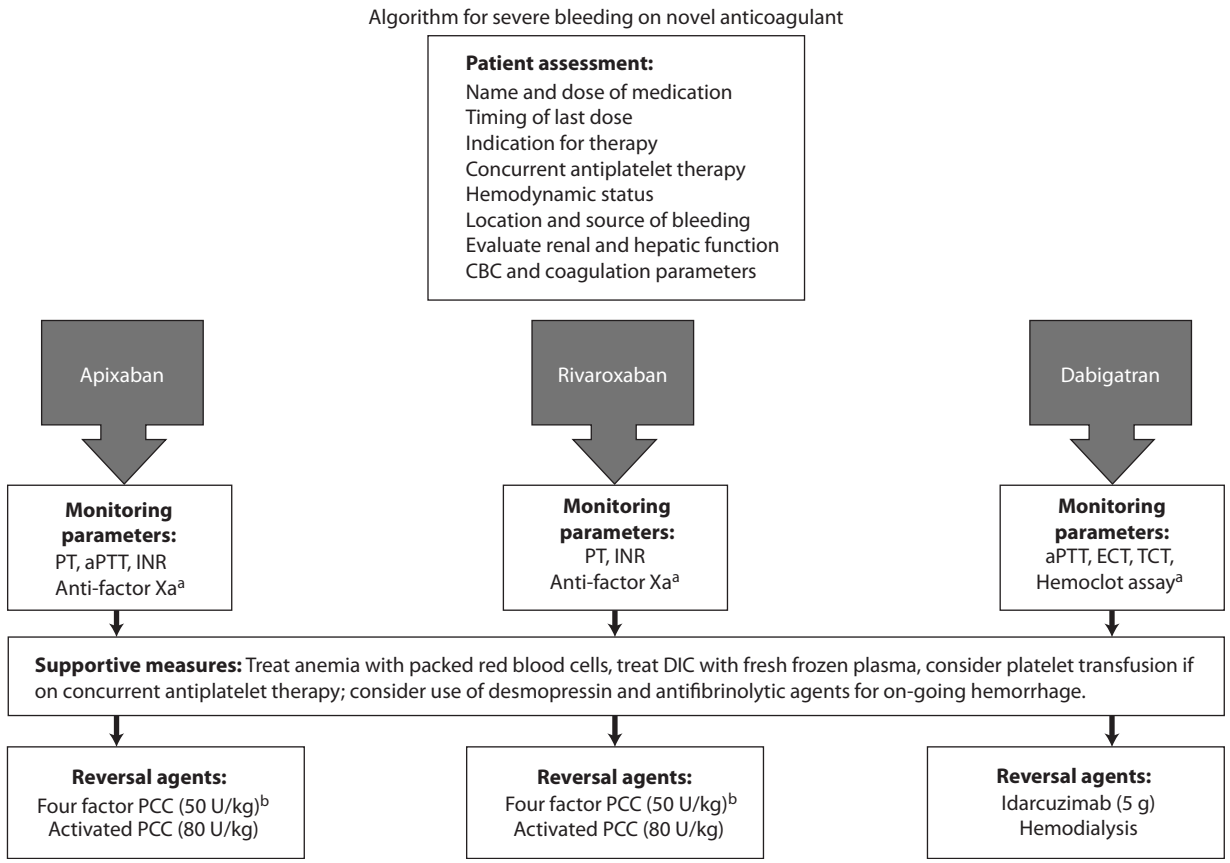

Figure 19.3 Reversal of novel anticoagulants. [a]Preferred monitoring parameter. [b]Preferred reversal agent. (Reproduced and modified with permission from Knepper J et al. *J Vasc Surg Venous Lymphat Disord* 2013;1(4):418–26.)

WARFASA study of 402 patients, recurrence rates of 6.6%/year versus 11.2%/year (hazard ratio [HR]: 0.58, $P = 0.02$) were found, while in the ASPIRE study of 822 patients, recurrence rates of 4.8%/year versus 6.5%/year (HR: 0.74, $P = 0.09$) were found.[24,25] Combining studies, there was a 32% reduction in the rate of recurrence of VTE (7.5%/year vs. 5.1%/year; HR: 0.68, $P = 0.008$) and a 34% reduction in the rate of major vascular events (recurrent VTE, myocardial infarction, stroke, cardiovascular disease death; 8.7%/year vs. 5.7%/year; HR: 0.66, $P = 0.002$), without an increase in major bleeding.[26,27] Interestingly, when compared to the new anticoagulants for extended treatments, the decrease in recurrence of 32% is much less than the 83%–88% decrease in recurrence with the new agents.[28] These data suggest that patients at increased risk of bleeding from anticoagulation or a moderate increase in thrombosis might benefit from long-term therapy with ASA (Table 19.2, Figure 19.4).

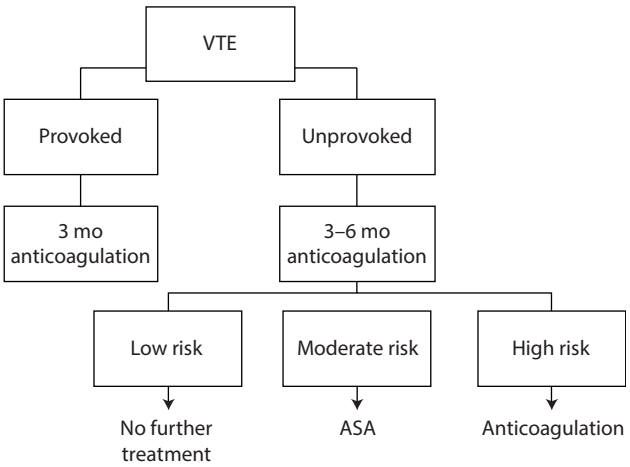

Figure 19.4 Incorporation of aspirin (ASA) into venous thromboembolism (VTE) extended treatment paradigm. (Reproduced with permission from Wakefield TW, Obi A, Henke PK, *Circulation* 2014:130(13):1031–3.)

19.4 DURATION OF THERAPY

The duration of anticoagulation depends on a number of factors, including the thrombotic risks at presentation, continuing risk factors for thrombosis, the type of thrombosis (idiopathic or provoked), how often thrombosis has occurred, the level of D-dimer measured approximately 1 month after stopping warfarin, and the status of the veins when stopping anticoagulation.[2,29] The recommended duration of anticoagulation after a first episode of provoked VTE is 3 months for both proximal and distal thrombi, although under certain circumstances, distal thrombi may not require treatment (Table 19.2).[2] For asymptomatic

patients with calf-level DVT and no risk factors, serial ultrasound imaging is preferred over anticoagulation. On the other hand, in symptomatic calf-level DVT, anticoagulation is recommended (Table 19.2).[2] After a second episode of VTE, prolonged oral anticoagulation is recommended, unless the patient is very young at the time of presentation or there are other mitigating factors (Tabel 19.2). VTE recurrence is more common with heterozygous factor V Leiden combined with a prothrombin 20210A mutation, or homozygous states of each, protein C or protein S deficiency (especially with a family history), antithrombin deficiency, antiphospholipid antibodies, and unresolved cancer.[30] In these circumstances, long-term oral anticoagulation is recommended. When they occur in isolation, the most common hypercoagulable states—heterozygous factor V Leiden and prothrombin 20210A—do not carry the same risk for recurrence as their homozygous counterparts. For these conditions, the length of oral anticoagulation is shortened.[31] In certain circumstances, such as active cancer, the use of LMWH is superior to warfarin for long-term treatment, at least when given over a 6-month period of time.[2]

Regarding unprovoked (idiopathic) DVT, the recommended length of treatment is extended therapy for more than 3 months, especially in those patients at low bleeding risk (grade 2B, Table 19.2). If indefinite therapy is considered in patients with idiopathic VTE, decision making may be aided by D-dimer testing 1 month after completion of warfarin therapy. An elevated D-dimer suggests ongoing increased risk, indicating resumption of full-dose anticoagulation. In one study of patients with idiopathic VTE, a low rate (6.2%) of recurrence of VTE was found when the D-dimer was normal at 1 month after discontinuation of warfarin, but a 15% rate of recurrence was found among those with abnormal D-dimer. Resumption of warfarin among those with abnormal D-dimer reduced the recurrence rate to 2.9%.[32] Similar findings have been reported in other studies. The use of repeat (serial) lower extremity ultrasound has also been proposed as a test for whether to continue anticoagulation beyond the usual timeframe, although its usefulness is less certain and the ability to quantify this effect clinically is difficult. For a second unprovoked VTE, recommendations are for anticoagulant therapy beyond 3 months in patients with a low bleeding risk (grade 1B). Criteria that have been described for discontinuing anticoagulation are given a level of evidence of 1B–2B, depending on the clinical situation. Acute DVT of the leg in the setting of active cancer should be treated with extended anticoagulation rather than 3 months of treatment if the risk of bleeding is not high (Table 19.2).

19.5 COMPLICATIONS

The most common complication of anticoagulation is bleeding. With standard heparin, bleeding occurs in approximately 10% of patients over the first 5 days. Major bleeding with UFH has been reported at a rate of 2.0%–4.5%, while for LMWH, this rate is between 1.5% and 4.7%.[33] With oral anticoagulation, major bleeding with warfarin has been reported at a rate of between 1.6% and 2.0%, and for all bleeding, this rate is between 8.5% and 10.3%. For the NOACs, major bleeding rates of 0.6%–1.4% and major and non-major bleeding rates of 4.3%–9.4% have been reported.[34]

Another potentially devastating complication is heparin-induced thrombocytopenia (HIT). This syndrome occurs in 0.6%–30% of patients. Morbidity and mortality rates have decreased with early diagnosis and appropriate treatment. Although HIT usually begins 3–14 days after the start of heparin treatment, it can occur earlier if the patient has been exposed to heparin previously. In terms of pathophysiology, a heparin-dependent antibody binds to platelets, activating them with the release of pro-coagulant microparticles, leading to thrombosis and thrombocytopenia.[35] Although the incidence and severity of the thrombosis appears to be less with LMWH than standard UFH, both bovine and porcine UFH and LMWH have been associated with HIT.[36] Even slight exposure to heparin, such as a heparin coating on indwelling catheters, can also lead to the clinical manifestations of the syndrome. The diagnosis should be suspected when thrombosis occurs during heparin or LMWH therapy, with a 50% or greater drop in platelet count, or when the platelet count falls below 100,000.[37] Heparin induced thrombocytopenia and thrombosis syndrome (HITTS) is defined as HIT associated with episodes of thrombosis.

A highly sensitive but poorly specific diagnostic test is the enzyme-linked immunosorbent assay (ELISA), which detects the anti-heparin antibody in plasma. A more specific but less sensitive test is the serotonin release assay. Often a combination of both tests gives the best diagnostic accuracy. When the diagnosis is made, heparin must be stopped and oral anticoagulation with warfarin should not be given until an adequate alternative anticoagulant is given and established. Additionally, warfarin should not be given until the platelet count has normalized, or at least returned to 150,000. LMWHs cannot be substituted for standard heparin in patients with HIT, as they demonstrate high cross-reactivity with standard heparin antibodies. The direct thrombin inhibitor argatroban has been FDA approved as an alternative agent. Although fondaparinux (Arixtra) has also been found to be effective for the treatment of HIT in some cases, it is not FDA approved for this indication. The use of these alternative agents is given either a 2C or 1C level of evidence according to the 2012 ACCP guidelines.

19.6 NON-PHARMACOLOGIC TREATMENTS

The use of strong compression and early ambulation after DVT treatment can significantly reduce the pain and swelling resulting from the DVT. It has been shown that the rate and severity of PTS after proximal DVT can be decreased by approximately 50% with the use of compression stockings.[38] In addition, walking with good compression does not increase the risk of PE, while significantly decreasing the incidence and severity of PTS.[39] However, a recent

multicenter randomized trial has challenged this concept. This study concluded that stockings do not prevent PTS after a first proximal DVT.[40] This large randomized study, although of great interest, brings up many questions, and its data should be confirmed in other studies before no longer recommending stockings after DVT (in our opinion).

19.7 AGGRESSIVE THERAPIES

For DVT treatment, the goals are to prevent the extension/recurrence of DVT, prevent PE, and minimize the late sequel of thrombosis, namely PTS. Standard anticoagulation accomplishes the first two goals, but not the third goal. PTS occurs in up to 30% of patients after DVT, and in an even higher percentage of patients with iliofemoral DVT.[41] More aggressive therapies for extensive thrombosis are thus indicated. Patients who present with DVT that could potentially result in significant long-term pain and swelling or limb loss due to ischemia, or who are clinically unstable due to PE (hypotensive, tachycardia, hypoxia, and tachypnea), may benefit from initial treatment beyond simple anticoagulation. Patients in this situation are best managed in the inpatient setting. Options for management include catheter-directed thrombolysis (CDT, with or without a mechanical device), thrombectomy, and systemic thrombolysis.

Experimentally, the thrombosis initiates an inflammatory response in the vein wall that leads to vein wall fibrosis and valvular dysfunction. Prolonged contact of the thrombus with the vein wall increases damage.[42] Thus, removing the thrombus should be an excellent solution to decreasing this interaction, although, depending on the timing of treatment initiation, it may not completely eliminate alterations in the vein wall. For example, the longer a thrombus is in contact with a vein valve, the more chance there is that this valve will no longer function.[43]

Venous thrombectomy—removal of thrombus with a catheter under direct operative vision—has proved superior to anticoagulation over 6 months to 10 years as measured by venous patency and the prevention of venous reflux.[44] Catheter-directed thrombolysis has been employed in many non-randomized studies, and in small, randomized trials was more effective than standard therapy for improving quality of life. Results are optimized further by combining catheter-directed thrombolysis with mechanical devices.[45,46] The devices include the Angiojet rheolytic catheter, Trellis balloon occlusion catheter, and the EKOS ultrasound accelerated catheter. These various devices hasten thrombolysis and decrease the amount of thrombolytic agent needed, thus decreasing bleeding potential. Additionally, the use of venous stents for iliac venous obstruction has been shown to decrease the incidence of PTS and chronic venous insufficiency.[47] The Attract Trial, which compares catheter-directed pharmacomechanical thrombolysis to standard anticoagulation for significant iliofemoral venous thrombosis, has finished recruitment. This study will evaluate anatomic, physiologic, and quality-of-life endpoints, along with complications. Its results should help direct therapy and determine the characteristics of patients to whom physicians should apply more aggressive treatment. At present, aggressive therapy is not recommended by the ACCP 2016 guidelines, although it is noted that such therapies may be pursued by patients who place a high value on prevention of PTS and low value on cost and risk associated with CDT (Table 19.2).[48] Current evidence to support the use of catheter-directed thrombolysis or more aggressive treatments with mechanical and surgical thrombectomies for acute iliofemoral DVT is discussed in more detail in Chapter 20.

For acute PE, evidence exists that thrombolysis is indicated when there is hemodynamic compromise from the embolism.[49] In controlled trials, systemic thrombolysis has been shown to improve hemodynamics, imaging, and echocardiography faster than heparin alone; however, mortality is not improved. The significant risk of systemic bleeding must be balanced against the relatively uncertain benefit of systemic thrombolytics. The risk of dying from PE is estimated at 70% if associated with cardiopulmonary arrest and 30% if associated with hypotension requiring inotropic support. In cases of hemodynamic instability, and in the absence of a high risk of bleeding, systemic thrombolysis has been recommended (tissue plasminogen activator [t-PA] 100 mg over 2 hours or 50 mg over ≤15 minutes) (Table 19.2). Consensus does not exist on whether thrombolysis should be used in situations in which there is no hemodynamic compromise but evidence of right heart dysfunction, or if there are positive biomarkers.[50] Future studies will address these situations.[50] Until then, in selected patients with submassive PE (evidence of right ventricle strain on echocardiogram, worsening clinical status after anticoagulation instituted, and/or relative hypotension with a systolic blood pressure drop of >40 mmHg), systemic thrombolysis can be considered if the patient is at very low risk of bleeding. As thrombolysis for PE becomes more localized, with catheters placed into the pulmonary circulation being associated with less systemic bleeding potential, it is likely that indications for pulmonary thrombolysis will broaden, as discussed in much more detail in Chapter 21.

19.8 SPECIAL SITUATIONS

19.8.1 Anticoagulation and pregnancy

The incidence of VTE associated with pregnancy is not precisely known, but it is believed to be substantially greater than in non-pregnant women. Approximately two-thirds of DVTs occur before delivery, and are distributed fairly uniformly throughout the pregnancy, but 40%–60% of PEs occurs in the 4–6 weeks after delivery. Symptomatic VTE is estimated at 5–12 per 10,000 pregnancies, and in the first 6 weeks postpartum, VTE is estimated at 3–7 per 10,000 deliveries. This translates to a 7- to 10-fold increase in antepartum and a 15- to 25-fold increase in postpartum VTE compared to non-pregnant patients of the same age.[51] DVT has a marked predilection for the left leg in pregnancy because of compression effects on the left iliac

vein by the overlying right iliac artery being pushed by the gravid uterus.

VTE in pregnancy appears to be strongly associated with thrombophilia. The most important thrombophilias are factor V Leiden, prothrombin gene mutation, anticardiolipin antibody elevation, antithrombin deficiency, and protein C and protein S deficiencies. However, routine thrombophilia screening does not seem to be cost effective in this group of patients.[52]

LMWH is safe and effective for the treatment of VTE during pregnancy and in the postpartum period. It is superior to warfarin due to the potential risk for embryopathy with warfarin (between 6 and 12 weeks' gestation) and risk of intracranial hemorrhage at the time of delivery, and it is preferred to UFH. Warfarin for VTE should be discontinued in favor of LMWH when pregnancy is planned or discovered. As UFH and LMWH do not cross the placenta, they can be continued throughout pregnancy. Although heparin anticoagulation could increase the risk of abruption, it causes neither teratogenicity nor fetal bleeding. Patients with a need for ongoing anticoagulation may reinitiate warfarin 12 weeks after delivery. Warfarin does not cross into breast milk in an active form, and thus it is not contraindicated and may be used during nursing.

19.8.2 Testing for thrombophilias

Identifying thrombophilias can guide the assessment of risk of future VTE events and provide guidance for therapeutic decisions regarding duration of anticoagulation. Guidelines and expert opinions suggest testing in some of the following populations: first episode of idiopathic thrombosis at 50 years of age or younger; history of two or more episodes of recurrent thrombosis, especially if the events were unprovoked; thrombosis in an unusual site (e.g., cerebral or mesenteric); positive family history with two or more first-degree relatives with documented venous thrombosis; women who develop thrombosis during pregnancy or in the setting of a hormonal agent; and women who have unexplained recurrent pregnancy loss.[53] The advantages of testing include improving the understanding of the pathogenesis of thrombosis, identifying and counseling affected family members, and obviating the need for expensive diagnostic testing, such as computed tomography scans, looking for malignancy. The disadvantages include the infrequent identification of patients with defects whose management would change, the potential for overaggressive management, insurance implications, and the cost of testing. Data from the large RIETE Registry have suggested that thrombophilia testing for a first episode of VTE is not advisable.[31]

Several genetic thrombophilias are now known, and their testing requires knowledge of specific interactions if testing is going to be carried out. Acute thrombosis and pregnancy can transiently reduce the levels of antithrombin, proteins C, and protein S. Therefore, these assays should be delayed by at least 6 weeks from the acute event or until a similar time into the postpartum phase. Heparin treatment can reduce antithrombin activity and antigen levels, and interfere with the interpretation of clot-based assays for a lupus anticoagulant. Warfarin can increase antithrombin levels, and will reduce protein C and protein S levels, as they are vitamin K-dependent factors. The effect from warfarin may persist for up to 6 weeks after its discontinuation. Importantly, ELISAs for antiphospholipid antibodies and molecular diagnostic testing for factor V Leiden and prothrombin gene mutations are not affected by anticoagulation, and may be performed at any time.

19.9 IVC FILTERS

Traditional indications for the use of IVC filters include a contraindication to, a complication of, or a failure of, anticoagulation. Overall, protection from PE is greater than 95% using cone-shaped, wire-based permanent filters in the IVC.[54] With the success of these filters, indications have expanded for some to include the presence of free-floating thrombus tails, prophylactic use when the risk of anticoagulation is excessive and when the risk of PE is thought to be high, and even for facilitating the use of peri-operative epidural anesthesia. IVC filters can be either permanent or optional (retrievable). Today, over a dozen IVC filters are FDA approved. Most filters are placed in the infrarenal location in the IVC. However, they may be placed suprarenally or in the superior vena cava. Indications for suprarenal placement include active pregnancy, in women of childbearing age, or in previous device failure filled with thrombus. Currently, only one randomized prospective study is available on the use of IVC filters as a treatment of DVT (which is not how filters are traditionally used).[55] Chapter 26 presents current indications, techniques, and results of IVC filters in detail, and includes recommendations of the American Venous Forum.

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● = Key primary paper
★ = Major review article

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20

Catheter-directed thrombolysis, mechanical thrombectomy, and surgery for the treatment of acute iliofemoral deep venous thrombosis

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20.1 INTRODUCTION

Venous thromboembolic disease affects over 900,000 individuals annually in the United States,[1] and remains a major source of morbidity and mortality throughout the world. Current therapy focuses on preventing the embolization of deep venous thrombosis (DVT), for which anticoagulation remains the cornerstone of treatment. Anticoagulation alone has been shown to reduce the incidence of pulmonary embolism (PE) and death in multiple randomized trials,[2] thus reducing the early complications associated with DVT. However, anticoagulation does not prevent or treat the development of post-thrombotic syndrome (PTS),[3–5] the most significant late complication of venous thromboembolic disease.

PTS is defined as a constellation of signs and symptoms in the affected extremity that occur after acute DVT; PTS is generally evident within the first few months after the diagnosis (and treatment) of DVT.[6] Clinical manifestations progress over time and include chronic pain, edema, varicosities, pigmentation, eczema, and ulceration in severe cases, which have a significant impact on quality of life.[7–9] The reported incidence of PTS varies, due in part to the variability and precision of the follow-up of patients after their acute DVT. In the United States, PTS is estimated to affect up to half of all people who have a DVT. PTS affects up to 6 million individuals, and ulceration exists in 400,000–500,000 patients who have suffered a DVT.[10] A large body of evidence reveals that PTS is more prevalent and severe following iliofemoral DVT if treatment involves anticoagulation alone.[4,6]

20.2 RATIONALE FOR REMOVAL OF THROMBUS

Ambulatory venous hypertension is the underlying pathophysiology of chronic venous disease.[5,11] Valvular incompetence and venous obstruction—consequences of iliofemoral DVT—are associated with the most severe post-thrombotic morbidity.[12] Thus, the underlying rationale for thrombus removal in patients with iliofemoral DVT is that eliminating the acute clot avoids or reduces chronic venous obstruction (Figure 20.1), resulting in marked reduction of the PTS.[4,12,13]

20.3 PUBLISHED GUIDELINES AND EVIDENCE

In 2012, the Society for Vascular Surgery published guidelines titled *Early Thrombus Removal Strategies for Acute Deep Venous Thrombosis: Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum*.[14]

2.1 We suggest a strategy of early thrombus removal in selected patients meeting the following criteria: (a) first episode of acute iliofemoral deep venous thrombosis, (b) symptoms <14

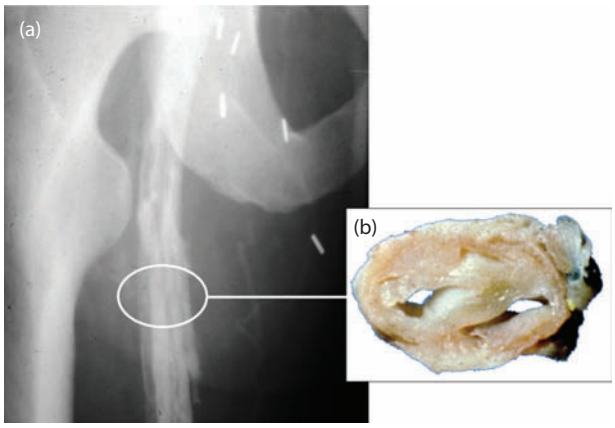

Figure 20.1 (**a** and **b**) Post-thrombotic venous disease illustrating the inability to identify obstruction as part of the pathophysiology of chronic venous disease. This patient had suffered from iliofemoral deep venous thrombosis 10 years earlier and was treated with anticoagulation alone. Severe post-thrombotic syndrome developed, and the patient underwent multiple hospitalizations for venous ulceration. An ascending phlebogram showed recanalization of the iliofemoral venous system; however, the radiologist's interpretation was that there was "no obstruction" of the deep venous system, and a 3-second maximal venous outflow test was "normal." A classic Linton procedure was performed and showed (insert) the cross-section of the femoral vein at the corresponding location on the phlebogram, just below the profunda femoris vein.

days, (c) a low risk of bleeding, and (d) ambulatory with good functional capacity and an acceptable life expectancy (Grade 2C).

In 2014, the American Heart Association (AHA) released a consensus statement entitled *The Postthrombotic Syndrome: Evidence-Based Prevention, Diagnosis, and Treatment Strategies*. Their recommendations for thrombolysis and endovascular approaches to acute DVT for the prevention of PTS state the following[6]:

> [Catheter-directed thrombolysis] and [pharmacomechanical catheter-directed thrombolysis] in experienced centers, may be considered in select patients with acute (<14 days) symptomatic, extensive proximal DVT who have good functional capacity, >1 year life expectancy, and low expected bleeding risk (Class IIb, Level of Evidence B).

Controversies surrounding the use of thrombolytic therapy to prevent the development of PTS persist. Most notably, the American College of Chest Physicians (ACCP) Consensus Committee has wavered on its recommendation regarding the use of thrombolysis for treatment of proximal DVT. In the *Antithrombotic Therapy for VTE Disease*, published in 2012, the ninth ACCP guideline recommendation states the following[15]:

> 2.9 In patients with acute *proximal DVT* of the leg, we suggest anticoagulation therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).

This redacts the eighth ACCP Consensus Committee recommendation published in 2008 for thrombus removal in patients with proximal DVT. At the time, prevailing evidence suggested that operative venous thrombectomy or CDT was recommended for patients with acute iliofemoral DVT to reduce acute symptoms and post-thrombotic morbidity (grade 2B).[2] The eighth ACCP consensus committee recognized that iliofemoral DVT was an important subset of patients deserving of added attention for a treatment strategy of thrombus removal.

Both the AHA and ACCP base their recommendations on the available published research. In this case, the strict method to include "evidence" used by the ACCP in 2012 compared to 2008 excluded all non-randomized controlled trials and did not include other evidence. Despite the available evidence, the use of the decided-upon criteria resulted in no study or treatment meeting the ACCP 2012 criteria for a grade 1A recommendation for any treatment of acute venous thromboembolic disease. Unfortunately, the ninth ACCP edition reverted to the generic "proximal DVT" classification and did not recognize iliofemoral deep venous thrombosis (IFDVT) as an important subset of patients facing more frequent and severe post-thrombotic morbidity.

Much of the evidence supporting thrombolysis for the treatment of iliofemoral DVT to prevent PTS is from single-center, non-randomized studies, although a more recent multicenter trial showed benefits of CDT. In the Catheter-Directed Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) trial, 209 patients were randomized to CDT plus anticoagulation or anticoagulation alone.[4] The addition of CDT resulted in a significant reduction in PTS compared to anticoagulation alone. In the Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial, pharmacomechanical catheter directed thrombolysis (PCDT) plus anticoagulation was tested against anticoagulation alone in 183 patients with DVT. Once again, PCDT plus anticoagulation showed a significant reduction in risk of PTS in the treatment group. The use of a non-standard measure of PTS and non-blinding of the clinical observers limits the strength of these results.[6]

The National Institutes of Health (NIH) has sponsored the Acute Venous Thrombosis: Thrombosis Removal with Adjunctive Catheter-directed Thrombolysis (ATTRACT) trial. This is a multicenter, randomized, open-label, assessor-blinded, parallel, two-arm, controlled clinical trial.[16,17] ATTRACT met its recruitment goal of randomizing 692 patients in December of 2014. Patients were stratified at entry to iliofemoral DVT or femoropopliteal DVT

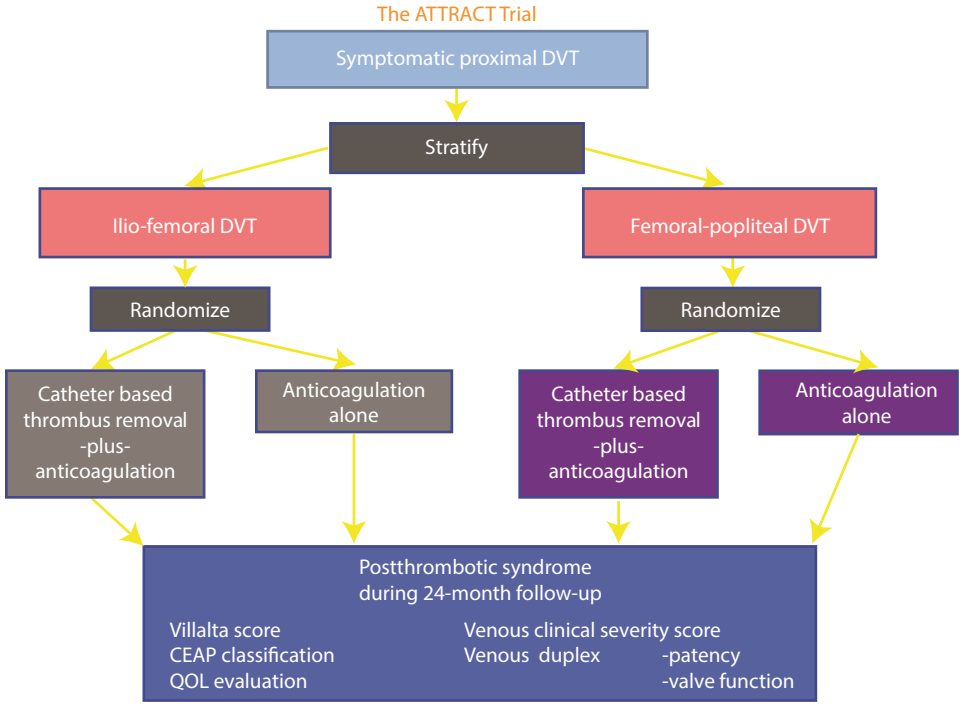

Figure 20.2 Algorithm of the protocol of the ATTRACT trial. DVT: deep venous thrombosis; QOL: quality of life.

(Figure 20.2). A total of 692 patients have been randomized. The ATTRACT trial is now into its 2-year follow-up phase for assessing its primary efficacy endpoint of PTS. Results are anticipated in early 2017.

Based upon all of the available evidence to date, and based upon the increased safety of CDT infusing low doses of a plasminogen activation in high volumes of saline (1 mg in 50–100 cc/hour), which improves efficacy, we would suggest that CDT for iliofemoral DVT be given a strong recommendation (level 1) supported by grade B evidence.

20.4 PRE-TREATMENT EVALUATION

After the diagnosis of acute DVT is established, all patients should be placed on anticoagulation therapy immediately, followed by leg elevation and leg compression.[18–20] After anticoagulation and compression, ambulation is encouraged. Patients with iliofemoral DVT who are eligible for anticoagulation and are ambulatory should be considered for thrombus removal. In patients with normal renal function, a contrast-enhanced computed tomography (CT) scan of the head, chest, abdomen, and pelvis is performed. Approximately 50% of these patients will have an asymptomatic pulmonary embolus. Although such emboli may not change the treatment plan, the value of establishing the diagnosis is often not appreciated until 3–5 days later when pleuritic chest pain develops in up to 25% of asymptomatic PE patients.[21] Without a previous diagnosis of PE, physicians might suspect that the result of pleuritic chest pain represents a "treatment failure" or an embolic complication of either lytic therapy or venous thrombectomy, rather than a delayed manifestation of a pre-existing PE. Additionally, the CT scan often identifies other thoracic, abdominal, or pelvic pathologies (see Figure 20.3b). Martinez and colleagues reviewed the results of CT scan evaluations for 47 patients with iliofemoral DVT and found PE in 48% and other unexpected thoracic, abdominal, or pelvic pathologies in 23%.[22] Renal cell carcinoma, adrenal tumors, retroperitoneal lymphoma, pulmonary adenocarcinoma, hepatic metastases, iliac vein aneurysms, and vena caval atresias were identified on CT as unanticipated sources and risk factors for iliofemoral DVT. Whether by CT or by duplex scan, imaging of the vena cava is important for assessing the degree of vena caval involvement with thrombus. If offering catheter-based techniques, a vena caval filter is recommended for patients with free-floating, non-occlusive vena caval thrombus. If operating, either proximal balloon occlusion of the inferior vena cava (IVC) or caval filtration is appropriate in those patients with free-floating thrombus. The majority of patients with iliofemoral DVT do not require an IVC filter.

Patients with extensive venous thrombosis frequently have a clinically obvious etiology (trauma), a known thrombophilia, or perhaps an occult cancer. However, those with an unprovoked VTE frequently undergo a full hereditary thrombophilia evaluation. Although we routinely performed a full battery of hereditary thrombophilia testing earlier in our experience, we now know that it is unnecessary, as the patient's extensive DVT imparts such substantial risk for future venous thromboembolic events that the risk conferred by the acute thrombotic event often exceeds the risk

of any identified hereditary thrombophilia.[23] However, testing for an acquired thrombophilia is warranted. A serious consequence of a negative thrombophilia evaluation is physician underestimation of future thrombotic risk. However, thrombophilia testing is important in first-degree female relatives of childbearing potential, especially for factor V Leiden, prothrombin, 20210 mutation, and antithrombin, as these test results may impact future care during pregnancy. Additionally, testing for an acquired thrombophilia, such as antiphospholipid antibodies, is warranted.

After the extent of the disease has been established, contraindications to either surgical or catheter-based techniques should be objectively reviewed. In general, the majority of patients with iliofemoral DVT should be offered a strategy of thrombus removal. Individuals with occlusive thrombus of the common femoral vein have effectively obliterated venous drainage from the lower extremity and are subject to severe post-thrombotic morbidity. Although most patients with acute DVT are treated as outpatients, those with occlusion of the common femoral vein and/or iliac vein should be hospitalized for an appropriate procedure designed to restore patency and provide unobstructed venous drainage from their common femoral vein into their vena cava. Our algorithm for the management of iliofemoral DVT is outlined in Figure 20.4.

20.5 INTRATHROMBUS CDT

The technique of CDT has evolved over the past several years. Our preferred approach is generally through an ultrasound-guided popliteal vein puncture with antegrade passage of the infusion catheter. Patients who have distal popliteal and tibial vein thrombosis are now approached through ultrasound-guided posterior tibial vein access. Adjunctive mechanical techniques are routinely used to shorten the duration of lysis and speed clot resolution. The dose and volume of the plasminogen activator that is delivered has also evolved. Since the activation of fibrin-bound plasminogen is not dose dependent, its exposure to the plasminogen activator appears to be the most important factor. The volume of lytic solution has increased over the years, with a decrease in the concentration (dose) of the plasminogen activator. It is now our preference to increase the volume of lytic infusion to 80–100 mL/hour. The larger volume is intended to saturate the thrombus, exposing more fibrin-bound plasminogen to the plasminogen activator. One milligram of recombinant tissue plasminogen activator (rtPA) is delivered in 100 mL of saline. Phlebograms are generally repeated at 12-hour intervals and are used to monitor the success of lysis, reposition catheters, and perform other mechanical interventions. Following successful

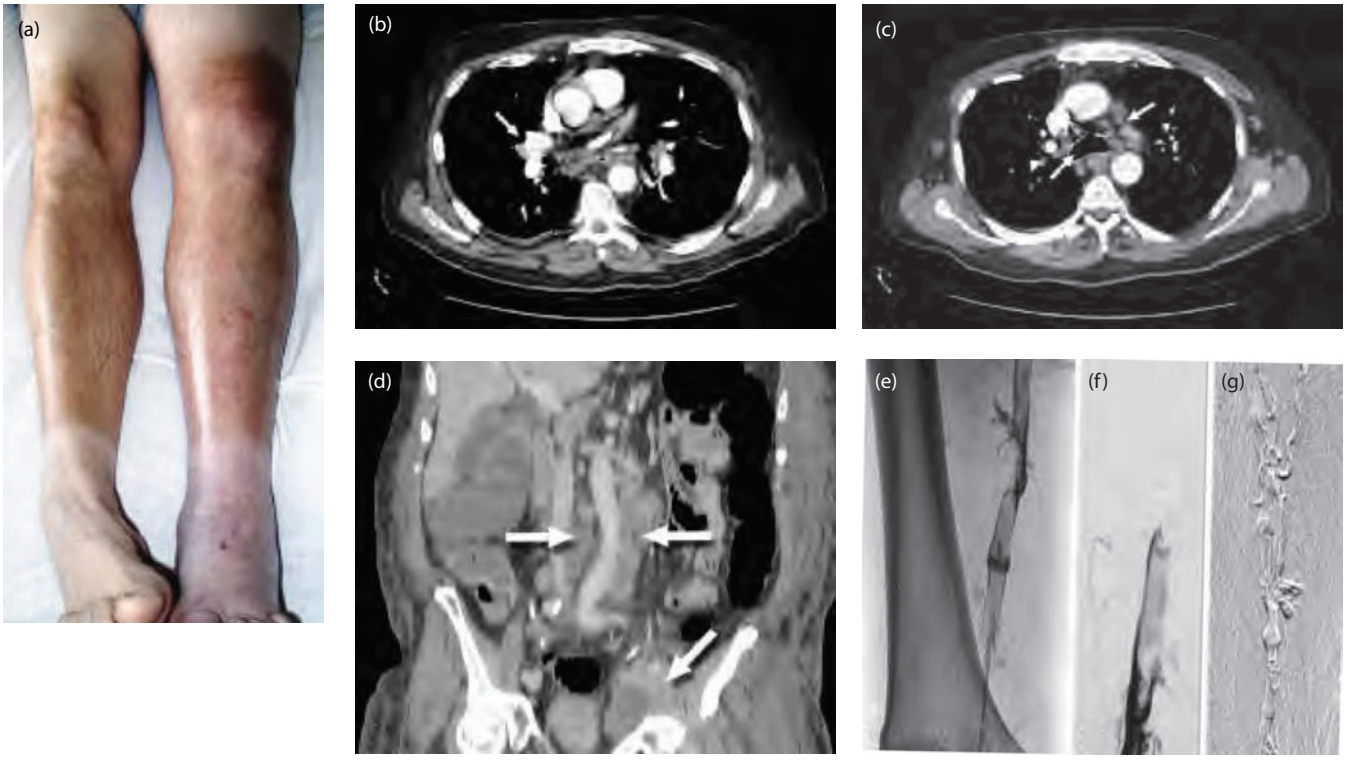

Figure 20.3 A 65-year-old white man was referred with phlegmasia cerulea dolens of his left leg **(a)** 36 hours after major abdominal laparotomy. Venous duplex demonstrated a clot in the posterior tibial veins extending to the external iliac vein. A contrast-enhanced computed tomography scan of the chest, abdomen, and pelvis was performed and demonstrated asymptomatic pulmonary emboli **(b)** and mediastinal **(c)**, retroperitoneal (**c**, arrows), and pelvic lymphadenopathy (**d**, arrows). The extensive thrombus is demonstrated by a catheter phlebogram of the femoral vein (**e** and **f**) and the silhouette of the calf thrombus **(g)** by the catheter in the posterior tibial vein at the ankle. (*Continued*)

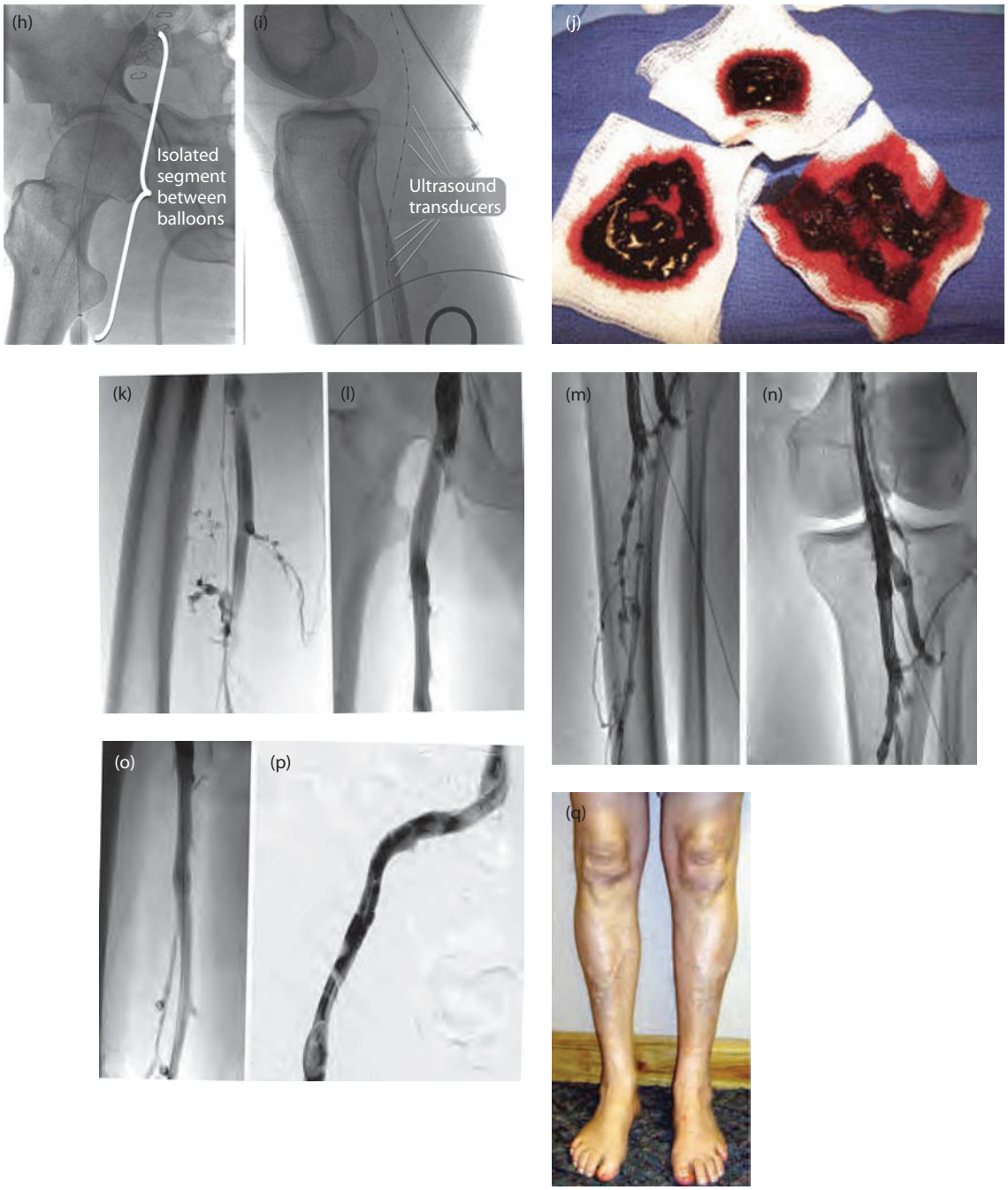

Figure 20.3 (Continued) The bulk of the thrombus from the proximal popliteal vein to the common iliac vein was treated with the Trellis catheter via an ultrasound-guided popliteal vein approach **(h)**. The clot in the posterior tibial and popliteal veins was treated with the EKOS EndoWave system **(i)**. Liquefied and fragmented thrombus resulting from isolated segmental pharmacomechanical thrombolysis was aspirated via the Trellis catheter **(j)**. Segmental phlebography is performed to check the results of treatment before moving to an adjacent thrombosed segment (**k** and **l**). Residual thrombus is removed by rheolytic thrombectomy with the AngioJet, and the iliac vein compression is treated with a stent. A completion phlebogram shows patency of the calf, popliteal, femoral, and iliac veins, as well as supple valve cusps, thus suggesting that valve function persists **(m–p)**. When catheter-based techniques are completed, a catheter is left in the popliteal vein (or posterior tibial vein if distal access is used) for infusion of unfractionated heparin for 24 hours. The concept is that the high concentration of heparin being infused into the target vein will increase its binding to residual thrombus, endothelium, and subendothelial collagen, thereby reducing the risk of thrombosis. The patient was treated with systemic chemotherapy for his underlying lymphoma. At 16 months **(q)**, the patient was asymptomatic, had no post-thrombotic symptoms, maintained lower extremity venous patency with normal valve function, and fortunately had no evidence of lymphoma recurrence.

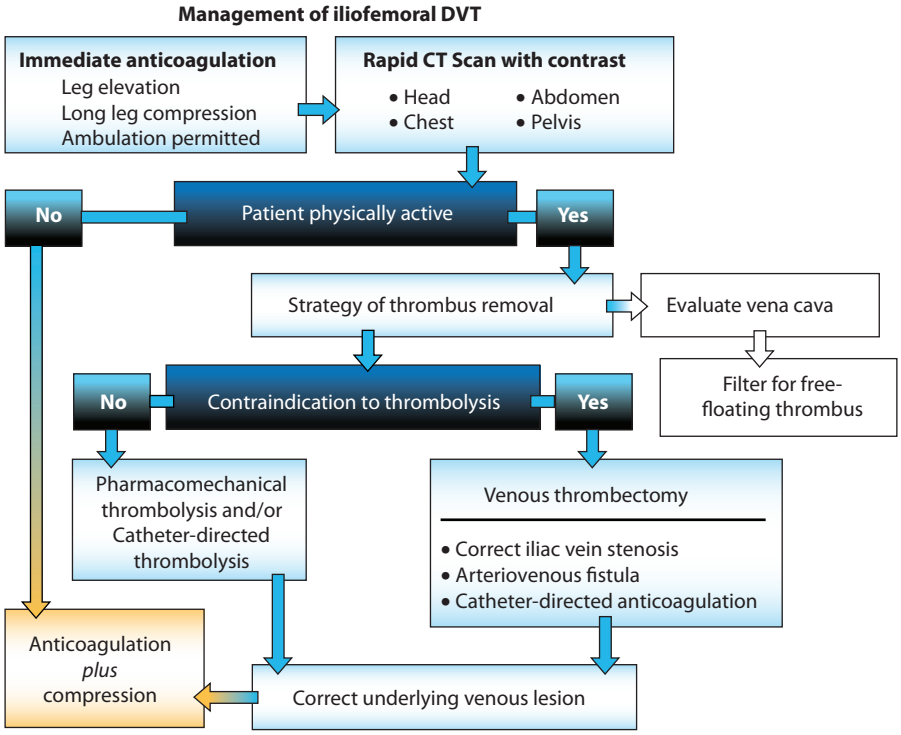

Figure 20.4 Suggested management protocol for patients with iliofemoral deep venous thrombosis. CT: computed tomography; DVT: deep venous thrombosis.

thrombolysis, the venous system is examined with completion phlebography. If an underlying stenosis exists, which is frequently observed in the left common iliac vein where it is compressed by the right common iliac artery, the vein is balloon dilated and stented. The addition of intravascular ultrasonography has improved the evaluation of iliac compression and the precision of stent deployment. Residual areas of stenosis must be corrected to achieve long-term success; otherwise, the patient faces a high risk of re-thrombosis. If a stent is used, it should be sized appropriately to the projected normal diameter of the recipient vein.

20.6 PHARMACOMECHANICAL THROMBOLYSIS

The adjunctive use of mechanical techniques is rapidly becoming the standard for catheter-based management of extensive venous thrombosis.[24–30] Percutaneous mechanical thrombectomy alone is less successful than CDT, and is associated with unacceptably high pulmonary embolic complications. A prospective evaluation of pulse-spray pharmacomechanical thrombolysis of thrombosed hemodialysis grafts found that PE occurred in 18% of patients treated with a plasminogen activator pulse-spray solution versus 64% of patients treated with a heparinized saline pulse-spray solution ($P = 0.04$).[24] Since thrombosed hemodialysis grafts are in direct communication with the venous circulation, they can be considered similar to proximal veins with acute DVT. Observations would likely be magnified when treating thrombosed veins larger than the 6-mm hemodialysis graft. In an experimental model, Greenberg and associates[25] evaluated mechanical, pharmacomechanical, and pharmacologic thrombolysis. Their findings are consistent with anecdotal clinical observations as well as the results reported by Kinney et al.[24] They reported that pulse-spray mechanical thrombectomy was associated with the largest number and greatest size of distal emboli. When urokinase was added to the solution, the embolic particles diminished in number and size and increased the speed of lysis and reperfusion.

Vedantham et al.[26] evaluated the effectiveness of mechanical thrombectomy alone and in combination with pharmacologic thrombolysis in 28 limbs of patients with acute DVT. They evaluated multiple devices, including the Amplatz (ev3, Inc.), AngioJet (Possis Medical), Trerotola (Arrow International), and Oasis (Boston Scientific/Medi-tech) catheters. Venography was performed at each step of the procedure. A total of 26% of the thrombus was removed by mechanical thrombectomy alone, whereas adding a plasminogen activator solution to the mechanical technique (pharmacomechanical) removed 82% of the thrombus.

Lin et al.[27] reported their 8-year experience with pharmacomechanical thrombolysis using a rheolytic thrombectomy catheter. Of their 98 patients, 46 received CDT alone and 52 underwent pharmacomechanical thrombolysis. Pharmacomechanical thrombolysis with the AngioJet catheter (Boston Scientific) was associated with significantly fewer phlebograms, shorter intensive care unit stays, shorter

hospital stays, and fewer blood transfusions. Bleeding complications were not different between the two groups. A smaller patient group treated by rheolytic thrombectomy was reported by Kasirajan et al.,[28] who demonstrated that mechanical thrombectomy alone was less effective than combined pharmacomechanical thrombolysis.

CDT alone was associated with the slowest reperfusion but the fewest distal emboli. In general, mechanical thrombectomy alone most often is inadequate. Although rheolytic pharmacomechanical techniques have been helpful in many patients for clearing a difficult lesion, hemolytic complications are common, and occasionally result in anemia and renal dysfunction. A device designed for isolated segmental and controlled pharmacomechanical thrombolysis is the Trellis catheter (Covidien). This hybrid catheter isolates the thrombosed vein segment between two occluding balloons after the introduction of a dispersion wire. A lytic agent is infused into the thrombus between the occluding balloons. The intervening catheter shaft assumes a spiral configuration, which is then motor-activated to rotate at 3500 rpm. After 15–20 minutes, the liquefied thrombus and remaining fragments can be aspirated through the sheath. Phlebographic evaluation was performed before moving on to treat additional thrombosed vein segments. The advantages of such a device include its ability to incorporate mechanical and pharmacological therapies, and to treat patients who have traditional contraindications to higher doses of thrombolytic agents, as much of the lytic infusate can be aspirated. The clot is more rapidly lysed and treatment times are significantly shortened. Martinez-Trabal showed that patients treated with isolated segmental pharmacomechanical thrombolysis had a significantly more rapid lysis time, with a reduction in the dose of plasminogen activator.[29,30] Unfortunately, the Trellis catheter is no longer available.

An adjunct to CDT is the incorporation of ultrasound transducers into the infusion catheter. Ultrasound waves generated during infusion of the plasminogen activator increase the surface area of fibrin and speed lysis. Several reports have emerged indicating that an infusion catheter with ultrasound transducers built into the infusion end of the catheter can be used to accelerate thrombolysis.[31–33] *In vitro* studies have demonstrated that ultrasound enhances the fibrinolytic activity of tissue plasminogen activators (t-PA).[32,34,35] The potential mechanism for augmented clot lysis has been extrapolated from *in vitro* studies showing that ultrasound produces clot fragmentation in the presence of t-PA and, consequently, more t-PA binds to fibrin binding sites because of the larger available surface area.[36,37] The concept of a transducer tip catheter that delivers a fibrinolytic drug in combination with high-frequency, low-intensity ultrasound has been studied by Engelberger et al.[38] In a single-center randomized and controlled trial of patients with PE, Engelberger et al.[38] showed that fixed-dose, low-intensity ultrasound-assisted thrombolysis was a safe and effective treatment for PE. They reported that their experience with ultrasound-accelerated thrombolysis for iliofemoral DVT followed by routine stenting of residual stenosis resulted in low bleeding rates, high patency rates, and a low rate of PTS.[39]

The same authors investigated the added benefit of ultrasound to CDT in patients with iliofemoral DVT. They randomized 48 patients with acute iliofemoral DVT to receive CDT or ultrasound-accelerated thrombolysis.[40] All patients had the ultrasound infusion catheter inserted into the thrombosed iliac veins. Only those randomized to the ultrasound-accelerated group had the ultrasound activated. After their target of 15 hours of treatment, the authors found that patients had 54% and 55% thrombus load reductions with CDT and ultrasound-accelerated thrombolysis, respectively. There were no differences between treatment groups in any of the other outcomes evaluated.

The patient with phlegmasia cerulea dolens described in Figure 20.3 illustrates the advantage of using isolated segmental pharmacomechanical thrombolysis to potentially shorten treatment duration and limit exposure to the thrombolytic agent, thereby maximizing the chance of a safe and successful outcome. As this patient was treated before the study published by Engelberger et al.,[40] we cannot conclude that ultrasound assisted thrombolysis (USAT) achieved better results than would have been achieved with CDT by the drip technique. As technology continues to improve, lytic infusion times will shorten, more patients will be offered a treatment strategy that includes thrombus removal (Figure 20.4), and many more patients will be spared their otherwise certain post-thrombotic morbidity.

20.7 OPERATIVE VENOUS THROMBECTOMY

Although operative venous thrombectomy is infrequently required because of the increased safety and effectiveness of CDT for IFDVT, it remains a valuable treatment option in selected patients. Such patients include those with multiple trauma, and active bleeding in those at high risk for bleeding into a critical site (intracranial and intraocular). What follows is a description of our current technique.

General anesthesia is usually recommended for patients undergoing operative venous thrombectomy. A longitudinal inguinal incision exposes the common femoral, femoral, saphenofemoral junction, and profunda femoris vein or veins (Figure 20.5a). A longitudinal venotomy of the common femoral vein is recommended to ensure access to the origin of the saphenous and profunda femoris branches. If infrainguinal thrombus is present, the leg is elevated and compressed with a tightly wrapped rubber bandage, the foot is dorsiflexed, and the calf and thigh are squeezed. If all infrainguinal thrombus is removed, which is clinically evident when it occurs, balloon thrombectomy of the iliofemoral venous system is performed.

If the infrainguinal thrombus persists and a guidewire can be advanced distally, an infrainguinal thrombectomy can be performed using an over-the-wire balloon thrombectomy catheter. If a guidewire cannot be passed through

the infraingual valves, a cut-down is performed to expose the distal posterior tibial vein. A No. 3 Fogarty catheter is advanced from the distal posterior tibial vein to and through the common femoral venotomy. The Silastic stem of an intravenous catheter (12–14 gauge) is amputated from its hub and slid halfway onto the balloon catheter. Another balloon catheter (No. 4 Fogarty) is placed in the opposite end of the Silastic sheath (Figure 20.5a). Pressure is applied to the two balloons by a single operating surgeon to ensure that the catheters remain secure inside the sheath. The No. 4 balloon catheter is guided distally through the thrombosed venous valves and clotted veins (Figure 20.5b) to the level of the posterior tibial venotomy (Figure 20.5c). Alternatively, if an over-the-wire balloon thrombectomy catheter is available, a guidewire can be passed proximally from the distal posterior tibial vein and the infrainguinal thrombectomy performed, with passage repeated as necessary (Figures 20.5d and e).

After infrainguinal balloon catheter thrombectomy, the infrainguinal venous system is flushed by placing a large red rubber catheter into the proximal posterior tibial vein and vigorously flushing with a heparin–saline solution, using a bulb syringe to hydraulically force residual thrombus from the deep venous system (Figure 20.5f). Frequently, an impressive amount of additional thrombus will be retrieved with this maneuver. Once the infrainguinal venous system is adequately cleared, a vascular clamp is applied below the femoral venotomy and the infrainguinal venous system is filled with dilute plasminogen activator solution consisting of approximately 4–6 mg of rtPA in 200 mL of saline. The plasminogen activator solution remains in the infrainguinal veins for the remainder of the procedure. This amount of local rtPA will bind to fibrin-bound plasminogen in the residual thrombus and promote further clot dissolution; however, this dose will not cause a systemic lytic response due to circulating plasminogen activator and plasmin inhibitors. If the infrainguinal venous thrombectomy is not successful because of older thrombus or chronic disease, the femoral vein is ligated and divided below the profunda femoris vein. Patency of the profunda is ensured by direct thrombectomy if necessary.

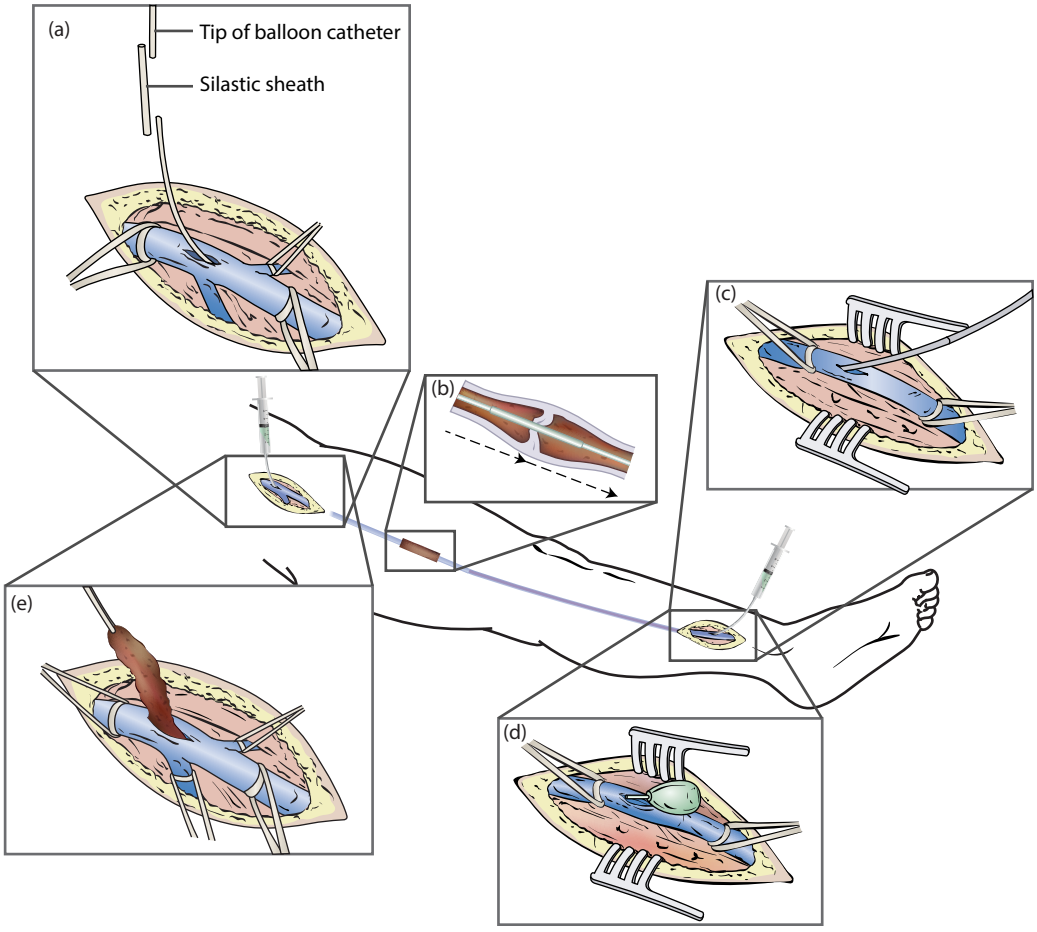

Figure 20.5 Surgical repair of venous thrombosis. **(a)** Longitudinal inguinal incision to expose the common femoral vein, femoral vein, saphenofemoral junction, and profunda femoris vein. (**b** and **c**) The balloon catheter is guided distally through the thrombosed venous valves and clotted veins to the level of the posterior tibial venotomy. (**d** and **e**) Performance of infrainguinal venous thrombectomy, with passage of the balloon catheter repeated as necessary.

(*Continued*)

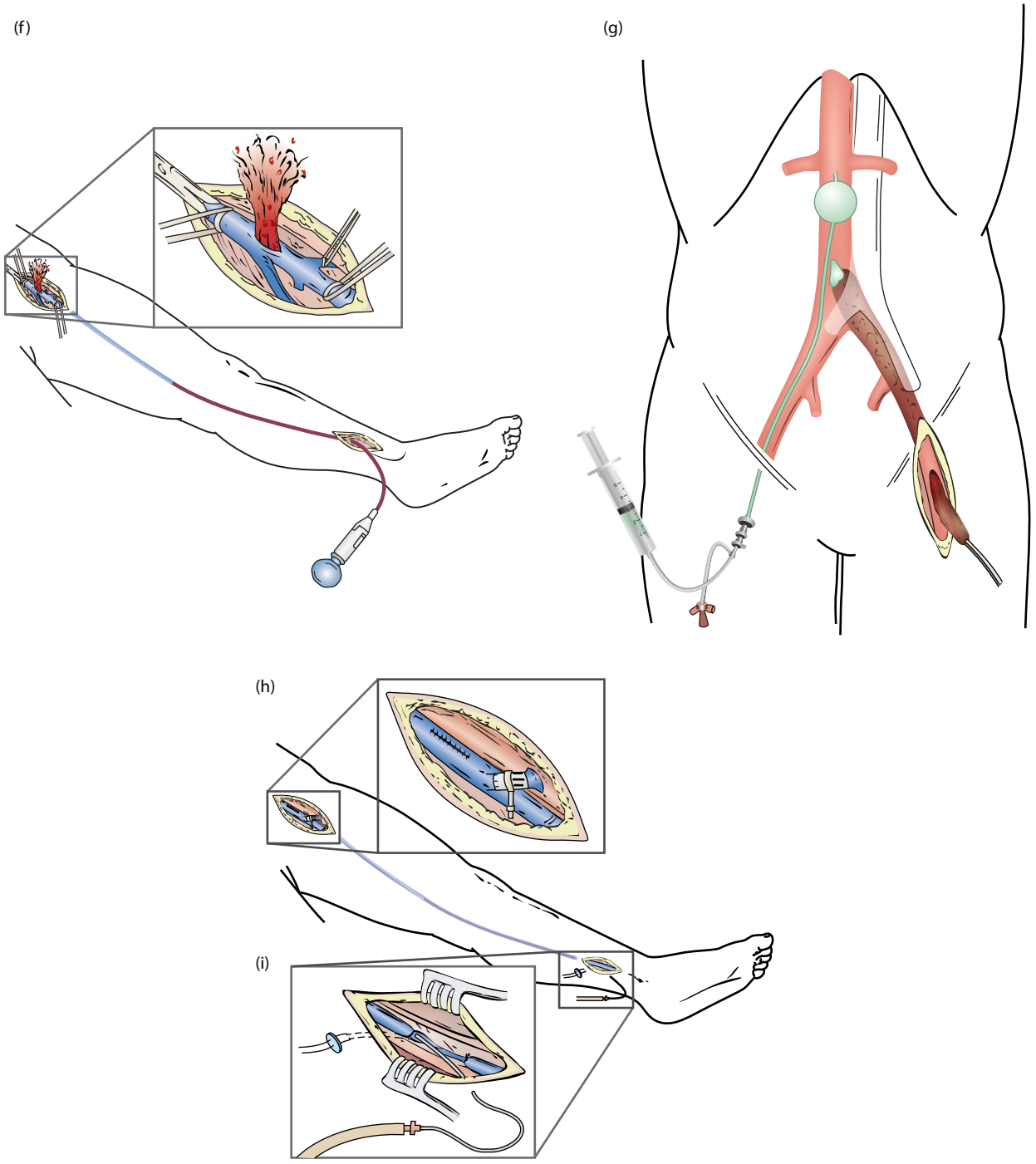

Figure 20.5 (Continued) **(f)** After infrainguinal balloon catheter thrombectomy, flushing of the infrainguinal venous system with a heparin–saline solution is performed by placing a large red rubber catheter into the proximal posterior tibial vein and flushing vigorously with a bulb syringe. After flushing is complete, 250–300 cc of saline with 3–4 mg rtPA is infused into the deep venous system after the clamp is reapplied to the distal common femoral vein (CFV). The proximal thrombectomy is then performed. **(g)** Ilio-caval thrombectomy can be performed with a protective balloon catheter inflated above the caval thrombus, if it exists, as an alternative to vena caval filtration. A large venous thrombectomy catheter is used, with an 8–10-Fr balloon. **(h)** Placement of a piece of polytetrafluoroethylene or Silastic wrap around the saphenous arteriovenous fistula. A large, permanent monofilament suture is looped and clipped with approximately 2 cm left in the subcutaneous tissue. This serves to limit dilation of the arteriovenous fistula and is also a guide for dissection should surgical disconnection of the arteriovenous fistula become necessary. **(i)** Placement of a small infusion catheter (pediatric feeding tube) into the wound via a separate stab incision in the skin. It is inserted and fixed in the proximal posterior tibial vein for infusion of unfractionated heparin directly into the thombectomized vein.

Iliofemoral venous thrombectomy is then performed by passing a No. 8 or 10 venous thrombectomy balloon catheter partially into the iliac vein for several passes to remove the bulk of the thrombus before advancing the catheter into the vena cava. The proximal thrombectomy is always performed under fluoroscopic guidance, with contrast material in the balloon, especially if a vena caval filter is present, there is clot in the vena cava, or resistance to catheter passage is encountered. During this part of the procedure, the anesthesiologist applies positive end-expiratory pressure to further reduce the risk of pulmonary embolization. If a clot is present in the vena cava, caval thrombectomy can be performed with a protective balloon catheter inflated above the thrombus as an alternative to vena caval filtration (Figure 20.5g).

After completion of the iliofemoral venous thrombectomy, intraoperative phlebography/fluoroscopy is performed to evaluate for an underlying iliac vein stenosis and to assess the nature of the venous drainage into the vena cava. Intravascular ultrasound is better than single-view phlebography for detecting iliac vein stenosis. Any underlying iliac vein stenosis is corrected by balloon angioplasty and stenting if venous recoil occurs. If an iliac vein stent is used, a 14-mm diameter or larger stent is recommended for the common iliac vein and 12-mm diameter or larger stent for the external iliac vein.

Once the venotomy is closed, an end-to-side arteriovenous fistula (AVF) is constructed by anastomosing the amputated end of the proximal saphenous vein or a large proximal branch of the saphenous vein to the side of the superficial femoral artery. The anastomosis should be limited to 3.5–4.0 mm in diameter. The purpose of the AVF is to increase venous velocity but not venous pressure. Common femoral vein pressure is recorded before and after the AVF is opened. No increase in venous pressure should be observed when the AVF is opened. If the pressure increases, the proximal iliac vein should be re-evaluated for residual stenosis or obstruction and the proximal lesion corrected. If the pressure remains elevated, the AVF is constricted to decrease flow and normalize pressure.

A piece of polytetrafluoroethylene or bovine pericardium is wrapped around the saphenous AVF and a large permanent monofilament suture (No. 0) looped and clipped with approximately 2 cm left in the subcutaneous tissue (Figure 20.5h). This will serve as a guide for future dissection in the event that operative closure of the AVF becomes necessary, although most, if not all, AVFs do not require closure. Since the AVF is limited and cannot enlarge, we consider it permanent. Clinical experience has shown a re-thrombosis rate of 12%–18% following elective closure of AVFs. These AVFs may also be closed with obliteration of the fistula using an endovascular intervention.

If serous wound accumulation is observed, a diligent search for transected lymphatics is performed, with careful ligation and coagulation. A closed suction drain is generally placed in the wound to evacuate serosanguineous fluid that may accumulate post-operatively. The drain exits through a separate puncture site adjacent to the incision. The wound is closed with multilayered running absorbable sutures to achieve hemostatic and lymphostatic wound closure and ensure elimination of dead space.

The distal posterior tibial vein is ligated. A small infusion catheter (pediatric feeding tube) is brought into the wound via a separate stab incision in the skin and inserted and fixed in the proximal posterior tibial vein (Figure 20.5i). This catheter is used for post-operative anticoagulation with unfractionated heparin (UFH) and pre-discharge phlebography. Anticoagulation via this catheter ensures maximum heparin concentration in the affected veins during their period of greatest thrombogenicity. A 2–0 monofilament suture is looped around the proximal posterior tibial vein (and catheter) and both ends exit the skin adjacent to the wound. The ends of the suture are passed through the holes of a sterile button, which is secured snugly to the skin when the catheter is removed. Upward tension on the ends of the suture obliterates the proximal posterior tibial vein at the time of catheter removal and eliminates the risk of bleeding; the suture is tied and secured above the skin by the button. As mentioned, before removal of the catheter, an ascending phlebogram is performed through the catheter to assess phlebographic patency.

Antibiotic ointment is applied to all wounds beneath sterile dressings. The patient's leg is wrapped snugly with sterile gauze and multilayered elastic bandages from the base of the toes to the groin. The posterior tibial vein catheter exits between the layers of the bandage, but is secured so that the patient can ambulate using an intravenous pole on wheels to support infusion of UFH.

20.8 POST-OPERATIVE CARE

Therapeutic anticoagulation is continued with UFH through the posterior tibial vein catheter attached to a pump on an intravenous pole with wheels so that the patient can ambulate. Before removal of the posterior tibial vein catheter, an ascending phlebogram is performed. Oral anticoagulation is begun when the patient awakens and resumes oral intake. Heparin infusion is continued for an overlap of 4–5 days until the international normalized ratio reaches 2–3. Oral anticoagulation is continued for an extended period, generally for a period of 1 year or more.

Intermittent pneumatic compression garments are used on both legs post-operatively when the patient is not ambulating. Before discharge, the patient is fitted for 30–40-mmHg ankle gradient below-knee compression stockings and instructed to wear the stockings from waking in the morning until bedtime. Randomized trials have demonstrated at least a 50% reduction in post-thrombotic morbidity with the use of 30–40-mmHg ankle gradient compression stockings.[18,19]

When the patient is fully recovered and back to baseline activity, repeat venous duplex and venous function studies are performed to evaluate ultrasonic patency and vein valve function, which serve as a baseline for future studies.

Guidelines 3.4.0 of the American Venous Forum on catheter-directed thrombolysis and venous thrombectomy for acute deep vein thrombosis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.4.1	In patients with symptomatic deep venous thrombosis and large thrombus burden, particularly in iliofemoral deep venous thrombosis, we recommend a treatment strategy that includes thrombus removal.	1	B
3.4.2	In patients with symptomatic iliofemoral deep venous thrombosis with symptoms of <14 days' duration, we recommend catheter-directed thrombolysis if appropriate expertise and resources are available to reduce acute symptoms and post-thrombotic morbidity.	1	B
3.4.3	We suggest pharmacomechanical thrombolysis, with thrombus fragmentation and aspiration, over catheter-directed thrombolysis alone in the treatment of iliofemoral deep venous thrombosis to shorten treatment time, if appropriate expertise and resources are available.	2	B
3.4.4	In patients with acute deep venous thrombosis, systemic thrombolysis is not suggested.	2	B
3.4.5	For patients with symptomatic iliofemoral deep venous thrombosis who are not candidates for catheter-directed thrombolysis, we recommend surgical thrombectomy.	1	B

Note: Guideline recommendations and suggestions are included in this table. All evidence to the date of the writing of this chapter is considered; therefore, the strength of these recommendations may differ from previously published guidelines.[2,14,15,41] We are certain that the results of the ATTRACT trial will have a major impact on future guidelines.

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● = Key primary paper
★ = Major review article
◆ = Guideline

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Endovascular and surgical management of acute pulmonary embolism

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21.1 INTRODUCTION

Venous thromboembolic events (VTEs) are clinically important causes of morbidity and mortality, occurring in 0.8–1 per 1000 person-years. This results in >250,000 admissions for a VTE annually in the United States. A third of these admissions will be for pulmonary embolism (PE) at a rate of approximately 0.45 per 1000 person-years.[1,2] The morbidity of acute pulmonary PE is significant, and this diagnosis confers a 15% 28-day mortality rate.[1] To direct treatment, PE is classified by prognostic clinical factors (Table 21.1), with stratification into massive and submassive categories on the basis of hemodynamics. For all groups, the initial treatment for any PE is immediate anticoagulation with unfractionated heparin or, preferentially, with low-molecular-weight heparin.[3] Treatment of low-risk PE remains anticoagulation therapy alone.[4] Patients with massive PE are preferentially treated with thrombolysis, if not contraindicated.[4] However, there is debate regarding the optimal modality of thrombolytic delivery: by peripheral systemic or by catheter-directed approaches. Finally, the preferred approach for the treatment of submassive PE with thrombolysis and/or the application of catheter-based treatment (CBT) remains intensely debated. The goal of this discussion is to review the interventional approaches for acute PE for use in clinical practice in massive and submassive PE.

21.2 PATHOPHYSIOLOGY OF ACUTE PE

The hemodynamic response to acute PE will vary for each patient based on several factors. In addition to the magnitude of the thromboembolic load, humoral factors, including serotonin, thrombin, and histamine release, contribute to the potential for hemodynamic embarrassment. The patient's cardiopulmonary reserve also plays a large role in the tolerance of an acute embolic event. Thus, a smaller PE may result in cardiovascular collapse in a patient with existing cardiopulmonary disease. Conversely, large thrombus burdens may be tolerated in healthy individuals. Therefore, a patient-specific approach based on the acute PE stratification (Table 21.1) is needed to guide appropriate treatment.[5]

Acute PE results in increased pulmonary vascular resistance due to two factors. Physical obstruction of the pulmonary vessels increases pulmonary artery (PA) pressures proportional to the thrombus load. Additionally, the pulmonary vascular bed vasoconstricts in response to hypoxemia. The combination of these two factors results in a high-pressure circuit. PA pressures are known to increase when 25%–30% of the pulmonary vasculature is occluded by thrombus.[5,6] Mean PA pressures of 30–40 mmHg are classified as severe pulmonary hypertension. In a previously healthy individual, 40 mmHg may represent the maximum pressure that the right ventricle (RV) can generate. However, pre-existing RV hypertrophy may allow the RV to overcome higher PA pressure.[6]

The obstruction of blood flow through the pulmonary arteries results in increased dead space ventilation. However, compensatory hyperventilation usually compensates to remove CO_2 and can also increase PaO_2. However, mismatch between ventilation and perfusion, intracardiac or intrapulmonary shunting of mixed venous blood, and alveolar hypoventilation may result in hypoxemia in patients suffering from PE.[6]

Increased RV afterload generated by the extent of thrombus and hypoxemic vasoconstriction can cause significant

Table 21.1 Classification of acute pulmonary embolism

Risk	Definition	
Massive	Sustained hypotension for >15 minutes or inotropic support due to the PE	
	Pulselessness	
	Persistent profound bradycardia (<40 bpm) with evidence of shock	
Submassive	No systemic hypotension, but either RV dysfunction or myocardial necrosis	
	RV dysfunction:	RV dilation (four-chamber RV diameter/LV diameter >0.9 by US or CT)
		Elevated BNP (>90 pg/mL)
		Elevated N-terminal proBNP (>500 pg/mL)
		ECG changes
	Myocardial necrosis:	Elevated troponin I (>0.4 ng/mL)
		Elevated troponin T (>01 ng/mL)
Low risk	No clinical markers for adverse prognosis used to define massive or submassive	

Source: Adapted from Jaff MR, McMurtry MS, Archer SL. *Circulation* 2011;16(123):1788–830.
Note: PE: Pulmonary embolism; bpm: beats per minute; RV: right ventricle; LV: left ventricle; US: ultrasound; CT: computed tomography; BNP: brain natriuretic peptide; ECG: electrocardiogram.

RV strain. This results in RV dilation, hypokinesis, tricuspid regurgitation, myocardial ischemia, and ultimately right heart failure. Right ventricular dilation also leads to intraventricular septal flattening, which can impair left ventricular (LV) function. These factors can then result in systemic hypotension from reduced LV preload and overall LV function, compounding myocardial ischemia. This process occurs over time, such that hemodynamic collapse may actually occur after 12–48 hours of relative "normotension" and hemodynamic stability.[5,7]

21.3 INDICATIONS FOR INTERVENTION

Given the pathological milieu of acute PE, treatment needs to address: (1) prevention of new thrombus formation; (2) clearance of the obstructing thrombus from the PA (either rapidly or over time); and (3) reducing RV dysfunction when present. Current guidelines recommend thrombolysis for patients with low bleeding risk who have massive PE. In addition, patients with submassive PE who are thought to be at risk for adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) may be considered for thrombolysis (Figure 21.1).[3,4] However, some patients have a contraindication to systemic thrombolysis (recent intracranial hemorrhage or surgery, recent spinal surgery, recent head trauma, intracranial neoplasm, uncontrolled hypertension, or active or recent bleeding). In addition, systemic thrombolysis carries a 20% risk of bleeding and a 3%–5% risk of hemorrhagic stroke.[8] Moreover, there may be insufficient time to allow for infusion and the effect of systemic thrombolytics in the acute setting. Finally, some patients will fail to improve despite thrombolytic treatment. In these instances, alternative treatments for expediting thrombus removal and/or reducing thrombolytic dosage, such as CBT or surgical embolectomy, remain important treatment considerations.

In massive and submassive PE, RV outflow obstruction can cause severe RV strain. Therefore, interventional efforts to remove the obstructing thrombus can potentially reverse this pathological state faster than systemic thrombolytic infusion. Percutaneous CBTs and open embolectomy can debulk the offending thrombus, expedite thrombolysis, improve lung perfusion, and/or improve right heart strain over heparin therapy alone, if systemic thrombolytics are not possible. Some CBTs may use low-dose or zero thrombolytics to minimize bleeding risk. Although CBTs are appealing for expedited care, they currently remain second-line therapies to systemic thrombolysis as the initial treatment. No additional benefit of CBTs has been proven over systemic thrombolysis. However, they remain recommended over no intervention (i.e., systemic thrombolysis) in conjunction with anticoagulation for massive and submassive PE.[3]

Due to the multitude of approaches for the treatment of PE, the concept of a PE response team has emerged as a multidisciplinary coordinated effort to streamline and improve the evolving and complex care of acute PE.[9] This multidisciplinary approach may lead to broader national efforts at improving processes and outcomes for PE.

21.4 FRAGMENTATION AND SUCTION THROMBECTOMY

The most widely used simple technique is the use of rational pigtail fragmentation (Figure 21.2). This technique requires femoral or jugular venous access. A guidewire is passed into the pulmonary vasculature through the thrombus. In comparison to a traditional pigtail catheter, for fragmentation of acute PE, the catheter has an oval side hole on its outer curvature. This allows the catheter to be advanced over the wire and the wire is used as an axis around which to rotate (Figure 21.2b). An 8-mm catheter may be useful for segmental branches and a 12-mm catheter for the main right and

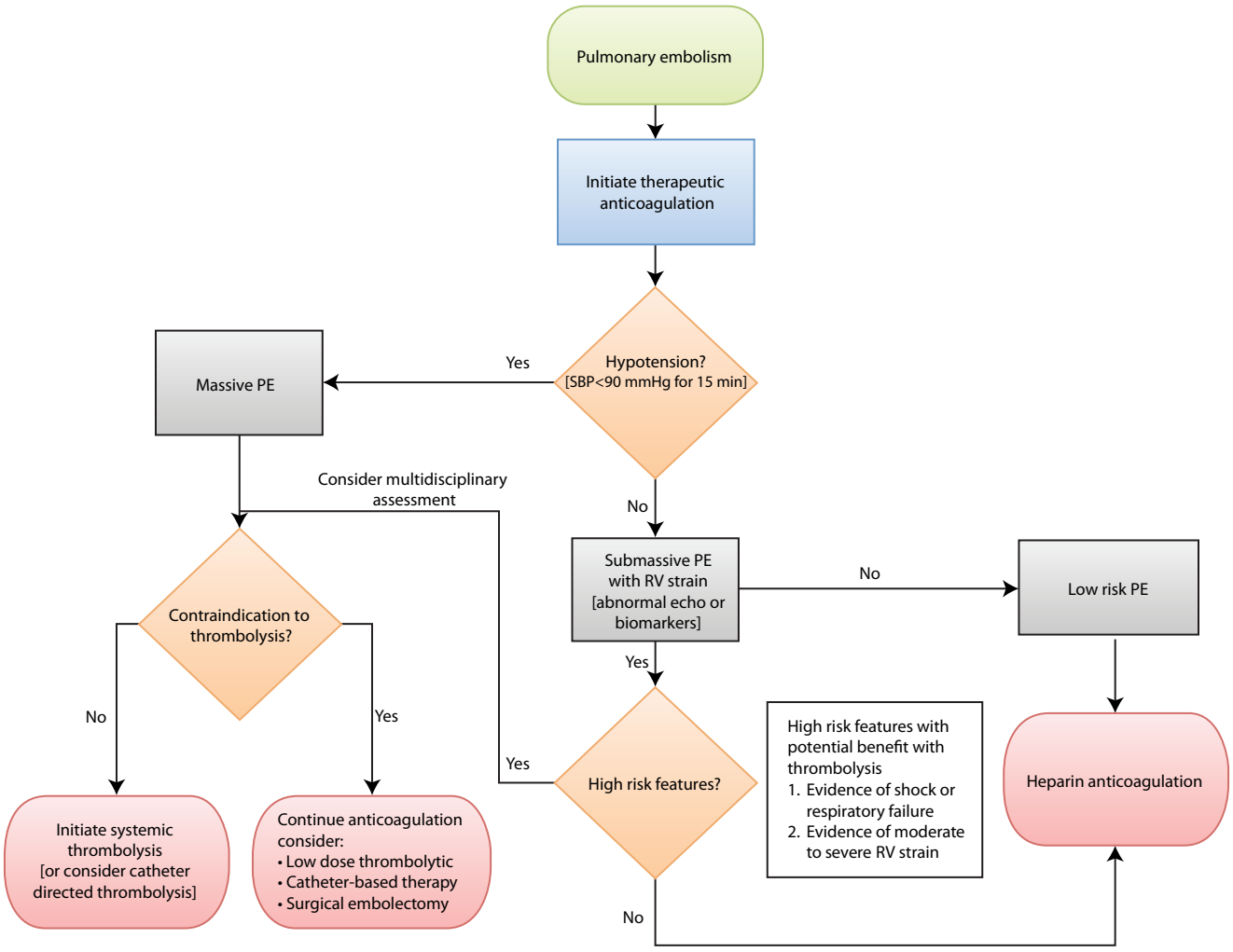

Figure 21.1 Treatment algorithm for pulmonary embolism. PE: pulmonary embolism; SBP: systolic blood pressure.

left pulmonary arteries.[8,10] This procedure can be performed in less than 30 minutes, resulting in rapid fragmentation of the thrombus. This technique embolizes the thrombus distally into smaller branches to restore partial perfusion of large vessels, improving pulmonary hemodynamics (Figure 21.2c). Additionally, this intervention increases the surface area of the thrombus for fibrinolytic activity. In a review of interventional techniques, pulmonary fragmentation appears to be clinically effective 80% of the time, with few complications.[11] Finally, additional fragmentation can be accomplished by deploying an angioplasty balloon (9–14 mm) into the thrombus.[12] The balloon must be undersized compared to the vessel in which it is used to avoid complications.[8]

In addition to fragmentation, it may be possible to remove the thrombus by aspiration from smaller vessels. This can be accomplished with any end-hole guide catheter (8 or 9 Fr) placed into the thrombus with the application of negative pressure by means of a syringe. In a review of CDT treatments, suction thrombectomy, with or without fragmentation, was technically successful in 40%–100% of cases.[11]

21.5 MECHANICAL THROMBECTOMY DEVICES

The most well-known catheter thrombectomy device is the AngioJet system (Boston Scientific, Marborough, MA). The AngioJet is a rheolytic mechanical thrombectomy device based on Bernoulli's principle. It creates a low-pressure zone (up to −600 mmHg) in a region of high jet velocity. The thrombus is fragmented and brought back into the catheter for removal. This can be combined with tissue plasminogen activator (tPA) infusion for a pharmacomechanical thrombectomy, whereby tPA is laced into the thrombus (using either 10 or 20 mg tPA and the appropriate AngioJet pulse spray-enabled catheter). Then, saline is used for standard rheolytic thrombectomy. The device has several catheter sizes for peripheral and coronary use. Most catheters are 6 Fr compatible or less (4 Fr

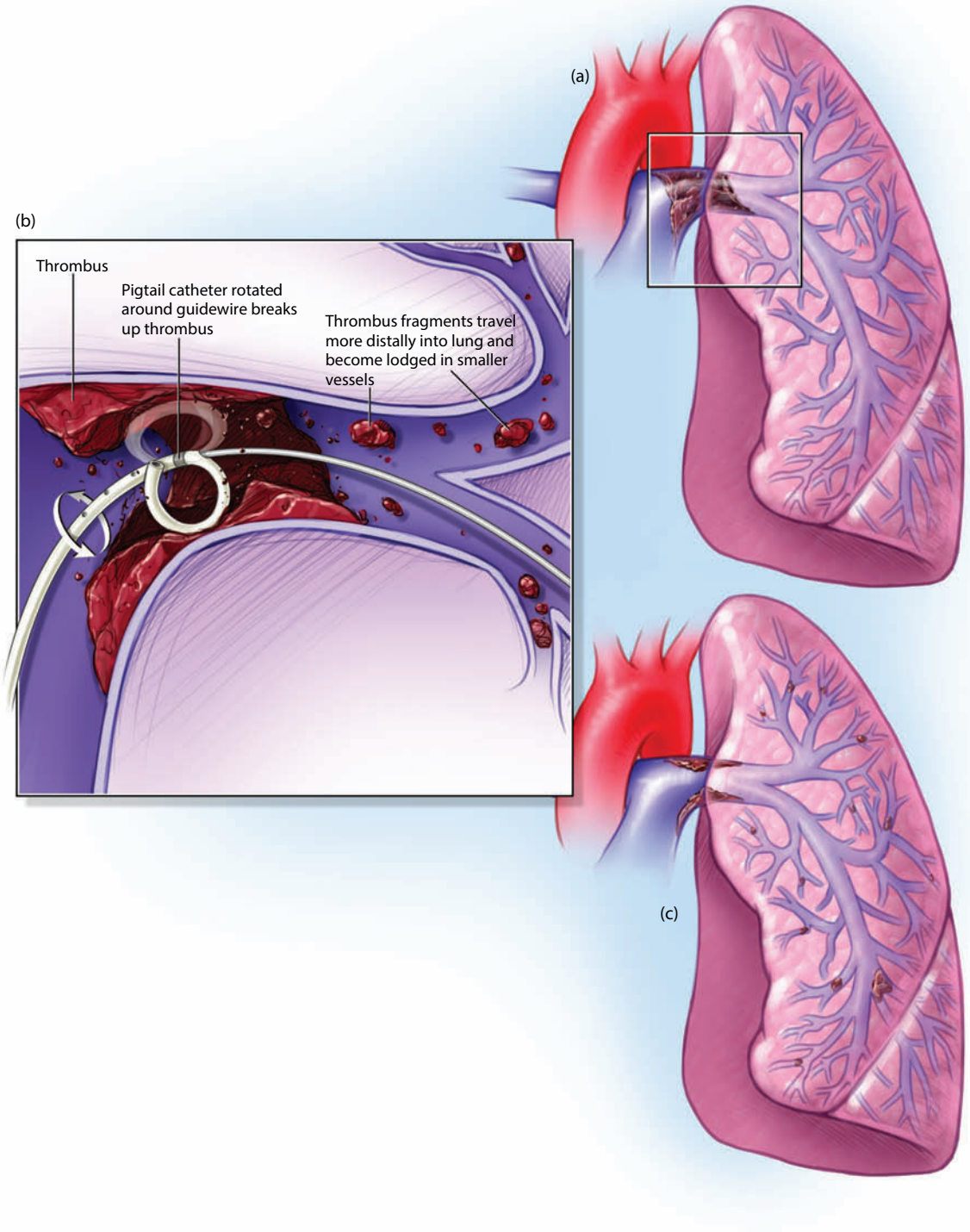

Figure 21.2 Pigtail fragmentation for pulmonary embolism. **(a)** Large pulmonary embolism in the main left pulmonary artery obstructing flow. **(b)** Pigtail catheter is rotated around the wire axis to fragment the thrombus causing distal embolization but restoring flow through the main pulmonary artery. **(c)** Flow restored with small distal embolization of thrombus.

for coronary use) and require the AngioJet pump tower to function. This device does not currently have a Food and Drug Administration (FDA) indication for PE. In spite of its successful use in the periphery and the initial enthusiasm from good technical success in the treatment of PE,[13,14] significant complications have been encountered when it is used in the pulmonary circulation. A systematic review of all catheter-directed therapies for PE demonstrated that use of the AngioJet for PE resulted in 76% of all reported complications, even though it was only used in 11% of cases.

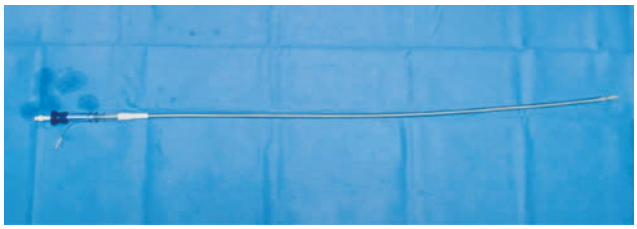

Figure 21.3 AngioVac cannula.

Major and minor complications occurred in 40% and 28% of patients, respectively. These complications included bradycardia, heart block, asystole, deep coughing, renal insufficiency, hemoglobinuria, and hemoptysis, as well as five procedure-related deaths.[8,11,15] Although the cause of these complications is unknown, possible hypotheses include the release of adenosine and potassium from hemolysis, or activation of stretch receptors by the jets. The device now carries a black box warning about risks of adverse events and death when used for PE. Thus, it should not be used in this setting, since other options with lower risk are readily available (e.g., fragmentation).

Other thrombectomy devices have been used for the treatment of PE. The Helix Clot Buster was approved for use in thrombosed dialysis access, and had been used off-label for PE. However, the device is no longer available in the United States. Additionally, The Aspirex catheter (Straub Medical, Wangs, Switzerland) is a newer device with potential for application in PE, although it is not available in the United States currently (it carries a venous indication internationally). This device has a high-speed rotating spiral in the body of the catheter that creates negative pressure. It allows maceration and aspiration of the thrombus. It has been shown to be effective during *in vitro* and *in vivo* testing[16] and in initial clinical reports for PE.[17] Additionally, the Indigo system (Penumbra, Inc., Alameda, CA) has developed a large directional catheter for suction thrombectomy, however limited data on its use is available to date.

Finally, the AngioVac device (Angiodynamics, Latham, NY) is a promising emerging catheter-based modality for the treatment of PE. Based on the instructions for use, the AngioVac (Figure 21.3) is a venous drainage cannula for extracorporeal bypass (up to 6 hours). It carries an additional indication for the removal of unwanted intravascular material (soft thrombus or embolus). It is a 22-Fr coil-reinforced cannula with a funneled balloon-actuated tip to direct the thrombus into the cannula (Figure 21.4). It is attached to a specially designed filter that can be connected to any veno-venous bypass centrifugal pump. A second venous access is necessary for venous return to complete the circuit, as the device can drain up to 5 L per minute (Figure 21.4). The device is advanced through a 24-Fr Dryseal sheath (W.L. Gore, Flagstaff, AZ) from the jugular or femoral approach to enter the pulmonary vasculature. Single reports attest to the feasibility of this device for acute PE.[18] The only published institutional series of 14 patients treated with AngioVac by Donaldson et al. included five patients treated for PE. However, placement of the catheter in the PA was only performed in three patients.[19] Only one of these three patients had complete evacuation of the mass, and two of the five PE cases had adjunctive catheter-directed thrombolysis performed. Acute drops in hematocrit were common in this series (11/14), as was need for transfusion (five patients) and access site hematomas (two patients).

The authors' institution has used the AngioVac for PE cases where thrombolytic treatment is contraindicated and treatment is warranted (massive or submassive PE with risk for deterioration). In our limited experience, a jugular approach is preferred and can be accessed percutaneously. The use of a stiff, pre-curved wire (such as a manually curved Amplatz wire [Boston Scientific, Natick, MA]) is necessary to direct the device from the RV into the PA (Figure 21.5). Extreme care must be taken as RV rupture has been reported with this technique. Treatment is limited to the first 2 cm of the main right and left pulmonary arteries, although theoretically further distal thrombus may be able to be extracted due to the drainage force of the device. Additionally, due to the RV outflow obstruction created by the device, the patient should be placed on temporary peripheral extracorporeal membrane oxygenation (ECMO) for safety. This can be weaned immediately after the procedure, before case completion. For simplicity, the AngioVac drainage can be linked to the ECMO circuit (Figure 21.6). Overall, this device presents a promising modality for quickly removing thrombus from the PA without the need for thrombolysis. However, large doses of heparin are needed for the veno-venous bypass circuit to obtain an activated clotting time (ACT) > 350 seconds. Additionally, there is a risk of dilutional anemia from the fluid the circuit adds to the patient's intravascular volume. Finally, coordination with cardiac surgery is a prerequisite, due to the risks of injury to the heart or pulmonary vessels and the need for ECMO.

21.6 CATHETER-DIRECTED THROMBOLYSIS

In an attempt to reduce the need for large systemic tPA infusions (typically 50–100 mg over 1–2 hours) in the treatment of PE, the delivery of local thrombolytic agents has been proposed as a potentially safer option, and can be used as a standalone treatment or as an adjunct in nearly two-thirds of all reported CDTs for massive and submassive PE.[11] This is performed after femoral or jugular access and catheterization of the pulmonary vasculature. A multi-holed lytic catheter (UniFuse [Angiodynamics, Lytham, NY]) is then placed within the thrombus, and a thrombolytic agent (urokinase or, more commonly, tPA) is infused unilaterally or bilaterally (Figure 21.7). For tPA, 1–2 mg/hour is typically delivered for approximately 15 hours, and then a follow-up pulmonary arteriogram is performed. This can usually be done with <30 mg of tPA, hence carrying a theoretically lower risk of bleeding complications. If extended infusions (>24 hours) are planned, fibrinogen levels should be monitored. If the fibrinogen levels fall precipitously (>50%), or

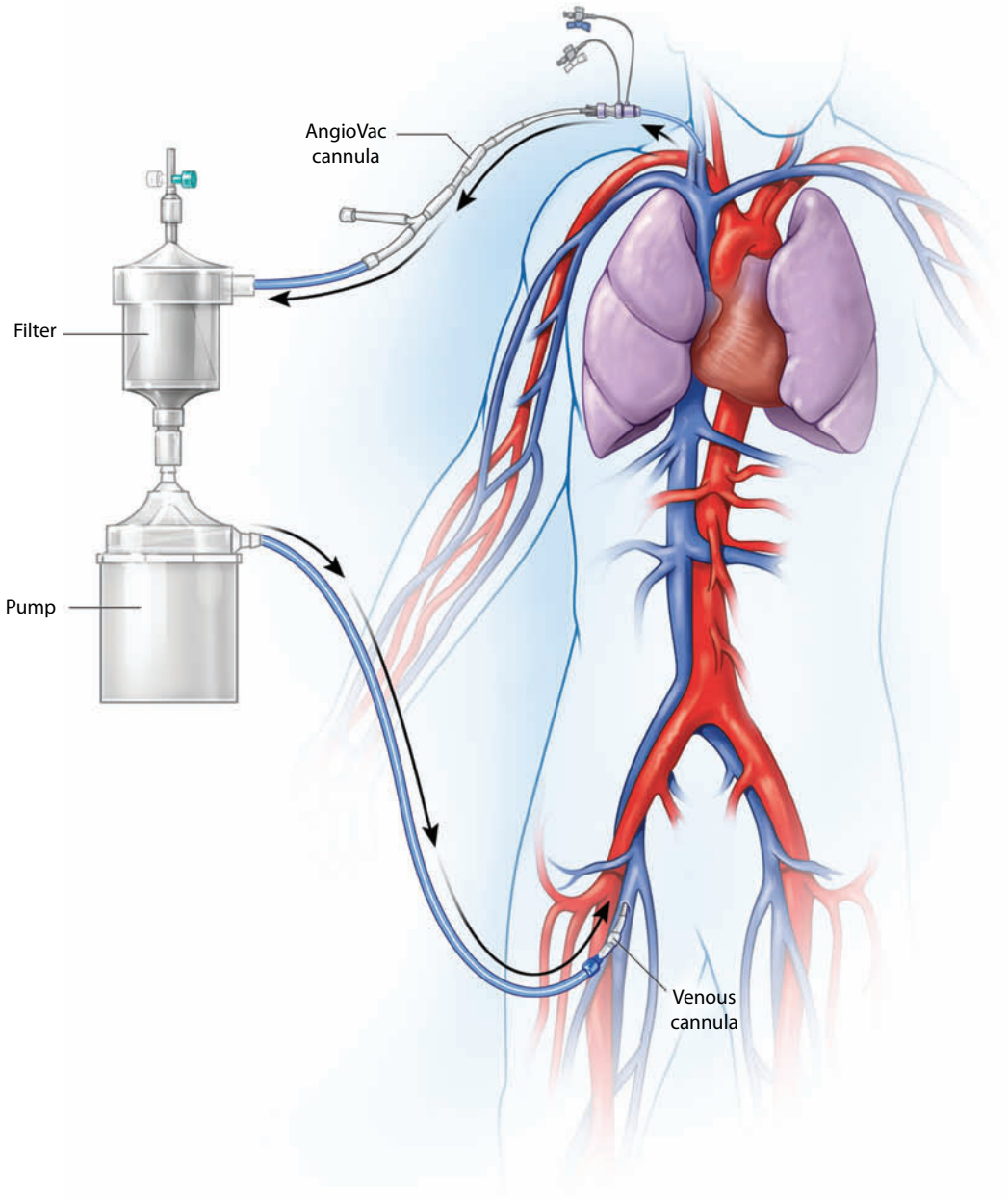

Figure 21.4 AngioVac setup for venous thrombectomy. Jugular access is obtained and the blood drawn through the specially designed filter via a centrifugal pump that returns the blood to the femoral vein through a standard venous cannula.

are under 200 mg/dL, the dose should be reduced or the infusion stopped. In a meta-analysis of CDT series, the frequency of success was higher if at least 80% of patients received locally delivered thrombolytic therapy during the procedure (91.2% vs. 82.8%, $P = 0.01$) or for an extended period of time (89.2% vs. 84.2%, $P = 0.045$). However, the included studies were quite heterogeneous, making a definitive benefit of catheter-directed thrombolytic treatment over other CDTs difficult to prove.[11]

To improve delivery of tPA to the pulmonary vasculature and decrease tPA infusions times (and subsequently tPA doses), ultrasound-assisted thrombolysis (USAT) for the treatment of massive and submassive PE may be used. Currently, the EkoSonic Endovascular System (EKOS Corp., Bothwell, WA) is the only USAT device that is approved for use in the United States. The use of ultrasound energy results in reversible disaggregation of non-cross-linked fibrin fibers and opens up sites for tPA binding in order to facilitate drug effect. Additionally, ultrasound pressure waves may increase thrombus penetration by acoustic streaming.[20] This can be done unilaterally or bilaterally, the latter of which is more common. The USAT catheter is 6-Fr compatible; however, if bilateral treatment is planned, a 10-Fr femoral venous sheath is necessary. The pulmonary vasculature is selected

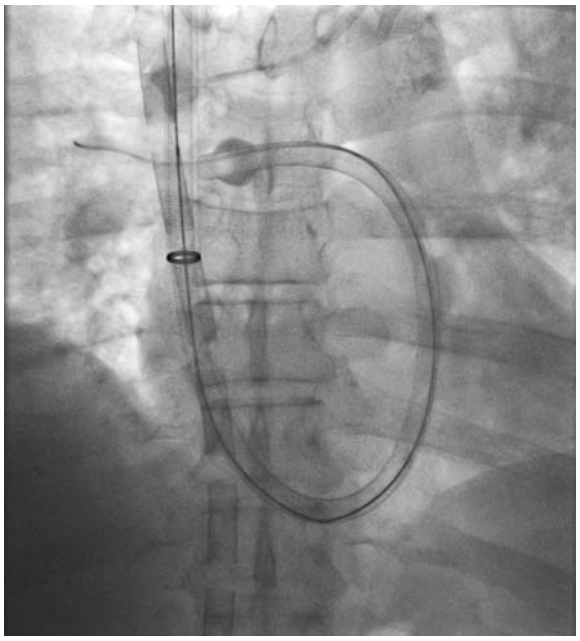

Figure 21.5 AngioVac in the right main pulmonary artery via a right jugular approach.

using standard techniques. Once wire access to the lobar branches is obtained, the infusion catheter is advanced over the wire and the ultrasound core is inserted that delivers high-frequency (2.2 GHz), low energy (0.5 W per transducer) ultrasound waves.[20]

The ULTIMA trial is the only randomized trial of treatment with USAT to date.[21] This trial randomized 59 patients with intermediate-risk PE (RV/LV ratio ≥1.0) to heparin therapy or heparin plus USAT with the EkoSonic Endovascular System to deliver either unilateral or bilateral tPA at 1 mg/hour for 15 hours. The primary endpoint was the RV/LV ratio change from baseline to 24 hours after treatment. In the USAT group, placement of the catheter was successful in 100% of patients (87% received bilateral catheter placement). There was a significant difference in the RV/LV ratio for the USAT group (1.28 ± 0.19 to 0.99 ± 0.17 [$P < 0.001$] vs. heparin 1.2 ± 0.14 to 1.17 ± 0.2 [$P = 0.31$]). The mean RV/LV ratio difference was 0.3 ± 0.2 for USAT compared to 0.03 ± 0.16 for the heparin group ($P < 0.001$). However, these differences were not significant at 90 days. Most RV hemodynamics were significantly improved at 24 hours with USAT compared to heparin treatment. Mean hospital stay was not different. At 90 days, mortality was

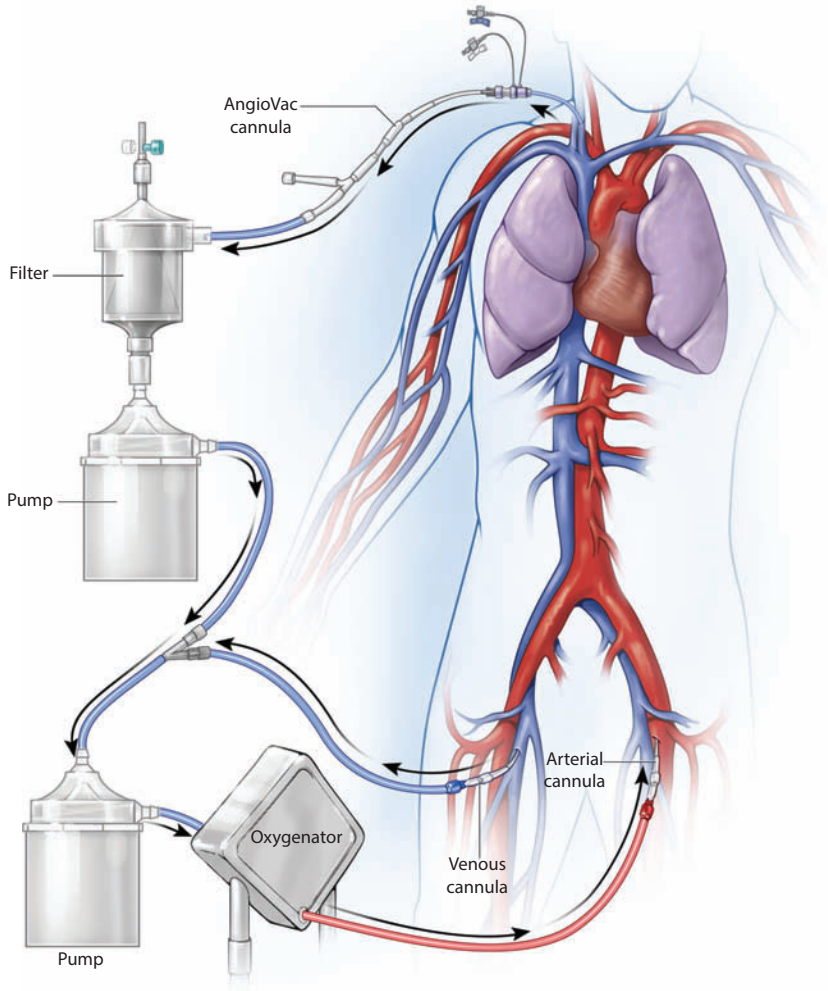

Figure 21.6 AngioVac set up with extracorporeal membrane oxygenation.

Figure 21.7 Bilateral placement of EKOS catheters into the right and left pulmonary arteries.

not different and no major bleeding occurred. Four minor bleeding events occurred with USAT and one occurred in the heparin-only group.[21]

In several larger retrospective series (Table 21.2), USAT had similar effects on RV/LV ratio improvement. Engelberger et al. reported on 52 patients with intermediate- and high-risk PE. The RV/LV ratio decreased from 1.42 ± 0.21 to 1.06 ± 0.23 after 24 hours ($P < 0.001$). The greatest benefit appeared to be in high-risk patients. Complications included a 3.8% mortality rate, major bleeding in 3.8% of patients, and minor bleeding in 21% of patients.[22] Additionally, Kennedy et al. reported on 60 patients treated with USAT. All patients had successful catheter placement. Complete thrombolysis occurred in 57% of cases and PA pressures decreased significantly. Their series reported a 5% mortality rate.[23] McCabe et al. reported on 53 patients with similar improvements in RV/LV ratio, PA pressures, and a 9.4% bleeding rate.[24] Other series that have been reviewed have shown that USAT can be performed with bleeding rates of 2%–20% and low mortality.[20] Finally, in the only report to compare USAT to standard catheter-directed thrombolytic treatment, Lin et al. reported more complete thrombolysis, shorter infusion times (17.4 ± 5.2 vs. 25.3 ± 7.3 (h), $P = 0.03$), lower tPA doses (17.2 ± 2.4 vs. 25.4 ± 5.3 (mg), $P = 0.03$), and lower bleeding complications (0% vs. 21%, $P = 0.02$) with USAT compared to standard catheter-directed thrombolysis.[25]

Overall, these studies demonstrate the feasibility of USAT for the treatment of intermediate-risk PE. However, there are no randomized trials of USAT compared to standard catheter-directed thrombolytic infusion. Additionally, the endpoints for these studies are usually markers of cardiac and pulmonary hemodynamics. They represent surrogate endpoints without clear correlation to long-term outcomes. There has been no long-term mortality or morbidity benefit demonstrated with many of these techniques to date, which would support changing current guidelines for treatment in submassive PE. Further efforts are necessary to delineate the patients who will receive the most benefit from these techniques.

21.7 SURGICAL PULMONARY EMBOLECTOMY

Surgical pulmonary embolectomy (SPE) remains a viable and effective means of treating massive acute PE, as well as submassive acute PE with adverse prognosis, when thrombolysis is contraindicated. These are often best performed in centers with experience in these procedures, as candidates for this procedure are inherently unstable. Historically, SPE was reserved for massive PE with hemodynamic instability and when standard treatment had failed, or thrombolytics were contraindicated, as a last-line effort. It is not unexpected that those selected for treatment have been reported to have a poor prognosis. However, outcomes of SPE have greatly improved, and may offer benefits over medical therapy or attempts at repeated thrombolytic treatment.[26] In a literature review by Stein et al. of SPE from 1985 to 2005, average mortality declined from 32% to 20% over this period, although there were slightly fewer patients with pre-operative cardiac arrest in the latter group (33% vs. 27%). Not surprisingly, those undergoing surgery with pre-operative cardiac arrest had a 59% mortality rate compared to 20% for those who did not have a pre-operative arrest.[27]

More recently, Leacche et al. reported on 47 patients undergoing emergent SPE at Brigham and Women's Hospital, which has taken an aggressive approach to SPE.[28] Nearly all (95%) had RV dysfunction by echo, and indications included a contraindication to anticoagulation (47%), failed medical treatment (10%), and RV hemodynamic dysfunction (32%). Their technique includes mandatory transesophageal echocardiogram (TEE) to assess RV function and the presence of patent foramen ovale (PFO) and atrial septal defects (ASDs; these would change operative cannulation and myocardial protective strategies). After median sternotomy, patients are placed in cardiopulmonary bypass with normothermia and without cardioplegic arrest (unless PFO or ASD is present). A longitudinal or transverse PA arteriotomy is made and clots are removed under direct visualization with forceps and suction. Fogarty catheters are avoided to prevent distal vessel injury. An inferior vena cava filter is placed at the end of the case. Thirty-day mortality occurred in three patients (6%), of which two had a pre-operative cardiac arrest, and

Table 21.2 Prior studies of ultrasound assisted thrombolysis

Study	Year	Type	Number of patients	Patient population	Treatment	Outcomes	Major bleeding	Minor bleeding	Mortality
Kucher et al.[21]	2014	RCT	59	Intermediate-risk acute PE (RV/LV ≥1)	USAT (EkoS with10 mg tPA) and heparin versus heparin therapy alone	Change in RV/LV ratio: USAT 1.28 ± 0.19 to 0.99 ± 0.17 ($P < 0.001$); heparin 1.2 ± 0.14 to 1.17 ± 0.2 ($P = 0.31$)	0%	10% USAT, 3% heparin	1 death (1.7%) in heparin group at 90 days
Engelberger et al.[22]	2013	Retrospective review	52	Intermediate-risk (38) and high-risk (14) PE	USAT with tPA 10 mg per side for 15 hours	ND	3.80%	21%	3.8% at 90 days
Kennedy et al.[23]	2013	Retrospective review	60	Intermediate-risk (48) and high-risk (12) PE	USAT with tPA 35.1 ± 11.1 mg over 19.6 ± 6 hours	Complete lysis 57%, near complete lysis 41%, partial lysis 1.7%	1.70%	1.70%	7% at 90 days
McCabe et al.[24]	2015	Retrospective review	53	Intermediate-risk PE	USAT with tPA 24 ± 9 mg over 15.9 ± 3 hours	Reduced RV/LV ratio (1.12 ± 0.3 to 0.98 ± 0.2 [$P = 0.03$]) and significantly reduced PA systolic (51.4 ± 15.5 to 40 ± 10.8) and mean pressure (33.8 ± 10.5 to 27 ± 7.6 [$P < 0.01$])	9.4% overall bleeding		0% at discharge
Lin et al.[25]	2009	Retrospective review	25	Massive PE treated with USAT (11) vs. CDT (14)	Urokinase and tPA	USAT complete lysis 100% vs. CDT 50%. Miller score not different	0% for USAT vs. 21% ($n = 3$) for CDT		USAT 9.1% (1) vs. CDT 14.2% (2)

Note: RCT: randomized controlled trial; RV: right ventricle; LV: left ventricle; USAT: ultrasound-assisted thrombolysis; tPA: tissue plasminogen activator; PE: pulmonary embolism; ND: no data; PA: pulmonary artery; CDT: catheter-directed thrombolysis.

two of the three that died needed a RV assist device. Other complications included two patients requiring reoperation and two deep sternal wound infections. Median follow-up was 27 months, and the 1- and 3-year survival rates were 86% (95% CI: 70%–90%) and 83% (95% CI: 66%–92%), respectively. Most late deaths were due to cancer.[28] Based on these encouraging results, the authors have extended SPE for submassive PE patients with massive proximal clot burden and RV dysfunction. This aggressive approach has been replicated by others, with comparable outcomes.[29]

Overall, SPE remains a viable and potentially critical component of comprehensive care in acute PE. Patients should be referred before the onset of cardiogenic shock and have large central thrombus burdens (within the main trunk or right or left main PA). Surgery can be performed with normothermia and with or without bypass, aortic cross clamping, and cardioplegic arrest. Only visualized thrombus is removed and inferior vena cava filters are placed at case completion due to the risk of recurrent PE.[4,28] As outcomes with this re-emerging technique have improved, this remains a viable treatment options for those with massive and submassive PE, making a coordinated multidisciplinary approach to PE critical to tailoring treatment based on patient factors and institutional expertise.

Guidelines 3.5.0 of the American Venous Forum on the endovascular and surgical management of acute pulmonary embolism

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.5.1	We recommend therapeutic anticoagulation with subcutaneous LMWH, subcutaneous fondaparinux, or IV UFH for initial anticoagulation of acute PE.	1	A
3.5.2	Anticoagulation alone is recommended for low-risk PE or submassive PE with mild RV dysfunction.	1	B
3.5.3	Thrombolysis is recommended for massive PE if bleeding risk is acceptable.	1	B
3.5.4	Thrombolysis is suggested for submassive acute PE that is felt to have poor prognosis if bleeding risk is acceptable.	2	C
3.5.5	Catheter thrombectomy, thrombus fragmentation, or surgical embolectomy is recommended for patients with massive PE and contraindications for thrombolysis depending on local expertise.	1	C
3.5.6	Catheter thrombectomy, thrombus fragmentation, or surgical embolectomy is recommended for patients with massive PE and who remain unstable after thrombolysis if local expertise is available.	1	C
3.5.7	Catheter thrombectomy or surgical embolectomy is suggested for patients with submassive PE judged to have poor prognosis.	2	C
3.5.8	We recommend against catheter thrombectomy or surgical embolectomy for low-risk PE or submassive PE with minor RV dysfunction.	2	C

Source: Adapted from Jaff MR et al. *Circulation* 2011;123(16):1788–830.
Note: LMWH: low-molecular-weight heparin; IV: intravenous; UFH: unfractionated heparin; PE: pulmonary embolism; RV: right ventricle.

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● = Key primary paper
★ = Major review article

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22

Treatment algorithms for acute venous thromboembolism: Current guidelines

ANDREA T. OBI AND THOMAS W. WAKEFIELD

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22.1 INTRODUCTION

Venous thromboembolism (VTE) is a source of major morbidity and mortality. The incidence of VTE exceeds 1/1000, and there are an estimated 200,000 first lifetime cases diagnosed in the United States every year. The 7-day mortality of patients suffering from VTE is 25%, with up to a third of patients with pulmonary embolism (PE) dying suddenly. VTE is the fourth leading cause of death in Western society and the third leading cause of cardiovascular death behind myocardial infarction and stroke. Of those individuals surviving their event, approximately 30% will develop recurrent VTE within 10 years, and greater than 20%–30% will develop the post-phlebitic syndrome over this time period (even higher with iliofemoral deep vein thrombosis [DVT]). VTE is more frequent in the elderly, and the incidence of thrombosis increases significantly beyond 60 years of age. As our population ages, the VTE incidence will increase.

Clearly, VTE is a problem that is encountered by a wide variety of patients and providers. This chapter is intended to guide those involved in patient care by providing direct access to easy-to-use algorithms for commonly encountered clinical scenarios. Standardized treatment management plans are defined through the algorithms. These may decrease practice variation and be useful with inexperienced staff, and may provide some control over risk management. As a word of caution, algorithms sometimes fail to account for diagnostic uncertainty, unique clinical circumstances, and patient preference/anxiety, and may perform differently amongst different populations or when used by different care providers. Clinician and patient acceptance are required in order to use algorithms, and every effort has been made to ensure that the algorithms listed utilize tests that are widely available and have been validated for the disease process being evaluated. The following algorithms and supporting text are obtained from Chapters 18, 19, 20, 21, 23, 24, 25, 26, 27, and 28; key references are as listed at the conclusion of each chapter.

22.2 PROPHYLAXIS

VTE can be prevented, particularly in the hospitalized patient (see Chapter 23). Appropriately delivered prophylaxis is cost-effective, reduces VTE by 50%–70%, and carries an acceptably low risk of hemorrhage. Without DVT prophylaxis, VTE rates are high for both surgical and non-surgical hospitalized patients. Although the incidence of VTE varies by both patient and procedure, VTE may occur in up to 20% of surgical patients. As more than 28 million surgical procedures are performed each year in the United States, and more than 35 million non-surgical patients are admitted each year to U.S. hospitals, this is a major health problem. With the evolution toward expanded outpatient delivery of medical and surgical services, only the sickest patients are hospitalized. The thrombotic event rate may be as high as 16% in these non-surgical patients without prophylaxis. PE accounts for nearly 10% of all hospital deaths and is one of the most preventable causes of mortality. PE may occur without prior warning, and sudden death may be the initial symptom of disease. According to

recent guidelines, low-dose unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux, are safe and effective prophylaxis strategies for hospitalized patients with other medical conditions. For bleeding patients or those who are at low risk of VTE development, mechanical compression (intermittent pneumatic compression) is indicated (Figure 22.1). For patients at moderate and high risk of VTE, Figure 22.1 provides recommendations for thromboprophylaxis regimens.

22.3 DIAGNOSIS

The diagnostic workup of a suspected VTE depends on the degree of clinical suspicion of DVT or PE (see Chapter 18). Several validated scoring systems exist to aid the clinician in determining the pre-test probability of such a diagnosis, most notably the Well's score for DVT (Table 22.1) and PE (Table 22.2) and the Antwerp score for PE (Table 22.3). A score resulting in a low or moderate probability of DVT or PE should guide the clinician to D-dimer as the initial "rule-out" test (Figures 22.2 and 22.3). A high probability should trigger a more aggressive workup with duplex ultrasound (Figure 22.2) if DVT is suspected, or PE protocol computed tomography (CT) (Figure 22.3) if PE is suspected. Importantly, modern-day diagnosis should include only noninvasive testing with a low risk profile. There is little to no role for invasive tests, such as lower extremity venography or pulmonary angiography, except under unusual circumstances or when invasive interventions are planned.

22.4 TREATMENT OF DVT

The mainstay of therapy for the diagnosis of acute VTE is prompt anticoagulation (see Chapter 19). Generally,

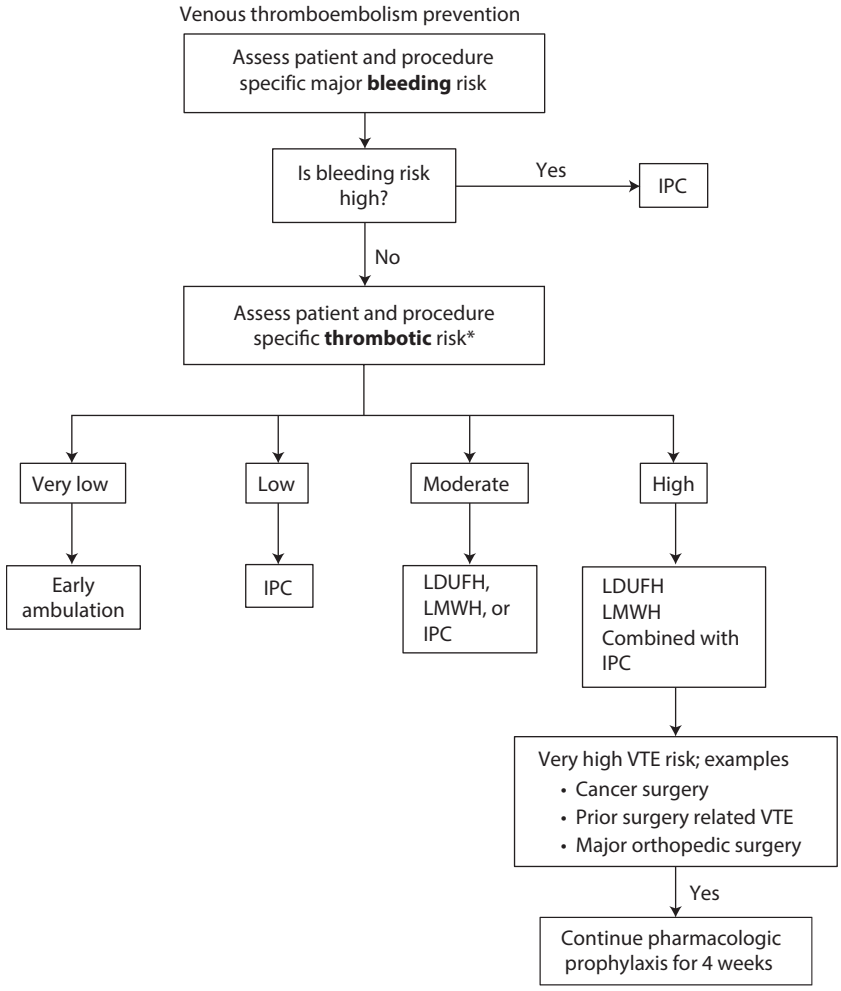

Figure 22.1 Practical approach to thromboprophylaxis in the hospitalized patient. IPC: intermittent pneumatic compression; LDUFH: low-dose unfractionated heparin; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VTE: venous thromboembolism.

Table 22.1 Wells et al. clinical model for predicting the pre-test clinical probability of deep vein thrombosis[a]

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	−2

Source: Reprinted with permission from Wells PS et al. *N Engl J Med* 2003;349(13):1227–35.

[a] A score of 2 or higher indicates that the probability of deep vein thrombosis is likely; a score of less than 2 indicates that the probability of deep vein thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

Table 22.2 Wells et al. short clinical score list for pulmonary embolism

Criteria	Score
Clinical signs and symptoms of deep vein thrombosis: minimal swelling of the leg and pain on palpation of the deep leg veins	3.0
Pulmonary embolism more likely than an alternative diagnosis	3.0
Heart beat frequency >100 beats per minute	1.5
Recent immobilization or surgery within <4 weeks	1.5
Documented history of deep vein thrombosis and/or pulmonary embolism	1.5
Hemoptysis	1.0
Recent history of malignancy within <6 months (treatment or palliative treatment)	1.0
Clinical score for pulmonary embolism	
Low	≤2
Moderate	2.0–6.0
High	≥6

Source: From Michiels JJ et al. *Semin Vasc Med* 2002;2(4):345–51. With permission.

Table 22.3 Antwerp clinical score list for pulmonary embolism

Criteria	Score
Age >60 years	0.5
One or more risk factors for venous thromboembolism	1.5
One or more eliciting circumstances for venous thromboembolism	1.0
Respiratory signs and symptoms	
Dyspnea	1.5
Pleuritic pain	1.0
Non-retrosternal, non-pleural chest pain	1.0
P_aO_2 <92% (<3 L O_2)	1.0
Hemoptysis	1.0
Pleural rub	1.0
Cardiac and other signs and symptoms	
Heart beat frequency >100 beats per minute	1.0
Temperature 37.5°C and 38.6°C	1.0
Chest X-ray: atelectasis and/or unilateral diaphragm elevation suspicious for pulmonary embolism and no other explanation	1.0
Leg symptoms suspicious of deep vein thrombosis (swelling, pain, etc.) (clinical score of Wells et al. for deep vein thrombosis)	3.0
Signs of circulatory and/or respiratory insufficiency: 1, 2, or 3	6.0
1. Hypotension (systolic <90 mmHg and heart frequency >100 beats per minute)	
2. Respiratory insufficiency (artificial breathing >3 L O_2)	
3. Recent decompensation cordis right	
Clinical score for pulmonary embolism	
Low	≤3
Moderate	3.0–6.0
High	≥6

Source: From Michiels JJ et al. *Semin Vasc Med* 2002;2(4):345–51. With permission.

LMWH is preferred, although unfractionated heparin remains an excellent option in patients with renal insufficiency or if there is concern regarding bleeding risk, given its shorter half-life and more reliable reversal with protamine. Figure 22.4 outlines decision making regarding a variety of commonly encountered comorbid conditions presenting with DVT, such as pregnancy and cancer.

22.5 TREATMENT OF ILIOFEMORAL DVT

Management following a diagnosis of iliofemoral DVT (Figure 22.5) is anticoagulation therapy along with leg elevation and compression; ambulation is encouraged (see Chapter 19).

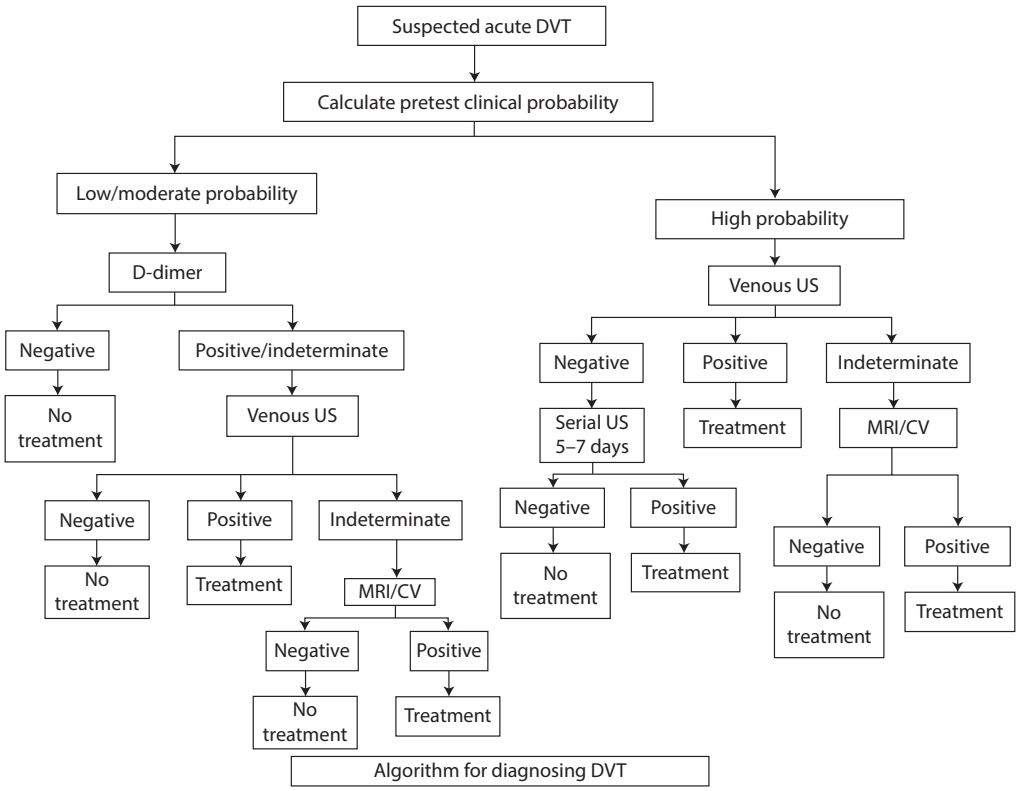

Figure 22.2 Algorithm for diagnostic workup of suspected DVT. Note that the pre-test probability can be calculated utilizing the Well's score (described in the text). In patients for whom the D-dimer is likely to be elevated from other sources (recent surgery or trauma), it is reasonable to proceed directly to ultrasound, even with low suspicion. CV: contrast venography; DVT: deep vein thrombosis; MRI: magnetic resonance imaging; US: ultrasound.

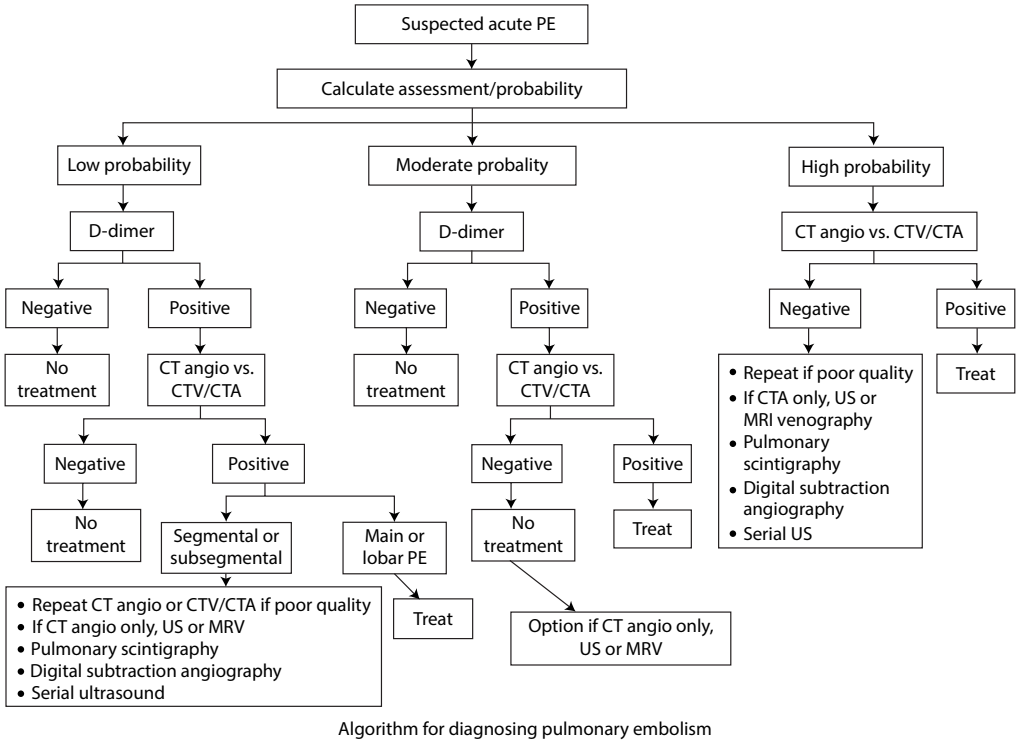

Figure 22.3 Algorithm for diagnostic workup of suspected PE. CT: computed tomography; CTA: CT angiogram; CTV: CT venogram; MRI: magnetic resonance imaging; MRV: magnetic resonance venography; PE: pulmonary embolism; US: ultrasound. (Adapted with permission from Stein PD et al.; PIOPED II Investigators. *Radiology* 2007;242(1):15–21.[3])

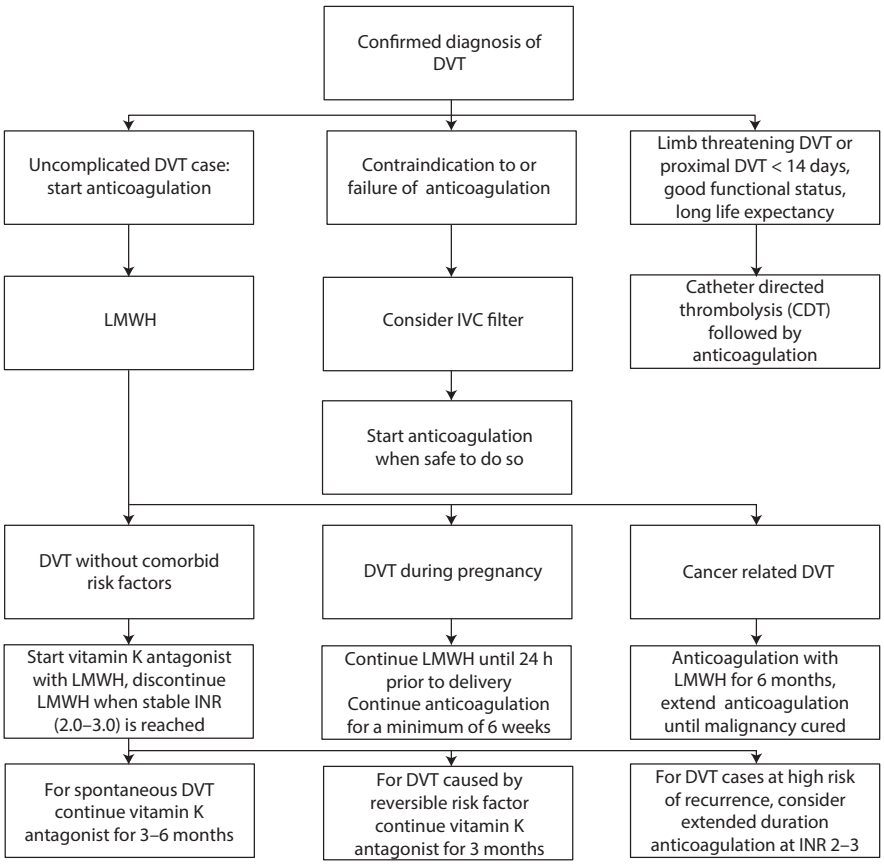

Figure 22.4 Management of acute DVT as recommended by ACCP guidelines, does not include management of new oral anticoagulants. Of note, some of the new oral anticoagulants do not require a LMWH bridge, and are not monitored with INRs. CDT: catheter-directed thrombolysis; DVT: deep vein thrombosis; INR: international normalized ratio; IVC: inferior vena cava; LMWH: low-molecular-weight heparin.

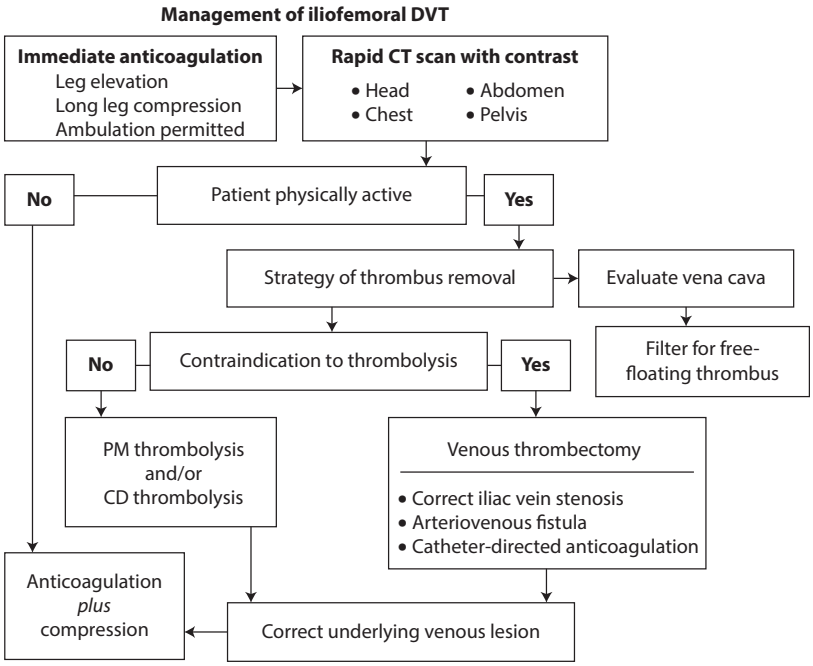

Figure 22.5 Management of acute occlusive proximal DVT. Aggressive therapies should only be considered in individuals who are mobile, with long life expectancy. CD: catheter-directed; CT: computed tomography; DVT: deep vein thrombosis; PM: pharmacomechanical.

Patients with iliofemoral DVT who are ambulatory should be considered for thrombus removal (Figure 22.5). Imaging of the inferior vena cava (IVC) by CT or duplex imaging is important in order to assess the degree of IVC involvement. An IVC filter is recommended for patients with free-floating, non-occlusive IVC thrombus. After the extent of the disease has been established, contraindications to either surgical or catheter-based techniques should be reviewed. The majority of patients with iliofemoral DVT should be offered thrombus removal via a catheter-directed approach. Patients with occlusive thrombus of the femoral vein involving the profunda femoris have obliterated venous drainage from the lower extremity and often exhibit severe post-thrombotic morbidity. Although most patients receiving anticoagulation may be treated as outpatients, those with common femoral vein and/or iliac vein occlusion should be hospitalized and undergo a procedure in order to restore patency and provide unobstructed venous drainage into the IVC from their lower extremity.

22.6 TREATMENT OF PE

For acute PE, treatment needs to address: (1) prevention of new thrombus; (2) clearance of obstructing thrombus from the pulmonary artery (either rapidly or over time); and (3) reduction of right ventricular (RV) dysfunction when present (see Chapter 21). Thrombolysis is recommended for patients with low bleeding risk who have massive PE. In addition, patients with sub-massive PE with new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis may be considered for thrombolysis (Figure 22.6). Catheter-based therapy or surgical embolectomy, however, may be recommended in a number of circumstances. These include a contraindication to systemic thrombolysis (recent intracranial hemorrhage or surgery, recent spinal surgery, recent head trauma, intracranial neoplasm, uncontrolled hypertension, or active or recent bleeding), a significant risk of bleeding, or insufficient time to allow infusion and the effect of systemic thrombolytics in the acute setting. Finally, some

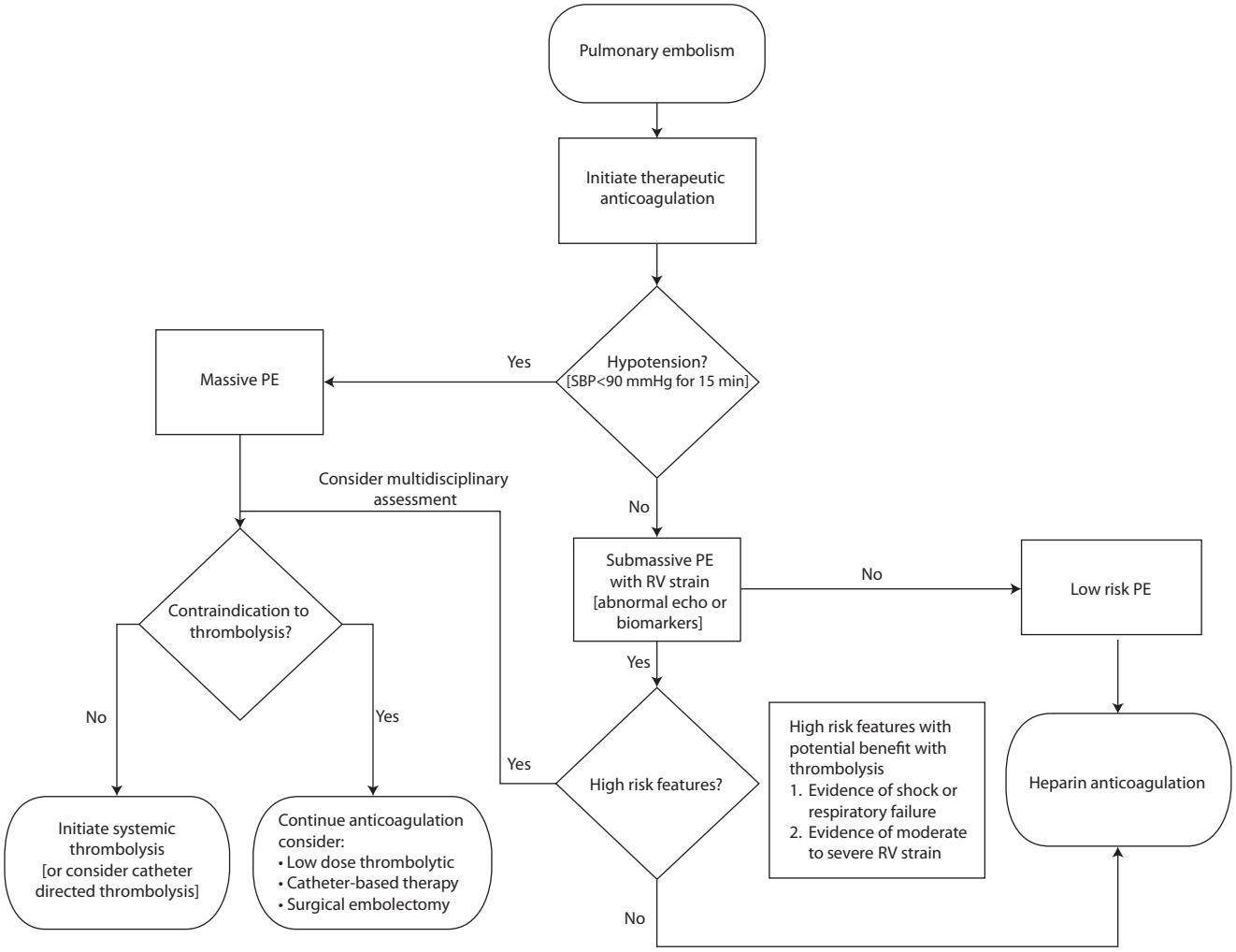

Figure 22.6 Management of PE, depending on the presentation massive, submassive, or low risk.

patients will fail to improve despite thrombolytic treatment and require more aggressive therapy, such as catheter-based therapy or surgical embolectomy.

22.7 SUPERFICIAL VENOUS THROMBOPHLEBITIS

When seeking a diagnosis of DVT, occasionally a patient with the diagnosis of isolated superficial venous thrombophlebitis (SVT) will be encountered (see Chapter 27) (Figure 22.7). If concurrent DVT exists, the patient should be managed as outlined in Figures 22.4 and 22.5. Patients with milder forms of isolated SVT are best managed with non-steroidal anti-inflammatory drugs, compression and warm compresses, and ambulation. Those with moderate disease should be managed more aggressively with either prophylactic LMWH or fondaparinux (Figure 22.7). This is defined as SVT located 3 cm distal to the saphenofemoral junction (SFJ) and at least 5 cm in length. If the patient develops DVT or PE, therapeutic anticoagulation should be considered (Figures 22.4 and 22.5). For patients that cannot tolerate anticoagulation, great saphenous vein (GSV) disconnection and ligation are appropriate at the SFJ when thrombus burden is moderate. Surgical treatment with GSV ablation and phlebectomies of the involved branch varicosities should be considered for patients with symptomatic SVT and evidence of venous insufficiency (confirmed by duplex ultrasound). However, this is most effectively performed after the phlebitis has resolved, usually within 3 to 6 months of the acute event.

22.8 SEVERE BLEEDING FROM NOVEL ANTICOAGULANTS

With the approval of the direct thrombin inhibitor dabigatran and the direct Xa inhibitors apixaban, rivaroxaban and edoxaban for the treatment of acute DVT, the clinician should be prepared to encounter the occasional patient with a severe bleeding complication or who needs urgent reversal of coagulopathy for emergent surgical intervention or in the setting of major trauma (see Chapter 19).

The approach for the reversal of the new oral anticoagulants should be determined by the patient's clinical status (Figure 22.8). In the case of non-urgent reversal, treatment involves withholding the anticoagulant for 2–4 days. In the setting of major bleeding, withholding therapy is not sufficient, and additional measures should be taken. Proposed reversal measures include the administration of activated charcoal (dabigatran only) in the event of overdose, the administration of fresh-frozen plasma, and treatment with activated or inactive four-factor prothrombin complex concentrates (PCC), recombinant factor VIIa (rFVIIa), and hemodialysis (for dabigatran only). Taking into consideration the risk of continued bleeding versus the risk of thrombosis, a sensible approach would be to initiate four-factor PCC in the case of major bleeding from rivaroxaban or apixaban, with the initiation of a pro-hemostatic agent (aPCC [activated PCC] or rFVIIa) if coagulopathy fails to reverse. In the case of major bleeding from dabigatran, the data regarding the use of rFVIIa and aPCC are largely equivocal, likely because activated factor VIIa is a component of aPCC. A reversal agent has now been Food and Drug Administration approved for dabigatran (idarucizumab), although this is not widely available at all hospitals, and a number of agents are under development for the anti-Xa inhibitors.

22.9 ASPIRIN FOR EXTENDED VTE TREATMENT

Traditionally, there has been little role for the use of aspirin (ASA) in the treatment or prevention of VTE (see Chapter

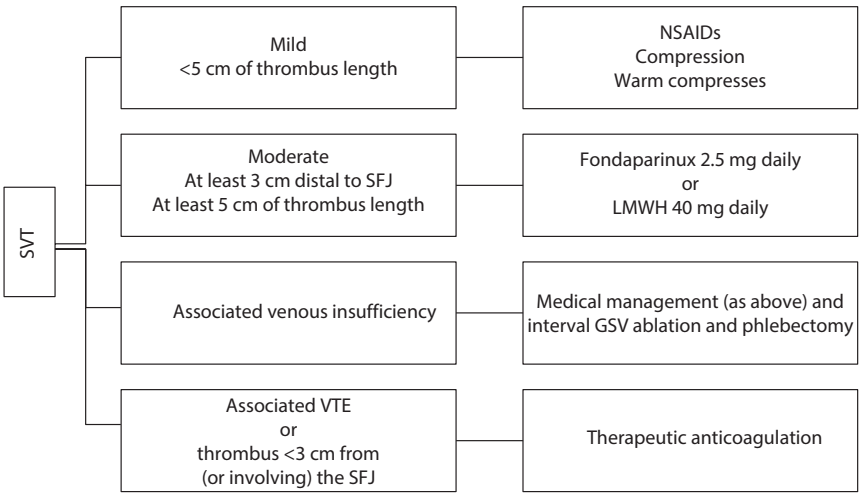

Figure 22.7 Management of SVT. GSV: great saphenous vein; LMWH: low-molecular-weight heparin; NSAID: non-steroidal anti-inflammatory drug; SFJ: saphenofemoral junction; SVT: superficial venous thrombosis; VTE: venous thromboembolism. (Reproduced with permission from Karthanos C et al. Superficial vein thrombosis in patients with varicose veins: Role of thrombophilia factors, age and body mass. *Eur J Vasc Endovasc Surg* 2012;43:355–58.[4])

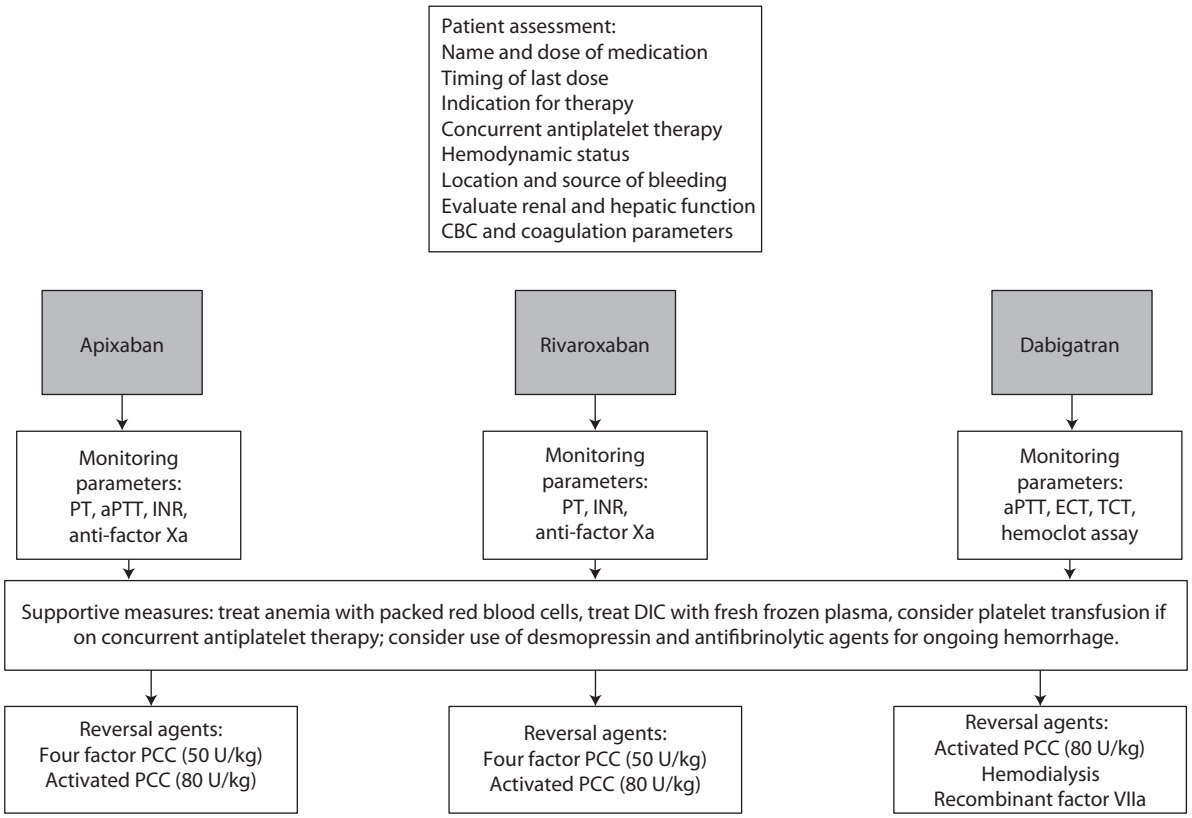

Figure 22.8 Reversal of novel anticoagulants. aPTT: activated partial thromboplastin time; CBC: complete blood count test; DIC: disseminated intravascular coagulation; ECT: ecarin clotting time; INR: international normalized ratio; PCC: prothrombin complex concentrate; PT: prothrombin time; TCT: thrombin clotting time. (Reproduced with permission from Knepper J et al. A systematic update on the state of novel anticoagulants and a primer on reversal and bridging. *J Vasc Surg: Venous Lymphat Disord* 2013;1(4):418–26.[6])

19). However, the new INSPIRE trial has reintroduced ASA as a potentially useful adjunct in patients who are at moderate risk of recurrent VTE (Figure 22.9). For patients who have a provoked DVT, 3 months of anticoagulation is adequate. For those patients with unprovoked (idiopathic) VTE and a high risk of recurrence, who would normally need long-term or life-long anticoagulation, he or she should remain on either oral vitamin K antagonist or one of the novel oral anticoagulants, and not undergo ASA therapy. For patients with unprovoked VTE and moderate risk of recurrence, the use of one baby ASA per day, rather than nothing, would be indicated. For patients with an unprovoked VTE and low risk of recurrence, no further therapy is indicated. The primary challenge faced by clinicians is differentiating the low-risk patient from the moderate-risk patient. Factors that have been found to be important include male gender, elevated D-dimer, significant residual scar tissue, presence of significant thrombophilia or, importantly, multiple thrombophilia states, age >65 years, and presence of post-thrombotic syndrome (least important in our opinion). Therefore, if the patient has one or more risk factor for recurrence from this group, then one baby ASA a day is indicated.

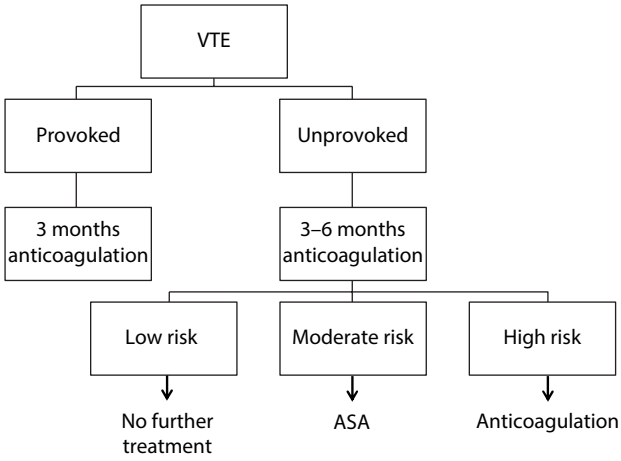

Figure 22.9 Incorporation of ASA into the VTE extended treatment paradigm. ASA: aspirin; VTE: venous thromboembolism. (Reproduced with permission from Wakefield TW, Obi A, and Henke PK. An aspirin a day to keep the clots away: Can aspirin prevent recurrent thrombosis in extended treatment for VTE? *Circulation* 2014; 130(3):1031–33.[5])

22.10 CENTRAL VENOUS THROMBOSIS

Acute central venous thrombosis associated with pacemaker wires, central venous catheters, or dialysis catheters is usually asymptomatic (see Chapter 25). Diagnosis starts with a clinical examination, followed by a duplex ultrasound examination. Once the diagnosis of upper extremity DVT is confirmed, the mainstay of treatment is anticoagulation. There is a limited role for thrombectomy or thrombolysis, except in the setting of phlegmasia, in which the viability of the limb is jeopardized (Figure 22.10). Thrombus prevention is best obtained by placing the catheter tip at the junction of the right atrium with the superior vena cava. Improving catheter and wire profiles by making them less thrombogenic may also play a role in decreasing central venous thrombosis.

22.11 EFFORT THROMBOSIS

For patients with thrombosis associated with thoracic outlet obstruction, the best initial procedure (more accurately, having the best chance of success) is defined by the duration of symptoms, whereas the subsequent method of thoracic outlet decompression is defined by the status of the residual vein and symptoms (see Chapter 24). Decompression should immediately follow thrombolysis (Figure 22.11). Note that in a patient with chronic thrombus who cannot be recanalized and is not significantly symptomatic, first rib resection is favored. Discussion is individualized, and the advantages and disadvantages of both resection and leaving the rib alone are unusually closely discussed.

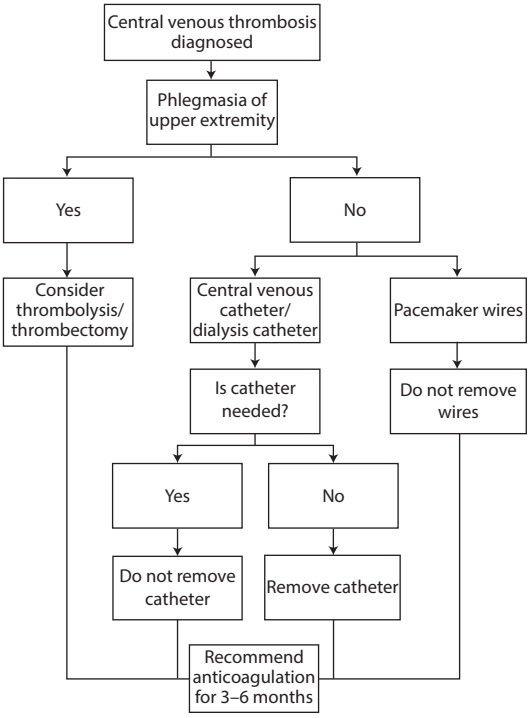

Figure 22.10 Management of upper extremity deep vein thrombosis. Note that if the patient is unable to undergo anticoagulation, consider superior vena cava filter placement.

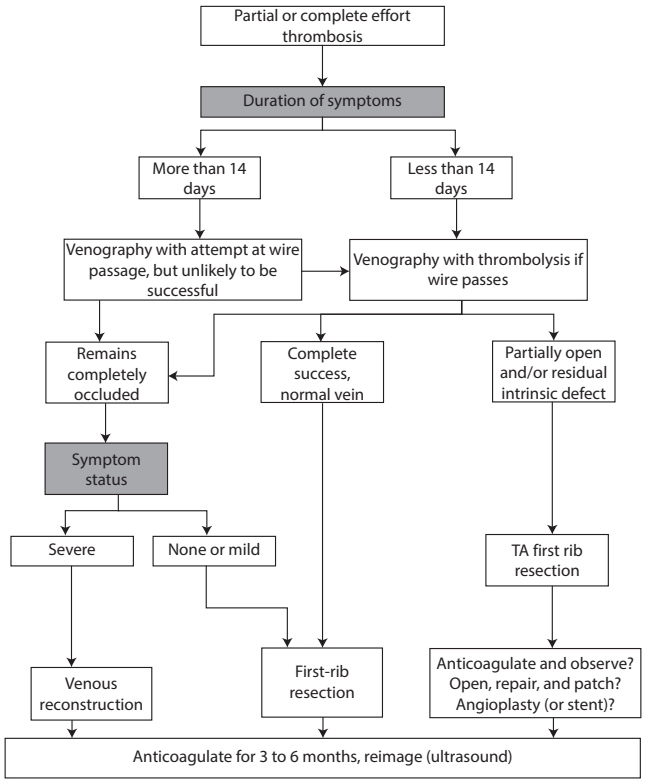

Figure 22.11 Management of venous effort thrombosis, also known as Page–Schroetter disease.

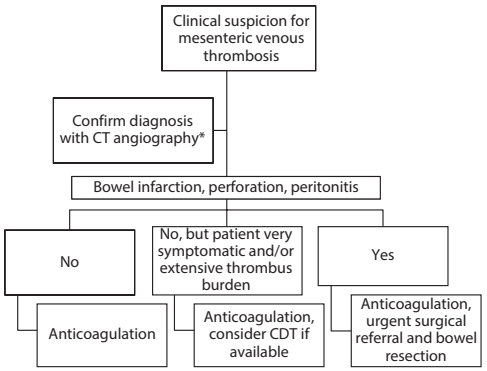

Figure 22.12 Management of mesenteric venous thrombosis. Magnetic resonance angiography or ultrasound may serve as alternative imaging modalities if CT angiography is not possible. Note that catheter-directed therapies may be available at select institutions. Only rarely will thrombus be amenable to operative thrombectomy. CDT: catheter-directed thrombolysis; CT: computed tomography.

22.12 MESENTERIC VENOUS THROMBOSIS

Clinical observations suggest that immediate anticoagulation with heparin for mesenteric venous thrombosis

(MVT) early in the course of the disease improves survival, reduces thrombus propagation, and reduces recurrence (see Chapter 28) (Figure 22.12). Gastrointestinal bleeding is not necessarily a contraindication to anticoagulant therapy, whereas the risk of bleeding must be weighed against the risk of bowel infarction. Observational studies suggest that chronic anticoagulant use reduces the incidence of recurrent venous thrombosis by a third. In general, anticoagulation should be continued until provoking factors have been eliminated, if possible. In those patients whose MVT can be attributed to temporary risk factors, 3 months of anticoagulants is likely to be reasonable. Expert opinion would suggest that antibiotic therapy should be provided for patients with signs or symptoms of bowel compromise.

Endovascular therapies may be pursued for selected patients with acute MVT that is diagnosed early in the course of the disease before bowel infarction or peritonitis develop (Figure 22.12). Mechanical thrombectomy may be combined with lytic therapy. The need for surgical intervention in patients with MVT is not universal and may be necessary for only a minority. Acute mesenteric ischemia accompanied by peritonitis or bowel infarction is an accepted indication for surgical intervention and resection of involved bowel. The key to successful surgery is to resect sufficient bowel to ensure proper anastomotic healing and halt thrombus propagation, while preserving as much viable intestine as possible. Often, the surgical procedure is staged with a repeat ("second-look") laparotomy performed 1 day later. Post-operatively, anticoagulants should be initiated as soon as hemostasis is ensured. Thrombectomy remains a potential treatment option for selected patients, yet must be pursued quickly, as thrombus maturation (beyond 3 days) reduces its success.

22.13 IVC FILTERS

Vena caval filters provide protection against PE without the significant morbidity and mortality associated with a surgical procedure (see Chapter 26). They should be used in patients who are at risk of PE, but for whom anticoagulation is contraindicated, has failed, or is associated with complications (Figure 22.13). IVC filter placement carries low morbidity and mortality. Multiple studies have demonstrated the efficacy of filters in preventing PE, although these filters may cause progression/recurrence of DVT, along with IVC thrombosis. The rates of these complications are device specific. There has been a recent increase in the placement of retrievable filters for the prophylaxis of PE in patients with time-limited contraindications to anticoagulation. The benefits with this practice are theoretical and need to be objectively studied. The type of filter used should be tailored to

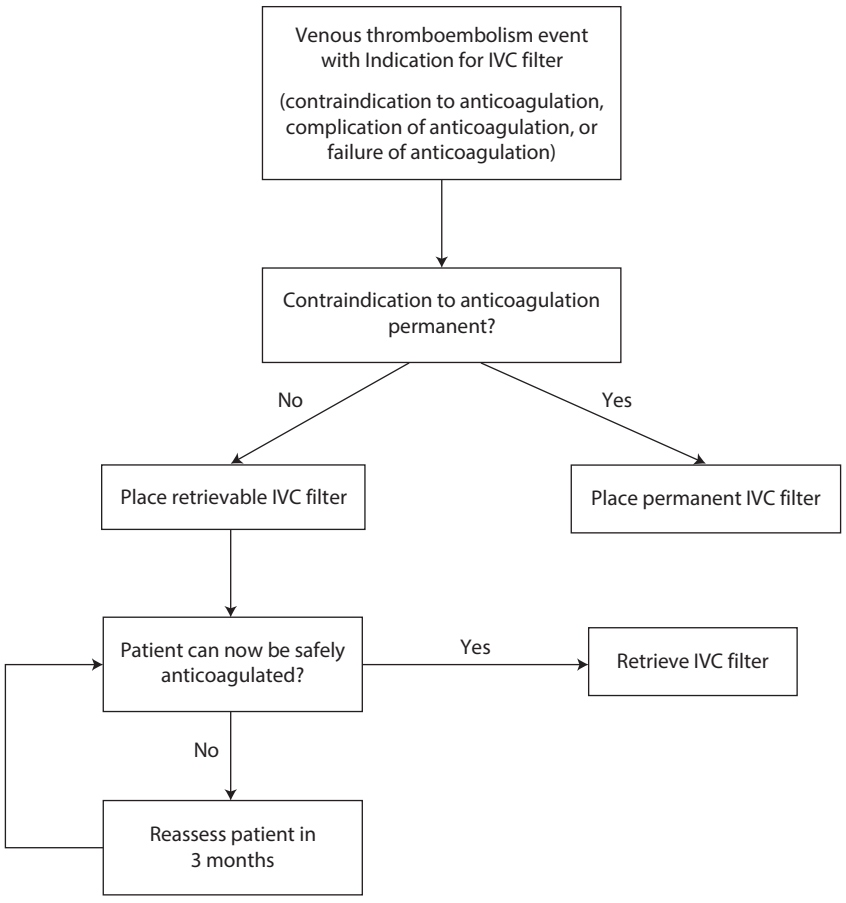

Figure 22.13 Algorithm for decision making regarding the type of IVC filter. IVC: inferior vena cava.

Guidelines 3.6.0 of the American Venous Forum on treatment algorithms for acute deep venous thrombosis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality
3.6.1	Low-molecular-weight heparin (LMWH) is now preferred over standard unfractionated heparin (UFH) for the initial treatment of deep vein thrombosis (DVT).	1	A
3.6.2	The criteria for the discontinuation of oral anticoagulation include thrombosis risk, residual thrombus burden, and coagulation system activation (as suggested by D-dimer measurements).	1	A
3.6.3	Heparin-induced thrombocytopenia remains a problem with all heparin preparations, but is more frequent with UFH than LMWH. Alternative agents include hirudin, argatroban and fondaparinux.	1	C
3.6.4	The use of strong compression and early ambulation after DVT treatment can significantly reduce the long-term morbidity of pain and swelling resulting from the DVT.	1	A

each patient. Major efforts toward identifying those patients who are at highest risk of significant PE and so should receive filters should occur. Efforts must also continue to be directed toward improving methods of thromboprophylaxis, since no filter can influence the development or course of the underlying thrombosis.

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23

Current recommendations for the prevention of deep venous thrombosis

ROBERT D. MCBANE AND JOHN A. HEIT

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23.1 INTRODUCTION

Venous thromboembolism (VTE) represents a major cause of morbidity and mortality in the United States.[1–3] The incidence of VTE exceeds 1 per 1000, with approximately 201,000 first life-time cases diagnosed annually in this country. The 7-day mortality of patients suffering a thrombotic event is 25% and up to 35% of patients with pulmonary embolism (PE) die suddenly. VTE is, therefore, the fourth leading cause of death in Western society, and the third leading cause of cardiovascular death behind myocardial infarction and stroke. Furthermore, VTE is both a recurrent disease and a morbid disease. Of those individuals surviving the thrombotic event, 30% will develop recurrent VTE within 10 years and 20%–30% will develop the post-phlebitic syndrome over this time period. VTE is typically a disease of elderly people, with the incidence of thrombotic events increasing significantly beyond 60 years of age (Figure 23.1). As our population ages, the expected number of VTEs annually will increase. Despite advances in radiographic detection, expanded knowledge of risk factors, and anticoagulant development, the incidence of VTE has been relatively constant over the past several decades (Figure 23.2).

Yet, VTE can be a preventable disease particularly in the hospitalized patient.[4] Appropriately delivered prophylaxis is cost-effective, reduces VTE rates by 50%–70%, and carries an acceptably low risk of hemorrhage. Without prophylaxis, VTE rates are high for both surgical and non-surgical hospitalized patients. Although the incidence of VTE varies by both patient- and surgery-specific variables, without prophylaxis, venous thrombotic events may occur in up to 20% of surgical patients. Underscoring the magnitude of this disease is the fact than more than 28 million surgical procedures are performed each year in the United States.[5] Furthermore, more than 35 million non-surgical patients are admitted each year to U.S. hospitals. PE accounts for nearly 10% of all hospital deaths and is one of the most common preventable causes of mortality. Often, these pulmonary emboli occur without prior warning, and sudden death may be the initial symptom of disease. With the evolution toward expanded outpatient delivery of medical and surgical services, only the sickest and frailest of patients are hospitalized. The thrombotic event rate may be as high as 16% in these non-surgical patients if no prophylaxis is given.[4,5]

In summary, VTE is the most common preventable cause of death and suffering. Providing appropriate VTE prophylaxis is the highest-ranked safety practice for patients who are at risk. The aims of this chapter are therefore to outline the risk factors for VTE, review the efficacy and safety of various prophylactic regimens, and provide recommendations regarding the most suitable prophylaxis based on the estimated risk.

23.2 RISK FACTORS FOR VTE

A number of patient characteristics have been identified as independent risk factors for VTE (Box 23.1).[3] Increasing age is a major risk factor for VTE. There is a direct relationship with increasing age and the annual incidence of VTE for both men and women (Figure 23.1). Beyond the fifth decade of life, the incidence increases precipitously. Below this age, VTE is relatively uncommon. PE accounts for an increasing proportion of VTE with increasing age for both genders, which has important implications for the future of the United States

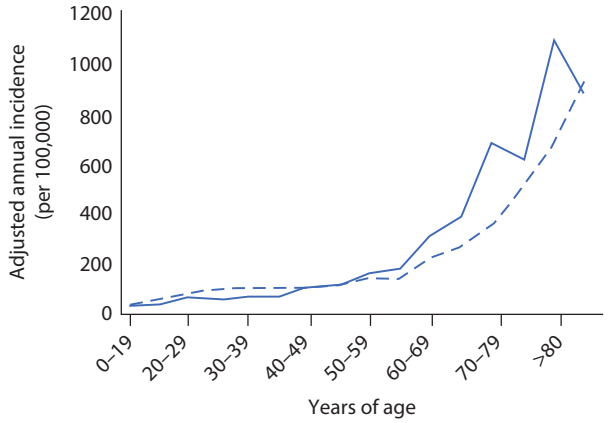

Figure 23.1 Annual incidence of venous thromboembolism adjusted for age and gender in Olmsted County MN, 1966–1990 (males: solid line; females: dashed line). (Adapted from Silverstein MD et al. *Arch Intern Med* 1998;158(6):585–93.)

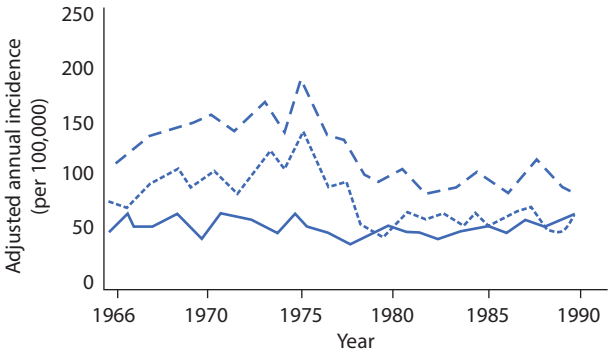

Figure 23.2 Annual incidence of venous thromboembolism (VTE) over time in Olmsted County MN, 1966–1990 (all VTE: dashed line; pulmonary embolism ± deep vein thrombosis: dotted line; deep vein thrombosis alone: solid line). (Adapted from Silverstein MD et al. *Arch Intern Med* 1998;158(6):585–93.)

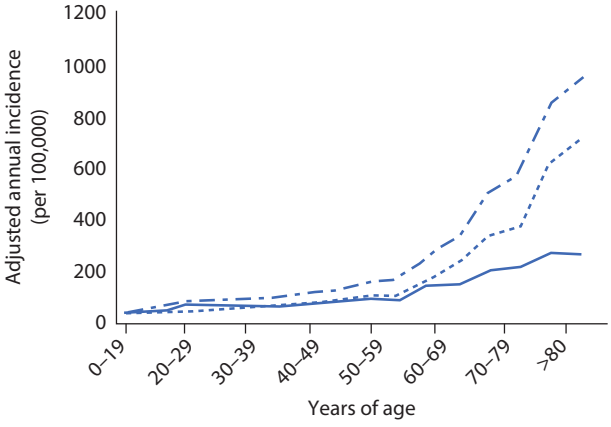

Figure 23.3 Annual incidence of venous thromboembolism (VTE) adjusted for age in Olmsted County MN, 1966–1990 (all VTE: short/long dashed line; pulmonary embolism ± deep vein thrombosis: dotted line; deep vein thrombosis alone: solid line). (Adapted from Silverstein MD et al. *Arch Intern Med* 1998;158(6):585–93.)

BOX 23.1: Clinical risk factors for venous thromboembolism

General risk factors

Increasing age
Trauma
Surgery
Leg immobilization or paralysis
Central venous catheter or transvenous pacemaker
Hospital or nursing home confinement
Prior superficial vein thrombosis
Varicose veins

Acquired or secondary thrombophilia

Malignancy
Myeloproliferative disorders
Heparin-induced thrombocytopenia
Nephrotic syndrome
Disseminated intravascular coagulation
Hormonal contraceptives and replacement
Lupus anticoagulant and antiphospholipid antibody syndrome
Pregnancy and postpartum state
Chemotherapy
Inflammatory bowel disease
Thromboangiitis obliterans (Buerger's disease)
Behçet's syndrome

Primary or familial thrombophilia

Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Activated protein C resistance and factor V Leiden mutation
Prothrombin G20210A mutation
Elevated factor VIII
Hyperhomocysteinemia

(Figure 23.3). As the average U.S. population age increases, VTE mortality is likely to increase because of the significantly worse survival after PE. VTE incidence also varies by ethnicity. The incidence is highest among Caucasians and African–Americans. Hispanic–Americans carry an intermediate risk, with the lowest-risk racial group being Asian–Americans. The incidence among Native Americans is unknown. Other important and independent risk factors for VTE include surgery, trauma, hospital or nursing home confinement, malignancy (with and without concurrent chemotherapy), prior central vein catheterization or transvenous pacemaker (for upper extremity deep venous thrombosis [DVT]), prior superficial thrombosis, varicose veins, and neurological disease with extremity paresis (Box 23.1). Severe liver disease may be protective, possibly because of reduced synthesis of pro-coagulant factors. The absolute incidence of VTE is strongly and directly related to body mass index, and inversely related to physical activity.[6]

23.2.1 Hospitalization

The VTE risk profile of contemporary hospitalized patients has gradually increased, with most carrying more than one recognized risk factor. Furthermore, most cases of VTE occur in the peri-hospitalization period. In the DVT Free registry, a large, multicenter, prospective ultrasound study of 5451 patients, nearly 60% of VTEs were diagnosed within the peri-hospitalization period, and 38% occurred within 3 months of surgery.[7] The combined identification of patients who are at risk for VTE and the implementation of prophylactic therapy for VTE prevention represent prudent and proven means of reducing VTE for most hospitalized patients. Most hospitalized patients have more than one risk factor for venous thrombosis, and these risk factors are likely additive in nature. Although surgery and trauma represent the most potent acquired risk factors for VTE, the majority of thrombotic events occur in non-surgical patients. For the non-surgical hospitalized patient, major risk factors include New York Heart Association class III–IV heart failure, chronic obstructive pulmonary disease exacerbation, sepsis, advanced age, history of prior VTE, cancer, stroke with limb paresis, and bed rest.[2,3]

23.2.2 Surgical factors

Surgery represents a major risk for VTE, and varies by the type, duration, and indication for surgery, type of anesthesia, associated risk factors, and patient-specific variables, including age.[2,3,8–10] In general, patients requiring anesthesia have a 22-fold increased risk of VTE. From a surgical perspective, the highest risk is associated with orthopedic procedures, especially hip or knee replacement, hip fracture surgery, and trauma surgery, including patients with spinal cord injury. Patient-specific variables include cancer, congenital thrombophilia, prior history of VTE, obesity, and increasing age (>60 years).[9] In general, spinal/epidural anesthesia carries a lower risk than general anesthesia.[11] Outpatient surgery has a lower associated risk than inpatient surgery.[9] Patients undergoing vascular surgery may have less risk than other surgeries, possibly because of the intra-operative use of heparin therapy. Aortic surgery carries a higher risk than distal bypass surgery.[12,13]

The Caprini risk model stratifies surgical patient risk of VTE into four categories: very low (0–1 points), low (2 points), moderate (3–4 points), and high (≥5 points).[14–16] This tool assesses nearly 40 factors, and can be a helpful framework for determining which patients would benefit from VTE prophylaxis and which strategy will be most appropriate for each given patient. An easy-to-use online risk calculator is available for rapid risk assessment, as is a smartphone app.[17]

23.2.3 Hormonal manipulation

It is estimated that more than 100 million women worldwide use hormonal contraception. VTE is one of the most disconcerting complications of oral contraception (OCP).[18] For women in their teens, twenties, and thirties, the anticipated incidence of VTE ranges from 1 in 100,000 to 1 in 10,000 with increasing age. The risk of VTE in OCP users is between three- and six-fold greater than in non-users. This risk is exponentially higher in carriers of factor V Leiden or prothrombin G20210A gene mutations.[18–20] The greatest risk occurs in the first 6–12 months of therapy, particularly in first-time users.[18] The risk remains until the third month following discontinuation. The risk of VTE is directly proportional to the estrogen dose. The risk is also related to the progesterone type. A number of studies have shown that third-generation OCPs confer greater VTE risk than second-generation agents. Progesterone-only OCPs are associated with a lower risk than combination preparations.[21] Both the transdermal patch and vaginal ring route of delivery carry increased thrombotic risk. The limited data suggest that transdermal progesterone implants may carry less risk relative to oral preparations; however, the risk is increased relative to non-users. The levonorgestrel-releasing intrauterine device (IUD) is the only hormone-based contraception which has not been shown to confer increased VTE risk.[22]

Both postmenopausal hormone-replacement therapy (HRT) and selective estrogen receptor modulator use (tamoxifen and raloxifene) are associated with an increased risk of VTE. Data from three large randomized controlled studies enrolling more than 30,000 women have shown that oral HRT is associated with a two- to three-fold increased rate of VTE compared with non-users.[23–25] The risk appears to be highest in the first 6–12 months of therapy.

Conjugated equine estrogen used alone carries a lower risk of VTE than the combined use of estrogen and medroxyprogesterone acetate (adjusted hazard ratio: 0.59, 95% CI: 0.37–0.94 for the comparison).[23] Inherited thrombophilic states increase the risk of VTE exponentially in HRT users compared with non-users. For example, combining HRT with factor V Leiden increases the risk by 15-fold.[26]

23.2.4 Pregnancy

Pregnancy increases the incidence of VTE in women by three- to six-fold.[27,28] The rate of venous thrombosis following pregnancy is 172–199 per 100,000 deliveries.[29,30] The risk is higher following cesarean section than vaginal delivery. This increased risk of VTE may relate to high estrogen levels, venous stasis, pelvic trauma with delivery, and acquired hypercoagulability. This acquired thrombophilia has been attributed to elevated pro-coagulant variables (fibrinogen, von Willebrand factor, and factor VIII), as well as decreased natural anticoagulants such as protein S. Risk factors associated with thrombosis during pregnancy include increasing age (>35 years), immobility, obesity, and prior VTE. African–Americans appear to have a greater risk than Caucasians.[30] DVT in the left leg occurs three-times more frequently than the right leg, previously explained by left iliac compression by the right iliac artery. Furthermore, DVT is approximately three-times more frequent than PE in these women.[29] The puerperium, which encompasses the

6-week window following delivery, is a higher risk period than the pregnancy itself.

23.2.5 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a generally accepted risk factor for VTE. However, the mechanism underlying this association remains unclear. The reported incidence of VTE in this disease is difficult to ascertain, in that most studies are limited by referral bias. In one population-based study in Manitoba, Canada, the incidence was 0.5%, which was significantly greater than expected compared with the general population for both DVT (incidence rate ratio [IRR]: 3.5, 95% CI: 2.9–4.3) and PE (IRR: 3.3, 95% CI: 2.5–4.3).[31] Although the risk of VTE may be associated with disease activity, half of patients experiencing thrombosis have inactive disease at the time of the event.[32–34] Surgery, especially colorectal surgery, carries an increased risk of VTE in patients with IBD. In the Canadian Colorectal DVT Prophylaxis Trial, the rate of VTE following surgery for IBD was 9% in patients receiving unfractionated heparin (UFH) compared with 3% for those receiving low-molecular-weight heparin (LMWH).[35]

23.2.6 Nephrotic syndrome

Thrombosis is a major source of morbidity in patients with nephrotic syndrome.[36,37] Renal vein thrombosis is the most common site of venous thrombosis, occurring in approximately 35% of patients with nephrotic syndrome. Thrombosis in other venous segments can be seen in 20% of cases. Urinary excretion of antithrombin, platelet hyperreactivity, and elevated plasma viscosity are listed as pathophysiological mechanisms of thrombosis in these patients. In general, renal vein thrombosis occurs as a consequence of underlying disease or cancer of the kidney.[38]

23.2.7 Malignancy

The incidence of VTE in patients with an active malignancy may be as high as 11%. Individuals with cancers involving the pancreas, gastrointestinal tract, ovary, prostate, and lung are particularly prone to developing VTE. All malignancies, including hematologic malignancies, carry this association to some degree. The one exception to this rule is that of non-melanoma skin cancer. Patients with active malignancy undergoing surgery are at increased risk, with an incidence of thrombosis approaching 40%. Compared with non-cancer-related surgery, the risk of post-operative DVT is increased twofold, with a threefold increased risk of fatal PE. Thrombosis may be the first manifestation of malignancy in some individuals. Trousseau's syndrome, or migratory thrombophlebitis, is a prime example. In the now classic study by Prandoni et al.,[39] the prevalence of malignancy among 153 patients with idiopathic VTE was 3.3% at clinical presentation of the thrombus. During the 2-year follow-up period, a new cancer diagnosis was confirmed in 7.6% of patients with idiopathic VTE compared with 1.9% of patients with secondary thrombosis. If recurrent VTE occurred during this time period, the incidence of new malignancy was 17.1%. Underlying cancer is particularly relevant for those patients presenting with organ vein thrombosis or bilateral lower extremity DVT.[40] Risk estimation for patients with cancer can be accomplished using an online calculator.[41] The Khorana score is a simple validated risk model for predicting rates of VTE in cancer outpatients receiving chemotherapy, using baseline clinical and laboratory variables.[42] This risk model incorporates five predictive variables for VTE including: site of cancer (2 points for very-high-risk site; 1 point for high-risk site); platelet count $\geq 350 \times 10^9$/L (1 point); hemoglobin <10 g/dL and/or use of erythropoiesis-stimulating agents (1 point); leukocyte count $>11 \times 10^9$/L (1 point); and body mass index ≥ 35 kg/m^2 (1 point). Based on their score, patients are then defined as low (0 points), intermediate (1 – 2 points), or high risk (≥3 points). Rates of VTE over the ensuing 2.5 months were 0.3%–0.8% in the low-risk group, 1.8%–2% in the intermediate-risk group, and 6.7%–7.1% in the high-risk group. Very-high-risk cancer sites include stomach and pancreas cancers. High-risk cancer sites include lung, lymphoma, gynecologic, bladder, and testicular cancers.

23.2.8 Travel

The association between prolonged travel and VTE is controversial. Documented associations have been shown primarily by retrospective studies assessing the history of recent travel in patients with a new VTE. The association appears to be related to duration of travel, with one study showing increased risk only when travel exceeded 10 hours.[43] In another study, only 56 of 135 million travelers flying to Paris had a confirmed PE for corresponding rates of 1:100 million passengers who traveled for fewer than 6 hours and 1:700,000 passengers who traveled for more than 6 hours.[44] Most individuals with VTE associated with prolonged travel have additional risk factors for thrombosis.[3,4] Ascribing causality to travel alone may therefore be incorrect.

23.3 VTE PROPHYLAXIS METHODS AND REGIMENS

In general, the provision, type, and duration of prophylaxis should reflect the individual patient's risk of VTE balanced against the risk of major bleeding associated with the exposure. VTE prophylaxis may be divided into two general strategies: primary (mechanical and pharmacological) and secondary or "surveillance" prophylaxis. Surveillance prophylaxis is defined as a strategy of serially screening for asymptomatic DVT, usually with duplex ultrasound. In this latter strategy, only patients discovered to have DVT are treated. Ultrasound screening for asymptomatic venous thrombosis, however, has limited sensitivity for this indication. Furthermore, this strategy does nothing to prevent venous thrombosis and is limited to the inpatient setting. In

this current medical era in which prompt hospital discharge is the standard, this strategy is ineffective at preventing VTE after discharge. In summary, surveillance strategies are neither effective nor cost-effective. Withholding primary prophylaxis in lieu of surveillance prophylaxis with duplex ultrasonography is therefore not prudent.

23.3.1 Mechanical prophylaxis

Non-pharmacological methods of VTE prophylaxis include elastic compressive stockings (ELS), intermittent pneumatic compression (IPC) devices, leg elevation, and early ambulation. Each of these methods promote venous emptying and thus reduce static venous blood pooling. Both ELS and IPC devices have been shown to reduce venous thrombotic events. One recent meta-analysis of 19 randomized trials, including 1681 patients undergoing general and orthopedic surgery, revealed a 12% absolute risk reduction for developing DVT (21% vs. 9%) favoring graduated compression stockings.[45] In this analysis, proximal DVT was reduced from 5% to 1% favoring the use of stockings. The incidence of PE was also reduced from 5% to 2%.

In a study of 798 intensive care unit (ICU) patients, the use of IPC was associated with a significantly lower VTE rate compared to those not using these devices.[46] In a meta-analysis of 70 trials including 16,164 hospitalized patients, the absolute risk reduction for DVT was 9.4% favoring IPC use (7.3% vs. 16.7%).[47] PE rates were also reduced (1.2% vs. 2.8%). There are limited data directly comparing types of IPC and the impact of VTE reduction. From the limited data available, calf–thigh compression and plantar compression appear to be similarly effective.[48]

The use of each of these interventions is primarily advocated for those situations where the risk of bleeding may be sufficiently high as to avoid the use of pharmacological agents (grade 2C).[9] They should also be employed in combination with pharmacological agents for those patients at very high risk of VTE (grade 2C).[9] Indeed, adding pharmacological prophylaxis to IPC may further reduce VTE rates by nearly 50% compared to IPC alone.[47]

23.3.2 Inferior vena cava filters

The routine placement of inferior vena cava (IVC) filters should be discouraged for the indication of venous thrombosis prophylaxis.[9,10,49,50] IVC filter placement should be reserved for patients with clear indications. These indications include acute VTE in the face of urgent/emergent surgery or other circumstances prohibiting anticoagulant delivery (class I; level of evidence B).[50] For this purpose, an "acute" DVT is defined as one occurring within 1 month of the urgent/emergent surgery. Other indications include verifiable anticoagulant failure. An IVC filter may be suitable prophylaxis for the multiple-trauma patient with bleeding risk precluding pharmacologic prophylaxis (grade 2C). Trauma patients may have extensive leg injuries that may preclude the use of IPC and ELS. A number of retrievable filters have been developed and approved by the Food and Drug Administration (FDA). The advent of these retrievable IVC filters has increased enthusiasm for pre-operative placement of these devices, which could then be removed post-operatively. Although attractive, the appropriate use of retrievable IVC filters for this indication has not been established. At this time, the indications for temporary, retrievable, or optional IVC filters are the same as those for permanent IVC filters (grade 2C).[49]

23.3.3 Pharmacological prophylaxis methods

Pharmacological prophylaxis can be broadly divided into several categories, including the use of heparinoids, vitamin K antagonists, and oral factor inhibitors. Antiplatelet agents such as aspirin, dipyridimole, or thienopyridines have either been ineffective or inferior to other agents for the prevention of venous thrombosis. Current guidelines recommend against their use for this indication.

23.3.3.1 UNFRACTIONATED HEPARIN

The heparins include UFH, LMWH, and the synthetic pentasaccharide fondaparinux. The anticoagulant properties of each of these agents are achieved through activation of the circulating endogenous inhibitor, antithrombin (formerly antithrombin III). UFH is a highly negatively charged proteoglycan extracted from either porcine or bovine intestinal mucosa. Each preparation contains a heterogeneous mixture of heparin molecules of variable lengths and molecular weights ranging from 5000 to 50,000 Da.[51] A specific pentasaccharide sequence within the UFH molecule binds antithrombin at the heparin binding site, thus activating the inhibitor. Only about 15%–25% of heparin molecules within any heparin preparation contain this specific pentasaccharide sequence, however, and therefore much of the heparin is ineffective for this purpose. This point will become important when discussing fondaparinux. UFH binds both antithrombin and thrombin, forming a ternary structure that enhances the affinity of antithrombin for thrombin by 1000-fold. Once formed, the thrombin–antithrombin complex is essentially irreversible. Heparin dissociates from the complex and is then free to participate in another round of antithrombin activation. Antithrombin also effectively inhibits the coagulant activities of factors IXa, Xa, and XIa. Non-specific binding to a variety of cells and plasma proteins neutralizes the anticoagulant activity of heparin. For these reasons, the volume of distribution and efficacy varies among individuals. Despite this, subcutaneous low-dose UFH prophylaxis is safe and effective for moderate-risk general surgical patients. For high- and very-high-risk patients, low-dose UFH is effective, but provides inadequate risk reduction. In these higher-risk patients, the post-operative increase in "acute-phase reactant" plasma proteins causes an increase in heparin non-specific binding and a reduction in the heparin anticoagulant effect. Realization of this problem led to the development of the

adjusted-dose UFH regimen, whereby the post-operative dose of heparin is increased to maintain the activated partial thromboplastin time in the upper normal range. Although this regimen has proven very effective in high-risk patients, it has not been adopted widely because of the inconvenience of monitoring and repeated dose adjustment. Low-dose heparin is associated with an increased incidence of post-operative wound hematoma. In addition, there is a small but definite risk of heparin-induced thrombocytopenia and thrombosis (HITT), a potentially devastating thrombotic complication.[52] Consequently, the platelet count should be monitored at least every other day and the heparin stopped if the platelet count decreases by 30%–50% of the baseline count.

23.3.3.2 LOW-MOLECULAR-WEIGHT HEPARIN

LMWH is derived by either enzymatic or chemical depolymerization of standard heparin to achieve a preparation with more uniform molecular weight. Thus, the average molecular weight of LMWH is between 4000 and 6000 Da.[51] The pharmacologic advantage of LMWH is that the net electrical charge is more neutral, thus substantially reducing non-specific protein or cellular binding. Absorption after subcutaneous injection is virtually complete. Consequently, the anticoagulant response after a LMWH subcutaneous injection is predictable and reproducible, such that laboratory monitoring and dose adjustment are rarely necessary. LMWHs provide very effective prophylaxis for high- and very-high-risk surgical patients. In North America, the initial LMWH dose usually is given 12–24 hours after surgery, whereas in Europe, a dose is given 10–12 hours before surgery. There does not appear to be a significant advantage of one approach over the other according to randomized trial data. In the current absence of randomized controlled trial data, one LMWH cannot be recommended over another. At similar antithrombotic doses, LMWH causes less bleeding than UFH. However, among patients receiving total hip and knee replacement, LMWH causes more bleeding than adjusted-dose warfarin. Although the incidence of heparin induced thrombocytopenia (HIT) is less frequent with LMWH than with UFH, there is substantial cross-reactivity, and HITT patients cannot be switched safely to LMWH. Currently, the LMWH cost per dose is approximately 10-fold greater than UFH.

23.3.3.3 FONDAPARINUX

Fondaparinux is a synthetic pentasaccharide with sequence specificity for the antithrombin heparin binding site.[53] It is given subcutaneously on a semi-weight-adjusted scale. Once given, absorption is rapid, complete, and predictable, with 94% of the drug protein bound to antithrombin. The half-life of the drug is quite long at between 17 and 22 hours. It is renally excreted and therefore may not be suitable for patients with renal insufficiency. Because of its very small molecular weight and neutral electrical charge, protamine is ineffective at neutralizing this drug. In trials of hip and knee replacement surgery, fondaparinux compared very favorably with other LMWHs in the reduction of thrombotic events and bleeding complications. Fondaparinux appears to be superior to other pharmacological agents in hip fracture surgery. The daily cost of fondaparinux is similar to other LMWHs. Although it does not appear to cause heparin-induced thrombocytopenia (HIT), it remains unclear whether this would be an acceptable alternative to heparinoids in the setting of HIT with or without thrombosis.

23.3.3.4 WARFARIN

Warfarin is an oral anticoagulant that acts by inhibiting the post-translational vitamin K-dependent carboxylation of glutamic acid residues of hepatically synthesized clotting factors and anticoagulant proteins.[54] These include factors II, VII, IX, and X, and the anticoagulant proteins C and S. Carboxylation enables protein incorporation of calcium, which is necessary for proper folding and activation. In the absence of calcium, these proteins cannot become activated and functionality is lost. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K-dependent clotting factor by approximately 30%–50%. A decrease in concentration of clotting factors is sequential and is related to the half-lives of the individual factors. The overall anticoagulant effect is generally seen between 24 and 48 hours after drug administration. However, the peak anticoagulant effect may be delayed by 72–96 hours. Regular monitoring of warfarin therapy is performed to improve both the safety and efficacy of this drug. The prothrombin time international normalized ratio (INR) is a clot-based assay that directly correlates with the clotting factor activity. Therapeutic warfarin for most indications is associated with INR values between 2 and 3.

Warfarin has a narrow therapeutic range, with the risk of major hemorrhage increasing substantially when INR values exceed 5. For INR levels below 1.5, antithrombotic efficacy is lost. Warfarin therapy may be affected by factors such as other drugs and dietary vitamin K, such that dosage should be adjusted by periodic determinations of prothrombin time (PT)/INR. The initiation of warfarin treatment is problematic because of variations in dose response. Physiological and pharmacological factors, such as interacting drugs or illnesses that affect the pharmacokinetics or pharmacodynamics of warfarin, dietary or gastrointestinal factors that affect the availability of vitamin K, or physiological factors that affect the synthetic or metabolic fate of the vitamin K-dependent coagulation factors, can affect the warfarin therapy.[37] The bleeding rate (including fatal, major, and minor bleeding events) of warfarin therapy is 7.6–16.5 per 100 patient–years. Major or life-threatening bleeds occur at a rate of 1.3–2.7 per 100 patient–years.[38–40] Although major bleeding can occur at therapeutic levels, the risk of bleeding rises with increasing intensity of anticoagulation.

23.3.3.5 ASPIRIN

The use of aspirin for VTE prophylaxis has been studied extensively, with only modest benefits observed. Perhaps

the best trial was performed in orthopedic patients undergoing major joint surgery. The PEP trial randomized 17,444 patients undergoing hip fracture surgery or total hip arthroplasty to aspirin 162 mg daily or placebo continued for 35 days.[55] Drug allocation in this study could be added to "routine practice" antithrombotic prophylaxis at the discretion of the local investigator. A modest but significant VTE reduction of 0.9% was observed in the aspirin group (1.6%) compared to the placebo group (2.5%). There was no difference in bleeding requiring reoperation between groups. Interestingly, patients randomized to low-dose aspirin in this study had an increased rate of non-fatal myocardial infarction. In summary, aspirin may provide modest risk reduction following major joint surgery when added to other prophylaxis therapies (grade 1B).[10] In patients undergoing non-orthopedic surgery or requiring DVT prophylaxis during hospitalization, there is no confirmed role of low-dose aspirin as a prophylaxis agent.

23.3.3.6 DIRECT FACTOR INHIBITORS

There are currently four direct thrombin inhibitors available for clinical use. Three of these inhibitors—argatroban, bivalirudin, desirudin—are parenteral, and the fourth—dabigatran—is oral. There are also now three oral direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban), of which two are FDA approved for VTE prophylaxis (apixaban and rivaroxaban).

23.3.3.7 BIVALIRUDIN

Bivalirudin, a 20-amino acid synthetic polypeptide analog of hirudin, has a terminal half-life of 25 minutes after intravenous injection and only a fraction is excreted via the kidneys. It has been evaluated primarily in patients undergoing percutaneous coronary intervention for coronary artery disease, and this is its current FDA approval. In a phase 2, dose-escalating trial of 222 patients undergoing total hip and knee replacement surgery, Hirulog (1.0 mg/kg every 8 hours) provided very low rates of total DVT (17%) and proximal DVT (2%), with bleeding rates <5%.[56]

23.3.3.8 ARGATROBAN

Argatroban is a peptidomimetic arginine derivative that binds non-covalently to the active site of thrombin to form a reversible complex.[51,52] The plasma half-life of argatroban is 45 minutes, and the drug is metabolized in the liver in a process that generates several active intermediates. Although this drug is safely used in patients with renal insufficiently, it should be used very cautiously (if at all) in those with hepatic insufficiency. The FDA approval of this drug is for the indication of HIT.

23.3.3.9 DABIGATRAN

Dabigatran etexilate is a prodrug which, once metabolized to its active form dabigatran, directly inhibits thrombin. Upon oral ingestion, dabigatran bioavailability is limited, with a time to peak concentration of 2 hours.[57] Dabigatran has a half-life of 12–17 hours and is not metabolized by the cytochrome P450 system. Drug absorption is poor, at approximately 7%, and is dependent upon gastric pH. To facilitate drug absorption, dabigatran is formulated by coating the drug around tartaric acid spherules. The tartaric acid promotes local pH changes at the gastrointestinal mucosal level. This formulation may promote gastritis and associated gastrointestinal upset. Dabigatran capsules must be swallowed intact to avoid changes of drug absorption. The P-glycoprotein system, which serves to secrete orally absorbed medications back into the intestinal lumen, is the only known mechanism through which drug interactions may play a role. Induction of this system (e.g., rifampin) serves to reduce circulation levels of dabigatran, whereas inhibition (e.g., amiodarone, dronedarone, ketoconazole, and verapamil) may increase circulating blood levels by up to 50%.

Dabigatran has been compared to enoxaparin in four trials that evaluated VTE prophylaxis following major orthopedic surgery.[58–61] These included two trials following total knee replacement—RE-MODEL ($n = 2076$) and RE-MOBILZE ($n = 2615$)—and two trials following total hip replacement—RE-NOVATE ($n = 3494$) and RE-NOVATE II ($n = 2055$). Three trials found dabigatran (150 mg or 220 mg once daily) to have efficacy rates which were non-inferior to enoxaparin (30 mg twice daily or 40 mg daily) for preventing VTE, with similar rates of major bleeding.[58–60] In the RE-MOBILIZE trial of total knee replacement, VTE rates were higher in both dabigatran arms, with similar bleeding rates. Dabigatran is FDA approved for VTE treatment, but not for the prophylaxis indication.

23.3.3.10 RIVAROXABAN

Rivaroxaban (Xarelto) is an oral direct factor Xa inhibitor which impairs coagulation by inhibiting the conversion of prothrombin to thrombin.[62] Upon oral ingestion, rivaroxaban is 80% bioavailable, with a time to peak concentration of 2–4 hours. Its elimination half-life is between 7 and 11 hours. A significant portion of rivaroxaban is metabolized through the liver's CYP450 system, primarily through CYP3A4 and CYP2J2. Potential drug interactions include medications which inhibit or promote the CYP3A4 or P-glycoprotein pathways. Rivaroxaban is contraindicated in patients with moderate to severe hepatic impairment (Child–Pugh B and C) or in patients with any degree of hepatic disease with coagulopathy. A total of 66% is also excreted via the kidney and, as a result, cautious use is warranted in patients with creatinine clearances of 30–50 mL/minute, and it should not be used in patients with creatinine clearances of less than 30 mL/minute. This drug is not dialyzable due to its high plasma protein binding (92%–95%). Use of rivaroxaban is not appropriate for all patient populations, and the risks and benefits need to be considered carefully.

The RECORD trials compared rivaroxaban 10 mg daily to enoxaparin (40 mg daily or 30 mg twice daily) for VTE prophylaxis in patients undergoing hip (RECORD 1 and 2) or knee (RECORD 3 and 4) replacement surgery.[63–66]

Treatment duration was 35 days for hip arthroplasty and 10–15 days for knee arthroplasty. RECORD 2 compared extended-duration (31–39 days) rivaroxaban with 10–14 days of enoxaparin for hip arthroplasty. RECORD 1, 3, and 4 found that rivaroxaban therapy reduced DVT, PE, or death without increased bleeding rates. RECORD 2 found that extended-duration rivaroxaban was more effective than 10–14 days of enoxaparin, without increased bleeding complications. The recommended dose of rivaroxaban for DVT prophylaxis following hip or knee arthroplasty is 10 mg daily, with the first dose given 6–10 hours after homeostasis is achieved, for a duration of 12 days for knee arthroplasty and 25 days for hip arthroplasty. In summary, rivaroxaban prophylaxis has a good efficacy and safety profile for VTE prophylaxis in orthopedic surgery arena.

23.3.3.11 APIXABAN

Apixaban (Eliquis) is an oral direct factor Xa inhibitor.[67] The drug is approximately 50% absorbed through the gastrointestinal tract, and absorption is not impacted by food. Apixaban is fully active 1–3 hours after administration. Drug metabolism is accomplished in the liver primarily through the CYP3A4 pathway; therefore, blood levels of apixaban are influenced by drugs that impact the activity of these enzymes. Drug levels are also influenced by inducers and inhibitors of the P-glycoprotein system. Elimination occurs through the kidneys (27%), biliary tract, and direct intestinal excretion.

Apixaban (2.5 mg twice daily) has been compared to enoxaparin in three trials of VTE prophylaxis following total joint replacement.[68–70] These trials include the ADVANCE-1 (vs. enoxaparin 30 mg twice daily) and ADVANCE-2 (vs. enoxaparin 40 mg once daily) trials of total knee replacement. The ADVANCE-3 trial compared apixaban to enoxaparin 40 mg once daily after total hip replacement. For these trials, apixaban had superior efficacy with similar safety compared to once-daily enoxaparin 40 mg. Compared to twice-daily enoxaparin (30 mg twice daily), apixaban was shown to have superior safety with similar efficacy. The recommended dose of apixaban for DVT prophylaxis following hip or knee arthroplasty is 2.5 mg twice daily. The first dose is given 12–24 hours post-operatively once homeostasis is achieved, for a duration of 10–14 days for knee arthroplasty and 35 days for hip arthroplasty. In summary, apixaban prophylaxis has a good efficacy and safety profile for VTE prophylaxis following orthopedic surgery.

23.4 PROPHYLAXIS RECOMMENDATIONS

23.4.1 General surgery

The risk of venous thrombosis following general surgery varies depending on the extent and nature of the procedure and the presence of the patient-specific risk factors previously discussed (Box 23.1).[9] Patients are thus stratified into very-low-, low-, moderate-, high-, and very-high-risk groups (Box 23.2). The Caprini VTE risk calculator is an easy-to-use electronic tool providing prompt risk assessment and general guidance for the assessment and management of these patients.[14–16] For very-low-risk patients (Caprini score 0), the risk of VTE is sufficiently low such that early ambulation alone is satisfactory (grade 1B). For low-risk patients (Caprini score 1–2), IPC pumping is recommended (grade 2C). For moderate-risk patients (Caprini score 3–4), VTE prophylaxis may include low-dose UFH, prophylactic-dose LMWH, or intermittent pneumatic compression pumping (grade 2B). For high-risk general surgery patients (Caprini score ≥5), either low-dose heparin or prophylactic-dose LMWH should be used. For patients undergoing cancer-related surgery, pharmacological prophylaxis should be extended for 4 weeks post-operatively (grade 1B). For surgery patients at high risk of major bleeding, mechanical prophylaxis with IPC pumping is recommended over pharmacologic prophylaxis.[10]

BOX 23.2: Risk stratification in surgical patients

Low risk
- Minor surgery, age <40 years, no additional risk

Moderate risk
- Major surgery, age >40 years, no additional risk

High risk
- Major surgery, age >40 years, with additional risk or myocardial infarction (MI)

Very high risk
- Major surgery, >40 years, with additional risk

Additional risk
- Prior venous thromboembolism
- Cancer
- Molecular hypercoagulable state
- Hip or knee arthroplasty
- Hip fracture surgery
- Major trauma
- Spinal cord injury

Colorectal surgery, particularly for the indication of malignancy resection, is associated with an increased risk of postoperative VTE. In the ENOXACAN study, 631 patients undergoing colorectal surgery for malignancy were randomized to receive either low-dose UFH (5000 U three times daily) or enoxaparin (40 mg daily).[71] All thrombotic events were confirmed by either venography or pulmonary scintigraphy. Patients were followed for 3 months. Venous thrombosis rates were equivalent for both groups (UFH 18.2% vs. LMWH 14.7%). Major hemorrhage was also equivalent (UFH 2.9% vs. LMWH 4.1%). Similar results were noted in the Canadian Colorectal DVT Prophylaxis Trial, in which 936 patients undergoing colorectal surgery for malignancy ($n = 475$) or IBD ($n = 584$) were enrolled.[72]

VTE rates (9.4% for both) and major hemorrhage rates (1.5% vs. 2.7%) were nearly identical for the low-dose UFH and enoxaparin groups. The FX140 investigators compared two LMWHs in patients undergoing colorectal surgery for cancer.[73] In this study, 1271 patients were randomized to either nadroparin (2850 IU/day) or enoxaparin (40 mg/day). Although VTE rates were similar between groups, bleeding complications were more common in enoxaparin-treated patients. In summary, the rates of VTE following colorectal surgery are high and mandate aggressive prophylaxis. UFH (5000 U three times daily) and LMWH (>3400 U/day) have similar efficacies and are both acceptable for this indication.

23.4.2 Vascular surgery

Patients undergoing vascular surgery may have less risk than those undergoing other surgeries. For patients in whom the risk of bleeding is high, IPC combined is a reasonable prophylaxis choice (grade 2C). The risk of VTE in patients undergoing vascular surgery is directly related to patient age, abdominal vascular procedures, limb salvage procedures, surgical duration, and operative venous trauma. Risk categorization is otherwise similar to that of general surgery (Box 23.2). For patients not receiving prophylaxis, the rates of DVT can be substantial. For example, in those patients assessed by venography, the rates vary from 18% to 42%.[74,75] In a cohort of 50 patients undergoing vascular surgery, the VTE rates were assessed by serial ultrasound performed pre-operatively and again prior to hospital discharge. Thrombotic event rates were highest following an abdominal procedure (41%) and lowest in those undergoing peripheral bypass procedures (18%).[75] Calf vein DVTs were four-times more common than more proximal thrombotic events. The VTE prophylaxis recommendations for general surgery can be extrapolated to the patient undergoing vascular surgery. By definition, most vascular patients carry considerable medical comorbidities, including extensive coronary disease, myocardial dysfunction, and obstructive pulmonary disease, which increase the risk of venous thrombosis and enhance the mortality rate of patients suffering from a PE. Vascular patients are furthermore unique in that they frequently receive systemic heparin anticoagulation during the course of their surgery. Consequently, pre-operative low-dose heparin or intra-operative IPC are unwarranted. Nevertheless, patients undergoing thoracic or thoraco-abdominal aortic reconstructions or other complicated vascular surgeries (i.e., ruptured aortic aneurysm repair, major vascular amputations, or major venous reconstructions) frequently require extended ICU support. The mobility of these patients is limited, and they often suffer multi-organ system failure. Although there are no vascular surgery-specific data, extrapolation from other ICU patients suggests that the VTE risk is high and warrants prophylaxis. Either low-dose heparin or LMWH are appropriate pharmacologic prophylaxis strategies (grade 1B).

23.4.3 Orthopedic surgery

23.4.3.1 TOTAL HIP REPLACEMENT

As our population ages and becomes increasingly obese, the need for total joint replacement is only anticipated to increase. Prevention of VTE in these elderly, obese, and sometime frail patients is therefore paramount. Vitamin K antagonists are widely used for this purpose in total hip arthroplasty. The advantages of warfarin in this setting include proven efficacy, a delayed onset of action, titratable response, acceptable bleeding risk, wide availability and familiarity.[10] The goal INR should be adjusted to values between 2.0 and 3.0. Whether initiated pre- or post-operatively, the efficacy of warfarin therapy is maintained. Multiple trials have shown that LMWH is safe and effective for prophylaxis after total hip replacement. Vitamin K antagonists have been compared with LMWH in several trials with mixed results. Two trials showed an advantage of LMWH over warfarin,[76,77] whereas three additional trials showed no difference.[78–80] Fondaparinux is an acceptable alternative agent that appears to be at least as effective as the LMWH enoxaparin for this indication.[81,82] Post-operative bleeding rates were similar in these two trials. In summary, either LMWH, fondaparinux (2.5 mg/day), or vitamin K antagonism with warfarin (goal INR: 2.0–3.0) are acceptable prophylactic regimens for this indication (grade 1B). Based on the RECORD and ADVANCE trials, both rivaroxaban and apixaban are likewise acceptable options for this indication.[63,64,70] Neither dabigatran nor edoxaban are FDA approved for VTE prophylaxis following hip replacement surgery.

23.4.3.2 TOTAL KNEE REPLACEMENT

Total knee replacement surgery appears to carry a greater risk of VTE than total hip replacement surgery.[10] Although the rate of venographic-confirmed DVT in patients undergoing this procedure is as high as 50%, the rate of symptomatic DVT is much lower, particularly if appropriate prophylaxis is used. Adjusted-dose vitamin K antagonists provide effective prophylaxis in patients undergoing total knee replacement surgery, with symptomatic VTE occurring in 1.0%–1.3% of patients.[83,84] A number of trials have compared coumarin derivatives with LMWH. LMWH has been consistently more effective than warfarin for the reduction of VTE, but results in a higher bleeding rate.[78,85–87] Consequently, the choice of LMWH or adjusted-dose warfarin depends on the estimated VTE and bleeding risks. IPC provides effective adjunctive non-pharmacological prophylaxis for total knee replacement patients. Fondaparinux is an acceptable alternative agent with approximately equal efficacy compared with enoxaparin.[88,89] In summary, either LMWH, fondaparinux (2.5 mg/day), or vitamin K antagonism with warfarin (goal INR: 2.0–3.0) are acceptable prophylactic regimens for this indication (grade 1B).[10] The RECORD and ADVANCE trials justify the use of either rivaroxaban or apixaban as reasonable alternative agents.[65,66,68,69] Neither dabigatran nor edoxaban are FDA approved for VTE prophylaxis following knee replacement surgery.

23.4.3.3 HIP FRACTURE SURGERY

Hip fracture surgery is associated with a very high risk of post-operative VTE, with venographic rates approaching 50%.[10] Symptomatic proximal DVT rates are approximately 25%, and fatal PE occurs at a rate of between 1.4% and 7.5%. Prophylaxis of hip fracture patients remains a major challenge because of the risk of bleeding associated with recent trauma. The risk of DVT is increased if hospital admission is delayed for more than 2 days after hip fracture. Moreover, the risk of fatal PE is reduced if hip fracture patients are operated on within 24 hours of their injury. Either adjusted-dose warfarin or LMWH prophylaxis is recommended, and should be administered as soon as the patient is clinically stable. Fondaparinux may be the preferred prophylactic agent for this indication. Compared with LMWH, fondaparinux reduced the rate of proximal DVT (0.9% vs. 4.3%) with an equivalent rate of major hemorrhage (2.2% for both groups).[90] In summary, fondaparinux, LMWH, or vitamin K antagonism with warfarin are acceptable prophylactic regimens for this indication (grade 1B).[10] According to the guidelines, IPC pumping is a perhaps lesser though acceptable alternative (grade 1C).[10] Patients undergoing hip fracture surgery were not specifically included in the RECORD 1 or 2 trials of rivaroxaban, and therefore the efficacy and safety of this agent in this setting are not clear. Likewise, in the ADVANCE 3 trial of apixaban, patients with hip fracture were not included. Given the results of these three trials of elective total hip replacement surgery, the use of either rivaroxaban or apixaban may be acceptable alternative agents for hip fracture surgery VTE prophylaxis.[63,64,70]

23.4.3.4 KNEE ARTHROSCOPY

Arthroscopic knee surgery is the most common orthopedic procedure performed in the United States.[10] The rate of symptomatic venous thrombosis following this procedure is extremely low, with published rates of less than 0.005%. The recommendations for VTE prophylaxis following knee arthroscopy are therefore limited to early ambulation for most patients (grade 2B).[10]

23.4.3.5 OPTIMAL DURATION OF PROPHYLAXIS

The optimal duration of prophylaxis following orthopedic surgery remains uncertain, and is a topic of ongoing debate.[91–93] Although VTE prophylaxis is typically stopped at hospital discharge, two-thirds of venous thrombotic events occur after hospital discharge.[91] The risk of VTE may persist for up to 3 months following surgery. Most trials continued prophylaxis for at least 7–10 days. However, the current duration of post-operative hospitalization is often 4 days or fewer, which may provide an inadequate duration of prophylaxis. In a meta-analysis of nine trials of extended-duration prophylaxis (30–42 days), the odds ratio (OR) of VTE rates was significantly reduced (OR: 0.38, 95% CI: 0.24–0.61).[92] This risk reduction was greater for patients undergoing total hip replacement than for total knee replacement. Extended-duration prophylaxis was not associated with an excessive rate of major hemorrhage. Based on these combined data, the current American College of Chest Physicians (ACCP) guidelines include a firm recommendation that all patients receive 10 days of appropriate VTE prophylaxis following total joint replacement or hip fracture surgery (grade 1B).[10] For patients undergoing total hip arthroplasty or hip fracture surgery, prophylaxis should be continued for 4 weeks, particularly in patients with continuing VTE risk factors (e.g., a previous history of VTE, obesity, continued immobilization, or bilateral simultaneous total knee replacement; grade 2B).[10]

23.4.4 Neurosurgery

The risk of VTE following neurosurgery is increased with intracranial procedures, malignancy, long surgical duration, limb paresis, and advanced age.[9] Rates of symptomatic VTE range from 3.7% to 19% depending on the presence of these variables.[94–96] IPC has been the prophylaxis of choice for elective neurosurgery patients, since even minimal bleeding could be catastrophic (grade 2C).[9] When considering prophylaxis strategies, rates of VTE must be weighed against the risk of intracranial hemorrhage, which is estimated at approximately 1%.[97] Low-dose UFH or LMWH are acceptable prophylactic agents for high-risk patients (grade 2C).[9,96,98] In one study of 150 patients undergoing craniotomy for brain tumor resection, the use of either agent completely eliminated symptomatic DVT as assessed by pre-discharge duplex ultrasonography.[91] In another study of 100 patients undergoing craniotomy, there was no significant difference in post-operative hemorrhage or VTE between heparin and dalteparin groups.[98] Notably, nearly 80% of VTE cases following neurosurgery occur following hospital discharge.[99]

23.4.5 Acute spinal cord injury with leg paralysis

Spinal cord injury with limb paresis carries an increased risk of both symptomatic and asymptomatic VTE, which may be twofold higher compared to major trauma without spinal cord injury.[100–107] PE remains the third leading cause of death in these patients.[108,109] Major risk factors for VTE in patients suffering from spinal cord injury include increased age, lower extremity fracture, and delayed use of prophylaxis. The period of greatest risk for VTE is the first 2 weeks after injury, with symptomatic PE rarely occurring beyond 3 months. Consequently, the prophylaxis duration in the absence of other risk factors should be 3 months from the date of the injury.[99] In a meta-analysis of studies assessing VTE prophylaxis strategies following spinal cord injury, LMWH was associated with reduced rates of PE, with a trend toward reduced major bleeding compared to low dose unfractionated heparin (LDUH).[110] Compared to no prophylaxis, the efficacy of LDUH could not be established; however, only 101 patients were analyzed, limiting interpretations of these results. In a retrospective cohort study design, two doses of tinzaparin (3500 or 4500 U daily) were

compared to enoxaparin 40 mg daily in 140 spinal cord injury patients.[111] Both enoxaparin and the higher tinzaparin doses were associated with reduced VTE rates. Starting prophylaxis early in the hospital stay was associated with lower event rates compared to later initiation. Based on the available evidence, LMWH provides effective prophylaxis for patients with acute spinal cord injury and paralysis (grade 2C).[9] These agents should be initiated once adequate hemostasis has been confirmed. Due to the increased risk of VTE in this population, IPC should be added when feasible (grade 2C).[9] For those patients in whom pharmacological prophylaxis cannot be safely used because of excessive bleeding risk, IPC should be employed (grade 1C). The bleeding risk should be reassessed regularly, adding pharmacological prophylaxis when feasible (grade 2C).

23.4.6 Multiple trauma

Asymptomatic DVT is common in trauma patients (injury severity score [ISS] >9). Using venography, one study of 349 trauma patients found a high DVT prevalence after lower extremity fractures (69%), spinal cord injury (62%), or isolated injury to the face, chest, or abdomen (50%).[112] None of these patients received prophylaxis. Other investigators using ultrasound found a 15.9% incidence of popliteal and calf vein DVT in 698 trauma patients.[113] Importantly, 35.7% of these showed signs of propagation over time. Risk factors for propagation included high ISS scores, age <62 years, ICU admission, and need for an operation. In a randomized trial of 344 trauma patients (ISS > 9), enoxaparin (30 mg twice daily) was compared with heparin (5000 U twice daily) for the prevention of VTE.[114] Venographically confirmed proximal DVT was significantly lower in the enoxaparin group (6%) compared with the heparin group (15%). Major bleeding was not significantly different (enoxaparin 3.9% vs. heparin 0.7%). For these reasons, LMWH prophylaxis is recommended for trauma patients in whom it is safe from a hemostasis standpoint (grade 2C). Based on the available data, however, low-dose UFH is also given the same level of support in the recent guidelines, and may be used for this indication (grade 2C).[9]

IPC was compared with LMWH (enoxaparin 30 mg twice daily) in 442 trauma patients (ISS >9).[115] In this study, ultrasound was performed within 24 hours of admission to establish the presence of pre-existing DVT, and weekly thereafter, or as indicated when DVT was suspected. Six patients who had IPC and one who received LMWH suffered a DVT ($P = 0.122$). There was one PE in each group. The combined incidence of major and minor bleeding did not differ significantly between the intervention groups. For those patients at very high risk of VTE, IPC should be added to pharmacologic prophylaxis (grade 2C).[9]

When considering VTE prophylaxis in trauma patients, the risk of major hemorrhage must be assessed as part of the decision-making process. There are trauma patients for whom pharmacological prophylaxis may be inappropriate due to an excessive bleeding risk. These include patients with severe head injury, liver or spleen laceration or trauma, spinal cord injury (particularly those with epidural hematoma), and trauma-associated coagulopathy and severe thrombocytopenia. For these patients, IPC is recommended until bleeding variables are normalized (grade 2C). If IPC is not feasible because of leg trauma, prophylactic IVC filter placement may be appropriate in selected patients who cannot tolerate any of the other three recommended modalities.[49] IVC filter therapy is not recommended as a primary prophylaxis for unselected trauma patients (grade 2C). The advent of retrievable filters has been felt by many to be an attractive option for high-risk trauma patients. One study compared the rates of filter placement, filter-related complications, and PE before and after the introduction of retrievable filters at the authors' institution.[116] With the introduction of retrievable filters at their institution, the rate of filter placement tripled, yet there was no significant difference in the rate of PE. Thus far, there are no randomized trials to provide guidance for the correct use of these filters in the setting of trauma.

23.4.7 Neuraxial anesthesia

Neuraxial anesthesia carries the rare but potentially devastating complication of perispinal hematoma in patients receiving prophylactic or therapeutic anticoagulation.[117–119] This complication may result in paraplegia, as delicate neural tissues are compressed by bleeding within the confined space of the spinal column. Signs and symptoms to look for include severe back pain with progressive lower extremity weakness or numbness, and bowel or bladder dysfunction. Diagnosis of this complication requires diligence with clinical scrutiny, as detection may be obscured by the anesthesia delivery. Perispinal hematomas have been described following the use of either LMWH or UFH. The risk exists for both the insertion and removal of perispinal anesthesia delivery catheters. Risk factors for perispinal hematoma include advanced age, vertebral column malalignment, traumatic insertions, and a history of prior bleeding diathesis. Other factors suspected of predisposing patients to spinal hematoma include enoxaparin overdose, commencing enoxaparin prior to the establishment of hemostasis, and use of concurrent medications known to increase bleeding. In general, it is best to wait 12 hours from the last LMWH injection (if at a twice-daily dose) or 18 hours (if at a daily dose) before either insertion or retrieval. More than 2 hours should elapse from the time of catheter manipulation before re-initiation of anticoagulants. If the spinal access was traumatic, this time interval should be extended.

In a review of neuraxial complications associated with concurrent LMWH or heparinoid prophylaxis and regional anesthesia or analgesia, the following recommendations were provided for patients receiving an initial LMWH dose before surgery:

- Regional anesthesia should be avoided in patients with a clinical bleeding disorder or in patients receiving other drugs which potentially may impair hemostasis

(e.g., aspirin or non-steroidal anti-inflammatory drugs, platelet inhibitors, or other anticoagulants).
- Insertion of the spinal needle should be delayed for 10–12 hours after the initial LMWH injection.
- Regional anesthesia should be avoided in patients with a hemorrhagic aspirate (e.g., "bloody tap") during the initial spinal needle placement.
- A single-dose spinal anesthetic is preferred over continuous epidural anesthesia.
- For patients receiving continuous anesthesia, the epidural catheter should be left indwelling overnight and be removed the following day.
- LMWH should be delayed for at least 2 hours after spinal needle placement or catheter removal.

The timing of neuraxial anesthesia relative to the use of direct oral factor inhibitor therapy is also an important variable, with limited information to guide clinicians. Each of the respective package inserts contains a black box warning regarding spinal and epidural hematomas with the use of these agents and neuraxial interventions. The timing of drug discontinuation prior to neuraxial anesthesia is not known. For rivaroxaban, catheter removal should be delayed for at least 18 hours after discontinuing this drug and should not be restarted for at least 6 hours following retrieval. For apixaban, catheter removal should be delayed for at least 24 hours after drug discontinuation and should not be restarted for at least 5 hours following retrieval. If a traumatic puncture is experienced, the timing of any drug re-initiation should be delayed for at least 24–48 hours. For dabigatran and edoxaban, the FDA-approved package insert offers no specific timing suggestions, whereas optimal timing between the drug administration and neuraxial procedures is not known. Regardless of the agent, patients should be carefully monitored for signs or symptoms of neurological impairment, with prompt assessment and intervention should any occur.

For patients in whom spinal hematoma is suspected, diagnostic imaging and definitive surgical therapy must be performed as rapidly as possible in order to avoid permanent paresis. In summary, all patients receiving neuraxial anesthesia and anticoagulant prophylaxis should be monitored carefully and frequently for early signs of cord compression.

23.4.8 Acute stroke with lower extremity paralysis

Low-dose heparin and LMWH are effective as prophylaxis after acute stroke with paresis or paralysis. IPC combined with low-dose heparin is a more effective prophylaxis than low-dose heparin alone.[120] In a randomized controlled trial of 2876 patients suffering stroke, the CLOTS 3 investigators compared IPC to no therapy. After 6 months of follow-up, IPC therapy was associated with an absolute reduction of proximal DVT from 8.5% to 3.6% favoring treatment.[121] Current guidelines recommend subcutaneous heparin prophylaxis for immobilized patients to prevent DVT (class 1; level of evidence A).[122]

For patients who cannot receive anticoagulant prophylaxis, the use of aspirin is a reasonable alternative (class IIa; level of evidence A). In the patient with stroke associated with cerebral hemorrhage in whom anticoagulation cannot be safely delivered, IPC may be an appropriate alternative. Using a stroke registry study methodology, hematoma volumes were assessed by serial computed tomography imaging in 73 patients with intracranial hemorrhage and/or intraventricular hemorrhage who received LMWH or UFH prophylaxis.[123] Hematoma growth was identified in only two patients. The authors concluded that pharmacological DVT prophylaxis can be safely given to patients with intracranial hemorrhage (ICH) and/or intraventricular hemorrhage in the subacute period without risk of hematoma growth.

23.4.9 Acutely ill hospitalized patients

VTE is a recognized complication of hospitalization and is a leading cause of morbidity and mortality in the acutely ill patient.[124] Estimated rates of as high as 20% have been suggested in the absence of appropriate VTE prophylaxis.

In medically ill patients, thromboprophylaxis has been shown to reduce the composite endpoint of symptomatic and asymptomatic venous thromboembolic events. A group of 1102 hospitalized patients were randomized to receive daily enoxaparin (20 mg or 40 mg) or placebo for up to 14 days.[124] Combined symptomatic and asymptomatic VTE rates were significantly lower in the enoxaparin 40 mg group (5.5%) compared to placebo (14.9%). This benefit was maintained at up to 3 months of follow-up. There was no difference in major bleeding. The lower enoxaparin dose was ineffective. Similar efficacy and safety outcomes were noted in randomized trials of dalteparin (5000 IU daily) and fondaparinux (2.5 mg daily) compared to placebo in acutely ill hospitalized patients.[125,126]

However, an improved survival advantage with thromboprophylaxis in medically ill patients has not been definitively shown. In the LIFENOX study, 8307 patients were randomly assigned to receive enoxaparin or placebo plus graduated elastic stockings in order to reduce the primary efficacy outcome of all-cause mortality at 30 days.[127] There was no difference in death rates for those patients receiving LMWH (4.9%) versus those who did not (4.8%). There was also no difference in major bleeding (0.4% vs. 0.3%) between groups.

Numerous randomized trials have demonstrated the safety, efficacy, and cost-effectiveness of thromboprophylaxis in hospitalized patients, and yet appropriate VTE prophylaxis delivery is underutilized in both medically and surgically hospitalized patients. In the multinational cross-sectional ENDORSE study, which surveyed 68,183 patients (55% medical and 45% surgical), only half of high-risk patients (58.5% surgical and 39.5% medical patients) received guideline-endorsed VTE prophylaxis.[128] Useful interventions to improve rates of VTE prophylaxis use

include system-wide educational activities with real-time alerts to providers. Multifaceted strategies were more effective than single interventions.[129]

In summary, according to the recent guidelines, low-dose UFH, LMWH, or fondaparinux are safe and effective prophylaxis strategies for hospitalized patients with other general medical conditions (grade 1B).[9] For bleeding patients, IPC would be expected to provide similar prophylaxis efficacy (grade 2C).

23.5 CONCLUSIONS

In summary, VTE is the most common preventable cause of death and suffering. Providing appropriate VTE prophylaxis is the highest-ranked safety practice for patients who are at risk. Recognition of the patient who is at risk, and delivery of appropriate prophylaxis, is imperative in order to reduce the incidence of VTE (including fatal PE) in hospitalized patients.

Guidelines 3.7.0 of the American Venous Forum on current recommendations for the prevention of deep venous thrombosis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.7.1	When the risk of bleeding from pharmacological agents is high, we suggest using non-pharmacological methods of venous thromboembolism prophylaxis, including elastic compressive stockings, intermittent pneumatic compression devices, leg elevation, and early ambulation. Each of these reduces venous thrombotic events by approximately 20%.	2	C
3.7.2	For patients at very high risk of venous thromboembolism, we suggest non-pharmacological methods of venous thromboembolism prophylaxis in combination with pharmacological agents.	2	C
3.7.3	For patients with acute venous thromboembolism within 1 month who undergo urgent/emergency surgery, or if other circumstances prohibit anticoagulation, we recommend placement of an inferior vena cava filter.	1	B
3.7.4	We suggest against inferior vena cava filter therapy as primary prophylaxis for unselected trauma patients.	2	C
3.7.5	We suggest that the indications for temporary, retrievable, or optional inferior vena cava filters are the same as those for permanent inferior vena cava filters.	2	C
3.7.6	Aspirin may provide modest risk reduction following major joint surgery when added to other prophylaxis therapies.	1	B
3.7.7	For very-low-risk patients (Caprini score 0), the risk of venous thromboembolism is sufficiently low that early ambulation alone is recommended.	1	B
3.7.8	For low-risk patients (Caprini score 1–2), intermittent pneumatic compression pumping is suggested.	2	C
3.7.9	For moderate-risk patients (Caprini score 3–4), we suggest low-dose unfractionated heparin, prophylactic-dose low-molecular-weight heparin, or intermittent pneumatic compression pumping.	2	B
3.7.10	For high-risk general surgery patients (Caprini score ≥5), either low-dose heparin or prophylactic-dose low-molecular-weight heparin is recommended.	1	B
3.7.11	For patients undergoing cancer-related surgery, we recommend pharmacological prophylaxis extended for 4 weeks post-operatively.	1	B
3.7.12	For surgery patients at high risk of major bleeding, mechanical prophylaxis with intermittent pneumatic compression pumping is suggested over pharmacological prophylaxis.	2	C

Continued

Guidelines 3.7.0 of the American Venous Forum on current recommendations for the prevention of deep venous thrombosis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.7.13	Following total joint replacement or hip fracture surgery, we recommend appropriate venous thromboembolism prophylaxis for 10 days	1	A
3.7.14	For patients undergoing total hip arthroplasty, we recommend either low-molecular-weight heparin, fondaparinux (2.5 mg/day), or vitamin K antagonism with warfarin (goal international normalized ratio: 2.0–3.0) for prophylactic regimens. Based on the RECORD and ADVANCE trials, both rivaroxaban and apixaban are similarly acceptable options for this indication. Neither dabigatran nor edoxaban are Food and Drug Administration approved for venous thromboembolism prophylaxis following hip replacement surgery.	1	B
3.7.15	For patients undergoing total knee replacement surgery, either low-molecular-weight heparin, fondaparinux (2.5 mg/day), or vitamin K antagonism with warfarin (goal international normalized ratio: 2.0–3.0) are recommended as prophylactic regimens for this indication. The RECORD and ADVANCE trials justify the use of either rivaroxaban or apixaban as reasonable alternative agents. Neither dabigatran nor edoxaban are Food and Drug. Administration approved for venous thromboembolism prophylaxis following knee replacement surgery	1	B
3.7.16	For patients undergoing hip fracture surgery, fondaparinux, low-molecular-weight heparin, or vitamin K antagonism with warfarin are recommended as prophylactic regimens for this indication.	1	B
3.7.17	For patients undergoing hip fracture surgery, intermittent pneumatic compression pumping is recommended as an acceptable alternative for patients at high risk of major bleeding.	1	C
3.7.18	Low-dose unfractionated heparin, low-molecular-weight heparin, or fondaparinux are recommended as safe and effective prophylaxis strategies for hospitalized patients with other general medical conditions.	1	B
3.7.19	For bleeding patients, we suggest intermittent pneumatic compression for thrombosis prophylaxis.	2	C

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● = Key primary paper
★ = Major review article
♦ = Major guideline

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24

Axillo-subclavian venous thrombosis in the setting of thoracic outlet syndrome

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24.1 INTRODUCTION

Axillosubclavian vein thrombosis (Paget–Schroetter syndrome) is the most common manifestation of venous thoracic outlet syndrome (VTOS). The subclavian vein passes through the anterior part of the thoracic outlet, where the first rib and clavicle are bound to the sternum and to each other by the costoclavicular ligament and subclavius tendon (Figures 24.1 and 24.2). The vein in this area can become chronically injured if certain environmental conditions are met, most commonly exercise with the arms over the head, and the vein can then thrombose; this condition is thus also termed "effort thrombosis."[1]

In the past, axillosubclavian vein thrombosis was considered just another form of deep vein thrombosis and was treated with anticoagulation and arm elevation alone. However, this proved to result in unacceptably poor outcomes. Chronic disability and persistent symptoms of upper extremity venous obstruction are present in between 25% and 77% of affected patients so treated, and pulmonary embolism can occur in 6%–15% of patients with acute thrombosis.[1–5] Because of these poor results, Machleder at the University of California, Los Angeles (UCLA) and several others began to aggressively treat these patients with catheter-directed thrombolysis in the 1970s, and today, this has become the standard of care for acute (within 14 days or so) thrombosis.[6,7] Although Machleder's original algorithm incorporated a 6–12-week interval between thrombolysis and rib removal, the prevailing opinion today is that first rib removal and intervention for any underlying venous abnormality at the costoclavicular junction (CCJ) should be done within days after thrombolysis, to reduce the risk of recurrent thrombosis.[8,9]

24.2 THROMBOLYSIS

24.2.1 Indication

Most believe that any spontaneous acute axillosubclavian thrombus represents VTOS and should be aggressively treated. Modern techniques instill a thrombolytic agent directly within the thrombus, and bleeding complications are rare. The results of catheter-directed thrombolytic therapy for any thrombosis are highly dependent on the chronicity of the thrombus. Contemporary series report rates of near-complete thrombus clearance when acute thrombosis of the axillosubclavian segment is treated, with low rates of hemorrhagic complications.[1,10] By contrast, once the thrombus has been present for 14 days or so, it is much more difficult to remove the obstruction by any means. Thus, a short interval from symptom onset to initiation of thrombolysis (days to a week or so) is critical for therapy.

Some patients present late after symptom onset (or are treated with anticoagulation before referral to an expert

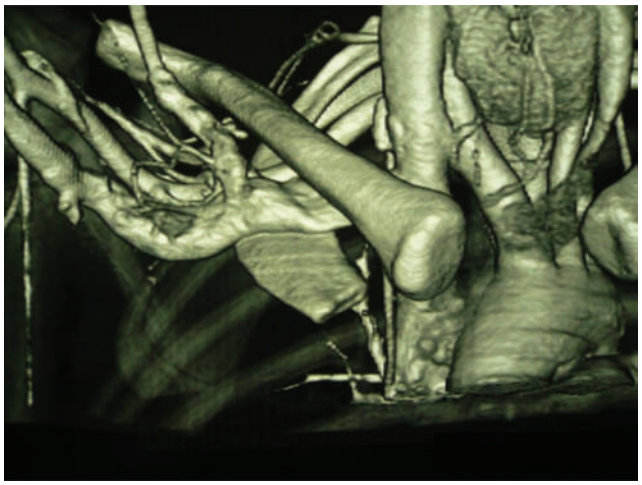

Figure 24.1 Computed tomography reconstruction of a patient with right-sided venous thoracic outlet syndrome showing the point of compression at the anterior thoracic outlet (the "void" just above the compressed vein is the subtracted subclavius muscle, illustrating the importance of this structure). Note that the right arm is in a raised position. Courtesy of Wallace Foster, MBBS, FRACS, Royal Brisbane and Women's Hospital, Brisbane, Australia. (From Illig KA et al. *Ann Vasc Surg* 2015;29:698–703; Glass C. VTOS in the patient requiring chronic hemodialysis access. In: Illig KA, Thompson RW, Freischlag JA, Donahue DD, Jordan SE, Edgelow PI, eds. *Thoracic Outlet Syndrome*, Springer-Verlag, London, 2013, 355–9. With permission.)

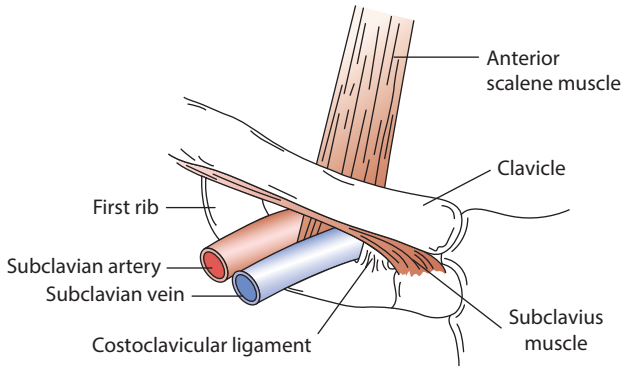

Figure 24.2 Drawing of the anterior portion of the thoracic outlet (costoclavicular junction) on the right, showing the vein at the fulcrum of the lever produced by the clavicle and first rib. Note the proximities of the subclavian muscle and costoclavicular ligament. (From Sanders RJ, Haug CE. *Thoracic Outlet Syndrome: A Common Sequela of Neck Injuries.* Philadelphia, PA: JB Lippincott, 1991, 237. With permission.)

in VTOS). While some attempt lysis, Freischlag and colleagues have shown excellent long-term results with anticoagulation and first rib resection alone, the rationale being to make room for collaterals and enable the possibility of spontaneous recanalization.[11,12]

24.2.2 Technical points

Prior to initiating thrombolysis, occlusion of the axillosubclavian segment should be confirmed with a central venogram. It is essential to cannulate a deep vein (either one of the brachial veins or the basilic vein) when performing the venogram; access via the cephalic vein will result in inability to treat any thrombus peripheral to the cephalic arch. An obvious first step is to achieve wire passage through the thrombus and re-enter the normal vein (usually innominate) central to all thrombus; again, this is much easier when the thrombus is in the acute phase.

Once wire passage has been obtained, either conventional or pharmacomechanical thrombolysis can be performed. Conventional thrombolysis is usually done with recombinant tissue plasminogen activator (tPA) at 1 mg/hour and a low-dose heparin infusion. Repetitive laboratory studies are not needed. A control venogram is performed in 12–24 hours to evaluate the effectiveness of thrombolysis; a positive result is usually obvious by dramatic relief of clinical symptoms. An alternative is pharmacomechanical thrombolysis. We have been satisfied with the AngioJet system (Medrad, Inc., Warrendale, PA), in which lacing of the thrombus with tPA (PowerPulse mode) is followed by physical removal by Venturi-effect suction. If debulking is successful but some thrombus remains, overnight conventional lysis can be performed and the results assessed. Other tools for pharmacomechanical thrombolysis include the Trerotola percutaneous thrombectomy device (Arrow International, Reading, PA) that macerates and fragments the clot, and the Trellis device (Bacchus Vascular, Santa Clara, CA) that isolates and removes a segment of clot with much less theoretical embolization. All seem to work fairly well, although none have shown superiority over any of the others.

Once all thrombus has been removed, the vein should be assessed for its baseline pre-thrombosis status. Usually, there will be residual fixed damage at the CCJ, caused by repetitive trauma in this area (Figure 24.3). Rarely, there will be a normal-appearing vein. In this situation, the venogram should be repeated with the arm elevated, which will often

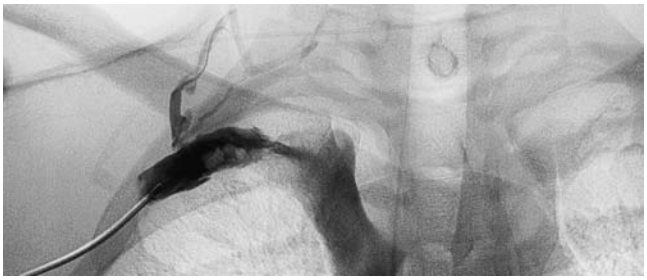

Figure 24.3 Venogram of a 20-year-old baseball player showing some recanalization of a completely occluded subclavian vein after 24 hours of catheter-directed thrombolysis. He underwent first rib resection 2 days later after heparin was discontinued.

"unmask" the compression. If the venogram is normal, the area can be further interrogated using intravascular ultrasound or with an appropriately sized balloon to identify a waist or obstruction. If absolutely no lesion is revealed after lytic therapy, the rib may be left in place, and a search for other causes (trauma, a recent intravenous or peripherally inserted catheter (PIC) line, or a hypercoagulable state) should be undertaken, but this situation is rare. In the vast majority of cases, an extrinsic stenosis and/or fixed venous injury is demonstrated, and virtually all authors recommend rib resection in this situation.

24.3 MANAGEMENT AFTER THROMBOLYSIS: TREATMENT OF EXTRINSIC COMPRESSION

After partial or successful thrombolysis, two factors must be addressed: the bony compression originally causing the problem and the intrinsic venous damage.

The original problem is caused by compression of the subclavian vein by the anterior junction of the clavicle and first rib at the CCJ (Figures 24.1 and 24.2), and less commonly by a cervical rib, hypertrophied anterior scalene muscle, elongated C7 process, or hypertrophied subclavius muscle. Stents in this area have been definitively proven to have insufficient radial force and strength to withstand this pressure,[1] and virtually all agree that bony decompression is required. While the clavicle can be resected with surprisingly little morbidity,[13] it is easiest and cosmetically appropriate to remove the first rib. There is a minority opinion that the rib can be left alone after a first episode of thrombosis,[14] but short-term recurrence rates approach 30% when the underlying condition responsible for the venous occlusion is neglected.[7] A recent meta-analysis clearly shows that removing the rib after successful lysis results in significantly improved outcomes,[15] and this is the policy followed by most clinicians today.

Although it was once standard to delay therapy by 3 months after thrombolysis in order to allow inflammation to recede and to assess the residual venous abnormality and the effect it has on the patient, current opinion is firmly in favor of earlier intervention, now defined as hours to days.[1] It is estimated that as many as a third of patients will suffer recurrent thrombosis during this interval, and early intervention has clearly been shown to be safe.

In patients with subacute and chronic axillosubclavian thrombosis, months after an acute episode, there are data to suggest that, even if thrombolysis is not indicated or not attempted, there may be still be a benefit to first rib resection. Freischlag and colleagues retrospectively evaluated outcomes following first rib resection in this situation.[12] The mean time from initial presentation was 3.8 months in patients undergoing pre-operative endovascular intervention, and 6.2 months in those having been anticoagulated only. At 1 year after rib resection, 91% of all patients had patent vessels (by ultrasound) and improvement in symptoms. The authors hypothesized that even when the vein is chronically occluded, first rib resection may enable recanalization and clinical amelioration.

There are several surgical approaches to first rib resection: transaxillary, infraclavicular, and supraclavicular approaches.

The transaxillary approach[16] has the advantage of direct visualization and exposure of the costoclavicular space and the site of venous compression. It also allows the operator to perform an external venolysis when necessary in the presence of extrinsic venous compression. In addition, it offers excellent cosmesis. However, the indications may be limited when more extensive reconstruction of the vein is necessary. In addition, there is a significant risk of long thoracic nerve injury.

The CCJ may also be decompressed using the infraclavicular approach.[17] This allows excellent visualization of the vein to reconstruct and first rib anteriorly. Other benefits include minimal manipulation of the brachial plexus, phrenic nerve, and subclavian artery, which are not involved in VTOS, along with the ability to keep the patient in the supine position for venography and thrombolysis.

24.4 MANAGEMENT AFTER THROMBOLYSIS: TREATMENT OF THE SUBCLAVIAN VEIN ABNORMALITY

Once the rib is removed, final venograms in the neutral and shoulder abducted positions should be performed. A few patients with no abnormalities of the subclavian vein in either position should be treated with a 3–6-month course of oral anticoagulation. Any extrinsic compressive lesion should have been eliminated by the operative procedure, but the majority of patients will have an intrinsic lesion of the subclavian vein. The pivotal question that must be addressed is whether the subclavian vein needs to be treated. No data on this matter exist. Most recommendations are based on symptom status; patients with persistent signs of venous obstruction, active lifestyles, and/or physically demanding vocations should have venous intervention after successful thrombolysis.

The available options for treating intrinsic subclavian vein lesions include percutaneous transluminal angioplasty with or without stent placement post-operatively, open patch venoplasty, or venous bypass at the time of thoracic outlet decompression. Some authors have suggested balloon angioplasty or stenting for residual stenosis of >50%.[18] Fibrotic lesions at the costoclavicular space are very resistant to balloon angioplasty, often requiring inflations of over 10 atmospheres. The venogram in Figure 24.4 depicts a patient with significant clinical obstruction after thrombolysis and first rib resection who underwent percutaneous balloon angioplasty with moderate symptomatic improvement. One year later, the patient returned with more severe venous obstructive symptoms and was treated with stenting (Figure 24.5). The image shows the stent prior to balloon expansion.

Figure 24.4 Venogram of a patient after thrombolysis and first rib resection showing residual obstruction of the subclavian vein due to intrinsic, chronic injury. She was treated with balloon venoplasty with partial relief of obstructive symptoms.

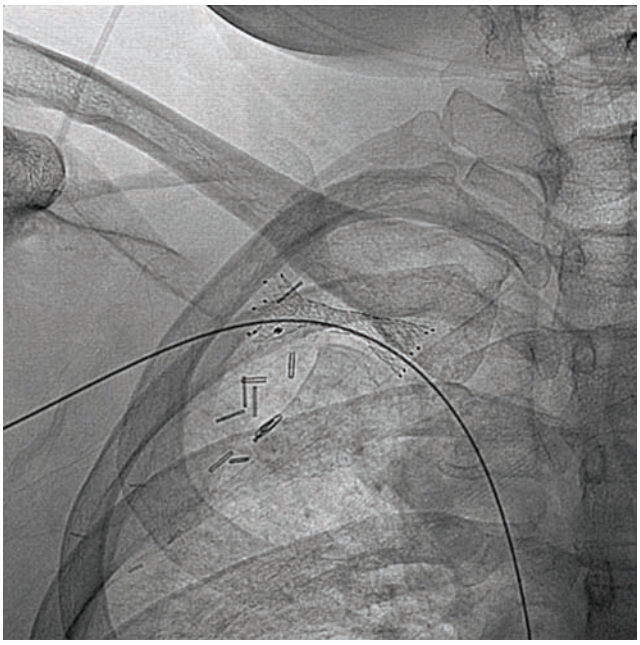

Figure 24.5 The patient in Figure 24.4 returned 1 year later with more severe symptoms of obstruction; the vein remained patent but was highly stenotic. A stent was placed (shown prior to balloon expansion) and dilated, with good long-term results.

Notably, stent placement prior to operative decompression should be condemned, as the stents are subject to compression between the clavicle and first rib, fracture, and recurrent thrombosis. Stenting following decompression, for example, where significant residual stenosis exists despite balloon dilatation, may be safer. However, some evidence has shown that the failure rates exceed those of the uninstrumented vein.[19]

The need for operative repair of the subclavian vein has been reduced significantly by catheter-based therapies performed immediately after thrombolysis and first rib resection. Open repair is reserved for those patients with disabling symptoms who have failed percutaneous therapy.

For some rare physiology or anatomy reasons, thrombolysis might be not effective even when the thrombus can be crossed with a wire and catheter-directed drug administration is possible. These patients, if highly symptomatic, can be considered for more aggressive intervention. Options in this situation include interposition grafting with the femoral vein, a spiral or panel saphenous vein conduit, or occasionally a prosthetic graft. Data on patency rates for the latter are sparse, but in the authors' opinion, a prosthetic graft does not fare well in this situation. The jugular vein can also be transposed to the patent subclavian vein peripheral to the occlusion. All of these techniques usually require wide exposure of the subclavian vein via an anterior approach. Two such options are available: subtotal claviculectomy, which is quite well tolerated,[13] and limited first interspaced sternotomy with "clavicular rotation," popularized by Molina (Figure 24.6).[20]

No reliable data exist as to when venous repair is needed. Some authors suggest that the vein should be repaired in all circumstances,[10] while most surgeons today are against the intervention in the absence of severe symptoms and residual defects. Theoretically, an important exception to this rule is when a CCJ stenosis exists in a patient with an ipsilateral arteriovenous fistula. In this situation the flow is much higher than in a patient with VTOS (1000–2000 cc/minute

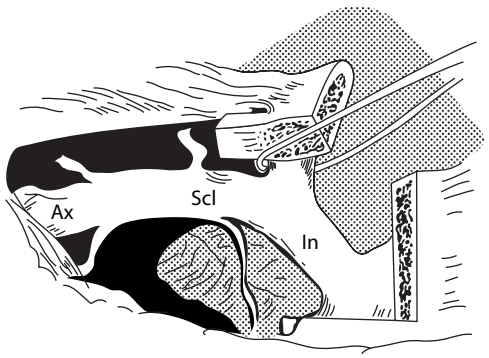

Figure 24.6 Wide exposure of the axillary, jugular, and innominate veins can be obtained by performing first space sternotomy (after rib excision) and rotation of the resulting structure cephalad (right side shown). Note that the sternoclavicular joint is not disrupted. Closure is then obtained with two perpendicularly oriented sternal wires. Ax: axillary vein; In: innominate vein; Scl: subclavian vein. (From Molina JE. *J Vasc Surg* 1998;27:576–81. With permission.)

as opposed to about 80 cc/minute), and this high flow has a much greater potential for turbulence and resulting intimal hyperplasia. Although no data exist on this matter, it is the authors' belief that stenosis in this situation should be more aggressively treated.[21,22]

24.4.1 Anticoagulation

A hypercoagulable state has been identified in only 6%–15% of patients treated for axillosubclavian thrombosis. However, following a thrombotic event, the involved venous segment is likely to be thrombogenic, at least transiently. For this reason, full anticoagulation with heparin should be continued post-operatively to prevent recurrent thrombosis. In the immediate post-operative period, patients should receive either a Lovenox or heparin drip while converting to Coumadin. Alternatively, a direct thrombin inhibitor (dabigatran) or selective factor Xa inhibitor (rivaroxaban or apixaban) can be used, although no data exist on efficacy and safety in this situation. Patients should be maintained on anticoagulation for 3–6 months. Duplex ultrasound can be used for surveillance.

24.5 RESULTS

Molina et al. reported the results of 114 patients treated for effort thrombosis of the subclavian vein. There was 100% success in re-establishing the flow and normal caliber of the subclavian vein in the 97 patients who presented early after thrombosis and had thrombolysis followed by immediate open surgery, which included resection of the medial portion of the first rib with or (in most patients) without partial median sternotomy. Venous reconstruction was usually performed with vein patch angioplasty. Seven patients required balloon plasty and stenting. Early primary assisted patency was 100%. Only 29% of the patients had successful surgery if the procedure was delayed.[10]

The Dartmouth group reviewed their experience with 36 patients treated for axillosubclavian vein thrombosis from 1988 to 2008. The overall patency rates were excellent: 100% and 94% after 1 and 5 years, respectively. Seven patients did require re-intervention: four received additional lytic therapy, two were stented, and one had venoplasty.[18]

Urschel and Patel presented the largest published series of patients with axillosubclavian vein thrombosis. Presentation varied with 608 patients included. However, most of them were treated within 6 weeks of thrombosis, with thrombolysis and immediate decompression. While patency was not recorded, 97% of their patients had good to excellent results. By contrast, only 16 of 36 patients (44%) treated with anticoagulation alone had good to excellent results, and 72% required delayed decompression due to recurrent intractable symptoms. Only 57% of those presenting after 6 weeks and managed with attempted thrombolysis and decompression had good to excellent results.[23]

Finally, a recent meta-analysis analyzed results in 684 patients with axillosubclavian vein thrombosis presenting

Guidelines 3.8.0 of the American Venous Forum on the management of axillosubclavian venous thrombosis in the setting of thoracic outlet syndrome

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.8.1	For primary axillosubclavian venous thrombosis in patients with venous thoracic outlet syndrome, we recommend venous thrombolysis followed by thoracic outlet decompression. This combination is safe and effective.	1	B
3.8.2	We recommend against stenting of the subclavian vein for venous thoracic outlet as an alternative to operative decompression.	1	A
3.8.3	Stenting of the subclavian vein after surgical decompression for venous thoracic outlet syndrome is recommended for significant refractory lesions, but evidence as to the long-term safety of this approach is lacking.	1	C
3.8.4	For patients with residual stenosis following thrombolysis and first rib resection for subclavian vein thrombosis in the setting of venous thoracic outlet syndrome, we recommend observation alone, as most of these patients will do well clinically and many will recanalize/remodel.	1	C
3.8.5	For patients with costoclavicular junction stenosis in the setting of an ipsilateral arteriovenous (AV) fistula and swelling, pain, or dysfunction, we recommend thoracic outlet decompression and endolumenal intervention; this approach is safe and effective.	1	B

within 14 days and undergoing thrombolysis. A total of 516 patients underwent first rib resection, with or without concomitant endovascular treatment. In this group, 95% had full symptom resolution and 94% of veins were subsequently patent as assessed by duplex ultrasonography. Only 54% of patients who did not undergo rib resection had long-term symptom relief, and 48% had patency of axillo-subclavian vein documented, in spite of the fact that more than 40% of these patients underwent rib resection later.[15] The available data firmly support the concept that the best possible results are obtained by early thrombolysis followed by expeditious thoracic outlet decompression and subsequent anticoagulation.

24.6 CONCLUSIONS

Treatment of subclavian venous thrombosis due to thoracic outlet syndrome has significantly evolved over the past half century. Anticoagulation alone is unacceptable, although a surprisingly high number of non-specialists are not aware of this concept. Current consensus recommends catheter-directed thrombolysis within 14 days of symptoms onset,

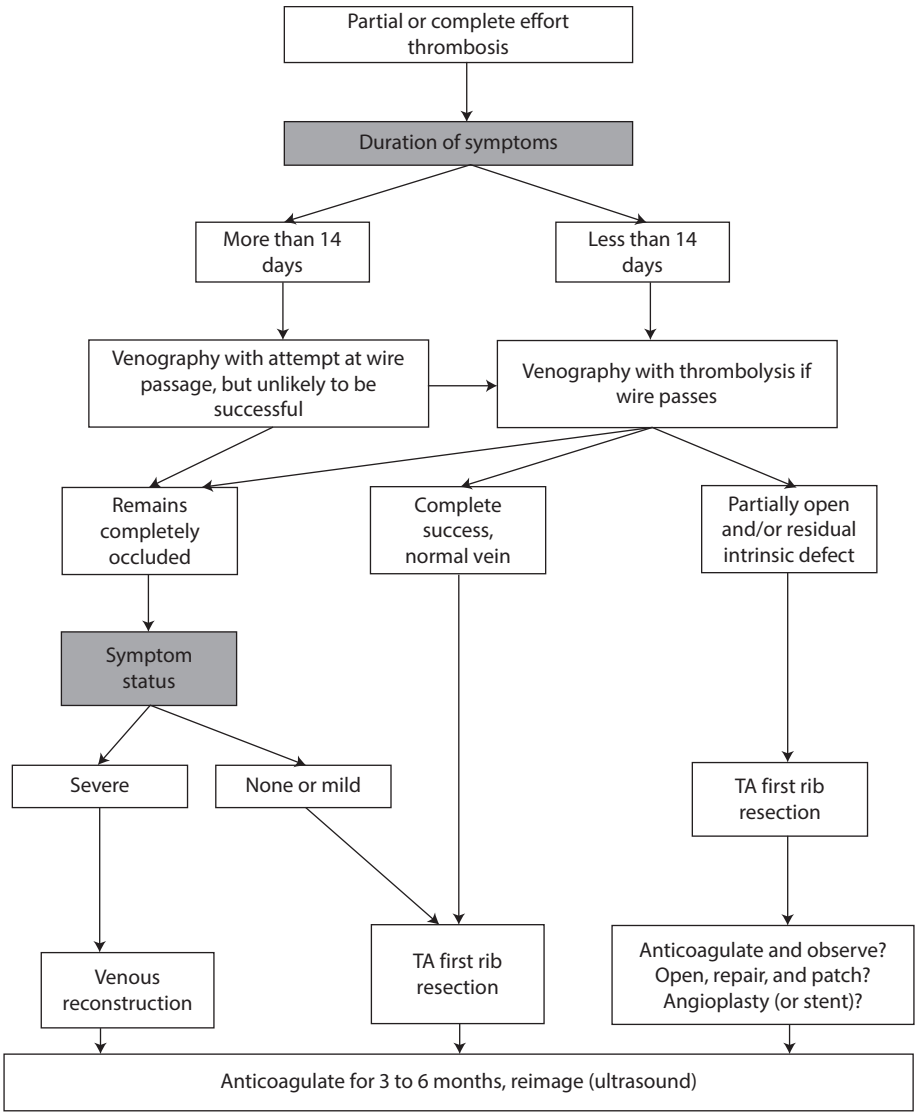

Figure 24.7 Algorithm for the treatment of patients with partial or complete effort thrombosis. The best initial procedure (more accurately, best chance of success) is defined by the duration of symptoms, whereas the subsequent method of thoracic outlet decompression is defined by the status of the residual vein and residual symptoms. Timing of decompression is not defined in our protocol, although we believe decompression should immediately follow thrombolysis. Note that in a patient with chronic thrombus who cannot be recanalized and is not significantly symptomatic, we tend to favor first rib resection (after Harthun NL. Management of the patient who presents late after thrombosis. In: Illig KA, Thompson RW, Freischlag JA, Donahue DD, Jordan SE, Edgelow PI, eds. *Thoracic Outlet Syndrome*, Springer-Verlag, London, 2013, 391–4; and de Leon RA et al., *Ann Vasc Surg* 2008;22:395–401, 2008, above), but it should be noted that this discussion is individualized and the advantages and disadvantages of both resection and leaving the rib alone are unusually closely discussed. TA: transaxillary. (From Illig KA, Doyle AJ. *J Vasc Surg* 2010;51:1539–47. With permission.)

followed by thoracic outlet decompression (by means of first rib resection when complex reconstruction is not needed) within a day or so of lysis, and subsequent temporary anticoagulation. Minor subclavian vein abnormalities should not be treated, while very-high-grade lesions or those associated with persistent symptoms should likely be repaired (Figure 24.7). Patients with chronic thrombus may do better with rib resection as well, although the data are less robust. Using this algorithm, good long-term results, defined as an essentially normal life, can be expected in 95% or more of patients.

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● = Key primary paper
★ = Major review article

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25

Acute central venous thrombosis in the setting of central lines, pacemaker wires, and dialysis catheters

SYED ALI RIZVI, ANIL HINGORANI, AND ENRICO ASCHER

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25.1 INTRODUCTION

Acute central venous thrombosis (CVT) is an important topic with a global effect. It can be divided into two causes: primary or secondary. Whereas primary causes are due to effort thrombosis or thoracic outlet syndrome, secondary causes are mostly due to either malignancy or indwelling catheters. Secondary causes of thrombosis have become the most likely source of this disease process.

Acute CVT lends itself to significant discussion because the use of central venous access for the placement of catheters and the treatment of cardiac arrhythmias with pacing wires and defibrillators has been rapidly increasing worldwide over the last few decades. Approximately 5 million central venous catheters (CVCs) are inserted yearly in the United States alone.[1] They are utilized to administer various fluids, medications, blood products, and antibiotics, to perform hemodialysis, and to monitor hemodynamics and provide parenteral nutrition. In addition, there are currently over 2 million patients with pacemakers worldwide.[2] All of these instruments carry significant potential to cause central venous trauma which can lead to CVT. In an autopsy study of 72 cancer patients, cannulated vessels compared to contralateral non-cannulated vessels had a markedly increased incidence of venous thrombosis of 36% compared to 1.2%, respectively.[3,4]

Prior to 1966, the incidence of upper extremity deep vein thrombosis (UEDVT) was understood to be 2% of all deep vein thromboses (DVTs). Yet, in a study based on a large prospective registry of consecutive patients with acute symptomatic DVT—the Computerized Registry of Patients with Venous Thromboembolism (RIETE)—the authors identified the prevalence of UEDVT as 512 among 11,564 DVT patients (4.4%). Increasing literature has now focused on the cause of UEDVT as being catheter related. The same study also demonstrated that 228 of those 512 UEDVT patients (45%) had catheter-related UEDVT.[5] Furthermore, UEDVT has been associated with complications of pulmonary embolism (PE), post-thrombotic syndrome (PTS), and death.[6]

As a consequence, our discussion in this chapter will focus on acute CVT in the setting of upper extremity central venous lines, dialysis catheters, and pacemaker wires. The diagnosis and treatment of lower extremity DVT is discussed elsewhere.

25.2 EPIDEMIOLOGY

25.2.1 Demographics

The RIETE registry comprises the largest set of prospectively collected data on patients with DVT. Its review has demonstrated that patients with UEDVT compared to patients with lower extremity DVT are younger (54 ± 19 vs. 66 ± 17 years), more often male (59% vs. 52%), weigh less (71 ± 14 vs. 74 ± 14 kg), have less frequent recent history of DVT (7% vs. 17%), and more commonly have cancer (38% vs. 20%).

In a study by Hingorani et al. in 1997, 546 patients with UEDVT were analyzed.[6] The average age of the patients was

64 (±17) years. They were more often females (66%) and had a history of cancer (22%). The overall mortality rate in this group was 29% at 2 months. Furthermore, another study compared 430 patients with lower extremity DVT and 52 patients with UEDVT over a 1-year period.[7] The authors of this study also noted higher 6-month mortality in the group with UEDVT (48%) than in those with lower extremity DVT (13%) ($P < 0.002$). No study has clearly examined the role of race in the development of UEDVT.

25.2.2 CVC-Related UEDVT

In the previously discussed study, utilizing duplex ultrasonography as part of the workup for arm swelling or PE, Hingorani et al. found 170 patients with UEDVT.[6] This retrospective study demonstrated concurrent CVC or pacemakers in 110 (65%) UEDVT patients. Furthermore, the same authors showed in a later study that the risk of mortality within 3 months of diagnosis of UEDVT was as high as 34%.[8] Finally, Kuter demonstrated that patients with CVC-related infection had a greater likelihood of having thrombosis than patients without CVC-related infection, with an odds ratio (OR) of 4.1 (95% CI: 1.5–11.4).[3]

25.2.3 Cancer population

In 2004, a review by Kuter of CVC-related thrombosis in the cancer population demonstrated that CVC-related thrombosis occurred in 41% (range: 12%–74%) of all cancer patients.[3] These results were based on 12 studies and 607 patients. The author demonstrated a higher incidence of asymptomatic thrombi as compared to symptomatic thrombi (29%; range: 5%–62%) (12%; range: 5%–54%). The same paper also referenced an article in which longitudinal analysis was performed on cancer patients to evaluate the timing of thrombosis. Serial venography was performed at 8, 30 and 105 days after catheter insertion on 95 patients. The authors found that by 8, 30, and 105 days, 64%, 65%, and 66% of all CVCs were found to have thrombosis, respectively.[3]

25.3 CLINICAL PRESENTATION

The most common presentation of patients with UEDVT is asymptomatic. The symptoms of UEDVT are usually reflective of the local effects of the thrombosis or embolization. In symptomatic patients, one or more of the following may be present: swelling of the extremity, face, and neck; pain of the extremity or neck; numbness; headache; paresthesia; engorgement of chest wall, neck, and extremity veins; jaw pain; and erythema.[9–15] Symptoms can be highly variable among patients, and can range from mild to debilitating. In rare cases, phlegmasia cerulea dolens has also been reported.[16,17]

25.3.1 Pulmonary embolism

Ventilation perfusion scans were performed in a study to determine the risk of PE among all patients with symptomatic and asymptomatic UEDVT. The study demonstrated that 13 of 86 patients (15.1%) were found to have a PE. The most common underlying diseases for these patients were cancer (31.4%), acute myocardial infarction (15.1%), acquired immune deficiency syndrome (8.1%), pneumonia (7.0%), acute pancreatitis (5.8%), and heart failure (5.8%). In another study, the authors attributed the risk of PE to be 5% of all UEDVTs and up to 20% in patients with CVC-associated UEDVT. The authors also discussed the need to develop less thrombogenic catheters to minimize the risk of UEDVT and PE.[18,19] Study by Monreal et al. have demonstrated the risk of PE as ranging between 4% and 15%.[18] Additionally, findings from the RIETE registry have also demonstrated that patients with UEDVT are associated with less severe symptoms of PE as compared to those with lower extremity DVT (9.0% vs. 29%; OR: 0.24; 95% CI: 0.18–0.33).

Furthermore, a retrospective review by Hingorani et al. in 2005 demonstrated that, of 465 patients diagnosed with UEDVT based on duplex ultrasonography, 327 patients were found to have catheter- or pacemaker-related UEDVT.[7] The authors failed to find a correlation between the site of UEDVT (internal jugular, axillary, brachial, or subclavian veins) and PE or mortality. They commented that patient mortality may not be related to the DVT itself; rather, it may be related to the underlying comorbid conditions.

25.3.2 Post-thrombotic syndrome

PTS has been defined in studies as persistent significant swelling with pitting edema, and is also a known complication of UEDVT. In 1997, Hingorani et al. demonstrated that among 170 patients diagnosed with UEDVT, with a mean follow-up of 13 months, 4% of the patients presented with symptoms consistent with PTS.[6] However, this rate has been previously described to be as high as 35% in patients with UEDVT. Data specifically related to catheter-associated PTS are lacking.

25.4 RISK FACTORS

25.4.1 Risk with CVCs

Risk factors for CVC-related thrombosis can be patient related, insertion related, catheter related, or a combination of any of these factors. In 1970, Tilney and Griffiths documented the first series of patients with indwelling catheter-related UEDVT.[15] Their study included 48 patients over a 25-year period who were found to have UEDVT. They found that 31 of 48 UEDVTs (64.6%) were associated with indwelling catheters. That study forewarned the increasing incidence of such occlusions as methods for long-term central venous access were becoming more widely used. Timsit et al. later published a prospective, multicenter study which reported that the risk of thrombosis increased with one or more of the following factors: age ≥65 years ($P = 0.001$); the internal jugular vein route for access ($P = 0.005$); and the absence of therapeutic anticoagulation at catheter placement ($P = 0.04$). In this study, there was no correlation

found between number of lumens and CVC-related thrombosis ($P = 0.91$).[20]

In 1988, Horattas et al. documented their 6-year retrospective review of all patients that presented to their facility with a diagnosis of UEDVT. They demonstrated 33 of 804 DVT patients (4%) had UEDVT and four of 33 patients with UEDVT (12%) had PE. The authors indicated that the risk of UEDVT was related to catheter presence in 13 of 33 (39%) patients. The authors also demonstrated that the risk of UEDVT increased with multiple punctures, large-bore catheters, the type of catheter material, and the duration of placement of the catheter.[21]

A 2013 review article by Murray et al. demonstrated a positive correlation between CVT and patient-related risk factors, including previous history of venous thromboembolism, inherited thrombophilia, malignancy, and presence of an acute infection.[10] Furthermore, their paper cites a prospective study on hematological malignancy in which CVC-related thrombosis increased in the presence of catheter-related infection. That study was performed using 105 consecutive patients undergoing intensive chemotherapy and addressed the risk of CVC-related infection and thrombosis.[22] All patients whose clinical examination of the upper extremity was suspicious for DVT underwent duplex ultrasonography or venography. The authors demonstrated that the risk of thrombosis increased markedly in those with catheter-related infection compared to those without catheter-related infection (relative risk [RR]: 17.6; 95% CI: 4.1–74.1). Thus, it is important to understand that catheter infection has a significant role in CVC-related thrombosis.

25.4.2 Risk with peripherally inserted CVCs

Peripherally inserted CVCs (PICCs) have been able to provide convenient long-term intravenous access for patients. In a retrospective analysis, Liem et al. reviewed all upper extremity venous duplex ultrasonography evaluations completed over a 1-year period at their vascular laboratory in order to identify patients with newly diagnosed UEDVT and a PICC placement ≤30 days from the examination.[23] They found that of the 831 completed scans, 154 (18.5%; 138 patients) scans were positive for UEDVT. PICC-associated DVT occurred in 54 of the 154 (35%) patients with UEDVT. These 54 PICC-associated DVTs occurred among the 1862 (2.6%) patients with PICC line placement during that time period. Previous large retrospective studies have also demonstrated that the incidence of UEDVT ranges from 1.6% to 3.5% among all PICC placements.[23] This study also found that large PICC diameter (≥5 Fr) had an OR of 3.9 (95% CI: 1.1–13.9; $P = 0.037$) and concurrent malignancy had an OR of 4.1 (95% CI: 1.9–8.9; $P < 0.001$) for developing UEDVT. The authors concluded that although the percentage of PICC-associated UEDVT is low, the increasing number of PICC placements lends itself to an overall increase in the number of patients that experience PICC-associated UEDVT.

Other authors have addressed the risk of UEDVT associated with PICC as compared to other CVCs. Chopra et al. completed a systematic review and documented that from a meta-analysis of 11 studies with 3788 patients, PICC lines were associated with an increased risk of DVT compared to other CVCs (OR: 2.55; 95% CI: 1.54–4.23; $P < 0.0001$). The number needed to harm for PICCs compared to CVCs was 26 (95% CI: 13–71).[24]

In another study, PICC line diameters and flow rates were analyzed.[25] The authors demonstrated in a fluid analysis model that the risk of thrombosis increased as a function of catheter size. This study documented that venous flow may be reduced by up to 80% with a 6-Fr catheter. Additionally, recent prospective studies have also shown an increased rate of symptomatic DVT with increasing PICC size from 4 Fr (1.0%–2.9%) to 6 Fr (8.8%–9.8%).[25]

25.4.3 Risk factors in pediatrics

A large retrospective cohort study examining the incidence of CVC thrombosis in pediatric patients found that 3.2% of CVCs were associated with thrombosis (2.8% DVT and 0.4% superficial vein thrombosis). This review examined 24 studies with 11,479 children. The study reported that 50% of all venous thromboses in children occur in those patients with CVCs. They demonstrated in 815 patients with catheters that increasing age (OR: 1.08; 95% CI: 1.03–1.13; $P = 0.002$), renal dialysis (OR: 3.2; 95% CI: 1.09–9.66; $P = 0.035$), and diagnosis of inflammatory bowel disease (IBD) or short bowel syndrome (OR: 4.3; 95% CI: 1.2–15.0; $P = 0.02$) increased the risk of thrombosis.[26] In addition, they found that the risk of CVC-related venous thrombosis ranges from 1.7% to 81.0% in various subgroups (such as patients with cancer, hemophilia, critical illness, children with IBD, and hospitalized and outpatient settings).

25.4.4 Risk with pacemaker wires

Patients with cardiac devices such as wires for pacing or defibrillation are also at significant risk for UEDVT. The first study to demonstrate symptomatic UEDVT being associated with transvenous pacing documented five patients with symptomatic UEDVT of the 212 patients with pacemakers (2%). These patients were treated with anticoagulation and arm elevation.[27] More recently, van Rooden et al. performed a study to document the interval of time between pacemaker placement and UEDVT by performing routine duplex ultrasonography before placement and then at 3, 6, and 12 months after placement. The study demonstrated that UEDVT was seen in 34 of 145 patients (23%). Most patients were found to have UEDVT within the first 3 months of lead implantation (20 of 34 patients [59%]).[28] The study also demonstrated a RR of 3.8 (95% CI: 1.0–15.0) for thrombosis in patients with multiple leads (27.4%) as compared with a single lead (7.2%).

The study by Korkeila et al. found that pacemaker implantation induced a transient hypercoagulable state, but the patient's degree of hypercoagulability did not predict subsequent venous thromboembolism. The authors concluded

that thrombosis formation with pacemaker leads was likely to involve the three components of Virchow's triad: stasis, hypercoagulability, and endothelial damage.[29,30] The same finding has been echoed by other studies.

25.4.5 Site selection

There have been a number of studies that have addressed site selection for CVC-related complications and specifically thrombosis. In one of these studies, the internal jugular vein route had a decreased incidence of malposition as compared to the subclavian vein route: 5.3% versus 9.3% (RR: 0.66; 95% CI: 0.44–0.99).[31] The study also found no difference in thrombotic events. In another study, Martin et al. addressed the risk of UEDVT in a prospective controlled trial with axillary vein cannulation and found the incidence of CVT to be 11%.[32]

25.4.5.1 LATERALITY

Debourdeau et al. presented a review article and found three studies that included CVCs and thrombosis in cancer patients.[33] One study was a prospective controlled trial in solid cancers among patients with tunneled catheters. It evaluated 5447 patients and found left-sided subclavian and jugular vein versus right subclavian vein access routes carry an increased RR of 2.6 ($P < 0.001$). Another study examined 122 patients with solid tumors or hematological malignancies and found that the risks of thrombosis in left-sided versus right-sided access equaled 19% versus 5%, respectively (RR: 4.4; $P = 0.04$). Finally, the third study sampled 334 patients with solid tumors or hematological malignancies and also found left-sided versus right-sided CVC thrombosis, which resulted in rates of UEDVT of 25.6% versus 6.8%, respectively ($P < 0.001$). Thus, left-sided access may carry a higher risk of catheter-associated UEDVT in cancer patients.

25.4.5.2 JUGULAR OR SUBCLAVIAN

A Cochrane review completed in 2012 by Ge et al. attempted to ascertain which vascular access site was associated with thrombosis.[9] They found three randomized controlled trials relevant to this topic. In comparing the internal jugular vein route versus the subclavian route for long-term access in cancer patients, the authors found no difference in thrombotic complications ($n = 240$; RR: 1.97; 95% CI: 0.87–4.48). Comparing femoral versus subclavian routes for short-term CVCs, the results showed that femoral access (21.55%, 25/116 patients) had significantly increased thrombotic complications compared to subclavian access (1.87%, 2/107) ($n = 223$; RR: 11.53; 95% CI: 2.80–47.52). Finally, by comparing the femoral site to the internal jugular vein in hemodialysis patients for short-term needs, the analysis found that there was no difference in thrombotic events between these groups. This analysis demonstrated that subclavian and internal jugular vein routes have similar long-term catheter-related thrombotic complications. The subclavian route was preferred to the femoral route for short-term CVC access. There were no randomized controlled trials addressing CVT and catheter site location for either pacemaker or long-term hemodialysis catheter needs.

25.4.5.3 PRE-EXISTING CENTRAL LINES AND CATHETERS

There has been a traditional fear of inserting a hemodialysis catheter on the ipsilateral side as a pacemaker or other CVC due to the risk of venous thrombosis or wire dislodgement. However, Jung et al. presented interesting findings during their retrospective review of 600 dialysis catheters over 10 years.[34] They found that in all 39 patients with preexisting CVCs ($n = 19$) or pacemaker wires ($n = 20$), the insertion of a tunneled dialysis catheter ipsilateral to the side of other CVC or pacemaker wires failed to reveal malfunction, infection, or dislodgement of the lines or wires. Thus, the authors recommended that in patients with anticipation of a need for arteriovenous fistula placement on one side, it is safe to place a hemodialysis catheter on the side ipsilateral to the cardiac pacing wire or CVC.[34]

25.5 DIAGNOSIS

Determination of thrombosis using duplex ultrasonography can demonstrate an acute UEDVT by the absence of augmentation of flow with respiration and other augmentation maneuvers, inability to compress the vein whenever applicable, and hypoechoic signals.[6] Baskin et al. presented a review article in 2009 and found that duplex ultrasonography exhibited a sensitivity of 78%–100% and a specificity of 86%–100% for the diagnosis of symptomatic UEDVT in an adult population.[11] In another study, a prospective analysis was performed in 66 children with acute lymphoblastic leukemia.[11] The study compared bilateral venography and duplex ultrasonography in the diagnosis of asymptomatic UEDVT. The authors demonstrated that UEDVT occurred in 29% of patients and the sensitivities of duplex ultrasonography and venography were 37% and 79%, respectively. They postulated that the lower duplex ultrasonography sensitivity was due to its inability to detect subclavian thrombosis, while venography may miss internal jugular thrombosis. The authors suggested using a combination of methods if suspicion remained elevated. In addition, a 2013 review article by Murray et al. of cancer patients with thrombosis demonstrated that the sensitivity of duplex ultrasonography may drop to 56% if proximal subclavian or brachiocephalic veins need to be assessed.[10]

Nevertheless, due to its noninvasive nature and cost advantage, duplex ultrasonography is initially recommended. If the duplex examination fails to reveal any thrombosis and clinical suspicion remains high, either computed tomography venography or magnetic resonance venography (MRV) may be needed to confirm diagnosis. Finally, venography remains the gold standard for the diagnosis of central vein thrombosis.

For patients with pacemaker wires, MRV is often contraindicated, and as such, another option for diagnosing thrombosis is transesophageal echocardiogram (TEE). In their 2010 study, Korkeila et al. performed TEE at 6 months

post-implantation of pacemakers and found approximately 9% of patients to have either thrombus in the right atrium or the central veins.[29] However, routine evaluation by TEE is of limited value due to its invasive nature and cost. Therefore, duplex ultrasonography is suggested as the first-line tool for the investigation.

25.6 PREDICTING PROBABILITY

While there is no clear way of knowing if a patient will develop catheter-related thrombosis, there have been attempts to use biomarkers, hematological tests, and clinical examination to identify patients who may be at higher risk of thrombosis.

In a prospective study enrolling 212 patients with hematological malignancy undergoing intensive chemotherapy, Boersma et al. found that the incidence of symptomatic CVC thrombosis is approximately 9%. High factor VIII levels ($P = 0.023$), leukocytosis ($P = 0.042$), and plasminogen activator inhibitor-1 levels above the 75th percentile of the population ($P = 0.008$) were all significantly related to symptomatic thrombosis. The authors suggested the use of further thromboprophylactic measures in this subset of patients.[35]

In another study, the authors conducted a retrospective review of all patients over a 5-year period who underwent duplex ultrasonography of the upper extremity to evaluate for thrombosis. Forty of 177 (23%) upper extremities that underwent scanning were found to have UEDVT. History of prior central venous catheterization predicted UEDVT with an OR of 7.0 ($P = 0.001$).[36]

In a separate study, Constans' Clinical Decision Score for predicting UEDVT assessed the risk as 12%, 20%, and 70% based on 1 point being assigned for each of the following three risk factors: presence of a CVC or pacemaker wire in the venous system; localized pain; and unilateral edema. A reduction of 1 point is assigned if some other diagnosis is at least as likely to be present as thrombosis.[37]

25.7 TREATMENT OF CVT

Most of the data for UEDVT treatment has been extrapolated using what we know from lower extremity DVT. As such, anticoagulation has historically been the treatment of choice.

The standard for anticoagulation is heparin as a bridge to vitamin K antagonists. In pediatrics, low-molecular-weight heparin may be unpredictable in its effect, and we may need to consider measuring anti-Xa levels. In addition, novel oral anticoagulants have proved their effectiveness in lower extremity DVT and should be strongly considered as enhanced alternatives.

UEDVT associated with catheters or wires should be treated with 3–6 months of anticoagulation. If the patient does not need a central line, including a PICC, the recommendation is to remove it.[30,33,38] Furthermore, wires for pacing and defibrillation need not be removed. Finally, in those patients who are unable to complete anticoagulation, one may consider placement of a superior vena cava (SVC) filter to prevent PE.[12,33,39]

The American College of Chest Physicians guidelines recommend against the use of compression in symptomatic patients. Furthermore, the safety and efficacy of thrombolytics and thrombectomy are not clearly established based on the available data. Their use may be beneficial for phlegmasia.[40]

25.8 PREVENTION OF CATHETER-RELATED CVT

The French National Federation of Cancer Centers workgroup on Standards, Options, and Recommendations reviewed 36 publications (studies between 1990 and 2007) in order to establish their guidelines on the prevention of CVC-related thrombosis. Their analysis found that catheter position is the most important factor, and recommended that the distal tip of all CVCs should be at the junction of the right atrium and SVC.[17]

While some studies have advocated the routine use of anticoagulation for the prevention of thrombosis,[12,19] most recent data fail to replicate the data that were published in the original trial, and routine anticoagulation for prophylaxis is not recommended.[33] Similarly, there is also no role for anticoagulation in the pacemaker population. Although studies have showed that anticoagulation prophylaxis trended towards less thrombosis in a small series, there has not been clear identification of the role of anticoagulation for prophylaxis.[33] In the study by D'Ambrosio et al., the authors performed a meta-analysis and found that anticoagulation use in cancer patients with CVCs had a lower risk of symptomatic CVC-related venous thrombosis than the control group (RR: 0.61; 95% CI: 0.42–0.88).[13] In a different series of patients, the 1994 study by Monreal et al. showed that prophylaxis with dalteparin starting 2 hours before CVC insertion in cancer patients reduced the risk for UEDVT.[19] Catheter thrombogenecity has also been discussed. Murray et al. demonstrated that polyethylene catheters are more thrombogenic than polyurethane catheters.[10] Furthermore, the authors found that rigid catheters may damage venous walls, whereas softer ones may be more compliant and remain in the optimal location, leading to improved thrombotic outcomes.

Data on heparin-bonded catheters are scarce and largely inconclusive regarding thrombus prophylaxis.[41] Indeed, heparin-bonded catheters have not been demonstrated to be prophylactic against UEDVT in adult patients.[42] In the pediatric population, a Cochrane review examined two studies: one with 97 patients and the other with 209 patients. Both studies randomized participants to heparin-bonded catheters and non-heparin-bonded catheters. The review found no difference in catheter-related thrombosis (RR: 0.34; 95% CI: 0.01–7.68).[43]

25.9 CONCLUSION

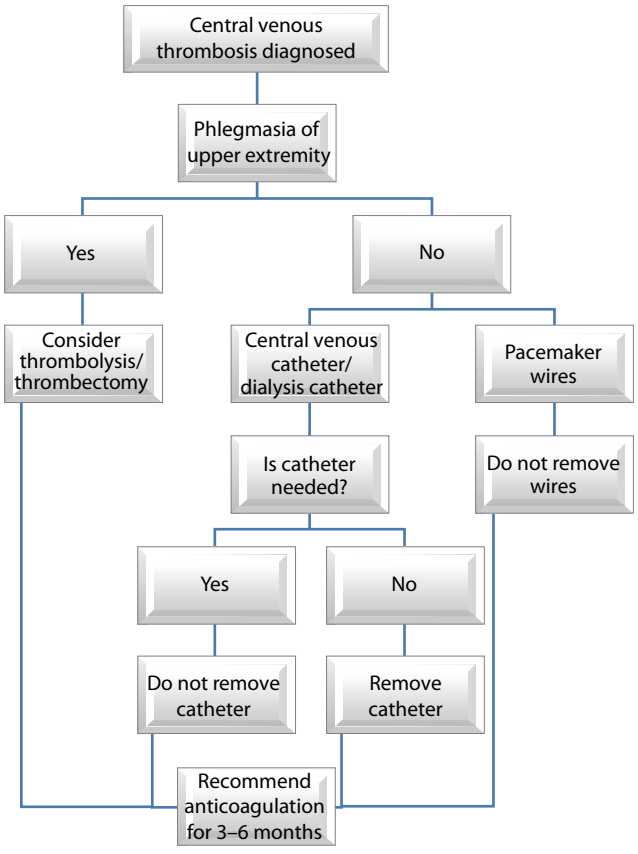
Virchow's triad is of importance in the development of CVT. Indwelling catheters inherently contribute to each of the components of the triad. They are foreign objects to the venous system and may contribute to its local hypercoagulability. Furthermore, catheter or pacemaker wire presence

Guidelines 3.9.0 of the American Venous Forum for the management of acute central venous thrombosis in the setting of central lines, pacemaker wires, and dialysis catheters

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.9.1	To decrease the risk of central venous thrombosis, we recommend placement of the tip of the central venous catheter at the junction of the right atrium and superior vena cava.	1	B
3.9.2	We recommend 3–6 months of anticoagulation for the treatment of symptomatic acute central venous thrombosis in the setting of central lines, pacemaker wires, or dialysis catheters. Removal of the central line or catheter is recommended only if they are no longer needed.	1	B

in the lumen may cause stasis due to low flow in the vessel lumen. In addition, their initial insertion and presence carries the potential to cause endothelial damage.

Acute CVT is usually asymptomatic. Diagnosis starts with a clinical examination, followed by duplex ultrasonography. Once the diagnosis of UEDVT is confirmed, the mainstay of treatment is anticoagulation. There are limited roles for thrombectomy or thrombolysis. Furthermore, prevention of thrombosis is best achieved by placing the CVC tip at the junction of the right atrium and SVC. Finally, improving catheter and wire profiles to be less thrombogenic may have a role in decreasing the prevalence of CVT. Treatment algorithm for CVT associated with pacemaker wires, CVCs or dialysis catheters are presented in Figure 25.1.



*If patient unable to undergo anticoagulation, consider SVC filter placement.

Figure 25.1 Treatment algorithm for CVT associated with pacemaker wires, CVCs or dialysis catheters.

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● = Key primary paper
★ = Major review article
◆ = Guideline

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26

Indications, techniques, and results of inferior vena cava filters

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26.1 INTRODUCTION

The majority of pulmonary emboli (PE) arise from thrombosis in the deep veins of the legs and pelvis. The first-line therapy for venous thromboembolism (VTE) is pharmacologic anticoagulation, but in instances where anticoagulation is contraindicated or therapeutic anticoagulation cannot be achieved, an alternative treatment strategy is required. This subset of patients requires placement of venous filter devices that provide partial interruption of the inferior vena cava (IVC) to prevent PE. The goal of IVC filter placement is to trap clinically significant thromboemboli without causing complete occlusion of the IVC. The advent of retrievable IVC filters has played a significant part in broadening the indications for the use of IVC filters to include prophylactic placement. Although this practice remains controversial, appropriately selected patients can benefit from IVC filter placement. In this chapter, we discuss the indications, clinical use, efficacy, insertion techniques, and complications of IVC filters.

26.2 BACKGROUND

John Hunter introduced one of the earliest techniques for the management of lower extremity thrombophlebitis in the 1700s with ligation of the femoral veins to prevent clot propagation. However, it was not until 1846, with Rudolph Virchow's suggestion that thrombus in the pulmonary venous system was of embolic origin, that venous occlusion was approached as a strategy for PE prevention. Bottini is credited with the first successful caval ligation in a setting of trauma, but Homan was the first to hypothesize that embolization of lower extremity thrombus could be prevented through bilateral ligation of the femoral veins.[1] When these techniques failed to prevent recurrent PE, Collins and Nelson,[2] and subsequently Homan,[3] proposed infrarenal ligation of the IVC as a strategy for PE prevention. Early IVC ligation involved a laparotomy under general anesthesia in patients with significant pulmonary hypertension, right heart failure, and associated oxygenation deficits, and thus was associated with unacceptably high mortality, ranging from 4% in low-risk patients to 39% in patients with significant cardiac disease.[4] Morbidity from the procedure was also substantial and included lower extremity edema, stasis ulceration, and post-thrombotic syndrome. Also of significance, ligation of the IVC was associated with an incidence of recurrent PE of up to 15% through the development of collateral vessels around the ligated segment. Surgical vena caval interruption techniques involving suture or staple grids, and external caval clips were also later developed in an effort to preserve channels for blood flow in the IVC while entrapping significant thrombus within caval segments. These techniques, although improvements from IVC ligation, were also fraught with complications, yet remained standards of therapy until less morbid treatments became available.

In the late 1960s, the Mobin–Uddin umbrella was introduced and became widely utilized because of its efficacy

and ease of placement compared to the contemporary surgical treatment options. The Mobin–Uddin umbrella consisted of a silicone disc with multiple holes and six stainless steel struts to maintain the appropriate geometry when deployed. Although it effectively prevented PE, it did so at the expense of caval patency and was associated with an IVC occlusion rate as high as 65%.[5] There were also significant problems with caval fixation that resulted in migration of the device into the right heart or pulmonary artery. As a result, it was later withdrawn from the market.

The Greenfield filter was first used in 1972 to provide protection against PE and is the benchmark to which all other filters are currently compared. The long-term patency rate of the Greenfield filter is as high as 95%,[6] which is likely due to the conical design that enables a high thrombus volume to area reduction ratio. This design allows up to 70% of the cone volume to be occupied with thrombus before a 50% obstruction in IVC cross-sectional area and significant reduction in blood flow occurs. The original 24-French (Fr) stainless steel filter was developed for operative insertion via a femoral or internal jugular venotomy under local anesthesia. The operative procedure required general anesthesia with a pre-operative venacavogram performed to assess for caval anomalies and to allow identification of the appropriate site for placement. This naturally led to the development of lower-profile systems that allowed for rapid and safe percutaneous delivery and deployment of the filter. The increasing convenience and reduced procedural cost of IVC filter placement has led to a surge in use of these devices, with an increase of 111% over the 10-year period prior to 2008.[7]

26.3 INDICATIONS FOR IVC FILTER PLACEMENT

It is well established that the first-line therapy for the treatment of VTE is anticoagulation.[8,9] Consequently, the most widely accepted indications for IVC filter placement require the presence of a VTE and contraindication to systemic anticoagulation. Indications for IVC filter placement are traditionally divided into absolute indications, relative indications, and prophylactic indications. Absolute indications for IVC filter placement are well established and follow common sense. These indications include the presence of VTE and one of the following: a baseline contraindication to anticoagulation, a complication from anticoagulation, or a recurrent deep venous thrombosis (DVT) or PE despite adequate (therapeutic) anticoagulation. There is considerable controversy surrounding numerous relative and prophylactic indications for IVC filter placement, which is reflected by variation in guidelines from the American College of Chest Physicians (ACCP), the American Heart Association (AHA), and the Society of Interventional Radiology (SIR). The indications for IVC filter placement are summarized in Table 26.1, and discussed in detail below.

Table 26.1 Indications for inferior vena cava filter placement

- Common indications:
  - Contraindication to anticoagulation in patients with pulmonary embolism (PE)/deep venous thrombosis (DVT)
  - Complications of anticoagulation
  - Failure of anticoagulation due to progression of DVT, recurrent PE, or noncompliance
  - Massive, life-threatening PE with residual DVT despite anticoagulation
  - Free-floating thrombus in inferior vena cava (IVC) iliac, or pelvic veins
  - Chronic, recurrent PE with pulmonary hypertension and cor pulmonale
- Indications specifically for prophylactic IVC filter:
  - Patients with prior PE with significantly increased risk for second PE or those with poor cardiopulmonary reserve
  - Patients with a significant burden of proximal DVT or free-floating thrombus
  - Patients at high risk for complications of thromboembolism like malignancies and major/multiple trauma
  - Patients who cannot receive anticoagulants, such as those with internal organ injury or active internal bleeding
  - Multiple risk factors for DVT in a pre-operative patient

26.3.1 Absolute indications (requires presence of VTE)

Contraindication to anticoagulation is the most frequently cited reason for selecting IVC filter placement over standard anticoagulation therapy. Major contraindications to anticoagulation are serious active bleeding, recent spinal cord or brain injury, recent stroke, surgery, or trauma. Advanced age and pregnancy are also considered as relative contraindications to anticoagulation, but remain controversial. Many contraindications to anticoagulation therapy are self-limited or are reversed over time, allowing a course of anticoagulation to be completed at a later time. The latter advocates the increased use of retrievable IVC filters.

Complications secondary to anticoagulation include bleeding or, in rare cases, an adverse reaction to the anticoagulant used. Up to 5%–10% of patients treated with intravenous heparin will develop a bleeding complication over the duration of therapy. The severity of bleeding is variable, but appears to be dose dependent and varies with the patient's inherent risk (i.e., prior surgery or trauma, predisposing clinical factors, or underlying hemostatic conditions).[10,11] In addition to bleeding complications, heparin-induced thrombocytopenia develops in 1.1%–2.9% of patients receiving unfractionated heparin.[12]

Should this occur, all heparin must be discontinued, even that which is used for flushing lines and catheters, as the condition responds to cessation of therapy. Rarely, patients may develop sensitivity to heparin with the development of a cutaneous rash or anaphylaxis. The incidence of these complications is much lower with the use of low-molecular-weight heparins, but they do occur. Alternatives to heparin should be considered.

Bleeding may also occur in up to 10% of patients treated with warfarin (Coumadin). The degree of bleeding is most often associated with the inactivation of the clotting cascade as indicated by an elevated international normalized ratio (INR). Patients with significantly elevated INRs are more likely to develop major hemorrhagic complications than those with mildly elevated levels.[13] Routine monitoring and dietary counseling will help to prevent such complications. Monitoring should also be undertaken when there has been a change in concomitant medications. Several drugs have either a synergistic or antagonistic interaction with warfarin, resulting in decreased efficacy or increased risk of adverse events. In addition to bleeding complications, a small number of patients develop warfarin-associated skin necrosis, which usually is seen early and in the absence of adequate concurrent heparin treatment. This is most likely to occur in areas of increased subcutaneous fat and may also be associated with the "blue toe" syndrome. Should this develop, the drug must be promptly discontinued.[14]

Recurrent VTE while on therapeutic anticoagulation is considered a failure of anticoagulation, and is another common indication for filter placement. Prior to determining that anticoagulation has failed, it should be established that the patient was adequately anticoagulated to begin with. Many times, failures of anticoagulation are failures to reach therapeutic drug levels. The patient who develops recurrence or extension of thromboembolism while anticoagulated may, in fact, not be adequately anticoagulated or simply non-compliant. In order to reduce this risk, patients should be monitored closely during the initiation of therapy with heparin to ensure that they are therapeutic within the first 24 hours. For low-molecular-weight heparin, patients become therapeutic with an appropriate weight-based dose. Nomograms have been developed to ensure that this takes place.[15,16] For patients on warfarin, the INR must be closely monitored to ensure that patients remain sufficiently anticoagulated for the duration of their treatment course. A subset of patients with warfarin resistance who demonstrate an inability to achieve a therapeutic INR should also be considered for IVC filter placement.

Recently, several new oral anticoagulants (NOACs) have been developed for treatment of VTE. These NOACs include the direct thrombin inhibitor dabigatran and the direct anti-Xa inhibitors rivaroxaban, apixaban, and edoxaban. All of these drugs are currently approved for both stroke prevention in atrial fibrillation and the treatment of VTE. The increasing use of NOACs for the treatment of VTE is relevant to this chapter for several reasons. Like heparin-derived products and warfarin, the primary complication of NOAC therapy is bleeding; thus, IVC filters may be indicated in patients taking NOACs. Additionally, there is no standard method of monitoring patient response to NOAC therapy. One of the purported advantages of this new class of drugs is that, unlike warfarin, regular monitoring of these drugs is not required. However, the inability to assess for therapeutic drug levels makes it extraordinarily challenging to establish whether a patient with a recurrent VTE on NOAC therapy was adequately anticoagulated at the time of the VTE event. Lastly, the growing use of NOACs for VTE treatment may influence future guidelines regarding the management of VTE. At present, failure of a single agent has been considered an indication for IVC filter placement. However, as more oral therapies emerge for the treatment of VTE, future guidelines may require failure of multiple pharmacologic modalities prior to use of an IVC filter.

26.3.2 Relative indications (VTE required)

The relative indications for IVC filter placement also require the confirmed presence of VTE, in addition to risk factors for future PE or cardiopulmonary compromise. Such indications include individuals with a DVT and poor cardiopulmonary reserve such as pulmonary hypertension or cor pulmonale, who are unlikely to tolerate the hemodynamic and respiratory stress of a PE. Similarly, patients with residual DVT who have experienced a massive PE may not tolerate additional pulmonary insult, and therefore may benefit from IVC filter placement. Patients with a large, free-floating iliocaval thrombus (typically greater than 6 cm) may also be considered for filter placement, as a large thrombus with high embolic risk could lead to a massive PE. Other relative indications for IVC filter placement include patients with a VTE and relative contraindications to anticoagulation, as is demonstrated by poor adherence to medications or by those with ataxia or a high fall risk. Additionally, patients with a high peri-procedural risk of PE, including those undergoing pulmonary thromboembolectomy, and patients with DVT and a large clot burden undergoing thrombolysis, could benefit from IVC filter placement.

There is ongoing debate with regard to the relative indications for IVC filter placement. Current AHA guidelines identify just one relative indication for IVC filter use: an acute PE in a setting of poor pulmonary reserve.[9] Additionally, the AHA guidelines state that IVC filters should *not* routinely be used as an adjunct to anticoagulation or in a setting of fibrinolysis. The ACCP has slightly more liberalized guidelines, with relative indications for IVC filter use including unstable patients with acute PE, massive PE treated with thrombolysis/thrombectomy, or chronic PE treated with thromboendarterectomy.[8] The SIR offers the most inclusive set of recommendations for IVC filter use, with the multidisciplinary consensus conference guidelines from 2007 and quality improvement guidelines from 2011 identifying all of the above indications.

26.3.3 Prophylactic indications (no VTE required)

Indications for prophylactic IVC filter placement remain highly controversial. Only the SIR guidelines recommend the use of IVC filters in a prophylactic setting, and the ACCP guidelines explicitly recommend against the use of prophylactic IVC filters. Nevertheless, there are certain populations that may benefit from the placement of an IVC filter, even in the absence of DVT. These indications are discussed below.

Certain trauma patients may be at excessively high risk of DVT, and thus are possible candidates for prophylactic IVC filters.[17] The constellation of traumatic injuries that constitutes high risk includes brain injury, spinal cord injury, and pelvic and lower extremity long bone fractures. These injuries carry a 50-fold increase in thromboembolic complications compared to other trauma patients.[18,19] The use of IVC filters in these patients has been criticized. By itself, the filter protects against PE, but does nothing to prevent additional episodes of thrombosis or to treat existing DVT. There are also concerns about increased health care costs and procedural morbidity/mortality.[18,20–24]

Certain surgical patients that may benefit from prophylactic IVC filter placement include patients undergoing bariatric surgery or spinal surgery. The incidence of PE in bariatric surgery patients is reported to be 1%–4%, but may be even higher in super-obese patients. This has remained unchanged despite the near-universal institution of pharmacomechanical prophylaxis measures. Several small retrospective studies have suggested IVC filter placement reduces the incidence of PE in bariatric surgery patients, but the practice remains controversial, and a recent systematic review concluded IVC filter placement offered no benefit for protection from PE.[25] The rate of PE after spinal surgery is reportedly as high as 13%; therefore, this patient population may benefit from pre-operative prophylactic IVC filter placement. Several small retrospective studies support this contention[26,27]; however, the quality of evidence at this time is low.

Malignancy has long been known to carry a significantly increased risk of VTE. The reported incidence of PE in the literature is somewhere between 7% and 50% in patients with malignancy.[28] Two studies have estimated the risks of PE in cancer patients to be approximately 3.6-fold higher than in patients without malignancy.[29,30] These same patients that are at increased risk of VTE also appear to be at increased risk of bleeding while receiving anticoagulation therapy.[29,31,32] Debate regarding the use of IVC filters in the setting of malignancy has persisted since the 1990s. Despite frequent use for this indication and continued attempts to clarify their role, the proper use of IVC filters in the setting of malignancy remains a point of contention.

Immobility is an established risk factor for VTE, with prolonged immobility leading to a 4.9-fold increased risk of PE.[33] While pharmacoprophylaxis and sequential compression devices may reduce the incidence of PE, certain individuals that have a contraindication to anticoagulation may benefit from IVC filter placement. For example, patients with severe stroke can have prolonged immobility and, due to risk of intracerebral hemorrhage, cannot receive anticoagulation. There are limited data demonstrating the efficacy of IVC filters in preventing PE in patients with restricted mobility. However, given the low risk of complications associated with IVC filters, these devices should be considered in immobilized patients who cannot receive anticoagulation.[34]

26.4 CONTRAINDICATIONS TO IVC FILTER PLACEMENT

The only absolute contraindications to IVC filter insertion are complete thrombosis of the IVC and inability to gain access to the IVC due to severe venous obstruction. A relative contraindication is uncorrectable, severe coagulopathy or thrombocytopenia, in which case surgical venotomy and surgical placement may be safer, although IVC filters with low-profile delivery devices may be useful in these cases. Careful evaluation of the risks versus benefits of filter placement should be done in such patients. Special situations requiring caution prior to filter placement include: patients with untreated or uncontrolled bacteremia, who should be treated with immediate and appropriate antibiotic treatment, and filter placement in pediatric patients and pregnant women, due to uncertain long-term effects and the durability of the filters. Again, retrievable filters may have a role in these patients depending on the specifics of these cases. If an IVC filter must be placed in a pregnant woman or woman of child-bearing age, placement of the filter in the suprarenal position should be considered to avoid the potential complication of compression of the filter by the enlarging uterus.

26.5 FILTER CHARACTERISTICS—WHICH ONE IS AN IDEAL FILTER?

Several designs of filters in various size and shapes are available for clinical use. The availability of such a wide range of filters suggests that not one type is by itself ideal. The characteristics of an ideal filter are described in Table 26.2. The most important desirable factors are high filtering efficiency (large and small emboli) without impedance of blood flow, stability of positioning and structure, and a low rate of associated morbidity.

26.6 TYPES OF IVC FILTERS

26.6.1 Permanent filters

Permanent filters are placed with the intention of providing life-long protection from PE, and are thus designed with caval fixation in mind. The first widely used IVC filter was the Greenfield filter, which was originally introduced in 1972 as a permanent filter (Figure 26.1). It is constructed of

Table 26.2 Characteristics of an ideal filter

1. High filtering efficiency for both large and small emboli without impedance of blood flow
2. Stability of position/fixation and structural integrity
3. Low procedural morbidity, no mortality, and low cost
4. Ideal biomechanical property: biocompatible, non-thrombogenic, and magnetic resonance imaging compatible
5. Ideal delivery system: small caliber and easy deployment with ability to reposition
6. Safe retrievability when no longer needed

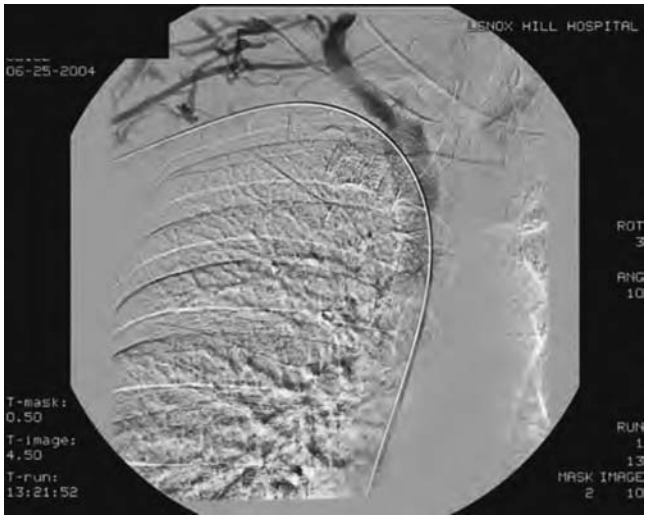

Figure 26.1 The original stainless steel Greenfield filter first used in 1972. (Used with permission from Rutherford RB, Ed., *Vascular Surgery* (4th Ed), W.B. Saunders Company, Philadelphia, 1995.)

stainless steel and was originally intended for open surgical placement via a 28-Fr sheath. It has been discontinued from clinical use and replaced with a lower-profile system. In addition to the Greenfield filter, several other permanent IVC filters are available for clinical use (Table 26.3). Brief descriptions of available permanent IVC filters are included below and in Figure 26.2.

26.6.2 Titanium Greenfield filter

The titanium version of the Greenfield filter has a conical configuration consisting of six struts that is compressed into a 12-Fr carrier (14.3-Fr outer diameter) sheath. The sheath is inserted with a guidewire, but actual filter deployment occurs without the use of a guidewire, unlike the original and stainless steel over-the-wire design. The filter is designed for IVC diameters smaller than 28 mm. The filter comes in femoral and jugular versions.

26.6.3 Stainless steel over-the-wire Greenfield filter

The filter has six stainless steel struts that are press-fitted into a cylindrical cap with a hole that the guidewire can pass through. This filter is placed over a centering guidewire to address frequently encountered instances of filter tilting and asymmetry with the titanium version. The hooks of four of the legs point superiorly, and two opposite hooks point inferiorly to prevent migration. The hooks are also "recurved," forming a complete circle before protruding to decrease the degree of hook penetration. There are separate femoral and jugular versions of this filter. The filter is safe for magnetic resonance imaging, but causes a significant amount of artifact.

Table 26.3 Permanent inferior vena cava filters

Name	Manufacturer	Year introduced	FDA approval
Titanium Greenfield	Boston Scientific/Medi-tech, Natick, MA	1988	1989
Over-the-wire stainless steel Greenfield	Boston Scientific/Medi-tech, Natick, MA	1994	1995
VenaTech/LGM	B. Braun Medical, Evanston, IL	1986	1989
Low-profile VenaTech	B. Braun, Boulogne, France	2000	2001
Simon Nitinol	Bard, Covington, GA	1988	1990
TrapEase	Cordis, Miami, FL	1998	2000
Bird's nest	Cook, Bloomington, IN	1982	1989

Name	Delivery system size	Maximum diameter	Length	Material	MRI compatibility
Titanium Greenfield	14.3 Fr	38 mm	47 mm	Titanium	Compatible
Over-the-Wire stainless steel Greenfield	15 Fr	32 mm	49 mm	Stainless steel	Not compatible
VenaTech/LGM	14.6 Fr	30 mm	38 mm	Phynox	Compatible
Low-profile VenaTech	9 Fr	40 mm	43 mm	Phynox	Compatible
Simon Nitinol	9 Fr	28 mm	45 mm	Nitinol	Compatible
TrapEase	8 Fr	35 mm	50–65 mm	Nitinol	Compatible
Bird's nest	14 Fr	40 mm	70–110 mm	Stainless	Not compatible; creates large artifacts

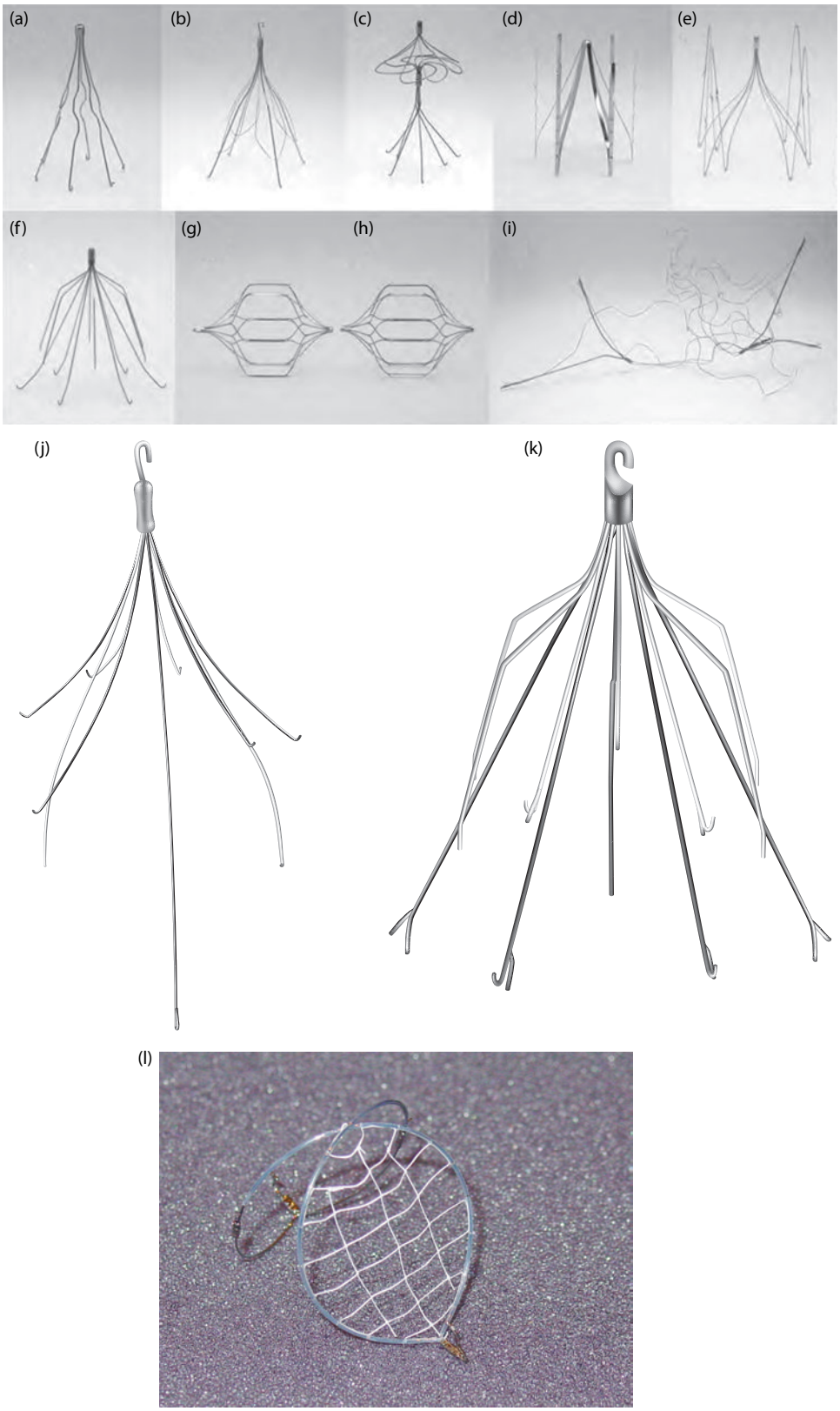

Figure 26.2 Various available filters. **(a)** Stainless steel Greenfield (Boston Scientific/Medi-Tech); **(b)** Günther Tulip MREye (Cook); **(c)** Simon Nitinol (Bard); **(d)** VenaTech LGM (B. Braun); **(e)** low-profile VenaTech (B. Braun); **(f)** OptEase (Cordis); **(g)** TrapEase (Cordis); **(h)** G2 Filter (Bard); **(i)** bird's nest (Cook); **(j)** ALN (ALN); **(k)** Denali (Bard); **(l)** Crux (Volcano). (Reprinted with permission from Getzen TM, Rectenwald JE. *J Natl Compr Canc Netw* 2006;4:881–8.)

26.6.4 VenaTech LGM and low-profile filter

This original LGM filter has a six-strut conical configuration with side rails containing hooklets that provide caval centering and fixation, respectively. The filter is designed for IVC diameters of 28 mm or less. The filter is loaded in an injection syringe, with the orientation of filter injection into the sheath determined by the access route (femoral or jugular). The low-profile filter replaces the LGM, and instead of six side struts as with the original VenaTech filter, this design uses eight Phynox wires formed in a conventional conical configuration with welded hooks, some oriented superiorly and others inferiorly. The lateral, side-rail configuration of these wires allows for caval centering and stabilizing. The low-profile filter can be deployed from femoral, jugular, or antecubital routes, and the low-profile design uses a cartridge injection system to properly orient the filter for femoral or jugular uses.

26.6.5 Simon Nitinol filter

The configuration of the filter uses a conical array of six struts with hooks at the base, and a daisy-wheel configuration of wires at the filter apex, in effect providing two levels of filtration. The filter daisy wheel has seven overlapping loops. The filter is manufactured from Nitinol (an alloy of nickel and titanium), which has unique thermal–mechanical memory properties that allow the filter to exist in the straightened but flexible form at room temperatures (<27°C) within the 7-Fr delivery carrier and reform into a predetermined designed filter shape at body temperatures. The filter is designed for IVC diameters of 28 mm and smaller. The filter can be deployed from femoral, jugular, or antecubital routes.

26.6.6 TrapEase filter

The TrapEase filter is a significant departure from the conical design introduced by Greenfield. It has a double-basket symmetric configuration with cephalad and caudad baskets in a six-diamond or trapezoidal shape and the baskets are then connected by six straight struts, which contain proximal and distal hooks for fixation within the IVC. The filter can be inserted by femoral, jugular, or antecubital approaches. The TrapEase IVC filter can be used in patients with IVC diameters of 30 mm and smaller. Recent data suggest that the TrapEase—and by association the retrievable version of this filter, the OptEase—may be associated with an excessive rate of IVC thrombosis.

26.6.7 Bird's nest filter

This filter consists of four stainless steel wires (25 cm long by 0.18 mm) attached to two V-shaped struts. The V-shaped struts have small barbs at the two ends to engage the IVC wall. During insertion, the four wires are extruded from the delivery system in a random distribution, simulating a bird's nest. The filter is approximately 7 cm long but, in practice, the deployed length varies by the amount of overlap of the "V" struts. It can be placed in IVCs with diameters as large as 40 mm. It can be placed by femoral or jugular routes. The filter generates the largest magnetic resonance imaging artifact of all the filter devices because of the stainless steel construction.

26.6.8 Optional retrievable filters

With optional retrievable IVC filters, the delivery system is completely removed and the venous system is re-accessed at a later date for retrieval of the filter if desired. The first retrievable filter to become commercially available was the Amplatz device, but this filter was removed from the market due to a high rate of IVC occlusion. Table 26.4 lists the commercially available retrievable IVC filters available in the United States. The time of retrieval for these filters varies with device, and there are multiple case reports of filter retrieval several months to years after placement. In general, retrieval of filters must be performed as soon after placement as clinically possible, because endothelialization of filter struts to the IVC wall has been described to occur as soon as 12 days after filter placement.[35]

26.6.9 Günther Tulip filter

This filter consists of four main struts configured as a cross with 1-mm-long hooks at the inferior end for IVC fixation. Each strut has an elongated wire loop that extends inferiorly three-quarters of the length from the apex to the hooked end of the four main cross struts. The filter is 30 mm in diameter and 50 mm long in the fully expanded state. Whereas the filter can be placed from either femoral or jugular access sites, retrieval is performed from the right jugular site with use of a retrieval snare and an 11-Fr sheath. It is recommended by the manufacturer that the filter removal is done within 14 days of implantation, but "conventional wisdom" suggests that removal out to 8 weeks is possible. Data suggest that the Günther Tulip may be safely removed at 30 days with minimal, if any, complications,[36] and removal out to 126 days after placement has been reported.[37]

26.6.10 Celect

The Celect is a cobalt–chromium filter that also consists of four main hooked struts for IVC fixation, as well as eight shorter secondary legs that provide additional outward support. The filter has a maximum diameter of 30 mm and is 45 mm long when deployed. It may be delivered via a jugular or femoral approach with a 7-Fr sheath, and retrieved using a looped snare through an 11-Fr sheath.

Table 26.4 Retrievable inferior vena cava filters

Name	Manufacturer	Year introduced	Delivery system size	Material	Magnetic resonance compatibility	Recommended time for retrieval	FDA approval for retrievable use
Gunther Tulip	Cook	1992 (available in the U.S. since 2001)	8.5 Fr	Elgiloy	Compatible	14 days	Approved
G2	Bard	2000	7.0 Fr	Nitinol	Compatible	60 days	Currently permanent use only
OptEase	Cordis	2003	6.0 Fr	Nitinol	Compatible	23 days	Approved

26.6.11 Recovery filter/Generation 2 filter/G2X/Meridian filter/ Eclipse/Denali

The Bard series of retrievable filters started with the Recovery Nitinol filter, which was the first filter to have a retrieval indication in the United States. The Recovery Nitinol filter was subsequently replaced by the Generation 2 (G2), which was later renamed the G2X. Both the Recovery and the G2 filters have two levels of filtration, similar to the Simon Nitinol filter. These filters have six arms and six legs (upper and lower filtering elements, respectively). The Recovery filter was retrieved from the right jugular vein approach with a retrieval cone that was fabricated from nine metal claws covered with urethane material. The G2 filter was modified by increasing its resting diameter, changing the angulation of the wires forming the upper filtering elements, and changing the metallic composition of the hooks attached to the lower filtering elements. Both the recovery and G2 filters were reported to have high rates of strut facture. One study noted that strut fracture occurred in 25% of Recovery filters and 12% of G2 filters, potentially leading to severe complications, including ventricular tachycardia and tamponade.[38] Both the Recovery and G2 filters were eventually removed from the market. Subsequent design changes led to the Eclipse, Meridian, and finally the Denali filters. Only the Eclipse and Denali are presently available for use in the United States. The Eclipse filter consists of 12 Nitinol wires originating from a central hooked nitinol ring. The two sets of legs provide two levels of filtration, with the longer legs providing fixation and the shorter legs providing stabilization. The filter can be deployed via a jugular or femoral approach in IVC diameters of up to 28 mm using a 7-Fr sheath. The Denali is a Nitinol filter consisting of 12 legs with two levels of filtration, much like the Eclipse. This filter has two longer anchors and four midsized legs with hooks and anchors that provide the first level of filtration. An additional six shorter legs stabilize the filter and provide a second level of filtration. The filter comes preloaded in a storage tube with a pusher. The delivery system uses an 8.4-Fr sheath and can be deployed in an IVC with a maximum diameter of 28 mm.

26.6.12 Option

The Option is an over-the-wire Nitinol filter that consists of six hooked struts for caval fixation. This is the lowest-profile filter currently available and utilizes a 5-Fr sheath that has an outer diameter of 6.5 Fr. The Option also has an optional 100-cm delivery sheath, and is the only IVC filter approved for popliteal access.

26.6.13 ALN

The ALN is a cone-shaped filter with three long, curvilinear centering struts and six shorter anchoring struts with curved hooks for fixation. The struts are all variable in length to prevent entanglement when loaded in the 7-Fr delivery sheath. The ALN filter is approved for use in caval diameters of up to 32 mm, and is available with or without a hook on the filter base for retrieval. The hooked system can be retrieved with a looped snare, while a pincer retrieval system is used for the non-hooked filter.

26.6.14 OptEase filter

The OptEase filter has a dual cone (symmetrical) design that is nearly identical to the TrapEase. The OptEase filter has been modified with the placement of unidirectional barbs and an apical hook for removal, and can be inserted from jugular or femoral routes with the same 6-Fr introducer sheath (by reorienting the filter). This filter is retrieved from the femoral vein only by snaring a small hook at the caudal end of the filter. Notably, in 2013, the Food and Drug Administration (FDA) issued a class I recall on OptEase filters due to confusion with the labeling of the filter and to avoid loading the filter backward. There were no problems with the device itself.

26.6.15 Crux

The Crux filter also varies significantly from the traditional conical filter design. The Crux is composed of a Nitinol frame made of two sinusoidal wave forms connected at the ends. When deployed, the filter forms a partially

sandwiched figure of 8 within the IVC. One loop contains a webbed expanded polytetrafluoroethylene (ePTFE) mesh to trap emboli. There are five tissue anchors along the outer frame that secure the filter in place. There are retrieval tails at either end of the filter, so that bidirectional retrieval can be performed.

26.7 TEMPORARY FILTERS

Temporary filters, by definition, remain attached to the delivery system. This facilitates retrieval, but the external portion increases the risk of infection. Temporary filters are not clinically available in the United States and are associated with poor outcomes in small European studies.[39,40] Two of the earliest caval interruption devices were designed for temporary use. These include the Eichelter sieve and the Moser balloon. These were soon abandoned in response to concern regarding the fate of trapped embolus.[4]

26.8 PERMANENT OR OPTIONALLY RETRIEVABLE?

The development of optional retrieval devices was largely driven by the results of the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) trial. The PREPIC trial was the first of only two randomized controlled trials involving IVC filters. The study was a multiinstitutional trial of 400 patients with confirmed acute proximal DVT that were randomized to receive either anticoagulation alone or anticoagulation and a permanent IVC filter. The initial 2-year results from the PREPIC found that at 12 days there were two PEs (1.1%) in the filter group compared to nine (4.8%) in the no-filter group ($P = 0.03$), resulting in an odds ratio (OR) of 0.22 (95% CI: 0.05–0.90). After 2 years, there were six PEs in the filter group compared to 12 in the no-filter group ($P = 0.16$). The overall incidence of recurrent DVT in the filter group was 20.8% compared to 11.6% in the no-filter group ($P = 0.02$), for an OR of 1.87 (95% CI: 1.10–3.20), although there was no significant difference in recurrent DVT at 1 year after enrollment.[41] The 8-year follow-up of the PREPIC trial found nine PEs (6.2%) in the filter group compared to 24 (15.1%) in the no-filter group ($P = 0.008$), resulting in an OR of 0.37 (95% CI: 0.17–0.79). Recurrent DVT occurred in 35.7% in the filter group, compared to 27.4% in the no-filter group ($P = 0.042$). At 8 years, there was no significant difference in mortality between the filter and no-filter groups, and no significant difference in incidence of post-thrombotic syndrome.[42] The results from PREPIC study suggested that IVC filters provide a reduction in risk of the development of PE when combined with anticoagulation, but no improvement in mortality. Furthermore, the benefit in terms of reduced risk of PE comes at the expense of an increased risk of recurrent DVT, although this did not translate to a higher risk of post-thrombotic syndrome.

While the PREPIC trial was heralded as the first randomized controlled trial to explore the benefits of IVC filter use in patients with DVT, the study had several notable flaws in its design and analysis. First, study participants were randomized using a 2×2 factorial design, so individuals were randomized to receive either enoxaparin or unfractionated heparin in addition to either an IVC filter or no filter. With enrollment of 400 patients, the study was underpowered for such an analysis.[43] Additionally, the PREPIC trial evaluated IVC filters only in patients who were concomitantly receiving anticoagulation, thus the population in which filters are most frequently deployed (patients who cannot be anticoagulated) was not examined.[44] Finally, the selection of the filter device was left up to the discretion of the physician, such that four different filter types were used in the trial.[45] Despite these weaknesses, the PREPIC study highlighted the fact that permanent IVC filter placement carries certain risks that could potentially be avoided with filter removal.

Expanding on the results of the PREPIC trial, the recently published PREPIC2 trial focused only on optional retrievable filters utilized over a narrow therapeutic window. In this study, 398 patients were randomized to receive either 6 months of anticoagulation alone or anticoagulation and an IVC filter. Those randomized to the filter group had the filter removed after 3 months, and then received an additional 6 months of anticoagulation. At 3 months, there was no significant difference in incidence of PE (3% with filter vs. 1.5% with no filter, $P = 0.50$), and at 6 months, there was no significant difference in mortality, PE, or recurrent DVT between the two groups.[46] The authors concluded that the use of retrievable IVC filters in addition to anticoagulation offers no benefit over anticoagulation alone.

The PREPIC2 study design was improved over the original PREPIC trial in that anticoagulation and filter type were standardized. However, the trial again failed to address the potential benefit of IVC filters in the population for which they are most frequently utilized: patients with VTE who cannot be anticoagulated. Furthermore, the study was not designed to address the issue of whether filter retrieval offered improved morbidity and fewer complications over permanent filter placement, since there was no study arm that included permanent filter placement. Additionally, the 6-month study period was not long enough to provide sufficient data for evaluating rates of recurrent DVT after retrieval, thus nothing can be inferred from the data regarding the incidence of recurrent DVT at this time.

The retrospective data available comparing permanent and optionally retrievable devices is equivocal at best. A cohort study of 702 patients found similar rates of recurrent PE in patients who received both permanent and optionally retrievable filters, suggesting that both types of filters are similarly effective. While no difference in incidence of recurrent DVT was noted, the mean follow-up in this study was only 11.5 months, and only 15.5% of the optionally retrievable group had the filters removed.[47] While optionally retrievable devices likely offer protection from PE that

is similar to permanent filters, it is unclear whether early retrieval offers any improvement in complication rate. In fact, there is some concern that optionally retrievable filters may be prone to higher device failure rates. In 2010, the FDA released a safety communication stating that from 2005 to 2010, over 900 adverse event reports were received, including IVC perforation, filter migration, filter fracture, and component embolization. The FDA statement, which was updated in 2014, recommended removal of retrievable filters as soon protection from PE is no longer required. A subsequent analysis of the FDA Manufacturer and User Facility Device Experience (MAUDE) database supported this statement, noting a significantly higher number of adverse events reported for retrievable filters compared to permanent filters from 2009 to 2012.[48]

In summary, optionally retrievable filters offer similar benefits to permanent filters and in general are associated with low morbidity. The selection of a permanent or an optionally retrievable filter should be considered on a case-by-case basis. Given the concern for a higher device failure rate, patients who receive an optionally retrievable device should have appropriate follow-up and the filters should be removed as soon as safely allowable. Optionally retrievable filters should only be considered in certain populations, including younger patients, patients with temporary contraindications to anticoagulation, and for prophylactic indications.

26.9 TECHNIQUES OF IVC FILTER PLACEMENT

Placement techniques for each of the filters differ, and the most appropriate step-by-step guide for placement can be found in the operator's instructions provided by the manufacturers. These directions should be reviewed prior to placement and followed carefully to ensure the safety of the patient. The usual steps involved in percutaneous filter placement are described in Table 26.5.

Table 26.5 Steps involved in radiological inferior vena cava filter placement

1. Pre-procedural evaluation:
   - Review indication and risk versus benefits of inferior vena cava (IVC) filter placement, including the duration for which the filter is likely to be needed
   - Review available duplex ultrasound/computed tomography/magnetic resonance imaging to evaluate presence of IVC, iliac, or femoral vein thrombus
   - Evaluate coagulation status
2. Preparation for filter placement:
   - Choose access based on the above evaluation
   - Perform inferior venacavogram; evaluate for IVC thrombus; identify level of renal veins; measure IVC diameter; detect venous anomalies
3. Choose appropriate filter and deploy according to operator's instructions provided by the manufacturer
4. Perform post-deployment radiographs
5. Follow-up recommendations

26.9.1 Venous access

The choice depends on the patency of the vein access site and sometimes operator preference. The right common femoral vein is the most common access site and affords a relatively straight course to the IVC. This is the preferred access site unless there is evidence of clot in the right femoral or iliac veins. The right jugular vein is another common access site through which most of the available filters can be deployed. Left femoral, jugular, antecubital, and more recently popliteal veins have all been used depending on the anatomy and type of the filter that is planned to be deployed. Placement of IVC filters through the left femoral and jugular approaches have been associated with a greater incidence of filter "tilt" with respect to the course of the IVC. Filters with low-profile delivery systems such as the TrapEase and Simon Nitinol filters (6 Fr) can be placed via the antecubital vein.[49] Alternative access sites have been described and are limited only by the surgeon's or interventionist's ingenuity. For example, the authors have placed Simon Nitinol filters through the right greater saphenous vein in morbidly obese patients, and Günther Tulip filters through a brachial approach with success in patients with bilateral femoral and jugular thrombosis.

26.9.2 Inferior venacavogram

Either iodine-based contrast or carbon dioxide is used to obtain a venogram via a marking pigtail catheter (Figure 26.3). A venacavogram is used to identify venous anomalies, measure caval diameter, exclude thrombus in the IVC, and identify the level of the renal veins. The opacification of the renal veins may be enhanced by the Valsalva maneuver. Except for bird's nest and the VenaTech low-profile filters, most of the commercially available filters are recommended for IVC diameters of 30 mm or less. When placing a filter in a patient with a megacava, two options for treatment exist: placement of a bird's nest or other filter type that is approved for a large vena cava, or placement of bilateral common iliac vein filters with devices that are approved for a vena cava of 28 mm in diameter or less.

Three major venous anomalies are of particular interest when placing an IVC filter. These are duplication of the IVC, circumaortic left renal vein, and left-sided IVC. These anomalies must be assessed prior to placing an IVC filter. Duplication of the IVC is seen in 0.2%–3.8% of the population and occurs due to persistence of both right and left cardinal veins. The cavae may be of equal size, although the right cava is usually larger. The left cava joins the right at

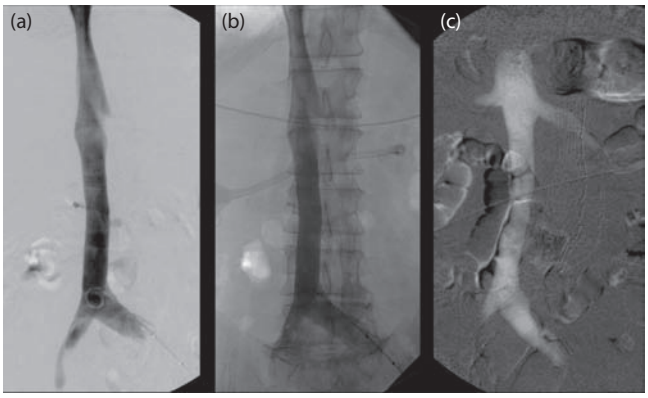

Figure 26.3 Inferior venacavogram performed prior to inferior vena cava filter placement showing normal caliber of the inferior vena cava and location of renal veins. **(a** and **b)** Inferior venacavogram using iodinated contrast media in digital subtraction mode and with bone landmarks to facilitate inferior vena cava filter placement. **(c)** Inferior venacavogram using carbon dioxide as the contrast medium in a patient with renal insufficiency.

the level of the left renal vein. This IVC variant can be safely excluded if contrast fills the left iliac vein on cavogram. If the left iliac vein is not seen on venogram and the left renal vein appears prominent, then a duplicated IVC should be actively ruled out prior to filter placement. If a duplicated cava is identified, then two options exist: two filters may be placed in both cavae or a suprarenal filter can be placed. Circumaortic renal vein occurs in 8.7% of the population, and the posterior component of the left renal vein is usually lower than the anterior one. The filter should be placed below the entry of all renal vein branches. Left-sided IVC is rare, with a prevalence of 0.2%–0.5%. The left cava crosses at the level of the renal vein to the right side, and the filter is deployed in the infrarenal location in such patients.

26.9.3 Intravascular ultrasound and transabdominal duplex ultrasound-guided placement of IVC filters

Bedside placement of IVC filters by using either transabdominal duplex or intravascular ultrasound (IVUS) guidance has been shown to be safe and effective.[50,51] These techniques are preferred and are especially useful in critically ill patients, those who are pregnant, those who have a contraindication to iodinated contrast media and CO_2 is not available, or those who exceed the safe weight limits of standard radiographic equipment.

26.9.4 Transabdominal duplex ultrasound technique

Transabdominal duplex ultrasonography is performed to determine the technical feasibility of bedside filter placement. Important findings to be noted on pre-procedural ultrasound include IVC diameter, absence of venous thrombosis, absence of venous anomalies, and the patency of the intended femoral vein access site. The IVC must be adequately visualized at the renal vein junction in both the transverse and the longitudinal axes. Identification of the right renal vein is critical because this usually represents the lowest renal vein. If venous anomalies or iliofemoral venous thrombosis is suspected, contrast venography is preferred to more precisely define the venous anatomy before filter placement.

The procedure is usually performed under local anesthesia. The femoral vein access is obtained and a 0.035-inch guidewire is advanced into the IVC. The filter introducer sheath is advanced over this wire to just above the renal vein confluence. The guidewire is removed to enable adequate visualization of the tip of the delivery catheter. The lowest renal vein/IVC junction is visualized transversely as the filter delivery catheter and sheath are slowly pulled back. When the tip of the filter delivery catheter disappears from the ultrasound view, the intended deployment position has been reached. This is visualized on longitudinal view, and under direct visualization, the filter is deployed. Full deployment is confirmed with dedicated duplex imaging and plain abdominal radiographs.

26.9.5 IVUS technique

Under local anesthesia, femoral vein access is obtained and a 9-Fr (longer than 25 cm) sheath is placed into the IVC over a 0.035-inch guidewire. An IVUS probe (15 MHz) is inserted over the guidewire to the level of the right atrium. With pullback technique, the level of renal veins, caval diameter, caval anomalies, caval thrombosis, and confluence of the iliac veins are identified. If the confluence of iliac veins is not clear, contralateral femoral vein access is obtained and IVUS is performed again to identify the above venous landmarks. Single or dual venous access techniques can be used for filter placement.

In the dual venous access technique, the IVUS probe is positioned just below the renal veins. Filter deployment is performed through a separate venous access, preferably through the contralateral femoral vein to reduce the incidence of access site thrombosis by dual puncture at a single common femoral vein. The filter delivery catheter and sheath are inserted to a level above the renal veins and pulled back to just below the renal veins. Correct placement is then confirmed by IVUS. Once the position is confirmed, the IVUS probe is pulled back and the filter is deployed.

In the single-vein, single-puncture technique, the IVUS probe is removed after the vein anatomy is interrogated. The length of the IVUS probe is then premeasured against the length of the filter delivery catheter that corresponds to the position of the filter delivery catheter when fully loaded in the sheath. Measurement guides on the IVUS probe mark this distance. The IVUS probe is then inserted into the

sheath up to this premeasured length, which represents the distance that the filter delivery catheter extends beyond the length of the sheath. The IVUS probe and sheath are pulled back together to a level just below the lowest renal vein as visualized by IVUS. In this regard, IVUS is guiding sheath positioning, which, because of the premeasured length, indirectly guides the intended filter position. Finally, the IVUS probe is removed, the filter delivery catheter is loaded into the sheath, and the IVC filter is deployed. Post-procedure abdominal X-rays are obtained to confirm the placement, position, and alignment of the filter.

26.10 FOLLOW-UP OF IVC FILTERS

Patients with vena caval filters should undergo follow-up on an annual basis until removed if retrievable, and indefinitely if permanent. The purpose of the examination is to evaluate the mechanical stability of the filter. In addition, the condition of the lower extremities is evaluated to monitor the ongoing risk for recurrent thrombosis. Because so many of these devices are placed by radiologists, it is important that the information about the filter placement is passed along to the patient's local physician so that arrangements for the appropriate studies can be made.

Patients with optionally retrievable filters placed for temporary risk of PE should be followed more rigorously. Although the recommended retrieval window varies by device, the FDA issued a safety statement in 2010 and again in 2014 recommending that retrievable filters be removed as soon as protection from PE is no longer required. These patients should be reassessed at 1–3-month intervals after filter deployment to determine whether ongoing protection from PE is warranted. A standardized surveillance program is highly recommended, as patients are otherwise much less likely to have the filter removed when appropriate.[52,53]

Traditionally, follow-up after IVC filter placement has included physical examination of the lower extremities to observe for edema, hyperpigmentation, skin ulceration, and other signs of post-thrombotic syndrome. In the past, anteroposterior and lateral radiographs of the filter were obtained at intervals and compared to previous studies for IVC filter follow-up to demonstrate the mechanical stability and physical integrity of the device. This practice is currently controversial as the long-term complications of established IVC filters are low. Newer filters, with fewer long-term data on fracture and migration rates, may be candidates for this more rigorous follow-up until these issues are firmly resolved.

Emergent follow-up should be obtained if the patient develops new bilateral lower extremity edema. Should this occur, a duplex scan of the vena cava is performed to look for thrombus in the filter or IVC. If the results of the ultrasound study are indeterminate, the patient should undergo a venacavogram to evaluate for caval obstruction. If occlusion is documented and felt to be of recent origin (less than 7 days), and the patient's medical condition allows, thrombolytic therapy may be attempted in order to treat the current symptoms and prevent later post-thrombotic syndrome. Patients who present with signs or symptoms of PE should also undergo venacavogram to determine the patency of the filter and the presence of trapped or propagating emboli. Rare propagation of thrombus above the level of the filter may be an indication for a second (suprarenal) filter rather than thrombolytic therapy.

26.11 COMPLICATIONS OF IVC FILTERS

Complications of IVC filter placement include those related directly to the procedure for placement or removal, and those related to the length of time the filter stays inside the IVC.[54] The incidence of complications varies and depends not only on filter type, but more importantly on the methods used to assess complications and the duration of follow-up. Table 26.6 lists the common complications associated with IVC filter placement. Fortunately, most of the complications associated with IVC filters are minor or infrequent. Access site thrombosis is the most common complication. With newer, smaller-sized delivery systems, the incidence of occlusive thrombosis of the access vein is low (2%–10%), although a non-occlusive femoral vein thrombus is seen more often (25%). IVC thrombosis is a serious and potentially fatal complication requiring emergent diagnosis and treatment. Thrombus may extend above the level of the filter, causing major PE and necessitating placement of an additional filter in the suprarenal IVC. IVC thrombosis may also cause phlegmasia cerulea dolens, a limb-threatening condition. While small clot burden may be treated with anticoagulation, large to complete caval thrombosis causing symptoms may need thrombolysis or stent placement in the IVC to restore patency and treat associated phlegmasia.

Table 26.6 Complications of inferior vena cava filter placement

Complication	Incidence (%)
1. Procedure-related complications: • Puncture site complications: bleeding, infection, thrombosis, or air embolism • Delivery system complications: filter malposition, tilting, or incomplete opening • Inferior vena cava wall penetration • Death	4–11
2. Filter migration to renal vein, heart, or pulmonary artery	3–69
3. Filter fracture	<1
4. New or worsened deep venous thrombosis	6–30
5. Inferior vena cava thrombosis	6–30
6. Recurrent/fatal pulmonary embolism	2–5
7. Venous insufficiency	10–30

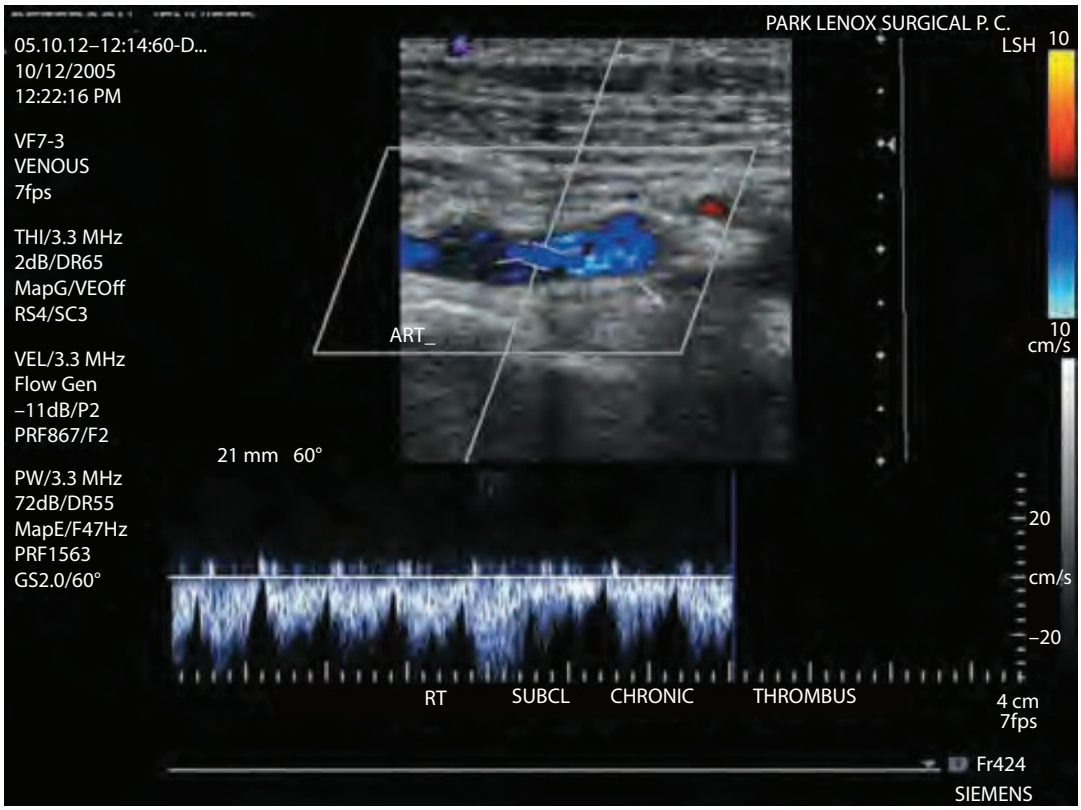

Figure 26.4 Results of experimental thromboembolism to the bird's nest, Simon Nitinol, and VenaTech filters in sheep, allowing sufficient time (30 days) for thrombus resolution. All filters show fibrous webbing.

Minor degrees of filter migration are of little concern. However, filter migration to the heart or pulmonary artery may be fatal due to the development of associated arrhythmias, acute myocardial infarction, pericardial tamponade, and cardiac valvular injury. Percutaneous retrieval or repositioning can be performed in these situations in an attempt to avoid emergent thoracotomy.

26.12 COMPARISON OF PERFORMANCE BETWEEN IVC FILTERS

Despite large numbers of clinical studies describing the effectiveness and safety of IVC filters, there are no studies that prospectively compare different filter designs. There is a misconception that because the published data for vena caval filters are similar, thus they are equivalent. Outcomes from *in vivo* animal studies demonstrated that this is not true. Figure 26.4 shows that thrombus resolution in the bird's nest, Simon Nitinol, and VenaTech filters results in heavy layers of fibrin webbing, while Figure 26.5 demonstrates the absence of webbing associated with the stainless steel and titanium Greenfield filters and an investigational device.

Comparing different designs is difficult due to variations in the populations studied, evaluation criteria, associated treatments, and the types and durations of follow-up.[55–57] Therefore, several guidelines have been published concerning reporting standards for filters.[58,59] Meta-analyses have shown the efficacy of filters in the prevention of PE, irrespective of the filter design.[60] Five major reports of objectively documented Greenfield filter patient outcomes have been published.[61–65] The follow-up included abdominal radiographs to determine the position of the filter and either

Figure 26.5 Results of experimental thromboembolism to the experimental filter, the percutaneous stainless steel Greenfield filter, and the titanium Greenfield filter in sheep with the same protocol as in Figure 26.4. All filters were clear of any residual fibrous tissue.

Table 26.7 Performance of different inferior vena cava filters

Filter	Number	Mean follow-up (months)	Recurrent pulmonary embolism (%)	Deep venous thrombosis (%)	Inferior vena cava thrombosis (%)	Post-phlebitic syndrome
Stainless-steel Greenfield	3184	18	2.6	5.9	3.6	19
Titanium Greenfield	511	5.8	3.1	22.7	6.5	14.4
Stainless steel over-the-wire Greenfield	599	26	2.6	7.3	1.7	2
Simon Nitinol	319	16.9	3.8	8.9	7.7	12.9
Bird's nest	1426	14.2	2.9	6	3.9	14
VenaTech/LGM	1050	12	3.4	32	11.2	41
Low-profile VenaTech	30	2.3	0	10.3	0	Not reported
TrapEase	65	6	0	45.7	2.8	Not reported
Gunther Tulip	83	4.5	3.6	Not reported	9.6	Not reported

Source: Angel LF et al. *J Vasc Interv Radiol* 2011;22(11):1522–30.e3; Hann CL and Streiff MB. *Blood Rev* 2005;19(4):179–202.

venographic or ultrasound studies to determine the patency of the filter. In addition, reports on subgroups of patients have also been published.[66,67] These reports have covered 27 years of experience with the stainless steel and the titanium Greenfield filters. In all, the patency rate has remained at 96% and the rate of recurrent PE has been between 3% and 5%.[4] The comparative efficacies and complications of different IVC filters are detailed in Table 26.7.

26.13 SUPRARENAL IVC AND SUPERIOR VENA CAVA FILTERS

Indications for suprarenal IVC filter placement are listed in Table 26.8. The efficacy and safety of Greenfield filters placed in a suprarenal position appear similar to those of filters placed conventionally in an infrarenal location.[6,68–70]

The role of a superior vena cava (SVC) filter in preventing PE is controversial. A few reports have described the benefits of such filter placement.[71–74] SVC thrombosis and guidewire entrapment during central line placement are potential complications of SVC filter placement. One recent systematic review reported serious, life-threatening complications (including SVC perforations, cardiac tamponade, aortic perforation, and recurrent pneumothorax) in 3.8% of SVC filters deployed. The rates of PE and associated mortality in patients with upper extremity DVT were 5.6% and 0.7%, respectively.[75] Therefore, the risks associated with SVC filter placement may outweigh any potential benefits in PE prevention.

Table 26.8 Indications for suprarenal inferior vena cava filter placement

- Renal vein or infrarenal vena cava or ovarian vein thrombosis
- During pregnancy or in women anticipating pregnancy
- Thrombus propagating proximal to a previously placed filter in an infrarenal location

Source: Caplin DM et al. *J Vasc Interv Radiol* 2011;22(11):1499–506.

26.14 CONCLUSION

Vena caval filters provide protection against PE without the significant morbidity and mortality associated with surgical interruption. They are intended for use in patients who are at risk of PE, but for whom anticoagulation is contraindicated or thought to be insufficient. IVC filter placement is a technically straightforward and safe procedure with an associated low morbidity and mortality. Multiple studies have demonstrated the efficacy of filters for preventing PE, although rarely IVC filters may cause progression or recurrence of DVT in lower extremities and IVC thrombosis. The rates of these complications are device specific, and it is important for physicians placing IVC filters to be familiar with the thrombosis, migration, and complication rates associated with the filter chosen for placement. There has been a recent surge in the placement of retrievable filters for the prophylaxis of PE in patients with time-limited contraindications to anticoagulation. The patient benefit associated with this practice is largely theoretical and needs to be objectively studied. The type of filter used should be tailored to each patient, with particular attention to the indication and the long-term results associated with the IVC filter chosen. The recent increase in the use of retrievable IVC filters is notable, and additional studies are required to document their safety and efficacy.

As improved techniques for the delivery of these devices, and new materials and designs, are developed, it is essential to keep in focus the indications and appropriate uses of these devices, including retrievable filters. Rather than focusing on the differences between the various devices (which will sort themselves out over time), the major effort ought to be directed toward identifying those patients who are at highest risk of significant PE. Efforts must also continue to be directed toward improving methods of thromboprophylaxis, since no filter can influence the development or course of the underlying disorder. This is clearly a case in which a well-planned offense is the best defense against this unnecessary source of morbidity and mortality.

Guidelines 3.10.0 of the American Venous Forum on the indications, techniques, and results of inferior vena cava filters

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.10.1	We recommend placement of inferior vena cava (IVC) filters: in patients with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) and a baseline contraindication to anticoagulation; in patients who suffer a complication from anticoagulation; in patients who develop recurrent DVT or PE despite adequate anticoagulation; and in patients who previously have had a massive PE and cannot tolerate further cardiopulmonary insult that would be associated with an additional PE.	1	A
3.10.2	We suggest placement of an IVC filter in patients with a free-floating thrombus greater than 5 cm in length within an iliac vein or the IVC.	2	B
3.10.3	We suggest prophylactic filters to patients if their associated medical conditions (malignancy or traumatic injuries) predispose them to DVT or PE.	2	B
3.10.4	We suggest caution in special situations prior to filter placement for patients with untreated or uncontrolled bacteremia, pediatric patients, and pregnant women, due to the uncertain long-term effects and durability of the filters.	2	C
3.10.5	We suggest bedside placement of IVC filters by using either transabdominal duplex or intravascular ultrasound guidance. Both have been shown to be safe and effective.	2	B
3.10.6	We suggest performing additional studies to document the safety and efficacy of the placement of retrievable filters in patients with time-limited contraindications to anticoagulation.	2	B
3.10.7	We suggest follow-up examination annually for patients with vena caval filters to evaluate the mechanical stability of the filter. In addition, the condition of the lower extremities is to be evaluated in order to monitor the ongoing risk for recurrent thrombosis.	2	B

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● = Key primary paper
★ = Major review article
◆ = Guideline

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27

Superficial thrombophlebitis

BENJAMIN JACOBS AND DAWN M. COLEMAN

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27.1 INTRODUCTION

Superficial venous thrombophlebitis (SVT) is common, although its incidence is likely underestimated, as many cases are subclinical and go unreported. There are a number of misconceptions about this diagnosis amongst physicians, the most pernicious of which is that it is entirely benign, offering no life- or limb-threatening complications. While this is true of some cases, SVT carries a risk of association and progression to deep vein thrombosis (DVT) and pulmonary embolism (PE). Consequently, a thorough understanding of the pathophysiology, diagnosis, and management of SVT is of great importance to the venous health physician.

27.2 EPIDEMIOLOGY

The incidence of SVT approximates 1:1000, although this is generally believed to reflect an underestimate. SVT affects almost 125,000 patients in the United States annually.[1] The average age at diagnosis ranges from 54 to 65 years; SVT affects females more than males.[2,3] The most commonly encountered risk factor is the presence of lower extremity varicose veins, occurring in 62% of SVT patients. Other associated risk factors include increasing age, obesity, tobacco use, previous history of DVT or SVT, pregnancy and the puerperium, oral contraceptives, hormone-replacement therapy, immobilization, recent surgery, and trauma.[4]

27.3 CLINICAL PRESENTATION

Patients will present in most cases with pain and erythema overlying the affected superficial vein, along with a palpable "cord" and edema of the surrounding soft tissue. Low-grade fever or malaise may be present. The superficial veins of the upper or lower extremities, the breast in the case of Mondor's disease, or the dorsal veins of the penis may all be affected by SVT. The most common locations affected by SVT include the great saphenous vein (GSV) and its tributaries, followed by the cephalic and basilic veins of the upper extremity.[4] The diagnosis of progression to DVT is often accompanied by a worsening of symptoms.[5]

27.4 ETIOLOGY

Traditionally, the pathophysiology of venous thromboembolic disease has been attributed to Virchow's triad of endothelial injury, stasis, and hypercoagulability. As our understanding of this triad has deepened, the importance of inflammatory mediators and broadened hypercoaguable states, like malignancy and obesity, has emerged. The etiology of SVT is complex and often multifactorial; it remains an area of active discovery.

27.4.1 Superficial thrombophlebitis and lower extremity varicosities

Lower extremity varicosities and lower extremity venous insufficiency are the most common risk factors for SVT. Varicose veins are comorbid with SVT in up to two-thirds of patients with SVT, and up to 70% of patients may have associated superficial venous insufficiency.[6] It has been reported that only 3%–20% of SVT patients with varicose veins will develop DVT, compared to 44%–60% of those without varicosities.[7–9] Therefore, it may be that SVT in patients with varicose veins has a different pathophysiology

from those without varicose veins. However, in a more recent study, no increased incidence of DVT or PE was noted when comparing patients with and without varicose veins in the 186 SVT patients identified.[2] Consequently, the question of whether SVT patients with or without associated varicose veins should be thought of as separate classifications remains ambiguous.[10] Conversely, addressing those patients with SVT involving varicose veins only is essential. This type of SVT may remain localized to the cluster of tributary varicosities or may, from time to time, extend into the GSV.[2] Superficial venous thrombosis is frequently found in varicose veins surrounding venous stasis ulcers.

27.4.2 Disease progression to DVT and PE

In as much as the primary threat to the patient with SVT is due to the potential for venous thromboembolism (VTE), it is important to clarify the connection between these entities. It has been shown that SVT can progress to DVT via proximal extension of thrombus into the deep system, but it also, perhaps counterintuitively, has been shown to arise in association with SVT in non-contiguous vessels.[2,3]

Concomitant DVT can be present but asymptomatic at presentation for SVT, and identified only on deep vein ultrasound studies. Decousus et al. noted that 25% of patients presenting with SVT demonstrated concomitant DVT at presentation, and importantly, almost half of these DVT cases were not contiguous with the SVT.[3] Of the 586 patients studied with isolated SVT, 10% went on to develop VTE during the study period. Across series, the incidence of proximal progression into the deep system ranges between 7% and 44%.[4,11] The most common route of extension is from the GSV via the saphenofemoral junction (SFJ) into the femoral vein.[9,12] Progression to VTE may also result from short saphenous vein SVT progression into the popliteal vein, and into the deep system via perforating veins.[4]

Chengelis et al. identified a group of 263 patients with isolated SVT without evidence of deep venous involvement by duplex ultrasound examination. Surveillance duplex ultrasonography performed approximately 1 week following SVT diagnosis revealed progression to deep venous involvement in 30 patients (11%) and specifically 16% of those with GSV SVT had extension into the femoral vein—most commonly via the SFJ (85%).[9] Proximity of superficial thrombus to the SFJ influences the likelihood of progression; SVT location within 1 cm of the SFJ confers a high risk of DVT progression.[5]

27.4.3 Associated hypercoagulability

Which patients, if any, presenting with SVT merit workup for hypercoaguable states remains an area of controversy and active research. There are no current guidelines that support concise recommendations. Martinelli et al.'s case–control study tested 63 'low-risk' patients (defined by the absence of malignancy, autoimmune disease, and lower extremity varicosities) for factor V Leiden mutation, prothrombin G20210A mutation, and deficiencies in antithrombin III (AT III), protein C, and protein S.[11] An increased risk of SVT was identified in patients with inherited coagulopathies. Risk of SVT was increased approximately six-fold for factor V Leiden mutation, four-fold for the prothrombin G20210A mutation, and 13-fold for the combined factor deficiencies. Similarly, de Moerloose et al. demonstrated that the presence of factor V Leiden mutation increased risk of SVT, although this was no longer statistically significant after controlling for obesity.[13] Additionally, patients with SVT not associated with lower extremity varicosities were more likely to have an inherited hypercoaguable state.

Another study of 29 patients with SVT investigated this relationship.[14] All patients underwent duplex ultrasonography of the superficial and deep venous systems. Patients with isolated SVT were treated with non-steroidal anti-inflammatory drugs (NSAIDs) and those with DVT were treated with heparin and warfarin. These patients had a similar coagulation profile performed that included protein C antigen and activity, activated protein C resistance, protein S antigen and activity, AT III, and the lupus anticoagulant. Twelve patients (41%) were found to have abnormal results consistent with a hypercoaguable state. Five of the patients (38%) with combined SVT and DVT and seven of the patients (44%) with SVT alone were found to be hypercoaguable. Four patients had decreased levels of AT III only and four patients were identified with activated protein C (APC) resistance. One patient had decreased protein C and protein S, and three patients had deficiencies of AT III, protein C, and protein S. The most prevalent anticoagulant deficiency was AT III. Furthermore, in a subsequent separate set of data examining patients with recurrent SVT, anticardiolipin antibodies were detected in 33% of patients.[15]

These findings and others suggest that patients with SVT may have an increased risk of an underlying hypercoaguable state, although not all studies have revealed such a strong association.[4,16,17] Consequently, whether routine testing of these patients is necessary remains unclear. It is reasonable to conclude that those patients presenting with SVT in the absence of any clear risk factor, especially if recurrent, merit such investigation.

27.4.4 Upper extremity SVT

The most common etiologic factor in upper extremity SVT is trauma associated with an intravenous cannula and intravenous infusions resulting in caustic endothelial damage. Treatment consists of cannula removal and warm compresses. The resultant lump may persist for months notwithstanding this treatment. Extension of upper extremity SVT into upper extremity DVT or PE is a very rare occurrence when compared with lower extremity SVT.[18]

27.4.5 Suppurative SVT

Suppurative SVT (SSVT) is also associated with the use of an intravenous cannula; however, SSVT may be lethal, given its association with septicemia. The associated signs and symptoms of SSVT include purulence at an intravenous site, fever, leukocytosis, and local intense pain.[19] Treatment consists of catheter removal, warm compresses, NSAIDs and broad-spectrum intravenous antibiotics (tailored to qualitative blood culture results). Surgery should be reserved for patients with SSVT who fail conservative management and require source control for persistent sepsis, including exploration, abscess drainage, and full venous resection to the extent that brisk back-bleeding is encountered.

27.4.6 Migratory SVT

Migratory thrombophlebitis was first described by Jadioux in 1845 as an entity characterized by repeated thrombosis developing in the superficial veins at varying sites, but most commonly in the lower extremity.[20] This entity may be associated with carcinoma and may precede diagnosis of the carcinoma by several years. Consequently, a workup for occult malignancy may, in fact, be warranted when the diagnosis of migratory thrombophlebitis is made.

27.4.7 Mondor's disease

Mondor's disease is defined as thrombophlebitis of the thoracoepigastric vein of the breast and chest wall. It can be associated with breast carcinoma or hypercoaguable state, although cases have been reported with no identifiable cause.[21] Recently, the term has also been applied to SVT of the dorsal vein of the penis.[22]

27.5 DIAGNOSIS

Duplex ultrasound scanning is the diagnostic modality of choice for the evaluation of DVT and SVT. The availability of reliable duplex ultrasonography of the deep and superficial venous systems has made routine determination of the location and extent of venous thrombosis accurate and practical. Furthermore, the extent of involvement of the deep and superficial systems can be more accurately assessed utilizing this modality; routine clinical examination may not precisely evaluate the proximal extent of the involvement of the deep or superficial systems. Duplex imaging of patients with SVT has revealed concomitant DVT in 5%–40% of patients.[2,23–26] It is important to note again that up to 25% of these patients' DVTs may not be contiguous with the SVT, or may even be in the contralateral lower extremity.[2] Consequently, bilateral imaging is necessary. Duplex ultrasound is also noninvasive, inexpensive, and may be easily repeated for surveillance examinations. Venography, alternatively, has fallen out of favor, with little indication.

27.6 TREATMENT

The extent of thrombus burden, thrombus location, the presence of concomitant DVT, and associated local infection should direct SVT treatment. Ambulation, warm compresses, elastic compression, intermittent elevation, and NSAIDs remain appropriate for cases of mild SVT in order to alleviate the inflammatory reaction.[27] While NSAIDs have been shown to significantly reduce the risk of SVT extension and/or recurrence by 67% compared to placebo, this therapy offers no protection against VTE, nor resolution of local signs and/or symptoms.[27,28]

Therapeutic anticoagulation and venous ligation or ablation have become increasingly popular for decreasing the risk of DVT in patients with SVT that demonstrate thrombus extension toward the level of the SFJ or carry additional risk factors for DVT extension. Historically, thrombus within 3 cm of the SFJ was felt to warrant surgical ligation of the SFJ with or without simultaneous GSV stripping/ligation, while more recent data support anticoagulation and compression over surgical measures.[29,30]

A 1999 prospective trial comparing various anticoagulant treatment groups (prophylactic unfractionated heparin, prophylactic low-molecular-weight heparin [LMWH], and therapeutic warfarin) to elastic compression alone or saphenous ligation identified lower rates of SVT extension in the anticoagulant treatment groups by surveillance imaging, without major bleeding complication.[31] Several contemporary trials have followed, further supporting the benefits of anticoagulation for SVT. The 2003 SVT Enoxaparin Study Group published their double-blind randomized trial comparing 8 days of treatment for SVT with prophylactic enoxaparin (40 mg) daily, therapeutic enoxaparin (1.5 mg/kg) daily, oral tenoxicam, and placebo for 8–12 days.[32] The incidence of deep and superficial venous thromboembolism was significantly decreased in all treatment groups (from 30.6% in the placebo group to 8.3% in the prophylactic enoxaparin group, 6.9% in the therapeutic enoxaparin group, and 14.9% in the tenoxicam group) without any hemorrhagic morbidity or heparin-induced thrombocytopenia. The randomized controlled Vesalio trial compared 1 month of prophylactic versus therapeutic doses of nadroparin for SVT.[33] These authors failed to demonstrate a difference in thrombus progression or VTE in either group, and moreover, they failed to meet recruitment goals, resulting in premature study termination.

A contemporary multicenter, randomized, double-blind, placebo-controlled trial reported on the safety and efficacy of fondaparinux for SVT.[34] Approximately 3000 patients with acute, symptomatic lower limb SVT involving a segment of at least 5 cm in length located at least 3 cm distal to the SFJ were assigned to 45 days of treatment with fondaparinux (2.5 mg subcutaneously daily) or placebo. The fondaparinux group demonstrated an 85% lower rate of PE or DVT than the placebo group after 77 days, along with a significantly reduced rate of symptomatic SVT recurrence

or extension to the SFJ without major hemorrhage or alternative morbidity.

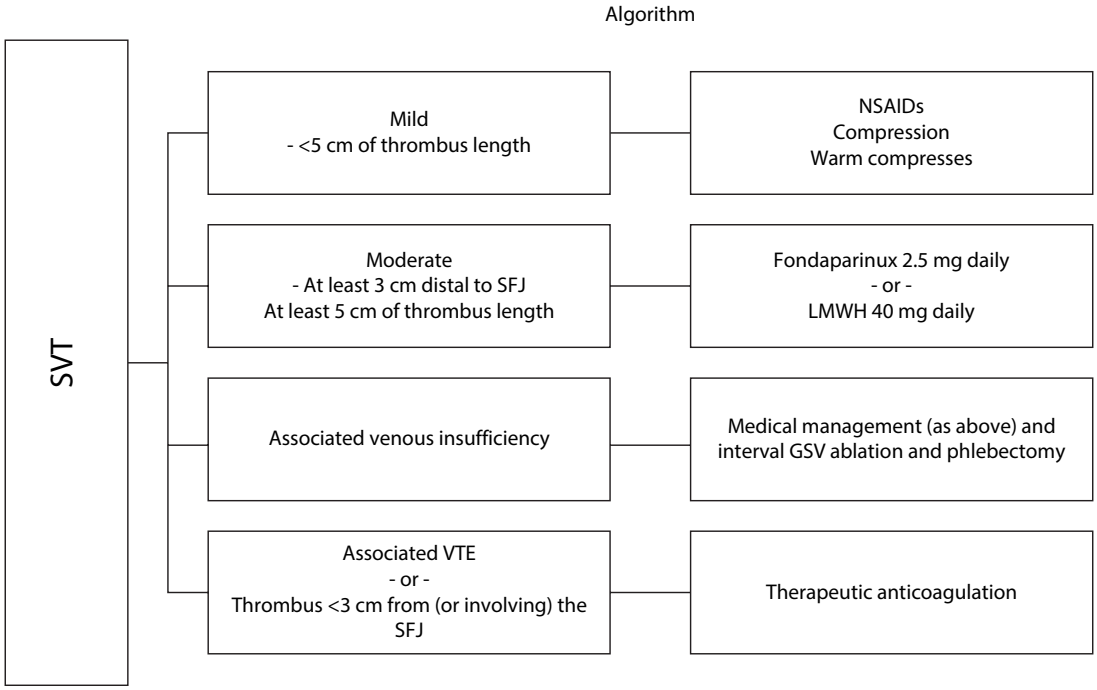
Most recently, a 14-day treatment course of dalteparin (200 U/kg at presentation followed by 10,000 U daily) for SVT was identified as superior to ibuprofen (800 mg three times daily) for both major upper and lower SVT.[35] Interestingly, this benefit was lost by the 3-month follow-up, and thrombus extension, including VTE, occurred in the time period following cessation of dalteparin and ibuprofen dosing, suggesting the treatment duration (2 weeks) may have been too brief. Finally, both therapies significantly reduced symptoms of pain during the treatment period and appeared safe without episodes of major or minor hemorrhage.

A 2013 Cochrane review including 30 randomized controlled trials and 6507 patients with SVT summarized that: both LMWH and NSAIDs reduce SVT extension and recurrence without any effect on symptomatic VTE; topical treatments relieve local symptoms; surgical treatment and elastic stockings offer a lower rate of VTE and SVT progression over elastic stockings alone; and fondaparinux appears to be an adequate treatment option as it offers a significant reduction in symptomatic VTE and SVT extension/recurrence.[36] The 2012 American College of Chest Physicians CHEST guidelines advocate medical treatment with a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (grade 2B) for patients with SVT of the lower limb that measures at least 5 cm in length, with grade 2C evidence favoring a daily dose of fondaparinux (2.5 mg) over a prophylactic dose of LMWH for patients with SVT being treated with anticoagulation.[37]

Finally, GSV disconnection and ligation at the SFJ remains appropriate for patients with SVT who cannot tolerate anticoagulation and demonstrate moderate thrombus burden (i.e., ≥5 cm in length or within 3 cm of the SFJ). Surgical treatment with GSV ablation and phlebectomies of the involved branch varicosities should be considered as the optimal treatments for patients with symptomatic SVT and evidence of venous insufficiency by duplex ultrasound in order to prevent recurrent phlebitis after the phlebitis has resolved, which is typically staged by 3–6 months.

27.7 CONCLUSION

In conclusion, SVT is common and carries a risk of association and progression to DVT and PE. The vein health physician must consider an individualized treatment plan. While patients with milder forms of SVT may be successfully managed with NSAIDs, compression, and warm compresses, those with moderate disease, defined as SVT located 3 cm distal to the SFJ and 5 cm in length, should be managed more aggressively, with either prophylactic LMWH or fondaparinux. Therapeutic anticoagulation should be considered for any patient that develops DVT or PE. For patients who cannot tolerate anticoagulation, GSV disconnection and ligation at the SFJ are appropriate when thrombus burden is moderate. Surgical treatment with GSV ablation and phlebectomies of the involved branch varicosities should be considered as the optimal treatments for patients with symptomatic SVT and evidence of venous insufficiency confirmed by duplex ultrasound, which is usually performed after the phlebitis has resolved.



Guidelines 3.11.0 of the American Venous Forum on superficial thrombophlebitis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.11.1	For saphenous vein thrombophlebitis within 3 cm of the saphenofemoral or saphenopopliteal junction, we recommend therapeutic anticoagulation.	1	B
3.11.2	For moderate thrombophlebitis with at least 5 cm thrombus length and at least 3 cm distal to the saphenofemoral junction, we recommend fondaparinux 2.5 mg daily or low-molecular-weight heparin 40 mg daily for 45 days.	1	B
3.11.3	For thrombophlebitis localized in the distal segment or in tributaries of the great saphenous vein with thrombus length <5 cm, we suggest ambulation, warm soaks, and non-steroidal anti-inflammatory agents.	2	B
3.11.4	For moderate thrombophlebitis as described above, or thrombophlebitis within 3 cm of the saphenofemoral junction, if anticoagulation is contraindicated, high ligation and division of the great saphenous vein is suggested.	2	B
3.11.5	In patients with saphenous thrombophlebitis, we suggest ablation once the inflammation resolved if there is evidence of venous insufficiency confirmed by duplex ultrasound scanning.	2	B

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Mesenteric vein thrombosis

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28.1 INTRODUCTION

Mesenteric vein thrombosis (MVT) was first described by Elliot in 1895.[1] Four decades later, Warren and Eberhard[2] recognized this as a distinct clinical entity and an important cause of bowel infarction. Now, 120 years after the first description, MVT remains a serious thrombotic disorder that is difficult to both diagnose and treat.[3] It is important to recognize very unique features of the mesenteric venous circulation that impact on the thrombotic process:

- There is a noticeable variation in mesenteric blood flow and viscosity associated with the time of day, nutrition intake, physical activity, emotional stress, diarrheal and/or vomiting related fluid loss, and dehydration from poor fluid intake.
- Mesenteric venous blood is rich in nutrients and intestinal elements such as microbial flora and both senescent and damaged cells.
- This circulation is subject to a number of blood-borne gastrointestinal peptides such as glucagon, vasoactive intestinal polypeptide (VIP), and cholecystokinin, which may further impact hemostasis and blood flow, particularly as mesenteric circulation is richly innervated by the sympathetic nervous system.
- The mesenteric veins do not contain venous valves, at least not in the larger channels.[4] This is important, as venous thrombi, occurring in the deep veins of the leg are thought to originate in the valve pockets; therefore, spatial and structural differences between leg vein and mesenteric vein thrombi might exist.
- Finally, the interrelationship of the mesenteric venous circulation with splenic and portal vein flow is such that a local pro-thrombotic milieu related to splenic or liver pathology (malignancy, inflammation, or infection) increases the propensity for thrombus propagation into the mesenteric venous segment. Thrombosis of one venous segment alters blood flow within the entire system; in particular, occlusion of the portal system will have a huge impact on venous blood stagnation within the mesenteric vein.

For these combined reasons, the mesenteric venous circulation is entirely unique and thrombosis occurring within this system should be considered as a distinct entity requiring special consideration and evaluation.

The incidence of MVT in the general population is poorly defined, but seems to be rather uncommon. Kazmers noted that MVT may be found in as few as one in 1000 laparotomies.[5] The incidence of MVT has increased in Sweden from 2.0 per 100,000 patient-years between 1970 and 1982 to 2.7 per 100,000 patient-years between 2000 and 2006.[6] The age at presentation varies from 45 to 80 years and both genders are equally represented.[3,5–14] Venous thrombosis may be limited to the mesenteric veins or may propagate to or from other regional vessels.[6–8,14] MVT accounts for 5%–15% of patients with intestinal ischemia.[9–12] The clinical course and symptomatology is determined by both the aggression of the thrombotic process and the extent of venous segments involved, determining the possibility of collateral circulation development. The superior mesenteric vein is much more frequently involved relative to the inferior mesenteric vein.[10]

Patients with acute MVT may note a sudden onset of abdominal pain, which may quickly progress within hours to include signs of peritonitis with bowel infarction. Patients with subacute onset present primarily with abdominal pain that has developed over days to weeks.[8–11] In these patients, neither bowel infarction nor chronic complications (variceal hemorrhage) are likely. Occasionally, however, patients with prominent and persistent abdominal pain

will develop intestinal infarction several days to weeks after the initial onset. Distinguishing between an acute and subacute presentation can be quite difficult.[7–9] It is for this reason that acute and subacute mesenteric venous thromboses are often discussed together. Patients with chronic MVT have minimal if any symptoms. The diagnosis is often made as an incidental finding on cross-sectional imaging studies when extensive venous collaterals are noted. Complications of portal vein or splenic vein thrombosis such as portal hypertension or esophageal variceal hemorrhage may also lead the clinician to MVT as the correct inciting etiology. This chapter will focus primarily on the acute form of MVT.

28.2 ETIOLOGY

Identification and treatment or elimination of the causal factors for MVT are central to clinical assessment and therapy. These factors can be generally categorized as inherited and therefore essentially permanent or acquired (Table 28.1). The acquired conditions may be transient, correctable, or permanent. Examples of transient acquired causes include pregnancy, surgery, and trauma. Predisposing conditions can be broadly divided into systemic or local. In patients with MVT, local causes such as abdominal or pelvic surgery, organ pathology involving the liver (cancer, cirrhosis, or hepatitis), pancreas (pancreatitis or cancer), and spleen (splenomegaly of different causes or splenectomy) are particularly relevant.[3,4,7,12,14,15] In general, provoked thromboembolic events attributed to transient or correctable acquired risk factors have a sufficiently low risk of recurrence such that prolonged anticoagulant therapy is neither necessary nor advisable.[16] For unprovoked thrombotic events, or for those with acquired and non-correctable risk factors, the risk of recurrence is deemed sufficiently high as to warrant prolonged secondary prevention with anticoagulants, assuming the risk of major bleeding is mild to moderate.[16] As our understanding and recognition of the factors involved in the genesis of venous thrombosis improves and as imaging modalities advance, the number of patients with unprovoked MVT should continue to decline.[3,5,6,12,14] However, the most recent international registry of splanchnic veins thrombosis including MVT showed that over 27% of cases were unprovoked.[17]

Table 28.1 Thrombophilia risk factors for mesenteric venous thrombosis

Inherited or Primary Thrombophilia
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Activated protein C resistance and factor V Leiden mutation
Prothrombin G20210A mutation
Elevated Factor VIII
Hyperhomocysteinemia from genetic defects in 5-methyltetrahydrofolate reductase
Acquired or Secondary Thrombophilia
Heparin induced thrombocytopenia
Disseminated intravascular coagulation (DIC)
Lupus anticoagulant and antiphospholipid antibody syndrome
Paroxysmal nocturnal hemoglobinuria
JAK2 (V617F) mutation
Hyperhomocysteinemia from acquired conditions, mainly vitamin deficiencies

Although there is a general acceptance that inherited or acquired thrombophilias either cause or contribute to MVT cases,[3,6,18] the precise role of these conditions remains unclear. Most studies have been retrospective in nature with incomplete coagulation assessment and limited by referral bias. Furthermore, in those patients in whom an underlying local etiology has been identified, coagulation testing is infrequently performed. Lastly, coagulation testing may be limited by the timing of assay acquisition, thus resulting in over- or under-estimation of coagulation defects. Test interpretation may be affected by the thrombus itself, hepatic ischemia secondary to the thrombus, or treatment with heparinoids or vitamin K antagonists.

Myeloproliferative neoplasms, including polycythemia vera, essential thrombocythemia, and primary myelofibrosis, are found in about a third of MVT cases and therefore are important considerations in the search for an underlying mechanism.[19] These disorders represent a stem cell-derived clonal myeloproliferation. The most common clinical manifestation of this malignancy and the cause of death is venous or arterial thrombosis.[20] The JAK2V617F sequence variation with gain of function that leads to independent proliferation is found in 90% of cases of polycythemia vera and up to 50% of cases of essential thrombocythemia. Screening for this mutation is therefore appropriate in the initial evaluation of patients who are suspected of having these disorders, including patients with MVT.[21–23] In fact, detection of the JAK2 sequence variation has replaced bone marrow examination as the first test to screen for myeloproliferative neoplasms.[22,24]

A good illustration of the role of thrombophilia in MVT patients is the analysis of 341 cases of splanchnic vein thrombosis, including 67 with MVT and 3621 control patients with leg deep vein thrombosis (DVT).[15] Factor V Leiden mutation was the most common thrombophilia in splanchnic vein thrombosis, particularly those with splenic vein thrombosis and MVT; one in every two cases with a homozygous mutation was a patient with MVT. Antiphospholipid antibody syndrome was the second most prevalent thrombophilia in these series; nearly 10% of those with MVT were diagnosed with this acquired thrombophilia. Over 7% of MVT patients were heterozygous carriers of the prothrombin G20210A mutation. There were only two MVT patients with antithrombin and one with protein S deficiencies. In this study, although the prevalence

of positive testing for thrombophilia was similar in MVT compared to leg DVT/pulmonary embolism, the prevalence of "strong thrombophilia," defined as deficiency of either antithrombin, protein C, or protein S, antiphospholipid antibody syndrome, homozygous factor V Leiden or prothrombin G20210A mutations, or compound heterozygous mutations of factor V Leiden and prothrombin G20210A, was greater in patients with splanchnic vein thrombosis.[15] This high prevalence was notably observed for patients with MVT. While the finding of "strong" thrombophilia usually mandates long-term secondary anticoagulation prophylaxis, this finding is of practical importance.

28.3 CLINICAL PRESENTATION

The onset of progressive abdominal pain in the patient with disproportionally few physical findings should prompt the clinician to think about MVT as a possible diagnosis. Although the durations of symptoms vary, the majority of patients will have had symptoms for more than 48 hours before seeking medical attention.[3] In those patients with ascites, MVT should be high in the differential diagnosis, particularly if thrombotic risk factors (e.g., oral contraceptive use or known malignancy) or historical factors such as a personal and/or family history of venous thromboembolic disease are present. The clinical manifestations depend largely on the extent of the thrombus, the size and number of vessels involved, the acuity of venous obstruction, and the extent of venous collateral development.[6,8] In general, the clinical signs and symptoms of intestinal ischemia due to MVT are non-specific. The pathophysiology includes mesenteric venous outflow obstruction that may lead to profound congestion and capillary malperfusion. This results in mesenteric ischemia with abdominal pain that is out of proportion to the physical findings.[3,5–15,25] The abdominal pain is often localized to the mid-abdomen and is described as "colicky," suggesting a compromised small bowel. Nausea, anorexia, vomiting, and diarrhea are also common. Hematemesis, hematochezia, or melena occur in about 15% of patients,[12] but occult blood is detectable in the stool in nearly 50%.[26] Abdominal distention is found in more than half of patients.[25] Peritoneal signs develop in a third to two-thirds of patients, although the initial physical findings may be entirely normal.[12] When fever, guarding, and rebound tenderness are found, intestinal infarction must be anticipated. Hemodynamic instability is a grave prognostic finding and may result from hypovolemia due to fluid collection within the bowel lumen or the development of ascites or septicemia.[12] Fluid resuscitation, early diagnosis confirmation, and prompt surgical attention are central to improving the outcomes of these unstable patients.

28.3.1 Diagnostic methods

Recent advances in imaging technology have increased the accuracy and frequency of MVT diagnosis and improved our understanding of its underlying causes. Nonetheless, this condition is frequently misdiagnosed initially or diagnosed late, and the outcome is often unfavorable.[11] In patients for whom the diagnosis of MVT is suspected, sensitive imaging modalities should be used early in the evaluation.

28.3.2 Computed tomography

Contrast-enhanced computed tomography (CT) is considered by many to be the test of choice for suspected cases of MVT.[27–30] The mesenteric vessels are well seen and the extent of bowel involvement can be simultaneously evaluated. Furthermore, other causes of abdominal pain can be excluded at the same time. An acute venous thrombus is identified as a central filling defect within the mesenteric vein (Figure 28.1). Engorgement of the superior mesenteric vein with varying degrees of wall enhancement may also be observed. Other CT findings are less specific and represent manifestations of the accompanying bowel ischemia. These include thickening of the small bowel wall and peritoneal fluid. If these non-specific signs are seen in the setting of MVT, bowel infarction should be strongly considered.

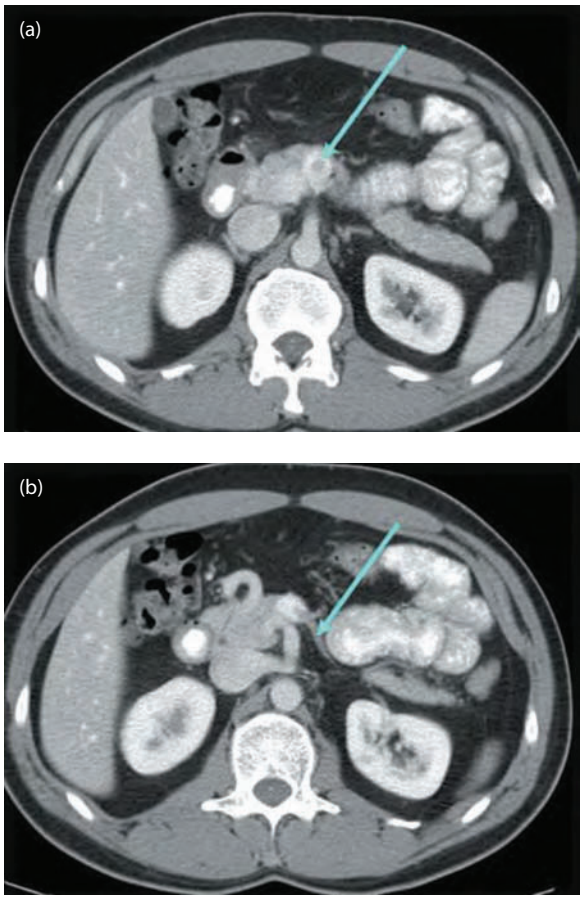

Figure 28.1 Computed tomography with intravenous contrast shows **(a)** nonocclusive thrombus projecting into the lumen of the superior mesenteric vein (SMV) up to the level of the confluence with the splenic vein and **(b)** thrombosis of a branch vessel of the SMV (arrow).

The sensitivity of contrast-enhanced CT imaging for MVT may be as high as 90%.[3,30] In those patients with early thrombosis involving small venous branches, the sensitivity is diminished. The new multi-row CT scanners offer the advantages of significantly shorter acquisition times, three-dimensional reconstruction, and reduced artifacts, thus improving the overall diagnostic accuracy.[30–32] This technique provides detailed assessment of both intra- and extraluminal abnormalities, mural thrombosis, and mesenteric edema. Metallic and non-metallic synthetic graft artifacts are reduced and the organ anatomy is well depicted.

28.3.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) also has excellent sensitivity and specificity for the diagnosis of MVT (Figure 28.2).[33] Advantages of this technique include no exposure to ionizing radiation and the ability to tailor the image acquisition to correspond to the desired vascular territory. The bowel and other organ integrity can be assessed at the same time. Limitations include signal degradation due to flow turbulence and motion- and metallic-related artifacts from vascular stents and vascular clips.[33–36]

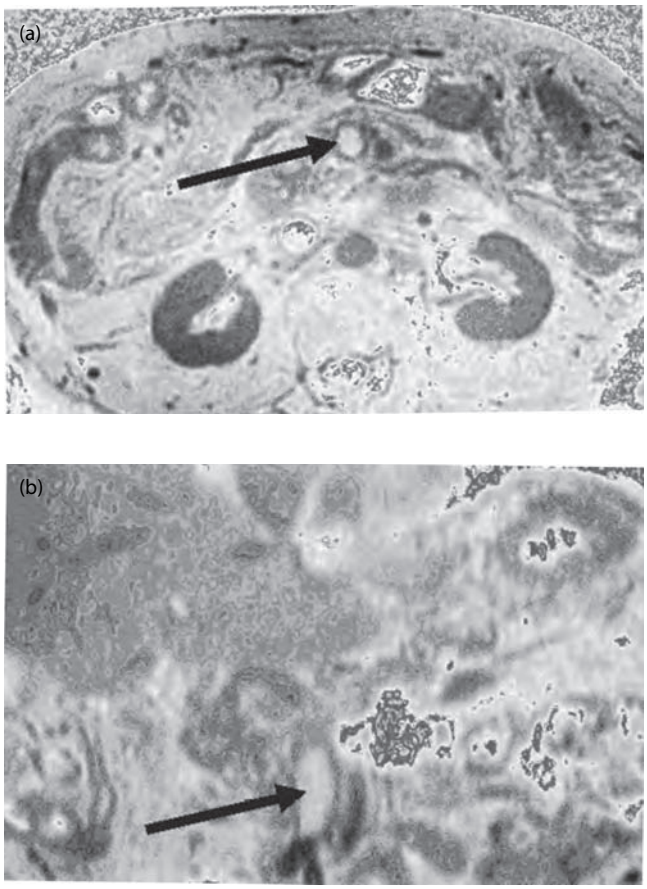

Figure 28.2 Magnetic resonance imaging (MRI) example of mesenteric vein thrombus. Contrast-enhanced MRI of the abdomen demonstrates an acute occlusive venous thrombus (arrows) involving the superior mesenteric vein (SMV) in both cross-sectional **(a)** and coronal **(b)** views. The SMV is distended with an acute-appearing thrombus.

28.3.4 Ultrasonography

Duplex ultrasound provides a sensitive and specific assessment of mesenteric blood flow in the evaluation of patients with suspected MVT.[27,33,37] Thrombus visualization within the mesenteric venous system confirms the diagnosis (Figure 28.3a and 28.3b). The lack of residual mesenteric venous flow by Doppler assessment is also quite specific for the diagnosis of MVT (Figure 28.3c and 28.3d). A thickened bowel wall, free intraperitoneal fluid, and biliary disease can also be demonstrated. Advantages include a noninvasive and inexpensive assessment that can be obtained urgently at the patient's bedside. There is neither nephrotoxic contrast nor ionizing radiation exposure during image acquisition. Limitations of this modality include operator skill and expertise, appropriate equipment capable of assessing slow flow states, and patient-specific variables, including unsuitable acoustic windows and overlying bowel gas. In addition, large periportal collateral vessels in portal venous thrombosis may be mistaken for a patent portal vein. Intravenous administration of ultrasound-compatible intravascular contrast agents in conjunction with grayscale harmonic imaging may increase vessel interrogation.[37] In experienced hands, duplex ultrasound is an invaluable technique for this purpose.

28.3.5 Venography

Although more invasive than the cross-sectional imaging modalities described, the advantages of conventional venography include an accurate assessment of mesenteric venous patency and flow direction, venous collaterals, and a comprehensive assessment of thrombus burden (Figure 28.4). Pressure gradients can be measured directly and endovascular therapies can be readily accomplished. Selective mesenteric angiography demonstrates impaired filling of the accompanying veins, arterial spasm, and prolonged opacification of the arterial arcades, all of which provide indirect evidence supporting the diagnosis.[27,38] The limitations of venography include the requirement of experienced personnel with appropriate imaging hardware. The evaluation includes transfer of a potentially unstable patient to a fluoroscopy suite for image acquisition, which is invasive and exposes the patient to both nephrotoxic contrast and ionizing radiation.

28.3.6 Abdominal radiographs

Although abdominal radiographs are abnormal in 50%–75% of patients, the findings are not specific for either bowel ischemia or MVT.[39] The most common findings include adynamic ileus with dilated, fluid-filled loops of bowel. Focal thickening of the mucosa ("thumb-printing") or mesentery and intramural or venous gas suggest advanced

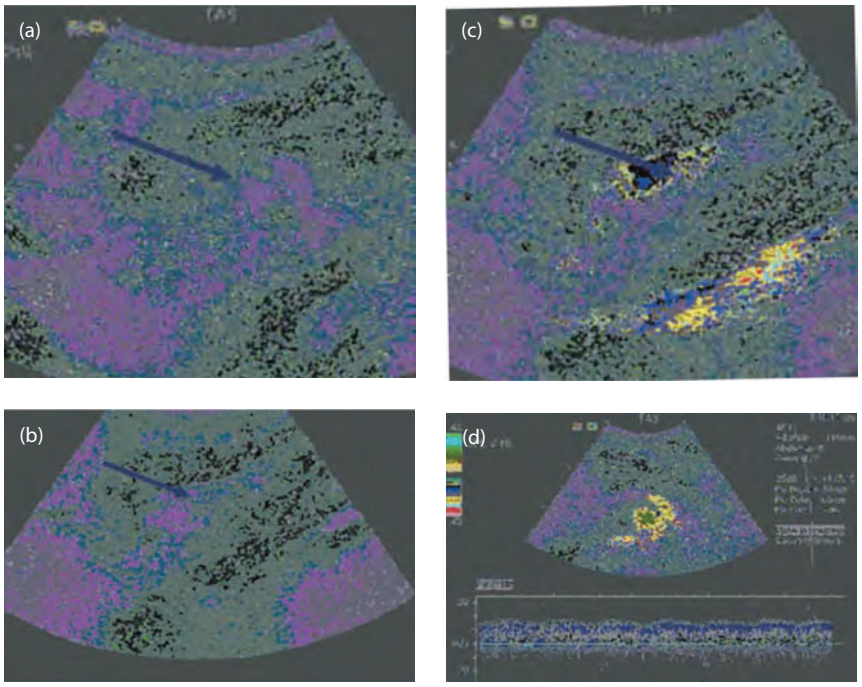

Figure 28.3 Duplex ultrasound example of mesenteric vein thrombosis. This duplex ultrasound example depicts an acute-appearing, non-occlusive thrombus (arrows) involving the superior mesenteric vein in cross-sectional **(a)** and longitudinal **(b)** views. Both color **(c)** and Doppler interrogation **(d)** of the venous segment reveal that the thrombus is incompletely obstructing mesenteric venous outflow.

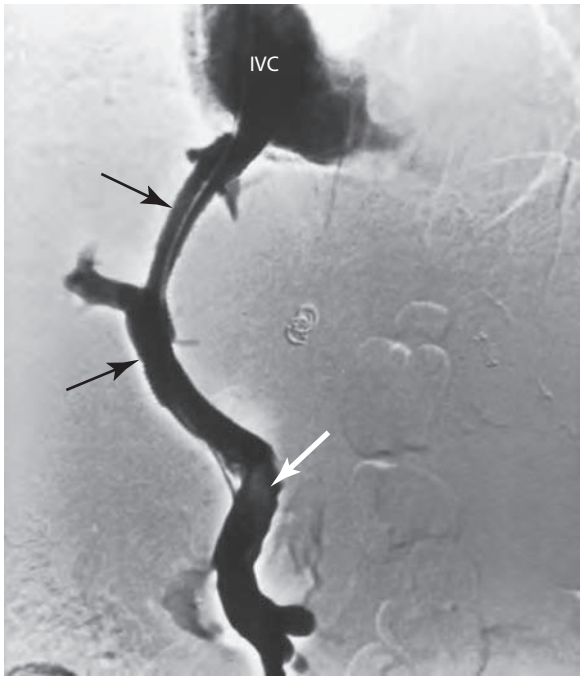

Figure 28.4 Venogram example of the transjugular intrahepatic portosystemic shunt (TIPS) procedure showing partially occlusive mesenteric venous thrombus (large white arrow). The stented communication (thin black arrows) with the inferior vena cava is readily apparent.

intestinal ischemia.[40] Barium contrast studies should be avoided in these patients.

In summary, there are a number of imaging studies to choose from in the evaluation of patients with suspected MVT. The choice involves a careful clinical assessment of the patient to determine the likelihood of MVT versus other diagnoses (assessing the pre-test probability of disease). For the stable patient with reasonable creatinine clearance, contrast-enhanced CT imaging will provide considerable clinical information. Contrast-enhanced MRI provides an excellent alternative for stable patients. For patients who are less stable, bedside duplex ultrasound will provide an assessment of mesenteric vascular patency. The ultimate choice of imaging will depend on the radiology expertise and machinery available at the institution that is caring for the patient. Discussion of the patient-specific variables with the attending radiologist prior to decision making is a very valuable and fruitful place to start.

28.3.7 Blood tests

Blood tests may be very helpful but are not very specific in the evaluation of patients with suspected MVT. The complete blood count with differentials is important for assessing both the hemoglobin and hematocrit in order to ensure that occult bleeding is not overlooked. Polycythemia rubra vera, essential thrombocythemia, leukemia, and other hematologic disorders which may predispose to venous thrombosis can also be screened for with this test. The white blood count will alert the physician to infections related to bowel infarction or perforation. Elevated serum lactate levels and metabolic acidosis

will help to identify those patients with a severely ischemic or infarcted bowel.[41] If levels are higher than 1000 U/L, acute pancreatitis should be considered. Transaminase elevation implies additional involvement of the portal or hepatic venous system. This is particularly relevant to the initiation of treatment with vitamin K antagonists. Fibrin D-dimer elevation may also be helpful in determining the timing of thrombosis. An acute thrombus is anticipated to be accompanied by significant D-dimer elevations. In the subacute or chronic setting, thrombosis evolution may no longer be associated with D-dimer abnormalities.

The timing of thrombophilia laboratory assessment may be a difficult decision to make. Ideally, one would obtain these types of tests once the thrombus has been appropriately treated and the patient is no longer taking warfarin or heparin. Typically, this type of testing (Table 28.1) would be performed more than 2 weeks after warfarin has been discontinued in order to maximize the test sensitivity and specificity.

28.4 TREATMENT

28.4.1 Medical management

The appropriate treatment of patients with MVT involves multidisciplinary input from both medical and surgical services. Clinical observations suggest that immediate anticoagulation with heparin early in the course of the disease, even intraoperatively, improves survival, reduces thrombus propagation, and reduces the risk of recurrence.[16,17,40] Gastrointestinal bleeding is not necessarily a contraindication to anticoagulant therapy, whereas the risk of bleeding must be weighed against the risk of bowel infarction. This decision requires careful and thorough patient evaluation, including measures of bowel ischemia, thrombus burden and acuity, collateral circulation, and an assessment of bleeding risk. Although improved survival rates have been shown among patients receiving anticoagulant therapy (63% vs. 44%), the need for chronic anticoagulant therapy in these patients is less clear.[14,42] Observational studies suggest that chronic anticoagulant use reduces the incidence of recurrent venous thrombosis by a third.[3,7,11,17] The efficacy and optimal duration of anticoagulant therapy, however, has not been defined by randomized trials. In general, anticoagulation should be continued until provoking factors have been eliminated if possible. In those patients whose MVT can be attributed to temporary risk factors, 3–6 months of anticoagulants is likely reasonable.[16,43] Expert opinion would suggest that antibiotic therapy should be provided for patients with signs or symptoms of bowel compromise.

28.4.2 Endovascular intervention

Endovascular therapies may be pursued for selected patients with acute MVT that is diagnosed early in the course of the disease before bowel infarction or peritonitis develop.[44–47] Candidates for this approach include those patients with acute and extensive mesenteric venous thrombosis with portal vein involvement for whom surgical thrombectomy or balloon embolectomy are not feasible options.[44] Catheter-directed thrombolysis requires gaining access either by cannulation of the portal venous system via a percutaneous transhepatic or transjugular approach, intraoperative catheterization, or through direct cannulation of the superior mesenteric artery. Indirect thrombolytic therapy via the mesenteric artery is particularly efficient for resolving thrombosis within capillaries and venules.[44–48] Mechanical thrombectomy could be combined with lytic therapy. Newer mechanical thrombectomy devices such as the AngioJet reholytic mechanical thrombectomy system (Possis Medical) have demonstrated promising efficacy in MVT treatment.[48] Although this represents an attractive alternative to surgical intervention which appears safe and effective, prospective studies with adequate patient numbers are necessary for a reliable assessment of this treatment method.

28.4.3 Surgical treatment

The need for surgical intervention in patients with MVT is not universal and may be necessary for only a minority.[3,6,14] Acute mesenteric ischemia accompanied by evidence of peritonitis or bowel infarction is an accepted indication for surgical intervention and resection of the involved bowel. The key to successful surgery is to resect sufficient bowel to ensure proper anastomic healing and halt thrombus propagation while preserving as much viable intestine as possible. The decision-making process may be complex and may require the technical skill and expertise of a surgeon who has familiarity with operations of this type. Management is dictated by the intraoperative findings, which range from segmental bowel ischemia to widespread mesenteric necrosis. Bowel perforation may or may not be present. Often, the surgical procedure is staged with a repeat ("second-look") laparotomy performed 1 day later.[49] Post-operatively, anticoagulants should be initiated as soon as hemostasis is adequately achieved. Under these circumstances, disease progression is uncommon. Thrombectomy remains a potential treatment option for selected patients, yet must be pursued quickly, as thrombus maturation (beyond 3 days) reduces the success of this operation.[50]

28.5 OUTCOMES

Reported mortality rates vary considerably and range from 2% to 50% within the follow-up range of 1 month to 5 years.[3,6,12–14,17] These studies, however, are either registries or retrospective analyses and are heterogeneous in nature, with varying proportions of acute and chronic, surgical, and non-surgical cases. Warren and Eberhard[2] compiled published reports of 75 cases of MVT, to which they added two of their own. In this historic description, the overall mortality rate was 58.8%. Of the 55 patients who underwent surgical resection, the mortality rate was 45.4%. Of the remaining 20 who were treated medically, only one patient survived to hospital discharge. More recent reports have yielded more favorable results with declining

mortality rates. Delay of diagnosis and intervention, post-surgical complications, and underlying malignancy carry worse prognoses.[11] The recurrence rate of venous thrombosis in these patients is not completely clear. Although the rates are said to be increased, Kumar and Kamath[8] reported only two recurrences among 30 patients with MVT limited to the superior mesenteric vein over a median follow-up of 18 months. Recurrent thrombosis was noted in five out of 39 patients with combined porto-mesenteric-splenic thrombosis during a median follow-up period of 27 months. These data suggest recurrence rates of 5%–6% per year. Morasch et al.[11] reported that all 22 long-term survivors of MVT (19 treated with warfarin) were thrombosis free at the last follow-up visit (mean 57.7-month period). Recently published results from the European International Registry of Splanchnic Vein Thrombosis (44% with MVT) reported rates of 3.8 per 100 patient-years for major bleeding, 7.3 per 100 patient-years for thrombotic events, and 10.3 per 100 patient-years for all-cause mortality. Anticoagulant treatment was associated with an essentially unchanged rate of major bleeding at 3.9 per 100 patient-years, but a lower rate of thrombotic events at 5.6 per 100 patient-years. When anticoagulation was discontinued, rates were 1.0 per 100 patient-years for bleeding and 10.5 per 100 patient-years for thrombosis recurrence. The highest rates of major bleeding and thrombotic events during the whole study period were observed in patients with cirrhosis (10.0 and 11.3 per 100 patient-years, respectively), while the lowest rates were observed in patients with thrombosis secondary to transient risk factors (0.5 and 3.2 per 100 patient-years, respectively).[17]

28.6 CONCLUSIONS

- MVT, although less common than arterial thrombosis, remains an important cause of mesenteric ischemia (5%–15%).
- MVT has lower morbidity and mortality than arterial mesenteric ischemia.
- The incidence of underlying thrombophilia in MVT is similar to leg thrombosis, but the higher incidence of "severe" thrombophilia observed in MVT impacts on recommendations for long-term anticoagulation.
- Both CT angiography and magnetic resonance angiography are recommended tests for MVT diagnosis.
- There is still a considerable delay in diagnosis because of a low degree of clinical suspicion and the non-specific clinical presentation.
- Immediate use of anticoagulation can improve outcomes, and if liver cirrhosis and esophageal/gastric varicosities are not present, an excessive bleeding rate is not observed.
- Surgery should be limited to patients with peritonitis or perforation, with the objective of conserving as much bowel as possible, yet ensuring viable margins.
- In patients with high-risk inherited thrombotic diathesis or another permanent risk for thrombosis, lifelong anticoagulation is a reasonable option; when the predisposing cause is temporary or can be eliminated, at least 3 months of anticoagulation is recommended.
- The long-term prognosis of patients without cancer or other life-threatening conditions is generally good.

Guidelines 3.12.0 of the American Venous Forum on mesenteric vein thrombosis

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.12.1	We recommend computed tomography angiography and magnetic resonance angiography for the diagnosis of mesenteric venous thrombosis (MVT).	1	B
3.12.2	We recommend immediate anticoagulation for the treatment of MVT to improve outcomes.	1	B
3.12.3	We recommend surgery for patients with MVT if they have evidence of peritonitis or perforation.	1	B
3.12.4	In patients with high-risk inherited thrombotic disorders or other permanent risk for thrombosis, we recommend long-term anticoagulation.	1	B

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● = Key primary paper
★ = Major review article

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Clinical presentation and assessment of patients with venous disease

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29.1 INTRODUCTION

Patients with venous disease represent a significant proportion of the patient population presenting to a vascular specialist. The nature of the disease is such that symptoms can be non-specific and difficult to assess. The ability to take an appropriate history and examination of the patient prior to organizing investigations is of paramount importance.

The assessment and clinical presentation of patients with venous disease have been covered by previously published guidelines.[1] In this chapter, we will review and expand on this topic.

29.2 THE UPPER LIMB

Vascular disorders of the upper extremity are less common than in the lower limb, affecting approximately 10% of the population.[2] The upper limb plays an important role in individuals with chronic disease (e.g., in the formation of arteriovenous fistulae and the administration of long-term intravenous therapy). Significant venous disease affecting the dominant arm can be life changing for an individual, and can potentially cause disability.

29.2.1 Trauma

Acute trauma and repetitive micro-trauma can both result in vascular disorders of the upper limb. This is particularly prevalent in middle-aged males employed in manual-type labor or young males involved in acute traumatic injury. Individuals working with handheld vibrating tools may be subject to chronic micro-trauma.

29.2.2 Intermittent subclavian/upper extremity vein obstruction

Although uncommon, compression of the subclavian vein can result in intermittent symptomatology including intermittent swelling, discomfort and tightness (relieved by rest), and abnormally prominent superficial veins. These symptoms are aggravated in the erect position or when the arm is raised (e.g., when typing, driving, or painting a ceiling).

Thoracic outlet syndrome (TOS) may present in this manner,[3] usually secondary to the presence of a cervical rib, a congenital fibrous band compressing neurovascular structures, or compression at the costoclavicular junction. TOS may be neurological or vascular in nature according to whether the brachial plexus or subclavian artery or vein is compressed. Patients with these symptoms should be evaluated with their shoulders in the neutral position and in specific stress tests to elicit signs and symptoms. These include braced in the military position (Figure 29.1) or with arms hyperabducted and externally rotated at the shoulder (Figure 29.2), as this will result in the subclavian vein being compressed by the scissor-like closure of the costoclavicular space. Arm discomfort, swelling, and venous distension in this position suggest intermittent venous outflow obstruction. However, as with arterial thoracic outlet obstruction, these findings can be reproduced in approximately 50% of otherwise normal individuals at the extremes of movement.[4] As subclavian vein thrombosis is a likely outcome of intermittent obstruction, active investigations with a view to surgical decompression are indicated. These maneuvers are useful in assessing patients, but have been reported to have low sensitivity and specificity.[5]

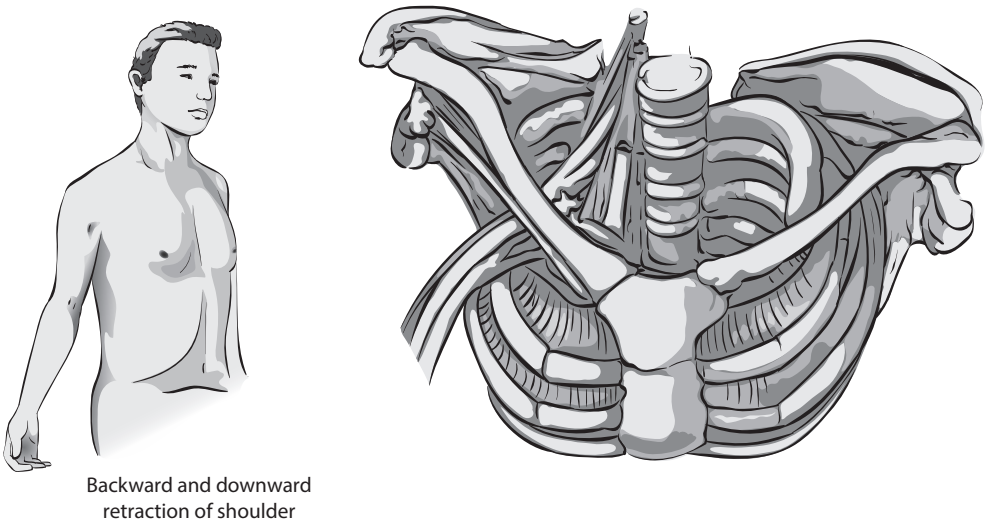

Figure 29.1 Compression of the subclavian vein in the military position. When the shoulder is retracted backward and downward, the subclavian vein is narrowed by the scissoring action of the clavicle and the first rib. (Adapted from Adams JT et al. *Surgery* 1968;63:147–65.)

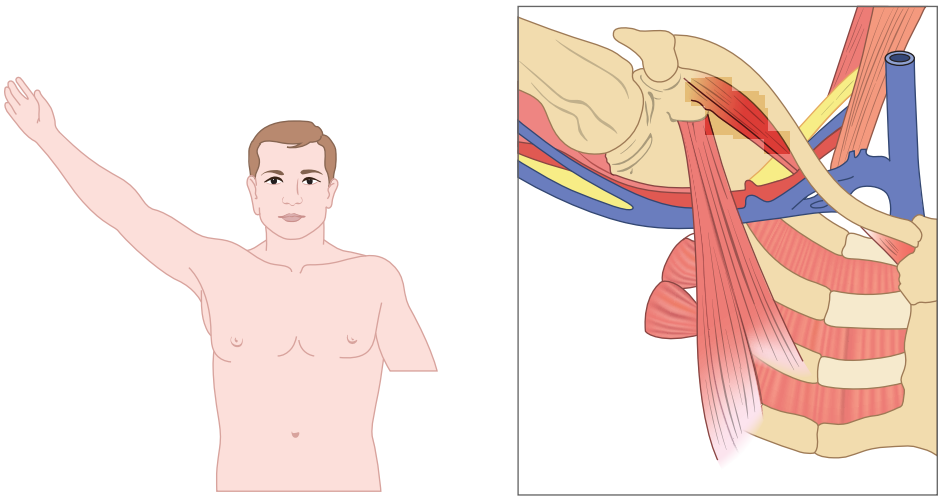

Figure 29.2 Compression of the subclavian vein with hyperabduction of the arm. With hyperabduction and external rotation of the arm, the clavicle rotates backward and downward and causes compression of the subclavian vein secondary to narrowing of the costoclavicular space. (Adapted from Adams JT et al. *Surgery* 1968;63:147–65.)

29.2.3 Subclavian/upper vein thrombosis

29.2.3.1 PRIMARY UPPER EXTREMITY DEEP VENOUS THROMBOSIS

Deep venous thrombosis (DVT) can arise as a result of hypercoagulable disorders or acute or recurrent trauma to a blood vessel.

Paget–Schroetter syndrome (effort vein thrombosis) describes a syndrome of axillosubclavian vein thrombosis associated with repetitive upper limb activities. The syndrome is due to repeated trauma to the endothelium of the subclavian vein, which may be secondary to the presence of the aforementioned congenital abnormalities, leading to the development of venous TOS. This syndrome is more common in young, healthy men undertaking manual work, preferentially involving the dominant arm. Patients are usually symptomatic, presenting with arm discomfort, swelling, and dilated veins across the shoulder and upper arm (Urschel's sign).[6] The arm may be pale, cyanotic, or red. Patients usually present acutely or subacutely, with sudden onset of symptoms. Often, patients can identify a precipitating event, such as a sports injury.

Pulmonary embolism (PE) following upper extremity DVT (UEDVT) has been reported to occur in 2%–35% of individuals.[7] Post-thrombotic syndrome, characterized by chronic pain, heaviness, and swelling, develops in up to

45% of individuals with UEDVT. Recurrent thrombosis is another significant complication. Considering the prevalence of UEDVT in young men and its preferential involvement of the dominant arm, it is important to bear in mind the degree of disability which can result.

Duplex ultrasound is a useful initial test; however, contrast computed tomography (CT) venography is the gold standard for diagnosis. Conservative management with anticoagulant therapy is suboptimal, with residual disability. Interventional treatment consists of catheter-directed thrombolysis with or without thoracic outlet decompression with or without venoplasty.[6]

29.2.3.2 SECONDARY UEDVT

DVT can result from direct trauma to the vessel—this can be iatrogenic or secondary to central venous cannulation, catheterization, or pacemaker insertion. Central venous catheters present a significant risk of thrombosis, which is reported to occur in 14%–18% of cases.[8] Recurrent intervention to the central veins can lead to stenosis and thrombosis. Unlike primary UEDVT, the onset of obstruction is gradual with recurrent intervention. Patients, therefore, have time to develop a collateral circulation and be asymptomatic. When present, the symptoms may be vague shoulder or neck discomfort or arm edema. Depending on the clinical situation, the first presentation may be a nonfunctioning line; venous duplex imaging or a "linogram" (contrast injection) can reveal the thrombosis. Treatment involves thrombolysis if the thrombus is extensive, or simply removal of the line and anticoagulation. Lines should be placed, if possible, in the internal jugular, cephalic, or external jugular vein, as chronic venous scarring with narrowing (stenosis) is particularly common following direct subclavian vein cannulation. A history of central venous cannulation is important in patients being considered for hemodialysis access and or arterial reconstruction using an arm vein due to the possibility of stenosis, especially in the case of prior subclavian vein usage. If present, postoperative limb swelling may result in significant patient morbidity.

29.2.3.2.1 Superficial venous thrombophlebitis

Superficial venous thrombophlebitis (SVT) is characterized by localized pain, redness, and swelling over a segment of a superficial vein. Iatrogenic injury, secondary to venous cannulation, is the most common cause, and is usually self-limiting. In some cases, the disease can be recurrent and persistent. Spontaneous thrombophlebitis, especially if recurrent, may be associated with malignant disease or thrombophilia. Upon examination, palpation will reveal tenderness over an underlying thrombus in the vein, with surrounding induration. If the thrombus in the vein is localized and not infected, there will not be significant distal swelling. Thrombus propagating to the deep veins is rare. A history of thrombophlebitis is important as it may have important consequences for venous access and the utility of an arm vein for arterial bypass.

29.2.3.2.2 Phlegmasia cerulea dolens

This typically occurs in patients with advanced malignancy, often being treated with chemotherapy via an indwelling central venous catheter. It is a variant of disseminated intravascular coagulation with thrombosis affecting not only the major veins, but also extending into the venules and the microcirculation. It is characterized by sudden, severe pain associated with intense swelling and discoloration of the affected limb. Development of a compartment syndrome is a potential complication and may even progress to venous gangrene requiring amputation. Further complications include PE and death.

29.2.3.2.3 Post-thrombotic syndromes

Post-thrombotic symptoms are reported in 30%–70% of patients following a primary subclavian vein thrombosis and consist of chronic discomfort, heaviness, and swelling, particularly in positions that compress collaterals in the costoclavicular space. However, the skin changes commonly found in the lower limb are extremely rare.

29.2.3.2.4 Arteriovenous malformations

These can be frequently misdiagnosed and are associated with localized limb hypertrophy. Examples include Klippel–Trenaunay syndrome (KTS) and Parkes–Weber syndrome (PWS); they usually affect the lower limb and are discussed in further detail below.

29.2.4 Examination findings

29.2.4.1 INSPECTION

Simply inspecting the arm and comparing it with the contralateral limb can yield useful clinical information. The examination process helps eliminate arterial, lymphatic, orthopedic, or rheumatologic pathology from the differential diagnoses.

Inspection should aim to identify the following: swelling, hypertrophy, discoloration, pallor, venous collaterals, prominent veins, scars and/or puncture sites, evidence of previous trauma, presence of indwelling lines, or cannulae.

29.2.4.2 PALPATION

1. To determine any difference in temperature
2. Tenderness over an inflamed superficial vein or in the supraclavicular fossa
3. Evidence of obstructing pathology in the axilla and/or supraclavicular fossa (e.g., enlarged lymph nodes or a palpable cervical rib)
4. Hard and "cord-like" veins suggesting previous thrombophlebitis
5. Presence of a full complement of pulses; presence of any abnormal pulsations, either venous or arterial (arteriovenous fistula or malformation)
6. Presence of a palpable thrill
7. Presence of pitting edema
8. Allen's test to confirm the arterial inflow to the hand and completeness of the palmar arch

29.2.4.3 PERCUSSION

The presence of incompetence can be assessed by the "tap test" of Chevrier. This is performed with the patient standing. One hand is placed on the proximal thigh, tapping dilated veins, whilst the other feels for a transmitted impulse in the veins of the lower leg. Venous return should flow from the foot to the groin. A palpable thrill in the lower leg veins is suggestive of continuity in the column of blood, implying the presence of non-functional valves and, therefore, venous incompetence.

29.2.4.4 AUSCULTATION

Listen for a continuous machinery murmur, which might indicate an arteriovenous malformation.

29.2.4.5 ADDITIONAL STEPS

The blood pressure should be measured in each arm and a full neurovascular examination should be performed. If the arm is swollen, the examination should include the axilla for lymphadenopathy and the breast to exclude malignancy. If there is concern about the adequacy of the deep venous outflow, the arm can be observed for swelling after application of a light superficial tourniquet. Symptoms of PE should prompt a full cardiorespiratory examination.

29.3 THE LOWER LIMB

Chronic venous disease is extremely common in the Western world, with variable incidence reported worldwide. Up to 80% of the general population will display evidence of venous disease, with 20%–64% suffering from varicose veins (VVs) and 1%–2% affected by venous ulceration.[9] Venous disease is known to negatively impact on quality of life[10] and has a significant association with depression.[11] Furthermore, European and U.S. data have estimated the cost of venous disease to be approximately 1%–2% of the total health care budget.[12]

29.3.1 Superficial venous thrombophlebitis

SVT is an unfortunate term because it tends to be dissociated from DVT when, in fact, the two commonly coexist as part of the venous thromboembolism spectrum.

SVT can occur spontaneously or secondary to trauma or intervention. Iatrogenic injury from intravenous cannulation and infusion of causative agents is the most common cause in normal veins. This can present as a tender lump or cord along the course of the vein. Treatment is via removal of the intravenous catheter, and resolution of the condition can take months. Iatrogenic thrombophlebitis may be complicated by bacterial infection, particularly in patients undergoing long-term intravenous cannulation. Septic phlebitis and suppurative thrombophlebitis are serious complications requiring antibiotic treatment and even surgical debridement in some cases. Systemic features and abscess formation are uncommon.

Occasionally, SVT can arise in association with a known or occult malignancy and, in this circumstance, is often migratory. It may also be associated with thrombophilia.

SVT can occur in diseased VVs in the form of sterile thrombosis. This is particularly common in pregnancy and presents as a hard, tender knot in the vein, with intense pain and overlying erythema. The inflammatory process can extend beyond the vein wall, resulting in bleeding.

If any clot propagates through junctional and non-junctional perforators, there is a significant risk of PE. Investigation of the deep veins (e.g., by duplex scan) is generally indicated, although symptoms of DVT may be absent.

On examination, signs of inflammation are present, including erythema, warmth, and tenderness (Figure 29.3). Upon resolution, there is often a residual mass or cord in the affected superficial vein.

29.3.2 Deep venous thrombosis

DVT leading to PE is the most common cause of potentially preventable death in adult patients, with an annual incidence of 1:1000 adults.[13] Risk factors include innate (age and hypercoagulability) and environmental (surgery, hospitalization, trauma, pregnancy, hormone therapy, obesity, and cancer) factors.

The mortality rate of those diagnosed with PE is approximately 10%. Cadaveric studies have, however, identified PE in up to 30% of individuals with a DVT, and this finding highlights the fact that many PEs are subclinical. In fact, CT pulmonary angiography is now identifying even more small subclinical pulmonary emboli.[14] Management depends upon prophylaxis, a high index of suspicion in "at-risk" patients regardless of symptoms, and early steps taken to provide a definitive diagnosis.

It is helpful to consider the development of DVT in two phases: embolic (early) and thrombotic (late). In the early phase, the thrombus is non-occlusive and not yet organized. As a result, there is no swelling, inflammation, or distension of superficial collateral veins, and the leg may appear quite normal

Figure 29.3 Superficial thrombophlebitis of the left thigh.

despite a significant risk of embolism. In the late phase, the thrombus becomes occlusive and incites a phlebitis, anchoring it to the vein wall; in addition, inflammatory signs and symptoms due to peri-phlebitis become apparent. The patient develops all the "typical" clinical features of DVT. At this stage, however, the risk of PE is low. The clinical diagnosis of DVT is difficult to make due to the poor sensitivity and specificity of "typical" signs. Even when symptoms are present, studies show that fewer than half of such patients have a DVT. Homans' sign (pain in the calf elicited upon passive dorsiflexion of the foot with the patient in the supine position with the knee flexed) is unreliable, painful, and should not be performed.

The Wells[15] scoring system is used to determine the probability of a patient having DVT before diagnostic tests are performed (Table 29.1). Patients with a score of 2 or more are more likely to have DVT.

Anatomically, it is useful to consider three patterns of disease (calf, femoral, and iliofemoral), although thrombosis is a dynamic process and proximal propagation is common.

Calf vein thrombosis is usually localized to one or two of the three major veins of the lower leg. Often, the thrombi are non-obstructive and, due to the pairing of tibial and peroneal veins, venous drainage may remain adequate. Calf tenderness may be present, but significant swelling is usually absent. In fact, most patients have no symptoms or signs whatsoever. About 20%, if untreated, may propagate into an above-knee deep vein. Calf vein thrombosis is the most common site of lower limb DVT and may propagate to the femoral vein. When the popliteal or femoral vein is involved, there may be swelling at the ankle and at the calf of greater than 1 cm in most patients, but this rarely extends above the patella unless outflow via the deep femoral vein is compromised.

Iliofemoral DVT may originate in the pelvic veins and not involve the distal femoral or calf veins in over 30% of patients. Consequently, duplex scanning commonly fails to detect it. Clinically, thigh swelling is present in addition to calf swelling. If the inferior vena cava is involved, signs and symptoms are usually bilateral. This type of thrombosis frequently has a marked inflammatory component, especially in pregnant women. Patients suspected of having this condition are best investigated via contrast CT venography or magnetic resonance venography.

Table 29.1 Clinical model for predicting the pre-test probability of deep venous thrombosis

Clinical characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep venous thrombosis	1
Alternative diagnosis at least as likely as deep venous thrombosis.	–2

Source: Adapted from Wells PS et al. *Lancet* 1997;350(9094): 1795–8.

Note: A score of 2 or higher indicates that the probability of deep venous thrombosis is likely; a score of less than 2 indicates that the probability of deep venous thrombosis is unlikely. In patients with symptoms in both legs, the more symptomatic leg is used.

29.3.3 Phlegmasia caerulea dolens

As described above with respect to the arm, extensive thrombosis may lead to phlegmasia, which in turn may precipitate venous gangrene. Phlegmasia of the lower limb sequesters a considerable proportion of the patient's blood and body fluids, especially if bilateral. This can result in severe systemic effects, which may include hypovolemic shock and renal failure.

29.3.4 Arteriovenous malformations

These most commonly affect the lower limb; KTS and PWS can present with abnormal varicosities.

KTS is a vascular malformation with capillary, venous, and lymphatic abnormalities. Patients characteristically exhibit the clinical triad of port wine stain, VVs, and limb hypertrophy. The lower limb is affected in approximately 70% of individuals.[16] Patients with KTS can present with SVT and bleeding from enlarged superficial veins. Typically, the VVs can present as anomalous veins or persistent embryonic veins; these are present in 72% of patients with KTS. The most common abnormality is the persistence of a lateral embryonic vein, identifiable in the lateral thigh and not joining the deep system. Abnormal medial or suprapubic veins are less common.[16]

Similarly to KTS, PWS usually affects the lower limb and is characterized by the presence of fast-flow arteriovenous fistulae. Patients present with cutaneous capillary malformations, limb hypertrophy and arteriovenous malformations. Superficial veins are prominent secondary to increased pressure. A bruit, or machinery murmur, is audible in the affected limb, and a thrill is palpable throughout the cardiac cycle.

29.3.5 Varicose veins

29.3.5.1 EPIDEMIOLOGY

VVs are extremely common, with risk factors including family history, age, and obesity. Their prevalence is expected to continue rising due to the aging population and obesity epidemic. VVs can be primary or secondary. Primary varicosities are due to incompetence in the superficial veins, often

located at the junctions between the superficial and deep venous systems (saphenofemoral, saphenopopliteal, or perforator incompetence). Secondary varicosities arise as a result of underlying pathology that has led to the development of venous hypertension in the superficial venous system. This includes DVT, deep venous incompetence, an intra-abdominal mass causing pressure on the pelvic veins, and obesity.

29.3.5.2 TRUNK VARICES

Trunk varices are VVs originating from the main stem and/or major tributaries of the great saphenous vein (GSV) and/or the small saphenous vein (SSV). These are the result of valvular incompetence and occur in the GSV distribution in 80% of individuals and the SSV distribution in 20%. They are usually ≥3 mm in diameter, lie subcutaneously, are palpable, and do not discolor the overlying skin. Although more women than men present for assessment and treatment of their VVs, the actual prevalence is roughly equal between the sexes.

29.3.5.3 RETICULAR VARICES

These lie deep in the dermis, are 2–3 mm in diameter, are not palpable, and may render the overlying skin darkish blue in color. They do not blanch on pressure. They may or may not be associated with trunk varices and are present in about 80% of the adult population.

29.3.5.4 TELANGIECTASIA

Also termed spider or hyphen web veins, they are intradermal, 1 mm or less in diameter, impalpable, blanching, and render the overlying skin purple or bright red. Again, they may be associated with trunk and reticular varices and are present in 80% of adults.

29.3.5.5 SYMPTOMS

The presentation of venous disease occurs across a spectrum, including asymptomatic disease, VVs, skin changes, and ulceration. This is best described and assessed via the CEAP (Clinical, Etiological, Anatomical, Pathophysiological) classification, an international system that enables the assessment of venous disease and its severity (Table 29.2).[17]

Thread and reticular veins can be unsightly but are not symptomatic. Although rarely life threatening, trunk VVs can have a significant detrimental effect on a patient's quality of life that should not be ignored.[10] The rate of depression with trunk VVs is more than double that of the general population.[11] This may be due in part to the cosmetic aspect and in part to the chronicity of the signs and symptoms of venous disease, which can interfere with patients' daily activities.

Previous local guidance in the U.K. advised general practitioners to refer a patient with VVs to secondary care only in the presence of what was defined as advanced disease (C4–C6). Lower CEAP grades were to be managed in the community with conservative measures, such as compression and lifestyle advice. Referral to secondary care was warranted in the presence of ulceration, bleeding, progressive skin changes, recurrent SVT, and symptoms having a severe impact on quality of life.

Table 29.2 CEAP classification

C: Clinical classification
C0: No visible or palpable signs of venous disease
C1: Telangiectasia or reticular veins
C2: Varicose veins
C3: Edema
C4a: Hyperpigmentation or eczema
C4b: Lipodermatosclerosis or atrophie blanche
C5: Healed venous ulcer
C6: Active venous ulcer
s: Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps
a: Asymptomatic

E: Etiological classification
Ec: Congenital
Ep: Primary (indeterminate cause)
Es: Secondary (e.g., post-thrombotic)
En: No venous cause identified

A: Anatomical classification
As: Superficial veins
Ap: Perforator veins
Ad: Deep veins
An: No venous location identified

P: pathophysiological classification
Pr: Reflux
Po: Obstruction
Pr,o: Reflux and obstruction
Pn: No venous pathophysiology identifiable

Source: Adapted from Eklöf B et al. *J Vasc Surg* 2004;40(6): 1248–52.

However, venous disease is a progressive disorder; the rate of C class disease progression from C2 disease to higher classes as reported by the Bonn Vein Study is 2% per annum.[18] This change in evidence has led national bodies to change referral pathways to all symptomatic disease with the aim of preventing, as opposed to treating, higher CEAP class stages. This is exemplified by the Society of Vascular Surgery (SVS) and the National Institute of Health and Care Excellence (NICE) guidelines (Table 29.3).[19]

Patients with VVs can be challenging to assess, as they may present with a wide variety of lower limb symptoms, including aching, a dragging feeling, heaviness and tension, swelling, tiredness, restless legs, nocturnal cramps, and itching. These symptoms are not specific to VVs and are extremely common in the general population. It is important to consider differential diagnoses (e.g., back pain) and arrange for the appropriate investigations to confirm the clinical suspicion. Management of patient expectations is paramount in the presence of non-specific symptoms, particularly when

Table 29.3 National Institute for Health and Care Excellence (NICE) guidance 2013

Referral to a vascular service
- Patients with symptomatic primary or recurrent varicose veins
- Patients with skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency
- Superficial venous thrombosis and suspected venous incompetence
- A venous leg ulcer
- A healed venous leg ulcer
- Immediate referral to a vascular service is warranted if there is a bleeding varicose vein

Imaging
- Duplex ultrasound should be used to confirm the diagnosis of varicose veins and the extent of truncal reflux and to plan treatment for individuals with suspected primary or recurrent varicose veins

Treatment
- Endothermal ablation (radiofrequency or laser) is first line
- If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy
- If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery
- If incompetent tributaries are present, consider treating them at the same time
- Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable
- Intervention should be avoided in pregnancy, where compression stockings should be offered

discussing treatment options. In a patient with evidence of reflux on venous duplex, it is important to inform them that intervention may not resolve their symptoms.

29.3.6 Chronic venous insufficiency

VVs are a manifestation of chronic venous disease. Chronic venous insufficiency (CVI) describes complications from the presence of high venous pressures in the lower limb, resulting in the cutaneous changes that are characteristic of the disease. Ultimately, this leads to skin damage, which may include ulceration of the lower leg.

29.3.6.1 SYMPTOMS

All of the symptoms described above for VVs may be associated with CVI, and there is a stronger relationship between symptoms and disease severity in this group. This group of patients is significantly older and, as such, comorbidities are more common, including peripheral vascular disease and diabetes. When assessing these patients, arterial disease and musculoskeletal problems should not be overlooked. Unlike patients with simple VVs, in whom actual swelling is unusual, the majority of patients with CVI have a degree of edema. This is usually of mixed etiology: venous hypertension, cardiac failure, and a degree of lymphedema. Severe pain is unusual and suggests that the patient may have coexisting arterial disease and/or infection.

29.3.6.2 HISTORY

This should explore the current episode of skin change/venous ulceration and any previous episodes. A history of vascular risk factors should be taken, including previous thrombotic episodes, vascular and non-vascular interventions to the lower limb, pelvis, and abdomen, malignancy, arterial risk factors, diabetes, autoimmune disease, and smoking. A general history, including family history, medications, and allergies, should also be taken. Furthermore, patients should be asked if symptoms of chronic venous disease are present, such as itching, restlessness, aching, heaviness, swelling, and fatigue.

29.3.6.3 EXAMINATION FINDINGS

29.3.6.3.1 Position

The patient should be examined standing under a good light and in a warm room. Patients may feel faint and a support should be available. The examiner should be sat on the floor or, ideally, on a small stool with the patient on a platform with a handrail for balance.

29.3.6.3.2 Inspection

VVs are dilated and tortuous, due to the pathological reflux commonly but not exclusively associated with a cephalad incompetent valve. The main trunks themselves may be dilated, but they are rarely tortuous, as they are supported by the deep fascia. The distribution of varices can give an indication as to whether they are GSV or SSV tributaries (or both) (Figure 29.4). However, in obese patients or those with previous surgical interventions, the anatomical connections may be less defined. In thin, athletic patients, highly visible and enlarged veins may be erroneously considered to be pathological. These are uniformly dilated and do not exhibit tortuosity. It is also important to note the presence of telangiectasia during inspection.

Veins lying in an abnormal distribution (such as laterally along the leg, vulval, or in the abdominal wall) are suggestive of a congenital cause, an underlying pathological process (e.g., intra-abdominal mass), or pelvic congestion syndrome.

The signs of CVI include corona phlebectatica, venous eczema, lipodermatosclerosis, hemosiderin deposition, and open (or healed) ulceration. These are most commonly found around the gaiter area, above the medial malleolus. Corona phlebectatica comprises a fan-shaped flare of small intradermal varices on the medial aspect of the ankle and foot. The apex of the flare is in the region of the one or more incompetent perforators and fans out towards the sole of the foot. Lipodermatosclerosis may be acute or chronic. In the acute phase, it is an inflammatory reaction that may be mistaken for cellulitis or phlebitis. It will overlie an area of

Figure 29.4 Varicose veins in the right great saphenous vein distribution.

perforator incompetence but, unlike cellulitis, the overlying skin will not be warm. In the chronic phase, the skin of the mid to lower calf is pigmented, shiny, hard to the touch, and fixed to the underlying chronically inflamed and contracted subcutaneous tissue. Surrounding dermatitis is common and may be a sensitivity reaction to topical medication applied to the area. White scar tissue (atrophie blanche) is often present. The site of lipodermatosclerosis relates to maximum ambulatory pressure, usually communicated by incompetent perforators. This also applies to the sites of ulceration, although as ulcers increase in size, this association becomes less defined. An ulcer characterized by a location or shape typical of pressure damage is an important pointer to coexisting arterial disease (see Table 29.4).

29.3.6.3.3 Palpation

Features such as temperature change, the presence of pulses or thrills, tenderness, induration, and edema provide useful information regarding the underlying disease process. The varicosities should also be palpated and an assessment of their course determined. In individuals with bilateral VVs, an abdominal and groin examination is essential to identify signs of intra-abdominal pathology.

Clinical tests such as the "tap" test of Chevrier or the Trendeleburg test have been used to help assess the patient with venous disease. The "tap" test of Chevrier consists of percussing over a varix while palpating caudally to help trace out the vein. A palpable transmitted impulse suggests an

Table 29.4 Differential diagnosis of leg ulceration

Clinical features	Arterial ulcer	Venous ulcer
Gender	Men > women	Women > men
Age	>60 years	40–60 years, but patients may not present until much older; multiple recurrences
Risk factors	Smoking, diabetes, hyperlipidemia, hypertension	Previous deep venous thrombosis, thrombophilia, varicose veins
Past medical history	Most have a clear history of peripheral, coronary, and cerebrovascular disease	>20% clear history of deep venous thrombosis. History suggestive of occult deep venous thrombosis is very common (e.g., leg swelling after childbirth, hip/knee replacement, or long bone fracture)
Symptomatology	Severe pain is present unless there is severe neuropathy. Pain may be relieved by dependency	Approximately 30% have pain, but it is not usually severe and may be relieved upon elevation
Site	Pressure areas (malleoli, heels, metatarsal heads, fifth metatarsal base)	Medial (70%) and lateral (20%) or both malleoli and gaiter area
Edge	Regular, "punched-out," indolent	Irregular, with neo-epithelium
Base	Deep, green (sloughy), or black (necrotic) with no granulation tissue, exposing major tendons, bones, and joint	Pink and granulating, may be covered in a yellow–green slough
Surrounding skin	Features of chronic ischemia (hairless, dry, pale)	Lipodermatosclerosis (pigmentation, induration, varicose eczema, atrophie blanche)
Veins	Empty, guttering on elevation	Full, usually varicose
Swelling	Absent	Present

Figure 29.5 Ulceration in the gaiter area of the left lower limb.

incompetent vein between the two sites. The Trendelenburg test consists of applying a tourniquet to the upper thigh to compress the GSV. The patient is then asked to stand, with the examiner assessing for superficial vein filling. The test can be repeated at different levels to identify the level of incompetence. Handheld Doppler can be used as an adjunct to insonate over the site of incompetence. Again, this was said to be useful in the obese patient, but has been found to have a sensitivity of as low as 56% at the saphenofemoral junction and 23% at the saphenopopliteal junction.[20] Overall, these tests have been found to be poorly predictive of venous anatomy, and should not be relied upon to plan surgery. Duplex scanning is the gold standard investigative tool allowing hemodynamic assessment of the superficial and deep venous systems.

29.3.6.3.4 Ulcer assessment

Ulcer assessment (Figure 29.5) should include:

1. Description of the ulcer, concentrating on the features outlined in Table 29.4
2. Pulse status and Ankle Brachial Index (ABI)

Guidelines 4.1.0 of the American Venous Forum on the clinical presentation and assessment of patients with venous disease

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Level of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.1.1	For clinical examination of the upper limb, we recommend inspection with comparison with the contralateral limb, palpation, auscultation, and examination of the axilla for adenopathy. In patients with adenopathy or swollen arms, we recommend examination of the breast to exclude malignancy.	1	B
4.1.2	For clinical examination of the lower limbs in patients with suspected acute deep venous thrombosis, we recommend inspection (edema, cyanosis, and varicosity), palpation (tenderness and pitting edema), auscultation (arterial bruit and heart and lung examination), and examination of the deep and superficial veins and calf muscles.	1	B
4.1.3	We suggest the use of the clinical scoring system of Wells to predict the pre-test probability of deep venous thrombosis.	2	B
4.1.4	For clinical examination of the lower limbs for varicosity and chronic venous insufficiency, we recommend inspection (varicosity, edema, skin discoloration, corona phlebectatica, ulcer, and lipodermatosclerosis), palpation (cord, varicosity, tenderness, induration, reflux, pulses, and thrill), auscultation (bruit), and examination of the groin and abdomen (masses, collateral veins, or lymphadenopathy) and ankle mobility.	1	B
4.1.5	Clinical presentation of patients with varicose veins may include symptoms like aching, heaviness and tension, sensation of swelling, tiredness, restless legs, nocturnal cramps, and itching. We suggest that there is little or no relationship between these symptoms and the presence and severity of varicose veins or the pattern and severity of reflux.	2	B

3. Gait and, in particular, ankle mobility
4. General physical examination

29.4 CONCLUSION

Venous disease is common and is often accompanied by non-specific symptoms, such as aching and swelling. This condition may be associated with a significant risk of morbidity, and can present in a variety of modalities depending on which portion of the venous system is affected. A thorough history and clinical examination can provide crucial information on the underlying pathology and help guide investigations and management.

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● = Published guideline
★ = Major review paper
◆ = Major primary paper

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30

Diagnostic algorithm for telangiectasia, varicose veins, and venous ulcers: Current guidelines

ROBERT B. MCLAFFERTY

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Chronic venous disease (CVD) is a common affliction, with telangiectasia being found in the large majority of people who are over 60 years old.[1] The diagnosis of telangiectasia, varicose veins, and venous ulcers starts with a well-rooted understanding of venous anatomy and pathophysiology, as outlined in previous chapters. While advances in physiologic testing, duplex imaging, and radiologic imaging continue to be made in the field of CVD, a thorough and directed history and physical examination can lead the physician to the proper clinical assessment, with supplementary tests as needed.

This chapter describes an orderly process of making a diagnosis for a patient with CVD. While simple problems can be diagnosed in a straightforward manner with little more than a reliance on a thorough history and physical examination, subtle and more serious disease may be present. Patients with intermediate to complex CVD may require more extensive diagnostic testing to better define the pathophysiology that is responsible for the signs and symptoms. Herein, guidelines are presented in order to put history, physical examination, physiologic venous testing, duplex imaging, and radiologic imaging into an orderly process for the practitioner. As a reminder, the diagnosis of CVD should be stratified according to clinical class, etiology, anatomic distribution, and pathophysiology (CEAP classification system; see Chapter 4).[2] This chapter will primarily focus on telangiectasia (clinical class 1), varicose veins (clinical class 2), and venous ulcers (clinical class 6). Additionally, given that numerous clinical practice guidelines have been previously published on the diagnosis and treatment of CVD, this chapter focuses on providing the clinician with a holistic amalgamation without GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria.[3–7]

30.1 HISTORY

In taking a complete history for CVD, the use of open-ended questions remains paramount to retrieving valid information about symptoms. This dictum may be even more useful for patients with telangiectasia and varicose veins. Excluding the more severe signs of CVD that can be readily evident as contributing to the patient's symptom complex, there can be a wide array of symptoms from patients with lesser degrees of CVD. By using simple questions such as "Can you describe what bothers you about your legs?" or even "What brings you to see me today?" one can start the cascade of allowing the patient to reveal subtle symptoms that previous practitioners may not have ascertained. After allowing the patient to describe any symptoms in an uninterrupted fashion, the physician can ask the patient to be more specific about certain aspects of the history. Finally, when open-ended questions yield no additional information, the physician can then proceed with directed questions and further obtain unmentioned details and pertinent negatives.

Symptoms from varicose veins are often vague. While some patients may be completely asymptomatic, many have symptoms that can be revealed with careful open-ended questioning. These include dull pain, aching, pressure, throbbing, heaviness, tiredness, restlessness, itching, burning, tension of the skin, cramping, and mild edema. Generally, these symptoms are exacerbated with limb dependency and relieved with elevation or rest. More severe

symptoms such as marked edema, dermatitis, hyperpigmentation, malleolar flair, corona phlebectatica, atrophie blanche, lipodermatosclerosis, ulceration, and skin erosion with hemorrhage can be present solely with superficial venous valvular incompetence, but often are seen with concomitant deep valvular insufficiency. Although telangiectasias are often assumed to by asymptomatic, their presence can illicit symptoms similar to varicose veins. Furthermore, their presence with correlative symptoms, in the absence of varicose veins by inspection, still might indicate more severe underlying CVD, to be revealed by physiologic testing.[8–11]

Important to the history following the detection of any symptoms related to telangiectasia and varicose veins are the severity and duration of symptoms. Other necessary questions include ascertaining information about a history of deep venous thrombosis, family history of venous diseases or "blood clots," bouts of superficial thrombophlebitis, occupation with regards to long durations of standing, previous venous surgery, presence of obesity (documenting body mass index), use of venotonic medications, history of constipation, history of trauma to the lower extremities, previous orthopedic surgeries, periods of prolonged bed rest, and the past use of compression hosiery. In females, pain can worsen during the menstrual cycle or pregnancy secondary to increased total body fluid volume and/or higher circulating levels of estrogen. Questions should also be focused on whether there are concomitant inguinal, perineum, vulvar, and/or vaginal varicosities present. For men, similarly, a history of varicocele should be sought. Patients should also be asked if any problems occur with walking. Rarely, patients will have concomitant peripheral arterial disease and exhibit symptoms of claudication (muscular leg pain with walking that is relieved by rest). Occasionally, patients may have symptoms from venous ambulatory hypertension. With this diagnosis, patients typically complain of a marked bursting pain in the calf muscles that is slow to abate with cessation of walking.

Confounding simultaneous diagnoses that can be challenging when teasing out diagnoses that are specific to CVD, particularly with the presence of varicose veins, including restless leg syndrome, causalgia, and other chronic pain syndromes of the lower extremities. The presence of these diagnoses could cause pause in procedural treatment and/or modify expectations for the relief of symptoms after treatment.

Patients presenting with venous ulcers should be questioned in a similar manner. Other pertinent questions relevant to a venous ulcer include location, size, appearance, and whether there are signs and symptoms of infection present. Past and current treatment regimens specific to the ulcer are also very important to document.

30.2 PHYSICAL EXAMINATION

The physical examination should take place in a warm, well-illuminated room with the patient in the standing position. With the patient's legs completely disrobed, careful inspection is carried out and patterns of telangiectasia, reticular veins, and varicose veins are noted. Clusters of telangiectasias can appear as skin blemishes or venous lakes. Often they are present in the lateral, posterior thigh, and popliteal fossa. Calf and thigh measurements should be performed. These help reveal more subtle problems with edema that may not be detected with simple visual assessment. Additionally, inspection for other, more serious signs of CVD in the gaiter area is performed. These include dermatitis, hyperpigmentation, malleolar flair, lipodermatosclerosis, cellulitis, atrophie blanche, corona phlebectatica, and evidence of healed or active ulceration. Location, size, depth, color, and number of ulcerations should be noted. The presence of an underlying congenital arteriovenous or venous malformation may be revealed by the presence of a well-demarcated, purplish pigmented area of the skin (port wine stain) or limb hypertrophy. Inspection should also concentrate on the presence of scars, particularly in the distribution of previous vein stripping, harvest, and/or phlebectomy.[8–11]

Occasionally, auscultation in the vicinity of varicose veins may reveal a bruit. Patients with a previous history of trauma to the lower extremity may have an arteriovenous fistula leading to varicose veins. A congenital arteriovenous or venous malformation can appear as a large, isolated, grape-like cluster of veins or as a moderate to large cluster of smaller vessels appearing with a reddish–bluish hue that penetrate more deeply into fatty and muscular layers of the limb. A bruit is not necessarily needed to confirm this etiology.

Palpation to aid in defining the extent and pattern of CVD is extremely important. Often, when in the standing position, other dilated veins that are incompetent and not readily visualized can be palpated. This may be true when only telangiectasia or venous ulcer is present by inspection. Palpation can also help define a more complete outline of varicose veins, particularly in the thigh region of obese patients. Not uncommonly, areas of old superficial thrombophlebitis can be palpated as cords that may or may not be contiguous with other varicose veins. A thrill can be palpated in some patients with a traumatic arteriovenous fistula. Careful palpation can also help ascertain more serious signs of infection by detecting the extent of dolor, tenderness, and induration. Outlining the extent of lipodermatosclerosis by palpation may also guide the physician as to which area to avoid for phlebectomy or to focus on for subendoscopic perforator surgery.

Patients should also be examined in the supine position. A complete abdominal examination may indicate mass with venous obstruction. Varicose veins that continue to be visualized or are slow to dissipate may also suggest the presence of significant venous obstruction. Pulse examination of the femoral, popliteal, dorsal pedal, and posterior tibial arteries should be performed.

30.3 LABORATORY EXAMINATION

Patients with CVD should have blood and/or urine testing depending on their history, physical examination, and

treatment plan. Patients with a history of recurrent venous thrombosis or venous ulcer before the age of 50 years or recurrent or recalcitrant venous ulcer may require complete screening for hypercoagulability (see Chapter 11).[12–14] Patients with long-standing venous stasis ulcers or those with suspected infection may require a complete blood count, metabolic panel, and inflammatory markers.

30.4 DIAGNOSTIC VASCULAR LABORATORY

Although history and physical examination play major roles in making the diagnosis of CVD, they provide little information regarding the pathophysiology of CVD. Indirect and direct noninvasive testing for CVD performed in the vascular laboratory by an experienced technologist can be of great assistance in expanding the diagnosis of the patient according to the CEAP classification. Delineation of venous reflux, obstruction, and calf muscle pump dysfunction are important to the diagnostic algorithm, particularly in the presence of varicose veins and venous ulcers. These tests may also be applicable to patients with telangiectasia, depending on accompanying leg symptoms.

30.4.1 Indirect noninvasive tests

There are a number of different indirect noninvasive venous vascular laboratory tests, of which the majority utilize some form of plethysmography (see Chapter 14) to help define the presence and distribution of reflux, obstruction, and calf muscle pump dysfunction.[15–17] Of these various tests, many vascular laboratories have the capacity to measure venous refill time and/or venous outflow. For patients with more advanced CVD and venous ulcers, selective use of venous plethysmography is recommended when direct noninvasive testing with the use of duplex ultrasound does not provide definitive diagnostic information.[6]

Typically, venous refill times are determined using photoplethysmography.[18,19] Following five consecutive plantar flexions of the ankle, blood is evacuated from the lower extremity and the venous pressure falls. If the valves are competent, refill to the baseline pressure through the arterial circuit takes longer than 23 seconds. Reaching the baseline plateau in 20 seconds or less indicates venous valvular reflux. Although stated as being imprecise, a thigh cuff can be placed and inflated to a pressure necessary to occlude the great saphenous vein and other superficial tributaries such as the anterior accessory vein (~40 mmHg). This maneuver may further delineate whether the deep venous valves are incompetent.

Venous outflow is typically measured with impedance and strain gauge plethysmography.[20,21] With the patient in the supine position and the legs elevated 15–20°, thigh cuffs are inflated to 50–80 mmHg to occlude venous outflow. When the venous capacitance pressure equalizes to the occluding pressure from the arterial inflow of blood, the cuffs are rapidly deflated. Just prior to cuff deflation, total venous capacitance is compared between the limbs. Limbs with acute or chronic thrombus may have less venous capacitance. The rate of decline over 3 seconds compared to the baseline capacitance also tests for venous outflow obstruction. A leg that is slow to empty could have thrombus more proximally. The presence of developed collateral venous circulation or venous duplicity can lead to a false-negative test.

Increasingly, air plethysmography is being used for its ability to diagnose calf muscle pump dysfunction.[22–24] Using an air-filled plastic bladder that surrounds the lower extremity, the system is calibrated with a known volume of air. Changes in air pressure within the bladder are recorded as maneuvers are made to change the venous capacitance and limb calf diameter. In someone with calf muscle pump failure, minimal blood ejects from the limb with each ankle dorsiflexion, yielding a markedly reduced ejection fraction and a high residual volume. Air plethysmography also evaluates other important physiologic parameters, including venous volume, venous filling index, and residual volume fraction (see Chapter 14).

30.4.2 Direct noninvasive tests

One of the most common direct noninvasive tests used to assess for venous valvular incompetence is described by van Bemmelen and colleagues.[25–27] Venous segments that are typically insonated for examination include common femoral, femoral, popliteal, posterior tibial, and great and small saphenous segments. With the patient using a handrail and dangling the leg in the standing position, duplex insonates the aforementioned venous segments with an appropriately sized cuff placed approximately 5 cm below the probe. Depending on cuff position, inflation pressures from 80 mmHg (thigh) to 120 mmHg (foot) are needed to overcome venous hydrostatic pressure and ensure complete venous evacuation. After maintaining an inflation for 3 seconds, the cuff is rapidly deflated within 0.3 seconds or less. Normal valves respond rapidly with cuff deflation, with 95% demonstrating complete cessation of reverse flow within 0.3 seconds. Therefore, reversal of flow that is greater than 0.5 seconds is considered abnormal. Typically, median reversal of flow times for incompetent valves is 3–4 seconds.

Identification of perforating veins may also be a valid need of the diagnostic evaluation. With the legs in an exaggerated reverse Trendelenburg or sitting position, the duplex can be used to visualize perforating veins along the medial calf. With calf compression or flexion, outward flow from the deep to the superficial venous system indicates incompetence. With the exception of identifying the location of perforating veins, this test is fraught with inaccuracy, as 21% of normal individuals have reversal of flow. Others have looked at the overall diameter of perforating veins, stating that incompetence is present if the diameter is greater than 3.5 mm.[28,29]

30.5 RADIOLOGIC IMAGING

Depending on the clinical scenario, venous obstruction can play a major role in contributing to the pathophysiology and symptom complex of initial-onset and recurrent varicose veins and more commonly in venous ulceration. Increased resistance to venous outflow in combination with valvular incompetence can be responsible for the more recalcitrant ulcer. Computed tomography or magnetic resonance imaging (MRI) can provide imaging to help make the diagnosis of venous obstruction possible.[30–35] Intravenous contrast is usually necessary for optimal evaluation of venous disorders when using computed tomography. Large zones of the body can be imaged over a very short period of time. However, flow artifacts can occur if homogeneous mixing does not occur between the blood and contrast. This is less true for the lower extremities compared to the large central veins in the thorax.

The most common compression syndrome is iliac vein compression syndrome or May–Thurner syndrome. Both modalities can provide accurate measurements of the degree of left common iliac vein compression by the right common iliac artery and further reveal other causes of compression, such as pelvic masses, bone spurs, iliac artery aneurysms, retroperitoneal fibrosis, and inflammatory processes. Each modality can also be useful for making the diagnosis of acute venous thrombosis. Moreover, they might provide an accurate picture of overall clot burden, particularly in certain circumstances when the duplex examination is limited, such as in the presence of large wounds, morbid obesity, and marked interstitial edema. MRI remains a better imaging modality if orthopedic hardware is present.

30.6 INVASIVE IMAGING

30.6.1 Contrast venography

When finalizing a diagnosis and contemplating either endovascular or operative treatment of venous pathology, particularly for that which is responsible for recalcitrant venous ulcer, contrast venography remains vital to providing correct information about venous anatomy, reflux, and obstruction. While detailed descriptions of ascending and descending venography are beyond the scope of this discussion, the techniques described by Rabinov and Paulin[36] and Kistner[37] serve as thorough overviews, respectively.

Ascending venography remains a primary technique for defining venous outflow obstruction. Depending on other previous diagnostic imaging studies (such as MRI) and possible simultaneous endovascular treatments to be performed, this technique may involve puncture of a foot vein, popliteal vein, femoral vein, or common femoral vein. The use of a tourniquet on the calf can assist in filling the deep veins of the lower extremity if performing ascending venography from the injection of a foot vein.

Descending venography remains the primary technique to anatomically define valvular reflux and function. To maximize visualization of the deep veins with this technique, the use of a tilt-table, Valsalva maneuver, and manual compression of the thigh may be helpful. Manual injection of 10–20-mL boluses of contrast is preferred, rather than the use of a high-powered injector. Contrast that freely travels retrograde with no valves visualized can be very helpful when contemplating possible treatments such as valve reconstruction or auto-transplantation.

Other salient points in optimizing the diagnostic potential of venography include: using selective and super-selective cannulation of venous tributaries to provide better venous filling; maximizing valve closure by keeping the patient supine when performing retrograde cannulation (ipsilateral or contralateral); and using larger amounts of contrast over longer periods of injection time. Multiple planar views at 90° obliquities (e.g., 45° left anterior oblique versus 45° right anterior oblique) can help further reveal a venous stenosis that is not appreciated fully on a typical

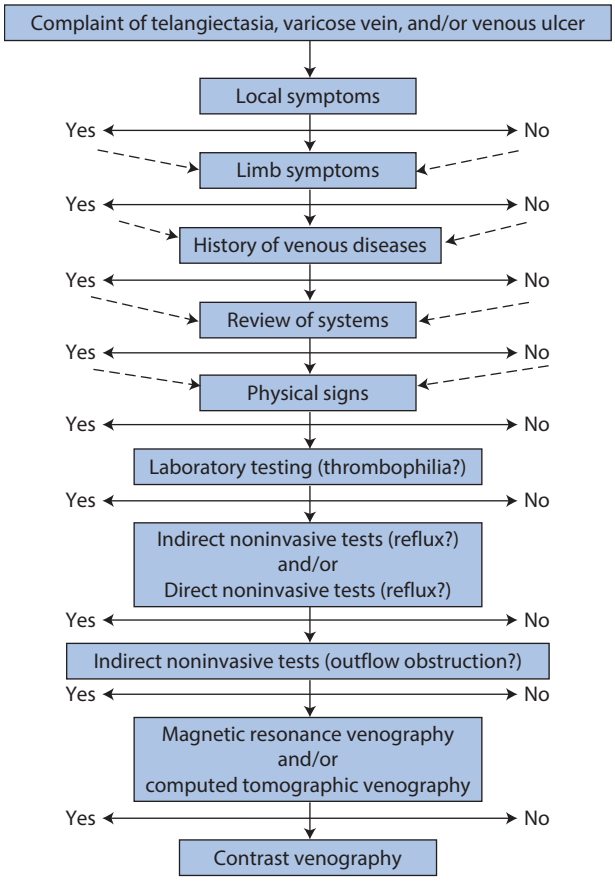

Figure 30.1 The suggested algorithm for the diagnosis of telangiectasia, varicose veins, and venous stasis ulcers may vary depending on presentation, history, and physical examination. Multiple diagnostic options and modalities exist and should follow this prescribed order, depending on the initial constellation of signs and symptoms. As determined by findings, treatment can commence at any stage after complete history and physical examination.

anterior–posterior image. When using a high-powered contrast injector for larger vein visualization, venous trauma can be avoided by using multi-side-hole catheters and decreasing the injection pressure to approximately half that of arterial injections (200–400 pounds/inch).

30.6.2 Intravascular ultrasound

In certain circumstances, venography even with different planar views may not be adequate for fully defining the degree of venous obstruction. Whether it is iliac vein compression syndrome or obstruction from residual chronic thrombus, intravascular ultrasound remains the method of choice for providing an accurate cross-sectional representation of present pathology, and may be more accurate than multiplanar venography to finitely specify where lesions begin and end.[38,39]

30.7 DIAGNOSTIC ALGORITHMS

From a practical standpoint for the clinician, patients typically come or are referred for evaluation because of the presence of spider veins (telangiectasias), varicose veins, or venous ulcers. Occasionally, chronic unilateral edema may be the sole complaint, but often, other associated signs of CVD may be present. Thus far, the discussion has provided a brief overview of the more common diagnostic tools that are typically available to help discern each aspect of the CEAP classification in patients with these conditions. These diagnostic tests and imaging studies help the physician with directing treatment, predicting prognosis, and providing a baseline for comparison during follow-up. The algorithm presented (Figure 30.1) is designed to help the health care professional provide complete care of these problems and further ensure that more significant underlying venous pathophysiology is addressed. Depending on a variety of treatment options that may be pursued for each particular constellation of symptoms, following the guidelines may vary from practitioner to practitioner. As prescribed by this chapter, the algorithm emphasizes diagnostic options in a logical order. Treatment options are outlined in other areas of this book and can occur at different stages of the algorithm, depending on the findings of diagnostic tests.

Guidelines 4.2.0 of the American Venous Forum on a diagnostic algorithm for telangiectasia, varicose veins, and venous ulcers

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.2.1	We recommend that in patients with telangiectasia, varicose veins, and chronic venous insufficiency, a complete history and detailed physical examination is complemented by duplex scanning of the deep, superficial, and (selectively) the perforating veins to evaluate valvular incompetence.	1	B
4.2.2	We recommend that in patients with telangiectasia, varicose veins, and chronic venous insufficiency, laboratory examination is needed selectively for those with a personal or family history of thrombophilia (screening for hypercoagulability) in patients with long-standing venous stasis ulcers (blood count and metabolic panel) and in cases of general anesthesia for the treatment of chronic venous disease.	1	B
4.2.3	In patients with telangiectasia, varicose veins, and chronic venous insufficiency, we recommend selective use of plethysmography, computed tomography, magnetic resonance imaging, ascending and descending venography, and intravascular ultrasound.	1	B
4.2.4	We suggest laboratory evaluation for thrombophilia in patients with a history of recurrent venous thrombosis and chronic recurrent venous leg ulcers.	2	C
4.2.5	We recommend arterial pulse examination and measurement of Ankle–Brachial Index in all patients with venous leg ulcer.	1	B

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● = Key primary paper
★ = Major review article
◆ = Formal publication of a management guideline

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31

Compression therapy for venous ulceration

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31.1 RATIONALE

Chronic venous insufficiency (CVI) is a notoriously difficult problem to treat and requires motivation on the part of the patients, physicians, and other health care professionals. Compression therapy is the standard first-line treatment for CVI and venous ulceration, and remains so despite progress in both ablative and reconstructive venous surgery. The goal of compression therapy is to facilitate rapid ulcer healing, maintain functional mobility of the patient, and prevent recurrence. Compression therapy is effective at promoting reasonably rapid ulcer healing (Figure 31.1). However, clearly not all patients heal rapidly or completely, and recurrence of ulceration remains a major problem irrespective of method of treatment. Risk factors for failure of treatment include advanced age, obesity, coexisting deep venous reflux or arterial insufficiency, long-standing or large ulcers, and multiple recurrences of ulceration.

Most forms of compression therapy are designed to allow the patient to remain ambulatory during treatment as opposed to a prolonged period of complete bed rest and lower extremity elevation. Ambulatory compression can be achieved using a variety of techniques, including elastic compression stockings, paste gauze boots (Unna's boot), and multilayer elastic wraps, dressings, and bandages. Pneumatic compression devices, applied primarily at night, are also employed in some patients.

31.2 MECHANISM

Ambulatory venous hypertension or the presence of elevated venous pressure at the ankle during exercise results in the tissue damage that is characteristic of severe chronic venous disease. The specific mechanisms at play is an area of active research and much has been elucidated regarding the factors that lead to valvular dysfunction, varicosities, lipodermatosclerosis, and ulceration (Figure 31.2a and b). Abnormal hemodynamics involving alterations in both pressure and shear stress within the venous system lead to an inflammatory cascade that eventually causes the characteristic findings of CVI. Low or zero shear stress can occur secondary to reflux from valve coaptation failure, outflow obstruction from venous thrombosis, and dilation and tortuosity of microvessels, as well as disruption of subcutaneous lymphatics (Figure 31.3a and b).[1] Current research continues to clarify the molecular mechanisms involved in CVI. A change in the shear stress on the endothelial surface increases adhesion molecules and leads to leukocyte margination, which in turn leads to activation of neutrophils and monocytes and propagates an inflammatory response. Capillary permeability results in the leakage of plasma proteins as well as cytokines into the extravascular space. A perivascular fibrin cuff forms, impeding wound healing, while cytokines, particularly tissue growth factor-β1, activate fibroblasts responsible for dermal tissue fibrosis (Figure 31.4).[2] Vascular endothelial growth factor (VEGF) has also been found to play a role in venous ulceration. VEGF is partially responsible for the increase in microvascular permeability, as well as proliferation of cutaneous capillaries that are tortuous, elongated, and glomerular in appearance. These abnormal capillaries are prone to injury in a milieu of poor wound healing.[3]

The abnormal hemodynamics and ambulatory venous hypertension must be overcome for compression therapy to be effective and healing to occur. Compression therapy should create internal pressures that are evenly distributed within the leg that maximize the effect of calf muscle contraction and thus optimize venous blood return to the heart. This is the concept of Pascal's Law, which states that pressure

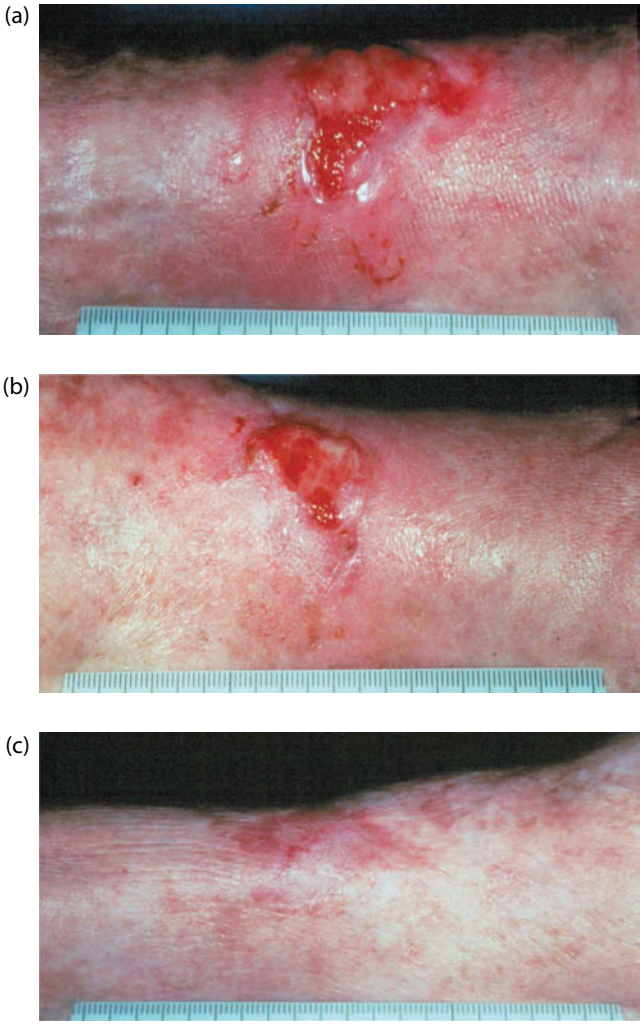

Figure 31.1 Stages of venous ulcer healing with compression therapy: **(a)** 1 month, **(b)** 2 months, **(c)** 3 months.

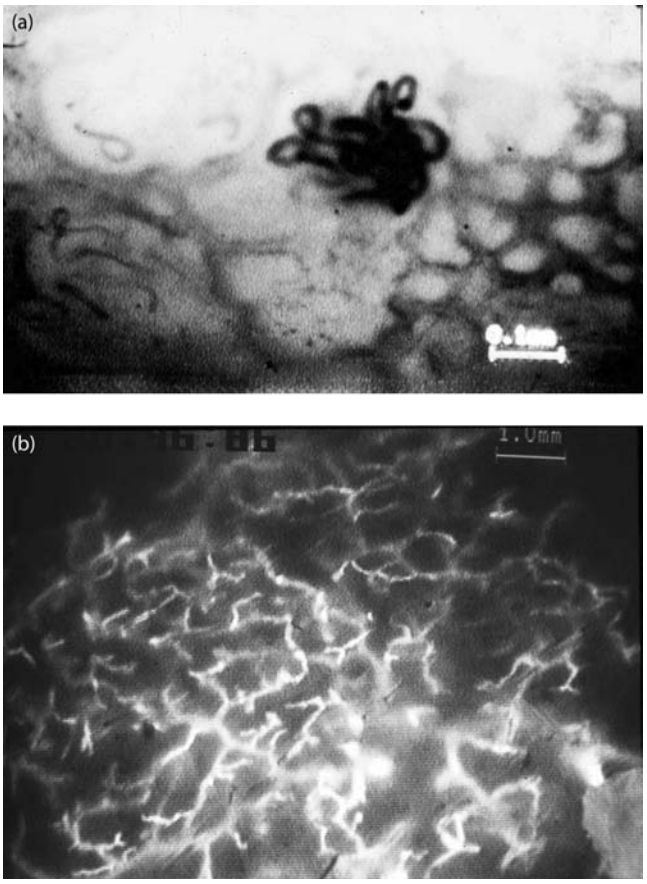

Figure 31.3 **(a)** Video microscopic image of a distorted, torturous medial malleolar microvessel in a patient with chronic venous disease. **(b)** Florescent video microscopy demonstrating disruption of perimalleolar subcutaneous lymphatics in a patient with venous disease.

Figure 31.2 **(a)** Lipodermatosclerosis. **(b)** Large venous ulcer in the medial malleolar region.

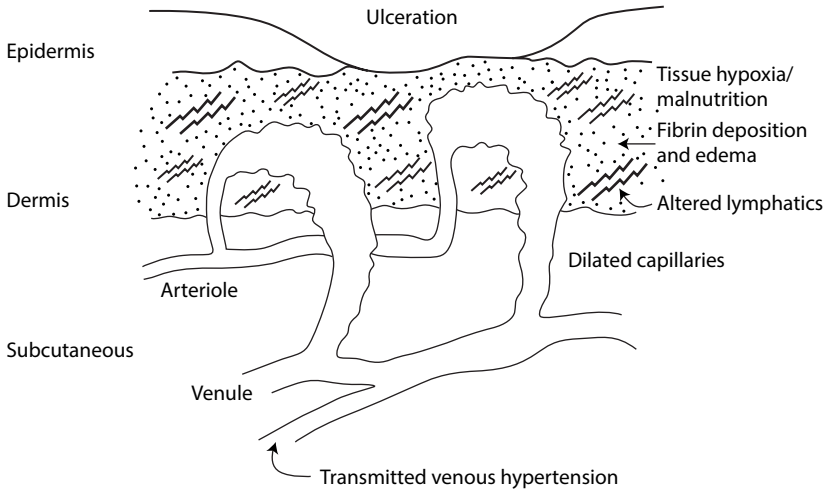

Figure 31.4 Abnormalities of capillary permeability are postulated to lead to leakage of plasma proteins, cytokines, and white cells into the extravascular space. Perivascular fibrin cuff formation may contribute to poor wound healing by inhibiting the diffusion of nutrients and oxygen to the cells.

applied to an enclosed system of an incompressible fluid is evenly distributed.[4] The rigidity of a compression dressing promotes fluid movement into the venous and lymphatic systems due to the pressure gradient created between the interstitial space and the intravascular space. The optimal pressure required to achieve a therapeutic hemodynamic effect is a matter of debate; however, the greater the pressure increase in the leg, the greater the force that pushes the fluid back towards the heart. Gravity governs intravenous pressure, which changes depending on the body position, and this must be counteracted. Physiologically, the pressure in a leg vein reflects the weight of the blood column between the site of measurement and the right atrium.[5] In the supine position, the venous pressure will be between 10 and 20 mmHg. Using a sphygmomanometer cuff containing an ultrasound-permeable window (Echo Cuff, VNUS Medical Technologies, Sunnyvale, CA), it can be demonstrated that in this position, lower leg veins will be narrowed by an external pressure of 10–20 mmHg and totally occluded by a pressure of 20–25 mmHg.[6] Venous narrowing by such low external pressures may explain the effect of thromboprophylactic stockings used in a recumbent patient. These stockings exert a pressure of between 15 and 20 mmHg and enhance venous blood flow velocity when the patient is supine. During standing, the intravenous pressure in the lower leg vein rises to around 60 mmHg, depending on the individual's height. An external pressure of around 35–40 mmHg has been shown to narrow the veins, but a pressure of more than 60 mmHg is necessary to occlude the veins totally.[6]

From these experiments, it may be concluded that major hemodynamic effects of compression in an upright subject may only be expected when the interface pressure of the compression device is higher than 35–40 mmHg. A safe upper limit of 60 mmHg for externally applied, *sustained* compression was proposed based on several microcirculatory investigations.[7] Intermittent pressure peaks can considerably exceed this upper limit.[8]

Compression improves venous pump function in patients with CVI (CEAP classes C3–C6), depending on the interface pressure.[9] Inelastic bandages that do not give way to changes of the leg circumference produce a more pronounced reduction of venous reflux as measured by air plethysmography compared to elastic material applied with the same resting pressure.[10] Inelastic bandages applied with a resting pressure of over 50 mmHg have been shown to demonstrate significant reductions in ambulatory venous pressure (Figure 31.5) as measured in patients with severe CVI walking on a treadmill.[11]

This effect may be explained by an intermittent occlusion of the leg veins exerted by the pressure peaks of 80 mmHg produced by an inelastic bandage during walking. Such effects cannot be achieved with elastic stockings that increase the interface pressure during walking to values only 3–8 mmHg higher than the resting pressure.[12]

A study regarding compression therapy use in ulcers secondary to both venous insufficiency as well as arterial insufficiency (Ankle Brachial Index [ABI] > 0.5, absolute ankle pressure >60 mmHg) showed that inelastic compression of up to 40 mmHg increases the venous pumping function to near normal without impedance of arterial perfusion. Investigations in this work included laser Doppler flux close to the ulcer and at the great toe, transcutaneous oxygen pressure on the dorsum of the foot, and toe pressures to assess arterial perfusion. The ejection fraction of the venous pump system was obtained to assess efficacy of compression on venous hemodynamics. Compression of 31–40 mmHg on the venous pump increased the ejection fraction from 33.9% to 62.6%. The arterial perfusion was not impeded and may have improved slightly given the raised arteriovenous gradient with increased venous return.[13]

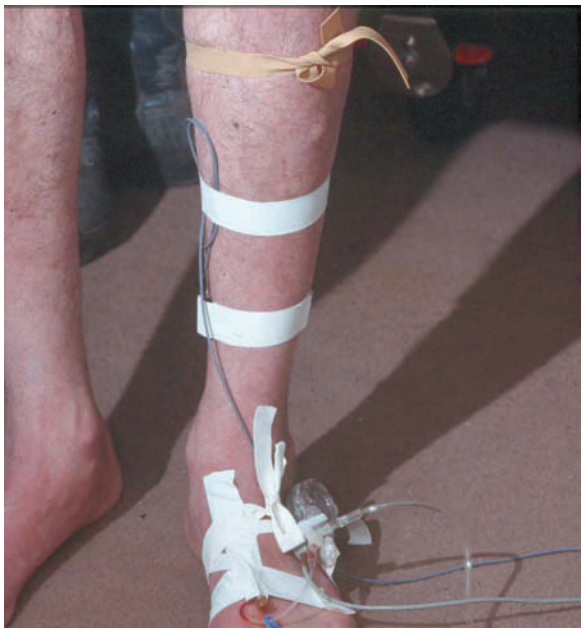

Figure 31.5 Ambulatory venous pressures can be measured with cannulation of a dorsal foot vein and a standard pressure transducer as deep venous pressures are transmitted directly to the dorsal veins of the foot.

There are many possible local cutaneous mechanisms explaining the benefit of compression therapy. Improvements in skin and subcutaneous tissue microcirculatory hemodynamics are postulated. A direct and favorable effect on subcutaneous pressures was also described.[14,15] Supine perimalleolar subcutaneous pressure increases with elastic compression. This should create a Starling gradient favoring resolution of edema by the movement of fluid from the interstitial space into the lymphatic circulation (Figure 31.6) and counteracting leakage of fluid out of the capillary. The observations correlate with the fact that elastic and nonelastic bandages reduce lower extremity edema in patients with CVI and venous ulceration. With edema reduction, the cutaneous and subcutaneous metabolism may improve because of enhanced diffusion of oxygen and other nutrients to the cellular elements of the skin and subcutaneous tissues, thereby promoting ulcer healing.

A number of biochemical abnormalities have now been implicated in the etiology and chronicity of venous ulceration. The effects of compression therapy on these alterations in biochemistry remain largely unknown. VEGF and tumor necrosis factor-α appear to participate in the tissue damage associated with chronic venous disease. Serum levels of both of these cytokines diminish in patients with venous ulcers treated with 4 weeks of compression therapy with four-layered bandaging. Reductions have correlated with ulcer healing as reflected by reduced ulcer size.[16]

31.3 PATIENT EVALUATION

Compression, like many other medical interventions, works best when patients understand their condition and the goals of therapy. Prior to the initiation of compression therapy for venous ulceration, patients must be educated about their chronic disease and the need to comply with their treatment plan in order to heal ulcers and prevent recurrence.

There are several possible causes of chronic leg ulcers. Only about 70% of leg ulcers have a venous origin. A definitive diagnosis of ulceration secondary to venous insufficiency must be made prior to undergoing treatment with

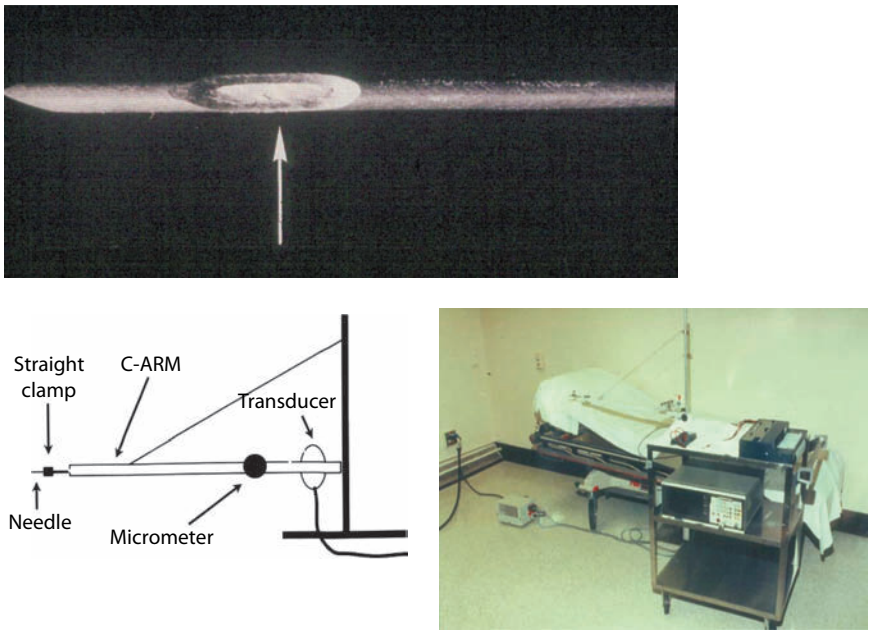

Figure 31.6 Needle with transducer used to study subcutaneous pressures exerted by external compression devices such as elastic stockings.

Figure 31.7 Duplex scanning to detect venous reflux in response to cuff deflation with the patient upright and non-weight bearing is the standard in most vascular laboratories for the detection of venous reflux of the lower extremity axial deep and superficial veins.

compression therapy. A detailed history should be obtained, including medications and other medical issues that may promote lower extremity edema and ulceration. Before the start of compressive therapy, venous insufficiency and/or venous obstruction should be documented in the noninvasive vascular laboratory (Figure 31.7) or, in selected cases, by venography.

Possible arterial insufficiency should also be assessed by physical examination or noninvasive studies prior to therapy beginning. Coexisting arterial insufficiency, especially if severe, is a recognized risk factor for the non-healing of venous ulceration.[17] Compression therapy can be counterproductive in the presence of arterial insufficiency, given that the already diminished skin perfusion pressure can be further decreased, resulting in an overall pro-ulcerogenic effect, as well as an increased risk of critical limb ischemia.[18] Compression therapy must be used with extreme caution in patients with arterial insufficiency and is essentially contraindicated in patients with an ankle brachial systolic blood pressure ratio of <0.5.

Finally, systemic conditions that affect wound healing and leg edema, such as diabetes mellitus, immunosuppression, and malnutrition, should be sought and improved as much as possible before or during the course of compression therapy. Strong compression applied to both lower extremities may shift a considerable amount of blood volume towards the heart, and is therefore potentially contraindicated in patients with severe cardiac dysfunction.

31.4 FORMS OF COMPRESSION THERAPY

31.4.1 Elastic stockings

Compression therapy is most commonly delivered with gradient elastic compression stockings. Gradient elastic compression stockings, initially developed by Conrad Jobst in the 1950s, were made to simulate the gradient hydrostatic forces exerted by water in a swimming pool. Elastic compression stockings are available in various compositions, strengths, and lengths, and can be customized for a particular patient.

The benefits of elastic compression stocking therapy for the treatment of CVI and healing of venous ulceration have been well documented. In a retrospective review of 113 venous ulcer patients, the use of below-knee, 30–40-mmHg elastic compression stockings, after first resolving edema and cellulitis if present, resulted in 93% ulcer healing. Complete ulcer healing occurred in 99 of 102 (97%) patients who were compliant with stocking use versus six of 11 patients (55%) who were non-compliant ($P < 0.0001$). The mean time to ulcer healing was 5 months. Ulcer recurrence was less frequent in patients who were compliant with their compression therapy. By life table analysis, the rate of ulcer recurrence was 29% at 5 years for compliant and 100% at 3 years for non-compliant patients.[19] In this cross-sectional study of venous ulcer patients, mean age was 59 years and 27% of ulcers were recurrent. Compliance with the use of stockings as instructed was very good. Not all centers, however, have had such favorable results with elastic compression stockings. Older, less compliant patients and populations with a higher percentage of recurrent or long-standing ulcers will likely not do as well.

Data on 3144 new chronic venous disease patients treated from 1998 to 2006 were reviewed to further characterize compliance with compression stockings. A total of 37% of patients reported either full or partial compliance; 63% did not use the stockings or abandoned them after a trial period. A total of 30% of non-compliant participants could not specify a reason for non-compliance; 25% did not have a prescription; 14% did not feel that the stockings helped; 13% reported the effect of binding/"cutting off" circulation; 8% felt that the stockings were too hot to wear; 2% reported limb soreness; 2% reported poor cosmetic appearance; 2% stated that they were unable to apply the stockings; 2% reported itching or contact dermatitis; and 2% were non-compliant due to cost.[20]

In addition to promoting ulcer healing, elastic compression therapy can also improve quality of life in patients with CVI. In a recent prospective study, 112 patients with CVI documented by duplex ultrasound were administered a questionnaire to quantify swelling, pain, skin discoloration, cosmesis, activity tolerance, depression, and sleep alterations. Patients were treated with 30–40-mmHg elastic compression stockings. Overall improvement in symptoms severity scores was observed at 1 month after initiation of treatment. Further ameliorations were noted at 16 months.[21]

Elastic stockings as a treatment for venous ulceration have the advantage over bandages that their effects are operator independent. Once applied, their effects are related to the strength of the stocking and independent of the patient. Stockings are less bulky than other forms of compression therapy and therefore perhaps more comfortable. They can

be worn with normal footwear and allow daily inspection of wounds. However, the stockings must be used to be effective and they are easily removed or "forgotten" by the noncompliant patient.

Patient compliance with compression therapy is crucial in treating venous leg ulcers. It begins with patient education, being reinforced at every visit to the office and the clinic. Many patients are initially intolerant of compression in areas of hypersensitivity adjacent to an active ulcer or at sites of previously healed ulcers. This can sometimes be overcome by initially fitting the patient with lower-strength stockings followed by higher-strength stockings over a period of several weeks. An obvious disadvantage is the added expense of the "introductory" stocking.

Patients may also have difficulty applying elastic stockings. Elderly, weak, or arthritic patients cannot easily apply elastic stockings. In one study of elderly (mean age: 72 years) and predominately female patients (69%), 15% of patients were incapable of applying stockings and 26% could only put them on with significant difficulty.[22] Obese patients frequently cannot reach their feet and are dependent on family members for application of the stocking. A number of aids have been developed to assist in the application of elastic stockings. With open-toe stockings, an inner silk sleeve can be placed over the patient's forefoot to allow the stocking to slide smoothly during application. The sleeve is removed through the toe opening after the stocking has been placed. Another device allows the patient to load the stocking onto a wire frame. The patient then steps into the stocking and pulls the device upward, applying the stocking to the leg (Figure 31.8).

Figure 31.8 The so-called Butler device can be used to aid in donning compression stockings. The patient loads the stocking onto the wire frame and then steps into the stocking and pulls the device upward, applying the stocking to the leg.

Recurrence of ulceration after healing can be lessened by the use of elastic stockings after the ulcer has healed.[19,22] However, in this case, an additional problem can be the unwillingness of insurers to provide coverage for elastic stockings, in spite of evidence of the cost-effectiveness of elastic stockings in preventing ulcer recurrence.[23]

Another indication of compression stockings is the prevention of post-thrombotic syndrome (PTS) observed in 25%–50% of patients following deep venous thrombosis (DVT). The clinical features are the same as those for CVI, and include a spectrum of symptoms and signs ranging from mild lower extremity swelling and discomfort to severe pain, to irreversible skin changes, and eventually ulceration.

Interestingly, the SOX trial, a recent randomized, placebo-controlled trial, questioned the use of compression stockings for the prevention of PTS in patients with a first-time proximal DVT.[24] The study was conducted from 2004 to 2010 and followed for 2 years 410 patients who were blinded and randomly assigned to either compression stockings with a pressure of 30–40 mmHg or placebo stockings with less than 5 mmHg of pressure. The cumulative incidence of PTS was 14.2% in patients with the active compression stockings versus 12.7% in the placebo arm, indicating no advantage of compression stockings for preventing PTS. This trial was in opposition to two previous trials that did show substantial benefit of compression in this indication; however, those trials were open label, single center, and smaller.[25,26] Therefore, while the utility of compression stockings for the prevention of PTS remains unclear, once PTS has developed, compression therapy remains a staple of treatment.

31.4.2 Paste boots

Another method of compression was invented by the German dermatologist Paul Gerson Unna in 1896. Unna's boot has been used for many years to treat venous ulcers and is available in many versions. Unna's boot is basically a form of compression bandages (see below). A typical Unna's boot-type dressing is a three- or four-layer dressing and requires application by trained personnel. A rolled gauze bandage impregnated with calamine, zinc oxide, glycerin, sorbitol, gelatin, and magnesium aluminum silicate is first applied with graded compression from the forefoot to just below the knee. Additional layers consist of a continuous gauze dressing followed by an outer layer of elastic wrap, also applied with graded compression. The bandage becomes stiff after drying and the rigidity may aid in preventing edema formation. The resting pressure, measured on the distal lower leg immediately after application, may be 50–60 mmHg in the supine position. Unna's boot is changed weekly or sooner if the patient experiences significant drainage from the ulcer bed. Once applied, Unna's boot requires minimal patient involvement and provides continuous compression and topical therapy. However, the Unna's boot has several disadvantages. It is uncomfortable to wear for some patients because of its bulkiness. This may affect patient compliance. In addition, the ulcer cannot be

monitored and the technique is labor intensive, with the degree of compression provided being operator dependent. Patients may also occasionally develop contact dermatitis to the components of Unna's boot that may require discontinuation of therapy. In a 15-year review of 998 patients with one or more venous ulcers treated with Unna's dressings, 73% of ulcers healed in patients who returned for more than one treatment. The median time to healing for individual ulcers was 9 weeks.[27] Unna's dressing has been compared with other forms of treatment. A randomized, prospective study comparing Unna's boot to polyurethane foam dressing in 36 patients with venous ulcers demonstrated a superior healing rate over 12 months in patients treated with Unna's boot (94.7% vs. 41.2%).[28]

31.4.3 Compressive bandages

The purported advantages of multilayered compressive dressings include maintenance of compression for a longer period of time, more even distribution of compression, and better absorption of wound exudates. The pressure delivered by a compressive bandage depends upon the radius of the limb to which it is applied, the number of layers applied, the elastic properties of the materials utilized in the bandage, and the wrapping technique of the health care personnel who apply the bandages. There are a wide variety of compression materials with different textures available, resulting in bandages in which the elastic properties and applied pressure are quite variable. Pressure, layers, components, and elastic properties (P-LA-C-E) are the deciding features that have to be considered when compression bandages are applied.

31.4.4 Pressure

The pressure developed beneath a bandage is governed by the tension in the fabric exerted by the bandager, the radius of curvature of the limb, and the number of layers applied.

Several instruments are available to measure the interface pressure exerted by a compression device on an individual leg. In the supine position, pressure ranges in the gaiter area can be classified according to proposals from a recent consensus conference (Table 31.1).[29] It must be stressed that the interface pressures exerted during standing and walking will increase in a manner that depends on the elastic property of the material. "Strong" and "very strong" bandages clearly produce higher interface pressure values than those obtained by compression stockings.

Table 31.1 Pressure ranges of compression bandages measured in the supine position at the medial aspect of the lower leg where the tendon changes into the muscular part of the gastrocnemius muscle

Recommendation	mmHg
Mild	<20
Moderate	20–40
Strong	40–60
Very strong	>60

31.4.5 Layers

Single-layer bandages will usually have an overlap of up to 50%. Multilayer bandages consist of several single layers.

31.4.6 Components

The components of a bandage are the different materials used for one compression bandage application. Besides their intended functions of padding, protection, or retention, they exert varying effects on the interface pressure and on the stiffness of the final bandage. Compression bandaging systems consist of at least two different bandaging materials applied over each other for the whole length of the leg (Figure 31.9).

31.4.7 Elastic properties

The usual differentiation between elastic and inelastic compression material is based on *in vitro* measurements using different extensometer devices and assessing the relationship between the power exerted to distend the bandage and the resulting stretch. Table 31.2 shows a classification system for single-layer, single-component materials.[29]

Several layers of elastic bandages will create a bandage with increasingly inelastic properties. The same is true

Figure 31.9 Application of the initial layer of a multilayer compressive wrap.

Table 31.2 Inelastic and elastic bandage materials

Inelastic	Elastic rigid	Short stretch	Long stretch
Extensibility (%)	0–10	10–100	>100
Examples	Zinc paste	Comprilan	Ace bandage
Velcro-band devices	Rosidal K	Surepress	(CircAid)

when two stockings are used over each other or when several components of different materials are applied. This is because of an increase in friction between the rough surfaces of different layers opposing the expansion of the elastic strain of the fibers. Typical examples of bandages with high friction are cohesive bandages that adhere to the underlying layer and are adhesive to the skin bandages.

Elasticity of the materials used in a compressive bandage (or stocking) is determined by *in vitro* measurements that quantify the power required to distend or stretch the bandage and the resulting extension of the bandage: a so-called hysteresis curve.[29,30] In general, an attempt is made to achieve a pressure of about 40 mmHg at the gaiter area. "Strong" bandage material will need to be stretched less than "weak" bandage material to achieve this goal.

Compressive bandages have varying degrees of stiffness, defined as the increase in pressure per centimeter increase in leg circumference.[30] A higher stiffness indicates relative inelasticity of the bandage. An inelastic bandage is defined as having a pressure increase of >10 mmHg when moving from a supine to standing position, whereas with an elastic bandage, the pressure increase is <10 mmHg. Relatively high-stiffness (inelastic) bandages include the Pütter bandage, which consists of two 5-m long short-stretch bandages applied to the leg in opposite directions (e.g., Comprilan, Rosidal K, and Pütter bandage). The inelastic kits are composed of padding, foam material, short-stretch bandages, and a protecting hose layer (Rosidal sys bandage). The main component of these bandages is cotton, which is permeable to air, very well tolerated, and can be washed and reused (Comprilan and Rosidal). Applying several elastic layers over each other creates a bandage system with high stiffness (Four-layer bandage and Profore). The final bandage, when used according to the manufacturers' instructions, will exert an interface pressure of about 40 mmHg on the distal lower leg in the resting position. The Coban2 layer kit consists of two layers with an adhesive surface. It is easy to apply and creates a stable, non-bulky bandage with high stiffness.

There are two main disadvantages of inelastic bandages. One is the loss of bandage pressure starting immediately after bandage application. The initial resting pressure will decrease by about 25% within 1 hour of application, mainly due to a decrease in the volume of the limb. The second disadvantage is the fact that a good inelastic compression bandage is not easy to apply. It requires skills that must be learned with proper training. Bandages with inelastic material should be applied with much higher initial tension than elastic bandages because of the fast pressure drop. An inadequate technique is the main reason for the poor clinical outcome described in several studies.[31]

Examples of elastic bandages are Ace-bandage, Surepress, and Perfekta. Proguide is a kit consisting of a padding layer and a specially designed elastic bandage. Elongation of the bandage material leads to only a small pressure increase.[7] Such bandages may exert a relatively high resting pressure, which will increase only minimally during walking ("low working pressure"). The main advantage of these bandages is that they are relatively easy to apply, whether by untrained staff or by the patients themselves. The main disadvantage is the high resting pressure and the uncomfortable feeling due to the constricting force of the elastic fibers. This high resting pressure might be responsible for skin damage, particularly in patients with arterial occlusive disease and overexposed pressure sites, such as over the dorsal ankle tendon.

Several points should be considered when compressive bandages are applied:

- Elastic bandages are easier to handle than inelastic bandages and may be applied by untrained staff or by patients themselves.
- Inelastic material should be applied with much higher resting pressure, pressing the bandage roll towards the leg as if molding clay. The patient is encouraged to immediately walk for at least 30 minutes to decrease edema and thereby decrease the pressure being exerted under the bandage.
- In patients with a small ankle circumference, bandages should be applied with much less tension using ample amounts of orthopedic wool padding to protect the tendon.
- The initial turn may start at the base of the toes or be placed around the ankle or between the heel and the dorsal tendon to fix the bandage. The ankle joint is always bandaged with maximal dorsal extension of the foot and the protruding tendon is carefully protected with cotton-wool.
- Overlapping can be carried out in a spiral fashion or with figures of eight.
- The proximal end of a knee-high bandage should cover the level of the fibular head.
- The bandage must be applied with no gaps so that each turn overlaps the previous turn by about 50%.
- Bandage materials must be non-allergenic to avoid the development of dermatitis.
- Pads can increase local pressure over ulcers or firm lipodermatosclerotic areas.
- Pain may indicate arterial ischemia. In such cases, the bandage must be removed immediately.
- Bandaging of the lower leg is sufficient for the majority of patients with chronic venous disorders.
- Walking exercises are essential to optimize the effect of compression therapy. However, compression is also able to reduce edema in immobile patients or in those with

severely restricted mobility. Inelastic fixed bandages are preferred for this indication because of the lower resting pressure.

- After some walking, the pressure will drop because of the immediate removal of edema. In the edematous phase, the bandage will loosen after a few days, and it should be renewed or over-wrapped with a short-stretch bandage. The same is advisable when exudate from the ulcer penetrates the bandage. This may occur particularly during the initial treatment phase, and the patient should be informed to come back if this happens. Generally, the bandage is changed every 7 days on average.

Stiffer, more inelastic bandages may have greater effects on measurements of deep venous hemodynamics. A study using air plethysmographic measurements of venous volume and venous filling index in limbs with venous ulcers treated with elastic long stretch versus inelastic short-stretch bandages found greater improvement in varicose veins and the venous filling index with the short-stretch, inelastic bandage.[10]

A clinical study of a relatively stiff bandaging system (multilayer wrap of orthopedic wool, crepe bandages, and Coban bandages) reported results in 148 ulcerated limbs (126 patients) that were refractory to simple wraps. At 12 weeks, 74% of ulcers had healed and measurements of compression declined only 10% over 1 week.[32]

A direct comparison between an elastic and inelastic bandaging regimen has been performed. The authors randomized 112 venous ulcer patients to an elastic or inelastic bandaging group ($n = 57$ and $n = 55$, respectively). Larger ulcers took longer to heal with the elastic compression, but complete healing at 26 weeks was no different: 58% for the elastic bandage arm versus 62% in the inelastic system arm.[33] Another study comparing multilayer bandaging versus relatively inelastic short-stretch bandaging for venous leg ulcers showed that ulcers treated with multilayer bandaging healed more quickly.[34]

Authors from Serbia reported dramatic results in healing very large venous ulcers with a heelless, open-toe, elastic, multilayered compression device knitted into a tubular configuration. A total of 138 patients with very large venous ulcers (20–210 cm^2) were randomized to treatment with the multilayered tubular device ($n = 72$) versus bandaging plus compression stockings ($n = 66$). Cumulative healing was 93% in the group treated with the multilayered tubular dressing and 51% in the other group.[35]

Clearly, multilayer compressive bandages can be effective for healing of venous ulcers. Stiffer, short-stretch bandages may have greater effects on deep venous hemodynamics and perhaps demonstrate faster healing than more elastic bandages. Whether this provides overall increased clinical efficacy remains to be determined. Direct comparisons between different multilayer bandaging systems and between those systems and other methods of compression are needed.

The Venous Ulcer Study IV (VenUS IV) looked at the clinical effectiveness and cost-effectiveness of compression two-layer hosiery versus four-layer compression bandages. This was a randomized controlled trial involving 453 participants from 34 centers in England and Northern Ireland. Study participants were stratified by ulcer duration and area, and then randomized to either hosiery or bandage compression therapy. The primary endpoint was time to ulcer healing, with a maximum follow-up of 12 months. Median time to healing was 99 days (95% CI: 84–126) in the hosiery group and 98 days (95% CI: 85–112) in the bandage group, indicating that both treatment options have essentially equivocal healing rates. The economic analysis, however, revealed a significant advantage to the hosiery group.[36]

31.4.8 Legging orthosis

CircAid is a legging orthosis consisting of multiple pliable, rigid, adjustable compression bands.[29] These bands wrap around the leg from the ankle to the knee and are held in place with Velcro (Figure 30.10). The device provides inelastic, rigid compression similar to an Unna boot with increased ease of application. Because the bands are adjustable, it can be tailored to the individual as limb edema decreases. The orthosis appears effective at promoting resolution of edema and is especially useful in patients who, for various reasons, are either unable or unwilling to wear compression stockings. This legging orthosis may be superior to elastic stockings at preventing limb swelling in patients with advanced venous insufficiency.[37]

Figure 31.10 Example of a CircAid compressive bandage. Compression can be varied according to how tightly the Velcro straps are pulled.

31.4.9 Pneumatic compression devices

Pneumatic compression devices can serve as adjuncts in the treatment of lower extremity lymphedema or venous ulceration. These devices may be particularly applicable to patients who have severe edema or morbid obesity. Relative contraindications are arterial insufficiency and uncontrolled congestive heart failure.

Pneumatic compression devices that provide sequential gradient intermittent pneumatic compression have received the most attention. Results suggest improvement in ulcer healing, but this might be facilitated by the fact that pump patients elevate their legs for longer on a daily basis than non-pump patients. The intermittent compression has not gained widespread acceptance, despite the results of the few studies in this area indicating that pneumatic compression may be useful in the treatment of venous ulcers, especially those refractory to previous treatment with ambulatory compression alone.[38,39]

31.5 STUDIES COMPARING SURGERY VERSUS COMPRESSION

The current literature highlights the difficulties of comparing various forms of compression therapy for venous ulcer treatment with venous surgery. At least two major reviews have concluded that insufficient evidence exists to favor one form of compression over another.[40,41] In addition, there is insufficient evidence to favor the use of adjunctive dressings, such as hydrocolloid dressings (DuoDERM), in addition to compression therapy to heal venous ulcers.[41] Comparisons are hampered by a low number of randomized controlled studies, different patient selection criteria, variable use of compression as an adjunct to surgical therapy, and potentially variable compliance with post-operative compression therapy.

The ESCHAR study evaluated the hemodynamic effects of added compression in patients with venous ulceration. Legs with open or recently healed venous ulcers were treated with multilayer compression bandages or superficial venous surgery plus compression ($n = 112$ legs vs. 102 legs, respectively). Venous refilling time as measured by photoplethysmography was the primary hemodynamic outcome. The ulcer healing rate was 64% at 24 weeks and nearly identical in the two groups. Although there was no benefit to surgery regarding ulcer healing, the ulcer recurrence rate was halved in those that underwent surgery.[42,43] The ESCHAR study results can be applied to the use of endovenous techniques.

In a study from Italy, Zamboni et al.[44] randomized 80 consecutive patients with 87 venous leg ulcers to treatment with compression or minimally invasive surgery. Healing was remarkable in both groups: 100% at 31 days in the surgical group compared with 96% at 63 days in the compression group ($P < 0.02$). Follow-up was 3 years and recurrence rates were 9% in the surgical group versus 38% in the compression group ($P < 0.05$). Quality of life was also better in the surgical group.

A British study randomized 76 patients with venous ulcer to treatment with a four-layer bandaging system or superficial venous surgery and a four-layer bandaging system. Healing occurred in 64% of the compression group and 68% of the surgical group ($P = 0.75$), with no significant difference in the time to ulcer healing and no differences in health-related quality of life.[45]

Why do these studies give such disparate results? The trials were similar in design, the patients nearly the same age, and the mean ulcer sizes no different, and yet the Italians stated that superficial venous surgery works as an adjunct to the treatment of venous ulcers, whereas the English concluded that superficial surgery added nothing to compression therapy. Details of the two studies may explain the different results. The Italians excluded ulcers >12 cm and patients with secondary reflux or deep venous reflux. The English patients had a mean of two previous episodes of venous ulceration. The Italian study did not provide

Guidelines 4.3.0 of the American Venous Forum on compression therapy for venous ulceration

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.3.1	We recommend compression therapy to heal venous ulcers.	1	A
4.3.2	We suggest compression therapy to decrease the risk of ulcer recurrence.	2	B
4.3.3	We suggest the use of multicomponent compression bandage over single-component bandages for the treatment of venous leg ulcers.	2	B
4.3.4	We suggest enforcing compliance since it is integral to the success of compression therapy.	2	A
4.3.5	We suggest use of intermittent pneumatic compression when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy.	2	C

information on previous episodes of venous ulceration. At this time, one is left to conclude that superficial venous surgery may improve the results of compression therapy for venous ulceration in certain, more favorable subgroups of patients with venous ulcers.

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● = Key primary paper
★ = Major review article

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32

Drug treatment of varicose veins, venous edema, and ulcers

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32.1 INTRODUCTION

The treatment of venous disease in the lower limbs has been revolutionized in the last two decades by the development of new methods of endovenous ablation. These are now widely incorporated into medical practice throughout the world and have led to considerable advantages for patients as well as for clinicians. Similar advances have not been achieved by drug therapy for varicose veins and chronic venous disease, although the development of orally active direct inhibitors of the clotting cascade have led to considerable advances in the management of venous thrombosis. No drug will cure varicose veins, although some benefit venous edema and ulceration. The greatest expansion of drug treatment in the management of venous disease has been the use of foamed sclerosants in the management of varicose veins, which is discussed in other chapters. The most economically important field of venous disease is leg ulceration. Presently available drugs have modest benefit in this disease and cannot be recommended in every patient. Research in the field of venous leg ulcers has not revealed any biological process that, when suppressed or enhanced by drug treatment, would dramatically enhance the process of wound healing.

32.2 VARICOSE VEINS AND EDEMA

Varicose veins are a common problem affecting about 25% of the adult population in westernized countries. This disease infrequently results in serious illness, although in some patients, severe skin changes (lipodermatosclerosis [LDS]) and leg ulceration may develop. Varicose veins are associated with a wide range of symptoms (aching, pain, cramps, restless legs, feeling of heaviness, itching, and feeling of swelling). The symptoms are commonly managed by elastic compression, sclerotherapy, surgery, or a venous ablation technique. Is drug treatment useful in managing any of the consequences of varicose veins?

In some countries drugs are widely prescribed, but in others few drugs are used in the treatment of varicose veins. A range of phlebotonic drugs is used (Table 32.1). The origin of these is from plants or synthetic sources. Little new evidence regarding the efficacy of these drugs on symptoms arising from varicose veins has been published in recent years. A Cochrane review of the efficacy of these drugs was published in 2005[1] and has not been updated subsequently. In all, 110 studies were considered for inclusion in the analysis; however, valid methodology and data were only present in 44 studies, covering a range of commonly prescribed drugs. The scope of this review included the following flavonoids: rutoside, French maritime pine bark extract, grape seed extract, Diosmin and Hesperidin, disodium flavonate, and the saponside centella asiatica. The synthetic products included were calcium dobesilate, fantazone, aminaftone, and chromocarbe. The overall findings were that there appeared to be an effect on edema, but amongst the symptoms mentioned above, only restless legs were moderated. For the more frequently prescribed drugs, the following effects were observed: calcium dobesilate reduced cramps and restless legs; Diosmin and Hesperidin benefitted trophic disorders as well as cramps and swelling; and rutosides were found to benefit edema. On the basis of their review, the authors concluded that there is insufficient evidence to support the global use of phlebotonics in the

Table 32.1 Classification of the main venoactive drugs

Group	Substance	Origin	Dosage (mg/day)	Number of doses/day
Benzopyrones				
α-benzopyrones	Coumarin	Melilot (*Melilotus officinalis* L.) Woodruff (*Asperula odorata* L.)	90 combined with troxerutin (540)	3
γ-benzopyrones (flavonoids)	Diosmin	*Citrus* spp. *Sophora japonica* L.	300–600	1 or 2
	Micronized purified flavonoid fraction		1000	1 or 2
	Rutin and rutosides	*Sophora japonica* L.	1000	1 or 2
	O-(β-hydroxyethyl)-rutosides (troxerutin, hydroxyrutoside [HR])	*Eucalyptus* spp. *Fagopyrum esculentum* Moench		
Saponins	Escin	Horse chestnut (*Aesculus hippocastanum* L.)	120, then 60	3
	Ruscus extract	Butcher's broom (*Ruscus aculeatus* L.)	2–3 tablets	2–3
Other plant extracts	Anthocyans	Bilberry (*Vaccinium mytrillus* L.)	116	2
	Proanthocyanidines (oligomers)	Grape pips (*Vitis vinifera*)	100–300	1–3
		Maritime pine (*Pinus maritima* Lank) (*Pycnogenol*)	300–360	3
	Ginkgo biloba	*Ginkgo biloba* L.	2 sachets (extracts of ginkgo, heptaminol and troxerutin)	2
Synthetic products	Dobesilate	Synthetic	1000–1500	2–3
	Benzarone	Synthetic	400–600	2–3
	Naftazone	Synthetic	30	1

Source: Reproduced from Ramelet AA et al. *Clin Hemorheol Microcirc* 2005;33:309–19.

management of the signs and symptoms described above. Fortunately, few side effects of this treatment have been reported.

Aescin (horse chestnut seed extract) is the subject of a separate Cochrane review.[2] The review was conducted in 2012, but no publication later than 2002 was included. The authors found evidence for efficacy on symptoms including leg pain, edema, itching, leg volume, and circumference in comparison with placebo. They recommended that, in view of the low frequency of adverse events, horse chestnut seed extract was appropriate for the short-term treatment of the symptoms of chronic venous disease.

A Cochrane review identified three studies addressing edema and varicose veins of the lower limbs in pregnancy.[3] One study (69 patients) showed that rutoside treatment reduced symptoms associated with varicose veins. A clinical trial (35 patients) addressing the use of stockings in pregnancy failed to reduce ankle edema.

A Cochrane review has addressed the efficacy of rutosides for the treatment of post-thrombotic syndrome.[4] Primary outcome measures were the occurrence of leg ulceration and deterioration of post-thrombotic syndrome. Secondary outcomes included reduction of edema, pain, recurrence of deep venous thrombosis or pulmonary embolism, compliance with therapy, and adverse effects. The authors concluded that there was no evidence that rutosides were superior to the use of placebo or elastic compression stockings.

In summary, phlebotonic drugs have a modest effect on the symptoms of chronic venous disease, including edema. These become less apparent or disappear when compression is used as a comparator treatment.

32.3 VENOUS ULCERS

Venous ulceration is conventionally managed by compression treatment, which may be combined with ablation

or surgery to varicose veins, perforating veins, and less frequently with deep vein reconstruction. Compression treatments have been found to lead to acceleration of healing with a greater proportion of healed ulcers. A significant problem remains in terms of the rate of recurrence of ulcers after healing with compression. Can this be reduced? Surgical ablation of incompetent superficial veins apparently does not lead to more rapid healing, but does prevent recurrence of ulceration.[5] This is certainly a very valuable adjunct to compression treatment. The costs of dressing a leg ulcer in the U.K. National Health Service are in the range of €6000–20,000 per year. This compares with the cost of surgical management of varicose veins of around €2000. Not all patients are prepared to undergo surgical treatment, especially the elderly. However, ultrasound-guided foam sclerotherapy has been reported to be effective in the management of venous ulceration by Pang et al.[6] These authors noted that healing of leg ulcers was achieved in 82% of patients following foam sclerotherapy to saphenous trunks and varices, with an ulcer recurrence rate of 4.9% at 2 years.

These are the standard methods of management, but is there any advantage of drug treatment in this group? A small number of drugs has been studied for activity in promoting leg ulcer healing and some are of historical interest only. The mechanisms of pathogenesis of venous ulcers have been investigated at length by several authors, including myself. Although many factors have been found to be involved in the inflammatory process leading to leg ulceration, it has not been possible to identify any "crucial" step which could readily be inhibited by pharmacological means. I believe that it is too simplistic to consider that such an easy solution could be found. Instead, it may be better to modify a range of processes observed in developing leg ulcers. This may lead to useful therapeutic advance.

32.4 DRUGS USED FOR VENOUS ULCERS

A range of drugs has been used in the management of leg ulcers. These may be given systemically or applied topically. In addition, a wide range of wound dressings has become available, some of which have "active" properties which might promote wound healing. Honey has been applied to leg ulcers as a wound dressing in the expectation that this will lead to more rapid healing. A recent Cochrane review has found that there is very limited evidence of efficacy for this treatment amongst low-quality studies.[7] A Cochrane review assessed the published data in 42 clinical trials in which hydrocolloid, foam, alginate, and hydrogel dressings were assessed.[8] The authors concluded that there was no evidence that any of these approaches accelerated wound healing when these were applied beneath compression. A further review has investigated published data concerning wound dressing and other topical applications.[9] The authors considered 68 studies for inclusion in their analysis and eliminated all but 20, excluding the remainder on the basis of poor study design. Eight studies addressed the use of wound dressings, but none showed conclusive advantage of any other dressing in accelerating wound healing. A further seven studies addressed the subject of topical growth factor application. The list of compounds applied topically included platelet lysate, keratinocyte lysate, vasoactive intestinal peptide, granulocyte colony-stimulating factor (G-CSF), and becaplemin. Of these, only G-CSF improved ulcer healing significantly, and these data were confined to one clinical trial. In five studies, human skin equivalents were investigated. These included Dermagraf, cultured keratinocytes, Apligraf, Epidex, and cultured epidermal allografts. Amongst these, evidence of improved healing was found in only one, a study of the use of Apligraf involving 275 patients.

In summary, wound dressings, growth factors, and human skin equivalents showed limited efficacy in accelerating wound healing in the trials included. I conclude that whilst wound dressings of modern design may facilitate the management of leg ulcers, none has the power to heal ulcers above the effects of compression bandaging applied alone. Topical growth factors have no consistent effect, and of the skin-equivalent dressings, only Apligraf has been shown to have beneficial effects for venous ulcers.

A further Cochrane review has considered the efficacy of antibiotics and antiseptics for venous leg ulcers.[10] No evidence was found for efficacy of topical antiseptic applications, honey, or silver-based products. Possible evidence exists of efficacy for cadexomer iodine. Antibiotics are considered in more detail below.

32.4.1 Systemic drugs for wound healing

Many drugs have been used in the hope of healing leg ulcers. I have included below those for which reasonable evidence of efficacy or lack of efficacy has been published.

32.4.1.1 ZINC AND VITAMINS

Greaves and Skillen, in an old but widely quoted paper, reported complete healing in 13 of 18 patients with previously intractable ulceration after a 4–month course of 220 mg zinc sulfate three times daily.[11] This might simply have reflected dietary inadequacy in this group. However, a Cochrane systematic review of zinc supplements considered six small trials which comprised the only available evidence.[12] No beneficial effect of oral zinc treatment on venous ulcer healing was found in these studies.

Adequate nutrition is essential for leg ulcer healing, as it is for wound healing of other types. A group of authors in the United States found deficiencies of vitamins A, E, carotenes, and zinc in patients being treated for venous leg ulcers.[13] They speculated that this reflected compromised nutritional status, which might influence leg ulcer healing rates. A further study found that the dietary intake of protein, vitamin C, and zinc may be inadequate in elderly patients with leg ulcers.[14] This has led to renewal of the suggestion that dietary supplements should be given to elderly

patients with leg ulcers[15]; however, a broader approach than single-vitamin supplements was used.

32.4.1.2 FIBRINOLYTIC THERAPY

The concept of an oxygen diffusion barrier causing skin hypoxia was first proposed by Browse and Burnand in 1982.[16] This theory led to attempts to reverse the damaging cutaneous effects of venous hypertension by enhancing fibrinolysis. The effect of stanozolol, an anabolic steroid with pro-fibrinolytic properties, was evaluated in 14 patients with long-standing LDS, without active ulceration.[17] After 3 months, all showed clinical improvement both subjectively and objectively (by mapping the area of LDS). Serum parameters of fibrinolytic activity improved in all cases. Fibrinolytic treatment for venous ulceration has been evaluated in one trial of 75 patients.[18] Patients were allocated to receive either stanozolol or placebo for up to 420 days, with conventional compression treatment in all cases. In an interim report, the authors found complete healing in 26 of 40 ulcers in the stanozolol group and 27 of 44 in the placebo group, indicating no benefit from active over placebo treatment. No further study has appeared in the 30 years since this publication. Stanozolol has been withdrawn from clinical use in the U.K.

In a further study, tissue plasminogen activator has been added as a topical treatment to leg ulcers as an ointment.[19] The presence of peri-capillary fibrin on skin biopsies was assessed before and after the treatment, but no difference was found. However, despite this, three out of six ulcers studied healed during the 12 weeks of the investigation.

Dermatan sulfate (DS) is a glycosaminoglycan which selectively catalyzes the inactivation of thrombin by heparin cofactor II without interacting with antithrombin III. DS does not interact with other coagulation factors and, unlike heparin, is able to inactivate thrombin bound to fibrin or to the surface of an injured vessel. Two DS-containing compounds—sulodexide and, particularly, mesoglycan—have been clinically studied in a number of trials and found to be effective in the treatment of venous and arterial leg diseases. Sulodexide is a highly purified glycosaminoglycan with pro-fibrinolytic properties.[20] A total of 235 patients were randomized to receive sulodexide or placebo for 3 months. The authors reported improved healing in the active treatment group compared to placebo. No further detailed work on this compound has been published.

32.4.1.3 ANTIBIOTICS

Venous ulcers contain a wide range of bacteria, and this has led some practitioners to use topical and systemic antibiotics in an attempt to eradicate the bacteria. This is probably a forlorn hope, since until the ulcer heals, bacteria will colonize the ulcer, although usually these are not the cause of the problem. There are some disadvantages to antibiotics as well. The use of topical antibiotics in leg ulcers may lead to the emergence of resistant organisms and the risk of sensitizing the patient to the antibiotic.[24,25] Some topical antiseptics and antibiotics exhibit cellular toxicity that exceeds their bactericidal activities and has been found to impair wound epithelialization.[26]

A Cochrane systematic review of the use of antibiotics and antiseptics (already mentioned above)[10] in chronic wounds has been published and includes an analysis of 45 clinical trials (4486 participants) of randomized design. Within this collection of trials were five addressing the use of systemic antibiotics, and the remainder assessed the use of topical antimicrobial drugs and antiseptics. No conclusive evidence of improved wound healing was found with systemic antibiotic treatment. However, the authors concluded that the limitations of the clinical trials were such that they could not determine whether systemic antibiotics could promote healing in patients with clinically infected ulcers. Lack of efficacy for most topical applications, with the possible exception of cadexomer iodine, was also found.

I accept that clinical infection of an ulcer should be treated, and this can be achieved by wound debridement combined with systemic antibiotics where evidence of cellulitis or septicemia is present.

32.4.1.4 DRUGS WHICH MODIFY LEUKOCYTE METABOLISM

The discovery of the involvement of leukocytes in the development of venous ulceration has opened new avenues of investigation in this area.[21] A number of drugs which modify white cell activation have been evaluated in patients with venous ulceration.

32.4.1.4.1 Pentoxifylline

Pentoxifylline is indicated in the management of peripheral arterial disease, but has also been used in the management of venous ulceration. Research on this drug indicates that it has a potent effect on the inhibition of cytokine-mediated neutrophil activation.[22] It has also been shown to reduce white cell adhesion to endothelium and to reduce the release of superoxide free radicals produced in the respiratory burst, which is characteristic of neutrophil degranulation.

A recent Cochrane review identified 12 clinical trials involving 572 patients in which pentoxifylline has been used with the aim of improving venous ulcer healing.[23] Overall, there was an absolute increase in healing of 21% (95% CI: 8%–34%) in favor of pentoxifylline as an adjuvant to compression. Healing in the control groups ranged from a high of 62.2% to a low of 16.67%, so the number needed to treat may range from 3 (95% CI: 2–12) to 11 (95% CI: 6–43). There is evidence that pentoxifylline may be useful in the management of leg ulcers, especially when combined with compression.

32.4.1.4.2 Prostaglandin E_1

Prostaglandin E_1 (PGE-1) has a number of profound effects on the microcirculation, including reduction of white cell activation, platelet aggregation inhibition, small vessel vasodilatation, and reduction of vessel wall cholesterol levels.[27] It has been evaluated in the treatment of various aspects of arterial disease; less work has been done on its use in venous

ulceration. An early trial of the use of intravenous PGE-1 in ulcers of both arterial and venous etiology reported improvement in four out of five venous ulcers on PGE-1 as opposed to four out of seven on placebo—hardly a dramatic result.[28] A further trial yielded more impressive findings.[29] A total of 44 patients with proven venous ulceration took part in a double-blind, placebo-controlled trial. Each received an infusion of PGE-1 (or placebo) over 3 hours daily for 6 weeks, in addition to standard dressings and compression bandaging. Those on PGE-1 showed a significant improvement in such parameters as edema reduction, symptoms, and "ulcer score," based on depth, diameter, etc. Perhaps more importantly, eight out of 20 patients on active treatment healed their ulcers completely within the trial period, whereas only two out of 22 controls did so.

A randomized, placebo-controlled, single-blind study from 2005 reported 87 patients with venous leg ulcers who were treated for 20 days with an infusion of PGE-1 (Prostavasin, Schwarz Pharma, Monheim, Germany) or placebo, in association with topical therapy. The healing of ulcers was followed for 120 days after the commencement of treatment. The main outcome measure was the number of healed ulcers at the end of the study period. In the active treatment group, all ulcers healed in under 100 days, whereas in the placebo group, only 84% did so by the end of the 120-day observation period ($P < 0.05$). This study demonstrates the effectiveness of PGE-1 in reducing the healing time of venous ulcers.[30] Subsequently, no further publication regarding the efficacy of this treatment has appeared.

32.4.1.4.3 Prostacyclin analogs

Iloprost (Schering, Berlin), a synthetic prostacyclin analog, has been used with success in the treatment of arterial and diabetic ulcers.[31] The mechanism of action of prostacyclin includes increased fibrinolytic activity,[32] reduced leukocyte aggregation, and adhesion to endothelium,[33,34] in addition to its better-known effects on platelet inhibition.[35] A study in which this was applied topically to venous ulcers was disappointing, with no difference observed between active treatment group and placebo.[36] In 2007, a report was published of a clinical trial in which patients with venous leg ulcers received a daily infusion of iloprost or saline for 3 weeks.[37] All patients received standard wound management combined with elastic compression. After 90 days, all patients in the iloprost group but only 50% in the control group had healed. After 150 days, 84% of patients in the control group had healed. The authors concluded that iloprost was effective at speeding venous ulcer healing. No further publication addressing the efficacy of iloprost in the management of venous leg ulcers has appeared subsequently.

32.4.1.4.4 Diosmin–hesperidin

This combination of flavonoid drugs has been used to manage the symptoms of chronic venous disease, including edema of the lower limbs, for many years. The use of this application has been summarized above. More recently, a number of clinical trials has been completed in which one flavonoid drug was used to treat patients with venous leg ulcers. Micronized purified flavonoid fraction (MPFF; Daflon 500 mg®, Servier, Gidy, France), which consists of 90% Diosmin and 10% flavonoids expressed as Hesperidin, has been shown to protect the microcirculation from damage secondary to raised ambulatory venous pressure.[38] It decreases the interaction between leukocytes and endothelial cells by inhibiting expression of endothelial intercellular adhesion molecule 1 and vascular cell adhesion molecule, as well as the surface expression of some leukocyte adhesion molecules (monocyte or neutrophil CD62L and CD11B).[39] There are few known side effects, and interactions with other drugs have not been reported.[38]

In a meta-analysis, clinical trials were sought in which MPFF had been used as an adjunctive therapy to compression and appropriate local care.[40] Outcome measures included time to ulcer healing and proportion of healed ulcers. Five prospective, randomized controlled studies in which 723 patients with venous ulcers were treated between 1996 and 2001 were identified. Conventional treatment (compression and local care) in addition to MPFF was compared to conventional treatment plus placebo in two studies ($n = 309$) or with conventional treatment alone in three studies ($n = 414$). The primary endpoint was complete ulcer healing at 6 months. The results are expressed as reduction of the relative risk (RRR) of healing with 95% confidence intervals. Since the desired treatment effect is increased ulcer healing, the RRR should be positive to indicate a benefit of adjunctive MPFF over conventional therapy alone.

At 6 months, the chance of healing ulcer was 32% better in patients treated with adjunctive MPFF than in those managed by conventional therapy alone (RRR: 32%; 95% CI: 3%–70%). This difference was present from month 2 (RRR: 44%; 95% CI: 7%–94%) and was associated with a shorter time to healing (16 weeks vs. 21 weeks; $P = 0.0034$). The benefit of MPFF was found in the subgroup of ulcers of between 5 and 10 cm^2 in area (RRR: 40%; 95% CI: 6%–87%), as it was in patients with ulcers of 6–12 months' duration (RRR: 44%; 95% CI: 6%–97%).

These results confirm that venous ulcer healing is accelerated by MPFF treatment. MPFF might be a useful adjunct to conventional therapy in large and long-standing ulcers which might otherwise be expected to heal slowly.

A Cochrane review has considered the efficacy of flavonoid drugs in promoting leg ulcer healing.[41] The authors included nine studies with 1075 participants and found evidence of the efficacy of flavonoid drugs for promoting leg ulcer healing. However, the authors commented on the poor quality of reporting of the trials of these drugs.

32.4.1.5 PLATELET INHIBITORS

32.4.1.5.1 Aspirin

The use of aspirin has been reported in a small number of patients undergoing treatment for leg ulceration.[42] This effect has never been substantiated in a clinical trial of any type and there is no evidence of efficacy for this purpose.

32.4.1.5.2 Ifetroban

Effects of the oral thromboxane A2 receptor antagonist ifetroban (250 mg daily) on the healing of chronic lower extremity venous stasis ulcers has been studied in a well-designed prospective, randomized, double-blind, placebo-controlled multicenter study.[43] This drug has a profound inhibitory effect on platelet activation. The results show no efficacy for influencing venous ulcer healing.

32.5 DRUG TREATMENT FOR CHRONIC VENOUS DISEASE

32.5.1 Varicose veins and edema

So when is it appropriate to prescribe phlebotonic drugs in patients with varicose veins or edema? In temperate climates, the use of compression stockings is generally considered to be the most appropriate conservative measure. However, in hot climates, the wearing of stockings is less acceptable for patients, who may find that they cause intolerable discomfort. There may be some rationale in prescribing phlebotonic drugs in these circumstances.

Diosmin and Hesperidin may be useful in trophic disorders, as well as cramps and swelling. Rutosides may benefit edema.[44]

32.5.2 Venous ulcers

A detailed strategy for the management of leg ulcers has been set out by the Society for Vascular Surgery and the American Venous Forum.[45] These recommend against the use of topical antimicrobial drugs (Guideline 4.15) in the routine management of leg ulcers. Treatment of the underlying cause of the leg ulcer, where feasible, is advised. As an ancillary measure, systemic treatment with pentoxifylline or MPFF is recommended (Guideline 7.2).

Compression treatment and surgery to treat incompetent superficial varices and perforating veins are the main lines of management in patients with venous leg ulcers. Only two drugs have been shown to have any influence on venous ulcer healing in a meta-analysis: pentoxifylline and MPFF. Both should be used in combination with compression and standard wound management. Efficacy is probably most apparent in large (5–10 cm), long-standing ulcers (more than 6 months). These drugs have few side effects and could be considered when compression alone has proved to be ineffective in countries where these compounds have been licensed.

PGE-1 has also been shown to have efficacy in promoting venous ulcer healing, but this is confined to one randomized controlled trial. In addition, this drug must be given by intravenous infusion and has some significant side effects. More detailed work is required before a recommendation can be made for its use in venous disease.

32.6 SUMMARY

- Varicose veins and edema are best managed by the use of compression, ablation techniques, or surgery to treat incompetent saphenous trunks, varices, and perforating veins.
- Some phlebotonic drugs improve the symptoms and edema associated with venous disease. These could be used in association with compression for the management of troublesome symptoms.
- Venous ulcers are best managed by strong compression and wound management. In patients with incompetent superficial veins and perforators, these should be managed by ablation techniques or surgery.
- Long-standing or large venous ulcers may benefit from treatment with either pentoxifylline of MPFF used in combination with compression.

Guidelines 4.4.0 of the American Venous Forum on the drug treatment of varicose veins, venous edema, and ulcers

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.4.1	We suggest venoactive drugs (Diosmin, Hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, horse chestnut seed extract [escin], ruscus, and dobesilate) in addition to compression for patients with pain and swelling due to chronic venous disease in countries where these drugs are available.	2	B
4.4.2	Long-standing or large venous ulcers may benefit from treatment with either pentoxifylline or micronized purified flavonoid fraction used in combination with compression.	1	B
4.4.3	We suggest Diosmin and Hesperidin in trophic disorders as well as cramps and swelling. We suggest rutosides in patients with venous edema.	2	B

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● = Key primary paper
★ = Major review article
◆ = Management guideline

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33

Liquid sclerotherapy for telangiectasia and varicose veins

EDWARD G. MACKAY

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33.1 INTRODUCTION

In recent years, many new treatment options for varicose veins have emerged, including endovenous thermoablation, microfoam sclerotherapy, mechanical chemical ablation, and cyanoacrylate glue ablation. These options will be covered in other chapters. Despite the new possibilities, however, liquid sclerotherapy serves as the main treatment option for small varicose veins (<3 mm) and for telangiectasia, also known as spider veins. In addition, liquid sclerotherapy may be indicated for larger veins in situations to which other options are not well suited. Although problems in small veins are generally considered to be cosmetic, they are nonetheless extremely important to patients. Additionally, some patients do describe symptoms of pain, burning, or swelling.

33.2 HISTORICAL REVIEW

Liquid sclerotherapy involves the injection of certain substances into the veins, with the goal of destroying the vein wall, resulting in sufficient damage to close the vein. As far back as 1682, there were attempts to treat veins with an injected substance, and from the middle of the nineteenth century onward, following the invention of the hypodermic syringe, there were efforts in Europe to test various sclerosants, but results were often poor, with patients suffering allergic reactions, high levels of pain, and tissue damage.[1] In the late 1920s and early 1930s, the use of sclerotherapy with a solution of quinine and urethane was reported at the Mayo Clinic.[2,3] Beginning in the 1930s, sodium morrhuate began to be used as a sclerosant. At the end of the 1930s, Smith reported poor long-term outcomes from sclerotherapy.[4] In the intervening years, however, with the introduction of different sclerosants and improved techniques for administering them, sclerotherapy results have improved. Sodium tetradecyl sulfate (STS), and polidocanol (PDL) have both been used widely in sclerotherapy for decades. PDL received Food and Drug Administration (FDA) marketing approval in 2010 and is sold in the United States under the trade name Asclera® (Merz North America, Inc.). STS, sold under the brand name Sotradecol® (Bioniche USA, Inc.), has been grandfathered in because of its long history of use.[5]

In 1993, Einarsson et al. reported the results of a randomized trial of 164 patients. Good results were seen in both compression sclerotherapy and surgical treatment groups immediately after procedures, but after 5 years, there was a much higher rate of treatment failures in the compression sclerotherapy group (74%) compared with the surgery group (10%).[6] Ultrasound-guided techniques kept improving the results, with foam sclerotherapy techniques eventually becoming comparable to surgical methods. This will be covered in a subsequent chapter.

33.3 DIAGNOSIS AND EXAMINATION

33.3.1 Clinical history

Patients often seek treatment for reticular veins (1–3 mm in diameter) and spider veins (<1 mm) for cosmetic reasons, but a complete history and physical are necessary to determine any underlying issues related to the patient's concerns. A careful history may reveal important information, such as reports of leg swelling, which may suggest potential venous insufficiency. It will also help determine whether

the problem falls into one of the categories of primary or familial, secondary or post-thrombotic, congenital or post-traumatic arteriovenous fistula, so that an appropriate CEAP (Clinical–Etiology–Anatomy–Pathophysiology) classification can be made.

A complete medical history must be taken to determine if a patient has any underlying medical problems or is on any medications that may affect treatment. It is particularly important to be alert to a history of deep venous thrombosis (DVT), hypercoagulable states, bleeding diathesis, or asthma. Medications that may affect results include anticoagulants and non-steroid anti-inflammatory drugs. Hormone replacements may also increase the risk of DVT.

33.3.2 Physical examination

A careful examination should be performed of the lower extremities to identify the locations of varicose, reticular, and spider veins (Figure 33.1). Noting the locations of the veins will give insight into the cause of the problem. Most spider veins are located on the lateral medial thigh. Corona phlebectatica at the ankle suggests saphenous insufficiency.[7] Evidence of bulging varicose veins deserves further evaluation with duplex examination. Other findings, such as port wine stains (Figure 33.2), hypertrophy of the soft tissue, and bone overgrowth of the extremity, may be suggestive of congenital malformations and indicate that further investigation may be needed with magnetic resonance imaging.

33.3.3 Laboratory examination

The history and physical will determine whether there is a need for further laboratory tests. If the patient has a history of DVT or there is a history of DVT in the family (parents or siblings), a hematology evaluation for thrombophilia should be considered.

Figure 33.1 Lateral venous plexus.

Figure 33.2 Port wine stain in patient with Klippel–Trenaunay syndrome.

33.3.4 Noninvasive vascular examination

Signs or symptoms of venous insufficiency, including varicose veins, require a venous duplex evaluation before any liquid sclerotherapy is considered. A complete examination of the deep and superficial system aims to determine if there is any evidence of DVT, either old or new reflux in the deep or superficial system, or superficial venous thrombosis. For patients with purely cosmetic telangiectasia, duplex imaging is rarely required if no other signs or symptoms (such as evidence of swelling, pigmentation around the ankle, or reports of leg fatigue) are present. Duplex mapping will be covered in another chapter.

More detailed examination with the use of magnetic resonance imaging or computed tomography venograms is indicated in case of suspected iliofemoral occlusive disease and vascular malformations, history of DVT, or physical findings of varicose veins on the abdomen/abdominal wall. Contrast venography is indicated only when considering intervention for pelvic or iliofemoral disease.

33.4 INDICATIONS

Liquid sclerotherapy is primarily used for small varicose veins and telangiectasias. It should not be performed until the source of venous insufficiency (if any) is appropriately treated.

Figure 33.3 Spider veins or telangiectasia of <1 mm.

Figure 33.4 Reticular veins of 1–3 mm.

Spider veins/telangiectasia of less than 1 mm in diameter (Figure 33.3) are generally cosmetic problems, although patients do sometimes complain of some symptoms related to them.

Small varicose veins of 1–3 mm can be treated after the source of venous reflux has been identified and taken care of (Figure 33.4). These reticular veins frequently feed into the spider veins, are largely asymptomatic, and are primarily of cosmetic concern.

Liquid sclerotherapy can be recommended for veins larger than 3 mm if there is a contraindication to foam sclerotherapy (such as right-to-left shunt) or surgical treatment.

Post-operative residual varicose veins over 3 mm can be managed successfully with liquid sclerotherapy if all other sources of reflux are treated.

33.5 CONTRAINDICATIONS

Contraindications of liquid sclerotherapy are listed below.

- Pregnancy; treatment should be delayed unless there is a major indication, such as a bleeding varicosity.
- Sedentary; mobility challenges.
- Severe systemic disease.
- Peripheral artery disease (PAD) with an Ankle Brachial Index of less than 0.8. The exception may be a venous ulcer with PAD.
- Febrile illness.
- Acute superficial venous thrombosis or DVT.

33.6 TREATMENT

The first step in treatment involves properly identifying the issue for which the patient is seeking care. If it is venous insufficiency, then the appropriate evaluation should be done to determine the cause of the problem. Treatment of venous insufficiency is covered in other chapters of this book. If venous insufficiency has been treated and the remaining complaint is related to small veins or cosmetic concerns, as in the case of spider telangiectasias, then liquid sclerotherapy may be indicated. Before sclerotherapy sessions begin, patients must be provided with sufficient information so that they can give informed consent. It is especially important that patients are aware of possible complications and are provided with a realistic assessment of outcomes to expect, as well as an understanding that treatment may involve a series of appointments. Once consent is given, photographs should be taken to provide baseline documentation of the areas to be treated.

33.6.1 Sclerosing agents

Sclerosing agents (Table 33.1) are divided into groups based on their mechanism of action. Osmotic agents work by dehydrating the endothelial cells. Examples include hypertonic saline 23.4%, glucose 75%, and sodium salicylate. Detergent solutions' mechanism of action involves damaging the surface lipids of endothelial cells. Detergent agents include STS, PDL, sodium morrhuate, and ethanolamine oleate. Corrosive agents damage the vessel wall. Examples of corrosive agents are sodium and potassium iodide, benzyl alcohol, 72% glycerin, and chromated glycerin.

33.6.2 Selection of sclerosant

In the United States, the FDA has approved several agents for sclerotherapy. These include the detergent solutions mentioned above. The two solutions currently used and marketed for liquid sclerotherapy are STS (Sotradecol) and PDL (Asclera). The PDL injection gained FDA approval in 2010.

Hypertonic saline 23.4% and glycerin 72% are used off-label for cosmetic spider veins.

Research to date does not appear to definitively prefer one sclerosant over another. In a 2010 review of the literature, David M. Duffy wrote: "All sclerosants represent a compromise between efficacy and toxicity, compounded by practitioner sophistication, patient-to-patient variability, and, as a practical matter, legal status."[8]

Carlin and Ratz reported a small randomized controlled trial comparing PDL, STS, saline 20% with heparin, and saline 0.9% (placebo). They concluded that PDL was as

Table 33.1 Sclerosing agent comparison

Agent	Manufacturer	Category	FDA approval	Strength	Advantages	Disadvantages
Hypertonic saline	Multiple	Osmotic	Off-label usage	++	Low risk of allergic reaction; wide availability; rapid response	Off-label; painful to inject; hyperpigmentation; necrosis; rapid dilution; not recommended for facial veins
Non-chromated glycerin	Compounded at pharmacy	Alcohol agent	Off-label usage	+	Low incidence of hyperpigmentation, necrosis, and allergic reaction	Weak sclerosing agent; typically only used for telangiectasia
Asclera (polidocanol)	Merz North America	Detergent	Approved	+++	FDA approved	Staining
Scleromate (sodium morrhuate)	Glenwood, LLC, Englewood, NJ	Detergent	Approved	+++	FDA approved	High incidence of skin necrosis and anaphylaxis
Sotradecol (sodium tetradecyl sulfate)	Bioniche USA, Lake Forest, IL (distributed by AngioDynamics, Inc., Queensboro, NY)	Detergent	Approved	+++++	FDA approved; low risk of allergic reaction; potent sclerosant	Potential necrosis with extravasation; telangiectasia matting

Source: Adapted from Gloviczki P et al. *J Vasc Surg* 2011;53(5):2S–48S.
Note: FDA: Food and Drug Administration.

Table 33.2 Indications and concentrations of sclerosing agents

Indications	STS (%)	Polidocanol (%)	HTS (%)	Glycerin (%)
Varicose veins >3 mm	1.0–3.0	1.0–3.0	–	–
Reticular veins 1–3 mm	0.5–0.75	0.5–1.0	11.7–23.4	–
Telangiectasias <1.0 mm	0.125–0.25	0.25–0.5	11.7–23.4	48–72

Note: STS: sodium tetradecyl sulfate; HTS: hypertonic saline.

effective as STS and saline with heparin, but was more easily tolerated by patients.[9]

In 2002, Goldman reported a study in which 129 patients were treated with varying concentrations of STS or PDL. Patients had an average of 70% improvement, and 70%–72% of them were satisfied with their results. No significant differences in adverse effects were reported, with the exception of a decrease in ulcerations and swelling in the PDL group.[10] The author concluded that both STS and PDL are safe and effective for varicose and telangiectatic leg veins.

33.6.3 Selection of the concentration of sclerosant

Effective sclerosis of the vein depends on contact between the appropriate concentration of the sclerosant and the vein wall for enough time to damage the wall and induce vasospasm. Too low a concentration or too little time may induce only thrombosis; too high a concentration may cause too intense a reaction, leading to a complication. Choosing an appropriate concentration comes with experience and should tend toward the lowest effective concentration; the suggested ranges are presented in the Table 33.2.

33.6.3.1 VEINS >3 MM

For veins larger than 3 mm, liquid sclerotherapy is not considered to be the best treatment. Superior options include foam sclerotherapy or surgery, which are discussed elsewhere in this book. If other methods cannot be performed, then liquid sclerotherapy with concentrations of 1%–3% STS or 1%–3% PDL could be attempted.

33.6.3.2 VEINS 1–3 MM

For reticular veins, 0.5%–0.75% STS, 0.5%–1.0% PDL, or 11.7%–23.4% hypertonic saline are generally accepted concentrations.

33.6.3.3 VEINS <1 MM (TELANGIECTASIAS)

Veins smaller than 1 mm can be treated with 0.125%–0.25% STS, 0.25%–0.5% PDL, 11.7%–23.4% hypertonic saline, or 50%–72% glycerin. Hypertonic saline and glycerin may be diluted with lidocaine.

33.6.4 Materials

Syringes: The choice of syringe will depend on personal preference as well as the type of sclerosant used. Typically, a 1–5-mL syringe is used. An advantage of a larger syringe is that it creates less pressure, which in turn results in less pain for the patient. Lower levels of pressure reduce the potential for extravasating of the sclerosant. If glycerin is being used, a smaller syringe may be needed to generate the pressure because of the high viscosity of the solution.

Needles: Very fine needles, such as 27–32 gauge, are recommended. They may be used alone or with a butterfly, which is helpful with larger veins where aspiration is required.

An antiseptic skin cleanser is used, such as alcohol.

Cotton balls or gauze pads: These are needed for compression and wiping up blood or the antiseptic.

Sclerosing agents: These should be clearly labeled, either in vials or syringes, with the type and concentration indicated.

A well-lit treatment room is needed.

Magnification: This can be obtained either with loupes (Figure 33.5) or other magnifying sources such as Syris surgical headlamps.

Emergency equipment: At a minimum, emergency supplies should include oxygen, epinephrine, steroids, and antihistamines.

33.6.4.1 OPTIONAL EQUIPMENT

Optional equipment includes polarized light sources, infrared visualization equipment, or vein lights.

33.6.5 Techniques

33.6.5.1 GENERAL CONSIDERATIONS

Treatment begins at the source of reflux; typically, this would involve either the surgical ablation or foam sclerotherapy

Figure 33.5 Loupes.

techniques that are covered in other chapter of this book. Liquid sclerotherapy proceeds according to the principle of addressing larger veins first then moving to smaller veins, moving from proximal to distal, while using the lowest effective concentration of sclerosant. Effective treatment of the larger feeder veins can also result in effective treatment of the smaller veins as the sclerosant travels through the system.

33.6.5.2 LARGE VEIN TREATMENT >3 MM

Treatment of the larger veins begins only after the source of refluxes, if any, have been addressed. As stated previously, large veins greater than 3 mm are best treated with other methods such as phlebectomy or foam sclerotherapy. If for some reason other methods are not available or recommended, then the sclerotherapy should start with marking the veins to be treated while the patient is standing. This step is done because once the patient lies down, the veins will flatten and may therefore be difficult to find. If ultrasound guidance is being used, however, this step is not needed.

The volume and concentration of sclerosant depend upon the size of the vein. The sclerosant is mixed with the blood in the vein and becomes diluted. Several steps can be taken to try to reduce the volume of blood in the vein to minimize this dilution: (1) use the "air block" technique in which air is injected to displace the blood immediately before the liquid is injected; (2) raise the patient's leg immediately after accessing the vein but before injection, as this will chase blood from the vein; and (3) immediately after injection, place a compression pad over the treated vein to slow the entry of blood into the vessel.

The concentration of the sclerosant should be 1%–3% STS or 2%–3% PDL. The volume of injection should be approximately 0.5–1.0 mL per site, but should not exceed 10 mL for the whole length of the vein. It is advisable to try to treat the entire vein in one session to prevent thrombosis of untreated segments. Patients should wear compression stockings for 1 week following treatment.

33.6.5.3 RETICULAR VEINS (1–3 MM)

Treating the reticular veins that are feeding into spider veins improves the global results. Often, reticular veins and spider veins have no obvious source of reflux on ultrasound. Sometimes on ultrasound, small perigeniculate or lateral thigh perforator veins are identified. Veins are usually visible to the naked eye with magnification, but there are other aids to seeing them better, such as infrared projection (Figure 33.6), vein lights, or polarized lights. When accessing the veins, aspiration of blood confirms proper needle placement. Per site, approximately 0.1–0.5 mL of the appropriate concentration of sclerosant should be injected. The next site of injection should be situated 5–15 cm from the previous site. This can be determined visually as the treated segment is usually in spasm and can no longer be identified. Concentrations to be used are 23.4% hypertonic saline, 0.5%–0.75% STS, or 0.75%–1.0% PDL. Foam sclerotherapy can also be used in reticular veins. This is discussed in another chapter in this book.

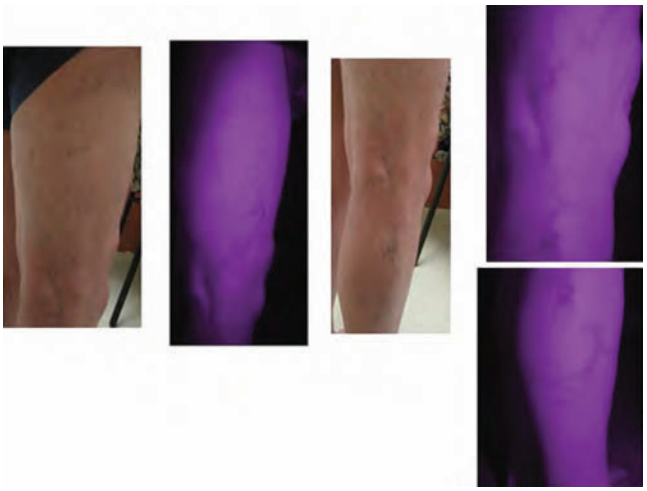

Figure 33.6 Infrared photograph of lateral varicose and perforating veins.

33.6.5.4 SPIDER VEINS

The key to treating spider veins is to visualize the needle entering the vein. Since aspiration is usually not possible for confirming needle placement, direct visualization is required. It is therefore important to have excellent lighting without glare. Magnification is also very helpful. Other aids include polarized lights, such as the Syris headlamp with magnification. The volume of injection depends on the length and size of the vein.

There should be minimal resistance, and once resistance is felt, the injection should stop. After the injection, the needle can be held in position with slight pressure on the plunger. This prevents blood from returning and increases contact time with the vein wall and sclerosant. Injection should be interrupted with any evidence of extravasation of the sclerosant. Additional pressure could be then applied after the injection to help produce apposition of the vein wall. This can be done manually or with cotton balls. Typical concentrations of sclerosant are 0.125%–0.25% for STS, 0.25%–0.5% for PDL, 11.4%–23.4% for hypertonic saline, or 48%–72% for glycerin. Total volume depends on the type and concentration of sclerosant, but 10 mL is typical for one session.

33.6.6 Compression

Compression following sclerotherapy reduces discomfort and side effects such as phlebitis. Compression stockings are generally used. Extra foam pads, cotton balls, or gauze can be placed to apply additional compression over the treated vein. These can be held in place with tape or wraps. This additional compression helps to coapt the vein walls and to avoid thrombosis, thereby diminishing the risks of postoperative pain and staining.

33.6.7 Post-sclerotherapy microthrombectomy

Following treatment, a thrombus may form in the vein despite adequate compression. The thrombus can be painful and could lead to staining. The unwanted effects of this complication can potentially be reduced by draining the thrombus in the first 2–3 weeks after treatment.[11] This can be done under local anesthesia and with the help of 18–22-gauge needles puncturing in the line along the vein and then using cotton swaps to compress the clot (Figure 33.7).

33.7 ADVERSE EVENTS

33.7.1 Pain

The most common complaint associated with sclerotherapy is pain. Several factors can be considered to minimize the amount of pain the patient will experience. (1) The choice of sclerosant will affect pain levels, with detergent sclerosants tending to result in less pain than the osmotic agents. If hypertonic saline—an osmotic agent—is used, lidocaine may be added to reduce the discomfort. (2) The use of the smallest-gauge needle that can penetrate the skin is advisable. Usually, 30–32-gauge needles work best. (3) The extravasation of the solution can be avoided by ensuring that the needle is correctly placed in the vein and the sclerosant is not injected too strongly or too rapidly. (4) Hypertonic saline has been associated with cramping at the injection site, so limiting the volume of injection at any one site may help. (5) Additional methods to reduce the discomfort include using topical local anesthetics, blowing cold air on the injection site, and placing ice packs immediately after the injection. It should be noted that the use of cooling with detergent solutions may affect their efficacy.

33.7.2 Visual changes

Visual changes or migraine auras are occasionally experienced at the time of treatment. These may be caused by the release of endothelin from the damaged endothelial cells. Such symptoms are more common in patients with a history of migraines or who have right-to-left shunts. These symptoms usually pass quickly.

33.7.3 Inflammatory responses

Localized inflammatory responses that lead to erythema, urticaria, and localized edema can be observed. These can be reduced by limiting the volume of sclerosant and using the appropriate concentration. A full-blown anaphylaxis reaction is possible, so an emergency kit that includes oxygen, epinephrine, antihistamines, and steroids should be on hand at the time of treatment.

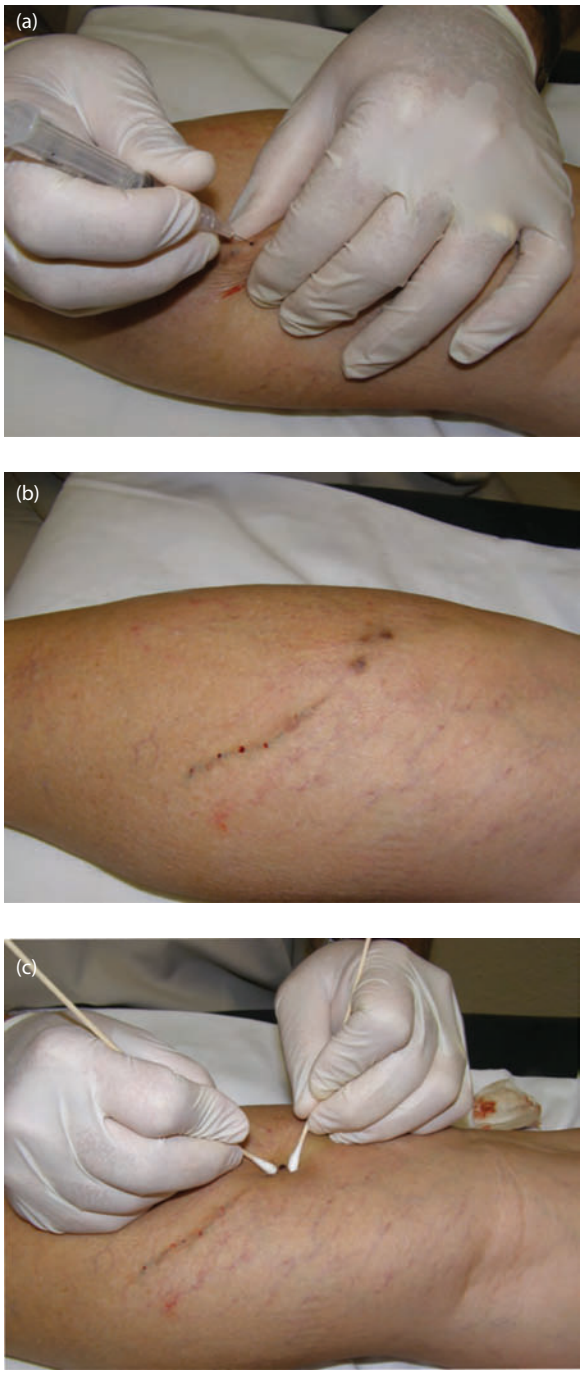

Figure 33.7 Post-sclerotherapy microphlebectomy: **(a)** puncture of the thrombosed telangiectatic vein with 30 gage hypodermic needle; **(b)** thrombus coming from telangiectatic vein; **(c)** more thrombus expressed from telangiectatic vein using cotton tip swab.

33.7.4 Hyperpigmentation

Hyperpigmentation is a brown stain related to the production of hemosiderin, which remains after the degradation of the thrombus at the site of the treated vein (Figure 33.8).[11] This can be minimized by post-sclerotherapy thrombectomy and usually resolves in just a few months. In some

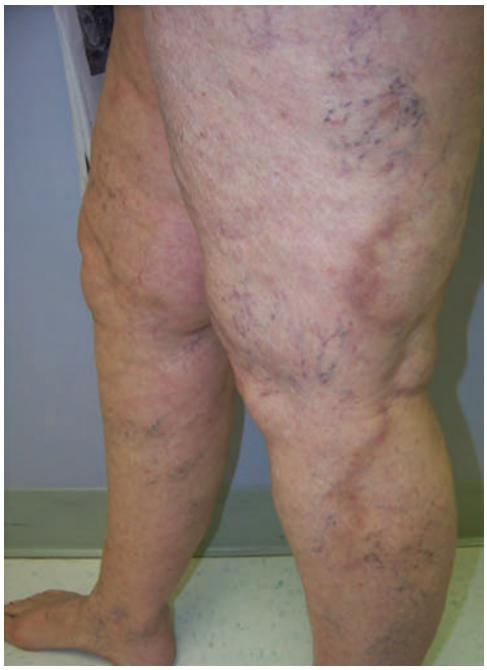

Figure 33.8 Adverse event: staining.

cases, for unknown reasons, the staining lasts much longer (1–2 years). Several theories to explain this phenomenon include the skin type of the patient, the use of too strong a solution leading to an intense inflammatory reaction and post-inflammatory pigmentation, or the use of too weak a solution leading to inadequate sclerosis, recanalized, persistent thrombosis, and pigmentation. Some sclerosants, such as hypertonic saline, seem to have a higher incidence of hyperpigmentation, possibly due to lysis of red cells.

33.7.5 Telangiectatic matting

Telangiectatic matting is a complication in which red or purple spider veins appear where either varicose or larger spider veins were treated (Figure 33.9). Although the cause cannot always be determined, inadequate treatment of an underlying source of reflux can frequently be found. Such sources could include an undetected saphenous incompetence, perforator vein incompetence, or a reticular vein. Ultrasound examination may help to determine the source; vein lights or infrared imaging may demonstrate a reticular vein not seen on ultrasound. If no source is found, the matting may resolve with time. Methods of treatment such as laser have been tried with some success.[12]

33.7.6 Skin necrosis

Sclerotherapy may induce skin necrosis (Figure 33.10). Possible causes include too high a concentration of sclerosant with extravasation, too much pressure applied to the syringe during injection leading to blanching, or injection of an arteriole. Preventive steps include use of the appropriate strength of sclerosant, very gentle pressure on the syringe

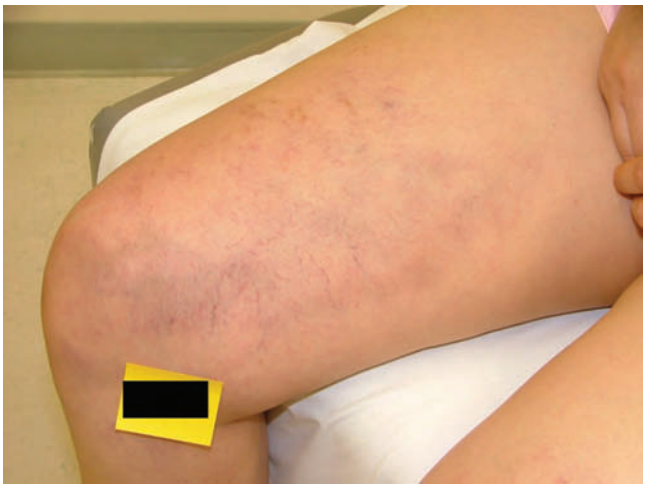

Figure 33.9 Adverse event: telangiectatic matting.

while directly visualizing the needle entering the spider vein, and aspiration to ensure that the injection is done in the varicose vein.

33.7.7 Thromboembolism

DVT is rarely seen with small varicose and spider veins, but DVT must be considered if unusual pain or swelling occurs in the post-operative period. Ultrasound should be done if any suspicion is aroused. The incidence of DVT increases when liquid or foam sclerotherapy is performed on larger veins with higher concentrations of sclerosant.

33.7.8 Intra-arterial injections

Short of an anaphylactic reaction, intra-arterial injection poses the greatest risk to the patient. This complication could lead to serious tissue loss, including the possible need for amputation. Every effort must be made to ensure that the needle placement is in a vein and not an artery. Certain

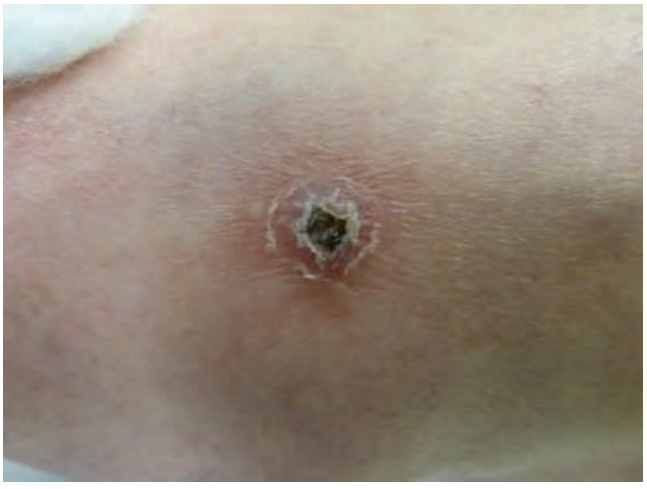

Figure 33.10 Adverse event: skin necrosis.

anatomic areas, such as around the ankle where the arteries are superficial, pose particular risk. Ultrasound-guided injections should be the rule for perforator veins or saphenous veins, as all perforator veins are accompanied by an artery, and with saphenous veins there are several locations where arteries are in close proximity. Ultrasound imaging alone may not be enough to prevent intra-arterial injection. Techniques such as aspiration of a small amount of blood can help ensure proper needle placement in the vein; the blood should come back very easily. Additionally, using an open hub technique may be helpful: when the syringe used for aspiration is taken off and replaced with a sclerosant syringe, there would be pulsatile back-bleeding if an artery is hit.

33.8 CLINICAL PRACTICE GUIDELINES

Current and previous clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum endorse sclerotherapy—either liquid or foam—for the treatment of telangiectasia, reticular veins, and varicose veins.[13] Liquid sclerotherapy remains the treatment of choice for reticular veins of <3 mm and for telangiectasia.

ACKNOWLEDGMENT

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Guidelines 4.5.0 of the American Venous Forum on liquid sclerotherapy for telangiectasia and varicose veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Level of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.5.1	We recommend liquid or foam sclerotherapy for telangiectasia, reticular veins, and varicose veins.	1	B
4.5.2	For the treatment of the incompetent saphenous vein, we recommend endovenous thermal ablation over chemical ablation with foam.	1	B

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●= Major review articles
★= Key primary papers
◆ = Guidelines

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34

Percutaneous laser therapy of telangiectasia and varicose veins

THOMAS M. PROEBSTLE

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34.1 INTRODUCTION

According to an epidemiologic study of more than 3000 randomly assigned persons in Germany,[1] only 9.6% of the population are free from any kind of varicosity, 31.3% suffer from clinically relevant varicose veins, venous edema, skin changes, or venous ulcer disease, and 59% have isolated leg telangiectasia.

Today, most people are aware of varicose veins and chronic venous diseases, with their associated risks such as deep vein thrombosis and lung embolism. The clinical symptoms and signs of advanced chronic venous disorders like pain and ulcers are known to the general population. Additionally, the development of a certain lifestyle during the last decades with increased awareness of body appearance, focusing on the cosmetic aspect of the legs, makes excellent if not outstanding cosmetic results an absolute requirement for many patients.

During the last decade, technology has progressed to such a degree that lasers and light sources for transcutaneous treatment of small varicosities and catheter-based systems for percutaneous treatment of clinically relevant varicose veins now meet most of these demands.

34.2 ETIOLOGY AND PATHOGENESIS

The etiology of venous disorders, including varicose veins and leg telangiectasia, is complex and still incompletely understood. Besides idiopathic causes, some acquired risk factors of varicose veins are known, and different diseases can also be involved in the development of varicose veins. For example, thrombophilia disorders may trigger deep vein thrombosis and subsequent new varicose veins associated with post-thrombotic deep vein reflux. Regarding the etiology and pathophysiology of varicose veins, the reader should consult Chapters 4 through 6. Leg telangiectasias are frequently idiopathic and mainly of cosmetic interest to the patient. However, as shown in Table 34.1, dermatologists are aware of a number of localized or systemic diseases, which may cause leg telangiectasia.[2,3] To know of these systemic diseases is important because some of their underlying conditions may be associated with skin hypersensitivity to light exposure and therefore any laser or intense pulsed light (IPL) treatment would not only be ineffective, but also potentially harmful to the patient, and therefore should be contraindicated.

34.3 CLINICAL MANIFESTATION AND CLASSIFICATION

The CEAP classification[4] offers a well-accepted system for the description of venous disease. However, it is less suitable for categorization of the clinically insignificant but cosmetically disturbing small veins. In the clinical stage C1, telangiectasia and reticular varicose veins with diameters below 3 mm represent a variety of small vessels that

Table 34.1 Causes of leg telangiectasia

Primary telangiectasia
Nevus flammeus
Klippel–Trenaunay syndrome
Neavus anemicus with telangiectasia
Angiomas and angiokeratomas
Angioma serpiginosum
Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome)
Ataxia telangiectasia (Louis–Bar syndrome)
Generalized essential telangiectasia
Hereditary benign telangiectasia
Spider telangiectasia
Bloom's syndrome

Secondary telangiectasia
Causes associated with chronic venous disease
Idiopathic telangiectasia (C1 according to CEAP classification)
Dermatitis/capillaritis alba (C4 according to CEAP classification)

Exogenous causes
Toxic exposure to infrared radiation, ultraviolet light or X-rays
Exposure to toxic or allergenic chemicals
Microbiological agents (e.g., acute [red] and chronic [bluish] *Borrelia* infection)
Blunt tissue trauma
Cutaneous drug reactions (e.g., corticosteroids)

Autoimmune disease
Lupus erythematosus
Dermatomyositis
Progressive systemic sclerosis
Morphea
Cryoglobulinemia

Causes with genetic background
Xeroderma pigmentosum
Goltz's syndrome
Congenital poikiloderma (Rothmund–Thomson syndrome)
Congenital neuroangiopathy (Maffucci syndrome)
Cutis marmorata telangiectatica congenital
Dyskeratosis congenita
Unilateral nevoid telangiectasia
Angiokeratoma corporis diffusum (M. Fabry)

sometimes require different treatment approaches. Several classifications have therefore been proposed to provide a more detailed view of them.

Initially, leg telangiectasias have been described morphologically by naming their pattern as linear, arborized or Besenreiser-type, spider or star-like, and punctiform or papular.[5] This morphologic view frequently helps to identify the origin of the telangiectasia, where it may be connected through a feeder vein with the more deeply located parts of the venous system, and where any treatment would probably be most effective.[6,7]

Table 34.2 Classification of leg telangiectasia according to Duffy[11] and Goldman[12]

Type 1	Telangiectasia, spider vein 0.1–1.0 mm diameter, color red to cyanotic
Type 1A	Telangiectatic matting 0.2 mm diameter, color red
Type 1B	Communicating telangiectasia Type 1 veins in direct communication with varicose veins of the saphenous system
Type 2	Mixed telangiectatic/varicose veins without direct communication with the saphenous system Diameter 1–6 mm, color cyanotic to blue
Type 3	Non-saphenous varicose veins (reticular veins) Diameter 2–8 mm, color blue to blue–green
Type 4	Saphenous varicose veins Usually diameter above 8 mm, color blue to blue–green

When laser treatment of telangiectasia was introduced, the concept of the thermal relaxation time and selective photothermolysis,[8] the diameter of the vessel became the most important parameter. Telangiectasias were separated into three groups: diameters below 0.2 mm, between 0.2 and 1 mm, and between 1 and 2 mm. Veins with diameters greater than 2 mm are named reticular veins.

Additionally, the color of the vessel provides important information. Due to general properties of light reflection and scattering, otherwise identical vessels appear more bluish if located deeper in the skin than those that are more superficial.[9] Furthermore, it has been demonstrated that red and blue telangiectasias differ significantly in their oxygen saturation,[10] implying that red vessels contain more arterialized blood than blue ones.

More recent classifications of telangiectasias and visible varicose veins[11,12] combine different aspects of the above-mentioned criteria to be most helpful in daily clinical use (Table 34.2).

34.4 PRE-TREATMENT DIAGNOSTICS AND REQUIREMENT

Before starting treatment of any venous disorder, a diagnostic workup including a physical examination, a patient interview, and a duplex Doppler ultrasound should be performed. During such a workup, the sources of pathological venous reflux in the deep veins, in perforators, and in the saphenous systems need to be identified, as well as regions of hemodynamically relevant obstruction, if there are any at all. Additionally, other reasons for the development of telangiectasias or visible varicose veins as listed in

Table 34.1 need to be identified to prevent harm from laser treatment.

After understanding the pathology of the leg's venous hemodynamics, if present, saphenous and perforator reflux need to be corrected first before small superficial vessels are addressed by any treatment modality. This strategy is based on the frequent connections of visible varicosities and deeper located incompetent veins,[6,7] and addresses venous hypertension in the potentially laser-targeted telangiectasia.

34.5 PATIENT SELECTION

Any patient presenting with telangiectasia can receive laser or IPL treatment as an alternative to sclerotherapy if there is no contraindications as discussed above (section 34.2) are present. Laser therapy is a modern, fast, and easy treatment which offers the patient a treatment without needle injury, without wound dressing and—in the hands of many physicians—also without post-treatment compression stockings. Unlike with sclerosants, there is no maximum total dose of laser light. Therefore, treatment of both legs in one session is possible. Laser or IPL treatment of telangiectasia are treatment options which combine perfectly with endovenous treatments of saphenous veins and are well suited for patients who seek minimal impairment of quality of life during and after treatment.

There are also indications for laser treatment in patients who are unable to receive sclerotherapy, and the typical reasons are:

- Needle-phobic patients
- Sclerotherapy-resistant telangiectasia
- Telangiectatic matting
- Patients with pronounced hyperpigmentation after sclerotherapy
- Intolerance to sclerosants

34.6 FUNDAMENTALS OF LIGHT–TISSUE INTERACTION

Successful treatment of telangiectasia with the use of lasers or IPL sources has to meet a number of conditions which are imposed by the physics of light–tissue interaction. The most important parameters and conditions are listed in Table 34.3.

Table 34.3 Confounders of successful laser or intense pulsed light treatment of telangiectasia

- Selection of wavelength according to the absorption characteristics of the target and overlying tissue
- Sufficient dosing of the laser energy in terms of laser fluence (J/cm^2) to achieve reliable vessel closure
- Selection of laser pulse duration not to exceed the thermal relaxation time of the target
- Oversizing of the beam diameter to correct the penetration depth for scattering losses
- Achievement of homogeneous volumetric target heating with an optimum combination of wavelength selection, adjustment of laser fluence, and pulse duration
- Adjustment of pulse duration with respect to the patient's pain perception
- Surface cooling for pain reduction and epidermal rescue

The selection of a wavelength determines principally whether the light energy can pass through overlaying skin tissue and thereby reach the target tissue, in this case a venous vessel of any given diameter at all. Between approximately 600 and 1200 nm, the human skin as a whole has a so-called optical window, an absorption minimum of the skin with an average absorption coefficient in the order of 5 cm^{-1}. The relevant chromophores of human skin that are responsible for the absorption of electromagnetic energy in this part of the spectrum are hemoglobin in the dermis and melanin in the overlaying epidermis. Water only starts to contribute at the infrared end of this part of the spectrum at wavelengths above 1000 nm. Figure 34.1 displays the most important absorption curves. Two examples of epidermal light absorption are given for fair skin and moderately tanned skin with epidermal volume fractions of melanocytes of 3% and 15%, respectively, calculated as described elsewhere.[13] In the dermis, the baseline absorption is characterized by the absorption profile of hemoglobin. Figure 34.1 shows the curve with an estimated dermal blood content of 0.2% and a hemoglobin concentration in the blood of 10 mmol/L. However, along the whole range of wavelengths, this absorption is about 100-fold weaker than the absorption of blood alone, which is the laser target in any transcutaneously treated vessel. As is easily seen, the 532-nm wavelength is about 100-fold more strongly absorbed by hemoglobin (231 cm^{-1}) than the 1064-nm wavelength (2.2 cm^{-1}).[14] The same is true of melanin, which absorbs the 532-nm wavelength about eight-fold more strongly (~400 cm^{-1}) than the 1064-nm wavelength (~50 cm^{-1}). Water absorption does not play a role in both wavelengths. In summary, the 532-nm wavelength penetrates significantly less deeply than the 1064-nm wavelength in both blood and bloodless skin (Figure 34.2).[14]

The amount of laser energy which finally reaches the target vessel determines whether the vessel will be permanently closed. When treating superficial veins, a sufficient fluence will elicit an immediate visible reaction, such as shrinkage or thrombosis of the vessel.[14] Proper ranges of fluence are wavelength dependent and start from 4 J/cm^2 for flashlamp pumped dye lasers when treating superficial vessels of 0.1 mm in diameter[15] and can reach 580 J/cm^2 in long-pulse neodymium-doped yttrium aluminum garnet (Nd:YAG) systems.[16]

When administering the desired amount of laser energy, the time in which it is delivered is also crucial. According to the principle of selective photothermolysis,[8] the laser pulse duration should not reach the thermal relaxation time of the

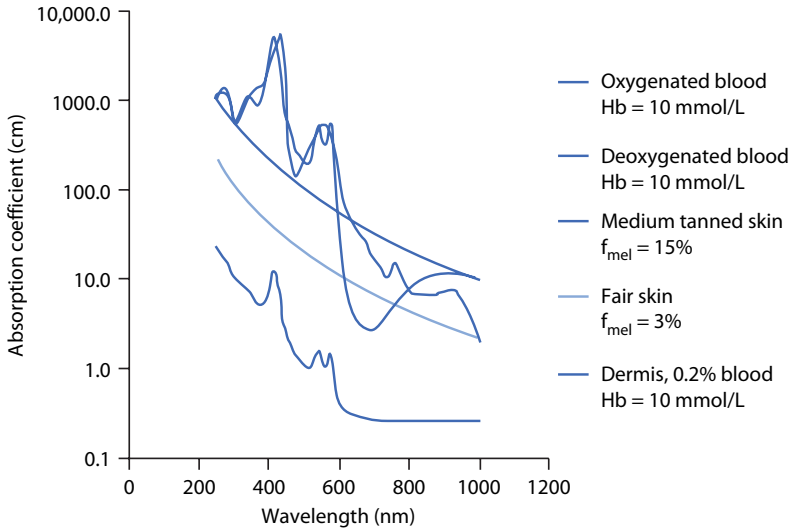

Figure 34.1 Absorption spectrum of blood with oxygenated and deoxygenated hemoglobin at a concentration of 10 mmol/L. Epidermal absorption of moderately tanned and fair skin is calculated with melanosome volume fractions (f_{mel}) of 15% and 3%, respectively. Dermal absorption is calculated with a blood volume fraction of 0.2% and oxygenated hemoglobin at a concentration of 10 mmol/L. All curves given in the wavelength range of between 250 and 1000 nm.

target tissue. Thermal relaxation describes the time course of heat transfer, usually by conduction, from the up-heated target structure to the cooler surrounding tissue. The equation describing this phenomenon is an e-function, with the thermal relaxation time as its time constant. Practically, this means that if administering laser pulses longer that the thermal relaxation time of the target tissue, the advantage of higher absorption in the target tissue is lost. The magnitude of the thermal relaxation time can be estimated as follows: its value in seconds is about the square of the target diameter (e.g., the thermal relaxation time is about 250 ms in a 0.5-mm diameter vessel or about 40 ms in a 0.2-mm diameter vessel). Actually, the thermal relaxation times are a little bit shorter than the estimates above, but in any case, actual pulse durations should stay below. However, one

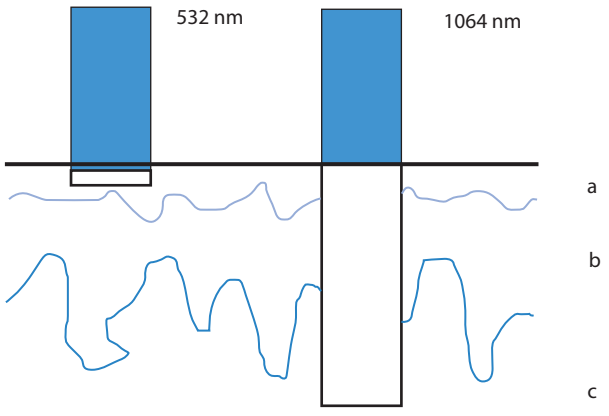

Figure 34.2 Semi-quantitative display of penetration depths of 532 nm and 1064 nm into human skin according to the absorption characteristics shown in Figure 34.1; a = epidermis, b = dermal layer, c = subcutaneous fat.

should not stay below the thermal relaxation time by too much. For example, for the 1064-nm ND:YAG laser, it has been shown that longer pulse durations of between 20 and 60 ms consistently produce better clinical results than 3-ms pulse durations in vessels with a mean diameter of 0.8 mm.[16] Histopathology supports these findings, showing marked shrinkage of perivascular collagen with longer pulses, while short pulses of 3 ms were only able to produce a thrombotic occlusion of the vessel. In conclusion, it seems that substantial heat damage around the target vein, or at least solid heat damage of the entire vessel wall, is a necessary condition to achieving instant and durable vein occlusions. On the other hand, longer durations of laser pulses are more painful than shorter pulses,[14] and therefore patients' pain sometimes does not allow for the administration of longer pulse durations; in particular, pulses above 100 ms duration are not tolerated by many patients.

Additionally, for successful laser ablation of leg telangiectasia, the actual penetration depth of laser light should be considered. Interestingly, this depth is not only dependent on the wavelength of the laser light and its absorption characteristics, but also on its scattering behavior. The actual penetration depth, therefore, can be increased by increasing the beam diameter (Figure 34.3). Due to the mentioned scatter effects, the originally cylindrical laser beam forms a pencil-like tip before being completely absorbed by surrounding tissue. However, because of the phenomenon of forward scattering itself, the vanishing of the laser beam takes longer and happens at greater tissue depth with larger beam diameters.

After considering the absorption of skin tissue and hemoglobin in general, the absorption characteristics of the target structure, and the geometry of the vein vessel itself, we need to take a closer look at the volumetric heating

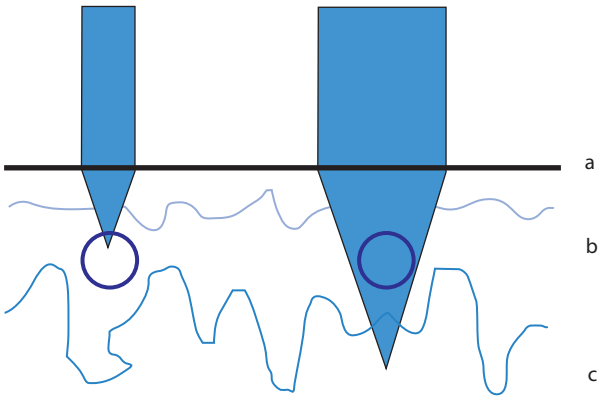

Figure 34.3 Semi-quantitative display of a penetration depth of 1064 nm into human skin according to different beam diameters. Penetration is deeper for larger beam diameters because of the physical effect of forward scattering (Mie scattering); a = epidermis, b = dermal layer, c = subcutaneous fat.

issue. If using a wavelength which is absorbed too highly by hemoglobin in vessels of larger diameter, the remote parts of the vessel do not become sufficiently heated because the energy is predominantly absorbed in the part that is first hit by the laser beam. In contrast, a wavelength which is absorbed more moderately by hemoglobin is able to heat up the vessel as a whole. Figure 34.4 displays this behavior for a 532-nm laser beam in comparison to a 1064-nm beam. For this reason, larger vessels with diameters in the order of 1 mm cannot be successfully treated with short laser wavelengths such as 532 nm, 585 nm, or even 595 nm.

To reduce pain and to minimize the risk of the numerous side effects elicited by heat damage of the skin, the use of skin cooling is mandatory today. Local use of ice cubes, the administration of cooled gel before laser treatment, or laser firing through ice cubes are historical methods that cannot guarantee reproducible results. Today, sophisticated dynamic spray cooling devices, chilled contact tips, or cool air generators are available.

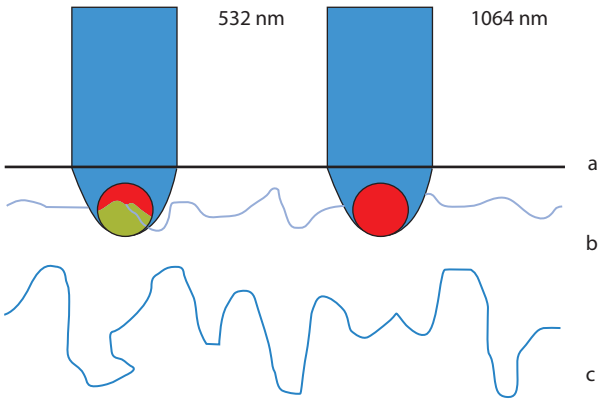

Figure 34.4 Semi-quantitative display of different volume heating effects of blood vessels caused by either 532-nm or 1064-nm irradiation. Due to the higher absorption of blood at 532 nm, larger vessels get heated only at the most superficial parts, producing a form of shield for more remote vessel parts, which stay cool. A 1064-nm wavelength heats the vessel more uniformly due to the lower absorption coefficient; a = epidermis, b = dermal layer, c = subcutaneous fat.

34.7 LASERS AND IPL FOR TRANSCUTANEOUS THERAPY OF TELANGIECTASIA

Meanwhile, treatment of telangiectatic vessels of the legs has reached a level which allows transcutaneous treatment in most of cases. There was an evolutionary change in laser parameters, particularly an increase of pulse duration and fluence and a move from visible light to near-infrared wavelengths. Today, a variety of laser and IPL systems are available for the treatment of leg telangiectasia of any diameter between 0.1 and 2.0 mm.

34.7.1 532-nm potassium titanyl phosphate Laser

The frequency-doubled 532-nm Nd:YAG laser system is particularly useful for the treatment of red leg telangiectasias with small diameters below 0.7 mm. It is most effective if used on skin types I–III and is problematic in tanned or dark-skinned patients because of the high absorption of melanin at this wavelength.

The 532-nm laser was initially used with fluences of between 14 and 20 J/cm^2, pulse durations of 10–15 ms and spot sizes of 3–5 mm in 50 patients with leg telangiectasias of varying diameters. A total of 83% of patients showed clearances of 50% or more after two treatments. With the abovementioned parameters and a chilled tip for contact cooling, the 532-nm potassium titanyl phosphate (KTP) laser proved to be less painful compared to laser systems with longer wavelengths.[17] In another 15-patient study, clinical results were corroborated on telangiectasias of less than 0.75-mm diameters. A clearance of more than 75% was achieved after two treatment sessions using a fluence of 16 J/cm^2 with 10-ms pulse duration and three passes over the same treatment area each session.[18] Another study confirmed the favorable pain and side effect profile, but found vessel clearance to be inferior to a long-pulse dye laser. The authors recommended the use of the KTP laser system in conjunction with sclerotherapy of larger feeding reticular veins.[19] However, when using a multi-pulse mode with three stacked pulses of 100-, 30-, and 30-ms durations (each separated by a gap of 250 ms), a fluence of 60 J/cm^2, and a beam diameter of 0.75 mm, clearance in leg telangiectasias of 0.5–1.0-mm diameters was 85% after three treatment sessions and 93% after four treatment sessions, most likely taking advantage of met-hemoglobin formation during the first of the three pulses.[20] In another work, no efficacy of the KTP laser was found on vessels with diameters of 0.7 mm or more.[21]

In another study, 79 areas of 20 female subjects (skin types I–III) were treated using a 532-nm KTP laser. A 5-mm diameter spot, fluences from 13 to 15 J/cm², and a pulse duration of 40 ms were used in two treatment session, 12 weeks apart. Blinded reviewers rated more than 50% improvements of telangiectasias in 69% of patients, and hyperpigmentation was observed in only 2%.[22]

34.7.2 578-nm copper bromide laser

The copper bromide laser is suited for red leg telangiectasia. In a study of 46 patients, 75%–100% clearance was achieved after an average of 1.7 treatments of vessels with diameters below 1.5 mm. Fluences were in the range of 50–55 J/cm², and a contact cooling system with a temperature of between 1°C and 4°C was used.[23]

34.7.3 Flashlamp pumped-pulse dye laser

This laser was the first to take advantage of the concept of selective photothermolysis and the first to achieve remarkable results in very small red vessels with diameters below 0.1 mm, like in telangiectatic matting. With a wavelength of 577 nm and pulse durations of 360 µs, this laser was shown to be suitable for the treatment of infantile hemangioma or port wine stains. It did not show remarkable effects on patients with leg telangiectasia.[24] When targeting blue leg telangiectasia with a wavelength of 585 nm and a pulse duration of 450 µs, it showed only very limited success, with a clearance rate of 30% and frequent hyperpigmentation thereafter.[25]

In the mid-1990s, dye lasers with 595-nm wavelengths and pulse durations of 1.5 ms were introduced. One study with fluences of 15 or 18 J/cm² showed clearance in up to 65% after a single treatment when treating vessels of between 0.6 and 1.1 mm in diameter.[26] Another study reported 100% clearance in leg telangiectasias of below 0.5 mm in diameter and 80% in vessels with diameters of between 0.5 and 1.0 mm.[27] In 10 patients, more than 75% clearance was achieved after three treatments every 6 weeks with minimal side effects using a 595-nm dye laser with a 1.5-ms pulse duration. Fluences of between 15 and 20 J/cm² were used on leg telangiectasias with diameters below 1.5 mm.[28] Wavelengths of 595 and 600 nm were compared in 87 patients with 257 treatment sites using 1.5-ms pulse durations and fluences of 16, 18, and 20 /cm². A clearance rate above 50% in up to 80% of patients was noted after a single treatment. The authors found best results with higher fluences on vessels of less than 0.5 mm in diameter. Pigment changes were noticed in 32% of cases.[29] The use of a dynamic cooling device in conjunction with a 595-nm wavelength and 1.5-ms pulse duration treatment reduced patient discomfort without diminishing the average clearance rate of 68%.[30] The introduction of dye lasers with pulse durations of 40 ms enabled treatment without or at least with diminished production of purpuric lesions after laser treatment. With the use of an extended pulse width of 40 ms and a fluence of 16 J/cm² and administering up to three passes over the same location during one session, after a total of two treatment sessions, 70% of leg vessels showed a clearance of 75%–100%. A −4°C air cooling system was used during treatment.[31] After only one treatment of submillimeter telangiectasia with the 595-nm dye laser at a 40-ms pulse duration with a fluence of 25 J/cm² and spray cooling, about half of patients had clearance of 50% or more. In the same study, 532-nm KTP laser treatment with a 50-ms pulse duration and a fluence of 20 J/cm² and contact cooling gave similar results.[32]

34.7.4 755-nm long-pulse alexandrite laser

The long-pulse alexandrite laser in the near-infrared at a wavelength of 755 nm proved to be most effective in a double-pulse mode (frequency: 1 Hz) at a fluence of 20 J/cm² with pulse durations of 5–10 ms.[33] Small vessels with diameters below 0.4 mm did not show significant response, while larger telangiectasias showed a 63% reduction after three treatments at 4-week intervals. Subsequent sclerotherapy improved laser results significantly. Another study showed that long-pulse alexandrite laser treatment at 3-ms pulse durations and fluences of 60–70 J/cm² for the treatment of veins of 0.3–3.0 mm in diameter frequently caused significant inflammatory skin reactions, purpura, and telangiectatic matting. Despite this side effect profile, only 33% of patients had more than 75% clearance after up to three treatment sessions.[34] When using the 755-nm alexandrite laser with a fluence of 90 J/cm², 15 of 20 patients had a clearance of between 25% and 75% of treated telangiectasias with diameters of 0.3–1.3 mm. However, in 75% of cases, hyperpigmentation was noted.[35]

34.7.5 Diode lasers of between 810 nm and 980 nm

No side effects but also no clearance of leg telangiectasia were observed in a study using an 810-nm diode laser with a 5-mm spot size and a pulse protocol of four consecutive stacked pulses (frequency: 2 Hz), each with a fluence of 3–4.5 J/cm².[36] Inconsistent results of only 29% of sites clearing by more than 75% were also reported by another group using an 810-nm long-pulse diode laser on vessels with diameters of between 0.3 and 3.0 mm.[34] Using a 940-nm diode laser with a 1-mm spot size, a pulse duration of 40–70 ms, and fluences of between 300 and 350 J/cm², a single treatment resulted in a clearance of more than 75% of treated telangiectasias in 12 of 26 patients (46%).[37] The same authors published the results of an additional 1-year follow-up with further improvement of clearing rates in 35% of patients.[38] Another group from France using spot diameters of between 0.5 and 1.5 mm, a pulse duration of between 10 and 70 ms, and fluences of slightly above 300 J/cm² found clearance rates of superior to 75% after up to three treatment sessions in only 13% of cases if vessel diameters were

below 0.4 mm, and in 88% of cases if vessel diameters were between 0.8 and 1.4 mm.[39] An 810-nm laser used with a 12-mm spot size, a pulse duration of 60 ms and fluences in the range of 80–100 J/cm^2 managed to completely clear 43% of spider veins after one session with two treatment passes.[40] A combination of a 915-nm diode laser with 1-MHz radiofrequency energy with up to three treatment sessions showed more than 75% clearance in 77% of treatment sites when using 80–140 J/cm^2 laser fluence and 80–100 J/cm^3 of radiofrequency energy with pulses of 100–300 ms in duration.[41] A 980-nm diode laser which was used with a contact cooling device, with fluences of between 300 and 500 J/cm^2 and pulse durations of 150 ms achieved up to 50% clearance in 60% of patients; however, with such long pulse durations, pain was pronounced in the majority of patients.[42]

34.7.6 1064-nm long-pulse Nd:YAG laser

The wavelength of 1064 nm shows less absorption in melanin compared to shorter laser wavelengths and is less absorbed by hemoglobin. Because of the relatively low hemoglobin absorption, laser energy can heat up the larger vessels as a whole. In 1999, Weiss and Weiss reported a study on 30 patients using a Nd:YAG laser at a 1064-nm wavelength with a pulse duration of 16 ms. They observed a 75% improvement after a single treatment in 0.5–3.0-mm diameter vessels.[43] Another study reported 64% clearance after a maximum of three treatment sessions using a 1064-nm Nd:YAG laser with a contact cooling device. The author used a 6-mm spot size, pulse durations of up to 14 ms and a fluence of 130 J/cm^2 to treat vessel diameters of between 0.2 and 4.0 mm.[44] A rate of 75%–100% clearance was achieved with a dual wavelength approach, when using the Nd:YAG system only for telangiectasias of 1.0–4.0 mm in diameter, but treating 0.1–1.0-mm vessels with a 550-nm IPL device.[45] Interestingly, in comparison to Sotradecol sclerotherapy, the long-pulse Nd:YAG laser had equal results in leg telangiectasias of 0.25–3.0 mm in diameter.[46] By utilizing a spray cooling device, long-pulse Nd:YAG treatment of leg veins of 0.3–3.0 mm in diameter showed clearance of more than 75% in 85% of treated sites after a maximum of three sessions.[47] This finding was corroborated in vein diameters of between 1.0 and 3.0 mm. With a single treatment using a fluence of 100 J/cm^2 and a pulse duration of 50 ms, a clearance of more than 75% was achieved in 66% of cases.[48] In a highly interesting approach taking advantage of met-hemoglobin formation using a non-uniform pulse sequence, a French group reported a clearance rate of 98% after three sessions. They used a 2-mm spot, fluences of between 300 and 360 J/cm^2, and a contact cooling device to treat blue leg telangiectasias of diameters between 1 and 2 mm.[49]

34.7.7 Combination of laser treatment after injecting telangiectasia

More recently, lasers have been used for combination treatment modalities after either a systemic intravenous injection of a green dye[50] or the injection of the target vessel with a polidocanol-based foam sclerosant.[51] Laser energies of an 810-nm diode or a 1064-nm Nd:YAG laser, respectively, were delivered.

In a prospective randomized trial, telangiectasias of 29 subjects were treated in the first arm with a 1064-nm Nd:YAG laser with fluences of between 160 and 240 J/cm^2, a pulse duration of 65 ms, and a 5-mm spot size, and in the second arm with a 810-nm diode laser after intravenous injection of 4 mg/kg body mass of an indocyanine green dye and using an fluence of 60–110 J/cm^2, a 48–87-ms pulse duration, and a 6-mm spot size. Blinded investigators and participants assessed clearance rate, cosmetic appearance, and adverse events up to 3 months after a single treatment session. Both investigators and participants ranked the clearance rates of the dye-augmented diode laser treatment greater than those after 1064-nm Nd:YAG treatment, but also rated the dye-augmented treatment as more painful.

In a randomized controlled trial in 320 female patients (skin types II–IV), polidocanol foam sclerotherapy of leg telangiectasia followed by 1064-nm Nd:YAG laser treatment was compared to polidocanol foam sclerotherapy alone.[51] Each patient received two single treatment sessions at a 3-week interval, with treatment of both legs occurring in full in each session. Up to 20 cc of foam prepared from a 0.3% polidocanol solution were injected per session. In the laser group, depending on the vessel diameter, a 2-mm spot size was used with a fluence of about 300 J/cm^2 or a 5-mm spot size was used with a fluence of around 60 J/cm^2. Depending on the diameter of the vessel, the pulse duration was chosen to be between 20 and 50 ms. Evaluation was performed by blinded analysis of photographs taken up to the 3-year follow-up and patients' self-assessment in 79 control legs and 517 legs treated with the foam–laser combination. Depending on the vessel diameter, clearance rates of the combination laser treatment were 89%–95%, while in the control group, after foam sclerotherapy alone, the corresponding clearance rates were only 15%–18%.

In a study in 60 patients, laser treatment of leg telangiectasias was evaluated with a unique coupled 585-nm dye laser and a 1064-nm Nd:YAG laser.[52] A spot diameter of 7 mm with pulses of 10 ms and a fluence of 9 J/cm^2 for the dye laser and pulses of 30 ms and a fluence of 80 J/cm^2 for the 1064-nm Nd:YAG were utilized. The time delays between sequential dye laser and Nd:YAG pulses were 125, 250, and 500 ms for vein diameters of 4, 3, and 2 mm, respectively. The patient satisfaction rate was 47 out of 60 patients. Blinded evaluation of clinical photographs as well as computerized analysis demonstrated good to very good improvements in 47 and 49 out of 60 patients, respectively.

34.7.8 Intense pulsed light

IPL sources do not make use of monochromatic light or of coherent light emission. They emit polychromatic light, which is defined by filters placed between the IPL source and the patient. In its initial phase, without concomitant

use of special cooling devices, side effects such as skin burns or hyperpigmentation could occur more easily than with today's devices. However, even in its early days, IPL was able to demonstrate excellent results on leg telangiectasia. In a multicenter trial treating 369 lesions in 159 patients, a clearance of more than 75% was achieved in 79% of vessels between 0.1 and 3 mm in diameter. The rate of adverse effects was low.[53] Another study showed that IPL is most effective in small red vessels with diameters of less than 0.2 mm, with an immediate clearance of 82%, while only 60% was achieved with IPL treatment of vessels between 0.5 and 1.0 mm in diameter.[54] In a more recent comparative study between Nd:YAG and IPL, the IPL treatment was judged to be more effective when diameters were below 1.0 mm, while larger veins were more effectively treated by the Nd:YAG laser.[55] Treatment combining IPL treatment for smaller vessels with diameters below 1.0 mm and Nd:YAG laser treatment for vessels with diameters above 1.0 mm was reported to be very successful.[45,56]

34.8 COOLING SYSTEMS

Skin cooling is crucial to minimizing thermal side effects on skin structures apart from telangiectasia. Today, icing of the skin cannot be judged as sufficiently reproducible, but is more reliable than the use of cooled gels. Gels provide a temperature decrease of only about 5°, can even disturb the spot geometry of the laser beam, and account for energy loss of about 35%.[29] Reliable and more effective techniques are contact cooling devices,[23,32,44] e.g., sapphire hand-pieces and dynamic spray cooling[30,32,47] using tetrafluoroethane or low-temperature air cooling devices[23,31,57]. In addition, for IPL, a collar contact cooling device improved clinical results, enabling the delivery of higher fluences with less pain.[58]

34.9 SIDE EFFECTS AND COMPLICATIONS

To identify patients who are prone to idiopathic hypersensitivity reactions after laser treatment, a test treatment of a small area is absolutely necessary before a full treatment session is administered. Furthermore, an informed consent from about the treatment-related risks should be signed by the patient. The most frequent side effects of laser treatment are:

- Transient or, rarely, permanent hyperpigmentation
- Telangiectatic matting
- Incomplete elimination of telangiectasia
- Treatment-related pain

Restricted to special laser types, particularly to the old type of flashlamp pumped dye lasers, is the side effect of purpura. As stated above, the long-pulse alexandrite laser therapy of leg telangiectasia is associated with pronounced inflammatory skin reactions under certain conditions. Hyperpigmentation can happen with the use of any laser or IPL source, but is more likely to happen after treatment of telangiectasia with shorter-wavelength lasers, such as 532-nm KTP devices. Patients with activation of their pigment system after sunny vacations, or who use sunbeds, should strictly avoid laser or IPL treatments. Conversely, sun exposure and use of sunbeds should be strictly avoided after laser therapy as long as any skin response is visible, usually for 3–4 weeks. Dark-skinned patients should be treated with particular caution, if treated at all.

A less frequent side effect of laser treatment is thrombosis of telangiectasia, which is mostly associated with vessel diameters above 1 mm. To accelerate the clearing of this phenomenon, thrombosis should be removed by needle puncture within the first week of treatment.

Rare complications of laser treatment include blistering of the skin with or without subsequent scarring. These side effects most frequently happen with overdosing of laser energy. Overdosing of laser or IPL can happen in conjunction with:

- Administration of too high fluences
- Inadvertent pulse stacking or inadvertent overlapping of pulses
- Intended pulse stacking with too small cooling intervals in between
- Inappropriate cooling of the skin surface during treatment

In addition, laser treatment of skin that is covered with lotions or ointments can result in skin burns and hyperpigmentation. Removal of all of these before laser treatment is therefore mandatory.

34.10 ALTERNATIVE TREATMENT OPTIONS FOR LEG TELANGIECTASIA

A serious alternative option to light-based systems or some of the described combination treatments of leg telangiectasia is sclerotherapy with various liquid or foam sclerosants. The technique of sclerotherapy is presented in detail in a different chapter of this book.

34.11 FUTURE DIRECTIONS

The laser and IPL treatment of leg telangiectasia offers significant potential to evolve. Bimodal wavelength approaches, longer pulse durations, and improved skin cooling contributed much to more effective laser and IPL treatment of leg telangiectasia.[59]

Despite a solid theoretical basis, concepts such as the exploitation of laser-induced met-hemoglobin formation are still not fully developed.[49,60] Similarly, feedback loops for the measurement of vessel and skin temperatures during laser treatment and subsequent online adjustment of laser fluences and skin cooling are technically possible, but have not yet been introduced into daily clinical practice. The same is true of automatic scanner systems which would direct the laser beam to the previously traced course of the target vessel.

Combination treatments consisting of laser treatment of telangiectatic vessels after systemic injection of a dye or a sclerosing foam at the treatment site look promising as well.[50,51] However, the scientific exploration of these concepts has only just begun.

34.12 SUMMARY

- Small leg telangiectasias: for diameters below 0.5 mm and telangiectatic matting, the flashlamp pumped dye laser at 595 nm is effective.[27,29,31] The KTP laser at 532 nm is suitable for vessel diameters below 0.7 mm.[18,21] Multi-pass treatment[18,31] or pulse stacking[20] may improve clinical results.
- Larger telangiectasias up to 3 mm diameter can be effectively treated by long-pulse Nd:YAG lasers with 1064-nm wavelengths.[43,46–48]
- The combination of laser treatment of leg telangiectasia with prior injection of a polidocanol foam seems to increase clearance rates dramatically.[51] Systemic injection of an indocyanine green dye prior to laser therapy may increase treatment success as well.[50]
- Effective skin cooling is mandatory to avoid thermal skin damage. Appropriate cooling devices are dynamic spray cooling,[30,32,47] contact cooling,[23,32,44] or cooled air.[31] Cooled gels do not provide sufficient or homogenous skin cooling.[29]
- In human skin, melanin is the main competing light absorber to hemoglobin[13]; therefore, laser treatment of telangiectasia can cause the side effect of long-lasting hyperpigmentation. An increased epidermal melanin content after sun exposure—a so-called tanned skin—therefore should be regarded as a contraindication to cosmetic laser treatment of leg telangiectasia.

Guidelines 4.6.0 of the American Venous Forum on the percutaneous laser therapy of telangiectasia and varicose veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.6.1	For telangiectasias with vein diameters below 0.5 mm and for telangiectatic matting, we recommend the flashlamp pumped dye lasers at a 595-nm wavelength.	1	C
4.6.2	For telangiectasias with diameters below 0.7 mm, we recommend the potassium titanyl phosphate laser at a 532-nm wavelength.	1	C
4.6.3	For large telangiectasias of up to 3 mm in vein diameter, we suggest treatment with long-pulse neodymium-doped yttrium aluminum garnet lasers at a 1064-nm wavelength.	2	C
4.6.4	During laser treatment, we recommend cooling to avoid thermal skin damage using dynamic spray cooling, contact cooling, or cooled air.	1	C
4.6.5	We do not recommend cosmetic laser treatment of leg telangiectasias in tanned skin with increased melanin content after sun exposure.	1	A

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● = Seminal primary paper
★ = Key review paper

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35

Foam sclerotherapy for ablation of the saphenous veins, varicose tributaries, and perforating veins

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35.1 INTRODUCTION

Since the last edition of the American Venous Forum (AVF) *Handbook of Venous Disorders* was published in 2008, there have been major advances in the endovenous management of varicose veins (VVs). Foam sclerotherapy (FS) is a versatile treatment that can be performed safely, quickly, and inexpensively in an office setting, and has become an important part of the phlebologist's armamentarium. The aim of this chapter is to

1. Briefly review the history of FS
2. Discuss the currently available sclerosants and techniques
3. Present the results of FS from large observational and randomized studies
4. Suggest how FS might fit within a multimodality endovenous treatment offer
5. Make some recommendations regarding further research

35.2 HISTORY

Sclerotherapy has been used to treat VVs since at least the 1850s. However, early sclerosants such as percholate of iron or mercury, iodine, tannins, and carbonic acid were associated with an unacceptably high incidence of serious, even life-threatening complications, such as tissue necrosis, sepsis, and pulmonary embolism. For this reason, it was not until the introduction of modern safe sclerosants, such as sodium tetradecyl sulfate (STS), in the 1960s that sclerotherapy gained widespread popularity. FS is thought to have been first described in 1939 by McAusland who, after shaking a bottle of sodium morrhuate, used the resultant froth to successfully treat telangiectasia. In 1944, Orbach described the "air block" technique in which an intravenous injection of air prior to the sclerosant was claimed to prevent dilution by blood and prolong endothelial contact. Sigg described a similar "foam block" technique in 1949. In 1950, Orbach noticed increased vasospasm (thought to be an important indicator of success) with FS when compared with liquid sclerotherapy (LS). In 1956, Flückiger emphasized the importance of leg elevation to empty the VVs of blood and advised the retrograde injection of foam, which could then be massaged along the leg in a proximal to distal direction. It was also noted that decreasing bubble size increased bubble surface area and endothelial contact, thereby producing more sclerosis with less sclerosant. In 1957, Mayer and Brücke described the use of a double piston syringe to produce what they termed "microfoam." In the 1990s, microfoam production was further refined by Cabrera, Monfreux, and Tessari, and Knight first introduced the concept of ultrasound-guided FS (UGFS).[1] Wollmann has reviewed the history of FS in more detail.[2]

35.3 SCLEROSANTS AND MECHANISM OF ACTION

In Europe, most phlebologists use "home-made" STS and/or polidocanol (PD) microfoam for FS. In the United States, Varithena, which is a commercially prepared 1% PD microfoam, has recently been approved by the Food and Drug Administration (FDA). Sclerosants produce endothelial damage, which exposes collagen and leads to activation of platelets and the intrinsic coagulation pathway. The resulting thrombosis and inflammation eventually results in fibrosis and obliteration of the vessel lumen. If intraluminal thrombosis is excessive, this can be associated with pain, dermal pigmentation, clot propagation (risk of deep vein thrombosis [DVT]) and recanalization. Detergent sclerosants such as STS and PD cause endothelial damage by altering cell wall surface tension, leading to rapid overhydration (maceration). STS is a long-chain fatty acid salt, is painless to inject, is usually used at concentrations of 1%–3%, and produces maceration within 1 second of exposure. PD is a urethane anesthetic agent, is painless to inject, is thought to be less likely (than STS) to produce extravasation necrosis, and is usually used at concentrations of 0.5%–3%. Injection of STS or PD as a foam, as opposed to a liquid, results in the displacement of blood, so minimizing deactivation (binding) by protein and maximizing contact with the endothelium ("foam block effect").[3] Both STS and PD are well tolerated, with similar side-effect profiles.[4]

35.4 FOAM PREPARATION TECHNIQUES

The Tessari (Tourbillon) technique is probably the most commonly use method for reproducibly making stable (in 1–2 minutes) microfoam (Figure 35.1).[5] Typically, two (2–10-mL) syringes are connected via a three-way tap. Room air is drawn into one syringe and liquid sclerosant into the other. The use of sterile air, nitrogen, or carbon dioxide has been advocated. However, they add cost and complexity and, due to a lack of evidence, there is a range of views as to whether these adjuncts confer any benefit in terms of safety or clinical effectiveness.[6] The air and sclerosant are mixed back and forth (usually around 20 times) through the three-way tap to produce the microfoam. The connector tap can be angulated to narrow the aperture in order to produce smaller bubbles and so more stable, and arguably more effective, microfoam. Alternatively, a 5-µm bacterial filter can be interposed between the two syringes. A number of other foam preparation methods have been described, such as the Hamel-Desnos et al.'s double syringe technique[7] and the Monfreux's "méthode MUS."[8] There is no clear evidence that one method is superior to the others, and cost and convenience are arguably the most important considerations. The most effective and commonly used gas-to-sclerosant ratios appear to be 4:1 or 5:2, but this is also an area where good-quality evidence is lacking. Low-silicone syringes and connectors are preferred as silicone destroys the surfactant arrangement of the foam lamellae, so making it less stable.[9] Varithena is a 1% PD foam made with a proprietary blend of "physiological" gases and dispensed from a pressurized container. Varithena bubbles are appreciably smaller than those found in "home-made" foam and this, together with the absence of nitrogen, may reduce the risks of air embolism.[10] However, thus far, clear evidence of benefit in terms of safety and clinical effectiveness compared to "home-made" foam appears to be lacking.

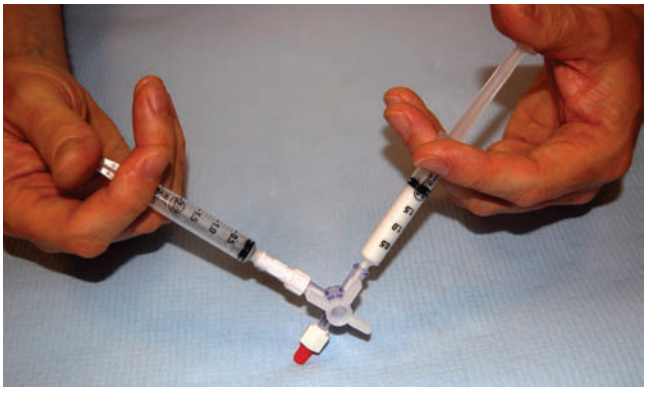

Figure 35.1 Tessari technique. Note the 5-µm filter between the syringe and tap for producing consistent microfoam.

35.5 TECHNIQUE

Many FS techniques have been advocated and there is no clear evidence as to which is the best. The authors have settled on a method that they have found to be simple, quick, safe, well-tolerated, and associated with excellent long-term (5–8-year) outcomes. As with all UGFS techniques, duplex ultrasound with a high-frequency (5–15-MHz) transducer and access to emergency resuscitation equipment in case of anaphylaxis (very rare) are required. The procedure starts by "marking up" the VV to be treated with the patient in a standing position. With the aim of introducing "fresh" microfoam at 10–20-cm intervals along the trunk and major tributary VV to be treated, intravenous cannulas are placed at strategic points under local anesthetic and ultrasound guidance with the patient in the supine and/or prone position. The size of cannulae to be used is determined by vein diameter and depth. In a patient with "standard" great saphenous vein (GSV) VVs, four cannulae are typically positioned in the GSV as follows: 10–15 cm below the saphenofemoral junction; just above the knee; just below the knee; and just above the ankle. In general, the greater the diameter of the GSV, the closer together the cannulae are placed. Where present, cannulae will also be placed in the anterior accessory saphenous vein and in all of the major tributaries. If there are extensive superficial varices, typically in the calf, then these too will be cannulated. In a patient with "standard"

small saphenous vein (SSV) VVs, the SSV is typically cannulated just distal to the saphenopopliteal junction, with the cannula pointing caudally to minimize entry of foam into the popliteal vein, and again in the distal SSV usually just above the ankle or at the point of the distal incompetence (Figure 35.2). The leg is then elevated to 45° in a sling to empty the superficial veins. The placement of cannulae as described above, rather than by direct injection with needle and syringe, allows the VV to be completely emptied of blood (so increasing the efficacy of the sclerosant) and virtually excludes the risk of extravasation. Microfoam aliquots (typically 2–3 mL, 1:4 gas-to-sclerosant ratio) are then injected via the cannulae, usually moving from proximal to distal. Typically, we use 3% STS for truncal veins, 1% STS for major tributaries, and 0.5%–1% STS for minor tributaries and superficial varices or very superficial truncal veins. The foam is injected slowly under direct ultrasound visualization so that venospasm is maximized and entry of foam into the deep system is minimized.[7] For larger truncal veins, we often perform a second injection in the proximal one or two truncal cannulae. The microfoam can be "milked" along the VV and into tributaries and varices using the ultrasound probe. Between injections, the patient is asked to plantarflex and dorsiflex their ankle to expel any foam that may have migrated into the deep system. The quantity of foam used depends on the extent of the veins to be treated, but in our practice, it would be unusual to use more than 16 mL 3% 1:4 air microfoam, which equates to 4 mL of 3% STS. There is a range of views as to whether it is necessary to perform manual compression of the saphenofemoral and saphenopopliteal junctions (e.g., using direct pressure from the ultrasound probe) in an attempt to prevent foam migration into the femoral and popliteal veins.[11] Having done this originally, the authors discontinued the practice because it was felt to be ineffective and potentially counterproductive by potentially allowing a sudden "bolus" of foam that has been trapped within the GSV/SSV to enter the deep veins. This change in practice has not been associated with any change in the side-effect profile or efficacy of the treatment. Regarding the treatment of perforators, the authors' practice is not to treat these directly, but rather to treat the superficial trunk directly distal and proximal whilst applying digital pressure over the perforator to prevent foam spilling into the distal deep venous system (as the risk of causing a DVT is probably greater than at the saphenofemoral junction because the flows are slower and the diameters smaller). However, others believe it is important to inject these perforators directly (under ultrasound guidance) with liquid sclerosant. Once the trunk, tributary, and variceal veins are observed on ultrasound to be in spasm and full of foam, the cannulas are removed and, while the leg remains elevated, a cotton wool roll is placed over the trunk to provide eccentric compression and the leg is wrapped in a cohesive, non-elastic, conforming bandage. The patient is then fitted with a European class 2, thigh-length stocking. We recommend that this bandaging/stocking stays in place undisturbed for 3 days (5 days if larger VVs have been treated). Thereafter, the bandages are removed and the stocking worn for a further 2–3 weeks. As is the case in many areas of FS practice, there is a wide range of views regarding the type and duration of post-procedure compression. Two recent randomized controlled trials (RCTs) have reported on this issue. One group compared bandaging for 24 hours and 5 days, both followed by a thromboembolic-deterrent stocking for the remainder of 2 weeks, and reported no advantage of prolonged compression bandaging in terms of phlebitis, skin discoloration, post-procedural pain, improvement in health-related quality of life (HRQL), and 6-week target vein occlusion rates.[12] The other study compared compression stockings (15–20 mmHg) worn during the day for 3 weeks with no compression and found no difference in occlusion rates, side effects (thrombophlebitis, inflammation, pain, and pigmentation), satisfaction scores, and HRQL.[13]

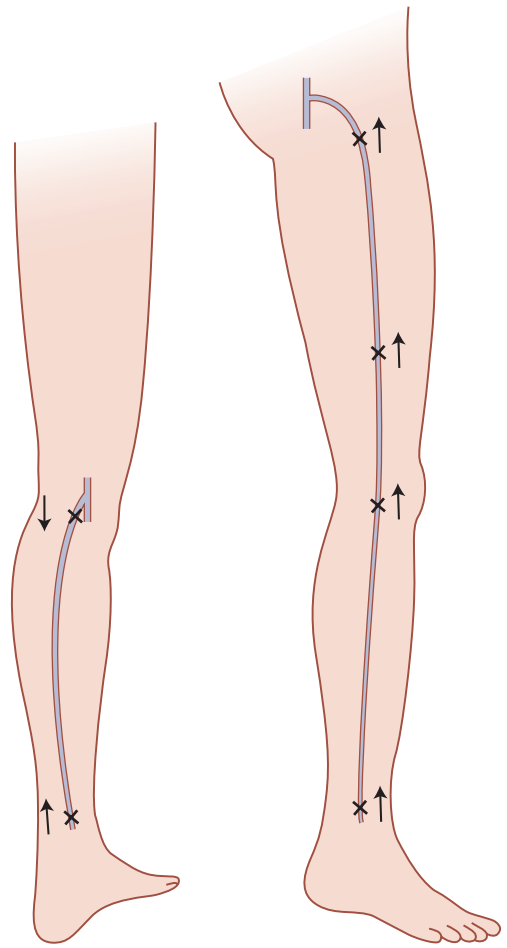

Figure 35.2 Schematic for great and small saphenous vein cannulation. Note the directions of the cannulae (arrows).

The phlebologist now has a wide variety of endovenous techniques to treat VVs, and these can be combined in imaginative ways so that the overall treatment offer is

tailored to the individual patient's needs, expectations, and desires. We aim to completely eradicate all superficial reflux at a single FS treatment session, as staged treatment is less convenient for the patient and less cost-effective. FS is particularly appropriate for complex recurrent disease associated with neovascularization, where the VVs to be treated are often too small, tortuous, and superficial to be treated easily by means of endothermal ablation (ETA) and where the versatility and adaptability of FS is a major advantage.

35.6 RESULTS OF FS

35.6.1 Observational case series

Numerous FS case series have been published. We have concentrated on the more recent papers, as FS techniques and results have continued to improve. In 2010, we reported that in a series of 344 legs with primary GSV reflux, a single session of FS led to the abolition of reflux in 95% of cases at 12 months.[14] In 2014, we reported that in a cohort of 391 legs treated by means of FS, only 15% required further treatment at a median follow-up of 71 months.[15] In 2009, Chapman-Smith and Browne reported a 4% clinical recurrence rate 5 years following FS and that 16.5% required repeat FS at between 1 and 2 years.[16] In 2012, a Taiwanese group reported a 90% occlusion rate at 38 months following two sessions.[17] With regard to recurrent VVs, we have reported a 93% occlusion rate following a single FS treatment in 91 legs affected by recurrent GSV reflux[18] and a 91% occlusion rate in 92 legs affected by recurrent SSV disease.[19] With regard to bilateral disease, a study published in 2012 by Bhogal and colleagues showed no difference in occlusion rates or complications between synchronous and metachronous bilateral FS.[20] However, as synchronous bilateral FS clearly requires a greater volume of microfoam to be injected in a single session, it seems sensible to restrict such treatment to patients with a limited burden of disease. Several groups, including our own, have confirmed that, when compared to conventional surgery (CS), FS is associated with quicker return to work and driving and with lower pain/analgesia requirements.[21] In summary, therefore, numerous observational case series attest to the safety and clinical efficacy of FS.

35.6.2 Randomized controlled trials

At the time this chapter was written, 17 RCTs have compared FS with CS, including phlebectomies, ETA using laser or radiofrequency energy, and LS. Bountouroglou and colleagues reported no differences between FS with CS after 3 months.[22] Kalodiki and coworkers also compared FS and CS, and at 3 and 5 years, found similar improvements in venous clinical severity scores and HRQL (SF-36 and Aberdeen Varicose Vein Score) and suggested that FS offered as a "dental care model" (treat as and when the problem appears) is a clinically effective and cost-effective treatment for VVs that is well tolerated by patients.[23] In a RCT of 60 patients published in 2009, Figueiredo et al. reported higher occlusion rates following FS (90%) than after CS (70%).[24] In 2012, Shadid and coworkers reported that in a large RCT, FS was not clinically inferior to CS at 2 years.[25] A further six publications have reported on four RCTs which have compared FS with ETA.[26–31] Although long-term occlusion rates following FS were lower, all of the endovenous techniques studied led to highly significant and broadly similar improvements in patient-reported outcome measures. Several trials have shown that FS is superior to LS for the treatment of truncal VVs and venous malformations.[7,32] Devereux and coworkers reported that the use of tumescence to reduce vein diameter prior to catheter-directed FS did not improve occlusion rates.[33] The recently published VANISH-2 trial suggests that at 12 months, the results of treatment with Varithena are similar to those seen after FS using STS and PD "home-made" microfoam in terms of symptoms, appearance, and occlusion rates on duplex ultrasound.[34] A summary of the major FS RCTs published since 2008 (the time of the last edition of the AVF *Handbook of Venous Disorders*) is displayed in Table 35.1.

35.7 CONTRAINDICATIONS AND SIDE EFFECTS

Contraindications to FS include:

- Previous serious drug allergy to the sclerosant
- Obstructed deep venous system
- Coagulopathy
- Peripheral arterial disease (ankle brachial pressure index <0.8)
- Pregnancy

Relative contraindications include:

- Planned long-haul flight within 4–6 weeks—possible increased risk of DVT
- Patent foramen ovale—possible increased risk of systemic side effects
- History of severe migraines—possible increased risk of migraine

The most common "side effects" of FS are lumpiness, localized phlebitis, and skin staining in association with excessive intraluminal thrombosis, which tends to occur most often within large and/or superficial VVs. These side effects can be mitigated by good technique, early ultrasound-guided aspiration under local anesthetic, and strong patient reassurance. Serious complications are very rare following FS. For example, the French PD study reported only eight (0.5%) muscular vein thromboses in a series of 1605 patients treated with FS.[35] Similarly, in a multicenter study of 1025 patients, Gillet et al. reported only 10 (1%) patients (five symptomatic) with DVT and one

Table 35.1 Summary of major randomized controlled trials of foam sclerotherapy from 2008

Authors	Sclerosant	Trial arms	Target vein	Follow-up	Conclusions
Brittenden et al.[31]	STS	UGFS: 212 EVLA: 292 CS: 294	GSV	6 months	QoL improves similarly in all treatments with similar treatment efficacy
Devereux et al.[33]	PD	UGFS with tumescence: 25 UGFS without tumescence: 25	GSV	12 months	No benefit of reducing vein diameter with tumescence analgesia pre-treatment
Lattimer et al.[29]	STS	UGFS: 50 EVLA: 50	GSV	3 + 12 months	UGFS less expensive with comparable effectiveness
Biemans et al.[30]	PD	UGFS: 80 EVLA: 80 CS: 80	GSV	12 months	QoL improved significantly with all treatments EVLA and CS better than UGFS according to occlusion on US
Shadid et al.[25]	STS	UFGS: 230 CS: 200	GSV	2 years	UGFS not inferior to CS when examining reflux associated with clinical symptoms
Yamaki et al. (2012)[47]	PD	UGFS: 51 Visual foam sclerotherapy: 52	GSV	6 months	UGFS and visual foam sclerotherapy equally effective
Kalodiki et al.[23]	STS	UGFS + SF ligation: 39 CS: 43	GSV	3 + 5 years	Treatments equally effective in VCSS and HRQL scores
Liu et al. (2011)[48]	PD	UGFS + SF ligation: 30 CS: 30	GSV	6 months	UGFS + SF ligation decreased treatment time, post-operative pain, and more rapid recovery
Rasmussen et al.[27]	PD	UGFS: 125 EVLA: 144 RFA: 148 CS: 125	GSV	1 + 3 years	All treatments efficacious with similar improvements in VCSS and QoL scores
Ukritmanoroat[32]	PD	50 patients all treated with LS and UGFS	All veins	90 days	Foam more effective than LS
Blaise et al. (2010)[49]	PD	UGFS 1% PD: 69 UGFS 3% PD: 70	GSV	3 years	1% and 3% equivalent in terms of efficacy
Figueiredo et al.[24]	PD	UGFS: 27 CS: 29	SSV + GSV	180 days	UGFS is a safe and effective option for venous treatments
Abela et al. (2008)[50]	STS	UGFS + SF ligation: 30 CS: 30 Invagination stripping: 30	GSV	2 weeks	UGFS + SF ligation give greater patient satisfaction and less post-operative pain
Ouvry et al. (2008)[51]	PD	UGFS: 47 LS: 48	GSV	2 years	Foam more effective than LS

Note: STS; sodium tetradecyl sulfate; PD: polidocanol; UGFS: ultrasound-guided foam sclerotherapy; LS: liquid sclerotherapy; EVLA: endovenous laser ablation; RFA: radiofrequency ablation; CS: conventional surgery; SF: saphenofemoral junction; GSV: great saphenous vein; SSV: small saphenous vein; QoL: quality of life; VCSS: venous clinical severity score; HRQL: health-related quality of life; US: ultrasound.

with a pulmonary embolism.[36] Abbassi-Ghadi and Hafez reported no DVTs and one PE in a series of 213 FS treatments.[37] Visual disturbances comprising unilateral/bilateral blurred vision, double vision, and scotoma have been reported in 0.09%–4.5% of patients undergoing FS[38]; the cause is unknown, but may relate to the release of vasoconstrictor chemicals from the damaged endothelium (PE).[39] Other neurological symptoms are extremely rare. A review of the literature of several studies and case reports involving 10,819 patients identified 15 transient ischemic attacks and 12 cerebrovascular accidents, with one fatality (reported as a case report in 1951). Two patients had residual weakness upon discharge from hospital and 11 of 16 transient ischemic attacks/cerebrovascular accidents were associated with a patent foramen ovale.[40] Symptoms often occurred minutes to hours after FS, and the longest was delayed to 5 days. The cause of these neurological symptoms remains incompletely defined, but foam bubbles passing into the cerebral circulation may be relevant in at least some cases.[41] Release of vasoactive moieties such as endothelin may also play a role.[42] Similar adverse events have been reported after CS and ETA procedures,[43,44] which perhaps suggest that at least some are coincidental and unrelated to the FS. Myocardial infarction has also been reported and may be unrelated or possibly the result of bubbles passing through a patent foramen ovale and into the coronary circulation.[45] Inadvertent intra-arterial injection has been reported 63 times in the literature and has led to amputation in 31 cases.[46] Overall, therefore, FS is an extremely safe treatment for VVs. However, it is suggested that patients are provided with written information on serious and common adverse events as part of the informed consent procedure prior to FS. Total foam volumes of up to 16 mL/treatment session for STS and 10 mL/treatment session for PD are licensed for use in European countries. Varithena is licensed in the United States for volumes of up to 15 mL/treatment session.

35.8 CONCLUSION

FS is a widely applicable and highly versatile clinically effective and cost-effective treatment for primary and recurrent VVs that can be safely performed in an office setting and is extremely well-tolerated by patients. However, further observational studies and RCTs are required to optimize patient selection, FS technique, and follow-up.

Guidelines 4.7.0 of the American Venous Forum on foam sclerotherapy

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.7.1	We recommend foam sclerotherapy in the treatment of truncal primary and recurrent varicose veins. This is applicable to patients with CEAP clinical grade C2–C6.	1	A
4.7.2	We recommend using ultrasound-guided foam sclerotherapy over liquid sclerotherapy for the treatment of truncal varicose veins.	1	B

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● = Major review article

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Techniques and results of the modern surgical treatment of the incompetent saphenous vein

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36.1 INTRODUCTION

A patient with an incompetent saphenous vein may be asymptomatic from a clinical perspective. The patient may have varicose veins of the lower extremities, defined as subcutaneous veins 3 mm or more in diameter visualized when the patient is standing.[1] Alternatively, there may be non-specific early signs of chronic venous disease or more advanced symptoms, such as severe edema or venous ulceration (clinical class C0–C6).

In the United States, about 23% of the adult population has varicose veins and 6% have advanced chronic venous disease, including skin changes and ulcerations. Based on the San Diego epidemiologic study, about 11 million men and 22 million women between the ages of 40 and 80 years have varicose veins, and 2 million adults have advanced disease.[2]

The incompetent saphenous vein may be an isolated finding or be associated with perforator and/or deep venous disease either of an occlusive or insufficient nature. Fortunately, widespread use of venous duplex scanning has aided in determining the likely reason(s) for the varicosities noted.[3] The CEAP clinical classification of C0 to C6 was 29%, 23%, 10%, 9%, 1.5%, and 0.5%, respectively, in the National Venous Screening Program which screened 2234 Americans. Reflux or obstruction was seen in 37% and 5% of participants, respectively.[4]

Varicose veins can be a cause of loss of working days, disability, and deterioration of health-related quality of life.[5] The annual medical cost of chronic venous disease in the United States has been estimated to be between $150 million and $1 billion.[5,6]

36.2 PERTINENT ANATOMY

The variability of lower extremity venous anatomy does add complexity to the operation, and has been discussed in prior chapters of this text, with illustrations. Some review of pertinent points for the open surgery is useful.

Two of the most important anatomic structures involved with open saphenous surgery would be the saphenofemoral junction (SFJ) and saphenopopliteal junction (SPJ), which have been retained in the current nomenclature of veins of the lower extremity.[7] It has been clarified that the proximal level of each junction corresponds to the valve located proximal to the saphenous opening (suprasaphenic valve) and the valve located about 3–5 cm distal to the saphenous opening.

The branches joining the great saphenous vein (GSV) at the confluence of the inguinal veins are the anterior accessory GSV, the external pudendal vein, the superficial circumflex iliac vein, and the superficial epigastric vein, as can the posterior accessory GSV (although it can join lower in the medial thigh), in addition to the posterior and anterior thigh circumflex veins occasionally. One anatomic dissection study found that there are at least four common variations to how these veins join, with incidence rates of the most common being 33%, 15%, 15%, and 13%, demonstrating how variability is actually the norm in this dissection.[8] The superficial external pudendal artery helps to mark the termination of the

GSV, and can lie anterior or posterior to the GSV as it enters the common femoral vein. Protection or ligation is required to prevent unwanted bleeding during an open procedure.

The GSV is doubled in the calf in 25% of the population and in the thigh in about 8%.[9] The posterior accessory GSV is a common tributary which begins posterior to the medial malleolus, ascending on the posteromedial aspect of the calf, and joins the GSV distal to the knee. It connects directly to the deep system via at least three prominent calf posterior perforating veins, and insufficiency in this vein may be an important component of a patient's symptoms. Knowledge that the anterior accessory GSV at the upper thigh courses deeply (superficial to the muscular fascia, like the GSV) to a hyperechoic fascia that resembles the GSV covering can aid the surgeon during anatomic dissection.[7] It is easily identified in that it courses more anteriorly than the GSV, with a path corresponding to the underlying femoral artery and veins. This is important since if this vein is insufficient, removal is required to affect a complete operation.

The saphenous nerve lies in close proximity to the GSV below the knee, and it is separate from it above that location. In 12% of cases, the nerve is directly next to the vein at the knee, so even in this location, there can be a risk of injury. Below the knee, the nerve lies next to the GSV except in a few patients (two of the 60 dissections preformed).[10] Its method of branching is forked toward the foot, so upward engagement is more likely than distal, providing some support for distal vein extraction during open operations.[11]

The SPJ lies deep in the fascia. In only about 75% of cases, the small saphenous vein (SSV) actually joins the popliteal vein; alternatively, it can join the gastrocnemius vein or progress in a more cephalad direction. Although the SPJ may be absent or rudimentary in about 25% of cases, when present, it generally joins the popliteal within 4 cm at or above the knee crease. In about 25% of cases, it is higher in location, and in about 1%, it is lower.[12] A termination in the upper calf by it either joining the gastrocnemius veins or GSV occurs in about 1% of cases.[13] There is often (70%) a thigh extension of the SSV that has a fascial compartment and follows the posterior femoral cutaneous nerve between the semitendinosis and biceps femoris muscles. It can terminate in the middle and upper thigh and equally into deep or superficial veins. It can connect to the GSV by way of the intersaphenous vein, formally known as the vein of Giacomini.[12,14] Knowledge that the SSV runs in the subcutaneous soft tissues in the lower two-thirds of the leg and then dives deep into the fascia is critical when dissecting in this area. Eliminating the deep dissection in favor of a more superficial to fascia ligation has been advocated, since there are no data to suggest that flush ligation results in a better outcome.[15] This is also one of the reasons the Society for Vascular Surgery (SVS)/American Venous Forum (AVF) guidelines committee recommends intra-operative duplex imaging as the safest way to identify the SSV during an operation.

The ultrasonic relationship of the sural nerve to the SSV has been extensively studied by Ricci and colleagues.[16] It lies close to the SSV in the distal leg, with a more distant relationship in the proximal calf, and is usually lateral to the vein in the facial compartment. It does not share a perivenous fascia with the vein as occurs in the case of the GSV and saphenous nerve. The posterior tibial nerve most commonly lies lateral to the SSV (in two-thirds of cases) and may actually twist around the SSV near the SPJ. The peroneal nerve always lies laterally, but can be in the zone of injury.[17,18]

36.3 INDICATIONS FOR SURGICAL PROCEDURES

The patient's symptom(s) determines the need for intervention, not an abnormality found on a diagnostic test. However, the diagnostic testing provides the confirmation that venous pathology is present and may be the underlying cause of the patient's complaints. Using the CEAP classification to define in detail your patient's venous condition provides a basis for the proper intervention to be chosen.[19] To place in perspective the current patient clinical state and to measure the result of an intervention, the patient's clinical severity score should be recorded.[20] A generic quality of life measurement tool allows comparison with other disease states and a general estimate of the ill effect of both the disease state and the effect of treatment. The Short Form 36-Item Health Survey (SF-16) has been successful in assessing the global well-being of patients with varicose veins.[21] There are several disease-specific quality of life scoring systems available, with some more heavily weighed to evaluating early-stage disease (varicose veins), such as the Aberdeen Varicose Vein Questionnaire, while others are more appropriate for characterizing patients with more advanced disease, such as the Charing Cross Venous Ulceration Questionaire.[22,23] The SVS Venous Clinical Severity Score is a physician-generated measurement tool which incorporates patient-reported, physician-observational, and clinical measurements in one scoring system, and has been recommended as the best estimate of symptom relief by the SVS/AVF guidelines.[15,20] The surgeon will need to provide the benefits to be gained over what period of time for the risks of surgical intervention. Ultimately, however, the patient will have to decide whether the symptom(s) he or she is experiencing is sufficiently severe to warrant the risk of open venous surgery.

Pertinent clinical guidelines provide evidence and guidance for the use of these procedures. For the treatment of the incompetent GSV, the SVS/AVF guidelines committee suggests high ligation and inversion stripping of the saphenous vein to the level of the knee (grade 2, level of evidence B). For treatment of SSV incompetence, the recommendation is high ligation of the vein at the knee crease, about 3–5 cm distal to the SPJ, with selective invagination stripping of the incompetent portion of the vein (grade 1, Level of evidence B).[15] Resolution of superficial reflux may aid in venous ulcer healing (grade 2, level of evidence C), will prevent recurrent venous ulceration (grade 1, level of evidence B), should be recommended to prevent recurrence in those with a prior venous ulceration which has healed, and is reasonable to

consider in a patient with skin that is at risk of venous ulceration (grade 2, level of evidence C).[24] The presence of deep or perforator insufficiency does not alter these recommendations. Finally, and in contradistinction to current payment structures, the data would support the contention that compression therapy is not the best primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation (grade 1, level of evidence B).[15,25]

There are certain conditions in which open surgery may be the preferred method of removing the pathologic saphenous vein, even though less invasive ablation techniques are available. In some locations, the expense of ablation technique devices is prohibitive and therefore open surgery provides a viable option for treatment.[26,27] Catheter-based therapy is ideal for straight, incompetent veins coursing within the saphenous canal. The anatomic variations that pose challenges for endovenous treatment are vein tortuosity and adherence to the overlying skin, which can be overcome with an open approach. Although stain resolution after endovascular interventions generally occurs spontaneously, it can persist for more than a year, resulting in cosmetically unacceptable outcomes in these adherent veins. In such cases, open surgery provides a potentially better method of care.[28] Patient preference may also be an indication due to the known long-term track record of open surgery and the potential for early recurrence after less invasive procedures.[29]

There may be situations in which recurrence post-ablation is due to saphenofemoral or saphenopopliteal reflux or neovascularization, which will require surgical exploration to treat.[30] Furthermore, open surgical intervention may be needed if arteriovenous fistulae develop post-ablation that are symptomatic. Symptoms are rare but may include severe limb edema, high-output cardiac failure, and steal syndrome. Asymptomatic patients may be followed with duplex ultrasound and may resolve spontaneously.[31]

36.4 CONTRAINDICATIONS

The lack of a patent vein being present into which the stripping device can be advanced is a contraindication to the performance of this procedure. The complete lack of a deep system capable of draining the lower leg of venous blood is a contraindication to saphenous vein removal. Although thought to be indicative of many of those with deep venous occlusive disease, the reality is that most patients with deep venous occlusive disease have sufficient reserve to allow saphenous removal when needed in order to treat the signs and symptoms of superficial disease.[32,33] Severe peripheral vascular occlusive disease must be taken into account whenever making incisions in the lower extremity, or healing will be an issue. If concerned with healing based on clinical and hemodynamic parameters, a more detailed investigation to eliminate arterial disease as a confounding variable in the patient's care is recommended. This is especially concerning in patients with venous ulceration and, in fact, an arterial pulse examination and measurement of ankle–brachial index is recommended in all of these patients.[24,34] In addition, associated medical conditions which might place the patient at higher risk of anesthetic complications (cardiac, pulmonary, and renal), increased bleeding or thrombotic events (uncorrectable coagulopathy, thrombophilias, cancer, and immobility), or infection (open wounds and systemic infection) must be appropriately considered and controlled in order to obtain optimal results. Multiple prior groin explorations is a relative contraindication to open surgery due to a higher risk of complications which include lymphatic leakage and major vascular injury.[35] In a retrospective study of 128 groin re-explorations for recurrent varicose veins, there was a 40% rate of wound complications.[36] Previous groin infection and radiation-induced scarring are important considerations when counseling patients about the risks of surgery. Pregnancy and breast feeding must always be considered as confounding variables, which might influence the patient's decision to proceed with an open procedure.

36.5 DIAGNOSIS

The initial indication that a pathologic saphenous system exists is based on patient symptoms. These include pain, swelling, heaviness, itching, skin discoloration, cramps, ulcers, and even overt bleeding from superficial veins which experienced a traumatic insult that can be slight or more intrusive. The psychological ramifications related to the unsightly appearance of varicose veins or other associated signs such as hyperpigmentation or ulceration affecting self-esteem are important considerations. A detailed history and physical examination is essential to establishing the diagnosis, noting obvious varicose veins, swelling, hyperpigmented skin, and present or past ulcers, so that the CEAP clinical classification can be documented.[19] One should make special note in female patients to rule out vulvar varicosities which are easily missed due to patient and/or physician reluctance to complete a proper examination. Physical examination can suggest SFJ or SPJ as well as perforator incompetence, but requires venous duplex imaging to confirm the clinical impression.

The critical need for venous duplex imaging prior to any saphenous intervention has become evident due to the variability of findings noted on the detailed imaging used in the conduct of certain ablation techniques.[37] Detailed imaging did not always confirm the clinical impression and, in fact, in some cases, the saphenous proper is not affected when it was considered the underlying etiology of the clinical findings.[38] The lower extremity venous duplex facilitates procedure planning and appropriate care. It completes much of the CEAP classification in terms of the etiology, anatomic distribution, and pathophysiology of the disease that is present. A detailed description of venous duplex imaging is contained in a prior chapter of this text and will not be readdressed here. The addition of other diagnostic modalities is generally not required, but based on unique patient conditions might include the need for magnetic resonance venography, computed tomography venography, venography, or intravenous ultrasonography.

36.6 TECHNIQUES

36.6.1 Anesthesia

Most patients opt for general or regional anesthesia (spinal or epidural), especially if a bilateral operation is planned. Others have employed the use of femoral nerve blocks with supplemental local anesthetic injections or tumescent anesthesia for unilateral procedures, but the manipulation required for the open procedure, especially around the deep veins in the groin, can be uncomfortable, if not painful for the patient. One dose of peri-operative antibiotic prophylaxis does decrease the risk of wound infection and wound-related complications, as demonstrated in a randomized controlled trial in patients undergoing groin dissection for the treatment of varicose veins.[39] The issue of peri-operative deep venous thrombosis (DVT) prophylaxis is best managed by using early and frequent ambulation in patients who are free of associated risk factors. In those patients with additional thromboembolic risk factors, such as thrombophilia, prior history of DVT or thrombophlebitis, and/or obesity, the recommendation is prophylaxis with low-molecular-weight heparin, low-dose unfractionated heparin, or fondaparinux.[15]

36.6.2 Operative procedure

36.6.2.1 PATIENT POSITIONING

36.6.2.1.1 GSV surgery

The patient is positioned in the supine position and the entire leg to umbilicus is prepped and draped in a routine sterile fashion to expose the entire leg and foot to the umbilicus. The initial dissection to expose the groin anatomy may be performed with the patient flat or slightly elevated. However, for the actually stripping of the vein from the body, the patient should be positioned in Trendelenburg to minimize vein distention and, therefore, blood loss.

36.6.2.1.2 SSV surgery

The patient is placed in the prone position for a bilateral procedure. A prone position is also quite acceptable for a unilateral procedure, but a semi-lateral position with the leg to be operated on facing upward on the operative field would suffice. Flexion of the knee relaxes the tight popliteal fascia for easier exposure. The initial dissection to expose the venous anatomy may be performed with the patient flat or slightly elevated. However, for the actual stripping of the vein from the body, the patient should be positioned in Trendelenburg to minimize vein distention and blood loss.

36.6.2.2 ELIMINATE PROXIMAL REFLUX: HIGH LIGATION AND DIVISION

36.6.2.2.1 Saphenofemoral junction

A transverse incision is made in the skin, 1–2 cm below the inguinal skin crease or somewhat higher in the obese patient. This approach facilitates easy closure at the completion of the operation via an incision, which is somewhat self-approximating (Figure 36.1A1, see arrow). The incision begins just medial to the femoral artery pulse and extends 3–5 cm medial so as to be centered over the saphenous and common femoral vein junction. Using cephalad and caudal retraction, the GSV and its branches, as well as the anterior common femoral vein, are visualized. The major branches of the GSV are the superficial circumflex iliac, superficial epigastric, external pudendal, and, in some cases, the anterior accessory GSVs. There is significant anatomic variability in how these veins converge near the SFJ, but this makes little difference to the ultimate goal of the operation, which is to ligate and divide each branch well off the trunk and often past their second branch points. The posterior accessory GSV is also ligated and divided if present in the dissection field. Occasionally, posterior and anterior thigh circumflex veins join the GSV and are likewise ligated and divided. All branches are ligated to the secondary branches by tradition, rather than this being a data-driven approach.[15,40] Care must be taken to visualize the superficial external pudendal artery and either protect it from harm or formally ligate and divide it in order to prevent undesirable arterial bleeding postoperatively. This artery helps to mark the termination of the GSV and can lie anterior or posterior to the GSV as it enters the common femoral vein (Figure 36.1A1 and 36.1A2). If not accomplished in the prior dissection, the anterior surface of the common femoral vein is formally visualized so as not to injure it during GSV ligation and to ensure that the vein to be stripped is not the common femoral vein. At this stage, the caudal GSV can be exposed via an overlying transverse incision centered over the vein (Figure 36.1B1) and situated just below the knee. Through this incision, the stripping device can be placed from caudal to cephalad and is seen to pass into the GSV at the groin incision. Except in obese patients, the rather rigid stripper can be palpated along the length of the GSV within the subcutaneous compartment it occupies. When satisfied that the anatomy has been correctly defined and dissected, the GSV is ligated flush on the common femoral vein with a double ligature or oversewn with a 5–0 prolene running suture (Figure 36.1A2) after securing it distally to the stripping device with a large silk tie. The GSV is divided to disconnect it from the deep system prior to stripping. Alternatively, some surgeons ligate the GSV on the common femoral vein, transect it, and pass the stripping device from cephalad to caudal.

36.6.2.2.2 Saphenopopliteal junction

A 4–6-cm transverse incision placed directly over the duplex-marked SPJ allows an incision to be best placed for later ligation and division of the SSV. The soft tissue is dissected in the transverse direction and then the deep fascia is incised in the longitudinal direction if flush ligation is the goal (see Figure 36.2A1). In the standard case, the SSV is subfascial rather than subcutaneous in location. The SSV is dissected and all tributaries ligated after clearly defining the popliteal vein (Figure 36.2A2). The tibial nerves pass near

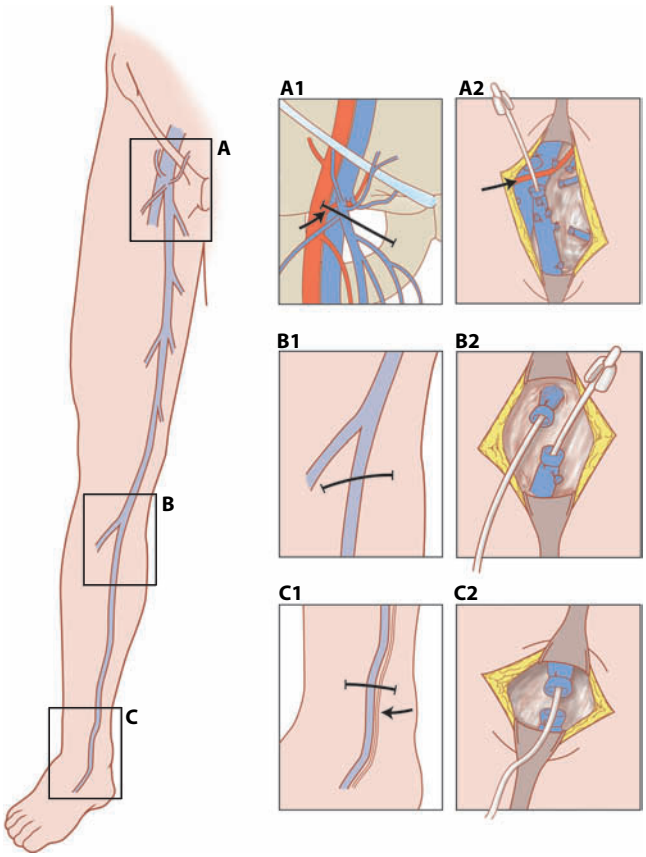

Figure 36.1 The supine patient's general anatomy is demonstrated in the long leg drawing. The top insert demonstrates (A1) the proximal great saphenous vein (GSV) with branches, with particular emphasis on the superficial external pudendal artery (arrow), which may be located above or below the insertion of the GSV into the common femoral vein. Lack of attention to the artery can result in unwanted bleeding. A2 depicts the ligation and division of all branches with flush ligation of the GSV on the common femoral vein and a Codman-type stripping device lying within the vein distally. B1 depicts a small incision centered over the GSV just below the knee to expose and control the vein. The saphenous nerve may lie close to the vein in this area and should be completely dissected away from the vein. B2 demonstrates the stripping passing upward to exit the GSV in the groin area (A2); in addition, a second stripper exits the distal vein for removal of the calf GSV if needed. In this depiction, a small head is attached to the distal stripper, but often the vein is simply tied to the small bullet on the end of the stripper. The vein is divided before stripping is undertaken. If vein removal was to not include the calf component, the distal vein would be ligated and divided. C1 is the artist's depiction of a small incision centered over the ankle GSV to expose and control it. Note the close proximity of the saphenous nerve to the vein (arrow); the nerve is dissected and removed away from the vein as much as possible. C2 shows the distal vein ligated with a proximal stripper in place and ligated to the vein. Before stripping, the vein is divided.

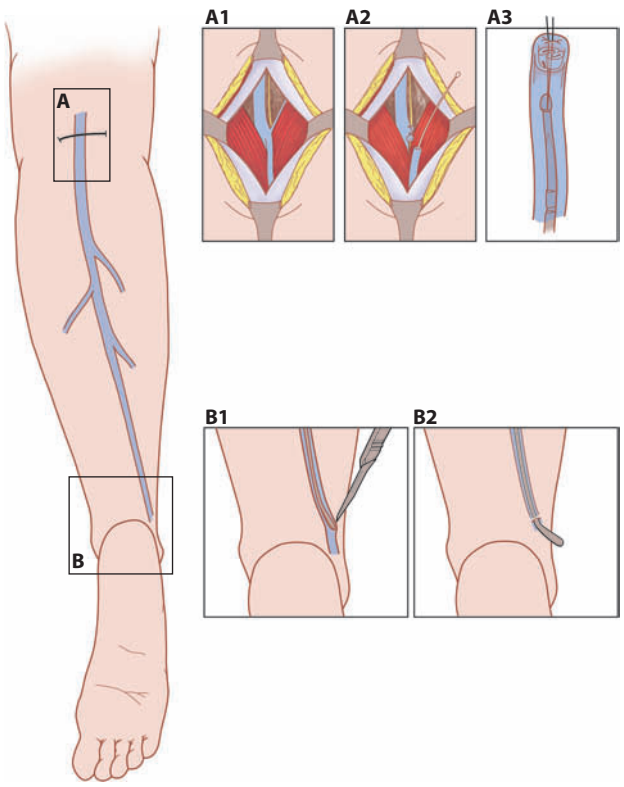

Figure 36.2 This artist's depiction shows the patient in a prone position with the general location of the small saphenous vein (SSV) beginning at the latter malleolus and terminating near the knee crease (incision proximal). A1 depicts the saphenopopliteal junction, which lies deep into the investing fascia rather than in the subcutaneous tissue in which the SSV lies in the more distal leg. Take special care to protect the tibial nerves (yellow structures next to the vein). It should also be understood that the intersaphenous vein may be a major proximal extension of the SSV. A2 shows the SSV ligated flush with the popliteal vein and a perforate–invaginate (PIN) stripper has been placed downward in the open distal SSV. A3 is a magnified view of the PIN stripper ligated to the SSV via a "floating knot" and the invagination process has begun. B1 demonstrates the proximally placed PIN stripper being forcefully pushed through the vein wall and subcutaneous tissues to indent the skin. An 11 blade or similar small knife punctures the skin, allowing the distal stripper to egress. B2 shows the distal PIN stripper exposed, which will be grasped and pulled downward, invaginating the vein from the body.

the popliteal vein and both structures must be identified and protected from harm. Ligation of the SSV flush on the popliteal vein can be accomplished before or after placement of the vein-stripping device via the distal vein. After stripper placement, the SSV can be ligated distally on the vein stripper at the time of flush ligation on the popliteal and the vein transected (Figure 36.2A2). If retrograde placement of the stripping device is planned, then flush ligation on the popliteal vein is performed and subsequently the distal saphenous vein can be opened for stripper placement.

36.6.2.3 REMOVAL OF THE INCOMPETENT VEIN: AXIAL STRIPPING

36.6.2.3.1 Great saphenous vein

Attempts to save the GSV using simple high ligation to prevent reflux into the incompetent system was fraught with rapid recurrent pathologic reflux and so was abandoned. Precise duplex imaging demonstrated a generally normal GSV devoid of reflux except at branch sites and has allowed a limited approach to the control of varicose veins. Unfortunately, primary axial GSV incompetence is generally associated with more advanced disease (C3–C6) and therefore removal of the pathologic vein is the best approach for long-term success. Removal of the vein to just below the knee is acceptable if there is no pre-operative reflux present into the calf and ankle. This limited stripping of the vein decreases saphenous nerve injury by minimizing the proximity of the two structures during stripping. However, if the entire vein demonstrates reflux on pre-operative duplex imaging, we would strip the below-knee GSV from the below-knee incision to the ankle, representing a conscious effort to dissect the saphenous nerve away from the vein at both incisions prior to stripping. We have observed minimal clinical consequences as a result of this approach, even though a careful neurologic examination will demonstrate some sensory deficiency.

Our general approach is to remove all incompetent GSV above and/or below the knee at the initial operation. If reflux stops at or just below the knee, a 1–2-cm long transverse incision is located a few centimeters below the knee and centered over the GSV to allow easy exposure (Figure 36.1B1). The vein is dissected from surrounding tissue with sufficient length to allow silk sutures to control bleeding from the vein proximally and distally to an opening in the anterior wall. Through the vein opening, the stripping device is placed cephalad into the vein and the proximal suture is used to tie the vein onto the stripping device. Vein stripper devices in general consist of a rather stiff and long wire with or without the ability to attach a "head" of various sizes to aid in vein removal. The various modifications have been named Codman, Myers, Varady, etc., and are available from a variety of manufacturers. The distal suture is tied to seal the distal vein and the stripper is passed upward until it is seen in the groin incision. We like to palpate the stripper within the subcutaneous saphenous compartment to provide some tactile impression that it lies in the correct position. We do this by grasping both ends of the stripping device and lifting upward to tether or bowstring it and allow improved palpation within the subcutaneous tissue. The vein in the knee area is divided to allow the vein to ultimately be pulled from the body in a downward direction. In the groin, the saphenous is flush ligated on the common femoral vein, the distal vein is ligated to the stripper, and the vein transected. When using one of the stripping devices (e.g., the Codman style device), variously sized heads may be placed on the stripper to aid in complete vein removal, but we generally choose the smallest available head to minimize the mass of tissue being removed and required to exit the distal incision. Others perform invagination stripping with excellent results, as described in more detail below.

If the calf GSV demonstrates significant reflux on pre-operative imaging, the GSV at the ankle is exposed via a 1-cm long transverse incision positioned 1 cm anteriorly and medially to the medial malleolus (Figure 36.1C1). The subcutaneous tissue is dissected from around the vein to separate the saphenous vein from the nerve and to allow a cephalad and caudal silk ligature to be placed around the vein. The caudal end of the vein is ligated and, with gentle traction on the cephalad suture, the anterior surface of the vein is opened, through which a stripping device can be advanced to the calf incision. The vein is ligated to the stripper at the ankle and the vein transected. Rather than ligating the saphenous vein at the calf incision, if only proximal stripping was planned, the vein is left open. The stripper is allowed to exit the vein, which is then ligated to it with a silk tie. We generally do not add a stripper head to the device in this location since the small obturator located on the device is generally sufficiently large to prevent the vein from pulling off it during invagination and extraction. The saphenous vein in the calf is divided to allow the vein to be removed from the body. Rather than stripping the entire saphenous vein with its accumulated bulk through the ankle incision, which might tend to drag the saphenous nerve with it, we have employed this two-incision technique for complete vein excision.

With the saphenous vein secured to the stripping device and transected proximally and distally to allow extraction, the patient is placed in a steep Trendelenburg position. The proximal vein is extracted first with gentle pressure held over the area during and somewhat after the stripping has taken place. The distal end of the stripper is grasped firmly and, with a constant and determined distal pull, the vein is removed from the body. After proximal pressure has secured acceptable hemostasis, the distal vein in removed in a similar fashion with external pressure again held to the point of hemostasis.

A technical modification that allows extraction of the saphenous from the body without a distal incision involves the use of a 3.5-mm diameter cryoprobe, which can be placed from proximal standard saphenous exposure into the distal vein and stops about 8 cm below the knee. When in place, liquid nitrous oxide is injected into the distal probe to freeze the probe tip to the veins at −85°C. The vein is then invaginated on itself by pulling the cryoprobe from distal to proximal, with the vein now trailing and being pulled from its compartmental bed. The proximal vein was already divided from its attachment with the common femoral vein to allow removal. Compression is applied and the proximal wound closed.[41,42]

36.6.2.3.2 Small saphenous vein

Extraction of the SSV may follow the same process as depicted for the GSV. The distal SSV may be exposed via

a transverse incision directed over the vein at the point of reflux termination as determined by pre-operative duplex imaging and marking. Alternatively, the vein may be exposed via a transverse incision located between the Achilles tendon and lateral malleolus at the high ankle. The sural nerve is not as closely adherent to the SSV as the saphenous nerve is to the GSV, but it can lie close to the SSV in the distal third of the leg. The nerve has small accompanying arteries and all must be protected from harm when dissecting the vein to allow ligation and stripping. After making the incision, the subcutaneous tissue is dissected to isolate the vein and to allow proximal and distal control with silk ties. The distal vein is ligated and the proximal vein opened to allow advancement of the stripper. The vein is ligated to the stripper and transected. The stripper is advanced and exits the vein at the knee vein incision. The vein is tied to the stripper in this location and, following ligation from the popliteal vein, the vein is transected. Following institution of the Trendelenburg position, the vein is pulled downward and from the body with external compression being applied for 2–5 minutes to control any bleeding. Alternatively, many surgeons will only remove about 10 cm or less from the proximal incision to prevent nerve injury and with the thought that recurrence is unlikely in this short vein.

An alternative method of stripping the SSV is depicted in Figure 36.2. Note that the same method could be used for stripping the GSV, although a few more incisions are required to allow visualization of the vein in its entirety. The method demonstrated is the perforate–invaginate (PIN) technique of Oesch. The SSV is ligated flush to the popliteal vein and a stainless steel semi-rigid PIN stripper (30 or 47.5 cm long) is back-loaded and passed retrograde down the vein. Retrograde bleeding is controlled by a suture encircling the vein with the stripper lying within it. The stripper is passed down the vein and past any area of reflux, at which point it is forcefully punctured through the vein and into the subcutaneous tissue, dimpling the skin. An 11 blade incises the skin via a stab incision, exposing the distal tip (Figure 36.2B1 and 36.2B2). The proximal vein is ligated to the stripper via a "floating knot." A silk suture is tied to the stripper, which is pulled a short distance into the vein, and then the suture encircles the vein, which is ligated and a long trailing component of the suture is left in place to allow vein removal if it breaks during stripping (Figure 36.2A3). The patient is placed in the Trendelenburg position during stripping. Pulling the distal stripper invaginates the vein, which eventually allows it to be pulled out from the distal incision. It is grasped and completely avulsed from the leg. Generally, no distal ligature is applied after vein transection. If the vein happens to break midway into its removal, the PIN stripper can be pulled into the vein via the trailing suture and the vein exposed, ligated to the stripper, and pulled into the proximal wound for removal. External compression provides hemostasis.

36.6.2.4 ADJUNCTIVE PROCEDURES, TECHNICAL CONSIDERATIONS, WOUND CLOSURE, DRESSINGS, AND POST-OPERATIVE CARE

At this point, branch varicosities can be removed via stab ablation, powered phlebectomy, or by other ablation techniques. In the majority of data that are available for estimating the overall results of open saphenous surgery, the branch varicosities that are addressed in some manner to provide complete care at a time when the patient has optimal anesthetic coverage. Incompetent perforator veins may also be addressed at this time via a variety of techniques.

If clinically indicated, bilateral surgery does not appear to increase the overall risk of complications in the patient.[43] High ligation alone as a treatment of a pathologically incompetent saphenous vein proved to be unsuccessful due to recurrent reflux and clinically apparent varicosities within a few years when compared to high ligation and stripping.[44] Dwerryhouse and colleagues reduced the need for reoperation from 20% with high ligation only to 6% with high ligation and stripping over 5 years.[45] Therefore, the addition of removal of the vein is an integral component of the open operative approach. Whether less invasive procedures such as the Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoiere (CHIVA) or Ablation Selective des Varices sous Anesthesie Locale (ASVAL) management of varicose veins will be more successful than simple high ligation is currently debatable and not championed in the United States. The former often employs ligation of the proximal saphenous in addition to ligation, division, and avulsion of incompetent varicose tributaries while maintaining the saphenous trunk, competent branches, and perforators.[46,47] The latter involves preservation of the incompetent saphenous and stab phlebectomy of all varicose tributaries.[48]

There has been debate as to whether the saphenous stump should be oversewn with a running suture versus simply ligated, and even whether a polytetrafluoroethylene (PTFE) patch should be placed over the ligated saphenous stump as a means of preventing neovasculogenesis in the groin with recurrent reflux.[49–52] The addition of the PTFE patch did add a significant complication risk to the procedure. The method of saphenous ligation likely has little impact on overall results. Current consensus would favor a secure closure of the saphenous stump, ligature, or oversewing with a non-absorbable suture, and no additional PTFE patch placement.[15]

The groin and posterior knee incisions used to provide high ligation can be closed with deep subcutaneous layers of interrupted 3–O absorbable sutures and a running subcuticular 4–O absorbable suture. The distal incisions used to expose the vein and allow stripper inversion and removal can be closed with one or two everting 4–O absorbable sutures. The incisions are covered with sterile flats and a compression wrap is applied from the foot to as much thigh circumferentially as possible, with slightly more compression distally

and tapering proximally. A sterile flat and dressing covers the groin wound. The patient is instructed to remove the dressing in 48 hours if desired and replace it with similar daily compression until seen in the clinic in about a week. Post-operative compression bandaging does reduce hematoma formation after vein stripping.[53] Use of compression stockings past 1 week has not been shown to be beneficial with respect to pain resolution, time to return to work, patient satisfaction, or wound complication rate.[54] The SVS/AVF guidelines committee recommends post-operative compression for a period of 1 week to reduce hematoma formation, pain, and swelling (grade 1, level of evidence B).[15]

The patient is discharged on the day of surgery after recovery from whichever anesthetic method was used. They are instructed to resume routine activities which do not involve heavy lifting or water sports. They can walk as desired rather than stand or sit for prolonged periods of time and, when reclining, should have their legs elevated to improve venous drainage. They should place a wedge between the boxspring and mattress to allow leg elevation above the head of about 4 inches when sleeping. A mild pain reliever is provided, but many patients use only an anti-inflammatory with good effect.[55] The patient is to be off work for 1–3 weeks, especially if they are involved in heavy labor occupations. Showering is permitted with proper leg wound protection. We generally see the patient in 5–7 days for wound inspection and examination. If all healing is progressing well, routine daily activities, including showering and light work duties, can be started. There are some data to suggest that high ligation and stripping in addition to stab phlebectomy to treat branch varicosities do require some time before returning to normal work activities. In one study, the average return to work time post-surgery was about 12 days.[56]

36.7 COMPLICATIONS

The risk of wound infections ranges from 1.5% to 16%.[57] In a retrospective study of 714 varicose vein surgeries in an outpatient setting spanning over 9 years, spinal anesthesia was found to be a significant risk factor for wound infection, with an odds ratio of 6.5. However, the discussion centered around the possibility that cigarette smoking was the actual risk factor, since spinal anesthesia was administered preferentially to this population. They had an overall incidence of 1.5%.[58] Another study which included 973 limbs treated in 599 patients reported a wound complication rate of 4%. Lymphatic complications occurred in 1.3% and all of the leaks were in patients undergoing groin re-explorations for recurrence. Two of the patients had lymphatic leak from phlebectomy sites. One patient had lymphedema.[35] A randomized controlled trial comparing prophylactic antibiotic use versus no antibiotics in high ligation and stripping with phlebectomies used an in-depth daily evaluation of the groin wound as assessed by a weighted scoring system composed of seven parameters. Based on a score that defines a wound infection, 9.9% in the treatment group and 18.2% in the control group experienced a wound infection. Two patients in the control group required incision and drainage of a wound abscess, and none require such an approach in the treatment group.[39] This study found two factors which increased the risk of a groin wound infection: obesity and current smoking.

Superficial nerves are at risk of injury due to their proximity to the veins being removed. The direction of stripping does affect nerve avulsion, as demonstrated by Ramasastry and colleagues, with much less risk if the direction of stripping is downward, since the branch points of the nerves are less likely to be engaged.[11] In fact, when stripping the entire saphenous vein downward, one investigator noted no objective nerve injury in 14 patients, while another demonstrated objective findings in upward stripping for an overall rate of injury of about 39%.[11,59,60] Stripping the vein only to the knee may eliminate this risk, but in 12% of cases, the nerve is on the vein at the knee.[10] Stripping to the knee is still associated with about a 7%–10% incidence of clinical saphenous nerve injury, so this approach does not eliminate the issue entirely.[35,60] Unfortunately, if you leave the below-knee vein in place, reflux and recurrent varicosities are risks which were noted in 4% of cases in one of the largest long-term follow-up studies available.[45] In fact, 29% of the patients in this study had duplex-confirmed reflux in the retained distal saphenous vein on follow-up, and the authors expressed a concern that this pathology may eventually be expressed as recurrent varicosities. In our own study, we preformed removal of all incompetent veins at the first operation, but via two separate incisions (an intervening knee incision). We observed a very small area of saphenous deficit in 58% of our cases (median 50 cm^2) around the medial malleolus or medial knee. A total of 54% of our patients with documented deficits did not recognize a problem, while four out of 26 still had symptoms, with only one noting moderate discomfort. None of our patients required recurrent surgery, although 29% had isolated cluster varicose veins.[61] No matter which approach is taken to remove the incompetent saphenous vein, the trade-off will be nerve injury risk versus recurrence in the retained saphenous vein. Common peroneal nerve injury occurred in 5%–7% of patients undergoing SSV ligation and stripping, with a sural nerve injury rate of 2%–4%.[15,62]

Injury to the femoral vein or artery is fortunately very rare (0.0017%–0.3%), but can be devastating, often because the problem is not promptly recognized and treated.[63] In one systemic review, 87 major vascular injuries were found, with about half being arterial in nature. In five cases, stripping of the femoral or popliteal vein occurred, and in 17 cases, stripping of the femoral artery was reported. Adherence to technique detail is apparent when considering that the stripper was inadvertently advanced into the deep artery or vein in these cases. Amputation can be the ultimate result if vascular repair is delayed or unsuccessful. Hagmuller from Germany reported an incidence of 0.02% of arterial injury and 1% of venous injury.[64] Critchley et al. reported one femoral vein injury among 599 patients in whom groin exploration was undertaken for the third time. They highlighted the risk of reoperation in a scarred groin.[35]

Thromboembolic complications including DVT or pulmonary embolism (PE) are rare, but can be serious in nature. Clinically apparent DVT and PE have been reported in series with maximal rates of about 0.5% and 0.17%, respectively.[35] In a more detailed prospective duplex study of 377 patients imaged before and at 2–4 weeks and 6–12 months post-surgery, acute DVT was detected in 20 patients (5.3%), with only eight being symptomatic (2.1%), and no clinical PE was observed.[65] Eighteen of the 20 cases were confined to the calf veins, with half completely resolved without reflux at 1 year. In a study comparing complications when stratified to younger or older than 65 years of age, there were no significant differences, but thromboembolism was seen only in the older group at a rate of 0.5%.[66] Protocols involving the use of graduated compression stockings for 6 weeks post-operatively with recommendations for early mobilization have been shown to decrease complications of venous thromboembolism from 0.7% to 0.2%. The PE rate decreased from 0.2% to 0% in this study.[67] When considering all of the available data, routine pre-operative prophylactic anticoagulation is not supported by Critchley et al. or the SVS/AVF guidelines committee members. The rate is low and generally not clinically significant when patients use compression and are allowed to ambulate early.[15,35] Based on their study findings, Critchley et al. started administering 40 mg of enoxaparin 1 day prior to surgery and continued this for 1 week post-operatively for patients with a history of venous thromboembolism.

36.8 RESULTS

Saphenous high ligation and stripping of the vein has been the gold standard for the treatment of saphenous incompetence for over a century, with only minor modifications over the decades. A randomized clinical trial has demonstrated that high ligation and stripping of the saphenous vein results in improved quality of life, cosmetic result, and relief of symptoms over that observed when using conservative management with compression garments only for the treatment of uncomplicated varicose veins.[25] A significant improvement in quality of life measurements was further confirmed by a randomized controlled trial report comparing open surgery to radiofrequency ablation.[39]

Recurrent varicose veins represent a failure of treatment to the patient and to the physician, especially when all has been done to eradicate the pathologic process at the first operation. Alternatively, they may reflect the chronicity of the disease process, but more likely they reflect some component of each. There are long-term data available regarding recurrence, which appears to be a progressive process. Clinical series with 2-, 5-, and >10-year follow-up data are available and note recurrent varicose veins at rates of 7%–37% at the 2-year follow-up, but up to approximately 50% and even 62% at 5 and 11 years, respectively.[40,45,68–76] The specific rates reported are subject to the rigors of patient inspection and the definition of recurrence, but these results do highlight the progressive nature of the disease even after an aggressive and extensive approach to intervention. This reality should be made clear to the patient prior to intervention in order to ensure a realistic expectations of outcomes.

For more advanced disease in which venous ulcer healing and prevention of recurrence are the markers of success, superficial vein surgery prevents recurrence. The ESCHAR trial randomized 500 patients with leg ulcers and isolated superficial or mixed superficial/deep reflux to compression only verses compression with high ligation, division, and saphenous stripping.[77,78] The rate of healing was the same at 4 months (65%), but at 12 months, the rate of ulcer recurrence was 28% in comparison to 12% when surgery was included in the patients' treatment ($P < 0.0001$), and the difference in ulcer recurrence was maintained at 4 years.

When compared to the less invasive techniques of radiofrequency or laser ablation that are now available to treat major saphenous reflux, early results (quality of life scores, associated pain, and recovery) favor the less invasive techniques; however, at 2 years, the clinical and hemodynamic results are similar.[56,79–82] Sclerotherapy, and even foam sclerotherapy, was less effective than surgery at eradicating major reflux.[83] A very recent large meta-analysis supported by the SVS and the AVF reviewed current data regarding these modalities for the treatment of saphenous incompetence. The analysis found surgery to be associated with a non-statistically significant reduction in varicose vein recurrence when compared to the other modalities, but with less early disability and pain associated with the less invasive techniques.[84]

36.9 CONCLUSIONS

The clinical consequences of saphenous vein incompetence is associated with significant medical consequences demonstrated as a negative impact on patient quality of life, ability to work, and costs of medical care. Venous duplex imaging is required to determine the etiology, anatomic distribution, and pathophysiology of the reflux that is present. The rapid rise of less invasive means to ablate the saphenous system and therefore eliminate reflux has relegated open surgery to a niche procedure in locales with finances insufficient to provide less invasive options. However, there are situations in which the cost of care, patient preference, and/or anatomic considerations reconfirm the open operation as a useful technique for the care of patients with saphenous insufficiency. Saphenous ablation—whatever form is taken to accomplish it—does provide patient relief that is better than compression alone and is proven to aid in the care of patients with advanced disease, especially those with venous ulceration. Knowledge of the anatomic variability of the lower leg superficial venous system is required for optimal open surgical results. The results of open saphenous surgery are quite comparable and, in some cases, superior to less invasive procedures in terms of long-term benefit, but such surgery is less well tolerated by patients and has higher morbidity in the short term. Current guidelines on surgical treatment of the incompetent varicose veins are listed below. Further guidelines on saphenous ablation in patients with venous ulcers are listed in Chapter 52.

Guidelines 4.8.0 of the American Venous Forum on the surgical treatment of the incompetent saphenous vein

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.8.1	For treatment of the incompetent saphenous vein in association with symptomatic varicose veins, we recommend saphenous vein ablation over compression therapy for appropriate candidates.	1	B
4.8.2	For treatment of the incompetent great saphenous vein in association with symptomatic varicose veins, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee.	2	B
4.8.3	For the treatment of the incompetent small saphenous vein associated with symptomatic various veins, we suggest high ligation at the knee crease 3–5 cm distal to the saphenopopliteal junction and selective stripping of the vein.	2	B
4.8.4	To decrease the risk of infection during open saphenous surgery, we recommend prophylactic systemic antibiotics.	1	B
4.8.5	To reduce swelling, hematoma formation, and pain, we recommend post-operative compression for a period of 1 week.	1	B

Note: For guidelines on saphenous and perforator ablation in the setting of venous ulcers, see Chapter 52.

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● = Key primary paper
★ = Major review article
◆ = Formal publication of a management guideline

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Radiofrequency treatment of the incompetent saphenous vein

ALAN M. DIETZEK AND STUART BLACKWOOD

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37.1 INTRODUCTION

Chronic venous disease (CVD) is one of the most common vascular diseases to affect a patient's health and quality of life (QoL). It is estimated that the prevalence of varicose veins is as high as 20%–60%[1] and that over 25 million Americans are concerned by chronic venous insufficiency (CVI).[2] The symptoms and signs of this disease are varied, and range from mild to disabling. They include varicose veins, leg swelling, skin discoloration, thickening of the skin, and, in the most advanced cases, ulceration. Consequently, CVD and its more severe form, CVI, have resulted in U.S. annual health care expenditures in the billions of dollars.[3]

Reflux in the great saphenous vein (GSV) is one of the most frequent causes of primary CVD. Prior to endovenous ablation, surgical stripping of the GSV was the accepted standard for the management of symptomatic superficial venous insufficiency. This intervention was associated with significant morbidity, post-operative pain, and prolonged recovery times. Radiofrequency ablation (RFA) for treatment of the incompetent saphenous vein was first introduced in Europe in 1998 and approved for use in the United States by the Food and Drug Administration (FDA) in 1999. RFA is a minimally invasive alternative to saphenous vein ligation and stripping. Since its introduction, the procedure has become increasingly popular as it offers equal efficacy, decreased morbidity, a milder recovery course, and greater patient satisfaction when compared to saphenous vein stripping.

Following stripping and ligation of the GSV at the saphenofemoral junction (SFJ), varicose vein recurrence affects 15%–30% of patients. The primary cause is neovascularization.[4] Following endovenous ablation via RFA, the neovascularization frequency is much reduced.[5,6] Pichot et al. performed detailed ultrasonographic analysis of the GSV in patients receiving RFA over a 2-year period. The most common observation at the SFJ was a short patent stump conducting anterograde tributary flow through the SFJ with an obliterated GSV trunk.[6] This patent stump is believed to serve as a conduit to preserve the normal physiologic flow from one or more patent tributaries such as those draining blood from abdominal and pudendal areas. Following RFA of the GSV, it has become clear that reflux at the SFJ can be eliminated without groin dissection or ligation of second- and third-order tributary branches. Preservation of such physiologic flow has been considered to be an advantage of endovenous procedures over traditional vein stripping as it causes less hemodynamic disturbance, which is thought to be one of the factors responsible for stimulating neovascularization following vein stripping.

Over the course of the past 15 years, there have been several randomized trials which have compared endovenous RFA with surgical stripping or endovenous laser therapy (EVLT) of the saphenous vein. All have demonstrated RFA to have equal or better outcomes, and will be reviewed in greater detail later in this chapter.[7–15] Until very recently, there has been only one RFA device available in the United States and approved by the FDA for use in superficial veins, albeit with modifications and different manufacturers over time (Closure and ClosurePlus™ [CP]—VNUS Medical Technologies, San Jose, CA; and ClosureFast™ [CLF]—Venefit™ Covidien, Mansfield, MA). All references to RFA in

this chapter are concerning these devices. At present, other RFA devices for use in saphenous vein ablation are under different phases of FDA evaluation. They will be briefly reviewed.

37.2 THE CLOSURE SYSTEM AND RFA PROCEDURE

37.2.1 Mechanism of action

The first-generation RFA catheters (CP) utilized bipolar electrodes at the tip of the catheter to apply to the vein wall an alternating electrical current at a frequency of 200–1200 kHz (Figure 37.1). The vein wall acted as a conductor with a known resistance, thus converting radiofrequency (RF) energy into thermal energy, resulting in heating of the vein wall. This caused denaturation of the collagen in the vein wall with resultant contraction of the vessel and obliteration of the vessel lumen. To transfer electrical current, there had to be good apposition of the catheter electrodes to the intraluminal vein wall.[16] With the RF energy activated, the catheter was withdrawn slowly (2–3 cm/minute) in order to ensure an adequate treatment to the vein wall. A thermocouple located on the electrodes monitored the temperature and provided continuous feedback to a generator, which, in turn, adjusted power delivery to maintain a temperature of either 85°C or 90°C. With widely accepted clinical success notwithstanding, the first-generation CP catheter suffered from very slow treatment times in comparison to laser ablation. Because of the necessarily slow catheter pullback speeds and not infrequent generator "shut-offs" when impedance surpassed a predetermined threshold, treatment times would often exceed 30 minutes. Additionally, results were occasionally inconsistent because of poor contact between the electrodes and the vein wall, with either ineffective closure of the saphenous vein or early recanalization.

In 2007, the current-generation CLF segmental ablation catheter replaced the bipolar electrode catheter. The CLF catheter has a 7-cm heating element at its tip which is heated to 1200°C by RF energy supplied through a RF generator (RFG) (Figure 37.2). During energy delivery, the catheter remains stationary for a period of 20 seconds. By conductive heat transfer, the vein wall segment in contact with the 7-cm catheter heating element reaches a temperature of 100–110°C. The catheter is then moved distally in 6.5-cm increments, thus achieving a 0.5-cm treatment overlap zone at each treated segment. This segmental technique significantly increases the procedure speed and effectiveness in part by eliminating operator variability. A 45-cm vein can be treated in 3–5 minutes, on par with the fastest endovenous laser protocol. A shorter 3-cm heating element design is available for shorter vein segments (Figure 37.2). The manufacturer currently produces a 60-cm length catheter for both sizes of heating elements and a longer 100-cm catheter option for the 7-cm heating element only.

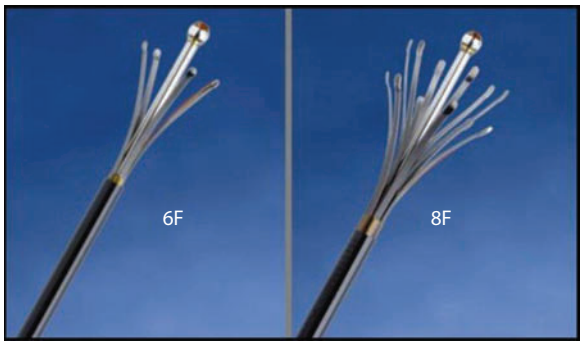

Figure 37.1 Bipolar heating element design of the original ClosurePlus device.

Although there have been significant changes in design since the first RFA device, the present segmental ablation catheter maintains the temperature feedback loop and thus controlled energy delivery. Impedance is monitored but not displayed. Displayed on the RFG are the temperature at the vein wall and the amount of power in watts required. High power (watts) may indicate poor contact with the vein wall, which is likely to occur with less-than-optimal exsanguination or poor vein compression onto the catheter. In this circumstance, the generator will display an advisory message prompting technical correction. The RFG (Figure 37.3) also allows close control of the temperature range to avoid undesirable effects of overheating such as boiling, coagulation, vaporization, and carbonization of the tissues. The procedural steps are quite simple, and, most importantly, there is no need for continuous pullback of the catheter during energy delivery. This eliminates most of the variability in energy delivery to the vein wall, thus ensuring consistent treatment outcomes.[17]

The endovenous RFA procedure is performed using both local anesthesia for vein access and perivenous tumescent anesthesia with or without sedation depending upon physician practice and patient anxiety. Percutaneous vein access is performed under duplex ultrasound guidance. Thermal damage to the vein wall leads to thrombosis and fibrosis of the vein and a durable closure of the vein over time. Less-than-optimal contact between the catheter and vein wall such as is seen with inappropriate treatment of aneurysmal segments of vein (>3 cm in diameter) using RFA may lead to superficial phlebitis in the short term and treatment failure in the long term, with restoration of flow and suboptimal clinical outcomes.

37.2.2 Technique of saphenous ablation: Using the segmental ablation catheter

Once venous access is obtained, a 7-Fr sheath is placed and the catheter is inserted through the sheath into the vein to be treated (Figure 37.4a and 37.4b). Any resistance to catheter passage through the vein should prompt alternative strategies to navigate venous tortuosity, as this will avoid patient discomfort and possible vein perforation.

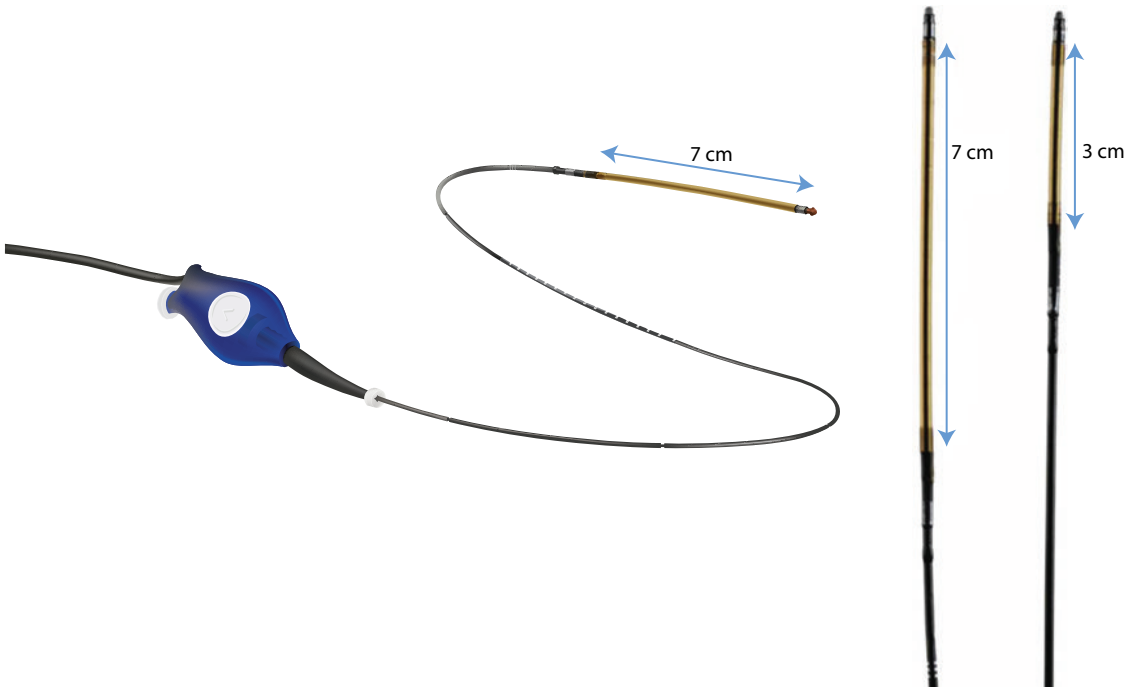

Figure 37.2 7- and 3-cm long heating elements of the newer ClosureFast segmental ablation catheter.

Techniques we employ routinely for this situation include gentle compression on the tissues over or proximal to the catheter tip to change its direction and or straightening or bending of the extremity to change the position of the vein. If these maneuvers fail either, a standard 0.025-inch or 0.018-inch guidewire will generally prove successful at crossing the tortuous segment. If all of these measures are unsuccessful, a second sheath is placed proximal to the tortuous vein segment. Together, these measures add no significant morbidity and very little time to the procedure. Once the entire vein is traversed with the RF catheter, the tip is pulled back to a minimum of 2 cm from the SFJ. When treating the small saphenous vein (SSV), the catheter tip is positioned at the point where the vein begins to turn down in its course towards the saphenopopliteal junction. This is usually significantly more than 2 cm from the junction. With the earlier-generation CP catheters, the tip was often positioned closer to the junction with either the femoral or popliteal veins because there was less forward heating with this catheter than the present CLF catheter (Figure 37.4c and 37.4f).

Figure 37.3 The new ClosureFast catheter and radiofrequency generator.

The key to the performance of almost all in-office vein procedures, other than sclerotherapy, is the use of tumescent anesthesia. This enables the delivery of large amounts of dilute anesthesia without the risk of lidocaine toxicity. Consequently, large treatment areas can be anesthetized for treatment. With the RF procedure, tumescent anesthesia is delivered into the perivenous space (Figure 37.4d through 37.4f). Adequate tumescence (approximately 10 mL/cm vein) is important for three reasons: first, it provides vein compression, which improves the vein wall to catheter contact that is necessary for RF ablation; second, it provides anesthesia and thereby improves patient comfort; and third, it acts as a heat sink around the treated vein, preventing injury to the surrounding skin and soft tissues and nerves. This is reflected in the extremely low incidence of skin burns and paresthesiae discussed later in this chapter. With the CLF catheter, energy delivery can be initiated by pressing a button on the catheter handle rather than on the generator (Figure 37.4g and 37.4i). This allows the operator to initiate treatment and eliminates the need for an assistant for this task as was necessary with earlier-generation

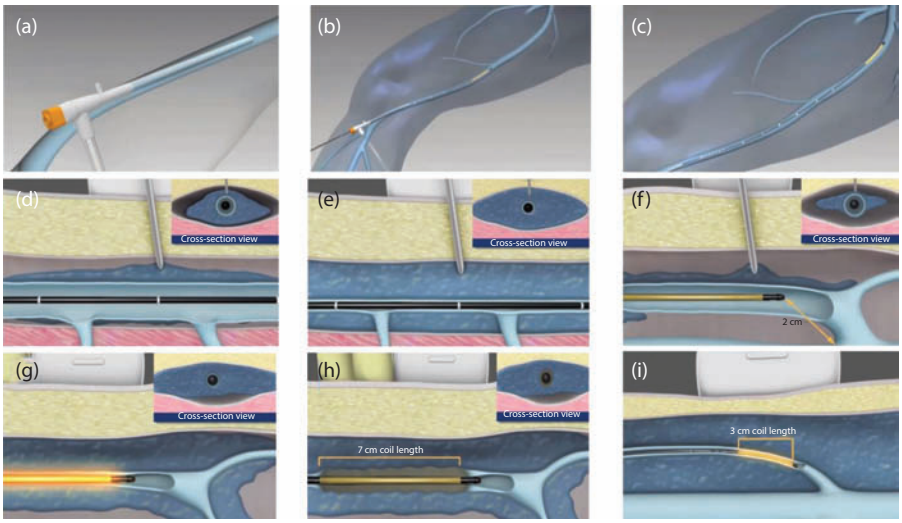

Figure 37.4 **(a–i)** Procedure technique of radiofrequency ablation using the segmental ablation catheter.

catheters. External compression over the heating element is important as an additional measure to bring the vein wall into contact with the heating element of the catheter, and can be achieved with most duplex probes (Figure 37.4g and 37.4h). With the default setting, the generator automatically terminates the energy delivery after 20 seconds. The catheter is then moved to the next 6.5-cm segment for treatment. Shaft markers on the catheter guide the catheter repositioning during the treatment. An additional energy cycle is applied at the first vein segment near the junction. We will also apply additional treatment cycles to dilated vein segments and to those areas with significant tributaries. After the catheter is moved out of the treatment zone, it should not be re-advanced into an acutely treated area. Immediate vein wall thickening and vein occlusion are expected on completion of the treatment.

37.2.3 Post-operative care

Patients are advised to ambulate immediately after the procedure, and it has been our practice to have patients wear compression hose for a minimum of 1 week, although admittedly there is little evidence to support this protocol. A completion duplex scan is then performed within 72 hours to assess for thrombus extension from the recently treated superficial vein into the deep system. The use of routine post-operative duplex scanning, however, is an area of some controversy as well, because of the very low incidence of deep vein thrombosis (DVT) following these procedures and the abundant evidence that most of these thrombus extensions resolve without treatment. Thus, why perform any testing? At the present time, we do so for medicolegal reasons. It has been suggested that most of these thrombus extensions are not true DVTs at all. In 2006, Kabnick et al. identified a new clinical entity named endovenous heat-induced thrombosis (EHIT) and suggested a protocol for treatment based on the degree of thrombus extension into the deep venous system.[18] Subsequent physician awareness and treatment modifications have reduced the incidence of clinically relevant EHIT after RFA to between 1% and 2%,[19] with symptomatic pulmonary embolism rates reportedly far lower at 0.03%.[20] New literature is emerging that suggests that the strategy of routine post-operative duplex may become obsolete as it appears to be cost-ineffective.[21]

37.3 RF PROCEDURE OUTCOMES

37.3.1 Saphenous vein occlusion

RFA treatment efficacy has been well documented, with short- to mid-term efficacy rates of 90%–100%.[7,8,12,14,22–29] The longest published follow-up results are from the VNUS Clinical Registry using first-generation bipolar technology and those from the recently reported latest-generation RF segmental ablation ClosureFast Registry. Both registries followed patients for up to 5 years and demonstrated vein occlusion rates of 87% and 94.9% and reflux free rates of 84% and 91.9%, respectively.[30,31]

Treatment efficacy with segmental ablation on large-diameter veins has also been evaluated, but only in the short term and in one publication.[32] In this study, the authors retrospectively reviewed their 6-month saphenous vein occlusion rates in veins ≤12 mm (mean: 8 ±2 mm) against veins >12 mm (mean: 17 ±4 mm) with the use of the segmental ablation catheter. Both groups achieved 100% vein occlusion.

37.3.2 Clinical outcomes (quality of life and patient satisfaction)

The treatment of saphenous vein reflux by RFA is less painful for patients than conventional surgery and patients recover faster. RFA appears to confer a mild benefit compared to laser in the early post-operative period, mostly related to pain,

Table 37.1 Effectiveness of radiofrequency ablation for varicose vein symptoms, impact on quality of life, and patient satisfaction with radiofrequency ablation

Study	Treatment (limbs)	Early occlusion rate	Maximum follow-up	Radiographic or clinical recurrence[a]	Patient satisfaction (QoL)[b]	
Rautio et al.[7]	CP (15)	NR	8 weeks	NR	Favored RFA at follow-up	8 weeks
	S&L (13)					
Lurie et al.[8]	CP (45)	95%	4 months	Not significantly different		3 and 7 days
	S&L (36)	100%				
Lurie et al.[24c]	CP (36)	NR	2 years			1 and 2 years
	S&L (29)	NR				
Perala et al.[9d]	CP (15)	NR	3 years		NR	
	S&L (13)	NR				
Hinchliffe et al.[10]	CP (16)	81%	6 weeks			
	S&L (16)	88%				
Kianifard et al.[11]	CP (55)	100%	1 year			
	S&L (55)	100%				
Stötter et al.[14]	CP (20)	95%	1 year		Favored RFA	
	S&L (20)	100%				
Subramonia et al.[13]	CP (47)	100%	5 weeks	NR		
	S&L (41)	83%				
Helmy ElKaffas et al.[12]	CP (90)	94.5%	2 years	Not significantly different	NR	
	S&L (90)	100%				

Note: QoL: quality of life; RFA: radiofrequency ablation; S&L: stripping and ligation; CP: ClosurePlus; NR: not reported.

[a] Venous Severity Improvements based on CEAP, VCSS.

[b] Survey methods included CIVIQ-2 (Chronic Venous Insufficiency Questionnaire-2), RAND-2 (RAND Short Form 36), AVVQ (Aberdeen Varicose Vein Questionnaire), EQ-5D (EuroQuol 5-Dimensional), and SF-12 (Short Form 12).

[c] Follow-up study of Lurie et al.[8]

[d] Follow-up study of Rautio et al.[7]

although this is generally short lived. Table 37.1 summarizes patient satisfaction based on randomized controlled trials comparing RFA to surgery or endovenous laser. Rautio et al. reported significantly less post-operative pain, quantified with a visual analog scale (VAS), in the RF group compared to the stripping group at rest ($P = 0.017$), in a standing position ($P = 0.026$), and when walking ($P = 0.036$), with the greatest differences at the 5th to the 14th post-operative day.[7] The analgesic needed in the RF patients was 0.4 ± 0.49 tablets of 600 mg ibuprofen per day, and in the stripping group was 1.30 ± 1.09 tablets ($P = 0.004$). Sick leaves were also significantly shorter in the RF group (6.5 ± 3.3 vs. 15.6 ± 6.0 days, $P < 0.001$), and physical function was restored faster in the RF patients, measured with RAND short form 36 QoL questionnaires. A multicenter study from five centers in the United States and Europe (EVOLVeS study) confirmed significant advantages of the closure procedure compared to conventional surgery, with less post-operative pain for up to 3 weeks, earlier return to activities and work, and better cosmetic results. Patients returned to either normal daily activities or to work at a mean time of 3 days, 8 days earlier than patients treated with surgery.[8] A 2-year follow-up study showed that QoL scores were superior in the RFA group at 1 year, and remained significantly better 2 years after treatment.[24] Similar clinical outcomes were observed at 2 years with RFA and surgery, as assessed by CEAP classification and Venous Clinical Severity Score (VCSS). The newer CLF catheter appears to confer the same mild convalescence as the previous generation catheters. The RECOVERY study compared patient recovery following saphenous RF versus EVLT with a 980-nm laser fiber in the immediate post-operative period with respect to pain, bruising, and pre-operative and post-operative QoL using the Chronic Venous Insufficiency Questionnaire-2 (CIVIQ-2) tool. Patients treated with RF did statistically better than EVLT patients in categories of pain, bruising, and QoL in the early post-operative period. This benefit disappeared at 30 days.[29] There was a greater reduction in VCSS at 48 hours (4.7 vs. 6.2), 1 week (4.2 vs. 5.9), and 2 weeks (4.0 vs. 5.3) for RFA as compared to laser. Reduced pain and post-operative edema were thought to be the main contributing factors to the improved VCSS ratings. The difference in VCSS ratings was also limited to 30 days.[8,24,29]

37.4 PROCEDURE SAFETY AND COMPLICATIONS

RFA was the first endovenous ablation technology available for wide clinical use. The procedure's safety was carefully investigated and reported in early and mid-term

publications.[7,8,14,23–26] A clinical registry was established in 1998 to monitor the procedure's safety and document treatment outcomes. As experience accumulated, a number of procedural modifications were implemented to minimize potential risks and increase treatment efficacy. A systematic review conducted by the Ontario Ministry of Health in 2011 found that approximately 2.9% (105/3664) of patients who undergo RFA of the saphenous vein will have a major adverse event.[33] However, of these patients, only 13.7% (504) were treated with the newer CLF device. Newer studies using the CLF catheter report complication rates of <2%, with most complications being minor, such as skin burns, paresthesiae, and thrombophlebitis (Table 37.2).

37.4.1 Superficial venous thrombophlebitis

Phlebitis can occur with the closure procedure as a result of residual blood trapped within vein segments. It is occasionally seen as a tender, erythematous, or ecchymotic band over the treated vein in the distal thigh and is self-limiting, with treatment needed only for symptom relief. In a comparative study of 667 RFA procedures, the rate of superficial venous thrombophlebitis (SVT) was 15% for the original CP catheter and 10% for the CLF catheter.[34] Similar rates of SVT were observed in a large randomized controlled trial comparing 500 patients treated with EVLT, RFA, foam sclerotherapy, and stripping of the GSV. SVT occurred in 12 patients (9.6%) undergoing RFA.[35] Other studies have found a lesser degree of phlebitis after RFA and a reduced incidence with the newer-generation catheter.[32,36] Calcagno et al. reported a 4% rate of clinically significant phlebitis after RFA,[32] and an industry-sponsored multicenter prospective study identified only two out of 254 limbs (0.8%) that had developed clinically significant SVT after ablation of the GSV using the CLF catheter.[36]

37.4.2 Bruises and burns

With the development of RFA, it became evident that thermal damage would be a major cause of side effects (major or minor). In early studies, full-thickness skin burns occurred in between 2%[23] and 4%[26] of treated limbs. Tumescent infiltration was introduced to address the skin burn risk. After the implementation of tumescent anesthesia, and with appropriate patient selection (see Section 37.5), skin burns are rarely observed today. Bruising is less frequent after RFA compared to stripping procedures. In one small randomized trial, 16 patients with bilateral recurrent GSV incompetence after high ligation were randomized to RFA on one leg versus conventional surgery with stripping of the GSV on the other leg. Bruising scores were measured using patient VAS, as well as digital image analysis software, to calculate the percentage of leg discolored after treatment. After conventional surgery, 21.8% of the leg was bruised compared to 11.9% ($P = 0.02$) with RFA using the CP catheter; in addition, patients also perceived less bruising based on a VAS.[10] More recently, this issue was re-examined using the newer CLF catheter in the RECOVERY study. Moderate to severe ecchymosis defined as >25% of the treated surface area occurred in one out of 46 (2.2%) of patients using the CLF catheter compared to 21 out of 41 (51.30%) patients treated with a 980-nm laser.[29]

37.4.3 Nerve damage and paresthesiae

Prior to the routine implementation of tumescent infiltration, paresthesia—often described as focal hypoesthesia—was reported in approximately 9%–19% of limbs within 1 week of the procedure, and this gradually resolved over time.[7,8,14,22–27] It must be noted that not all paresthesiae resolve; the Closure Study Group found a 15% rate of paresthesiae at 1 week (43/286), of which 5.6% (8/142) persisted at the 2-year follow-up.[30] Perivenous tumescent infiltration effectively eliminates this complication.[24] Limiting treatment to the above-knee saphenous vein also markedly decreases the risk of paresthesia by avoiding potential thermal injury to the saphenous nerve, which most often lies adjacent to the saphenous vein below the knee.[26] If the saphenous vein is to be treated below the knee, great care should be taken to administer adequate tumescent anesthetic and, if possible, to identify the saphenous nerve with duplex and separate it from the vein with tumescence.[5]

Table 37.2 Safety profile of radiofrequency ablation

Complication	ClosurePlus (selected studies)	ClosureFast (selected studies)
SVT	0.8%–15% [30,34–36]	0%–10% [32,34–37]
DVT	0%–3.5% [7,8,23,26,33,34] and 16%[a] [38]	0%–1% [34]
PE	0.02% [26]	0%–rare [33]
Thermal injury	0%–4% [26,33]	0% [33]
Nerve damage and paresthesiae (early and late)	9%–19% [7,8,14,22–27]	1%–3.4% [32,36,39]
Wound infections	0%–rare [33]	0%–rare [29,33]
Bleeding	0%–rare [33]	0%–rare [33]

Note: SVT: superficial venous thrombophlebitis; DVT: deep vein thrombosis; PE: pulmonary embolism.

[a] Most studies report 0%–2% rates, with one outlier study.

37.4.4 DVT and pulmonary embolism

DVT is always a potential risk of any surgical procedure. In a retrospective study, the incidence of DVT after open varicose vein surgery was approximately 5.3% in 377 patients.[40] The majority of DVTs in this study were in the calf and had no evidence of propagation or embolism. The situation is very different for thrombosis occurring in the setting of RFA. In the case of endovascular obliteration, thrombus can originate from the treated superficial vein and extend into the much larger femoral venous system. Careful catheter tip positioning is crucial and should be >2 cm distal to the SFJ and the ostium of the superficial epigastric tributary. This minimizes the risk of DVT and preserves physiologic blood flow from the tributary. Immediate and sufficient ambulation is emphasized, and routine ultrasound scanning within 72 hours post-operatively to rule out DVT is still recommended, although this practice is controversial, as discussed previously. DVT rates are reported to be 0%–2% in the majority of published series which are, for the most part, with the use of the earlier-generation bipolar catheters.[7,8,14,22–28] In one series, the DVT rate was 16.4% (12 of 73), but this is an exception from the experiences of others.[38] In a comparative study, there were no cases of DVT detected in those patients treated with the segmental ablation CLF catheter, whereas DVT occurred in 3.5% of cases treated with the previous-generation bipolar CP catheters.[34]

37.4.5 Wound infection

Wound infections are very rare complications of endovenous ablative procedures. In the RECOVERY study, for example, no patient in either group (laser vs. RFA) developed a wound infection.[29]

37.4.6 Bleeding and hematoma

Risk of bleeding appears to be small and not clinically significant in patients undergoing RFA of the saphenous vein. If there is any bleeding, it is minor and self-limiting. In one relatively small, non-randomized, prospective study, periprocedural bleeding in patients who underwent either EVLT or RFA while on anticoagulation ($n = 88$) was compared to that in a control group not on anticoagulation ($n = 92$). The authors found that the only group with a statistically significantly higher rate of bleeding was the group undergoing RFA while on "triple therapy" using aspirin, clopidogrel, and warfarin. No major bleeding occurred. The study was underpowered to detect a difference between the two different types of ablation techniques.[41]

37.5 CONTRAINDICATIONS TO RFA

Despite great enthusiasm regarding RFA for the treatment of GSV reflux and varicose veins, there are several important scenarios in which RFA might be not optimal or is contraindicated. Small-diameter (<2.5 mm) or tortuous veins, scarred veins, thrombosed veins, and aneurysmal veins may be contraindications for the RFA procedure, all for purely mechanical reasons. Acute thrombosis of the saphenous vein is a contraindication to RFA as the catheter should not be advanced directly through acute thrombus. In the case of small or tortuous veins, the catheter may not be able to traverse the lumen. Large aneurysmal segments of vein will not allow for adequate apposition between the vein wall and the heating element of the catheter. When treated with RFA, thrombus formation and SVT often occur. Therefore, aneurysmal segments are best managed by surgical excision. Treatment with RFA of diffusely enlarged saphenous veins of >2 cm is very uncommon and prone to fail unless certain measures are taken. Techniques used to overcome this problem include compression with ultrasound during heating, use of additional tumescence, Esmark exsanguination of the leg, adoption of the Trendelenburg position, and/or leg elevation throughout the procedure. In general, we would not recommend RFA for veins >2.5 cm in diameter. Failure to achieve satisfactory compression should prompt the surgeon to perform an alternative endovenous technique or high ligation and stripping of the saphenous vein. Patients who have previous chronic SVT of the saphenous vein who have had excessive scarring and synechiae formation within the vein may not be candidates simply because the catheter may not be able to pass through these areas. Another relative contraindication to RFA is a saphenous vein which is very superficial. In this circumstance, adequate tumescent anesthesia will prevent a skin burn, but will usually not prevent staining and dimpling of the overlying skin. This should be discussed in detail with the patient prior to the procedure and a surgical option should be offered. Other contraindications to RFA include pregnancy, inability to ambulate, poor general health, and acute DVT.

37.6 RECURRENCE RATES AND TREATMENT FAILURE

Treatment failure can be divided into two groups: hemodynamic failure and clinical failure. Early hemodynamic failure following surgical stripping is due to incomplete saphenous vein removal, whereas in the case of RFA, this is due to inadequate vein ablation. Delayed hemodynamic failure after surgery is primarily due to neovascularization and is recognized as one of the principal causes of recurrent reflux and disease progression after stripping of the saphenous vein.[42–45] It occurs in more than 50% of limbs with clinical recurrence and accounts for 85% of recurrent SFJ reflux.[46,47] Furthermore, 90% of observed neovascularization was already evident at 2 years.[47,48] Neovascularization was reported in one (2.8%) RFA limb and four (13.8%) stripped limbs ($P < 0.05$) in the EVOLVeS study.[8] A lower incidence of neovascularization with RFA was also reported by Pichot et al.[6] They carefully studied 63 limbs with a detailed ultrasound scan protocol and found no evidence of neovascularization at 2 years after RF treatment. Two major advantages of RFA that are thought to account for the low

incidence of neovascularization are no incision and surgical dissection of the groin resulting in angiogenic stimuli and minimal hemodynamic disturbance thanks to preservation of physiologic epigastric flow through the SFJ. Subsequent to RFA, recanalization of the vein is most often the culprit, but the actual recurrence of SFJ reflux is a more objective measure and provides important hemodynamic information that permits the detection and possible prediction of clinical recurrence. Reflux in tributary veins or perforator veins can also cause hemodynamic failure. Clinical failure occurs when symptoms do not resolve or recur, and is usually associated with the reappearance of varicose veins. Varicose vein recurrence rates after vein stripping have been reported between at 20% and 50% at 2–5 years,[4,46–51] and up to 70% of patients have some degree of recurrent symptoms by 10 years.[52] However, the varicose vein recurrence rate can be affected by several factors, including the completeness of varicosity removal at the time of initial surgery and the examiner's subjectivity. Interestingly, 5-year data from the VNUS Closure Registry revealed that hemodynamic failure did not result in symptom recurrence in most patients.[28] In a more recent study, however, symptom recurrence (relative risk [RR]: 2.75) and need for additional procedures (RR: 3.96) did correlate with recanalization as identified by duplex, but in the 17 out of 249 limbs with recanalization, no anatomic or patient-specific risk factors were found.[53]

37.7 OTHER RF DEVICES

37.7.1 RF-induced thermotherapy

RF-induced thermotherapy (RFiTT; Celon AG, Medical Instruments, Teltow, Germany) is a technique which utilizes bipolar RF via resistive heating of the vein wall. In the Laser and RFA Ablation (LARA) study, RFiTT ($n = 40$) was compared to EVLT with an 810-nm laser ($n = 34$). Occlusion was 95% in both groups at 10 days and 74% and 78% (P = non-significant) at 3 months in the ablation and laser groups, respectively. In patients who were their own controls, as they had bilateral disease with one leg treated by laser and other by RFiTT, post-operative pain and bruising were significantly less in the RFiTT legs in the first 2 weeks.[54] A much larger prospective, non-randomized, multicenter study included 462 patients (569 GSVs), with follow-up at between 180 and 360 days (mean: 290 ± 84 days). Complete occlusion was accomplished in 98.4% of patients at a mean follow-up of 290 days when experienced operators performed the procedure.[55]

37.7.2 F Care Systems: Endovenous RF

Endovenous RF (EVRF; F Care Systems, Antwerp, Belgium) is a monopolar RF device which applies continuous energy for ablation of the saphenous vein using the CR45i catheter at 4 MHz (25 W). In one unpublished, small, prospective, non-randomized study, 30 patients (54 GSVs) were treated with this technique. At the 1-month follow-up, 92% of patients had complete occlusion, 6% had partial occlusion without reflux, and 2% had partial occlusion with reflux.[56] Szabó (unpublished data) treated 313 patients (276 GSVs) in a single-center, prospective study, with early and mid-term results showing complete occlusion in 99% (275/276) of veins at 1 month. Patient satisfaction was 99% and there were no major complications such as DVT, thermal burns, or nerve injury.[57]

37.7.3 Other endovenous or minimally invasive treatment options

While saphenous RFA combines the benefits of a minimally invasive procedure with excellent clinical outcomes, new endovenous modalities continue to challenge RFA as the preferred technique for the treatment of the incompetent, symptomatic saphenous vein. These include tumescentless mechanochemical endovenous ablation (MOCA), chemical and glue ablations, and higher-wavelength laser fibers, covered laser fibers, and minimally invasive conventional surgical techniques. In one recent small, prospective study of 38 patients using glue—cyanoacrylate embolization (CAE) with the VenaSeal Sapheon Closure System (Sapheon, Inc., Morrisville, NC)—a 92% target vein closure rate was achieved without the need for tumescent anesthesia or post-operative compression stockings. These outcomes were maintained at the 2-year follow-up.[58] A randomized controlled trial published at the time of the writing of this chapter describes the immediate 3-month follow-up results of CAE ($n = 108$) versus segmental RFA ($n = 114$). The study showed non-inferiority of CAE to RFA, an adequate safety profile, less peri-procedural ecchymosis, and no need for tumescent anesthesia.[59] There was no statistical advantage to RFA where peri-procedural pain scores were concerned.

MOCA techniques employing the Clarivein Catheter (Vascular Insights, Madison, CT) use mechanical injury to the vein endothelium in combination with an infused liquid sclerosant. Early series have reported decreased pain and bruising with MOCA, with comparative vein occlusion rates to the CLF segmental ablation catheter.[60,61] More definitive answers as to whether these devices have equal efficacy and decreased pain compared to RFA will come from two randomized trials currently enrolling patients to compare MOCA with segmental RFA. These are the Mechanochemical Endovenous Ablation versus Radiofrequency Ablation in the Treatment of Primary Great Saphenous Vein Incompetence (MARADONA) study for the GSV[62] and the Mechanochemical Endovenous Ablation versus Radiofrequency Ablation in the Treatment of Primary Small Saphenous Vein Insufficiency (MESSI) study for the SSV.[63] These two trials are intended to compare peri-procedural pain and the efficacy of the MOCA compared with RFA.

37.8 CONCLUSIONS

Endovenous ablation is now arguably the standard for the treatment of saphenous vein incompetence. The evidence for the efficacy—both clinical and anatomic—of RFA of the GSV is quite robust and is derived from peer-reviewed journal articles including 14 randomized studies and their respective mid-term follow-up data. Nine of these studies compare RFA to open ligation and saphenous vein stripping[7–15] and five compare RFA to endovenous laser.[29,37,54,64,65] One trial compares results with all three major endovenous options (sclerotherapy, laser, and RFA) and conventional surgery.[35] These data have been systematically reviewed.[33,66] The most recent-generation RFA by segmental ablation has been rapidly adopted by clinicians because of its proven efficacy, short procedure times, and mild patient recovery profile as compared to both surgery and EVLT. Although there are now several additional modes of endovenous ablation, none have thus far been as thoroughly evaluated and well studied in the peer-reviewed literature as thermal RFA.

Guidelines 4.9.0 of the American Venous Forum on radiofrequency ablation of the incompetent saphenous vein

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.9.1	Endovenous thermal ablations (laser and radiofrequency ablations) are safe and effective, and we recommend them for the treatment of saphenous incompetence.[67]	1	B
4.9.2	Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery.[67]	1	B

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● = Major reviews
★ = Major primary papers
◆ = Clinical practice guidelines

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38

Laser treatment of the incompetent saphenous vein

NICK MORRISON

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38.1 INTRODUCTION

Lower extremity varicose vein disorders are most often associated with truncal venous insufficiency involving the saphenous system: the great saphenous vein (GSV), the small saphenous vein (SSV), and/or incompetent major tributaries or perforator veins. Varicose vein disorders have historically been treated with stripping of the saphenous vein and interruption/ligation and removal of the major tributary and perforator veins.[1] Since 1999, endovenous thermal ablation procedures have been found to be safe and effective methods of eliminating the proximal portion of the GSV, the SSV, and even tributary and perforating veins from the venous circulation, with faster recovery and better cosmetic results than stripping.[2,3] The currently available methods most commonly used to achieve thermal ablation of these incompetent veins are: the Venefit procedure using a radiofrequency (RF) catheter and generator (Medtronic, Minneapolis, MN); the RF-induced thermotherapy procedure using a bipolar RF system (Celon AF Medical Instruments, Teltow, Germany); the endovenous laser ablation procedure using a laser fiber and generator (various manufacturers); and the steam vein sclerosis procedure using heated vaporized water (CERMA SA, Archamps, France). The first three systems use electromagnetic energy, whereas the last utilizes steam. As with a stripping procedure, following these endovenous thermal ablation procedures, it is also necessary to treat any remaining incompetent portion of the GSV and/or SSV, perforating veins, and varicose tributaries, typically with either sclerotherapy and/or phlebectomy.[4] This chapter will primarily concern itself with endovenous laser ablation.

38.2 BACKGROUND

38.2.1 Animal studies

There are no reports of animal testing of laser technology in saphenous vein ablation prior to the initial publication of clinical case series. In 2002, Weiss[5] described *in vivo* caprine jugular veins treated with RF and pulsed-mode 810-nm diode lasers, with fluoroscopic and histologic examinations demonstrating extensive vein wall damage and frequent perforations with laser ablation compared with RF ablation. Min et al.[6] recorded temperatures outside the porcine vein during laser ablation with injected perivenous anesthetic (as is standard for human treatment), and demonstrated temperatures no higher than 40°C within 2 mm of the vein. Later, Fan and Anderson[7] treated blood-filled bovine saphenous veins with laser ablation, producing inconsistent transmural thermal damage with perforations, and concluded that direct thermal damage is the likely mechanism of vein wall destruction, not steam bubbles as had been previously postulated.[8]

38.2.2 Human studies

Prior to the publication of single-center case series reports of endovenous laser ablation of the incompetent saphenous vein, no multicenter clinical trials of the safety and efficacy of this procedure in humans were published. Since the initial published case series, some analyses of the pathophysiologic effects of laser ablation in humans have emerged. Proebstle et al.[9] reported on the heat injury seen in a GSV

that was removed following pulsed-mode laser ablation and found damage along the entire vein, noting more severe damage with perforations at the site of the laser pulses. Corcos et al.[10] described histopathologic changes in GSVs treated by laser ablation without perivenous anesthesia, in combination with saphenofemoral interruption and excision of a portion of vein for histologic examination. Full-thickness intimal thermal damage was seen in three-quarters of the veins, with transmural damage and/or perforation seen in a quarter of the veins. However, several veins had been subjected to more than one ablation period during treatment, thus limiting the importance of the findings.

Finally, in an attempt to quantify the risk of thermal damage to surrounding tissue during laser ablation after injection of perivenous anesthetic, Beale et al.[11] measured maximum temperatures of approximately 43°C in tissues 3–5 mm from the GSV during laser ablation. These findings were confirmed by Viarengo et al.[12]

38.3 PATIENT SELECTION

Inclusion criteria are: symptoms and physical signs of venous disorder; a duplex scan, performed by a fully qualified sonographer, showing a patent vein with reflux greater than 0.5 seconds; a patent deep venous system; a vein conducive to cannulation; and adequate patient mobility (Box 38.1).

Exclusion criteria are: arteriovenous malformations; restricted ambulation; acute infection; acute venous thrombosis[13]; and deep venous obstruction (Box 38.2).

As a surgeon's experience with endovenous ablation procedures increases, relative exclusion criteria may be relaxed, and patients with deep venous reflux, previous venous treatment, large-diameter veins, aneurysmal vein segments, vein tortuosity, or those on chronic anticoagulant therapy[14] or hormone-replacement therapy may be safely and successfully treated (Box 38.3).

Strong consideration of a thrombophilic condition should be given pre-operatively to patients with a history of deep vein thrombosis, recurrent episodes of acute superficial venous thrombophlebitis, multiple spontaneous abortions, or a strong family history of deep vein thrombosis or clotting disorders. The physician should be aware of the guidelines produced by the American College of Chest Physicians for the risk assessment for deep vein thrombosis,[15] as these guidelines may be helpful in selecting patients for laser ablation and in selecting which patients should receive prophylactic anticoagulation before undergoing endovenous laser ablation. While the risk of deep vein thrombosis following these procedures is low, such a potentially life-threatening outcome following the treatment of relatively benign disease could be catastrophic.

BOX 38.1: Clinical indications for laser ablation

- Superficial venous disorder
- Duplex scan with reflux >0.5 seconds
- Patent deep system
- Vein conducive to cannulation
- Adequate patient mobility

BOX 38.2: Exclusion criteria

- Arteriovenous malformation
- Restricted mobility
- Acute infection
- Acute venous thrombosis
- Deep venous obstruction

BOX 38.3: Relative exclusion criteria

- Deep venous reflux
- Previous treatment
- Large-diameter vein
- Anticoagulant therapy
- Hormone-replacement therapy
- Vein tortuosity
- Aneurysmal vein segments

38.4 TECHNOLOGY

Laser generators are available from various manufacturers, all of which appear to be effective at producing venous ablation (Table 38.1). Lower-wavelength lasers (up to 1300 nm) target hemoglobin as the primary chromophore. More recently, higher-wavelength lasers have been introduced which target water in the vein wall. Lower levels of energy are thus utilized in these systems, which results in less pain and bruising for patients.[16,17]

Each generator utilizes a laser fiber of varying sizes and designs. Earlier systems used bare-tipped fibers, while more recently, covered, centering, or radial fibers are more commonly used to reduce the risk of vein perforation and

Table 38.1 Laser generators

Wavelength	Name
810 nm	Varilase
940 nm	Dornier, Angiodynamics
980 nm	Angiodynamics
1320 nm	CoolTouch
1470 nm	Angiodynamics, Biolitec

subsequent patient bruising and discomfort by producing more uniform vein wall injury.[16–18]

38.5 PROCEDURE

Initially, endovenous laser ablation was performed in the hospital surgical or radiologic suite under general anesthesia or conscious sedation. However, over the past decade, these procedures have moved to the office setting under local anesthesia, with or without sedation. Furthermore, although the ablation procedure is often performed on veins other than saphenous veins, the technical details remain quite similar. The following description of the procedure for a saphenous vein (great or small) is given with the above in mind.

After obtaining informed consent, patients may be given an oral or intravenous sedative prior to the procedure. The patient is placed on an adjustable operating table (with Trendelenburg capability) in a patient gown and undergarments. The course of the saphenous vein, from the saphenofemoral or saphenopopliteal junction to the insertion site, is mapped by ultrasound. An insertion site is chosen to maximize treatment length, minimize risk of thermal damage to perivenous structures, and assure facile access. Most physicians will utilize a site in the distal thigh or proximal calf for the GSV, and the mid-calf to distal calf for the SSV.

If incompetent, the distal portion of the GSV or SSV saphenous veins are often not treated with endovenous laser ablation because of the increased risk of paresthesia from damage to the saphenous or sural nerve, which is in close proximity to the vein distally. However, distal thermal ablation is advocated by some investigators to eliminate the entire incompetent segment, with no or minimal increased incidence of nerve damage.[19] Access to the saphenous vein is generally gained using an ultrasound-guided, percutaneously placed needle. Venospasm will make access more difficult, so preventative maneuvers such as heating the access site locally, placing the patient in reverse Trendelenburg position, or the use of 2% nitropaste applied to the proposed insertion site prior to the sterile surgical preparation can be utilized to increase the chance of successful venous cannulation by dilating the vein and preventing venospasm. It is sometimes appropriate to choose a primary access site and a larger-diameter, secondary (back-up) access site in case access at the primary site is unsuccessful. Perivenous or intramural hematoma from unsuccessful attempts at cannulation may render that portion of the saphenous vein technically inaccessible, leading to the need for a secondary site. As the practitioner's ultrasound-guided technical skills improve, even small-diameter saphenous veins can be successfully cannulated.

The first attempt at cannulation of the vein is the most likely to be successful, so the insertion site should be carefully chosen to make access as ergonomically feasible as possible. Just below the knee, the GSV is relatively anterior. With the patient's operative leg externally rotated, this site becomes more advantageous than in the distal or mid-thigh (Figure 38.1). Even though the saphenous nerve is closer to the vein in this area, the laser sheath will protect this portion of vein, and thus limit the risk of thermal nerve damage.

Figure 38.1 Leg externally rotated with the insertion site covered with nitropaste.

The leg is cleansed from the most proximal treatment site to the insertion site with an antiseptic. The operative area is isolated with sterile drapes. After infiltration of local anesthetic at the insertion site, an introducer needle is inserted into the vein under ultrasound guidance. A micropuncture set can be used to gain access, and the caliber of sheath "stepped up" to accommodate the laser fiber. Using the Seldinger technique, after placement of a guidewire into the vein, a sheath is advanced into the vein over the guidewire until it is identified by ultrasound to be 3–4 cm below the saphenofemoral junction, or just inferior to the deep angulation of the SSV, where it will join the deep system. (Alternatively, the laser fiber may be advanced directly through the access needle and carefully guided to the same position without the use of the sheath and guidewire.) Occasionally, passage of the fiber may be impeded by vein tortuosity. Usually, straightening the leg or guiding the fiber by external compression/manipulation of the thigh will enable successful advancement. Segmental stenosis from previous sclerotherapy will also impede advancement of the fiber or guidewire. In this case, or if the vein is so tortuous as to not allow passage, a second, more proximal cannulation will enable treatment of first the proximal and then the distal segments of the saphenous vein.

Ultrasound-guided, high-volume, dilute anesthesia (0.05%–0.25% xylocaine with epinephrine/bicarbonate) is then injected into the saphenous compartment (Figure 38.2) along all but the most proximal portion of the treatment segment, completely surrounding the target vein to ensure adequate anesthetic effect, to compress the vein for better thermal effect, and to protect the perivenous structures from thermal damage. It is always necessary to clearly identify several important anatomic landmarks (Figure 38.3)

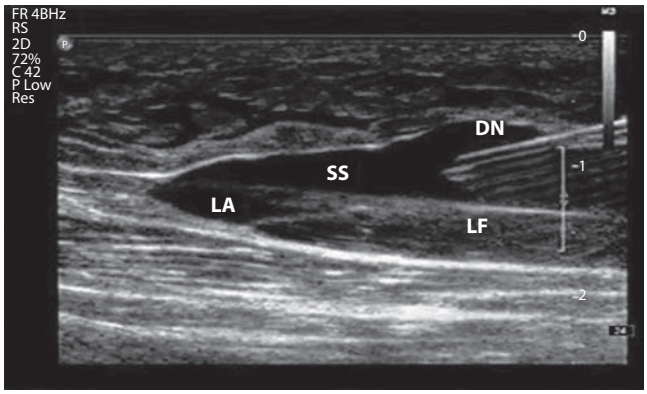

Figure 38.2 Longitudinal ultrasound image of dilute LA injected into SS. LA: local anesthesia; SS: saphenous sheath; DN: delivery needle; LF: laser fiber. (Courtesy of D. Neuhardt, Compudiagnostics.)

near the saphenofemoral junction prior to treatment to effect safe and adequate treatment of the GSV. However, one should be mindful that injection of the local anesthetic near the intended start of treatment will obscure these landmarks, severely limiting one's ability to see the safe final placement of the laser tip. The patient may then be placed in a Trendelenburg position to further empty the vein of residual blood, with the final position of the tip of the laser fiber confirmed by ultrasound (just inferior to the entrance of the superficial epigastric vein into the GSV—typically 2 cm below the saphenofemoral junction—for GSV treatment [Figure 38.4] and just inferior to the deep angulation of the SSV). The anesthetic solution is then injected into the tissue surrounding the proximal 3–4 cm of the saphenous vein.

The sheath and/or laser fiber are then withdrawn at a rate of 1–3 mm per second, more slowly for the proximal 10 cm and more quickly distally. The goal is to achieve successful ablation while at the same time minimizing the incidence of vein perforation, which is thought to contribute to post-operative

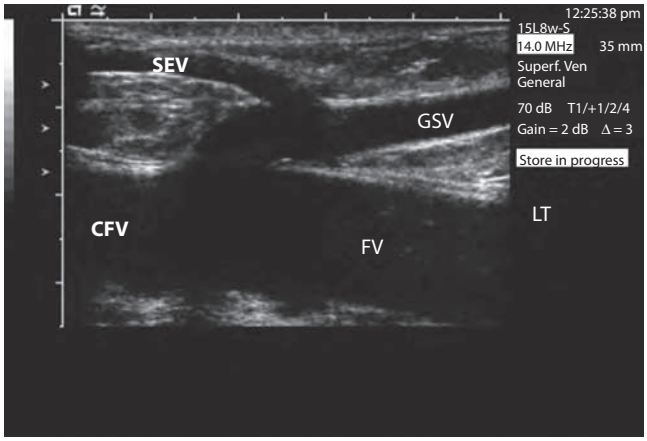

Figure 38.3 Longitudinal ultrasound image of the saphenofemoral junction area. SEV: superficial epigastric vein; GSV: great saphenous vein; CFV: common femoral vein; FV: femoral vein. (Courtesy of D. Neuhardt, Compudiagnostics.)

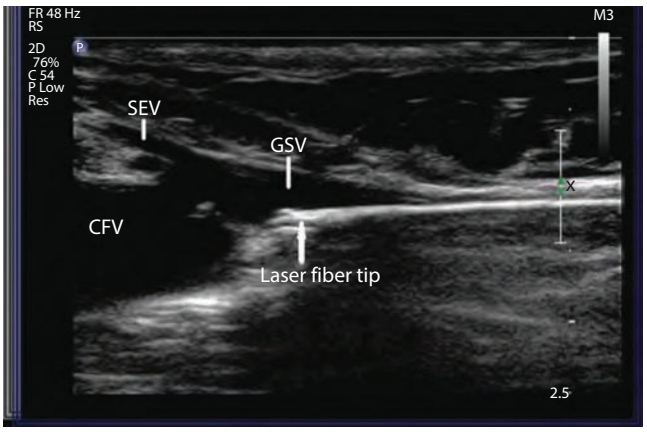

Figure 38.4 Longitudinal image of the saphenofemoral junction area with an appropriately positioned laser tip in the GSV. SEV: superficial epigastric vein; CFV: common femoral vein; GSV: great saphenous vein; laser tip: tip of the laser fiber just inferior to the entrance of the superficial epigastric vein into the great saphenous vein. (Courtesy of D. Neuhardt, Compudiagnostics.)

pain and bruising. Generally, delivering 60–100 J of laser energy per centimeter of vein treated for lower-wavelength lasers and 40–60 J per centimeter for higher-wavelength lasers will accomplish these goals. On conclusion of the procedure, Doppler confirmation of the patency of the common femoral artery and vein or popliteal artery and vein is recorded. By consensus, patients are generally placed in compression therapy (e.g., short-stretch bandages and/or 30–40-mmHg compression hose [thigh high or panty according to patient preference]). Compression is generally maintained for at least several days, if not longer, to minimize patient discomfort.[20] Adjunctive ligation of the saphenofemoral or saphenopopliteal junctions is not necessary.[21]

38.6 FOLLOW-UP

The necessity of follow-up duplex examination is not universally accepted.[22] However, because of the possibility of incomplete ablation or recurrent patency of the treated vein and the need for adjunctive treatment of the distal GSV and/or SSV, as well as the incompetent tributaries and perforator veins, color-flow Doppler ultrasound, interviews, and physical examinations at appropriate intervals are suggested to ensure a successful outcome.[23] More frequent follow-up visits will often reveal the need for adjunctive treatment earlier in the post-operative course.

38.7 OUTCOMES

38.7.1 Duplex outcomes (surrogate outcome markers)

Navarro et al.[24] published the first case series in 2001 on 40 veins treated with laser ablation under local perivenous anesthesia, reporting 100% complete ablation at a mean follow-up of 4.2 months, with no significant complications. Proebstle

Table 38.2 Mid-term anatomic and clinical outcomes following endovenous laser ablation

Authors	Number of veins	Follow-up period (months)	Successful ablation (%)	Significant complications
Chang and Chua[55]	252	19	96.8	36.5% paresthesia 4.8% skin burn 1.6% thrombophlebitis
Disselhof et al.[28]	93	≥24	84	2% thrombophlebitis
Nandhra et al.[38]	44	24	81.2	NA
Myers and Jolley[29]	404	36	80	0.2% severe pain 2.2% thromboembolism 0.3% nerve palsy
Rasmussen et al.[31]	137	60	82.1	NA 2.6% post-procedural pain
Samuel et al.[39]	38	60	92.1	2.6% hyperpigmentation

et al.[25] reported occlusion in all 41 SSVs treated at a mean follow-up period of 6 months. Similar short-term reports of successful ablation with lasers of different wavelengths have been published.[26,27] Few mid-term reports are available,[28] but most demonstrate similarly good results. In particular, Meyers and Jolley[29] have reported their carefully collected and statistically well-analyzed data, showing a secondary or assisted successful ablation rate of 97% at 4 years (Table 38.2).

38.7.2 Patient/physician-reported outcome measures

The movement in clinical trials towards a greater emphasis on quality of life outcome measurement tools is reflected in the endovenous laser literature comparing different ablation methods. Patient- and physician-reported outcome measurement tools are now commonly used to define successful treatment.

Marston et al.[30] reported improved CEAP classification (C, clinical; E, etiology; A, anatomy; P, pathophysiology) and Venous Clinical Severity Score (VCSS) following RF or laser ablation. In reporting 5-year results comparing endovenous laser with surgical ablation of the GSV, Rasmussen and colleagues noted no statistically significant difference in physician- or patient-reported outcome measures.[31] Shepherd et al. demonstrated less post-procedural pain following segmental RF ablation than with a lower-wavelength laser, but quality of life outcomes were similar at 6 weeks.[32]

Generally good outcomes have been reported when laser ablation is combined with other treatment modalities. Mekako et al.[33] have demonstrated the feasibility of performing laser ablation in concert with ambulatory phlebectomy. Neglén et al.[34] demonstrated good outcomes when combining laser ablation with deep vein stenting for superficial venous insufficiency and concomitant deep vein obstruction. Theivacumar and colleagues[35] have demonstrated that, in some patients, the incompetent GSV in the presence of a grossly incompetent anterior accessory saphenous vein will recover competence following ablation of the anterior accessory saphenous vein alone. Myers et al.[36] have advocated for laser ablation for incompetent major tributaries, while others have demonstrated the safety and efficacy of laser ablation for the incompetent vein of Giacomini.[37]

It has been assumed that most incompletely ablated veins will be seen in the first few months following treatment. However, we have identified recurrence in our own patients more than 6 years after apparently successful ablation, with recurrent symptoms and partially patent segments. Thus, it seems prudent to perform careful follow-up of these patients for 1 year and when recurrent symptoms occur.

Improvement in physician-reported measurement tools such as the revised VCSS and, even more importantly, improvement in patient-reported outcome measures are almost uniformly seen following endovenous laser ablation.[31,32,38,39] Included in many of the more recent laser ablation reports are generic health (Short Form 36 [SF-36] and Euroqol [EQ-5D]) and disease-specific quality of life measurement tools (Aberdeen Varicose Vein Questionnaire [AVVQ]).

38.7.3 Complications

Complications may be divided into intra-operative and post-operative adverse events. Intra-operative adverse events include technical challenges and adverse patient events (Box 38.4).

The technical challenges sometimes encountered are difficult access (venospasm and access location) and problems with advancing the wire/sheath/fiber (vein tortuosity, aneurysmal segments, or sclerosis from previous sclerotherapy).

BOX 38.4: Intra-operative adverse events

- Difficult access
- Difficult fiber advancement
- Vagal reaction/dysrhythmia
- Nerve pain
- Transient heat

BOX 38.5: Post-operative adverse events

- Ecchymosis
- Pain
- Paresthesia
- Infection
- Cutaneous thermal injury
- Superficial thrombophlebitis
- Deep vein thrombosis

Adverse patient events that may occur are dysrhythmia or vagal reaction (often because of anxiety), saphenous or sural nerve pain, or transient heat (the last two usually occur because of inadequate anesthetic infiltration).

Post-operative adverse events include bruising, pain, paresthesia, infection, skin burn, superficial thrombophlebitis, lymphedema, and deep vein thrombosis (Box 38.5). Anecdotal case reports of retained fiber/sheath,[40] stroke,[41] arteriovenous fistulae,[42] and death (personal communication) have been published.

Bruising is usually minimal, especially with the higher-wavelength lasers[16] and modified fibers,[30,35] and of limited duration.[16,18] The incidence of paresthesia is generally <1%,[43] and unlike after GSV or SSV stripping, it has been our experience that paresthesia following endovenous ablation is usually mild, short-lived, and limited to the distal thigh following GSV ablation and the distal calf, ankle, and foot following SSV ablation. Furthermore, it has been our observation that the rate of paresthesia is inversely related to the practitioner's experience with perivenous ultrasound-guided anesthesia. Infection and skin burns are rarely reported and are easily avoided with the perivenous anesthetic injected to separate the skin from the underlying vein to be treated. Superficial thrombophlebitis is generally reported in less than 10% of cases[43] and responds to the usual clinical measures of anti-inflammatory medication, compression, and ambulation. Lymphedema has not been reported, but we have seen it in our own center, and it is believed to be caused by unrecognized impaired lymphatic drainage that is usually present prior to any procedures. Treatment of this complication may include exercise, therapeutic lymphatic massage, and compression with multilayered short-stretch bandages, pneumatic compression devices, and compression hose.

Deep vein thrombosis is perhaps the most significant complication, although the incidence reported in the laser literature is quite low.[44] Most true deep vein thromboses develop in calf veins, and because they are considered to be "provoked," they are usually of limited clinical significance. More proximal deep vein thromboses do occur, however, and should be aggressively searched for and treated. Treatment is well explained elsewhere in this text. A thrombophilic condition should be considered in any patient who develops deep vein thrombosis in the post-operative period, especially if it is accompanied by a previous episode, family history, or history of multiple miscarriage.

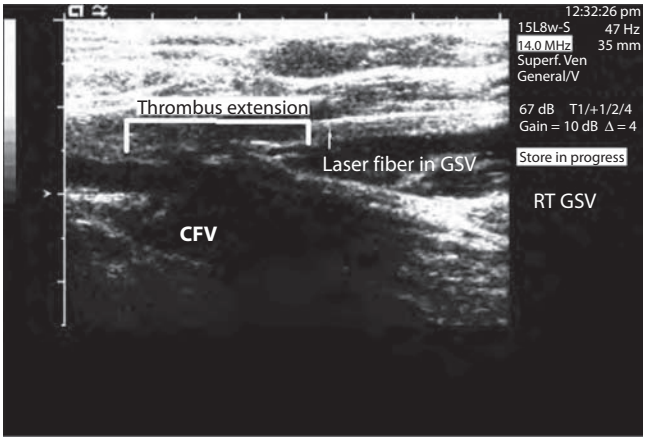

Figure 38.5 Thrombus extending from the great saphenous vein into the CFV. CFV: common femoral vein; Laser fiber in GSV: thrombus extending from laser fiber tip within the great saphenous vein with surrounding tumescent anesthesia. (Courtesy of D. Neuhardt, Compudiagnostics.)

A different thrombotic entity has been described by multiple authors as thrombus extensions from the saphenous veins into the common femoral or popliteal vein, identified early in the post-operative period by routine duplex follow-up examination. This complication has been described as endothermal heat-induced thrombosis[45] or post-ablation superficial thrombus extensions,[46] with categorization of these thrombi for treatment algorithms. However, such thrombus extensions (Figure 38.5) have rarely been associated with embolization, so it is unsettled as to how to manage them. As first reported by McMaster[22] and in more recent symposia discussions among venous experts, because of the number of routine duplex examinations needed to identify a clinically significant venous thromboembolism, these examinations being performed as a routine following endovenous saphenous ablation may not be warranted.

Recanalization of the laser-ablated vein does occur and may be identified at any time after treatment. However, patients remain asymptomatic for some time after it is detected on duplex ultrasound. Once recanalization occurs, the vein rarely goes on to complete occlusion.[47]

Recurrent varicose veins following laser ablation may be considered a complication or a natural progression of the disease process. This topic is covered later in the text and therefore will not be discussed here. It should be mentioned that depending upon the location of recurrence, endovenous laser ablation is sometimes included in the treatment.[48]

38.8 PERFORATOR VEIN LASER ABLATION

Controversy remains as to the role of perforator vein incompetence in the healing and subsequent recurrence rate of venous ulcers. Perforator laser ablation is

technically feasible, and some investigators have concluded that thermal ablation of superficial and perforator veins enhances healing and reduces the incidence of recurrence,[49,50] However, Marston[51] and Samuel et al.[52] have reported that, with limited evidence to substantiate a positive effect on ulcer healing, recurrence, or quality of life improvement, additional studies are required to define the role of perforator thermal ablation in C5 and C6 patients. Furthermore, it has been well-documented that when perforator and truncal vein incompetence coexist, perforator incompetence is often eliminated by treatment of the truncal vein alone.[53]

38.9 SUMMARY

Endovenous laser ablation is generally safe. Intra-operative and post-operative complications are uncommon and generally less frequently seen than with more traditional surgical procedures. Differences in methods of follow-up examination and in definitions of successful ablation may help explain the variance in results between published reports and those seen in the surgeon's own clinical setting. Randomized controlled trials comparing endovenous laser ablation with other modalities (with long-term follow-up) have demonstrated, and will continue to demonstrate, where these minimally invasive methods belong in the therapeutic armamentarium for the treatment of chronic venous disorders of the lower extremity. Office-based ablation techniques have been shown to be more cost effective than traditional operating room-based surgical treatment.[54] While some surgeons have previously expressed the view that none of these techniques has yet been shown to be better than conventional surgery in the long term, patient perceptions have uniformly been that minimal invasion is better.

Finally, careful follow-up post-laser ablation should result in more complete treatment of the patient's venous disorder, with better resolution of the patient's symptom complex. It is simply not appropriate to ablate only the proximal saphenous vein and expect long-lasting resolution of the patient's symptoms and varicosities. Unless one is committed to a program of meticulous follow-up and adjunctive treatment, the practitioner and the patient will be left with unsatisfactory results.

38.10 CONCLUSIONS

- Endovenous laser ablation of the saphenous vein effectively removes the target vein from the venous circulation.
- Endovenous laser ablation is safe and well tolerated, with a low incidence of significant complications reported.
- Adjunctive therapy to permanently eliminate the saphenous vein and all other sources of reflux disease is integral to the adequate control of superficial venous insufficiency.
- Careful follow-up will ensure the best results.
- Long-term outcome reports are necessary to conclude that endovenous laser ablation is a durably effective method of treating superficial venous insufficiency.
- Randomized controlled trials comparing endovenous laser ablation with other methods (including surgery, RF ablation, and chemical ablation) have demonstrated quality of life improvements equal to or better than other endovenous ablation methods.

Guidelines 4.10.0 of the American Venous Forum on laser treatment of the incompetent saphenous vein

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.10.1	Endovenous laser therapy of the great saphenous vein is safe and effective and we recommend it for the treatment of saphenous incompetence.	1	A
4.10.2	Clinical outcome after endovenous laser therapy up to 3 years is comparable to traditional stripping and ligation and we recommend it for the treatment of the incompetent great saphenous vein.	1	C

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● = Major primary paper
★ = Major review paper
◆ = Published guideline

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Emerging endovenous technology for chronic venous disease: Mechanical occlusion chemically assisted ablation (MOCA), cyanoacrylate embolization (CAE), and V block-assisted sclerotherapy (VBAS)

STEVE ELIAS

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39.1 INTRODUCTION

Endovenous ablative technologies continue to evolve, with the development of mechanical occlusion chemically assisted (MOCA) ablation, cyanoacrylate embolization (CAE), and V block-assisted sclerotherapy (VBAS). Currently, all endovenous technologies can be classified under two general categories: thermal tumescent (TT) or non-thermal non-tumescent (NTNT).[1] The TT technologies include radiofrequency, laser, and steam. NTNT technologies encompass MOCA ablation, CAE, VBAS, and polidocanol endovenous microfoam, with others emerging. The NTNT segment is the fastest growing due to some inherent advantages: minimal nerve or skin injury; safety when treating disease to the ankle; decreased patient discomfort due to the decreased needle sticks by avoiding tumescence; and the elimination of any capital equipment (generator). As with the TT techniques, all NTNT approaches can be performed in an office setting in under an hour. Patients can return to normal activity almost immediately (Table 39.1).[2,3]

The above advantages of NTNT do not sacrifice safety, efficacy, or clinical outcomes when compared to TT techniques. All technologies have been shown to significantly improve quality of life (QoL) measures.[4,5] We know that successful occlusion of an axial vein (great saphenous vein [GSV], small saphenous vein [SSV], and anterior accessory GSV, etc.) improves a patient's QoL no matter what technology is used.[6] In fact, the evidence is so compelling regarding QoL improvement that societal and government health agencies have recommended that endovenous ablation be the first modality of choice for symptomatic axial vein incompetence.[7,8] Successful ablation is not about treating the vein, it is about treating the patient. The idea of the occlusion rate being the primary endpoint has faded in recent years. The primary endpoint of "Did we improve patients' QoL?" is now at the forefront, as it should be. Physician-derived and patient-reported outcome measures are now what academics and third-party payers consider to be primary endpoints. We treat patients, not veins. With these concepts in mind, we can better understand where the NTNT technologies of MOCA ablation, CAE, and VBAS can be best utilized when caring for patients with vein disease.

39.2 MOCA ABLATION

39.2.1 Overview

MOCA ablation (ClariVein™) has the longest follow-up and was the first of the new NTNT technologies to be reported. The device was developed by Michael Tal and John Marano

Table 39.1 Thermal tumescent and non-thermal non-tumescent technologies

TT	NTNT
• Radiofrequency • Laser • Steam	• Mechanical occlusion chemically assisted • Cyanoacrylate embolization • V block-assisted sclerotherapy • Polidocanol endovenous microfoam
TT vs. NTNT	
TT (10%–15%)	**NTNT (85%–90%)**
• Bigger veins • Longer follow-up • Nerves/skin: concerns • Patient comfort: tumescence (learning curve)	• GSV/SSV/C6/below-knee GSV • Shorter follow-up but equal • Nerves/skin: no issue • Patient comfort: better • Shorter learning curve?

Note: TT: thermal tumescent; NTNT: non-thermal non-tumescent; GSV: great saphenous vein; SSV: small saphenous vein.

(Figure 39.1).[9] First-in-man evaluations were performed in February 2009.[10] There are two components to the device/technique: (1) mechanical damage to the endothelium by a rotating wire (Figures 39.2 and 39.3); and (2) chemical installation of a detergent liquid sclerosant (sodium tetradecyl sulfate [STS] or polidocanol) simultaneously. The mechanical disruption allows for penetration of the sclerosant so that medial damage and scarring can occur, which leads to occlusion.[11] The wire rotates at 3500 rpm and, in addition to causing endothelium damage, it also causes vein spasm so sclerosant is not being injected into a vein filled with blood (Figures 39.4 and 39.5). The technique not only

Figure 39.1 Mechanical occlusion chemically assisted ablation (ClariVein) device.

Figure 39.2 Mechanical occlusion chemically assisted ablation angled wire unsheathed.

consists of sclerotherapy. Each component—mechanical and chemical—is essential for good results. Each component alone yields poor results. The sclerosant exits the catheter sheath about 2 cm from the tip of the rotating wire, is pulled up the shaft of the wire, and is released from the tip, thus directly "injecting" sclerosant into the damaged vein

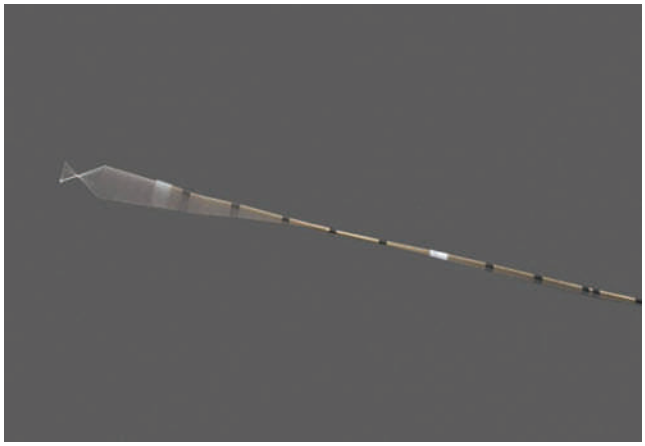

Figure 39.3 Mechanical occlusion chemically assisted ablation wire rotating.

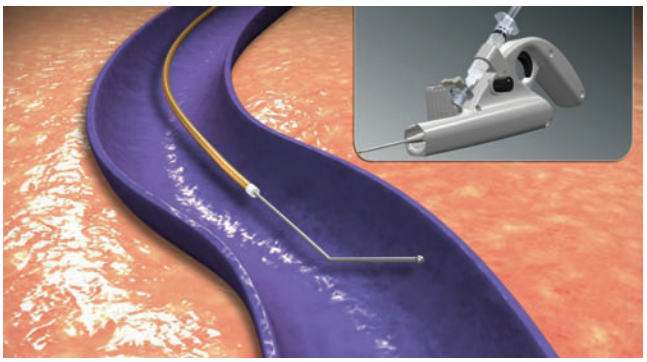

Figure 39.4 Mechanical occlusion chemically assisted ablation mechanism of action.

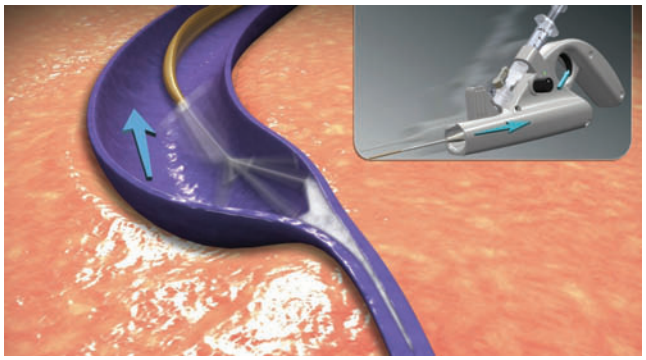

Figure 39.5 Mechanical occlusion chemically assisted ablation wire rotating/sclerosant injection.

wall (Figure 39.5). This action allows for sub-endothelial penetration of sclerosant to aid in media damage. One can think of the rotating wire as a sprinkler releasing sclerosant from the tip. In the original trial, all veins received 12 cc of 1.5% STS liquid. A pullback rate of 1.5 mm/second or 1 cm every 7 seconds was used. This was chosen because of the similarity to the existing laser pullback rates at that time. The volume of sclerosant used was irrespective of the length of the vein being treated. The occlusion rate was 96% at 1 year with minimal complications: no deep vein thrombosis (DVT), nerve, or skin damage. Venous Clinical Severity Score (VCSS) improved, as expected with an occluded GSV. Greater than 2–year follow-up was reported by the same group[12] with a 96% occlusion rate.

39.2.2 Technique

The technique has undergone some modifications since the original report as all new techniques or technologies do. Here are the current recommendations:

1. Micropuncture access with ultrasound (US) guidance.
2. Placement of a 4-Fr or 5-Fr micropuncture sheath into the vein.
3. No further wire or sheath exchanges required and no tumescence required.
4. Passage of the angled catheter portion of the device up the targeted vein.
5. Unsheathing of the wire and placement of the wire tip 2 cm from the saphenofemoral junction (SFJ) or just at the fascial curve of the saphenopopliteal junction (SPJ).
6. Attachment of the motor unit and the syringe containing sclerosant.
7. Volume of sclerosant determined by diameter and length treated (table available).
8. Begin rotation only, no injection for the first centimeter of pullback to induce vein spasm (i.e., from a position 2 cm to 3 cm from the SFJ).
9. After 1 cm of rotation only, begin drip infusion; the patient only feels vibration.
10. Maintain constant rate of pullback (1.5 mm/second) with continuous drip infusion.
11. Reload syringe when needed.
12. Post-treatment, have the patient flex ankles to wash out any sclerosant in the deep system.
13. Wrap legs as per your protocol. This author uses 4- and 6-inch Ace bandages from the mid-thigh.
14. Have patient ambulate; they may resume normal activity on the next day.

39.2.3 Technical pearls

The pullback rate is much more important for success than the sclerosant volume. When failures are analyzed, the operator often pulled too fast and did not allow enough time for sufficient vein damage. In the original study, all veins received 12 cc of 1.5% STS regardless of the length treated. No DVT occurred. Obviously, some veins received slightly too much and some received slightly too little damage, yet a 96% occlusion rate was achieved with no DVT/skin/nerve injury. The technique is forgiving of volume, but not forgiving of pullback rate. It is better to pull "too slow" and give "too much" sclerosant that the contrary. The type of detergent sclerosant does not affect outcomes. The Dutch have reported comparable results with polidocanol 2% and 1%.[13]

Confirm placement of the wire prior to starting treatment with US; US visualization is not routinely needed during the pullback. If there is a larger segment of vein (>8–10 mm), then the US probe is used to partially compress that section in order to improve vein wall contact. Routine pressure may lead to the rotating wire getting caught on the vein wall. If this happens (in perhaps 5% of cases), a quick jerk of the wire will free the catheter. This is akin to pulling a bandage quickly off the skin. You will know the catheter is getting caught when you hear the motor slow down and the patient experiencing a pulling sensation. The wire cannot be broken by pulling it.

If doing concomitant phlebectomy, this author recommends access and placement of the MOCA ablation device, but no treatment until the phlebectomy segment is completed; then the vein is treated. This sequence minimizes the potential dwell time of sclerosant in the deep system, thus minimizing the risk of DVT. There are no studies demonstrating this theoretical issue. The reported DVT rate worldwide is less than 0.5%.[14]

When imaging post-treatment, it is important to not only use US greyscale, but color-flow duplex as well. With MOCA ablation, the vein is immediately occluded, but it takes 3–6 months longer to contract (Figure 39.6). Therefore, any early US with greyscale will show a dilated vein. This finding is in contrast to TT ablation. The additional use of color-flow duplex will document the absence of flow.

As with most other endovenous treatments, the post-procedure compression and activity instructions have become less onerous. This author uses compression for 24 hours post-MOCA ablation and then only 3 days of compression when awake. Any and all activity is allowed the next day. These instructions apply when phlebectomy is not included.

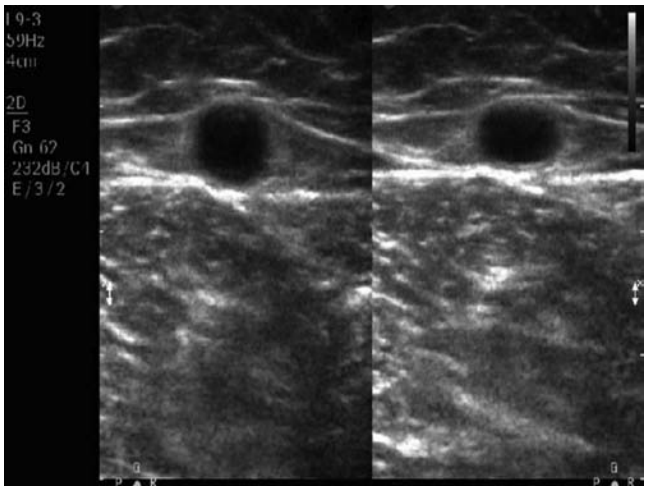

Figure 39.6 Ultrasound post-mechanical occlusion chemically assisted ablation at 6 months.

39.2.4 Results

To date, 16 articles have been published regarding MOCA ablation (ClariVein™) in the peer-reviewed literature and 60,000 procedures have been done worldwide. The results are overwhelmingly coincident with occlusion rates of greater than 90%, and improvements in QoL measures are significant.[15] Some specific studies which address specific topics will be discussed.

The longest follow-up has been by the author of the original clinical trial[12] at greater than 2 years. van Eekeren et al. reported similar results at 1 year when using polidocanol instead of STS. In addition, all of the QoL measures improved at 1 year.[16]

One of the advantages of any NTNT technology is safety and the lack of risk of nerve injury when treating any below-knee segment of vein. Boersma et al.[17] reported the 1-year results for MOCA ablation when treating the SSV. No nerve injury occurred and the occlusion rate was 94%. These results are encouraging in that SSV treatment has the concern of potential injury to three nerves: sural, tibial, and peroneal. Many physicians have been loath to treat the SSV due to nerve risk and DVT. This study did not experience either issue.

In terms of the management of more advanced disease states, C6 ulcer patients experience another advantage with NTNT technologies. In C6 patients, if the axial disease reflux is to the ankle, it is desirable to treat the entire pathologic segment. Tumescence is hard to place in an area of ulceration and significant lipodermatosclerosis. This author has used retrograde cannulation of the GSV in these circumstances with good results. Moore et al.[18] have reported on the use of MOCA ablation in a C6 patient with SSV incompetence with good results. Finally, two studies compared MOCA ablation to radiofrequency ablation. van Eekeren et al.[19] concluded that MOCA ablation yielded less postoperative pain, faster recovery, and sooner return to work than radiofrequency ablation. Bootun et al.[20] randomized 119 patients to MOCA or radiofrequency ablation. MOCA ablation had lower intra-operative pain scores with equal occlusion rates and QoL improvements compared to radiofrequency ablation.

39.2.5 Summary

MOCA ablation currently has the longest follow-up of any NTNT technology. Studies support its use for the great majority of incompetent superficial axial veins. All measures are as good if not better than comparative TT technologies. There are unique advantages of the NTNT techniques and of MOCA ablation specifically. At the conclusion of this chapter, a summary of the benefits, indications, and contraindications of all of the TT and NTNT technologies will be presented.

39.3 CAE (VENASEAL™)

39.3.1 Overview

CAE is another NTNT technology that has similar advantages to MOCA ablation: minimal nerve injury, no tumescence, and results that are equal to or better than TT techniques. The technology was developed by Rodney Raabe. A specially formulated cyanoacrylate (CA) adhesive is embolized into the target vein utilizing a catheter that does not allow solidification of the glue within it. Once in the vasculature, the glue sets and causes immediate occlusion. A foreign body reaction incites an inflammatory response in the vessel, ultimately leading to fibrotic occlusion.[21] The system consists of a delivery catheter/sheath and a delivery gun (Figure 39.7). First-in-man evaluations were conducted by Almeida et al.[22] The initial technique involved the extrusion of CA 2 cm from the SFJ. This proved to be a little too close, as there was egress of the material into the common femoral vein in almost 20% of cases. The current technique has undergone some modifications in order to minimize complications.

39.3.2 Technique

1. Access vein percutaneously and pass a long 0.035-inch guidewire to the SFJ or SPJ.
2. Insert a long 7-Fr sheath to within 5 cm of the SFJ.

Figure 39.7 Cyanoacrylate embolization (VenaSeal) system.

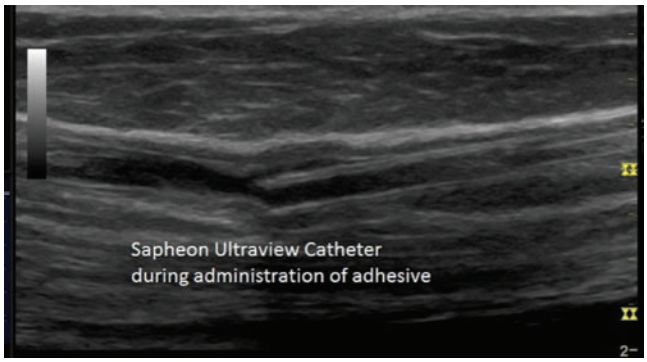

Figure 39.8 Cyanoacrylate embolization ultrasound catheter and adhesive delivery.

3. A 5-Fr delivery catheter is placed through the 7-Fr sheath and positioned 5 cm from the SFJ (Figure 39.8).
4. The delivery gun is attached and loaded with CA.
5. With each click of the delivery gun, 0.1 cc of CA is delivered.
6. The first injection is 5 cm from SFJ and the second is 1 cm distal (6 cm).
7. Pressure is applied for 3 minutes with the US probe over this area.
8. The catheter is moved distally 3 cm and another 0.1 cc is delivered.
9. Pressure is applied for 30 seconds to this segment.
10. Catheter is subsequently moved 3 cm, 0.1 cc is placed, and pressure is applied for 30 seconds each time.
11. The entire vein is segmentally treated to the insertion site.
12. Post-procedure compression is optional.
13. An average of 1.3–1.5 mL of CA is used.

39.3.3 Technical pearls

Being too close to the SFJ or SPJ can lend to glue placement in the common femoral/popliteal vein. The glue does not break down overtime, so theoretically this can be a permanent nidus for clot formation. Catheter position needs to be confirmed. Air pockets have been incorporated into the catheter for improved visualization and echogenicity. The 3-minute compression time is important to allow sufficient "setting" of the glue so that the SFJ/SPJ is thoroughly protected. Doing nothing for 3 minutes can seem like a long time for the operator, but be patient.

Nick Morrison, the principal investigator for the pivotal U.S. VeClose trial, offers two other technical thoughts. In the U.S. trial, epifascial veins were not treated, the thought process being that the inflammatory reaction could cause skin damage and the cord of glue might be felt through the patient's skin. Dr. Morrison also feels that one should avoid placement of glue immediately at the ostium of a large perforating vein to decrease the risk of deep system damage.

From a technical perspective, this NTNT method is analogous to the TT method of radiofrequency ablation; it is a segmental ablation. The pullback rate variable has been eliminated. This enables a more consistent and predictable delivery of glue to the vein. The operator places the CA, pulls the premeasured trigger, compresses, and moves to the next segment. Eliminating pullback rate concerns and removing tumescence simplifies the technique for both patient and physician.

39.3.4 Results

Initial studies were done in a swine model and reported in 2011.[23] A first-in-man study followed and 2-year follow-up was recently reported.[21] Thirty-eight patients were assessed initially and 24 were available for 2-year follow-up. An occlusion rate of 92% was achieved (Figure 39.9). More importantly, the VCSS was still significantly improved from baseline and edema and pain were improved. These procedures were conducted without tumescent anesthesia and no post-operative compression was employed.

The European multicenter eSCOPE trial reported a 92.9% occlusion rate at 12 months.[24] The VCSS and Aberdeen Varicose Vein Questionnaire showed subsequently improved scores. This highlights the importance of QoL measures as outcomes and not solely occlusion rates. As with all NTNT techniques, no nerve injury occurred. There was some form of phlebitis reaction in about 11% of patients. This study was conducted without post-operative compression.

The most recent trial as of this writing is the U.S. pivotal trial, VeClose.[25] This trial was a non-inferiority trial comparing CAE to radiofrequency ablation. All centers had significant radiofrequency technique experience and there was a roll-in period for CAE before trial entry so that investigators were over the learning curve. This trial did use post-operative compression as a fair comparison to radiofrequency ablation. The 6-month occlusion rates were essentially the same; radiofrequency ablation: 94%; CAE: 99%. More importantly, all measures of QoL were equal—pain during procedure, ecchymosis, VCSS, European Quality of Life 5 dimensions questionnaire (EQ-5D), and Aberdeen

Figure 39.9 Great saphenous vein at 6 months post-cyanoacrylate embolization.

Varicose Vein Questionnaire (AVVQ)—highlighting once again that a successfully closed GSV positively impacts patients.

39.3.5 Summary

CAE has similar results to MOCA ablation with similar advantages. It further simplifies a NTNT procedure by eliminating the variable of pullback rate as alluded to earlier. It may have the same theoretical benefit in ulcer patients that MOCA ablation has been shown to have. To date, this has not been reported for CAE. Superficial veins may exhibit more of a phlebitic reaction and some below-knee segments of the GSV and SSV are quite close to the skin. As of this writing, there have been no reports of the use of CAE in the SSV. Studies on these types of veins need to be done.

39.4 V BLOCK-ASSISTED SCLEROTHERAPY

39.4.1 Overview

VBAS can be conceptualized as an internal SFJ or SPJ ligation with concomitant sclerotherapy. It consists of a polytetrafluoroethylene-coated plug similar to a small vena cava filter (Figure 39.10) that is mounted on a preloaded delivery system (Figure 39.11). A proprietary dual-syringe system simultaneously exsanguinates and collapses the target vein while infusing a liquid sclerosant (Figure 39.12).[26] The V block plug is released 2 cm from the SFJ or SPJ and the simultaneous vein exsanguination and sclerosant infusion is begun. It only involves local anesthesia at the insertion site. The pullback rate of the catheter is relatively unimportant. As with the MOCA ablation device, some venous tributaries get secondarily treated when sclerosant egresses into them. Nerve injury has not been reported and the DVT rate is less than 0.5%.

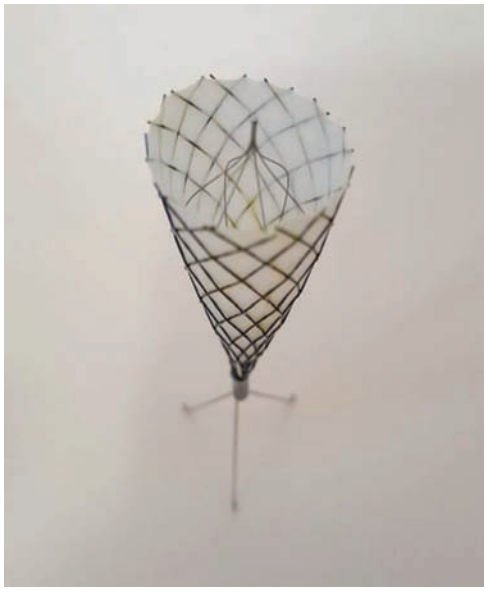

Figure 39.10 V block-assisted sclerotherapy device.

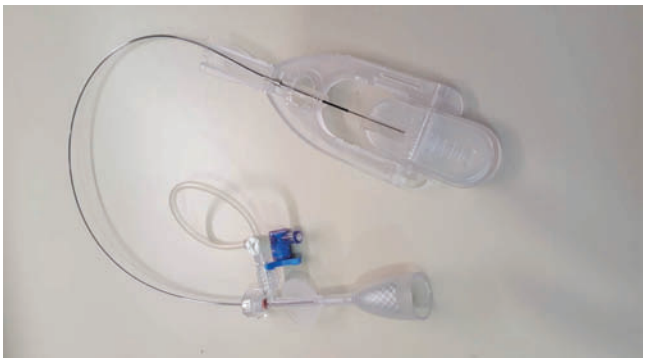

Figure 39.11 V block-assisted sclerotherapy delivery system.

Figure 39.12 V block-assisted sclerotherapy dual-syringe technique.

39.4.2 Technique

1. Micropuncture access.
2. Insertion of a 0.035-inch wire into the SFJ/SPJ.
3. Passage of a 6-Fr catheter 2 cm from the SFJ/SPJ.
4. The V block device is passed up the catheter and released 2 cm from the SFJ/SPJ (Figure 39.13).
5. The V block carrier is removed and dual a lumen catheter is passed up the sheath.
6. Dual syringe with sclerosant in the syringe is pulled back.

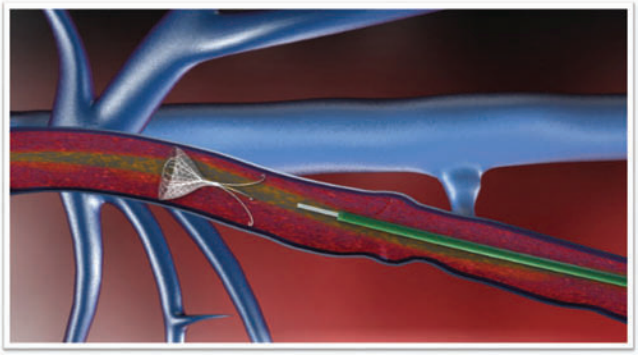

Figure 39.13 V block in the saphenofemoral junction position.

7. Pressure is kept on the syringe with the sclerosant.
8. The empty syringe aspirates blood and collapses the target vein.
9. The leg is wrapped as usual.

39.4.3 Technical pearls

Currently, the release mechanism for the V block needs two hands to accomplish placement. The procedure is done under US visualization; therefore, two people are required. The device has a tendency to advance by a short amount. This must be adjusted for prior to release. The device can easily be seen on US.

39.4.4 Results

Initial animal studies[24] demonstrated 100% occlusion in sheep GSVs at 90 days. Histological examination showed ablation of the lumen, good incorporation of the V block, and fibrosis of the target vein. The first-in-man study was reported by Ralf Kolvenbach at the VEITH Meeting of 2014. Fifty-two patients were enrolled in the study. He reported the results at 3 months in 18 patients. The occlusion rate was 94%. Minimal adverse events occurred, primarily consisting of a clinical phlebitic reaction. No DVT or nerve injury was reported. AVVQ scores improved as well. Further follow-up reporting should be available soon.

39.4.5 Summary

The VBAS technique is another promising NTNT technology; in theory, it should achieve the same improvements in QoL scores if the axial veins remain occluded. As mentioned, the delivery system needs to be improved and simplified so as to allow for accurate placement. A second generation is undergoing testing. This device can also treat below-knee disease safely.

39.5 DISCUSSION

Currently, the NTNT category is undergoing similar issues that the disruptive TT technologies experienced in the early 2000s. The NTNT technologies are the next wave of disruptive technology regarding the treatment of superficial venous disease. The use of tumescence is the most discomforting aspect of endovenous ablation for patients and physicians. Accurate placement of tumescence is the most difficult part of the learning curve. It is also the part of the procedure that patients find most uncomfortable. Eliminating tumescence is a laudable goal as long as outcomes are similar to TT results. As illustrated above, the literature does support similar outcomes with TT and NTNT technologies, at least in the mid-term. It should be kept in mind that superficial varicose vein disease is an incurable disease. The 5- or 10-year results, while important, are not as realistic when analyzing vein disease as compared to other disease states, because no vein specialist will tell patients that they are "cured." New disease is expected. New disease is treated.

It is this author's belief that any vein specialist needs to be facile with at least one TT and one NTNT technique. There are certain clinical scenarios in which one type of approach is more advantageous than another (Table 39.2). Most below-knee pathologies are better treated with NTNT techniques in order to minimize nerve and skin issues. As stated previously, if pathology and reflux include the ankle level, the NTNT techniques can safely accomplish treatment goals. This is even more advantageous with advanced C5 or C6 disease when tumescence is difficult to place in an area of skin changes or ulcer. Access can also be made retrograde from the knee level. MOCA ablation can also be safely used for epifascial veins because there is only a minor phlebitic reaction.

Almost any TT or NTNT technology can be safely used in the above-knee axial vein. However, this author feels that for large veins of greater than 10–12 mm, TT options are better. Veins of greater than 10–12 mm have been treated with success with NTNT technologies, but large veins in general require more energy and a thermal mode of action. Recanalized veins from previous thrombophlebitis or previous failed ablations are better treated with TT technologies for similar reasons (Table 39.2).

Specifically within the NTNT category, each technology has its own unique advantages and disadvantages.

These modalities may also have applications in other aspects of venous disease. For example, MOCA ablation, CAE, or VBAS with some modifications have the potential for treating ovarian vein incompetence or internal iliac vein branch incompetence causing pelvic congestion syndrome. Varicose veins are already treated with foam sclerotherapy, but CAE can also conceptually be used with perhaps some change in chemical structure.

Which NTNT technique is best? There is no one "best" technology. Many factors need to be considered: cost, reimbursement, vein specialist comfort with the technique, patient's experience, and the unique clinical/anatomical scenario. One thing is clear: all NTNT technologies positively impact on patients' QoL.

39.6 OVERALL SUMMARY

All new technologies and techniques undergo evolution from initial development to early adoption to general use. MOCA ablation, CAE, and VBAS are no exceptions. These techniques have been modified as more experience has accrued. This new class of ablation will persist and grow. The removal of tumescence from endovenous procedures is a goal that is worthwhile for patient and treating vein specialists. Whenever a technique is made simpler with equal or better results, everyone benefits.

The main challenge as of this writing is reimbursement for MOCA ablation, CAE, VBAS, and polidocanol endovenous microfoam. This story is familiar to all of us who began using the TT technologies of laser and radiofrequency

Table 39.2 Advantages and disadvantages of non-thermal non-tumescent technologies

NTNT technology	Advantages	Disadvantages
MOCA ablation	No foreign body left Uses approved liquid sclerosant Longest follow-up of all NTNT technologies Tortuous veins: angled wire Perforators: PAPS 60,000 patients worldwide	Need to pullback/inject simultaneously Longest learning curve Compression: 5 days
CAE	Segmental ablation Pullback rate variable eliminated Second longest follow-up No post-procedure compression Perforators: PAPS?	Foreign body left Phlebitic reaction Tortuous veins: difficult
VBAS	Pullback rate variable eliminated Uses approved liquid or foam sclerosant	Foreign body left Shortest follow-up Smallest number treated Tortuous veins: difficult Compression: 7 days
PEM	Pullback rate variable eliminated Tortuous veins: foam traverses Also treats branch varicosities Perforators: PAPS	Requires two people for procedure IFU: 2 weeks of compression Not indicated for small saphenous veins

Note: NTNT: non-thermal non-tumescent; MOCA: mechanical occlusion chemically assisted; CAE: cyanoacrylate embolization; IFU: instructions for use; VBAS: V block-assisted sclerotherapy; PAPS: percutaneous ablation of perforators; PEM: polidocanol endovenous microfoam.

Guidelines 4.11.0 of the American Venous Forum on emerging endovenous technology for chronic venous disease: mechanical occlusion chemically assisted (MOCA), cyanoacrylate embolization (CAE), V block assisted sclerotherapy (VBAS)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.11.1	We suggest MOCA for • SSV incompetence with diameter <10 mm • Mildly tortuous GSV/SSV due to steerable wire • BK GSV incompetence to the ankle for C2–C6 disease	2	B
4.11.2	We also suggest MOCA for epifascial axial vein incompetence.	2	C
4.11.3	We suggest CAE for • BK GSV incompetence in C2–C6 disease • SSV incompetence	2	C
4.11.4	We suggest against CAE treatment of epifascial axial veins.	2	C
4.11.5	We suggest VBAS for AK GSV incompetence with diameter <12 mm.	2	C
4.11.6	We suggest PEM for tortuous axial veins (GSV).	2	B
4.11.7	We suggest PEM for branch varicosities <6 mm.	2	C
4.11.8	As overall non-thermal non-tumescent technics (NTNT) guidelines we recommend MOCA, CAE, PEM for AK GSV treatment for diameters <12 mm.	1	B
4.11.9	We recommend thermal tumescent technologies for vein diameters >12 mm.	1	C
4.11.10	We suggest NTNT not be used for vein diameters >12 mm.	2	B
4.11.11	We suggest NTNT not be used for post thrombotic recanalized veins.	2	C

Note: PEM: polidocanol endovenous microfoam; SSV: short saphenous vein; GSV: great saphenous vein; BK: below-knee; AK: above-knee; TT: thermal tumescent; NTNT: non-thermal non-tumescent.

ablation in the early 2000s. If technologies show safety and efficacy and improve patients' lives, they ultimately are reimbursed. This should follow for the NTNT group as well.

Once the reimbursement hurdle is overcome, this author feels that 80%–85% of axial vein reflux will be treated by NTNT methods and 15%–20% will require TT methods. The data support a positive impact on patients' QoL when using NTNT methods. They allow us to more than adequately treat superficial axial disease. They enable us to have an impact on patients with vein disease. Any new technology needs to be held to the gold standard of helping patients, not just treating veins. These technologies achieve this. The future of endovenous ablation is the future of NTNT technologies—for now. We await the next disruptive technology.

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● = Key primary paper
★ = Major review article
◆ = Formal publication of a management guideline

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40

Phlebectomy

LOWELL S. KABNICK AND OMAR L. ESPONDA

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40.1 INTRODUCTION

Hippocrates performed the first phlebotomy to treat a varix about 2400 years ago. Since that time, procedures for the removal of varicose veins have evolved, with many modifications. Robert Muller, a Swiss dermatologist, refined the technique in 1956 and later discovered through surgical history that ambulatory phlebectomy was practiced by Aulus Cornelius Celsus 2000 years earlier. Although Muller's technique was adopted slowly, it is now considered the preferred method for the treatment of varicose veins. The procedure is performed under local anesthesia with little, if any, recovery time. In short, a small hook-like instrument, together with fine clamps, is employed to extract the varix from a small (~2-mm) incision. At the completion of the procedure, a dry sterile compression dressing or compression hose is applied post-operatively to the limb.

This chapter will cover the indications and contraindications of ambulatory phlebectomy. A detailed explanation of the procedure will be provided, as well as a description of potential complications and the regions in which phlebectomy is difficult to perform. For the reader to best gain expertise and shorten the learning curve, the author suggests not only reading this chapter, but also seeking out an expert in the field of phlebectomy to observe the procedure.

40.2 HISTORY

In 400 BC, Hippocrates was the first to conceptualize phlebectomy; several sequential punctures in the vein would be used to get rid of the "bad blood" that fed an ulcer.[1,2] However, it appears that Aulus Cornelius Celsus (56 BC–40 AD) was the first surgeon to actually perform phlebectomy. According to historians who researched and wrote the history of ambulatory phlebectomy, most of Celsus' writings have been lost to time. However, some of the documents that were discovered attributed and described Celsus' venous contributions.

Concerning phlebectomy, Celsus wrote, "The varicose veins were treated by exposure followed by avulsion with a blunt hook or by touch of the cautery."[3] Although he made large incisions, he used compressive bandages that allowed ambulation.

The current phlebectomy technique was first described by Robert Muller, a dermatology-trained phlebologist from Neuchâtel, Switzerland, who reinvented and refined the technique that we know today as ambulatory phlebectomy (Figure 40.1). Disappointing results of large vein sclerotherapy had prompted Dr. Muller to re-evaluate and change his technique. He noticed that phlebitis developed in a number of cases after injection, followed by recanalization and recurrent thrombus. Because of the fragility of the venous wall and the difficulty of removing these treated veins, he eliminated sclerotherapy and went directly to removal.

Muller began by using small hooks (made from broken forceps) to remove varicosities through small incisions. By 1956, he had perfected this technique, which he presented in 1967 to the French Society of Phlebology and in 1968 to the International Congress of Phlebology. These presentations were poorly received by most of the audience. Muller wrote, "It was a total fiasco. Everybody agreed that it was a ridiculous method, after which I could have buried myself together with the invention. However, a young colleague, Dr. Dortu, asked me to teach him the method."[4–6]

Figure 40.1 Dr. Robert Muller.

Since then, Muller and his disciples have taught this technique, which has spread slowly throughout the world. It was not until recently that Muller's phlebectomy technique was adopted in the United States as the procedure of choice to remove segments of varicose and some reticular veins. Over the years, Dr. Muller's technique and instrumentation have been imitated, given different names, reinvented using personal techniques, and perhaps improved.

40.3 DEFINITION OF AMBULATORY PHLEBECTOMY

The term "ambulatory phlebectomy," coined by Dr. Muller, refers to the technique in which varicose veins are extracted in an outpatient setting under local anesthesia using small punctures and hooks. This technique requires hemostatic compression and immediate ambulation.

Ambulatory phlebectomy, stab avulsion, stab phlebectomy, microphlebectomy, and microextraction are synonymous terms that define this ambulatory, outpatient technique. The Current Procedural Terminology code book of the American Medical Association lists three codes for the billing of the procedure: (1) 37765, stab phlebectomy of varicose veins, one extremity, 10–20 stab incisions; (2) 37766, stab phlebectomy of varicose veins, one extremity, more than 20 incisions; and (3) 37799, for fewer than 10 incisions.[7] When discussing the procedure with a patient, we strongly recommend that the terms "ambulatory phlebectomy" or "microphlebectomy" be used. Stab avulsion and stab phlebectomy should be avoided as patients react with apprehension to those terms.

The objective of ambulatory phlebectomy is to provide definitive treatment for the removal of the target vein.

40.4 DIAGNOSTIC METHODS AND INDICATIONS

40.4.1 Diagnostic methods

A complete history should be taken and a physical examination performed for every patient, as well as a duplex ultrasound in most cases. Transillumination is very helpful for identifying varicose or reticular veins associated with telangiectasias. Common transilluminating devices include the Veinlite (TransLite, Sugar Land, TX) and VeinViewer by Luminetx (Memphis, TN).

40.4.2 Indications

Indications for ambulatory phlebectomy vary depending on the skill set and other techniques with which the phlebologist is comfortable. Patients of all ages are candidates for phlebectomy. The procedure may be medically or cosmetically indicated. Ambulatory phlebectomy can be performed solely or in conjunction with another procedure.

Varicose veins of any size and in any location, excluding the cephalad end of the great or small saphenous vein, are candidates for ambulatory phlebectomy. These include the epifascial great saphenous vein, collateral varicosities, and reticular veins. Also appropriate for ambulatory phlebectomy are regional venous networks, including accessory saphenous veins of the thigh, pudendal perineal veins, reticular veins of the lateral subdermic plexus and popliteal fossa, and foot and hand veins.[8,9] Dilated veins in other parts of the body, including the periorbital, abdominal, and chest areas, as well as medial thigh perforators and small lateral perforators, can be treated by this technique with success.[10]

Areas of difficulty for ambulatory phlebectomy are the knee, tibial, and foot areas, where the veins are tethered by connective tissue, making their removal somewhat arduous. Areas of caution are the following: the peripheral great saphenous vein in the saphenous nerve distribution and the small saphenous vein in the sural nerve region. Lateral varicosities by the fibular head are in the region of the peroneal nerve and should be approached with caution, as should many areas of the hand and foot.

40.4.3 Treatment strategies

Accepted treatment options in phlebology include compression therapy, sclerotherapy, ambulatory phlebectomy, endovenous thermal ablation, and topical laser. Each treatment modality has its advantages and indications; however, there is significant overlap.

Sclerotherapy is the closest alternative treatment strategy to ambulatory phlebectomy. At present, there is still a debate as to which is better, and a paucity of evidenced-based literature to support the superiority of either procedure. A single randomized controlled trial by de Roos et al.[11] demonstrated the superiority of ambulatory phlebectomy over

sclerotherapy for the treatment of the anterior thigh circumflex vein. However, there are flaws in the study. Debates regarding the superiority of the procedures usually end in a tie. The phlebologist must know both procedures.

40.4.4 Delayed versus simultaneous procedures

There is substantial controversy over whether ambulatory phlebectomy should be performed at the same time that truncal reflux is being abolished. Historically, the complete removal of any varicosities at the same time as great saphenous vein treatment has been dogma. In the early twentieth century, Homans[12] and Mayo[13] published papers stating that complete removal of varicosities was encouraged to prevent recurrence. The current scientific literature regarding timing of varicosity treatment after interruption of truncal reflux is scant; however, review of the literature reveals that simultaneous treatment of varicosities leads to higher patient satisfaction, early gains in quality of life, and a reduced need for further procedures.[14,15] The final decision on treatment strategy should rest with the clinician and the patient, as both delayed and simultaneous procedure pathways offer good outcomes.[14,15]

40.4.5 Benefits of ambulatory phlebectomy

Ambulatory phlebectomy is an economical, cosmetic, and effective method to remove veins. Improvements in anesthetic technique, namely the use of tumescent anesthesia, have limited the amount of pain both intra-operatively and post-operatively. Patients can return to daily activities after the procedure and return to work the next day. Because of the paucity of reported complications, the procedure is considered safe.[16–18] However, long-term results, even if presumed excellent, have not been well studied to date.

40.4.6 Contraindications

There are a limited number of contraindications to ambulatory phlebectomy. The following conditions should be considered as relative contraindications: infectious dermatitis or cellulitis in surrounding areas, severe peripheral edema, severe arterial insufficiency, serious illness, anticoagulation, hypercoagulable state, and pregnancy.

40.5 TECHNIQUE

40.5.1 Pre-operative preparation

All target veins should be traced while the patient is standing as they may be difficult or impossible to identify during recumbence. Surgical markers include those using gentian violet-colored solution (e.g., Vismark; Viscot Medical, East Hanover, NJ) surgical skin markers. Use of a permanent marker to trace the veins should be avoided because of the risk of tattooing. After the patient has been placed in the recumbent position, the vein marks can be adjusted using a transilluminator or an ultrasound if necessary. Because veins tend to shift, this subsequent adjustment adds to the efficacy and speed of extraction (Figure 40.2).[19]

Figure 40.2 The circle and dotted line tracing the vein were drawn with the patient in an erect position (blue arrows). The straight line was drawn with the patient in a recumbent position (red arrows).

40.5.2 Surgical plan

The timing of ambulatory phlebectomy depends on the nature and type of other venous procedures being performed. When ambulatory phlebectomy is coupled with saphenectomy or endochemical or endothermal ablation of the great or small saphenous veins, phlebectomy below the knee should be performed first. There can be a transient increase in endoluminal pressure in caudal veins during saphenous treatment, which could result in bleeding if ambulatory phlebectomy is performed during the same stage. During the procedure, this occurrence can be reduced by placing the patient in the Trendelenburg position. Depending on the physician and patient preferences, procedures can be staged, treating the great or small saphenous vein first, followed several weeks later by ambulatory phlebectomy. This method allows the existing truncal varicosities to decrease in size or disappear before further procedures.[20,21]

40.5.3 Anesthesia

Local anesthesia with or without epinephrine was used historically, but rarely today, to provide a painless phlebectomy. Most operators now suggest using tumescent anesthesia for ambulatory phlebectomy.

40.5.3.1 TUMESCENT ANESTHESIA

Tumescent Function: *adjective* Etymology: Latin *tumescent-*, *tumescens*, present participle of *tumescere* to swell up, inchoative of *tumere* to swell: somewhat swollen <*tumescent tissue*>[22]

J.A. Klein, a dermatologist, was the first to describe tumescent anesthesia in 1987.[23] His method utilized dilute local anesthesia as a way of creating a field block. Tumescent anesthesia exploits the principles of pharmacokinetics to achieve anesthesia of the epidermis, dermis, and subcutaneous tissues. The subcutaneous infiltration of a large volume of dilute buffered lidocaine and epinephrine causes the targeted tissue to become swollen and firm, or tumescent. Because the subcutaneous tissue is relatively avascular, a large volume of diluted epinephrine injected into this area produces widespread and prolonged vasoconstriction. Vasoconstriction appears to diminish the rate of systemic lidocaine absorption, thus reducing the peak plasma lidocaine concentration, reducing potential toxicity, and permitting a much larger dose of lidocaine to be administered.[23–26]

According to Klein, "In fact tumescent technique permits safe lidocaine dosage of at least 35 mg/kg of body weight and provides effective local anesthesia for as long as ten hours. The widely accepted 5–7 mg/kg safe maximum dose for lidocaine with epinephrine when administered subcutaneously has never been substantiated by a published scientific study."[26]

Klein and others observed that the pharmacokinetics of dilute lidocaine with epinephrine are different from those of 1%–2% lidocaine. With undiluted lidocaine, a measurable plasma level appears in 15 minutes and peaks soon after; lidocaine is metabolized in a few hours. Absorption of the tumescent solution is slower, causing peak plasma levels to occur many hours later, and thus the anesthetic effect is longer. Patients receiving large volumes can have plasma levels that peak in 4–14 hours and linger for longer than 24 hours.

40.5.3.2 PROCEDURE FOR ADMINISTERING TUMESCENT ANESTHESIA

In 1995, Cohn and coworkers[27] reported using the tumescent technique for local anesthesia while performing ambulatory phlebectomy. Three years later, Smith and Goldman[28] reported the use of tumescent anesthesia for ambulatory phlebectomy.

The infiltration of dilute anesthesia in a perivascular position—epidermal and dermal—serves several purposes: (1) the anesthetic effect is long lasting, and sensation returns slowly; (2) with the use of longer needles and dilute solution, fewer needle punctures are needed and less pain upon administration is observed; (3) the tumescent technique causes more compression of the surrounding tissues, leading to less hematoma and ecchymosis; (4) hydrodissection occurs around the vein, facilitating the removal; and (5) reduction of infection, usually limited to the incision site, is a result of the bacteriostatic and bactericidal properties of the lidocaine concentration.[29]

The methods of delivering and mixing of ingredients of tumescent anesthesia vary between operators. A typical solution formula is as follows: 445 mL of 0.9% saline, 50 mL of 1% lidocaine with 1:100,000 epinephrine, and 5 mL of 8.4% sodium bicarbonate.

Presently, most operators use a regular syringe, a self-filling syringe, or a peristaltic pump to deliver tumescent anesthesia. The last two methods facilitate delivery of higher volumes of tumescent anesthesia. Microcannulas or 22-G or 25-G 7-cm hypodermic or spinal needles are used for the delivery of the solution.

40.5.4 Procedural equipment

Incisions or punctures can be made with various devices, including hypodermic needles and surgical blades. The most common instruments are 18-G needles, number 11 blades, and standard 15° ophthalmologic blades (I-KNIFE® II Alcon, Fort Worth, TX). After phlebectomy is completed, 12 × 33-mm adhesive microporous surgical tapes (Steri-Strips™ 3M, Oakdale, MN) are placed to close the punctures.

Several different hooks are available for purchase, varying in size, shape, and sharpness. Commonly known hooks are the Muller, Oesch, Tretbar, Ramelet, Verady, Dortu-Martimbeau, and Kabnick hooks.[30] One particular phlebectomy instrument is not superior to another. It is important for the clinician to be comfortable with a particular set of hooks, making the selection after trying the gamut.

The clamps used for the vein extraction should have a fine tip so that they can grip close to the skin. A serrated face is helpful in maintaining firm traction without slippage. The operator should have at least three fine hemostat clamps available, but five or more are preferable (Figure 40.3).

40.5.5 Procedure

After the anesthetic has been injected into the perivenous tissues, an incision/puncture (~2 mm) is made near the vein (Figure 40.4). Most are oriented vertically, except around the knee, where they should be oriented along the tension

Figure 40.3 A typical surgical tray for phlebectomy.

Figure 40.4 Incision.

lines (Langer's lines). A blunt-tip spatula may be inserted into the opening, although this is not mandatory (Figure 40.5). It does, however, enable a hook to be inserted without interference from surrounding tissues and without enlarging the entrance hole. Once the hook has been inserted, the vein is grasped blindly and brought up and out of the opening (Figure 40.6a). If the vein is not extracted, the hook is maneuvered with finesse, in different angles, inserting and retracting the instrument through the incision until the vein is hooked. The operator should be aware that when attempting different angles at approaching the vein, he or she should execute the motion while paying attention to the depth. When just the perivascular connective tissue is hooked, that tissue is clamped with a hemostat and kept

Figure 40.5 Kabnick phlebectomy instrument with the spatula end used as a dissector.

in traction while the hooking maneuver is repeated until a venous loop is exteriorized. The vein is then grasped between clamps and transected by small scissors (Figure 40.6b and 40.6c). Using gentle traction on the hemostat in a "windshield wiper movement," one end of the varix is teased out of the puncture site. Successive hemostats are applied to the varix as it is extracted from its position, keeping in mind that the vein will eventually tear (Figure 40.6d). Very long segments can often be removed through a single puncture site. Once a segment has been extracted, the operator moves along the vein by a roughly equivalent distance and makes another incision, and the process is repeated. Any redundant perivascular tissue expressed out of the puncture site should be trimmed at skin level. If a hair-size nerve fiber is exteriorized, it is likely that the patient will experience an immediate sharp pain and burning sensation. If the nerve fiber has not been transected, the operator should reintroduce the nerve fiber into the incision and move on to another area to access the vein segment. After the procedure, some patients may develop areas of hypoesthesia that in most cases will resolve.[16]

The operator is encouraged to remove all parts of the varix without leaving isolated segments behind to reduce a possible inflammatory response from thrombosis of the retained segment. However, as long as most of the segment is removed, the patient should have an excellent result. There is rarely cause to ligate a vessel except when a perforator, peripheral foot or hand vessel, or large varix (>1 cm) is exposed (Figure 40.6e). Ligation of vessels may improve cosmetic results due to less bruising and subsequent staining. Perforating veins are recognized as branches in the vein, often with an orientation that is perpendicular to the skin and associated with a deep pulling sensation.

The puncture sites are covered with adhesive microporous surgical tape and sterile dressings and wrapped with a soft gauze roll and stretch bandages (Figure 40.7a through 40.7d).

40.5.6 Discharge recommendations

After ambulating and once vital signs are stable, the patient can be safely discharged from the facility. Discharge and follow-up recommendations to patient are as follows:

1. On the day of surgery, walk *ad libitum*.
2. Take acetaminophen or ibuprofen as needed for discomfort.
3. Wear the compression wraps continuously for 24 hours. After 24 hours, remove all of the dressing materials except the adhesive microporous surgical tape. The adhesive surgical tape should be left in place for 10–14 days.
4. Once the dressing is removed, apply the compression stocking(s) (class 2, 30–40 mmHg) for a minimum of 1 week during waking hours.
5. You may shower after 2 days. There is to be no tub bathing or swimming until the adhesive surgical tapes are removed.

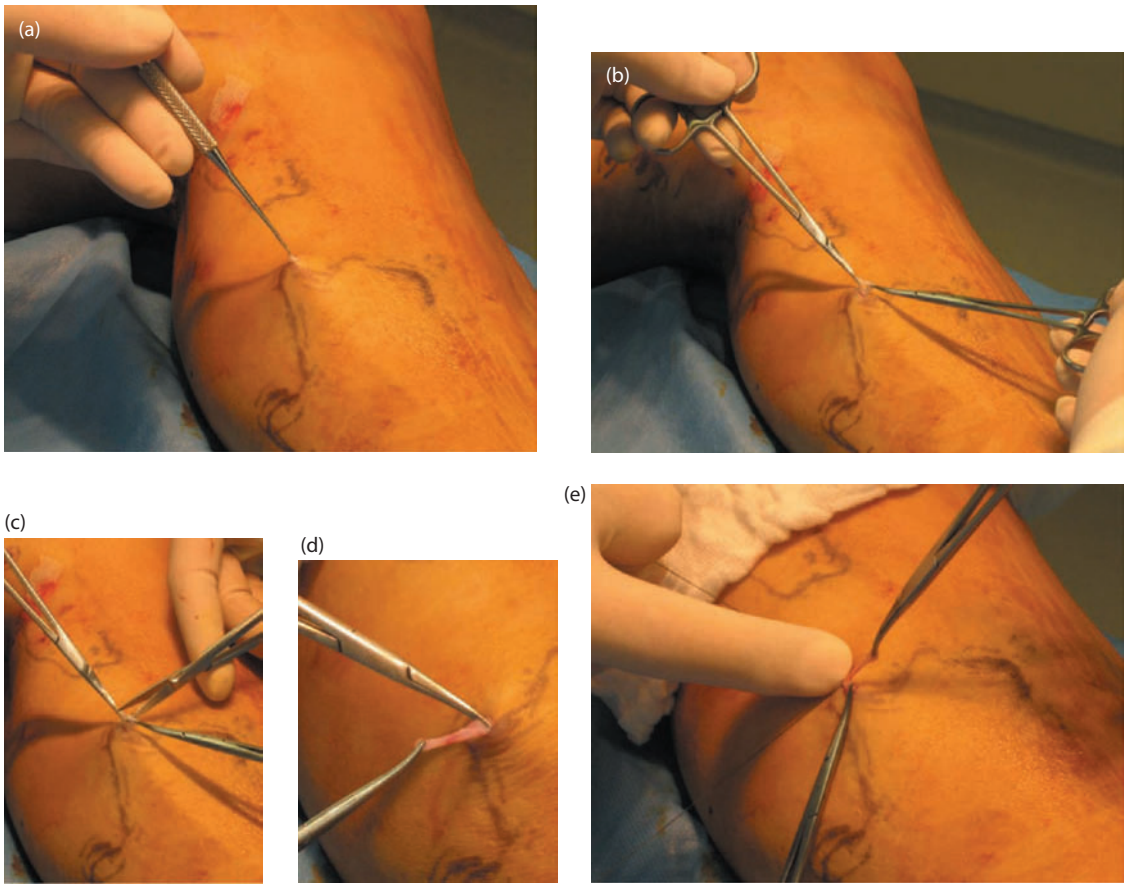

Figure 40.6 **(a)** Hook delivering the target vein above the skin surface. **(b)** Delivering a loop of vein and clamping proximally and distally. **(c)** Transection of the vein loop. **(d)** Gentle traction on the clamp. **(e)** Optional vein ligation.

6. There is to be no lower body or heavy aerobic exercise for 1 week. Return to activities of daily living as usual.
7. Follow-up is to take place in 2 weeks, 3 months, and 1 year.

40.6 COMPLICATIONS

Complications arising from ambulatory phlebectomy are quite rare, but can occur, as listed in Table 40.1.[17,18,20,31,32] There have been two large retrospective studies looking at the complications of phlebectomy. The first was a multicenter French study that reviewed 36,000 phlebectomies.[33] The second was a literature review by Ramelet[16] in 1997. He reported the complication rates of several different authors. The rates of complications vary widely, with skin blistering being the highest, ranging from 1.3% (1997 Olivencia report[18]) to 20% (1980 Gillet report[34]). Telangiectatic matting has varied in the different studies from 1.5% in the multicenter French review[33] to 9.5% in Trauchessec and Vergereau's report.[35] Some authors have reported telangiectatic matting to be as high as 2.4%. However, if we look at current reports, the common complications appear to change in frequency. Regardless, the most common complications are: development of telangiectasias, 2%; blistering, 0.5%; hyperpigmentation (limited), 0.01%; and missed varix, 0.3%.

There is an individual predisposition to developing telangiectasias; however, the exact pathophysiology of this reaction following microphlebectomy has not been elucidated. The incidence of hyperpigmentation depends on the size of the removed veins and the amount of shed blood. The incidence of skin blistering has decreased over time by proper bandage placement, as well as alternatives to skin tapes.

40.7 TRANSILLUMINATED POWERED PHLEBECTOMY

The proprietary name for the transilluminated powered phlebectomy (TIPP) device is the TriVex System (LeMaitre Vascular, Inc., Burlington, MA). The development of this device began in 1966, when Greg Spitz, a surgeon, took an arthroscopic shaver and applied it for the removal of varicose veins. Through many derivations, including transillumination and a delivery method for tumescent anesthesia, the present system was complete. The system contains a modified arthroscopic shaver and a transilluminator coupled with an irrigator that delivers tumescent anesthesia. The concept was developed to decrease the time for

Figure 40.7 **(a)** Placement of adhesive strips over vein extraction sites. **(b)** Sterile gauze placement. **(c)** Gauze wrap. **(d)** Stretch bandage placement.

ambulatory phlebectomy. Although there have been many modifications, the procedure remains virtually the same. Varicose clusters are transilluminated, anesthetized, morcellated, and aspirated (Figure 40.8a and 40.8b).

40.7.1 Study results

Studies of the TriVex System describe several modifications of the procedure to improve patient outcomes. Investigators have often compared manual phlebectomy with TIPP. Most authors indicate that the number of incisions is fewer with TIPP, and the operating time is faster. Ray-Chaudhuri et al.[36] compared post-operative pain scores, with the results after 14 days being 2.6 (manual) and 1.9 (TIPP), a difference that was not statistically significant. Cosmetic effect was also equal. In two randomized trials Aremu et al.[37] and Scavée et al.[38] demonstrated no difference in patient cosmetic scores or satisfaction. These conclusions were recognized by Spitz and coworkers[39] in their original reported findings. In addition, the authors agree that TIPP has a significant learning curve. The learning curve is associated with a higher number of missed veins along with an increased incidence of hematoma and other adverse events. These post-operative complications can be reduced by dissecting carefully along and parallel to the varicose vein, avoiding lateral movements, and using a lower oscillation frequency and a pulsing technique to allow for proper aspiration.[37,40] Other encountered complications after TIPP are skin perforation, nerve injury, deep vein thrombosis, incomplete vein resection, hypertrophic scarring, permanent skin discoloration, and wound infection.[41]

Traditionally, TIPP has been performed in an operating room under general or regional anesthesia with sedation; however, more recently, Spitz reported his experience with a series of 36 patients treated with TIPP in the office setting with good clinical outcomes.[42]

Although TIPP is presently utilized, compared with hook microphlebectomy, TIPP has not been proven to be simpler, more cost effective, less insulting to tissue, or better cosmetically.

40.8 CONCLUSIONS

Ambulatory phlebectomy has been adopted as the standard procedure and definitive treatment for the removal of varicose veins. This simple procedure has added a highly

Table 40.1 Potential complications arising from ambulatory phlebectomy[a]

Complication type	Complication
Anesthetic complications	Allergic reaction (e.g., to preservative or lidocaine)
	Emotionally labile patient
	Technique related (e.g., placement of injection)
Skin complications	Blister
	Dimpling
	Hypo- or hyper-pigmentation (incision)
	Induration
	Infection
	Pigmentation, transitory or permanent
Complications of compression bandage	Blisters
	Contact dermatitis
	Ischemia
	Skin necrosis
	Swelling
Vascular complications	Bleeding or seroma
	Deep vein thrombosis
	Matting
	Pulmonary embolism
	Superficial thrombosis
	Telangiectasias
Lymphatic complications	Lymphocele
	Lymphorrhea
	Persistent edema
Neurological complications	Dysesthesia (temporary or permanent)
	Nerve damage: saphenous, sural, peroneal nerves, etc.
	Temporary hypoesthesia
	Traumatic neuroma

[a] This list is compiled from the experience of several physicians: Jose Olivencia, Robert Muller, Stefano Ricci, Lowell Kabnick, and Michael Ombrellino.[17,18,20,31,32]

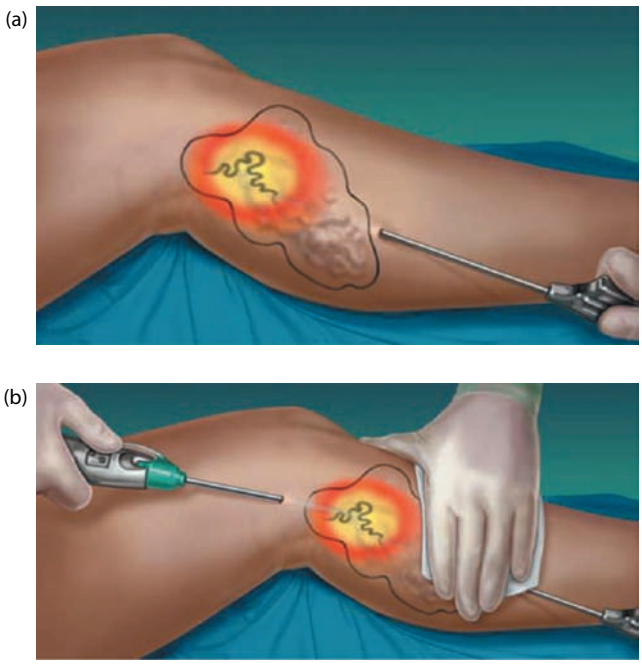

Figure 40.8 **(a)** Transillumination and instillation of tumescent anesthesia. **(b)** Removing vein placement of the TriVex resector and illuminator.

acceptable cosmetic dimension to the medical indication. Using accepted technique—ambulatory delivery, local anesthesia, 2-mm incisions, hook technique, and compression—patients will experience minimal recovery times and few, if any, complications (Figure 40.9a and b).

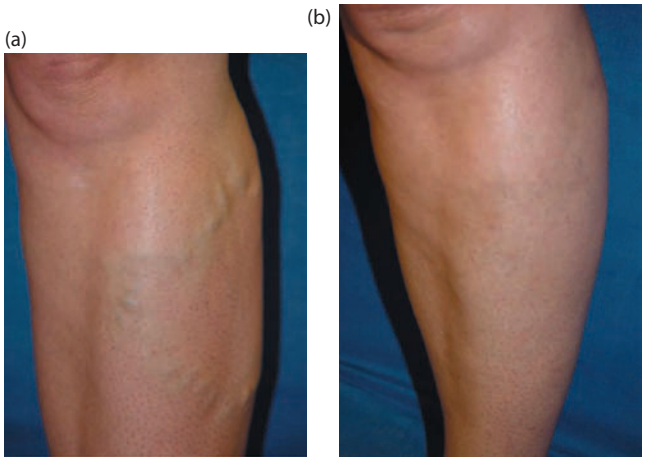

Figure 40.9 **(a)** Pre-operative photograph of varicose veins. **(b)** Post-operative view 12 weeks after phlebectomy.

Ambulatory phlebectomy can be staged or performed along with truncal ablation. Local or tumescent anesthesia is recommended when performing ambulatory phlebectomy. TIPP has been effective in multiple studies in treating varicose veins. Phlebectomy has been superior to sclerotherapy for varicose veins. Pre-operative mapping with transillumination in the recumbent position is accurate.

Guidelines 4.12.0 of the American Venous Forum on phlebectomy

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.12.1	We recommend ambulatory phlebectomy—an outpatient procedure performed under local anesthesia—as an effective and definitive treatment for varicose veins. The procedure is performed after saphenous ablation, either during the same procedure or, at a later stage.	1	B
4.12.2	Transilluminated powered phlebectomy has been effective in multiple studies for the treatment of varicose veins. We suggest it as an option.	2	C
4.12.3	We suggest phlebectomy over sclerotherapy for the treatment of varicose veins.	2	B

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● = Major primary paper
★ = Major review paper
◆ = Published guideline

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41

Recurrent varicose veins: Etiology and management

PAMELA S. KIM, ANGELA A. KOKKOSIS, AND ANTONIOS P. GASPARIS

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41.1 INTRODUCTION

Recurrence of varicose veins following surgical intervention is unfortunately a common and challenging problem. The prevalence of recurrent varicose veins has been reported to be between 20% and 65% after 2–11 years of follow-up. The rate of recurrences increases with time, and accounts for >20% of patients requiring venous surgery.[1–7]

Despite this knowledge, this is an issue which remains incompletely understood. In 1998, an international consensus meeting was held, which proposed guidelines for the definition, description, and treatment options for recurrent varicosities.[5,7,8]

According to the consensus meeting, a clinical definition of recurrent varices after surgery (REVAS) is "the presence of varicose veins in a lower limb previously operated on for varices with or without adjuvant therapies." This definition includes true recurrences and residual veins, as well as varicose veins as a consequence of disease progression.[8] In the more recently published VEIN-TERM consensus document, a new acronym was introduced to describe both recurrent and residual varices. Presence of varices after intervention (PREVAIT) serves as an all-inclusive term for varices that cannot be definitely classified as recurrent or residual.[9]

41.2 ETIOLOGY

The etiology and pathogenesis of recurrent varicose vein disease continues to be a source of debate. Residual disease, new disease, recurrent disease, and neovascularization, along with multiple contributing characteristics, have all been implicated in the formation of recurrence. Whatever the etiology, a source of reflux is identified in about 90% of the patients.[10]

The location of reflux is variable and is identified at the groin region in 37% of cases, at the thigh in 68%, at the popliteal fossa in 23%, at the lower leg in 85%, and in other areas in 11%. Reflux at the saphenofemoral junction (47.2%) and perforating veins (54.7%) has been found to be the most common factor associated with recurrent disease. Remote source of reflux from the pelvis is common (17%), but is often overlooked and should always be considered in multiparous women with recurrent disease. One or two sources of reflux are identified in 68% of patients, and more than two sources are identified in 22%.[10]

Disease can occur at the same site as a previous intervention or at a different site. The underlying etiology in each scenario can be variable and in some patients (15%) it can be mixed (Figure 41.1).[10] Site of disease and underlying etiology can affect treatment strategy.

Residual disease occurs due to tactical and technical error and was historically believed to be the most common cause of recurrent varicose vein disease (Figure 41.2). However, tactical error, which refers to inadequate preoperative evaluation and inappropriate surgery, is now considered to account for 4% of recurrences. Technical error, which refers to inadequate or incomplete surgical technique, accounts for 5.3% of recurrences. This is largely attributed to inexperience and poor technique.[4,5,8] Residual disease can be seen at the same or at different sites of treatment and is usually evident soon after treatment.

In a randomized trial of 133 limbs in the mid-1990s comparing saphenofemoral junction ligation with or without great saphenous vein (GSV) stripping, Jones et al. found that

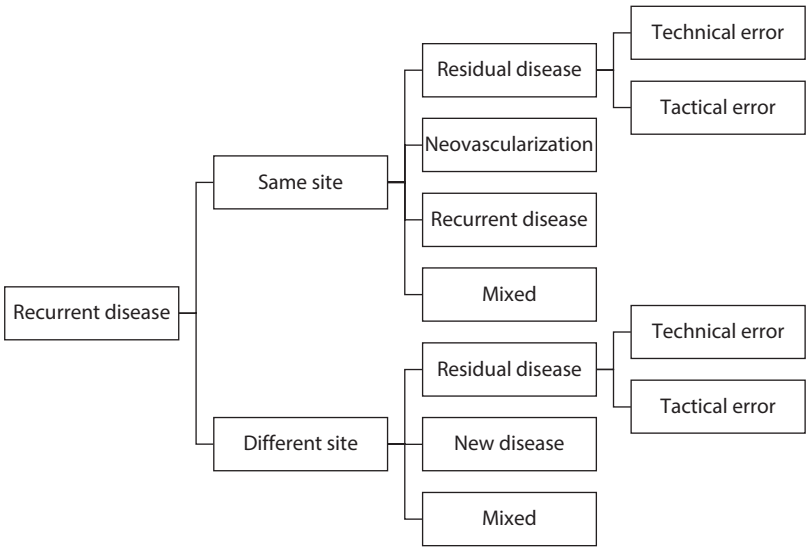

Figure 41.1 Etiology of recurrent varicose veins.

clinical recurrence at 2 years was higher in those without stripping (43% vs. 25%, $P = 0.04$).[11] Subsequently, Joshi et al. demonstrated that incomplete removal of the GSV is a common cause of recurrence. In a prospective study of 419 limbs that had previously undergone GSV ligation and stripping, there were varying lengths of residual GSV observed at re-operation, with the frequency of reflux in the residual GSV greater than at other sites ($P < 0.0001$) or for primary segmental deep venous incompetence ($P < 0.0001$).[12] However, the increasing use of duplex ultrasound imaging pre-operatively and peri-operatively, especially with the popularity of endovenous techniques, has reduced the rates of these errors.[4,5,8]

New disease is defined as the development of new varicosities in an area that has not been treated before (Figure 41.3). It occurs as a result of the development of venous reflux secondary to the natural evolution of the disease and accounts for up to 32% of recurrences.[10] Varicose vein disease is known to be a progressive and evolutionary entity, and thus is unavoidable.[4,5,7] When looking at recurrence patterns after endovenous laser treatment of saphenous vein reflux in 58 patients (79 limbs), the most common recurrence patterns leading to the varicose veins was new reflux in the anterior accessory saphenous and small saphenous veins.[13]

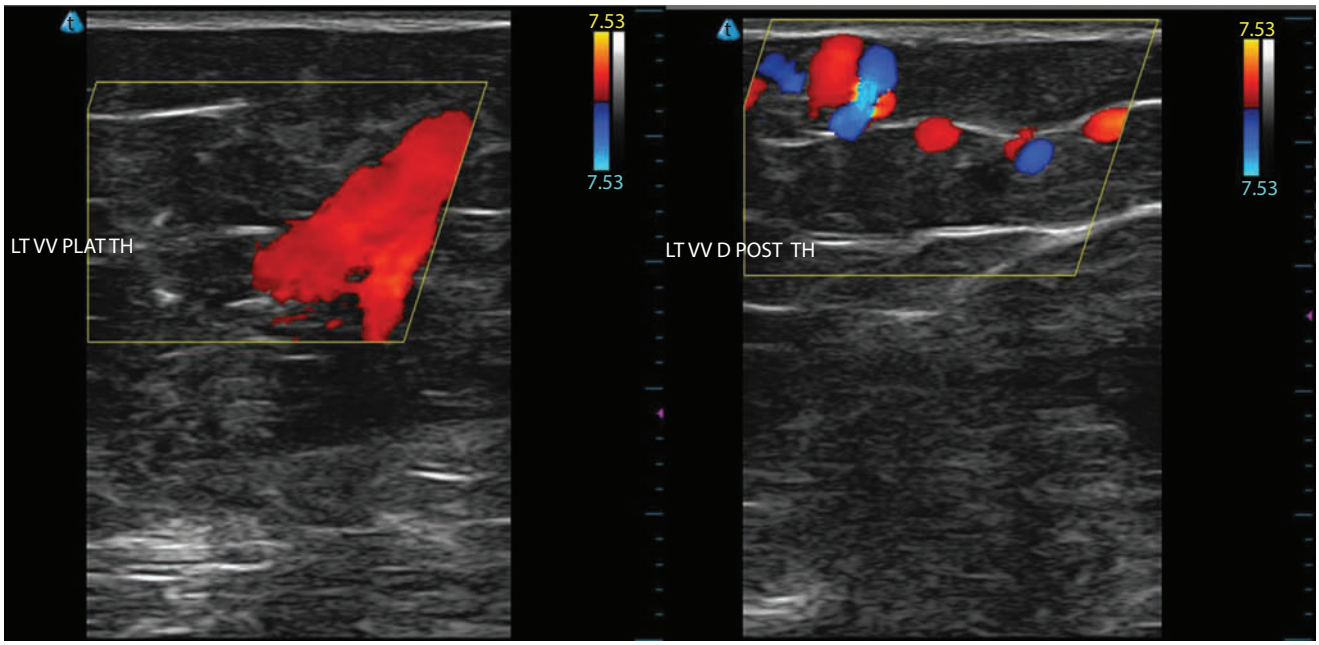

Figure 41.2 Residual disease—lateral thigh varicose veins with reflux in a 32-year-old female 6 weeks after laser ablation of the anterior accessory saphenous vein and phlebectomies.

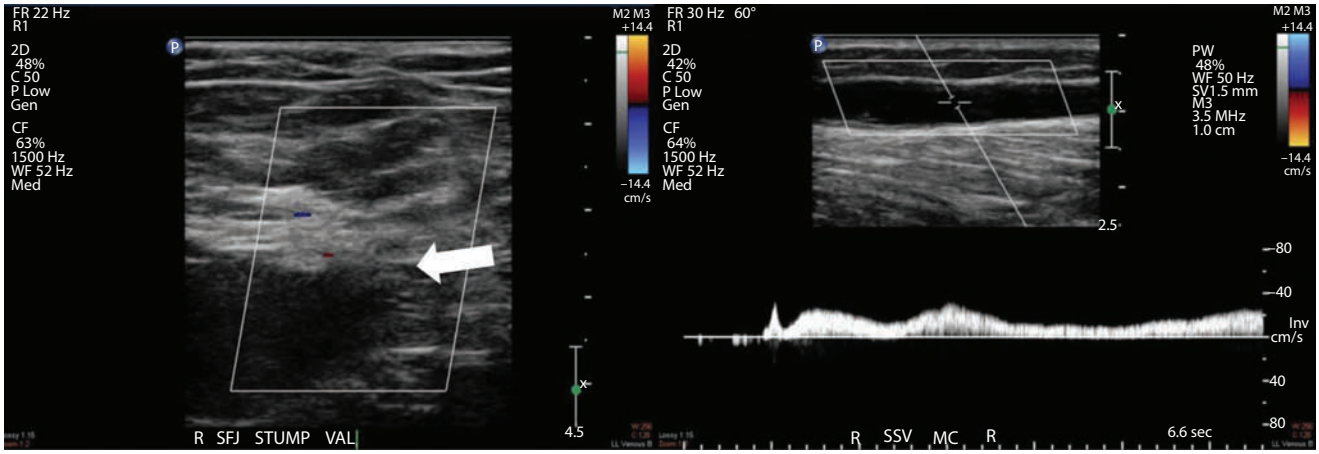

Figure 41.3 New disease—no reflux and absent great saphenous vein in the saphenofemoral junction (arrow) 3 years after radiofrequency ablation. Ipsilateral small saphenous vein reflux has developed that was not present 3 years ago.

While new disease occurs in remote sites, recurrent disease usually refers to new varicose veins that develop in the area that was previously treated (Figure 41.4). Recurrent veins are usually due to failure of treatment of the underlying source of reflux. Some examples include recurrent varicosities due to recanalization of a refluxing previously treated saphenous vein or recurrent veins following treatment in a patient with an untreated underlying pelvic source.[3–5] Elimination of the underlying refluxing source is crucial to the prevention of repeat recurrence.

Neovascularization, which is claimed to account for 13% of recurrent varicose veins, is a particularly debated topic. It refers to the presence of reflux in a previously ligated saphenofemoral junction or saphenopopliteal junction (Figure 41.5) and is caused by the development of incompetent serpentine veins linked with thigh or calf varicosities.[4,5,8] Several studies support neovascularization, demonstrating that it is the most common cause of recurrence if the GSV is not stripped (neovascularization at 43% with ligation alone vs. 25% after stripping, $P = 0.04$).[11] Even complete GSV stump resection and inversion suturing of the common femoral vein venotomy after GSV stripping does not decrease its incidence.[2] It is believed to be a result of angiogenesis following tissue trauma, or a consequence of a "hemodynamic paradox" triggered after elimination of saphenous reflux. Histologically, it is identified by an incomplete wall structure, multiple channel recurrences, and the absence of nerve fibers or neural markers.[14–16] However, other studies dispute the role of neovascularization. Egan et al. looked at duplex and operative findings in a consecutive series of 500 limbs undergoing re-operation for recurrent varicose veins that had previously undergone saphenofemoral junction surgery.[3] All recurrent varicose veins that had duplex-diagnosed neovascularization were associated with persistent reflux in the GSV stump or thigh GSV or both.[3] Regardless, neovascularization is credited as a factor in recurrent varicose vein disease following junctional ligation. With the use of endovenous interventions, which avoid surgical manipulation of the junction, the incidence of neovascularization has almost been eliminated. A recent Cochrane review

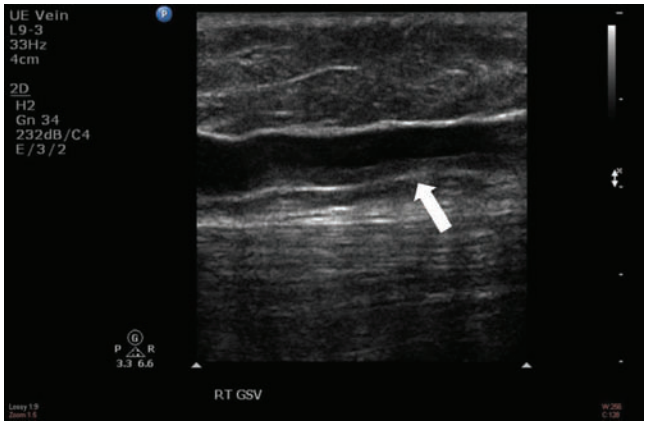

Figure 41.4 Recurrent disease—symptomatic right great saphenous vein recanalization with thickening of the vein wall (arrow) after laser ablation 6 months ago.

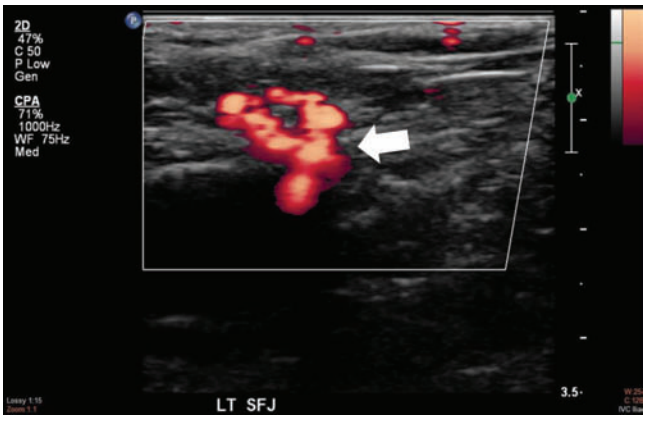

Figure 41.5 Neovascularization—48–year-old female with recurrent varicose veins 16 years after ligation and stripping of the left great saphenous vein. Serpentine vessels (arrow) with reflux in the area of the saphenofemoral junction.

shows that endovenous laser ablation has decreased the rates of neovascularization as compared to open surgery.[17]

Contributing factors such as of gender, family history, post-thrombotic syndrome, congenital factors, pregnancy, obesity, hormonal therapies, and lifestyle also need to be acknowledged. A patient's history of lifestyle factors such as standing for many hours are especially critical to consider, as a multi-institutional study of 199 lower limbs found that these factors had the highest prevalence in recurrence.[7,10]

Along with these factors, there is also some debate regarding the impact of the initial intervention on the possibility of recurrent disease. Overall, recurrence rates are comparable among all treatment modalities, including open surgery, endothermal ablation therapies, ultrasound-guided foam sclerotherapy, and CHIVA (Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire).[4,14,16–23] However, when compared to open surgery, neovascularization and recurrence may be less common after thermal ablation.[4,14,16–18]

41.3 CLASSIFICATION

The CEAP classification, in conjunction with the REVAS classification, is used to identify recurrent varicose veins. The CEAP classification consists of the clinical, etiological, anatomical, and pathophysiological factors of the disease. The REVAS classification adds additional elements to better define the recurrence (Table 41.1).[8]

41.4 DIAGNOSTICS

Recurrent varicose veins may be presented to the clinician in a variety of ways. Patients may notice remaining or new varicosities, or return with recurrent symptoms. Additionally, recurrent varicosities may be found at follow-up visits or picked up on routine post-procedure duplex ultrasound imaging.[8]

When recurrent varicose veins are suspected, it is essential to take a complete history and perform a physical examination. Attention must be paid to the date of previous interventions, the procedure or procedures performed, post-procedure therapy, and any complications. Any new history of deep vein thrombosis, superficial thrombophlebitis, hormonal changes, and other risk factors should also be reviewed, along with enquires into specific lower extremity complaints consistent with recurrent symptoms. Physical examination should include looking for telangiectasias, varicosities, skin changes, wounds, thrombophlebitis, edema, restricted range of motion, neurological abnormalities, the quality of arterial pulses, and the presence of scars in relation to recurrent veins.[8]

Duplex ultrasound imaging is the recommended method of assessing recurrent venous disease. It provides a noninvasive, reproducible method of viewing anatomy, valvular incompetence, and obstruction with sensitivity and specificity rates of >80% and a positive predictive value nearing 100%.[5,7,8] Duplex ultrasound enables the evaluation of the location of the varicosities, as well as the source of the recurrence (i.e., neovascularization or a perforator, residual, or re-analyzed refluxing saphenous vein).

Table 41.1 The recurrent varices after surgery classification

Topographic sites
g: groin
t: thigh
p: popliteal fossa
l: lower leg including ankle and foot
o: other
Sources of reflux
0: no identified source of reflux
1: pelvic and/or abdominal
2: saphenofemoral junction
3: thigh perforators
4: saphenopopliteal junction
5: a popliteal perforator
6: gastrocnemius veins
7: lower leg perforators
Reflux degree
R+: clinical significance probable
R–: clinical significance unlikely
R?: clinical significance uncertain
Nature of sources
Ss: same site of previous surgery
1: technical failure
2: tactical failure
3: neovascularization
4: uncertain or unknown
5: mixed
Ds: different/new site
1: persistent
2: new
3: uncertain or unknown
GSV AK: above the knee
GSV BK: below the knee
SSV: short saphenous vein
O: other
N: neither
Factors that may be contributory
gF: general factors (family history, obesity, pregnancy, oral contraceptives, or lifestyle)
sF: specific factors (primary deep venous incompetence, post-thrombotic syndrome, iliac vein compression, congenital vascular malformation, lymphatic abnormality, calf pump dysfunction, or other)

An assessment of how recurrent disease is impacting a patient's quality of life (QoL) is also important. Various methods, including the Venous Clinical Severity Score, the Aberdeen Varicose Vein Questionnaire, the EuroQol five dimensions questionnaire (EQ-5D) with a visual analog scale, or the Medical Outcomes Study Short Form 36, may be used. Although few studies directly address QoL after recurrence, studies which look at recurrence rates after

initial interventions show that QoL scores are still improved compared to before the initial procedure.[14,16,24–26]

41.5 TREATMENT

The management of recurrent varicose vein disease is a challenge and is frequently associated with overall reduced patient satisfaction. As such, patients should be told from the outset that treatment of their venous disease may not be confined to a single procedure, and appropriate follow-up care is essential.[7,25,27]

The basis of conservative management remains compression therapy and leg elevation. These noninvasive methods have long been used to manage venous hypertension and provide symptomatic relief. Medications to reduce inflammatory mediators are also available, although they are not routinely used.[5,8] In general, a more invasive intervention is now considered after recurrence occurs. This also improves patient satisfaction, as has been found by Pavei et al. They looked at 51 patients for an average of 5.8 years after re-intervention on recurrent varicose veins. More than 90% of the patients stated that they were quite satisfied to very satisfied after their re-intervention, and almost 80% of the patients felt that the results were good to very good.[7]

Redoing open surgery for recurrent varicose veins is more difficult, being complicated by distorted normal anatomy. It is also associated with an increased incidence of complications such as neurovascular injury and infection, leading to increased hospital costs and prolonged recovery.[5,28] A study of 67 lower limbs with recurrent varicosities of the GSV compared endovenous laser ablation to conventional surgery and showed that the surgery patients required more general and regional anesthesia ($P < 0.001$), with longer hospital stays ($P < 0.05$), and longer time off work ($P < 0.0001$). The wound infection rate was higher amongst the surgery patients (8% vs. 0%, $P < 0.05$), as was the paresthesia rate (27% vs. 13%, $P < 0.05$).[1] In a similar study of 116 lower limbs with recurrent varicosities of the small saphenous vein, there were more patients with sural nerve neuralgia in the surgery group (20%) than after endovenous laser ablation (9%), although this did not reach statistical significance.[29] As a result, less invasive approaches to treat recurrent varicose veins are currently advocated.

Radiofrequency ablation, endovenous laser ablation, and ultrasound-guided foam sclerotherapy have all been described as safe and effective options for the treatment of recurrent varicose veins.[28,30–32] At 3 months, there was a 96% success rate in the retreatment of GSVs by endothermal techniques, along with an improvement in QoL scores.[30] In another study with an 18-month follow-up period, no clinical recurrence and no recanalization of retreated GSVs or small saphenous veins were appreciated after endovenous laser ablation.[28] Ultrasound-guided foam sclerotherapy of above-knee and below-knee GSV reflux recurrence was also found to be effective with only one or two sessions at 1-year of follow-up.[31] In a 5-year prospective study of 203 limbs, Chapman-Smith and Browne demonstrated serial annual duplex ultrasound reduction in GSV diameter, which was maintained over time. There were 15.5% of limbs that required repeat sclerotherapy sessions at between 12 and 24 months, but less than 10% of limbs required repeat therapy in subsequent years.[32]

Treatment of varicose veins includes mini-phlebectomy or ultrasound-guided sclerotherapy. Phlebectomy for residual disease is an excellent option and is very successful. Recurrent varicose veins can be challenging, as the veins tend to be stuck in the subcutaneous tissue and are thin walled and therefore tear easily, making complete removal difficult. In this situation, ultrasound-guided sclerotherapy may be a better option. This is also the case with the treatment of neovascularization in the groin, as open surgical treatment is challenging (Figures 41.4 and 41.5).

41.6 CONCLUSIONS

REVAS remains a poorly understood pathology, but is unfortunately a common problem. As such, continued studies are essential to find the best therapies to treat and prevent recurrences. For now, minimally invasive endovenous interventions offer the best results in the treatment of this pathology.

Guidelines 4.13.0 of the American Venous Forum on the management of recurrent varicose veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.13.1	For a clinical description of varicose vein recurrence, we recommend using the recurrent varices after surgery classification.	1	B
4.13.2	For evaluation of varicose vein recurrence, we recommend duplex ultrasound scanning of the location of the varicosities as well as the source of the recurrence.	1	B
4.13.3	For treatment of varicose vein recurrence, we suggest endovenous techniques, ultrasound-guided foam sclerotherapy, or phlebectomies, depending on the etiology and extent of varices.	2	C

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● = Major primary paper
★ = Major review paper
◆ = Published guideline

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42

Treatment of varicose veins: Current guidelines

JOSE I. ALMEIDA

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42.1 INTRODUCTION

In the United States, an estimated 23% of the adult population has varicose veins, and 6% has more advanced chronic venous disease (CVD), including skin changes and healed or active venous ulcers.[1,2] In patients with CVD, a complete history and detailed physical examination are complemented by duplex scanning of the deep and superficial veins. The most important concept for the practitioner treating varicose veins to understand is that simple vein removal, without proper workup, will not yield good results. It is critical to recognize that bulging veins are usually associated with an underlying source of venous hypertension, and treatment of the source is as important as the vein removal itself. Prior to treatment, the physician must perform a thorough evaluation with duplex ultrasound imaging to identify the source of venous hypertension and its highest point of reflux. Venous plethysmography may be used selectively if physiologic information is also needed. Evaluation for thrombophilia is performed only in patients with recurrent deep venous thrombosis, thrombosis at a young age, or thrombosis in an unusual site. A quality of life assessment should be obtained with a disease-specific instrument to evaluate the severity of CVD and patient-reported outcomes after intervention.

Open surgical treatment of varicose veins with high ligation and stripping of the great saphenous vein (GSV) or small saphenous vein combined with excision of large varicose vein clusters has been the standard of care for over a century. Over the past 15 years, however, endovenous thermal ablation has largely replaced the classic high ligation and stripping operation in the United States. Varicose vein excision performed from multiple larger skin incisions[3] has also been abandoned, and stab phlebectomy and powered phlebectomy have been adopted.

42.2 CLINICAL EXAMINATION

The revised CEAP classification is recommended for documenting clinical class (C), etiology (E), anatomy (A), and pathophysiology (P). Patients with CVD are assigned into classes: C1, spider veins or telangiectasias; C2, varicose veins; C3, edema; C4a, pigmentation and/or eczema; C4b, lipodermatosclerosis and/or atrophie blanche; C5, healed ulcer; and C6, active ulcer.[4] This chapter will focus on the treatment of patients with varicose veins (i.e., C2 disease). The revised Venous Clinical Severity Score (rVCSS) is recommended for grading the severity of symptoms and signs of CVD. The rVCSS is the best currently available instrument for quantifying improvement and assessing changes in the severity of CVD during follow-up (short term, <1 year; mid-term, 1–3 years; long term, >3 years).[5]

42.3 NON-SURGICAL MANAGEMENT

If non-operative management is the desired treatment modality, phlebotonic drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chestnut seed extract [aescin]) in addition to compression hose are available for patients with pain and swelling due to CVD—in some countries, these drugs are not available. Readers should consult Chapter 32 for evidence of the efficacy of drug therapy. Although compression may improve symptoms, a large systematic review of compression hosiery for uncomplicated simple varicose veins concluded that: (1) evidence supporting compression garments to decrease progression or to prevent recurrence of varicose veins after treatment is lacking; and (2) patient non-compliance with compression therapy was high.[6] The need for a period of compression treatment before any operative intervention for C2 disease has been advocated by third-party

payers; however, data from the REACTIV trial contradict this policy. The REACTIV trial results support interventional treatment becoming more efficacious and cost effective.[7] Compression therapy using moderate pressure (20–30 mmHg) is recommended for patients with varicose veins who are not candidates for intervention.

42.4 INTERVENTIONS

42.4.1 Open venous surgery

42.4.1.1 HIGH LIGATION, DIVISION AND STRIPPING OF THE GREAT SAPHENOUS VEIN (GVS)

GSV reflux is the most common form of venous insufficiency in symptomatic patients and is most frequently responsible for varicose veins of the lower extremity.[8,9] The first objective in the treatment of varicose veins is therefore elimination of GSV reflux by its removal from the circulation. Although endothermal ablation is favored in the United States, in many countries, conventional surgery remains the standard of care.[10]

High ligation and stripping is performed through a small, oblique incision made in the groin crease, and the saphenofemoral junction (SFJ) is dissected, taking care not to injure the surrounding lymphatic tissue or the external pudendal artery. The anterior wall of the common femoral vein must be visualized in order to clearly identify the SFJ. Flush ligation of the saphenous vein is performed in order to minimize the chances of post-operative thrombus formation in the cul-de-sac of the saphenous vein stump. In addition, it is also important to avoid narrowing of the common femoral vein. A flexible plastic Codman stripper (without the removable acorn) is often used for invagination stripping. The saphenous vein is tied to the end of the stripper and the vein is invaginated into its lumen as the stripper is pulled down through a small incision made below the knee. The metallic Oesch perforate–invaginate (PIN) stripper is less traumatic and the procedure is performed under local tumescent anesthesia in the office.[11] The PIN stripper is passed via groin incision for inversion stripping and removed through a puncture wound below the knee. For treatment of the incompetent GSV, stripping of the saphenous vein should be done to the level of the knee because of an increased incidence of reported saphenous nerve injury if stripping is performed below the knee.[12] Cryostripping, whereby a cryoprobe is inserted into the saphenous vein, may minimize bleeding. After maintaining the freezing cycle for a couple of seconds, the GSV is invaginated with an upward tug and it is stripped toward the groin. Stripping of any technique is usually completed with a phlebectomy to remove the bulging varicose veins through a small stab wound. To reduce hematoma formation, pain, and swelling, a period of post-operative compression of 1–2 weeks is usually satisfactory.

42.4.1.1.1 Ambulatory selective varices ablation under local anesthesia (ASVAL)

The ambulatory selective varices ablation under local anesthesia (ASVAL) operation emphasizes preservation of the incompetent saphenous vein and relies on stab phlebectomy of all varicose tributaries to meet the treatment goals. This technique is most suitable for patients with less advanced C2 disease—in one study, 33% of patients had no symptoms and 91% had no trophic skin changes.[13]

42.4.1.1.2 Conservative hemodynamic treatment for chronic venous insufficiency (CHIVA)

The conservative hemodynamic treatment for chronic venous insufficiency (CHIVA) technique uses a hemodynamic approach based on the principles of preserving the saphenous vein and rerouting venous drainage into the deep system. The goal of CHIVA is to decrease the hydrostatic pressure in the saphenous veins and tributaries by strategic ligations placed in the superficial venous system; drainage of the superficial veins is preserved, usually via a reversed flow.[14] The CHIVA and ASVAL procedures have not gained acceptance worldwide and should be used selectively by surgeons trained in these techniques.

42.4.1.2 ENDOVASCULAR VENOUS SURGERY

42.4.1.2.1 Thermal Ablation

Endovenous thermal ablation of the GSV is safe and effective, with faster recovery and better cosmesis than surgical high ligation and stripping.[15,16] Endovenous thermal ablation causes a direct thermal injury to the vein wall resulting, in destruction of the endothelium, collagen denaturation of the media, and fibrotic and thrombotic occlusions of the vein. The two most popular methods of thermal ablation presently used are radiofrequency (RF) ablation, which uses a catheter to direct RF energy from a dedicated generator, and endovenous laser (EVL) ablation, which employs a laser fiber and generator.

RF ablation for the treatment of varicose veins was approved by the United States Food and Drug Administration (FDA) in 1999. The current RF catheter was introduced in 2007, and is more effective and faster to use than the first-generation device; this version does not need an irrigation system and the entire pull-back procedure takes 3–4 minutes. The endoluminal energy delivered by RF ablation provides heat transfer via conduction to the vein wall for injury.

Laser treatment was first recommended in 1989, but it took 10 years before the first successful clinical application of a diode laser for the treatment of varicose veins was reported—the technique was soon adopted and perfected in the United States and worldwide.[17,18] The endoluminal energy delivered by laser provides heat transfer via conduction and convection to the blood for injury.[19] Blood coagulates at 70–80°C, steam bubbles form at 100°C, and carbonization of coagulum is observed at 200–300°C. EVLs are available in different wavelengths. Currently available laser systems include hemoglobin-specific laser wavelengths (810, 940, and 980 nm) and water-specific laser wavelengths (1319, 1320, and 1470 nm). Amongst the EVL wavelengths, the data are not demonstrative of one wavelength being

superior to another. Device choice is a matter of physician preference.

RF and EVL ablation are similar techniques in many ways. Both RF and EVL ablation are catheter-based endovascular interventions which use electromagnetic energy to occlude (ablate) the treated vein by heat transfer. Both destroy the endoluminal surface of the incompetent truncal vein and heal by fibrosis. Both require local tumescent anesthesia and are done under sonographic guidance. Both are outpatient procedures that can be performed in an office setting. Patients complain less of pain and discomfort after thermal ablation and return to work earlier than after open surgical procedures.[20]

42.4.1.2.2 Sclerotherapy (liquid or foam)

Injection of a chemical into the vein to achieve endoluminal fibrosis and obstruction of the vein has been used for almost a century. Sclerotherapy lost popularity after a study from Europe demonstrated poorer clinical outcomes when sclerotherapy (liquid) was compared with surgery.[21] Chemical ablation re-entered the arena with the advent of foam sclerotherapy, which has improved efficacy. Sclerosant in the form of foam is more effective for saphenous vein closure when compared to its liquid counterpart[22,23] and is more readily visualized with ultrasound imaging (ultrasound-guided foam sclerotherapy). Until recently, physicians only had the option of compounding their own foam using a liquid–air mixture. Physicians began substituting carbon dioxide for air when case reports of paradoxical embolization began to surface in the literature.[24]

In a randomized trial involving 798 participants with primary varicose veins at 11 centers in the United Kingdom, the authors compared the outcomes of foam, laser, and surgical treatments. Primary outcomes at 6 months were disease-specific quality of life and generic quality of life, as measured by several scales. Secondary outcomes included complications and measures of clinical success. After adjustment for baseline scores and other covariates, the mean disease-specific quality of life was slightly worse after treatment with foam than after surgery ($P = 0.006$), but was similar in the laser and surgery groups. There were no significant differences between the surgery group and the foam or laser groups in measures of generic quality of life. The frequency of procedural complications was similar in the foam group (6%) and the surgery group (7%), but was lower in the laser group (1%) than in the surgery group ($P < 0.001$); the frequency of serious adverse events (approximately 3%) was similar among the groups. Measures of clinical success were similar among the groups, but successful ablation of the main trunks of the saphenous vein was less common in the foam group than in the surgery group ($P < 0.001$).[25]

42.4.1.2.3 Polidocanol endovenous microfoam

In order to mitigate nerve injuries and to reduce the number of injections required for the placement of perivenous tumescent anesthesia during thermal truncal vein ablation, non-thermal alternatives for truncal vein closure have generated some interest.

Polidocanol endovenous microfoam is a proprietary pharmaceutical-grade foam of an oxygen–carbon dioxide mixture that is dispensed from a proprietary canister device. Two placebo-controlled studies—VANISH 1 and 2—have demonstrated its satisfactory efficacy and tolerance.[26]

42.4.1.2.4 Mechanochemical ablation

This device associates a catheter with a fast-rotating thin wire tip and an infusion of liquid sclerosing agent. It can be applied along the saphenous trunk without local anesthesia and provides excellent immediate and mid-term closure rates.[27]

42.4.1.2.5 Endovenous glue

This system uses catheter-delivered glue (a proprietary formulation of n-butyl cyanoacrylate) to treat refluxing truncal veins. Short-term (3-month) closure of the target GSV was high (99%) in a recent pivotal trial[28] and was similar to that observed in a prior single-arm feasibility study (95%)[29] and in a prospective multicenter European study (96%).[30]

42.4.1.2.6 Steam ablation

Steam ablation using a catheter and generator has been introduced in Europe, but the available data are insufficient.[31]

42.4.2 Non-Truncal Veins

42.4.2.1 STAB PHLEBECTOMY

Elimination of an incompetent GSV reduces venous hypertension, relieves patient symptoms, and prevents or slows the progression of disease. However, GSV ablation alone is usually not sufficient for the elimination of all existing varicose veins. Stab phlebectomy is indicated for the removal of varicosed venous tributaries when visible and palpable on the surface of the skin. Stab phlebectomy is simple to perform, well tolerated, and can be used in conjunction with other treatment modalities.[32] Regarding the controversy as to whether to do GSV ablation with simultaneous or delayed phlebectomy, combined endovenous ablation and stab phlebectomy delivers improved clinical outcomes and a reduced need for further procedures, as well as early quality of life improvements.[33]

42.4.2.2 TRANSILLUMINATED POWERED PHLEBECTOMY (TIPP)

TIPP is an alternative to stab phlebectomy for extensive varicose veins. Instrumentation includes a central power unit with controls for irrigation pump and resection oscillation speeds; an illuminator hand-piece connects to the control unit using a fiber optic cable and provides high-intensity light for transillumination and delivery of tumescence irrigation; a resector hand-piece has both 4.5-mm and 5.5-mm options. Although no published data clearly show a statistically significant clinical advantage of TIPP over stab phlebectomy, except for in terms of fewer incisions, most studies reported on earlier-generation systems and techniques. In a randomized clinical trial, TIPP was compared to stab

phlebectomy in 188 limbs of 141 patients with varicose veins. At 6 and 12 months, there were no significant differences in cosmesis ($P = 0.955$ and $P = 0.088$, respectively) or recurrence ($P = 0.27$ and $P = 0.11$, respectively).[34]

With the newer-generation system and modified technique and learning curve adjustments, TIPP has become less traumatic, which may decrease potential complications and improve outcomes over those that have been previously reported. Until new trials are performed, any additional potential benefits of TIPP have yet to be substantiated.

42.4.2.3 SCLEROTHERAPY

In a randomized clinical trial comparing stab phlebectomy to compression sclerotherapy for the treatment of varicose veins, the 1-year recurrence rates amounted to one out of 48 for stab phlebectomy and 12 out of 48 for compression sclerotherapy ($P < 0.001$); at 2 years, six additional recurrences were found for compression sclerotherapy ($P < 0.001$).[35]

42.5 RECURRENT VARICOSE VEINS

Recurrent varicose veins after surgery were reported to have a 60% incidence at 34-year clinical follow-up.[36] Neovascularization was found to be as frequent as technical failure (20% vs. 19%), and the SFJ (47.2%) and leg perforators (54.7%) were the areas that were most often involved by recurrent reflux.[37] Stab phlebectomy, sclerotherapy, or endovenous thermal ablation of the accessory saphenous vein or perforating veins can be performed depending on the source, location, and extent of recurrence. A Cochrane review on sclerotherapy was published in 2006 and concluded that the evidence supports the current place of sclerotherapy in modern clinical practice, which is usually limited to the treatment of recurrent varicose veins following surgery and thread veins.[38]

42.6 OUTCOMES

Many clinical tools are available for evaluating the results of procedures on patient-focused outcomes, including symptom improvement, recurrence of varicosity, healing or recurrence of skin ulcers, improvements in the chronic, progressive symptoms of CVD, improved quality of life, and cosmetic improvements. At a minimum, the basic CEAP clinical classification in combination with the rVCSS should be used to follow patients in routine clinical practice.

Guidelines 4.14.0 of the American Venous Forum on the treatment of varicose veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.14.1	We suggest venoactive drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chestnut seed extract [aescin]) in addition to compression for patients with pain and swelling due to chronic venous disease in countries where these drugs are available.	2	B
4.14.2	We recommend thermal ablation or stripping as the primary treatment for varicose veins. We recommend compression therapy using moderate pressure (20–30 mmHg) for those who are not candidates for a procedure.	1	B
4.14.3	We recommend endovenous thermal ablation in preference to high ligation and stripping or foam sclerotherapy for the management of saphenous vein incompetence.	1	B
4.14.4	In highly selected patients, we suggest using non-thermal venous ablation procedures in preference to high ligation and stripping or endothermal venous ablation for the management of saphenous vein incompetence.	2	C
4.14.5	We suggest mini-phlebectomy, foam sclerotherapy, or endovenous thermal ablation for recurrent varicose veins.	2	B
4.14.6	We suggest mini-phlebectomy over sclerotherapy for the treatment of tributary varicosities once axial reflux has been addressed.	2	B
4.14.7	In clinical practice, we recommend that the basic CEAP clinical classification in combination with the revised Venous Clinical Severity Score should be used to follow outcomes.	1	B

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● = Key primary papers
★ = Major Review articles

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43

Surgical repair of primary deep vein valve incompetence

RAMESH K. TRIPATHI

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43.1 INTRODUCTION

The description of the first successful repair of the deep vein valve by Kistner[1,2] was a seminal event. Though initially controversial, it sparked a resurgence of interest in deep venous reflux disease, leading to important advances. Today, vein valve reconstruction is an established option in the treatment of deep venous reflux due to worldwide contributions to the evolving concepts and techniques. With the advent of newer imaging modalities and better understanding of reflux pathology, the field of deep venous valve reconstruction has been resurgent.

43.2 SURGICAL PATHOLOGY

Venous ulcer pathophysiology is based on venous hypertension that leads to microcirculatory anomalies and subsequent trophic lesions.[3] The aim of any treatment addressing venous ulcer (VU) is to reduce venous hypertension, both to obtain healing and to prevent recurrence.

In most papers dealing with venous ulceration, obstruction was still not identified as a leading cause of venous hypertension,[4,5] with reflux being the most frequent cause. Various reflux patterns were defined at the Vein Term Consensus Conference.[6] Axial reflux is mainly responsible for severe chronic venous insufficiency compared with segmental deep reflux, isolated or combined.[7]

Roughly half of the patient population undergoing valve repair will be found to have "primary" valve reflux and the other half will have secondary or post-thrombotic disease.[8,9]

Primary lesions of deep venous valves are classified into the subtypes listed in Figure 43.1. Very rarely, congenital anomalies such as tricuspid valves, absent valves, or duplicated refluxive conduits involving one or both limbs may be found. In "primary" valve reflux, the culprit can be vein wall dilatation or valve cup or cusp abnormalities. Often, valve attachment lines can be easily seen and traced on the surface of the vein from the outside. The valve angle where the two valve attachment lines come together at the commissure is widened and often obtuse (normally acute).[9,10] This may be seen at only one or both of the two commissures. The adventitia may be thick, in some cases obscuring the valve attachment lines. Internally, the valve cusps are redundant with excessive pleats and folds, thus failing to coapt properly (Figure 43.2) and allowing reflux. The texture of the valve cusps themselves appears normal and translucent.

In a subset of patients, distal deep vein thrombosis is seen below a "primary" refluxive valve.[11] It is not clear whether the thrombotic process is the result (from reflux stasis) or cause of the reflux. In most post-thrombotic series, new reflux develops in valves that are remote from the thrombus site for unknown reasons.[11–14]

43.3 INDICATIONS AND SELECTION OF PATIENTS

Deep valve repair should be reserved for patients who have exhausted other less intensive therapeutic options. Typically, a course of compression therapy would have been tried for a

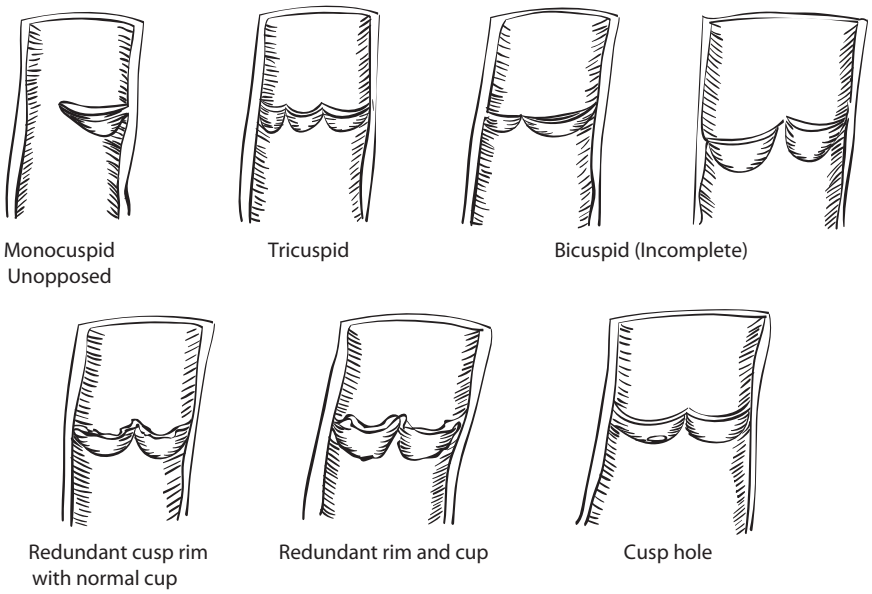

Figure 43.1 Valve station abnormalities in primary incompetence.

Figure 43.2 Redundant valve cusps with excessive pleats and folds that fail to coapt properly and allow reflux.

reasonable period of greater than 3 months. However, certain socioeconomic factors and special situations such as occupation or comorbidities may render long-term compression therapy impractical or impossible. Potential candidates for deep valve reconstruction should have symptoms of CEAP (C, clinical; E, etiology; A, anatomy; P, pathophysiology) clinical class 4 or higher. Pain is not adequately covered by the CEAP classification. About 10% of patients with deep valve reflux will have severe (visual analog scale >5) pain unaccompanied by other clinical manifestations. The severity of pain with or without other clinical features is an important consideration in case selection. Recurrent cellulitis and recurrent superficial or deep venous thromboses are less common indications. As most patients with deep venous reflux have other system involvement,[15] simpler procedures such as saphenous ablation and/or perforator interruption might have been carried out already. It is well known that venous disease often responds to partial correction, at least initially. Deep valve repair is indicated only when the initial approach fails.[13] Since chronic venous disease in general poses little risk to limb or life, this graduated approach makes sense.

43.4 PRE-OPERATIVE ASSESSMENT

Prospective candidates should undergo a general as well as a detailed venous evaluation. The latter should employ the CEAP classification system, with venous severity scoring. Current medications including hormones and anticoagulants are relevant. Adequacy of arterial perfusion should be ascertained.

A comprehensive set of investigations is necessary for initial assessment and follow-up. These include duplex scanning that should document axial deep venous reflux and a repairable reflexive valve (Figure 43.3a and b). Although there are no techniques to precisely quantify reflux at a single valve station, modern duplex scans can calculate reflux velocities and valve closure times. Valve closure times may have errors in clinical correlation and therefore other parameters are to be combined to assess reflux.[16–18] B-mode scanning can also delineate the type of valve abnormality

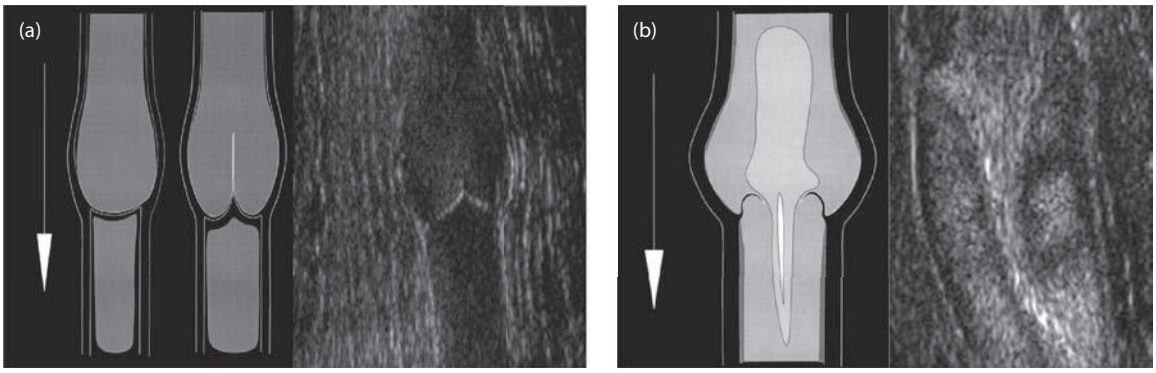

Figure 43.3 **(a)** Normal competent valves on schematics and B-mode flow. **(b)** An incompetent valve with the "scimitar sign" indicating severely prolapsed cusps.

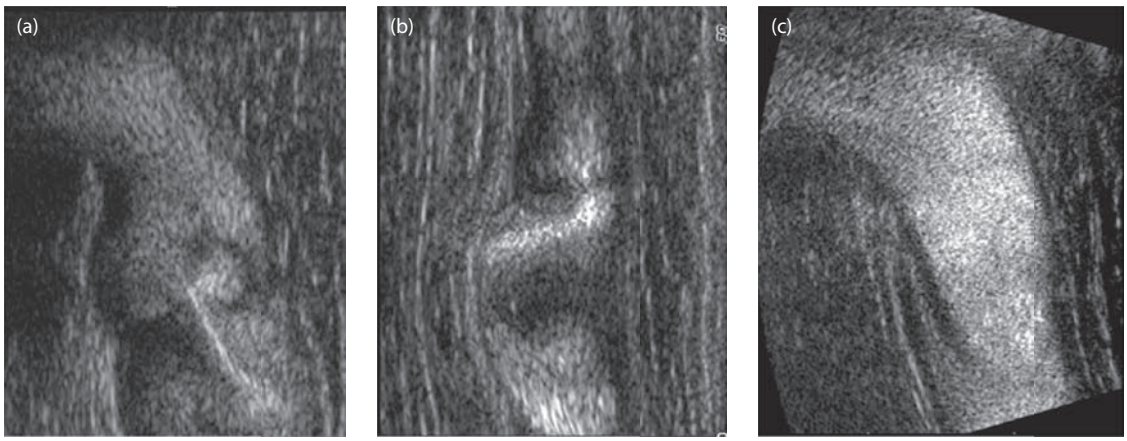

Figure 43.4 **(a)** Incompetent valve with reflux jet in the opposite direction to the cusps. **(b)** Single prolapsed cusp. Blood is directed towards the vein wall. Suitable for valvuloplasty. **(c)** Avalvular vein. No valve repair possible.

(Figure 43.4a–c).[19] It can also measure inter-valvar distances that can estimate the degree of plication/excision of venous valve required (Figure 43.5a and b).[19]

A global test such as ambulatory venous pressure or air plethysmography and contrast computed tomography/magnetic resonance venography studies are useful not only for quantifying venous hypertension, but also for ruling out any functional obstruction in the iliocaval region. The author uses a descending venogram pre-operatively to identify the valve to be repaired and intra-operatively to document abolition of reflux following valve repair (Figure 43.6a and b). Venography is no longer used to quantify reflux as the test has been found to be not very specific.[16,20]

The author advocates deep vein valve repair if the valve closure time is >3 cm/second and is associated with reflux velocities >5 cm/second by standing duplex scan with the patient performing the Valsalva maneuver. Crude estimation of reflux severity can be achieved by counting the number of refluxive venous segments (segment score) or the distal extent of uninterrupted reflux in the limb (Kistner reflux grades).[4,9,17] "Axial reflux" is frequently (in about 40%) but not exclusively associated with severe clinical presentation.[7] Venous filling time (VFT) in ambulatory venous pressure and venous filling index (VFI_{90}) measured

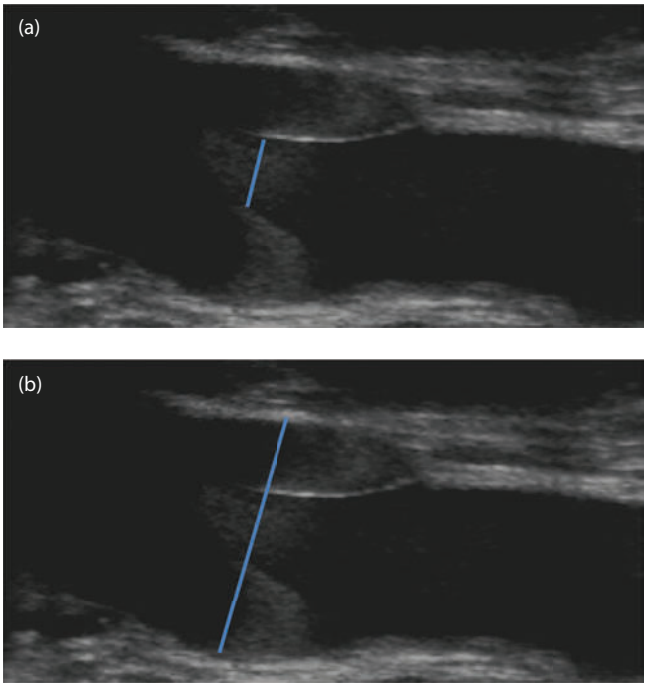

Figure 43.5 **(a)** Intervalvar distance. **(b)** Transcommissural diameter.

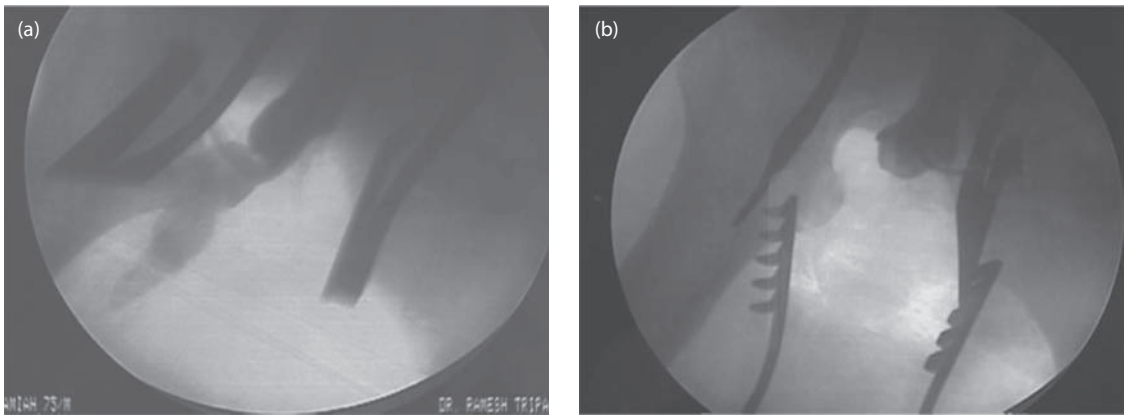

Figure 43.6 **(a)** Reflux at common femoral vein (CFV) valve on intra-operative descending venography. **(b)** Abolition of reflux after internal valvuloplasty.

by air plethysmography have been shown to correlate with the global severity of reflux and are useful outcome monitors.[4,17,21,22] Several quality of life measures that are specific for venous disease (Short Form 36 [SF 36], Venous Severity Scores, Venous Clinical Severity Scores, and Venous Disability Scores) are now available. A few of these are easy enough to be employed on a routine basis in venous practice.

A routine hypercoagulability workup is recommended to provide proper guidance for the duration and extent of post-operative anticoagulation.

43.5 SURGICAL TECHNIQUES

The patient is positioned supine with the femoral or popliteal (medial approach preferred) areas prepared following epidural anesthesia in the reversed Trendelenburg 45° position.

Pre-operative duplex imaging of deep venous reflux is carried out for valve measurements of deep vein diameters in inspiration and expiration and inter-valvar distance computation at multiple sites of possible valvular repair, and these sites on the skin are marked to enable intra-operative identification and localization.[19] Valves with most severe reflux are chosen for valvuloplasty. Multilevel repair is carried out when more than one valve is refluxing at greater than 3 seconds for valve closure time.

A femoral valve is invariably present below the take-off of the profunda femoris vein. This is the main target for repair. A second inconstant femoral valve may be found 2–5 cm below the first valve; a common femoral valve may also be present in some cases. When present, these extraneous valves provide convenient alternative or additional sites for repair through the same incision. A profunda femoris valve is commonly present (in about 85%) at the origin; in its absence, a more distal valve can be found 2–3 cm distally. In the popliteal vein, a valve is present in about 70% at the adductor tubercle level. A valve at the mid- or distal popliteal vein is found less frequently (in about 50%) in non-thrombotic cases. However, one or more valves are invariably present in the adjoining posterior tibial vein. Guidance to repairable valve station locations may be obtained from pre-operative venography or duplex, but not always.

43.6 IDENTIFICATION OF VALVE ATTACHMENT LINES

Once the target vein is exposed, the valve station may become readily apparent after a preliminary adventitial dissection. Through a combination of sharp and blunt dissection, the adventitia is peeled away (Figure 43.7). To prevent venospasm and vein trauma, excessive handling of the vein is avoided. Where possible, atraumatic vascular ring forceps should be used to handle the vein. After systemic heparinization (heparin 100 IU/kg body weight), atraumatic vascular clamps are applied on the vein segment above and below the target valve. Commissural apices should be clearly visible. Intact valve lines indicate the presence of valve cusps and a direct repair is almost always possible. Interrupted or absent valve attachment lines denote valve dissolution. This sign is so reliable that further time and effort does not need to be wasted in performing a venotomy to search for non-existent valve cusps. About 4 cm of the valve station and adjoining venous segments should be cleared of branches in preparation for both direct and indirect types of repairs. After the commisures are identified, a stay suture (7–0 Prolene) is taken at the apex of the commissure to guide the venotomy once the vein is collapsed.

43.7 STRIP TEST

Once the valve station is identified, a strip test is performed to confirm valve incompetence. With a bulldog clamp in place, the infravalvular segment is emptied upwards through the valve. If the valve is competent, the segment will remain collapsed. A refluxive valve will allow the segment to fill from above. The supravalvular segment may also be gently squeezed towards the valve to test its competence. An intra-operative descending venography confirms valvular incompetence at this stage (Figure 43.6).

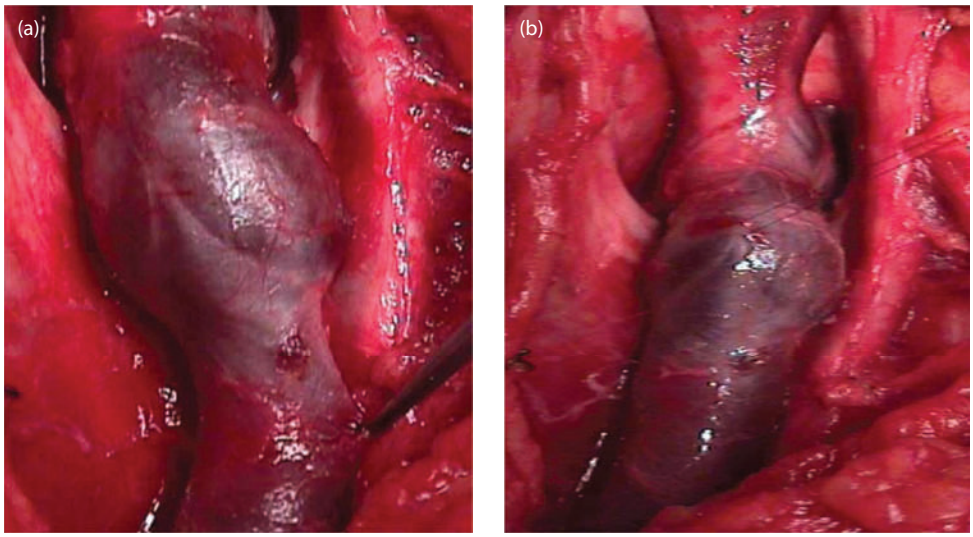

Figure 43.7 **(a)** Vein valve exposed after adventitial dissection. **(b)** 7–0 Prolene suture is placed at the commissural apex.

43.8 SPECIFIC VALVE RECONSTRUCTION TECHNIQUES

Descriptions of numerous techniques of valve reconstruction can be found in the literature. Most direct valve repair techniques in current use are variations/modifications of the basic internal or external techniques originally described by Kistner. A brief outline of the more common techniques in current use is provided below. The source manuscript should be consulted for finer details.

43.8.1 Internal valvuloplasty

43.8.1.1 REEFING TECHNIQUES

The original description by Kistner[1] utilized a longitudinal incision between the two valve cusps cutting through the anterior commissural apex (Figure 43.8). The incision is started 10–15 mm below the valve attachment lines and extended upwards through the commissural apex, keeping the cusps in view to avoid damage (the valves can droop or even prolapse down in some cases). The incision allows the valve station to be laid open like pages in a book, providing excellent exposure of redundant cusps. Frequent irrigation with saline is necessary to visualize the translucent valve cusps and their free edges. By using 7–0 polypropylene sutures, the valve edges are gathered like the pleats of a curtain and tacked to the commissural apex with the knot placed outside. A single double-needled suture can be used at the undivided posterior commissure. Separate sutures will be necessary at each half of the divided anterior commissure. Approximately 20% of the valve edges at each commissure will need to be tacked in this fashion. Some subjective judgment is required in deciding when enough valve tightening has been achieved, as valve competency cannot be tested until after the venotomy had been closed. Closure has to be meticulous, with everting sutures and good intimal apposition minimizing the chances of a potential nidus site for thrombus formation.

The valve can also be exposed through a supravalvular transverse incision[23,24] placed about 5 mm above the

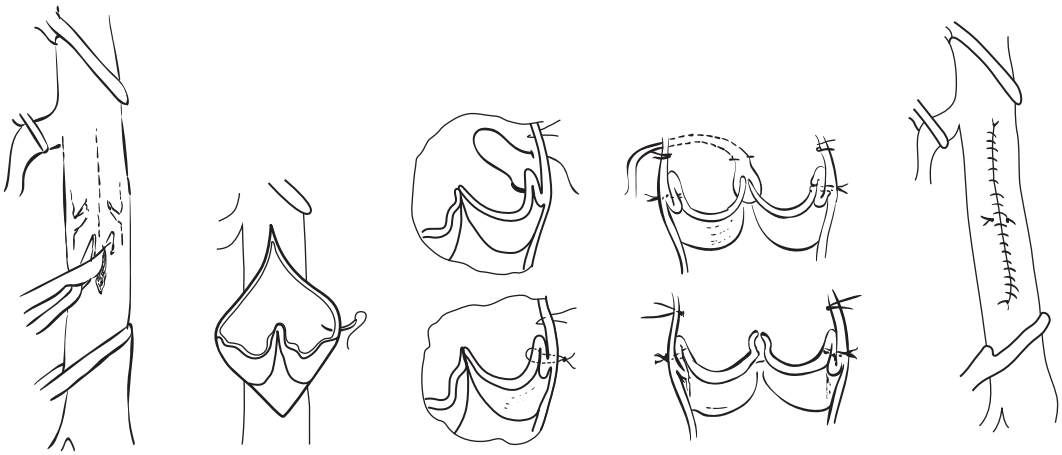

Figure 43.8 Longitudinal internal valvuloplasty by Kistner.

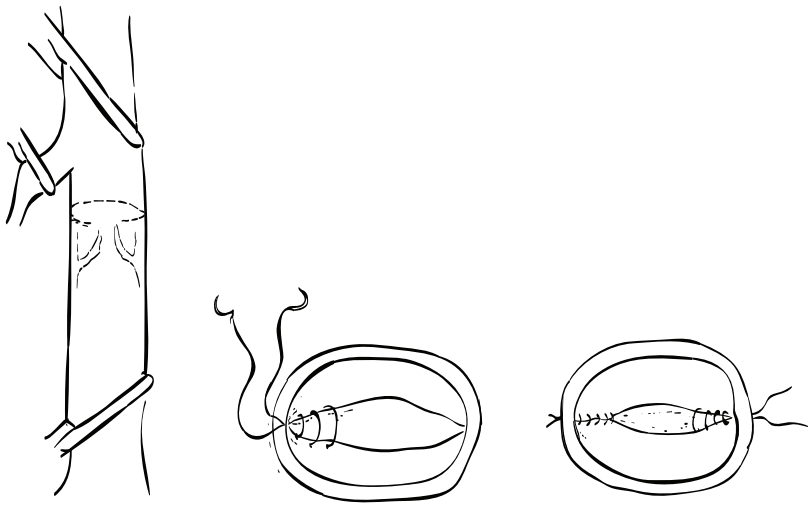

Figure 43.9 Transverse internal valvuloplasty by Raju.

commissural apex (Figure 43.9). Half a dozen or so stay sutures are placed through the lower cut edge for retraction; the same sutures can be used later for closure. This transverse incision is comparatively short, reducing suture line length but at the cost of somewhat reduced exposure. The annulus is not traversed, minimizing the chance of cusp damage during the venotomy; tightening of the valve cusps can be continuously monitored as the repair progresses and the endpoint can be gauged before the venotomy is closed.

Exposure can be further increased by converting the transverse incision into a "T"[2,25–27] towards the valve cusps (Figure 43.10). Extension into the valve sinus where there is relative stasis should be avoided.

The "trapdoor" incision (Figure 43.11)[28] provides even greater exposure than the longitudinal incision, limits valve injury, and allows unhindered evaluation of all of the components in the process of reflux and their correction. It also enables testing of reflux intra-operatively while having the option of correcting incompetence without having to take down the venotomy as in other techniques. However, its incision length is much greater, and this may increase the effort at faultless closure.

Despite the cited advantages and disadvantages, all of the described incisions seem to work well in the hands of their proponents, and the choice seems to be one of personal preference.

43.8.1.2 EXCISIONAL TECHNIQUE

Reduction internal valvuloplasty[19] is a departure from reefing techniques due to the problems of increased thrombosis, loss of valvular area on planimetry, and valve resorption. In this technique, the target deep vein for valve repair is exposed and dilated with heparin saline solution from a distally placed Venflon 23 gauge to prevent venospasm and allow visualization of valve commissures after adventitial dissection. Trapdoor venotomy is then carried out and the valves exposed. Redundancy of the valve is noted on either side of the mid-curve of the valve sweeping towards each commissure (Figure 43.12a) by measuring calipers that are guided by ultrasound intervalvar

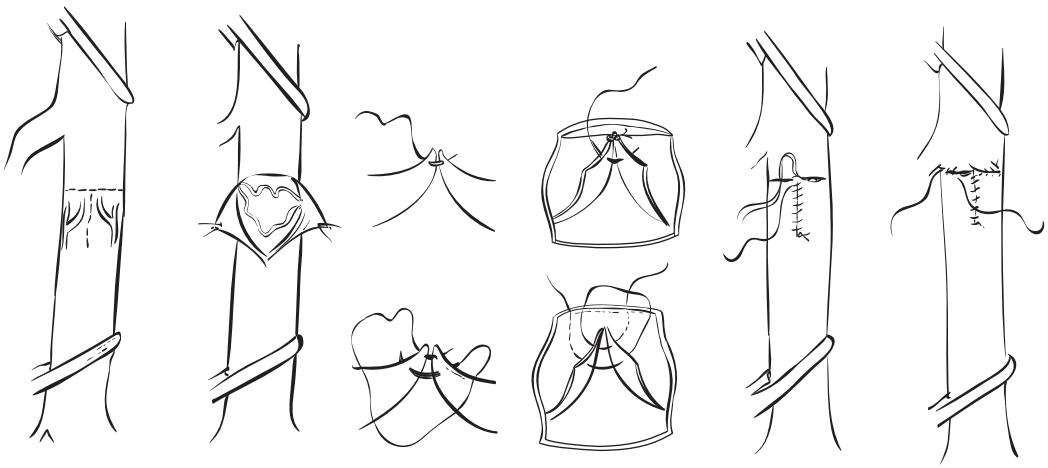

Figure 43.10 "T" internal valvuloplasty by Sottiurai (modified by Perrin).

Figure 43.11 Trapdoor internal valvuloplasty by Tripathi.

measurements. The redundant valve is then marked on the outer side of the mid-valvular line in a curvilinear sweep and the excessive valve is excised (Figure 43.12b). The edge of the excised valve is sutured to the venotomy edge on the outer aspect of the valve station (Figure 43.12b) by a running 7–0 Prolene (Ethicon, Johnson & Johnson, Cincinnati, OH) or CV8 (polytetrafluoroethylene [PTFE]) suture (WL Gore & Associates, Flagstaff, AZ) in a previously described "out–in–out" fashion.[29] At the same time, the surgeon ensures that the cup brim is taut and that there is no eversion, inversion, or folding (Figure 43.12c). The "trapdoor" is then closed with a 6–0 Prolene or CV7 (PTFE) suture as described earlier by the author,[29] and valve competence is checked by open (Figure 43.13a) as well as closed strip test techniques (Figure 43.13b). An intra-operative descending venography can also be done to confirm valve competency (Figure 43.6). The surgical repair and intra-operative assessments are performed in supine, reversed Trendelenburg (45°) with Valsalva maneuver where applicable. With experience, valve competency is readily achieved (Figure 43.14). However, there should be no hesitation regarding reopening the venotomy for placement of additional sutures if the valve is not completely competent. Precision, faultless technique and a mindset that accepts nothing less than a perfect repair are essential for success. Botched reconstructions can seldom be salvaged by reoperation at a later date at the same site because of edema, inflammatory response, thrombosis, and cicatrix formation at the repair site.

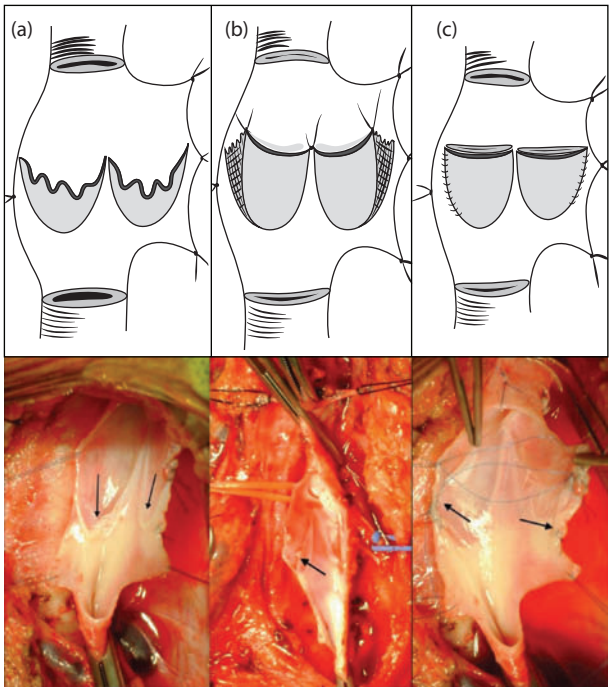

Figure 43.12 **(a–c)** Reduction internal valvuloplasty technique at the common femoral vein valve station.

43.8.2 External valvuloplasty

External valvuloplasty is a less invasive technique that may involve either adventitial or transcommissural plication of the valve cusps. It can be performed via three techniques:

1. Anterior commissural plication, as described by Nicolaides et al.[30]
2. Transcommissural plication, as described by Kistner/Raju (Figure 43.4)[31–33]
3. Angioscope-guided external valvuloplasty, as described by Hoshino/Gloviczki[34–37]

This technique[31] brings the two valve attachment lines together using externally placed sutures at each commissural end. The valve redundancy itself is not directly addressed. Starting at the commissural apex, continuous or interrupted transmural sutures are placed along the valve attachment lines, covering about 20% of the attachment line length at each end. This is usually at the point where the attachment lines curve sharply away from each other. Additional sutures may be required at one or both commissural sides to achieve competence. It is remarkable how a single additional suture would restore competence

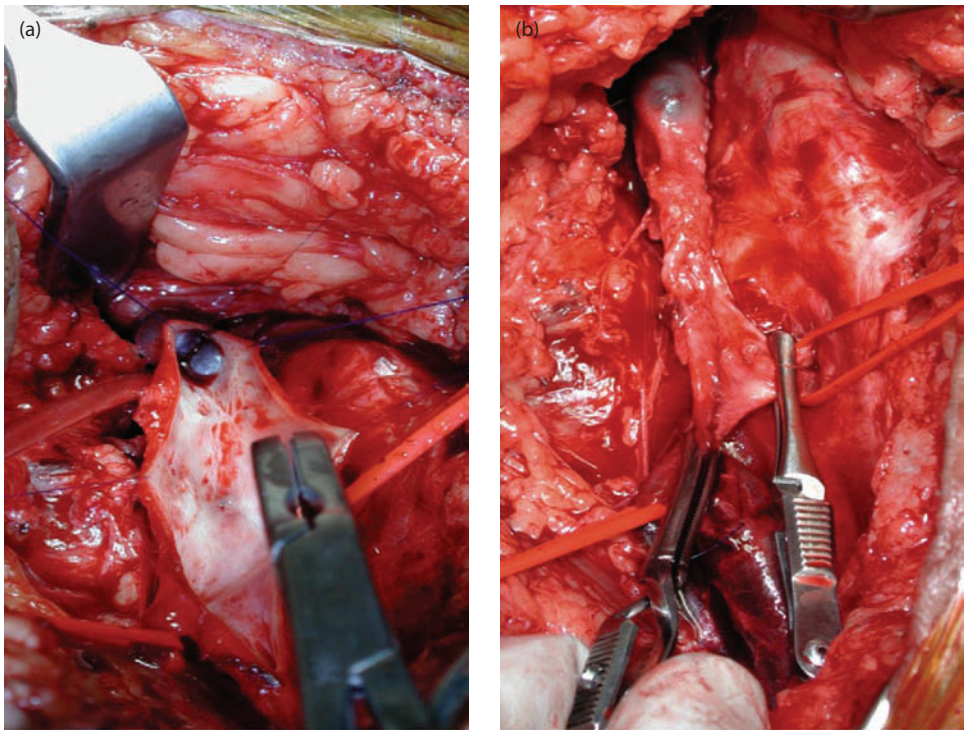

Figure 43.13 **(a)** Open competence check by partial closure of trapdoor valvuloplasty at the CFV. **(b)** Closed "vein strip" test of valve competency after closure of trapdoor valvuloplasty.

to a valve that had remained refluxive after a row of prior sutures. Creation of valve station stenosis during repair should be avoided; a relative stenosis of 10%–20% is occasionally necessary to achieve valve competence and is probably acceptable.

43.8.2.1 ANTERIOR COMMISSURAL VALVULOPLASTY

This technique, popularized in the United Kingdom by Nicolaides and Belcaro,[30] addresses mild reflux where anterior plication may be sufficient to reduce or abolish reflux, especially in conjunction with superficial reflux disease.

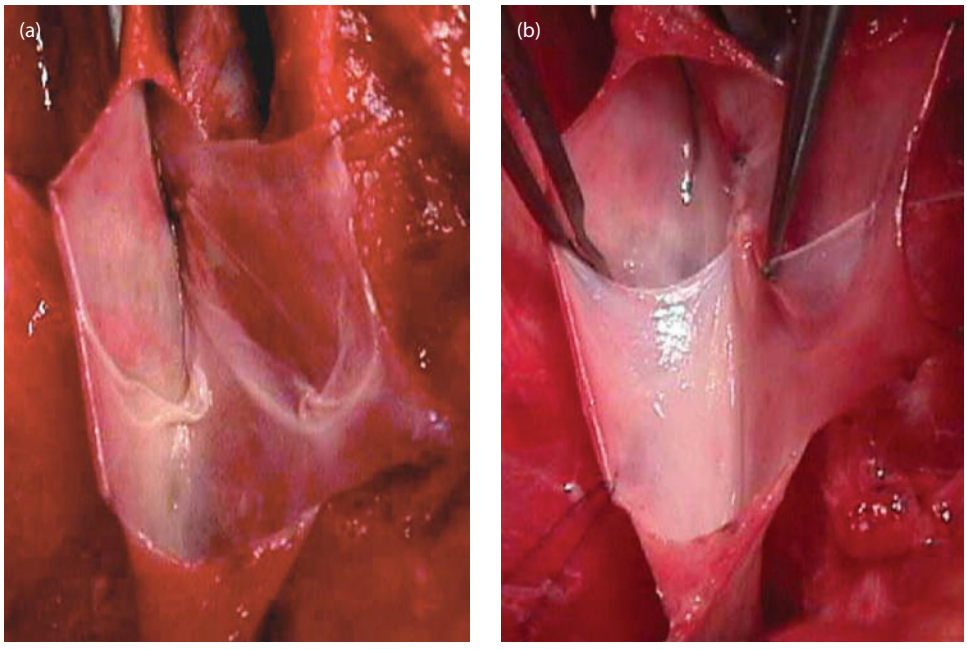

Figure 43.14 Repaired incompetent valves after trapdoor internal valvuloplasty: **(a)** before and **(b)** after intervention.

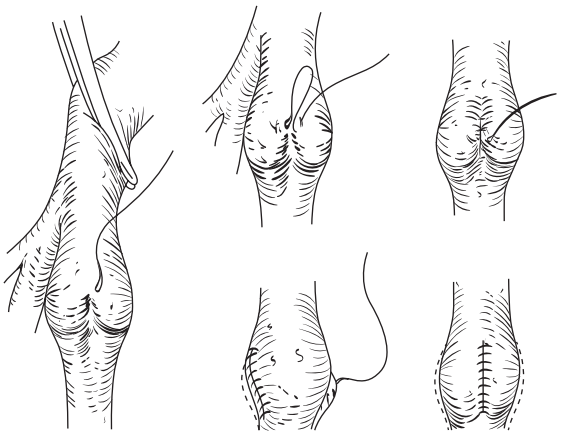

Figure 43.15 Anterior plication external valvuloplasty.

It may be applicable in small caliber veins. Long-term results are unsatisfactory and this procedure has largely been abandoned (Figure 43.15).

43.8.2.2 TRANSCOMMISSURAL VALVULOPLASTY

In this technique,[31–33] the valve attachments are clearly delineated first as described. Transluminal sutures are placed as in the angioscopic technique, but "blindly," without the aid of the angioscope or venotomy. Initial sutures near the commissural apex are shallow, as the free edges of the valve cusps do not extend very far into the lumen at this point. Farther down, they do extend further into the lumen, crossing it to the opposite commissure. Each subsequent suture should, therefore, be placed slightly deeper into the lumen than the previous one to catch the cusp edges. As each repair suture is tied, the slack valve cusps will tighten progressively. Despite the "blind" nature of the technique, valve competency can be routinely achieved, which can be continuously monitored after each suture is placed (Figure 43.16).

43.8.2.3 ANGIOSCOPIC REPAIR

First described by Gloviczki et al.[34] from the Mayo Clinic, this technique has gained many adherents.[33–35] It is an enhancement of the external repair technique; transluminal instead of transmural sutures are used along the valve attachment lines. By visualizing the valve apparatus with an angioscope introduced through a small venotomy above the valve station, the transluminal sutures not only appose the valve attachment lines, but also tighten the valve cusps. Angioscopic irrigation is required for proper visualization of the valve apparatus; a watertight purse string suture around the venotomy is required. Some extravasation of the irrigant into the vein wall at the venotomy site is common and minor intimal trauma from manipulation of the tip of the angioscope is unavoidable. It is actually quite difficult to direct the sutures under angioscopic visualization to catch the valve cusps. More often, angioscopic inspection merely confirms that the sutures have traversed the valve *after* they had been placed. It appears that transluminal sutures placed along the valve attachment lines usually tack or tether the redundant valve cusps; the angioscope is confirmatory, but not an aid in the actual placement of sutures. This insight led to the development of transcommissural valvuloplasty described above.

43.8.3 External banding

This is a method that utilizes an external wrap of PTFE or silicon to narrow the lumen, thus maintaining the approximation and competence of the valves.[38–41] The external sleeve may be anchored to the adventitia using sutures to prevent migration. Lane et al. proposed an external valvular stent Venocuff II™ (AllVascular Pty Ltd, Sydney, Australia).[38] This is a Dacron-reinforced silicon stent with an adjustable diameter that has been found to be far superior to Dacron and PTFE in animal models. Many authors have abandoned this procedure because of concerns regarding scarring and fibrosis of the treated vein.

43.8.3.1 ANTICOAGULATION

Prophylactic low-molecular-weight heparin (LMWH) started before surgery should be continued at least for 4 or 5 days afterwards, along with pneumatic compression and early ambulation. Primary cases with external repair may not need warfarin anticoagulation beyond peri-operative LMWH.[49] Most other cases will require post-operative warfarin anticoagulation for at least 3 months. Longer-term anticoagulation may be considered in patients with known thrombophilia or other risk factors for thrombosis.

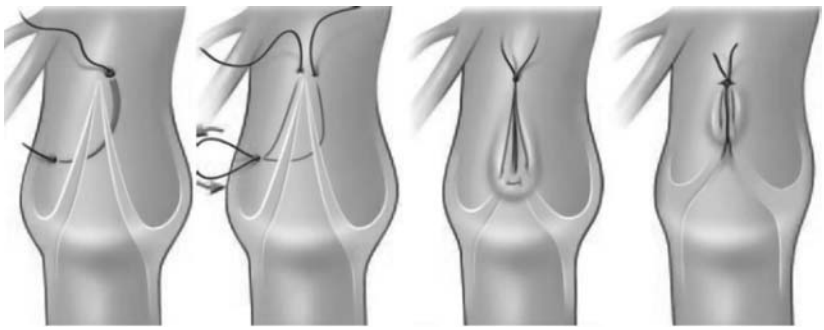

Figure 43.16 Transcommisural valvuloplasty.

43.8.3.2 MORBIDITY

Deep vein valve repairs are usually well tolerated with very low morbidity and mortality (<1%), with many authors reporting no mortality at all.[42] Hematoma and seroma formation may be seen in up to 15% of patients.[15,24,27,29] Deep vein thrombosis occurs in less than 10% of patients.[27,29] Wound infections have been seen in about 1%–7% of patients.[15,24,29] Pulmonary embolism and mortality are rare after valve reconstruction.

43.8.3.3 OUTCOME

Several good long-term clinical results have been published[8,10,15,17,24,27,29,43–50] that reflect the current practice and outcomes of deep venous valve repairs. In primary disease, long-term cumulative ulcer healing of about 60%–80% can be expected.[15,24,29] Resolution of pain and swelling are also excellent. Most patients are able to discard or limit stocking use after successful valve reconstruction. Hemodynamically, significant improvement in VFI_{90} (air plethysmography) can be expected following valve reconstruction.[20,42–48] Ambulatory venous pressure improves significantly after valve reconstruction and may normalize in some "primary" disease cases.[15,17,47] Clinical failures are associated with nonimprovement in ambulatory venous pressure parameters after valve reconstruction; ulcers seldom heal if VFT persists at below 5 seconds after surgery. Ambulatory venous pressure is influenced by multiple aspects of venous dynamics, including vein wall compliance.[43–45] Reflux is but one component, although it is a dominant one. Therefore, only improvement, not total normalization, is to be expected following a single valve reconstruction in a multifocal disease.

The results of internal and external valvuloplasty in primary deep valve insufficiency are shown in Tables 43.1 and 43.2. Internal valvuloplasty is credited to have a success rate of over 70% at the 5-year follow-up, and external valvuloplasty on the whole achieved less satisfactory results (40%–50%) if valve competency and freedom from ulceration are taken into account. In all the published series, an excellent correlation can be noted between clinical outcome and valve competency. The outcomes of other techniques are more difficult to assess—either angioscopy-assisted valvuloplasty[33–35] or cuffing[38–41] (Tables 43.1 and 43.2)—due to the fact that follow-up has not been long enough, with the exception of the series reported by Lane et al.[38]

43.9 CONTROVERSIES

43.9.1 Single versus multiple valve reconstructions

In symptomatic primary disease, multisystem, multilevel disease is often present. Whether a single valve repair is enough or whether multiple valve repairs at more than one location (e.g., femoral, popliteal, tibial, and profunda femoris) would yield better clinical and hemodynamic outcomes has long been a subject of controversy. Clinical experience indicates that a single valve repair at the femoral location provides durable clinical relief in about 70% (cumulative) of patients; however, hemodynamic improvement is often only partial, although significant. Some studies have hypothesized that multilevel valve repairs in the same axial system have better outcomes compared to single-level repair.[29] The theory suggests that there will be at least one functional valve station in a repair of two valves, thus improving overall outcome. In our 2-year study, we demonstrated that patients with primary refluxive disease undergoing single-level valvuloplasty could expect a 59.4% valve competence rate and a 54.7% ulcer healing rate ($P = 0.05$) compared to multilevel repairs with a 79.7% valve competence rate and a 72.9% ulcer healing rates. Our results suggest that multivalve repair does indeed fare better than a single-valve station repair in the same axial system in terms of maintaining the overall competency.

43.9.2 Preferred site for valve repair

Sottiurai and others[25,26,30] believe that the popliteal vein is the gatekeeper of the leg veins and recommend popliteal level repair. Although this is attractive in theory, there is no evidence to support this concept in hemodynamic data,[43,44] nor from any comparative clinical series. Kistner and Raju have recommended repair of the common femoral vein or termination at the superficial femoral level.[42,50] In the author's practice, the site that is chosen for valve reconstruction is at valve stations with maximum reflux diagnosed using duplex scan and descending venography. The author uses two-level repairs in patients with Kistner's grade III and IV reflux. The author also found that patients who underwent multilevel repairs had superior results to those undergoing single-level repairs, irrespective of the sites of repair. This gatekeeper concept may therefore not be valid any more. In the author's experience, as well as that of others,[24,28,49] femoral repairs had better clinical outcomes than repairs at other sites, including the popliteal location. All valve repairs show a steady functional deterioration over time.[8] The femoral valve showed less deterioration than other repair locations, including the popliteal.

43.9.3 Choice of technique

A direct valve repair technique should be used first if the valve structure is repairable. Internal valvuloplasty is a precise, direct technique with proven long-term efficacy. Even though internal valvuloplasty also deteriorates in terms of duplex competence over time, it decays less in relative terms than other valve reconstruction techniques.[8,29] Internal valvuloplasty is a time-consuming technique and may not be feasible in small-caliber veins. External or transcommissural techniques are fast and can be carried out in small-caliber veins; because of their speed, they will be preferred in multiple valve reconstruction. All things being equal, the choice of technique is largely governed by personal preference and the experience gained with a certain technique. This is as it should be, as there is a considerable learning curve in mastering valve reconstruction techniques.[50]

Table 43.1 Deep vein reconstruction results

First author, year	Surgical technique	Number of limbs (number of valves repaired)	Etiology PDVI/total	Follow-up, months (mean)	Ulcer recurrence or non-healed ulcer (%)	Hemodynamic results	
						Competent valves (%)	AVP/VRT
Lehtola, 2008	VI	12	5/12	24–78 (54)	–	(55)	–
	VE Transmur	7	3/7				
	VI + VE Transmur	1	0/1				
Masuda, 1994	VI	32	27/32	48–252 (127)	(28)	24/31 (77[a])	AVP ↑ 81% (mean) VRT ↑ 50% (mean)
Perrin, 2000	VI	85 (94)	65/85	12–96 (58)	10/35 (29)	72/94 (77)	AVP normalized 63% (mean)
Raju, 1996	VI	68 (71)	–	12–144	16/68 (26)	30/71 (42)	–
Raju, 1996	VE Transmur	47 (111)	–	12–70	14/47 (30)	72/111	–
Raju, 2000	VE Transco	141 (179)	98/141	1–42	(37)	(59)	AVP ↑ 15 % (mean) VRT normalized 100%
Rosales, 2006	VE Transmur	17 (40)	17/17	3–122 (60)	3/7 (43)	(52)	AVP ↑ 50 % (mean)
Sottiurai, 1996	VI	143	–	9–168 (81)	9/42 (21)	107/143 (75)	–
Tripathi, 2004	VI	90 (144)	118	(24)	(32)	(79.8)	–
	VE Transmur	12 (19)			(50)	(31.5)	–
Wang, 2006	VE Transmur	(40)	40/40	(36)	–	(91)	VRT ↑ 50% (mean)
Tripathi, 2014	VI RIVAL	25 (44)	44/44	1–24 (12)	3/25 (12)	42/44 (95.4)	–

Note: VI: internal valvuloplasty; VE Transmur: external transmural valvuloplasty; VE Transco: external transcommissural valvuloplasty; PDVI: primary deep venous insufficiency; AVP: ambulatory venous pressure; VRT: venous return time; ↑: increased; RIVAL: reduction internal valvuloplasty.

[a] Reflux absent or moderate (<1 second).

Table 43.2 Banding, cuffing, external stent, and wrapping results

First author, year, material	Number of limbs (number of valves repaired)	Site	Etiology PDVI/total	Follow-up, months (mean)	Ulcer recurrence or non-healed ulcer (%)	Hemodynamic results	
						Competent valves (%)	AVP/VRT
Akesson, 1999, Venocuff I®	20 (27)	F, P	7/20	5–32 (19)	2/10 (20) PTS	PVI 7/7 (100) PTS 7/10 (70)	PVI: AVP ↑ 10% (mean) VRT ↑ 10% (mean) PTS: AVP ↑ 10% (mean)
Camilli, 1994, Dacron®	54	F	54/54	4–63	–	41/54 (76)	–
Lane, 2003, Venocuff II®	42 (125)	F, P	36/42	64–141 (93)	(20)	(90)	AVP ↑? VRT ↑ 100% (mean)
Raju, 1996, Dacron®	(96)	F, P, T	–	12–134	6/22 (27)	60/72 (83)	–

Note: PDVI: primary deep venous insufficiency; PTS: post-thrombotic syndrome; PVI: primary valvular incompetence; F: femoral; P: popliteal; T: posterior tibial; AVP: ambulatory venous pressure; VRT: venous return time; ↑: increased.

43.10 CONCLUSIONS

In the era of endovascular advances, including the tremendous impact of iliac vein stenting in healing venous ulcers, a significant proportion of patients will have recurrent venous leg ulceration despite ablation of all superficial venous reflux and correction of deep venous obstruction. Apart from this subgroup, there is a smaller group of patients from ethnic subgroups (South Asian/Maori/Pacific Islander gene pools) who will have primary valvular insufficiency. These patients must be investigated for primary valvular incompetence and offered repair, as long-term results can be extremely satisfying.

Guidelines 4.15.0 of the American Venous Forum on surgical repair of deep vein valve incompetence for primary reflux

No.	Guideline	Grade of recommendation	Grade of evidence (A: high quality (strong/weak); B: moderate quality; C: low or very low quality)
4.15.1	For deep venous reflux with skin changes at risk of venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest individual valve repair for those who have axial reflux with structurally preserved deep venous valves, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. Valve reconstruction should be considered in primary valvular incompetence after less invasive therapies have failed.	2	C

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● = Key primary paper
★ = Major review article

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44

Surgical treatment of post-thrombotic valvular incompetence

OSCAR MALETI AND MARZIA LUGLI

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44.1 INTRODUCTION

Post-thrombotic syndrome (PTS) can develop in up to two-thirds of patients with extensive deep vein thrombosis (DVT).[1] The cause of PTS is chronic obstruction, valvular incompetence, or both, resulting in major hemodynamic disorders.

The obstruction is an endoluminal fibrosis. This, together with a rigid vein wall, leads to loss of compliance and increased resistance.[2] The valve damage leads to reflux. Reflux can be segmental (limited to the femoral, popliteal, crural, or calf veins) or axial (extending from the groin all the way to the calf).[3]

PTS can lead to severe chronic venous insufficiency (CVI)[4] which is frequently the result of both obstruction and valvular incompetence. Usually, obstruction is at the iliocaval level and valve damage is at the infrainguinal level all the way down to the calf veins.

In most patients, the thrombus dissolves following an episode of acute DVT, but this becomes complete in only a third of patients, and the percentage is even lower in patients with iliocaval thrombosis.[5]

Moreover, residual obstruction at the femoropopliteal level appears to be better compensated by collateral pathways compared with an obstruction at the iliac and common femoral levels. Loss of compliance occurs in addition to an increase in vein wall resistance and valve incompetence, which prevent normal emptying during ambulation. Obstruction and decreased compliance are directly responsible for an increased residual venous volume.[6]

Compression therapy can control signs and symptoms, but it is associated with high rates of venous ulcer recurrence, especially in non-compliant patients.[7]

A first attempt to restore equilibrium in the leg circulation should be to treat the proximal obstruction.[8] Secondly, if needed, correcting the reflux should be taken into account.[9,10]

At present, investigations are not available to distinguish between the respective roles of obstruction and reflux in determining signs and symptoms.[11] However, clinical results in treated patients reveal that ulcers are more frequently present in patients with reflux, while those with proximal obstruction have pain and venous claudication. The choice to begin by treating the proximal obstruction is usually dictated by the decision to apply the less invasive procedure first.

In PTS, the valves are usually destroyed and direct repair is rarely possible.[12] Consequently, the aim of surgical techniques in post-thrombotic valvular incompetence is to create a new competent axis.[13]

44.2 SURGICAL TECHNIQUES

Ligation of the deep veins was practiced previously to treat chronic post-thrombotic valvular incompetence. Ligation is not supported by data and we agree with recent recommendations of the vascular societies' guidelines that ligation of the femoral vein (FV) or popliteal vein (PV) to treat deep vein valve reflux should be abandoned as a routine treatment.

The surgical techniques that are applicable to treat post-thrombotic valvular incompetence are:

- Vein transposition
- Vein transplant
- Neovalve
- Artificial venous valve

44.2.1 Vein transposition

This technique transforms a devalvulated segment to a valvulated one when the anatomy for this is favorable. The technique is usually applied at the inguinal level.

First described by Kistner in 1979, the most common options are transposition of the incompetent FV to the profunda femoris vein (PFV) or to the great saphenous vein (GSV).[14,15]

44.2.1.1 TRANSPOSITION TO THE PFV: TECHNICAL DETAILS

For transposition of the FV onto the PFV, the femoral bifurcation is dissected first. A short segment of the common FV (CFV) is dissected, just enough for clamping, but a longer segment of the PFV and the FV need to be dissected for adequate transposition. It is crucial to identify the most proximal and competent valve of the PFV and to dissect the FV for a sufficient length for a transposition free of torsion and tension.

The FV is divided in the vicinity of the CVF and closed with a running suture, avoiding any residual stump.

The FV is subsequently anastomosed with the PFV, just distal to a competent valve of the PFV. If the FV has post-thrombotic trabeculae, those have to be excised before the anastomosis is done.

End-to-side anastomosis (Figure 44.1a) is more commonly practiced due to the size mismatch; however, end-to-end anastomosis (Figure 44.1b) is preferable for hemodynamic reasons, when possible. When the PFV divides into two smaller adjacent tributaries below the competent valve, a strategy such as that shown in Figure 44.2 can be applied.

44.2.1.2 TRANSPOSITION TO THE GSV: TECHNICAL DETAILS

If a competent GSV is available, we can transpose the FV to a site below the saphenofemoral junction (Figure 44.1c).

Given that the GSV is located in a subcutaneous area, it is preferable to transpose the saphenous vein itself in the subfascial area (Figure 44.1d). When the terminal and sub-terminal valves of the saphenous vein are competent, it is preferable to perform the anastomosis below both of these valves.

The GSV is dissected in its first portion for 5–10 cm. The FV divides immediately below the FV–PFV junction. An oblique end-to-end anastomosis is performed between the GSV and FV (Figure 44.3) to compensate for the size mismatch of the two veins.

The increased flow in the saphenous vein may lead to an overload in the saphenous vein itself, and this overload may lead to valve incompetence. To avoid this, a cuff can be applied below the competent saphenous valve in order to prevent post-procedural dilatation.

44.2.1.3 ADVANTAGES

- Easy to perform when a competent saphenous vein is available
- Good long-term results

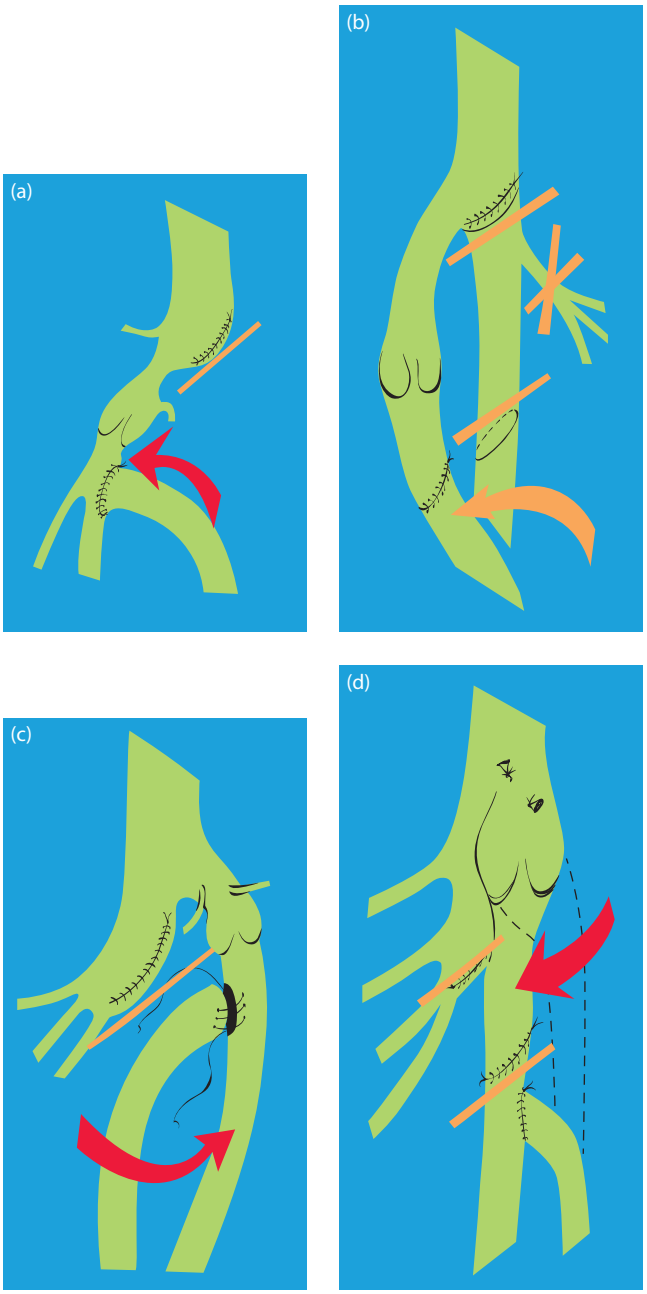

Figure 44.1 Femoral vein transposition **(a)** into the profunda femoris vein (end-to-side anastomosis); **(b)** into the profunda femoris vein (end-to-end anastomosis); **(c)** into the great saphenous vein (end-to-side anastomosis); and **(d)** into the great saphenous vein (end-to-end anastomosis).

44.2.1.4 DISADVANTAGES

- Discrepancy of caliber between the FV and GSV or PFV
- Adverse anatomy of deep veins system
- Competent valve only in the distal part of the PFV, requiring an extended dissection
- Incompetence of PFV and GSV after transposition due to increased caliber
- Risk of post-procedural lymphocele and lymphorrhea

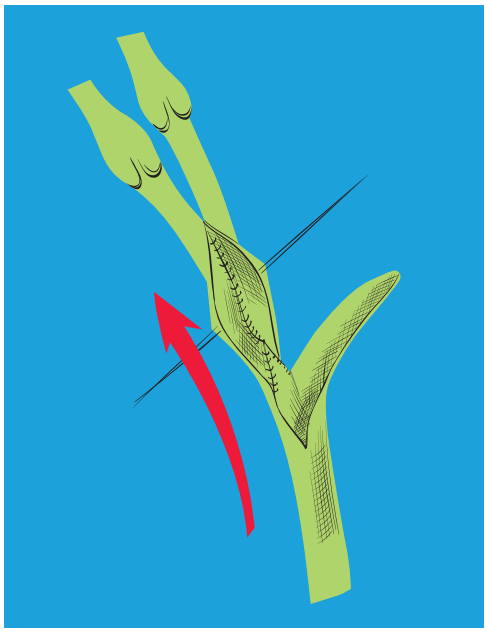

Figure 44.2 Transposition into the profunda femoris vein in the case of small parallel axes.

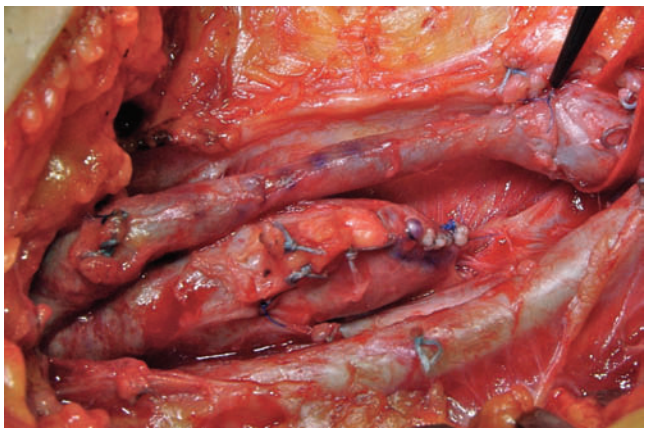

Figure 44.3 New axialization with the saphenous vein.

44.2.2 Vein transplant

The purpose is to insert a segment with a competent valve in the incompetent deep venous system. The donor is usually the axillary vein (AV), as first described by Raju,[16] or the brachial vein, as first described by Taheri et al.[17]

44.2.2.1 TECHNICAL DETAILS

The main potential drawbacks of this technique might be the incompetence of the donor segment or the caliber discrepancy.

A transverse incision at the apex of the armpit allows access to the AV in order to obtain a segment that is long enough for transplant. The vein dissection must be performed proximally as far as the rib level, and distally as far as the incision will allow.

It is not necessary to restore anatomical continuity, as available collateral pathways ensure good compensation; thus, complications related to the removal of the axillary portion are rare. Before procedure, the segment must be tested for the competence of the valve (or valves); in the event of valve incompetence, reconstructive bench surgery may be contemplated, but valve repair may be difficult.[18]

The AV must be implanted in the most suitable segment—FV or PV—depending on its caliber. Before implantation into the PV, we must be sure that there is not a second incompetent PV present. In such circumstances, if the PV is chosen for implant, the other refluxing axis must be ligated. The PV is accessed medially just as one would access the proximal popliteal artery. A posterior approach could also be an option, but it is more cumbersome since the AV segment is harvested in the supine position.

Peri-operative thrombosis is not rare, so the surgeon needs to avoid any tension or torsion and stenosis at the anastomosis.[19,20]

Interrupted sutures or two half-running sutures are preferred over a single continuous suture.

The diameter of the proximal anastomosis should be larger than the distal one, and a maximum distance should be maintained between the valve cusp and the proximal anastomosis (Figure 44.4).

44.2.2.2 ADVANTAGES

- Fewer post-operative complications, such as lymphocele and lymphorrhea, than with groin exposure

44.2.2.3 DISADVANTAGES

- Problems in the case of multiple PV incompetence
- Involves operation on the arm, removing a major axial vein
- Post-procedural thrombosis is frequent

44.2.3 Neovalve

The neovalve is a technique based on the principle of constructing a new, autologous valve by using the patient's venous wall.

44.2.3.1 TECHNICAL DETAILS

In a limited case series, Raju and Hardy created a *de novo* valve employing a valvulated portion of the saphenous vein or a tributary or the AV and inserting it into the FV. They reported very good results.[18]

Plagnol et al. used as a neovalve invagination of the GSV terminal section into the CFV.[21]

In the Maleti technique, the neovalve is obtained by dissecting the venous wall in order to create a flap (Figure 44.5).[22,23] Although applicable in valve agenesis, the neovalve is easier to perform in PTS because of the thickened vein wall. Due to the variable anatomical conditions of the wall or lesions, the standard approach is not an option. The possible localization and the method of neovalve creation must be precisely defined using high-resolution

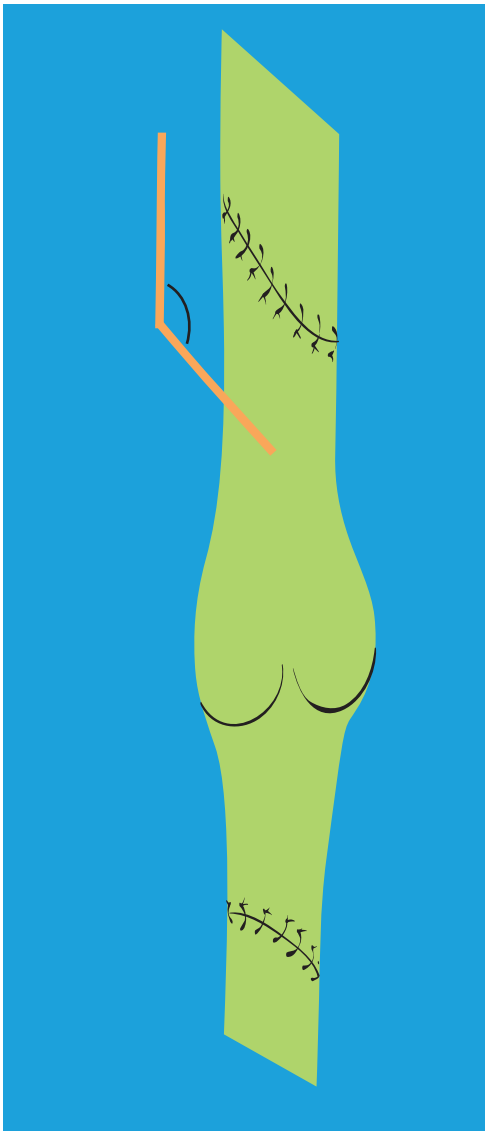

Figure 44.4 End-to-end sutures in a valve transplant.

ultrasound (US). The final decision is made only after phlebotomy.[24]

The post-thrombotic lesions can be varied: slight wall thickening, homogeneous or inhomogeneous; synechiae and septae; intraluminal fibrotic septum which creates a double channel; or considerable wall thickening with the fibrosis occupying a large part of the lumen. Except for the first condition, an endophlebectomy should usually be performed during the same operation.

The main risk with the neovalve is post-operative reattachment to the dissection site; this can be prevented by applying specific stitches, as shown in Figure 44.6.

The neovalve can be bicuspid or monocuspid, depending on the features of the wall. The monocusps must be longer to prevent leakage. We know that normal valve physiology is based on the shape of the valve itself and, given that the neovalve does not comply with this model, the washing action of the sinus is missing. This results in reduced movement in the flap, which in turn can lead to thrombosis in the sinus. Therefore, when applicable, a flap is created in front of a tributary to decrease the risk of thrombosis (Figure 44.7).

Some authors[25] suggest invaginating a portion of venous wall and reconstructing the wall with a polytetrafluoroethylene patch. The disadvantage of this technique is that, being open laterally, the flap is not able to decrease the hydrostatic pressure. However, as the volume of the reflux is reduced, the neovalve is partially functioning when associated with efficient deambulation.

44.2.3.2 ADVANTAGES

- An anti-reflux mechanism is created using the patient's own tissue.
- A surgical option when vein transposition and transplant are not available.

44.2.3.3 DISADVANTAGES

- Lack of standardization
- Frequent requirement for concomitant endophlebectomy
- Difficult to predict reconstruction site

44.2.4 Artificial venous valve

Many attempts to create venous valve substitutes have been performed over the years. Research is still underway and application in humans is not yet recommended.[26]

44.3 OUTCOMES

It is difficult to evaluate the clinical results of deep venous reconstructive surgery for reflux.

The main tools are the Villalta score and Venous Clinical Severity Score, but they have not been applied in most published series, so the outcomes are usually based on pain reduction and ulcer healing.

The results of transposition, transplantation, and neovalve are presented in the Tables 44.1,[27–32] 44.2,[19,,29,31-41] and 44.3,[21,23,25] respectively. As for artificial valve results, the bioprosthetic venous valve developed by the Portland team did not show valve competence at 1-year follow-up,[42] so the experimental phase continues.

44.4 PATIENT SELECTION AND SURGICAL INDICATIONS

Patients eligible for deep vein reconstructive procedures undergo a diagnostic protocol (Figure 44.8).

It is commonly believed that US can exhaustively investigate patients affected by CVI. However, this is a misconception. First of all, US will not detect proximal obstruction, which is frequently present. Secondly, the severity of the disease does not always correspond to the reflux elicited by means of a standard maneuver, such as calf compression or Valsalva.

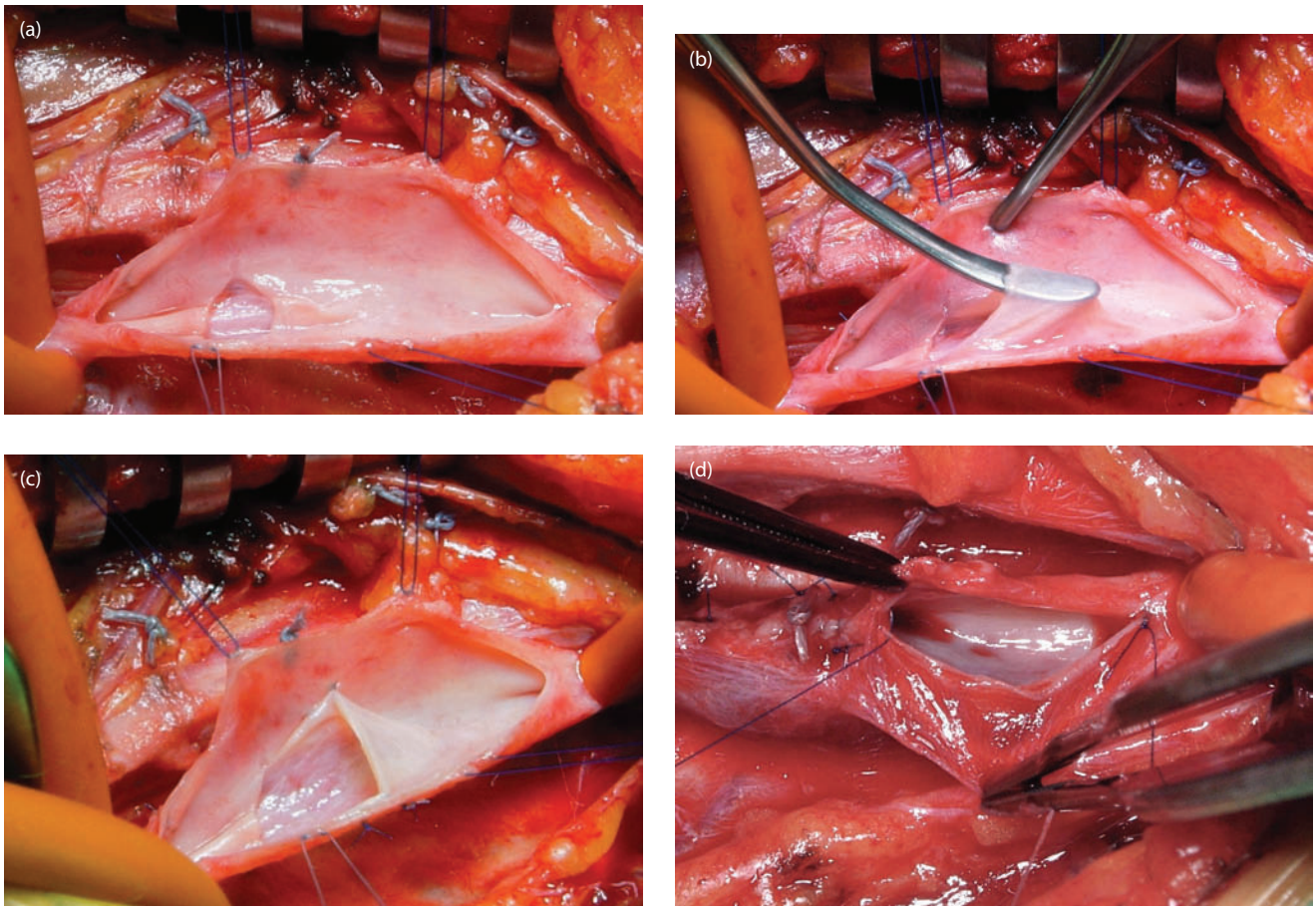

Figure 44.5 Neovalve according to Maleti. **(a)** Posterior transversal wall incision. **(b)** Parietal dissection. **(c)** Neovalve fixation in a semi-open position. **(d)** Neovalve competence verification.

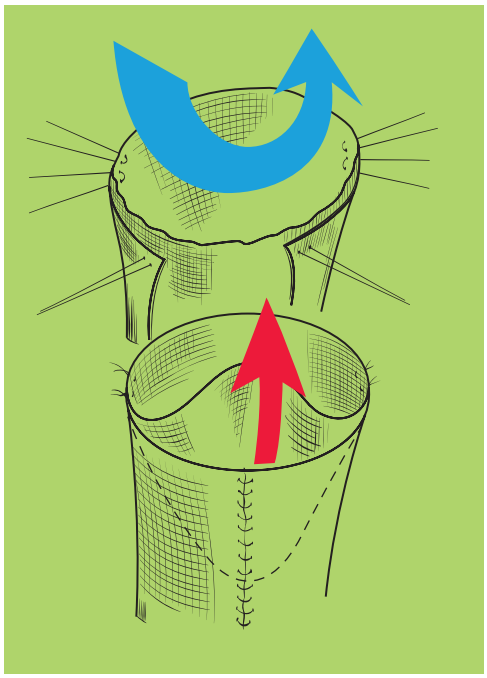

Figure 44.6 Technical details to prevent re-adhesion in the neovalve.

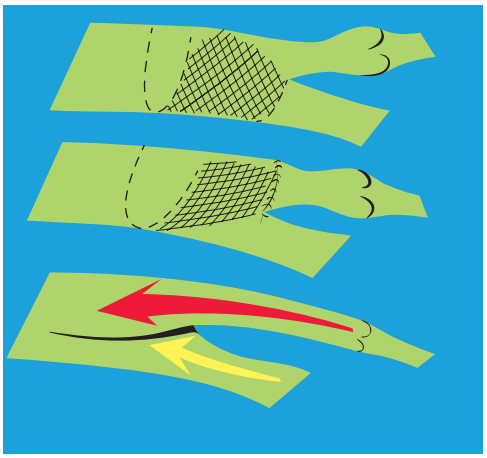

Figure 44.7 Neovalve based on competing flow (red arrow: flow from profunda vein; yellow arrow: flow from femoral vein). Observing laterally located tributaries, a wall dissection at the common femoral vein level is performed up to the origin of the femoral vein. The neovalve flap is divided at the femoral vein origin and sutured at the tributary ostium level.

Table 44.1 Transposition results

Author, year	Number of limbs	Follow-up months	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Johnson[27], 1981	12	12	4/12 (33)	2/2 (100)[a]
Masuda[28], 1994	14	48-252	7/14 (50)	10/13 (77)
Sottiurai[29], 1996	20	9-149	9/16 (56)	8/20 (40)
Cardon[30], 1999	16	24-120	4/9 (44)	12/16 (75)
Perrin[31], 2000	17	12-168	2/8 (25)	9/17 (53)
Lehtola[32], 2008	14	24-78	NA[b]	(43)

Note:
[a] Only 2 of 12 patients studied.
[b] Not available.

Table 44.2 Transplantation results

Author, year	Number of limbs	Follow-up months (mean)	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Taheri[33], 1986	71	NA	1/18 (6)	28/31 (90)
Eriksson[34], 1986	35	6-60	NA	11/35 (31)
Nash[35], 1988	25	NA	3/17 (18)	18/23 (77)
Bry[36], 1995	15	15-132	3/14 (21)	7/8 (87)
Mackiewicz[37], 1995	18	43-69	5/14 (36)	NA
Raju[19], 1996	54	12-180	NA	16/44 (36)
Sottiurai[29], 1996	18	7-144	6/9 (67)	6/18 (33)
Raju[38], 1999	83	12-180	(40) 6 years	(38) 4 years
Perrin[31], 2000	32	12-124 (66)	9/22 (41)	8/32 (25)
Tripathi[39], 2004	35	(24)	(45)	(41)
Lehtola[32], 2008	29	24-78 (54)	NA	(16)
Rosales[40], 2008	22 (including 3 double Tr, 2 Tr + other procedures)	6-108	NA	Tr GSV 14/26 Tr AV 3/6
Kabbani[41], 2011	19	(37)	6/8 (80)	8/19 (42)

Note: Tr: transplantation; GSV: great saphenous vein; AV: axillary vein.

Table 44.3 Neovalve results

Author, year	Technique	Number of limbs	Follow-up Months (mean)	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Plagnol[21], 1999	Bicuspid	44	6-47 (17)	3/32 (17)	38/44 (86)
Opie[25], 2008	Monocuspid	14	(48)	0/6	13/14 (92)
Maleti-Lugli[23], 2009	Monocuspid or Bicuspid	40 (19+21)	2-78 (28,5)	7/40 (17)	13/19 (68) 21/21 (100)

Therefore, when conservative and superficial venous treatments fail in C3–C6 patients the diagnostic protocol should be revised. We recommend contrast venography[3] and air plethysmography.[43] Venography provides information about proximal lesions (above the inguinal ligament) and is able to detect valve incompetence below the inguinal ligament. Air plethysmography brings data about calf muscle pump efficiency and venous resistance. When a proximal obstruction is strongly suspected and surgical correction is indicated, an intravascular US (IVUS)[44] investigation confirms the lesion before stenting.

If no proximal obstruction has been detected but a high plethysmography resistance exists, an IVUS may detect the lesions not revealed by venography. This strategy can be justified to reduce costs, since an optimal diagnostic protocol would involve venography and IVUS at the same time. A positive plethysmography test may suggest further investigations, while negative results do not exclude the possibility of clinically significant venous obstruction.[45]

Computed tomography and magnetic resonance venography are additional investigations used for the evaluation of lesions in the iliocaval veins.

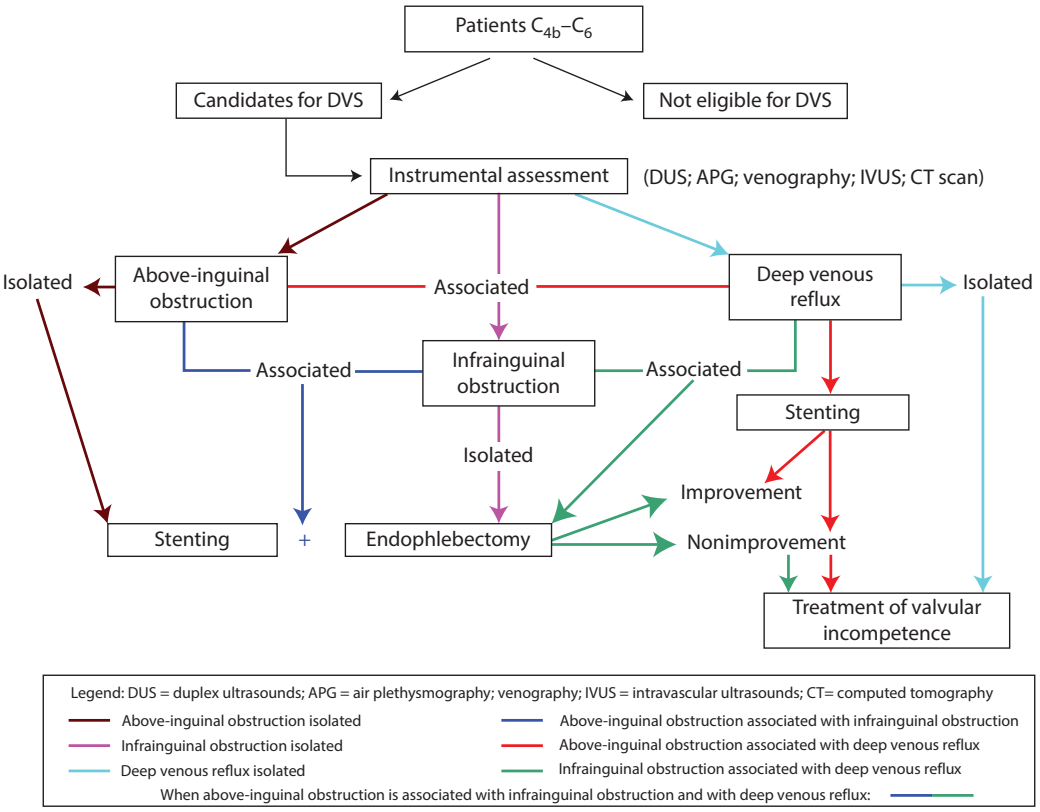

Figure 44.8 Diagnostic protocol and therapeutic strategy.

44.5 OPERATIVE PROCEDURE STRATEGY

To decide which strategy to apply, we need the following information:

- Presence or absence of proximal obstruction, including occlusion.
- Presence or absence of all axial reflux below the inguinal ligament, from groin to calf, via the femoropopliteal axis or by superficial or deep transfer.
- Presence or absence of proximal PFV competence.
- In case of PFV incompetence, identification of single or multiple re-entry points into the PV. It may be useful to determine the easiest access and the best way to occlude the re-entry point using an endovascular procedure.
- Presence and competence of great and small saphenous veins.
- PV anatomy (single or multiple channels) and competence.
- Diameter of the FV and PV.
- Femoropopliteal flow during exercise.
- Diameter and competence of the AV.
- Presence of endoluminal fibrosis, seen as a double channel at the femoropopliteal level.

Increased venous pressure as compared with the contralateral limb indicates proximal obstruction to venous flow. However, the pressure is usually not increased at rest, even when there is an obstruction. Besides resistance, other factors, such as flow, can be crucial. For example, the increased pressure may be due to a test-induced hyperemia. Venous obstruction should not be interpreted in the same way as arterial obstruction, given that the venous system is characterized by low pressure and velocity, and high volume and low resistance. In view of the latter, significant venous obstruction may occur with minimal symptoms, unlike in the arterial system.

The treatment of proximal obstruction can reduce the resistance, but it mainly increases the flow and decreases the venous volume in the limb. This can lead to a substantial improvement in hemodynamic signs and symptoms, despite the persistent associated distal valvular incompetence.

It is therefore essential to wait some months after treatment of proximal obstruction before treating the distal reflux.

44.6 CONCLUSIONS

In the absence of randomized trials, the level of evidence on the efficacy of surgical treatment of post-thrombotic valvular incompetence is low. It should be emphasized that the low complication rate, as well as the good results reported in the published series, indicate that deep venous reflux surgery should be given the place it deserves.

When addressing a pathology like PTS, where complete healing cannot be ensured, the purpose of surgery is to restore the limb to hemodynamic equilibrium when compressive therapy alone is unable to ensure a good quality of life. For these reasons, surgery is reserved for patients with severe CVI, clinical classes C4b–C6.

Extending this surgery to clinical classes C3 and C2s is not justified at present. In these patients, correction of any proximal obstruction may be indicated.

Guidelines 4.16.0 of the American Venous Forum on the surgical treatment of post-thrombotic valvular incompetence

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.16.1	Surgical treatment of post-thrombotic valvular incompetence is suggested in patients with infrainguinal deep venous reflux and skin changes at risk of venous leg ulcer (C4b) or healed/active venous leg ulcer (C5–C6), These procedures should be done in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.16.2	In a patient with advanced post-thrombotic syndrome (C4b, C5–C6), we suggest against ligation of the femoral or popliteal veins as a routine treatment.	2	C
4.16.3	In a patient with advanced post-thrombotic syndrome (C4b, C5–C6), we suggest individual valve repair in addition to standard compression therapy for those who have axial reflux with structurally preserved deep venous valves, to aid in venous ulcer healing and to prevent recurrence.	2	C
4.16.4	In a patient with advanced post-thrombotic syndrome (C4b, C5–C6), we suggest valve transposition or transplantation for those with absence of structurally preserved axial deep venous valves and competent outflow venous pathways that are anatomically appropriate for venous outflow. This procedure should be done in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence.	2	C
4.16.5	In a patient with advanced post-thrombotic syndrome (C4b, C5–C6), we suggest consideration of autogenous valve substitutes such as a neovalve by surgeons experienced in these techniques in those with no other option available. This procedure should be done in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C

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45

Endovascular reconstruction for primary iliac vein obstruction

PETER NEGLÉN

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In the complex make-up of the multifactorial etiology of chronic venous disease (CVD), the presence of venous obstruction has been ignored for decades. Reflux was emphasized and dominated the pathophysiology of CVD. The fact that an efficient, low-risk treatment is now available and that an iliac venous outflow obstruction has been shown to be an important contributor have changed the paradigm. The iliac and common femoral veins constitute the common outflow tract of the lower extremity, and chronic obstruction of this segment appears to result in more severe symptoms than does lower segmental blockage.[1,2] Obstruction in CVD is either non-occlusive (stenosis) or occlusive (occlusion) and primary (non-thrombotic) or post-thrombotic. Complete occlusion is a misnomer and should not be used.[3] Poor recanalization following acute deep vein thrombosis (DVT) of the common femoral and iliac veins, sometimes with inferior vena cava (IVC) involvement, is probably the most common cause of symptomatic chronic venous blockage. The thrombosis may be limited to the iliofemoral segment or contiguous from the calf to the iliac veins. Remaining obstruction is the principal cause of symptoms in approximately a third of post-thrombotic limbs.[4,5] Treatment of post-thrombotic iliac vein obstruction is discussed in Chapter 46. Less common causes of chronic blockage of the femoro-iliocaval vein include benign or malignant tumors, retroperitoneal fibrosis, iatrogenic injury, irradiation, cysts, and arterial aneurysms. Non-thrombotic iliac vein lesions (NIVLs) have a high prevalence in the asymptomatic general population. Kibbe et al. found that two-thirds of all patients studied had at least 25% compression of the left iliac vein.[6] This fact has raised skepticism as to whether or not the NIVL is even pathogenic, with the suggestion that it should be viewed as a "normal" anatomic variant that does not need treatment. There is, however, increasing evidence that this is not true.[7]

45.1 NON-THROMBOTIC, PRIMARY OBSTRUCTION

A so-called primary or non-thrombotic iliac vein obstruction (May–Thurner syndrome[8] or Cockett's or "iliac vein compression" syndrome[9]) has been described. Typically, a stenosis of the left proximal common iliac vein is caused by compression by the right common iliac artery with secondary band or web formation (Figures 45.1 and 45.2).[10] The prevailing concept is that this syndrome is only clinically expressed in the left lower extremity of predominantly young women of child-bearing age. This limitation is unsubstantiated. Clearly, no patient should be excluded from consideration of the syndrome based on age, sex, or bilateral or right side involvement since compression lesions are not uncommon in males, in elderly patients, and may involve the right limb. In our experience of treating iliofemoral obstruction in 938 limbs in 879 patients, 53% of limbs had non-thrombotic compression lesions (defined as absent history of DVT and no venographic or ultrasound findings indicating

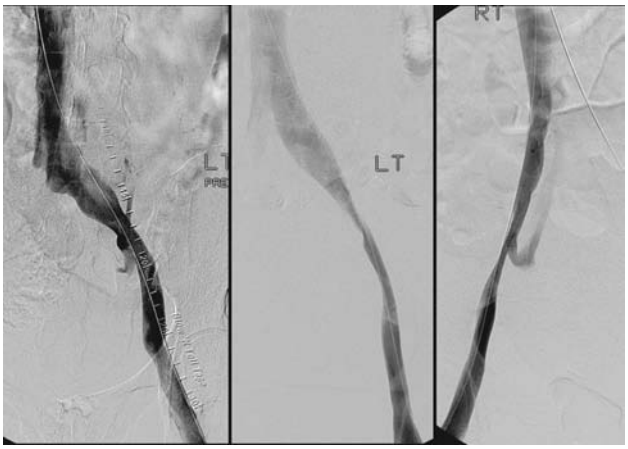

Figure 45.1 Transfemoral ascending venograms: anterior–posterior views. (Left) Findings suggesting compression of the left common iliac vein in an elderly woman with slight filling of the ascending lumbar and internal iliac veins. (Middle) Distal compression of the left external iliac vein in the sagittal plane (see also Figures 45.3c and 45.3d). (Right) Compression of the right distal common iliac and external iliac veins by the right iliac artery as it gradually traverses those veins.

previous DVT), 40% had post-thrombotic obstruction, and 7% had a combined etiology (a central NIVL with a post-thrombotic obstruction in the peripheral iliac vein). The ages of the patients with non-thrombotic blockage ranged from 18 to 90 years (median 54 years), 20% of patients were

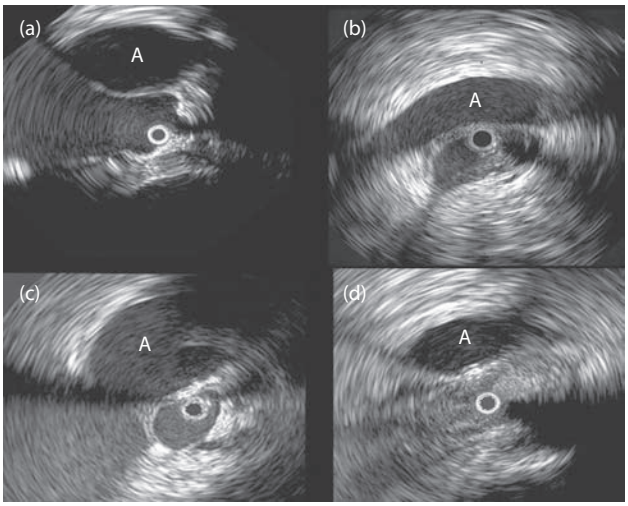

Figure 45.2 Images obtained by intravascular ultrasound (IVUS) at the site of an iliac vein compression. The black circle inside the vein represents the inserted IVUS catheter (the "A" marks the right common iliac artery). **(a)** The right common iliac artery crosses anterior to the left common iliac vein, in this case creating a moderate degree of compression. **(b)** Compression of the left common iliac vein with an intraluminal web formation. **(c)** A distinct septa underlying the compressing artery deforming and dividing the iliac venous lumen. **(d)** Acute thrombosis of the compressed venous segment.

men, and 25% of the symptomatic lower limbs were on the right side.[11] The obstruction is not only caused by an extrinsic compression by a crossing artery, but also by potential flow restrictions by concomitant intraluminal lesions and wall fibrosis. Thus, the term "compression lesion" should be replaced by the term NIVL.

45.2 CONNECTION BETWEEN NIVL, ACUTE DVT, AND RECANALIZATION

The important relationship between iliac vein compression lesions and the preponderance of left iliofemoral thrombosis was recognized early. Virchow attributed the marked left-sided predilection for DVT to stasis caused by compression of the left iliac vein by the right iliac artery against the fifth lumbar vertebral body.[12] Presence of intra-luminal obstruction to flow may enhance thrombus formation (Figure 45.2d). The NIVL may not only cause a thrombosis, but also affect the degree of resolution of the formed thrombus. Recanalization appears to be inhibited and more incomplete when an external compression is present.[13] Cockett et al observed that the obstructive lesion that precipitated the thrombosis impeded its resolution, and the post-thrombotic perivenous fibrosis appeared to develop excessively at the initiating lesion site, with the combination resulting in severe clinical presentation.[10,14] This observation is of great importance since it has been reported that 80% of limbs with iliofemoral DVT have underlying extrinsic iliac compression-type lesions detected by spiral computed tomography (CT) venography.[15] It is important to realize that a NIVL can cause symptoms of the lower limb without having had DVT.

45.3 EXTERNAL COMPRESSION AND INTRALUMINAL LESIONS

"Iliac vein compression syndrome" is a misleading nomenclature since the lesion is not only characterized by narrowing due to external compression, but also frequently by the presence of intraluminal lesions acting as weirs in the bloodstream (Figures 45.2b and 45.2c). As mentioned above, these lesions are now more appropriately named NIVLs. The origin still remains an enigma. A post-thrombotic etiology of the intraluminal lesions appears to be ruled out due to the absence of hemosiderin and other features of an organizing thrombus, even though secondary thrombosis at the site or distally is often associated.[8,10] The nature of these lesions was described by McMurrich in 1908 who called them an "adhesion" resulting in "fusion of the anterior and posterior wall of the vein." He thought the lesion was congenital and was surprised by its frequency (33%) in 107 unselected cadavers.[16] Ehrich and Krumbhaar confirmed the high prevalence of these obstructive intraluminal lesions (30% in 412 unselected autopsies), although they contested the etiology being congenital.[17] Although the theory of congenital etiology is not prevailing, there is some support for it. The presence of muscle, elastin, and collagen has been described

in these lesions in a layered structure, which would suggest an ontogenic, not traumatic origin.[10,17] The arterial crossover points also coincide with embryonic venous fusion sites where congenital webs and membranes may be present.[18] These occur more commonly on the left side. These early studies lay dormant until interest was revived by the detailed studies of May and Thurner in 1957.[8] Their studies supported the presently prevailing theory that the majority of NIVLs are probably traumatic from repeated pulsations of the intimately associated artery. They found a 22% incidence of iliac intraluminal lesions in 430 unselected cadavers. The morphology of the lesion varied from a thin membrane to "ridges, velums, chords, spurs or bridges" to total blockage. Interestingly, the anatomist DiDio had already described these lesion in his doctoral thesis in 1949 and also introduced the concept of the "venous spur" (personal communication by Alberto Caggiati). May and Thurner suggested that the predominant fibroblastic content of the lesion resulted from a proliferation of cells originating from the endothelium in response to chronic injury by the pulsating artery. Operating on these obstructions, Wanke had earlier observed a cicatricial sclerotic transformation of the common sheath secondary to iterative trauma and perivenous inflammation.[19] Arteriosclerotic inflammation of the artery at the vessel crossing may also affect the underlying vein and explain the finding of venous obstruction in elderly people. The increased incidence in women has been attributed to compression by the gravid uterus or increased lordosis. In the 1960s, Cockett et al. confirmed the high prevalence of the compressive iliac lesion in the general population (eight out of nine corrosion casts of the vein [88%] showed at least some degree of external compression) and 14% of 100 unselected cadavers had intraluminal lesions.[9,14]

45.4 ANATOMICAL ASPECTS

The exploration of iliofemoral veins with intravascular ultrasound (IVUS) has provided new information regarding the compression portion of the non-thrombotic iliac lesions.[11] Among 493 symptomatic lower limbs, a single central NIVL was present in the common iliac vein in 36% of limbs at the crossing of the right common iliac artery. A single peripheral NIVL was found at or near the internal iliac vein junction in 18% of lower limbs at the crossing of the internal iliac arteries. More interestingly, in 46% of limbs, central NIVLs were combined with a peripheral NIVL (Figure 45.3). The latter finding has implications for the extent of stenting in individual patients with "primary" obstruction. The central NIVL lesion was typically very focal (±1 cm) on the left side and was located at the iliocaval confluence. Contrarily, the right central NIVL was less focal (≤2 cm) and was located 1–2 cm distal to the iliocaval confluence. Below the focal lesion on the left side, a varying eccentric impression is also frequently observed of the cephalad two-thirds of the left common iliac vein, probably caused by the left common iliac artery. Not until just above the internal and external iliac vein confluence is the common iliac vein fully distended. This is an important observation since the fully distended vein should be used for reference for the choice of diameter of the stent to be inserted. This has also been observed on CT scan in asymptomatic individuals.[20] The central NIVL lesion was three-times more frequently observed on the left side, while the peripheral NIVL lesion was equally distributed bilaterally. The anatomical differences between the right and left pelvic vasculature may explain the variable distribution of proximal and distal obstructive lesions (Figure 45.4).[10] The level of aortic bifurcation is variable, which affects the relevant left side anatomy very little, but has a major effect on artery/vein course relationships on the right side. The right iliac artery always crosses the left common iliac vein abruptly, with the level of crossing showing minor variations (central left lesion). On the right side, the right iliac artery crosses the right common iliac vein only in 22% of cadavers, coursing "lazily" across the vein over a longer length (central right lesion) (Figure 45.4, inset). In three-quarters of limbs, the right common iliac artery crosses the right common iliac vein somewhat more abruptly low down at the internal–external iliac vein confluence (peripheral right lesion). In most cases, the right internal iliac artery does not cross the common or external iliac veins, because it originates before the iliac artery has crossed the vein. The left internal iliac artery always crosses abruptly across the left iliac vein (peripheral left lesion) (Figure 45.3c and 45.3d). These

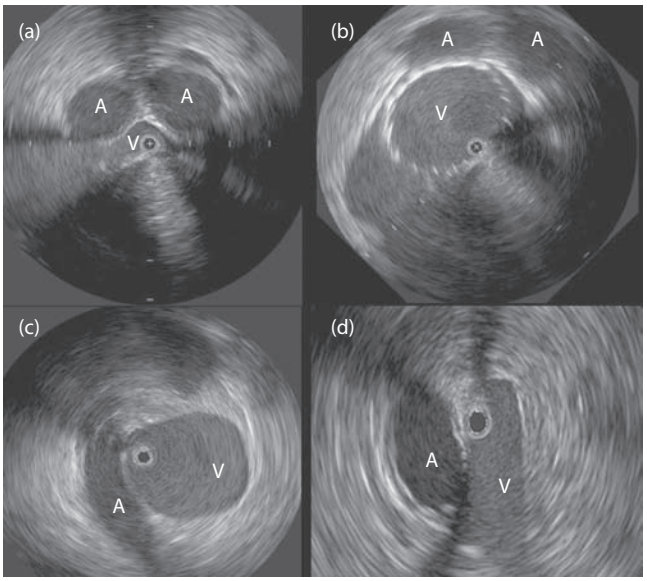

Figure 45.3 Images obtained by intravascular ultrasound (IVUS). The black circle inside the vein (V) represents the inserted IVUS catheter. **(a)** The distal inferior vena cava is compressed by a low aortic bifurcation (A) at the confluence of the iliac veins. **(b)** Same anatomic site post-stent placement. **(c)** The internal iliac artery (A) is seen crossing the external iliac vein (V) entering the pelvis. No compression of the vein is observed. **(d)** Significant compression of the external iliac vein is observed, as well as a distal non-thrombotic iliac vein lesion.

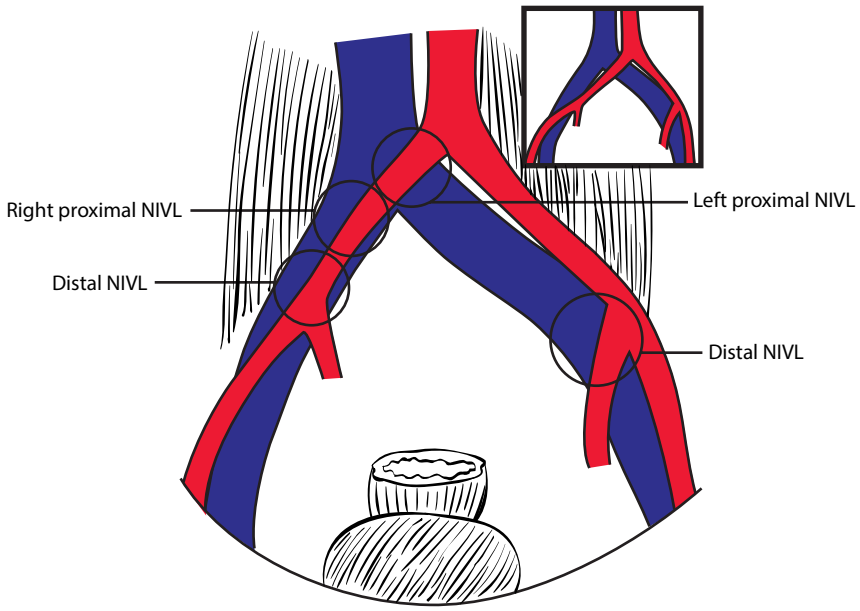

Figure 45.4 The relationships between the pelvic arteries and veins. The left-sided central lesion is related to the abrupt crossing of the left common iliac vein by the right common iliac artery. The subsequent course of the right common iliac artery is variable (see text). The minority pattern is shown in the larger drawing. Coursing gradually across the left common vein, the right common iliac artery may be related to the central and/or peripheral non-thrombotic iliac vein lesion (NIVL). In the majority pattern (inset), the right common iliac artery crosses the right common iliac vein more perpendicular and peripherally. It may still create a peripheral right NIVL, but will not cause a central right NIVL. The left internal iliac artery crossing may be related to the left distal NIVL.

anatomical variations may explain the greater frequency of proximal left compression lesions, the focal stenosis on the left, and the diffuse lesion on the right side, as well as the similar rates of the distal lesions occurring bilaterally.

45.5 PATHOPHYSIOLOGY OF NIVLs

The possibility that these limbs with "primary," non-thrombotic disease (NIVLs) may have had an isolated subclinical iliac vein thrombosis that initiated at the vessel crossing and then propagated distally into the external iliac vein cannot be excluded. On the other hand, limbs with obvious post-thrombotic disease may have had an underlying iliac vein compression resulting in an iliofemoral vein thrombosis.[14,15] Whatever the chain of events, it serves to remind us that patients complaining of leg pain and swelling and no history of previous DVT or other venous disease may have isolated iliac vein obstruction.

Non-thrombotic iliac lesions are ubiquitous in asymptomatic individuals. Why does a NIVL become symptomatic in some when it remains silent in most? This apparent contradiction can be resolved if NIVL is viewed as a permissive condition predisposing to the development of CVD. Permissive conditions are pathologies that may remain variably silent in and of themselves until additional insult or pathology is superimposed. Obstruction of major venous pathways cannot be considered a "normal variant," only clinically asymptomatic. There is extensive literature on pathologic and iatrogenic major venous interruptions. They are often clinically tolerated,[21,22] but not always.[23,24] There are numerous reports in the literature of silent congenital or acquired IVC occlusions being discovered incidentally on imaging studies, but that become symptomatic with the onset of distal thrombosis.[25,26] It is therefore not surprising that many NIVL obstructions remain asymptomatic, as this is probably a gradually progressive condition. Additional insult or pathology such as trauma, cellulitis, distal thrombosis, secondary lymphatic exhaustion, or, commonly, reflux may render the extremity symptomatic. The general principle in these complex pathologies is to treat the permissive condition first, which alone may provide relief, and to prevent recurrence. Correction of secondary pathology may be required only in recalcitrant and advanced cases. A total of 75% of limbs with NIVL and concurrent reflux experienced a good or excellent outcome in this series with stent placement alone, even when the reflux component, which was severe in many, was uncorrected. These results are supportive of the concept that NIVL plays a permissive role in the genesis of CVD symptoms.[11]

An alternative explanation for the observations presented here is to consider NIVL and distal reflux as a continuum in progressive hemodynamic deterioration of the venous system. Venous decompensation occurs when the hemodynamics cross a certain critical threshold and the patient become symptomatic. However, no conclusive connection between NIVLs and distal reflux has been established.

45.6 DIAGNOSIS OF NIVL

45.6.1 Hemodynamic tests

There is no "gold standard" for the assessment of venous obstruction. Unfortunately, it is not even known to what degree a single stenosis or multiple-level obstructions are hemodynamically significant or "critical" (i.e., increasing the peripheral venous hypertension). An elevation of pressure of only a few mmHg at the venular end of the capillary may result in venous symptoms. The concept of an arterially significant obstruction being a stenosis of >70%–80% is based on a decreased distal perfusion, since that degree of an arterial obstruction has a higher resistance than the tissue. Central resistance to flow is not an issue in the converging venous system, but increased peripheral venous hypertension is. Relief of this hypertension (decompression of the leg) is the basis of symptom relief. Ultrasound investigation and outflow fraction determinations by plethysmographic methods have been shown to be unreliable and play only a limited role. Although abnormal plethysmography findings may indicate obstruction to the venous outflow, significant blockage may exist in the presence of normal findings.[27,28] Even the invasive pressures (i.e., hand/foot pressure differential and reactive hyperemia pressure increase) and indirect resistance calculations appear insensitive and do not define the level of obstruction.[28] Unfortunately, it is presently impossible to detect borderline obstructions, which may be of hemodynamic importance. Thus, a positive hemodynamic test may indicate hemodynamic significance, but a normal test does not exclude it.

Different differential pressures can be measured during venogram. Only small pressure differences (2–5 mmHg) at rest may indicate significant obstruction. The venous circulation is a low-pressure, low-velocity, and large-volume vascular system, where the venous pressure is a function of not only resistance to the flow (degree of obstruction and collateral formation), but also depends to a higher degree on the flow velocity and magnitude of volume flow. The contralateral veins converge beyond the iliac obstructions, which may mitigate any IVC to femoral vein pressure gradient at rest. These pressure differences are certainly much lower than in the arterial system, and may be difficult to measure accurately.[29,30] The suggested pressure differentials to detect hemodynamic significance in the literature are set arbitrarily. In a supine position, especially during surgery, it is difficult to increase the venous outflow sufficiently to detect a borderline hemodynamic obstruction. Thus, pressure measurements during the intervention cannot assist in making a decision as to whether or not to continue with the placement of a stent.

45.6.2 Imaging studies

Since accurate hemodynamic tests are unavailable, diagnosis and treatment must be based on morphological findings. Post-thrombotic lesions are often obvious and found to a high degree using all imaging modalities. Findings of NIVL are less striking and can be missed. Spiral computerized tomography venography (CT-V) and magnetic resonance venography (MR-V) are frequently used; however, these modalities need to be validated versus IVUS, and their role in the workup of venous obstruction is not yet defined. The transfemoral venogram is often still used and may show definite obstruction and development of collaterals. A simple venogram is usually performed initially in the stent placement procedure. Findings in patients with NIVLs are often subtle in the anterior–posterior (AP) view and are only suggestive of an underlying obstruction (e.g., widening of the iliac vein [pancaking], "thinning" of the contrast dye resulting in a translucence of the area, partial intraluminal defect [septum], or a minimal filling of transpelvic collaterals). In 30%–40%, the AP image actually appears to be "normal."[11] Increased accuracy may be achieved with multiple-angled projections, which may reveal surprisingly tight stenosis on oblique projections, although the AP image is quite normal (Figure 45.5). However, even with oblique views the stenosis is missed in 5%–10% of limbs. The extent of a NIVL is still hard to delineate on venogram and venogram is a poor guide for the extent of stenting. Naturally, the hemodynamic impact of any detected stenosis is not known from morphologic studies. Any compensatory role of collateral formation is doubtful since blood flow through these meandering vessels can hardly replace the flow through the straighter main vein. The collaterals observed pre-stent often disappear promptly following stenting of a significant stenosis. The flow through the stent is obviously favored. The presence of collaterals in a symptomatic patient is usually to be considered an indicator of obstruction.

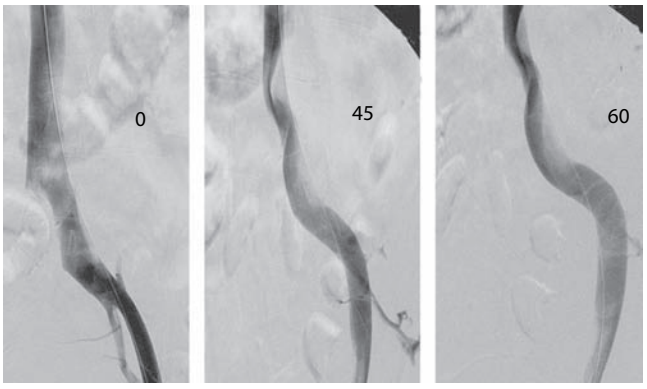

Figure 45.5 Transfemoral left venogram with multiple projections. (Left) Anterior–posterior view showing the absence of stenosis, a translucent left common iliac vein, and slight filling of collaterals. The stenosis is detected by rotation: (Middle) 45° oblique view; (Right) 60° oblique view. A typical "corkscrew" appearance is created by the impression of the artery on the vein. It is difficult to decide where the lesion starts and terminates on the venogram.

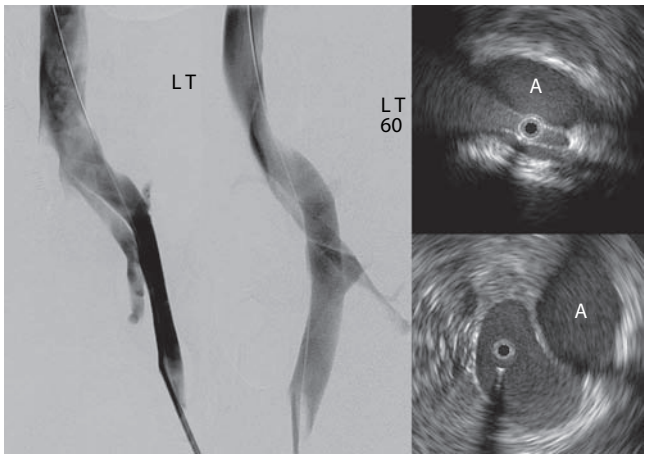

Figure 45.6 (Left) Transfemoral venogram in anterior–posterior (AP) and 60° oblique views. Note the absence of obvious obstruction in the AP view, which is exposed in the oblique view. (Right) Intravascular ultrasound (IVUS) images of the same patient with a central non-thrombotic iliac vein lesion clearly shown with the right common iliac artery (A) compressing the left common iliac vein (top) and the left common iliac artery (A) compressing the left iliac vein (bottom; see text). The black circle inside the vein represents the inserted IVUS catheter.

IVUS can detect only axial collaterals running close to the original vessel. Transpelvic collaterals will escape detection. Several studies have shown, however, that IVUS is superior to transfemoral venography in the detection of the extent and degree of obstruction, especially in patients with NIVL (Figure 45.6).[31–33] On average, the transfemoral venogram significantly underestimated the degree of stenosis by 30%. The venogram was actually considered "normal" in a quarter of limbs, despite the fact that IVUS showed >50% obstruction.[34] Interestingly, Cockett and colleagues made similar observations in the 1960s. Venography was diagnostic in only 65% of obstructed limbs in their material and collaterals were visualized only in 63%. It was noted that in 54% of symptomatic patients, transfemoral venography appeared "normal" with smooth contours of contrast in the iliac vein and without collaterals. The authors also noted that the absence of collateral formation should not negate consideration of a significant obstruction.[9,10,14] In addition, IVUS shows intraluminal details (e.g., trabeculations and webs), which may be hidden in the injected contrast dye. An external compression with the resulting deformity of the venous lumen can be directly visualized, and wall thickness and movement can be seen.

IVUS is clearly superior to transfemoral venography in providing adequate morphological information. It is presently the best available method for diagnosing clinically significant NIVL and also for guiding stent placement in these patients. Obstructions with >50% diameter stenosis on venogram or >50% area reduction and/or >50% minimum diameter stenosis on IVUS are indicated for stenting. This measurement has been arbitrarily chosen based on the fact that the majority of patients treated for this degree of obstruction improve clinically.

45.7 PATIENT SELECTION

There is no evidence that asymptomatic patients with incidental finding of a NIVL need any intervention. Patients with an acute iliac DVT secondary to compression should be treated according to the guidelines in Chapter 22. Patients with symptomatic non-thrombotic iliac lesions should be considered for stenting. The problem is to identify and select those patients. The most essential aspect is to be aware of the existence of iliac vein outflow obstruction and its importance—think obstruction! There are no specific symptoms per se that identify the presence of NIVL. Symptoms of proximal chronic venous obstruction may vary greatly, but only patients with significant symptoms belonging to severe C3 (swelling above knee) and C4–C6 of the CEAP classification should be investigated for iliac obstruction and considered for stenting. Obstruction has been shown to be important in the clinical expression of CVD, especially as pain. Negus et al. suggested that limb swelling and pain were related to the obstructive component, while limb ulceration resulted from valve reflux.[10] Ulcer is rarely seen with isolated obstruction, and formation of ulcer appears to require the presence of reflux.[7] Nevertheless, correction of outflow obstruction results in substantial symptom relief, including ulcer healing, even in the presence of reflux. A substantial number of patients with CVD complain of disabling limb pain and swelling without skin changes. The dominant pathophysiologic component in these patients may be obstruction rather than reflux, and it is possible that these symptoms are mainly attributable to the outflow blockage. "Venous claudication" is a condition described as an exercise-induced "tense" pain, which requires several minutes of rest and often leg elevation to achieve relief. There are no reports on the association of NIVL and complaints of venous claudication. Certainly, patients with significant outflow obstruction may have less dramatic symptoms with less distinct lower extremity pain and discomfort with decreased quality of life and moderate disability. Of particular interest are patients with primary reflux disease with pain out of proportion to the degree of reflux and when no reflux is found in patients with "venous pain." Patients with atypical varicose veins or early recurrence of varicose veins may have underlying obstruction. Women complaining of pelvic congestive syndrome who have not improved on ovarian embolization may be a group of patients that may improve on stenting of a non-thrombotic iliac vein obstruction, if present. Patients with obvious obstruction on duplex ultrasound scanning or other morphological studies and those with positive pressure studies should probably be considered for exploration by IVUS and stenting of the pelvic outflow. Absence of collaterals on morphological studies does not negate a significant stenosis, and presence of collaterals should not be a requirement for stenting of NIVLs.

45.8 THE STENTING PROCEDURE

The technique of stenting of NIVLs is outlined below, emphasizing a few important points (Figure 45.7).[33–35] The procedure may be performed under local anesthesia in a fully equipped endovascular or angiographic suite. External ultrasound for cannulation guidance is obligatory, and the availability of IVUS is preferred in order to diagnose the severity and extent of the NIVL and guide stent placement. The antegrade approach through an access in the thigh portion of the femoral vein or through the popliteal vein is preferred. Too high an access in the thigh/groin makes it impossible to find compression at the level of the inguinal ligament, if present. In contrast to arterial access at the thigh level, control of the venipuncture site is not a problem because of the low venous pressure. After cannulation, a guidewire is inserted, followed by the sheath (usually 9–11-Fr size) to accommodate the IVUS catheter, stent, and balloons. The NIVLs are usually simple to transverse with the guidewire. A transfemoral antegrade venography is performed using a power injector and with a subtraction technique. The compression of the iliac veins occurs in different planes. If IVUS is not going to be utilized, it is vital to perform several oblique venographic projections to reveal both sagittal and transverse compressions and assess the extent of the lesion to be stented. The reference vessel for assessment of the stent diameter is the fully expanded common iliac vein below the central NIVL and the fully expanded distal external iliac vein for the peripheral NIVL.

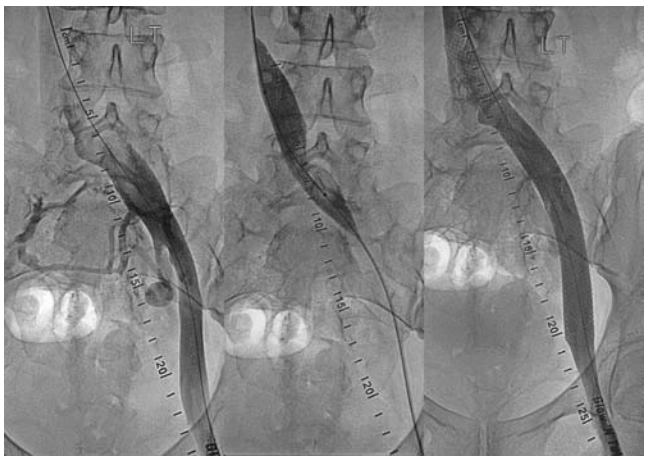

Figure 45.7 Stenting of a compression lesion. (Left) Transfemoral venogram showing a typical non-thrombotic vein lesion with pre-stent translucency at the vessel crossing and transpelvic collaterals. (Middle) Focal wasting of the balloon during inflation by the stenosis at pre-dilation prior to stent placement. (Right) Post-stent venogram revealing no stenosis or collaterals. Note that the Wallstent is placed well into the inferior vena cava to prevent retrograde migration. The stent is carried into the external iliac vein, since a significant stenosis was found on intravascular ultrasound at the external and internal iliac vein confluence.

The extent and degree of obstruction are more accurately delineated by IVUS. The importance is to re-establish the size of the normal vein at the level of the NIVL in order to properly decompress the lower limb. The entire obstruction is ultimately dilated with 14–18-mm high-pressure balloons. No clinical rupture of the vein has as yet been reported. Only self-expanded stents should be inserted. Owing to the size and radial strength requirements, braided stainless steel stents (Wallstent, Boston Scientific, Natick, MA) are most frequently used in the United States and have proven efficacy. However, new, dedicated venous Nitinol stents are available in Europe. These have not yet been assessed for long-term efficacy. Stenting of a stenosis adjacent to the confluence of the common iliac veins using Wallstents requires that the stent be placed well into the IVC to avoid early caudal migration and restenosis. Owing to its braided stent design, it will foreshorten on dilation or extend on insufficient dilation, which has to be taking into account when stents are overlapping or are expected to deploy at a certain level. With multiple focal stenosis, two or more stents are inserted without leaving skip areas, although the vein segments may appear normal between the central and peripheral lesions. If central and peripheral NIVLs are combined with compression by the inguinal ligament, the stent system must extend peripherally below the level of the inguinal ligament. The profunda femoris vein is easily identified by IVUS. If necessary, extension of the Wallstents across the groin crease into the common femoral vein just above the profunda orifice has not been found to jeopardize stent patency.

The peri-operative thrombosis prophylaxis may vary, but is fairly standardized in our hands. The patient receives 2500 U of dalteparin subcutaneously pre-operatively. During the procedure, 5000 U of unfractionated heparin is given intravenously. Most procedures are performed as outpatient procedures. Post-operatively, a foot compression device is applied, dalteparin 2500 U administered subcutaneously in the recovery room, and dalteparin 5000 U administered before discharge. Low-dose aspirin (81 mg *per os* daily) is started immediately post-operatively and continued. No vitamin K antagonists are necessary, unless findings on the IVUS support the presence of a previous DVT.

45.9 COMPLICATIONS AND THROMBOTIC EVENTS

Stenting of patients with "primary" obstruction is a well-tolerated procedure with extremely low morbidity and nil mortality.[36–38] The non-thrombotic complication rate related to the endovascular intervention of NIVL is minimal and, when it occurs, is related to the cannulation site. Of particular note is the near absence of early stent thrombosis (<30 days), as reported in several series, although only aspirin is administered for long-term stent maintenance. This is remarkable, considering the natural potential for thrombosis that exists in the venous system.

The extension of the stent into the IVC has raised concerns about relative obstruction to the venous outflow of the contralateral limb and subsequent thrombosis. The thrombosis rate was, however, was low (0.6%) in this study. This should be compared with the approximately 40% rate of proximal restenosis when a braided stent (Wallstent) was not extended into the IVC.[33]

45.10 STENT OUTCOME

The cumulative primary and secondary patency rates in 518 patients treated for symptomatic "primary" obstruction were 79% and 100% at 72 months, respectively. There were no thrombotic stent occlusions (Figure 45.8).[36] Ye et al. reported the same cumulative patency rates in 224 stented limbs to be 98% and 100%, respectively, at a mean follow-up of 4 years.[37] Missing associated lesions during stent correction of NIVL is a common reason for residual or recurrent symptoms that require repeat interventions. Re-interventions were mainly performed in order to balloon dilate in-stent restenosis, to add a stent that was central or peripheral to the existing stent system, or a combination of these procedures. The cumulative severe (>50%) in-stent stenosis rate was assessed in 270 limbs and remained low in the long term, with the cumulative rate at 72 months being 1%.[38] By contrast, Meng et al. reported non-cumulative occlusion and restenosis rates of 8% and 4%, respectively, in 231 patients followed for 3 months to 10 years (mean 46 months).[39] The cumulative primary patency rate at 5 years was 94%. The nature and mechanism of the development of in-stent recurrent stenosis (ISR) is not yet known, but is probably due to flow alterations and thrombus formation. Contrarily to the treatment of post-thrombotic iliac obstructions, the placement of stents in non-thrombotic iliac vein obstructions appears to be exceptionally safe, with a near absence of re-occlusion and development of in-stent stenosis in the long term.

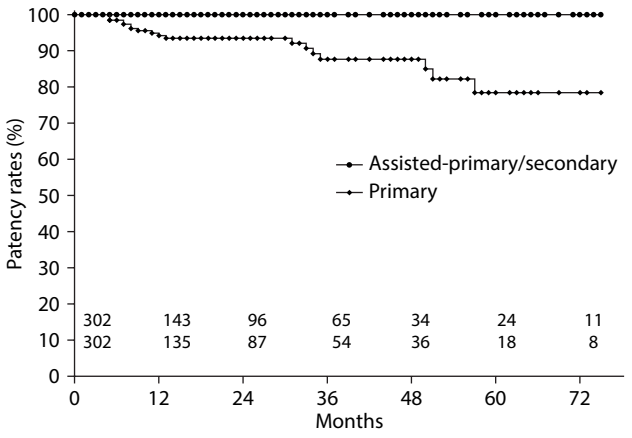

Figure 45.8 Cumulative primary, assisted primary, and secondary patency rates for stented limbs with non-thrombotic iliac vein lesions. The lower numbers represent total limbs at risk for each time interval (all standard error of means [SEM] <10%).

45.11 CLINICAL OUTCOME

Reports about clinical outcome after stent placement for isolated "primary" obstruction are few. Most studies mix thrombotic and non-thrombotic obstructions and include treatment of superficial reflux. Despite these caveats, patients stented for symptomatic NIVLs alone appear to have a favorable clinical outcome, particularly in terms of relief of pain and the healing of venous ulcers. Raju and Neglén reported cumulative results observed at 2.5 years after stent placement with complete relief of pain, complete relief of swelling, and sustained healing of leg ulcers of 77%, 53%, and 76%, respectively.[11] A later report showed a cumulative ulcer recurrence-free rate at 5 years of 62%.[36] Ye et al. showed non-cumulative rates of relief of pain and swelling and ulcer healing in 87%, 88%, and 74%, respectively, in 101 limbs at a median follow-up of 4 years.[37] Quality of life scores improved significantly in both studies. Interestingly, Neglén et al. showed nearly the same result in subgroups of limbs with NIVL alone and NIVL combined with reflux, with the reflux remaining untreated.[11] Although Meng et al. did not compare these subgroups directly, they found that patients with NIVL and varicose veins only had significant symptom relief in 13% of limbs after 2 months.[39] However, all patients with NIVL and great saphenous vein reflux had saphenous vein stripping in addition to stent placement (195/231 limbs, 84%). The rates of relief of swelling and ulcer healing were 84% and 85%, respectively, in the entire cohort at an average follow-up of 4 years. Long-term cumulative relief of pain, ulcer healing, and improved quality of life scores have been shown to be the same in stented limbs with NIVL and thrombotic obstruction, despite the observation that limbs with thrombotic obstruction clearly had more extensive venous disease with more severe obstruction and reflux more frequently involving multiple systems and levels than limbs with NIVL.[36]

45.12 CONCLUSIONS

Compression of the iliac veins is frequently found in asymptomatic individuals. Despite this observation, NIVL has been shown to play a role in patients with chronic venous insufficiency (C3–C6), as stenting of the lesion shows a favorable clinical outcome. The major obstacle to improving the selection of patient with a NIVL is the lack of a reliable test to measure a hemodynamically significant stenosis. The key for the physician is to be aware of the importance and possibility of venous blockage, and to perform investigations of the pelvic venous outflow. Of particular interest are patients with primary reflux disease with pain out of proportion to the degree of reflux, patients with suspicion of "venous pain" with no reflux, patients with atypical or early recurrence of varicose veins, and patients with pelvic

Guidelines 4.17.0 of the American Venous Forum on endovascular reconstruction for primary iliac vein obstruction

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.17.1	We recommend endovenous stenting as the current "method of choice" for the treatment of primary iliac vein obstruction.	1	B
4.17.2	To alleviate pain and swelling and promote sustained ulcer healing, we recommend venous stenting for the treatment of primary iliac vein obstruction. Venous stenting improves the quality of life of the patients.	1	B

congestive syndrome and no improvement after ovarian embolization. Patients with obvious obstruction on duplex ultrasound scanning or other morphological studies and those with positive pressure studies should probably be considered for exploration by IVUS and for stenting of the pelvic outflow.

The diagnosis and treatment must presently be based on invasive morphological investigations of the iliac venous outflow, although hemodynamic criteria would be preferred. IVUS investigation is the ultimate test and should be generously utilized in symptomatic patients with a suspicion of outflow obstruction. Limiting workup of patients with significant CVD only with duplex ultrasound will not suffice, especially when restricted to the infra-inguinal vein segments.

Stenting of the primary iliac vein obstruction can be performed with low morbidity, no mortality, long-term high patency rates, and a low rate of in-stent restenosis. Stenting of a primary iliac vein obstruction is a minimally invasive outpatient procedure and appears to result in marked clinical improvement whether or not an adjunct procedure in order to control superficial reflux is performed.[11,40,41] In the presence of combined iliac vein obstruction and superficial or deep reflux, therefore, the emerging course of treatment is to primarily correct the obstructive component.

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● = Key primary paper
★ = Major review article

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46

Endovascular treatment of post-thrombotic iliofemoral venous obstruction

ERIN H. MURPHY AND SESHADRI RAJU

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46.1 INTRODUCTION

Deep venous thrombosis (DVT) affects nearly 1,000,000 people annually in the United States.[1] Immediately following the index thrombotic event, patients are at risk of clot propagation and pulmonary emboli. As the risk of acute complications decreases, the risk of post-thrombotic syndrome (PTS) or secondary chronic venous hypertension increases. PTS consists of a constellation of symptoms of chronic venous disease which results from a prior episode of DVT. Symptoms range from mild swelling to intractable edema, limb heaviness, debilitating leg pain, pigmentation, venous claudication, chronic ulcers, and cellulitis. Pain and swelling are generally postural, worsening with prolonged leg dependency, and increasing as the day progresses.

PTS is most closely associated with proximal DVT, involving one or more segments above the popliteal vein, which is present in 80% of patients with symptomatic DVT.[2] In these patients, the incidence of PTS following DVT ranges from 20% to 50% in the literature.[3] At 5-year follow-up in patients who were managed with anticoagulation alone for acute DVT, up to 90% have been shown to have at least some evidence of chronic disease. Moderate-severity PTS with debilitating venous claudication has been reported in up to 44%, and severe PTS, characterized by lower extremity ulceration, is reported in 15%.[4,5] Overall, estimates have shown that venous ulceration secondary to PTS is currently present in about 5% of the population. Applied to current population statistics, this presently equates to over 15 million people in the United States.

The impact of this disease cannot be overstated and is immense for both the individual and the health care system. PTS has been universally associated with decreased quality of life,[5,6] workplace absenteeism,[7] dysfunction and disability, and increased chronic medical care and cost.[8,9] Moreover, self-reported quality of life scores in PTS patients parallel those expected in age-matched patients with serious chronic diseases such as diabetes, congestive heart failure, and chronic obstructive pulmonary disease.[6]

46.2 PRESENTATION AND ETIOLOGY

PTS is a distinct and separately identifiable entity from DVT and must be distinguished from the initial DVT episode. Symptoms within the first 3–6 months following an inciting DVT should be attributed to the index event. Only after this initial lead-in period has passed is it appropriate to assign the remaining symptoms to PTS rather than the acute DVT.[3] Alternatively, symptoms associated with the initial DVT episode may regress with anticoagulation, only to gradually worsen months or years later. In fact, while most patients who develop PTS do present in the initial few months to years post-inciting DVT episode,[9,10] it has been demonstrated that the risk for PTS continues to increase for the next 10–20 years.[11]

Understanding the mechanisms of PTS is essential to prevention as well as treatment. Overall, venous dysfunction is multifactorial and linked to underlying persistent outflow obstruction, venous reflux, and calf muscle dysfunction. These factors each contribute to PTS via the shared mechanism of increased ambulatory venous hypertension.

Persistent venous outflow obstruction is present in 70%–80% of cases of iliofemoral DVT as a result of either

failed or incomplete venous recanalization.[4,5] Persistent obstruction can overwhelm the ability of the calf muscle pump to lower ambulatory venous pressure and may eventually lead to valvular reflux. Deep venous reflux, whether attributable to persistent obstruction and subsequent elevation of pressure or to primary valvular damage from thrombosis and fibrosis, serves as another source of increased pressures in the calf and foot. Lastly, calf muscle pump dysfunction also likely contributes to worsening PTS symptoms by decreasing the efficacy of the venous pump. Over time, chronic venous hypertension may cause inflammatory-mediated muscle atrophy, denervation, and myopathy.[12] Furthermore, lower extremity swelling, pain, and ulceration can lead to a decrease in ambulation. In patients who become more sedentary secondary to their symptoms, calf muscle ejection fraction is significantly decreased by greater than 50% compared to control subjects or even limbs with prior iliofemoral DVT who have not become sedentary.[5]

While the factors contributing to PTS are apparent, what remains indistinct is the precise order of predominance of obstruction, reflux, and calf dysfunction in determining the occurrence and severity of PTS. Thus far, persistent obstruction appears to be one of the most important features of significant PTS. Early persistent obstruction, even for as short as 1–6 months,[13,14] is a consistent predictor of eventual PTS. Conversely, early catheter-directed thrombolysis is associated with a reduced incidence of PTS.[15] Furthermore, obstruction of the iliofemoral portion of the venous system—the common outflow channel of the leg—is associated with more severe PTS than persistent femoral–popliteal obstruction. The latter, which has a more developed collateral system, may compensate better, with less elevation of downstream pressures.

Interestingly, venous ulcers appear to have an association with pathological reflux. This may indicate that the underlying pathology differentiates itself in terms of disease presentation, with persistent obstruction leading primarily to pain and swelling, and reflux contributing to ulceration.[15,16] Neglen et al. demonstrated that ulcers were present in 24% of patients with obstruction and reflux versus only 5% of patients with obstruction alone.[16]

Importantly, Raju et al. demonstrated that iliac vein stenting for late chronic venous obstruction was sufficient to control symptoms even in the presence of persistent deep reflex. Specifically, ulcer healing rates of 54%, freedom from ulcer recurrence of 88%, freedom from dermatitis of 81%, and freedom from pain and swelling at 5 years of 78% and 55%, respectively, were observed.[17]

Most likely, the various etiologies interplay in an exponential rather than incremental way in the development of PTS. The diagnostic evaluation should therefore be thorough enough to evaluate all underlying pathology, including an evaluation of reflux and obstruction in both the deep and superficial systems.

46.3 DIAGNOSTIC EVALUATION

46.3.1 History and physical

Clinical evaluation with a detailed history and physical are paramount in the evaluation of patients with suspected PTS. Ultimately, it is the severity of clinical symptoms and examination findings that guide the necessity for intervention. Even the most extensive lesions are not treated unless the clinical presentation justifies it. History should include evaluation for symptoms and duration, medical comorbidities, ambulatory status, personal and family history of DVT or thrombophilia, anticoagulation use, and prior venous interventions (inferior vena cava [IVC] filters, venous ablations, thrombolysis, and thrombectomy). It should be noted that an absence of a documented DVT does not exclude a diagnosis of PTS, as the initial thrombotic episode may have been asymptomatic or undiagnosed. Postural symptoms of heaviness, tightness, swelling, and pain, which worsen with prolonged dependency and improve with elevation, support a venous etiology. Venous claudication is associated with severe disease and is described as a bursting-type pain with ambulation which resolves with rest and limb elevation. Significant swelling or chronic skin changes with malleolar pigmentation or lipodermatosclerosis provide further evidence of an underlying deep venous obstruction that is unlikely to be related to superficial reflux alone. Ulcers can be attributable to superficial disease, but often have a deep venous pathology component as well (Figure 46.1).

46.3.2 Laboratory evaluation

Laboratory evaluation for patients with suspected PTS includes a thrombophilia panel workup, coagulation panel, complete blood count, and basic metabolic panel, with attention to albumin and renal function.

46.3.3 Hemodynamic evaluation

Unfortunately, at this time, there is no ideal hemodynamic parameter in the laboratory or operating suite that can accurately predict the degree, or even presence, of significant underlying iliac vein obstruction. Thus, while abnormal alterations in venous plethysmography and invasive pressure measurements (arm–foot venous pressure and ambulatory venous pressure) can support underlying venous disease,[18–20] an absence of these findings does not rule it out. Furthermore, excellent clinical outcomes have been demonstrated despite a lack in significant pre- and post-stenting differences in hemodynamic test results, including ambulatory venous pressure, venous fill time, outflow fraction, and venous filling index.[16,21] Thus, the criteria for intervention are largely based on clinical symptoms in the presence of outflow stenosis.

Figure 46.1 Presentation of chronic venous disease. Patients with chronic venous disease may present with pain and swelling **(a)**, hyperpigmentation with lipodermatosclerosis **(b)**, and ulcers **(c)**.

46.3.4 Diagnostic imaging

Currently, in the evaluation of a PTS patient, duplex ultrasound is routinely performed and is helpful for documentation of infrainguinal obstruction and reflux in both the deep and superficial systems. However, when using ultrasound to diagnose iliac vein obstruction, there are limitations. Duplex is highly operator dependent with a significant learning curve for iliac vein visualization in the pelvis. This may make reliable and accurate imaging of the iliac vessels challenging in laboratories with a low volume of venous cases. Difficulty of visualization may be further increased by the presence of bowel gas or significant truncal obesity.

Perhaps most important, however, are the limitations in the current diagnostic criteria for the diagnosis of iliac vein obstruction with ultrasound. Current published criteria for stenosis are based on the identification of a 50% narrowing of the iliac vein when compared to adjacent normal venous segments.[22] The problem inherent in this technique with post-thrombotic vein patients is two-fold. First, venous stenosis in post-thrombotic patients is most often long, diffuse stenosis involving entire venous segments (i.e., entire common iliac vein or external iliac vein). This is in contrast to the focal lesions seen in non-thrombotic iliac vein lesions (NIVLs) or arterial segments. Thus, without an adjacent normal segment to reference, no stenosis will be identified, resulting in a false-negative interpretation (Figure 46.2). Second, while it is generally accepted in the arterial system that a 50% lesion is significant, studies have suggested that a much smaller degree of vein stenosis can elevate venous pressures behind the lesion, contributing to disease. Since criteria are not readily available to diagnose lesions of less than 50%, nor has the degree of hemodynamic significance yet been determined, ultrasound studies in these patients may also be interpreted as normal.

Transfemoral venography is commonly employed as an alternative or compliment to duplex ultrasound. This is an excellent tool for determining in-line flow and vessel patency. Imaging with venography may also demonstrate focal lesions. However, these are less common in PTS patients compared to NIVLs. Diffuse narrowing is sometimes apparent. Early collateral filling before the proximal ipsilateral iliac vein is a sign of proximal obstruction (Figure 46.3). Despite these advantages, venography is limited in the determination of stenosis. Images are generally obtained in an anterior–posterior (AP) plane, providing a projection of the vein from lateral wall to lateral wall. Since stenosis typically occurs disproportionally in the AP dimension in veins, lesions are not always discretely apparent.[23–25] Instead, lesions may appear as a broadening or thinning of contrast. Collaterals, which fill before the remainder of the ipsilateral iliac vein, may also be a sign of a significant proximal stenosis. Diffuse stenosis without adjacent focal lesions may again be interpreted

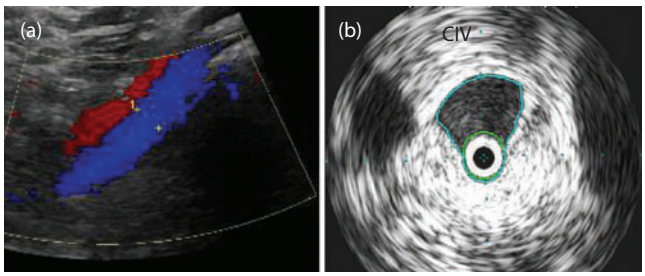

Figure 46.2 Using traditional diagnostic criteria, ultrasound can miss underlying diffuse stenosis when there is no focal narrowing. In this patient with diffuse stenosis, the duplex was normal **(a)**, despite a greater than 50% narrowing that was easily demonstrated with intravascular ultrasound **(b)**.

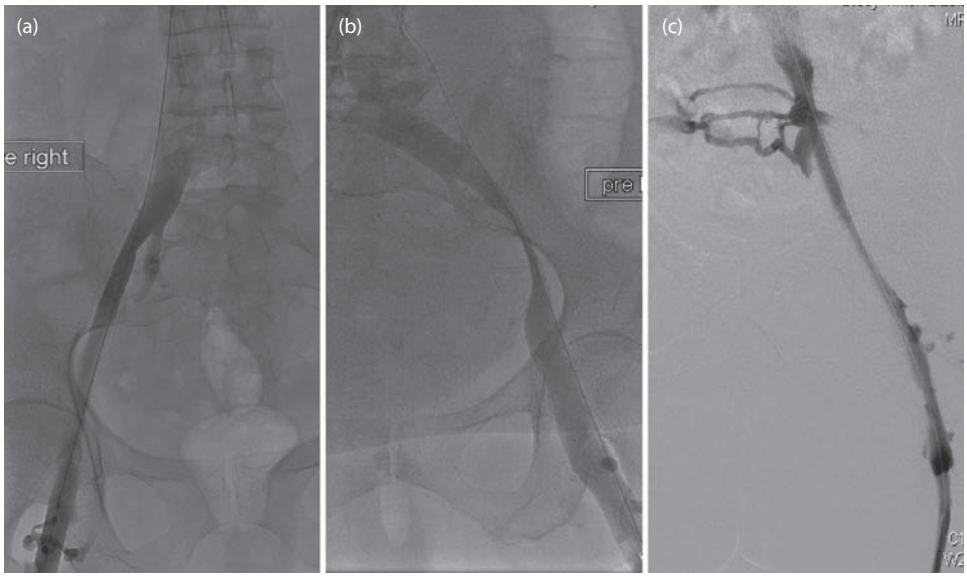

Figure 46.3 Signs of underlying iliofemoral venous stenosis on venogram. Venographic appearance of iliofemoral venous stenosis may include diffuse narrowing throughout an entire segment **(a)**, focal segmental stenosis seen here in the external iliac vein **(b)**, or the presence of collateral filling before the ipsilateral proximal common iliac vein **(c)**.

as normal. The overall accuracy of venography in the detection of non-occlusive iliac vein stenosis is around 50%[17] and is likely maximized by the operator reviewing all images.

Alternative, non-invasive venographic studies include computed tomographic venography and magnetic resonance venography. These studies are promising in that a cross-sectional image of the vessel is visible throughout its course, which may better delineate narrowing in the AP plane. Nonetheless, these studies are again subject to false interpretation as normal in patients with diffuse stenosis if the interpreting physicians seek discrete lesions to compare against adjacent segments. While it is our experience that a trained eye can recognize diffuse disease, well-conducted trials demonstrating the efficacy of these studies in the diagnosis of post-thrombotic iliac vein obstruction are lacking.

Ultimately, intravascular ultrasound (IVUS) remains the gold standard for diagnosis and is supported by a 90% sensitivity for the detection of iliac vein obstruction.[23,26] Once the suspicion for underlying iliac vein stenosis is high enough to warrant a procedure, IVUS can be used to confirm the diagnosis, as well as to guide the stenting procedure in the same setting.

46.4 INTERVENTION

Endovascular venoplasty with iliofemoral venous stenting has become first-line therapy for post-thrombotic iliofemoral venous obstructive lesions. In fact, with evidence that stenting alone can improve symptoms substantially without correction of the underlying deep venous reflux,[17] open venous valve reconstructions and bypasses have all but been eliminated.

Because of the low morbidity and high success of endovascular interventions to relieve venous obstruction in the common outflow tracks, this is a first step in patients who have PTS and obstruction. Superficial reflux may be treated at the same time or in a separate procedure with ablations if it is felt to be hemodynamically significant enough to be contributing to venous disease.

46.4.1 Technique

Access is obtained in the femoral vein of the mid- to upper thigh under ultrasound guidance. Occlusive disease of the femoral vein in the thigh is not uncommon in post-thrombotic patients, but does not preclude use of the vein for access. On rare occasions when access of the femoral vein fails, alternative access sites include the common femoral vein, profunda femoral vein, internal jugular vein, popliteal vein, or even the great saphenous vein.

Both intra-operative venography and IVUS are performed to guide the procedure. Venography provides a roadmap for the procedure, identifies cross-pelvic collateralization, and allows visualization of continuous flow. Slow flow with failure of contrast clearance or occlusion is easily demonstrated.

Occlusions are crossed with a glide wire and associated catheter. Use of long 6-Fr or 7-Fr support sheaths may be needed to help cross the occlusion. Different from the subintimal j-wire technique that is often used to cross arterial lesions, small intraluminal wire/catheter advancements are preferable in the vein.

Once wire access has been obtained across the occlusion or stenotic venous segments, IVUS is performed. IVUS is highly sensitive for iliac vein stenosis of both focal as well as long segment diffuse disease.[23,26] Slow venous flow below

an occlusion may also be noted with the presence of "snowflakes" in the IVUS image. With IVUS, diameter and area measurements are obtained in the common femoral vein, external iliac vein, common iliac vein, and IVC to determine the extent of PTS. These values are then compared to anatomic norms for each segment to determine the degree of stenosis. The anatomic norms that are used are 200, 150, and 125 mm^2 to correspond to the common iliac vein, external iliac vein, and common femoral vein, respectively. These areas are determined from average vein diameters of 16, 14, and 12 mm in the same vessels.[27] Most frequently, post-thrombotic disease will be segmental, involving the entire common iliac vein, external iliac vein, and/or common femoral vein. The location of the iliac vein bifurcation is noted. Additionally, a distal stent landing zone is determined at the time of the initial IVUS, before balloon dilatation, which will result in vasospasm. The landing zone should be in a relatively disease-free segment, or at least in the least diseased segment above the femoral bifurcation, where the superficial femoral vein is joined by the profunda femoral vein. In some patients, poor inflow secondary to post-thrombotic or occluded femoral and profunda femoral veins is noted. Stenting without an appropriate landing zone in open but stenotic patients should be avoided when possible. However, in the case of a recanalization of a chronic occlusion, stenting to the most robust segment of vein may still be beneficial and may remain patent despite a relative paucity of flow.

In cases where IVUS fails to demonstrate a significant lesion, balloon sizing should be performed. Undetected iliac vein stenosis can be picked up in 15% of patients that would have been missed by IVUS.[27] In this subset, stenosis is diagnosed with balloon wasting and should be stented.

The segments to be treated should be pre-dilated with a large, 16–18-mm balloon at high insufflation pressures in the range of 14–18 mmHg held at each station for 1–2 minutes. Notably, in severely diseased veins, pre-dilation should be performed from bottom to top in order to prevent difficulty in retrieving a balloon through stenotic segments. If the IVC was also recannalized, then larger balloons in the range of 22–24 mm are used for pre-dilation.

All stents currently used in the venous system are considered "off-label" and were initially designed for use elsewhere in the body. At our center, we primarily utilize Wallstents (Boston Scientific, Nantick, MA) in combination with Gianturco Z-stents (Cook, Bloomington, IN). Wallstents are first deployed from the iliac confluence down to the previously determined landing zone. Generally, 16-, 18-, or 20-mm Wallstents are used for iliac and common femoral veins. Z-stents, sized a minimum of 2 mm larger than the Wallstents, are deployed such that the upper 2 cm of the Z-stent rests in the IVC and the remainder is within the Wallstent in the common iliac vein. When stenting bilaterally, the Wallstents are deployed bilaterally to the iliocaval confluence, the first Z-stent is deployed into the IVC, and the second Z-stent is deployed such that it interdigitates with the first Z-stent. If the IVC is also stented, then larger, 22–24-mm Wallstents are used in the IVC landing zone above the confluence. These stents, like the iliac wall stents, are placed prior to the Z-stents so that the Z-stents may interdigitate into the caval stent. The use of Z-stents facilitates bilateral stenting and IVC stenting and prevents chronic jailing of the opposite iliac vein by Wallstent extension into the IVC.[28] Importantly, some form of stenting must extend into the IVC, or recurrence at the iliocaval junction is likely to occur. Alternative configurations to Z-stenting for bilateral stenting including the apposition technique, double-barrel stenting, and Y-fenestrations. While commonly performed, these approaches are not encouraged, as they have been associated with decreased patency and increased need for re-interventions (Figure 46.4).[29]

After stenting, the stents are balloon profiled. Repeat IVUS should demonstrate normalization of iliofemoral diameters, or larger balloons may be used to dilate the stents to a greater extent (Figure 46.5).

46.4.2 Post-operative management

Patients are generally discharged from the hospital on post-operative day 1. Patients are anticoagulated peri-operatively. Long-term anticoagulation is determined by standard criteria including documented thrombophilia, recanalization

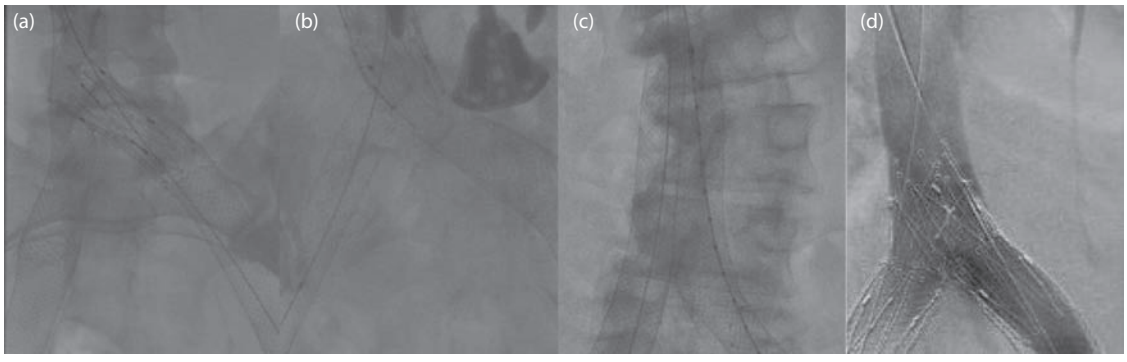

Figure 46.4 Bilateral stent configurations. Y-configurations **(a)**, apposition stenting **(b)**, and double-barrel stenting **(c)** are common configurations, but are associated with increased complications. Bilateral Z-stenting may decrease the need for re-interventions **(d)**.

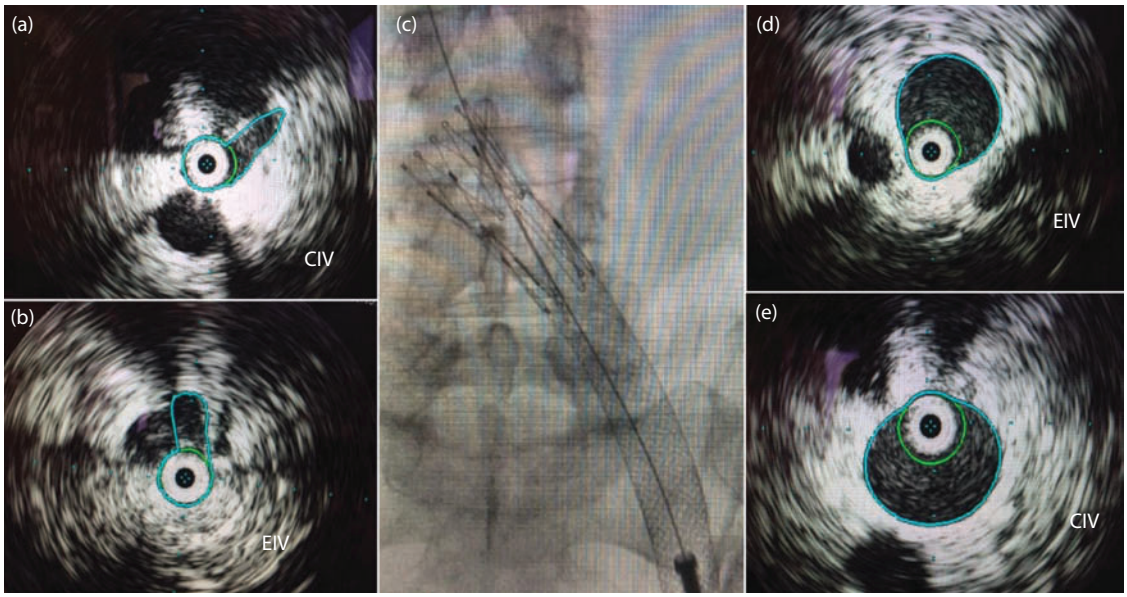

Figure 46.5 Iliofemoral venous stenting of a patient with post-thrombotic syndrome. Pre-intervention intravascular ultrasound demonstrated 65% stenosis of the external iliac vein **(a)** and 64% stenosis of the common iliac vein **(b)**. The final stent image is seen in **(c)**. Completion of intravascular ultrasound demonstrated well-expanded lumen throughout, with resolution of stenosis in the external iliac vein **(d)** and common iliac vein **(e)**.

for complete occlusions, recurrent thrombosis, or unprovoked thrombosis.

Stent surveillance is performed at routine intervals in our laboratory with duplex ultrasound and clinical examination. Duplex is performed on post-operative day 1, and then again at 1 month, 3 months, 6 months, 12 months, and yearly thereafter. In-stent restenosis (ISR) with significant build-up is first treated with a change or increase in the anticoagulation regimen. Persistent ISR or stent collapse without symptoms are monitored. When combined with an interval increase in symptoms paralleling the decrease in stent patency, patients are managed with repeat IVUS with possible stent dilation and/or stent extension depending on the findings at the time of reoperation.

46.5 OUTCOMES

Percutaneous interventions for PTS are safe and can be performed with minimal morbidity. A summary report on nearly 1500 cases demonstrated no deaths, no pulmonary emboli, access site complications in <1%, and bleeding requiring transfusion in 0.03%. The incidence of DVT was also no higher than the incidence in native veins.[30] Mild ISR is common, but severe ISR (>50%) occurs in only 10% of PTS patients.[30]

While cumulative stent patency is lower in post-thrombotic patients compared to their non-thrombotic counterparts, encouraging and sustaining results are still routine. Five-year primary, primary assisted, and cumulative secondary patency for stents in post-thrombotic, non-occluded veins have been reported at 57%, 80%, and 86%, respectively.[31] Overall reported secondary patency rates for post-thrombotic limbs at 4–7 years are 74%–89%.[30] Symptom relief is universal, with most patients reporting improved pain, swelling, and quality of life. Venous claudication should be expected to resolve after relief of iliac outflow obstruction, and improvements in ambulation are nearly universal.[18] At 5 years, cumulative complete relief of pain and swelling were reported at 62% and 32%, respectively.

Patients with chronic total occlusions requiring recanalization prior to stenting have the lowest stent patency, as expected. Nonetheless, even in this group, initial recanalization success remains high, as do the rewards. Successful percutaneous recanalization of occluded femoro-iliocaval lesions has been reported at 83%–95%.[30,32] Cumulative patency in the 139 limbs that were treated was 66% at 4 years, with rates of relief of pain and swelling at 3 years of 79% and 66%, respectively. Consequently, quality of life was markedly improved in these patients.[32] Among those series reporting recanalizations of occluded femoro-iliocaval lesions, cumulative secondary patency was slightly lower than that demonstrated in PTS patients without occlusion and ranged from 66% to 89% at 4–7 years of follow-up.[30]

Notably, occlusions generally occur in patients treated for post-thrombotic occlusions with poor inflow. Failure to recognize and treat common femoral disease by extension of the stent beyond the inguinal ligament increases the risk of re-thrombosis.[33] Stents should be extended to healthy vein or at least the best inflow possible, which is often just above the profunda vein. Stenting across the inguinal ligament has been demonstrated to be safe and necessary in many patients, without the stent fractures seen in the arterial system.[34] Interestingly, while hypercoagulable disorders are associated with a higher rate of initial thrombosis, they are not associated with an increased rate of stent occlusion.[31]

Ulcer healing in post-thrombotic patients is lower than in the non-thrombotic cohort; however, even in this disadvantaged group, a 60% 5-year cumulative healing rate has been demonstrated.[27] The most difficult ulcers to heal are post-thrombotic patients with large ulcers (greater than 1 inch) with significant deep venous reflux (defined as the presence of reflux in more than three venous segments). It should be noted that correction of superficial reflux with great saphenous vein ablation was performed simultaneously with stenting in patients with a great saphenous vein of greater than 5 mm with documented reflux. In patients with ulcers that do not heal, investigation and treatment for new developments of superficial reflux or in-stent stenosis should be performed. Some patients with large ulceration may require split-thickness skin grafts or vascularized flaps for coverage.

46.6 CONCLUSION

PTS is a treatable yet undermanaged, debilitating condition. Percutaneous intervention can be performed with relative ease, low morbidity, and zero expected mortality. Reasonable long-term patency is the rule, with limited need for re-interventions. Prolonged symptom relief including relief from pain and swelling and healing of ulcerations is also expected, along with improvements in quality of life and substantial decreases in venous-relate disability.

Guidelines 4.18.0 of the American Venous Forum on the endovascular treatment of lower extremity post-thrombotic iliofemoral venous obstruction

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.18.1	In a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis with or without lower extremity deep venous reflux disease that is associated with severe limb swelling (C3), with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend venous angioplasty and stent recanalization, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	1	B

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47

Endovascular reconstruction of inferior vena cava obstructions

YOUNG ERBEN AND HARALDUR BJARNASON

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47.1 INTRODUCTION

Endovascular management of iliac vein obstructions has become well accepted in recent years, with good technical and clinical outcomes.[1–8]

Obstructions of the common femoral veins (CFVs), iliac veins (IVs), or inferior vena cava (IVC) are associated with significant morbidity and mortality.[9,10] In the past, treatment options for chronic obstructions have mainly been conservative management based on compression therapy and leg elevation with or without the use of anticoagulation.[11] Surgical options are available, but have inconsistent outcomes, and not all patients are candidates for such treatment.[12–14]

It has been estimated that one person in 1000 of the general population will develop deep vein thrombosis (DVT) annually. In only 10% of those patients will the thrombus extend to the IVs,[15] which leads to an annual incidence of IV thrombosis of close to one in 10,000 of the population. Conservative treatment of IV thrombosis includes anticoagulation for 3–6 months or longer.[16] Many patients will be left with persistent venous occlusion, and these patients may be at considerable risk of developing severe postthrombotic syndrome.[17] Although the standard treatment for acute iliofemoral thrombosis has been anticoagulation, catheter-directed thrombolysis, with or without mechanical thrombectomy, has been shown to be effective in acute iliofemoral DVT. Even with thrombolytic treatment, a large proportion of patients will still need endovascular stents to be placed in conjunction with the thrombolytic procedure.[6,18–20] Occlusion of the IVC is expected in 0.2%–0.6% of the population[21] and represents 6% of patients undergoing treatment with endovascular stents[6] for chronic venous obstruction. To date, there are multiple publications that support the use of stents for the treatment of venous obstruction/occlusion in the IVs and IVC.

47.2 PATIENT SELECTION

Currently, recanalization and stenting of the obstructed IVs and the IVC is only offered to patients with symptoms due to the venous obstruction or in those who had previous DVT immediately distal to IVC or IV obstruction.

Ultrasound is, as a general rule, the most accessible and in many ways the best imaging study available for evaluation of the venous system outside of the body cavities. On ultrasound, the veins of the leg, popliteal vein, femoral vein (FV), and the CFV can be evaluated for patency and wall thickness. Duplex scanning will give functional information on both reflux and venous obstruction.

For imaging of the IVs and, in particular, the distal end of the IVC, ultrasound becomes significantly less dependable and sensitive. In these areas, ultrasound can in most cases indicate whether or not the vein is open. The Doppler waveform from the CFV will also give an indication of the status of the proximal IVs.[22] Other alternative modalities such as ascending venography, computed tomography, and magnetic resonance imaging (MRI) can be helpful in the evaluation of the IVs and the IVC. These imaging methods are discussed in detail in Chapters 15 and 16.

Ascending venography gives a very good anatomic image of the deep veins in the leg, knee, and thigh. The CFV is also well visualized, but the IVs and the IVC are often poorly opacified because of the diluted contrast and

because the blood is often diverted away by collaterals because of central obstruction. The great saphenous vein can also be well evaluated, which is another important point in the evaluation of the possible candidate for IVC recanalization.

Contrast-enhanced computed tomography (CT) is often very helpful in the evaluation of a patient with obstruction of the IV or IVC (Figure 47.1). CT can reveal underlying lesions such as a tumor, iliocaval compression syndrome (May–Thurner syndrome), retroperitoneal fibrosis, or an aneurysm compressing the vein. Acute thrombosis of the pelvic veins or IVC can also be diagnosed with contrast-enhanced CT. Contrast mixture artifacts may mimic thrombus in the veins. Therefore, caution is needed when diagnosing acute venous thrombosis based on a CT because non-opacified blood mixes with the enhanced blood, which can resemble thrombosis. The same type of artifacts can also be seen on MRI.

MRI can be used to evaluate the IVs and the IVC. There is less experience with MRI than with other modalities (Figure 47.2). MRI sequences have been reported that can directly demonstrate acute thrombus (6 months or less).[23]

Noninvasive tests such as air plethysmography have been applied to diagnose and follow-up venous disorders.[24] These functional tests can be part of surveillance after intervention. There are mixed reports on the usefulness of these tests when it comes to documenting obstruction, and some reports have indicated that the correlation with hemodynamic improvement after successful endovascular stent procedures might not be good.[25]

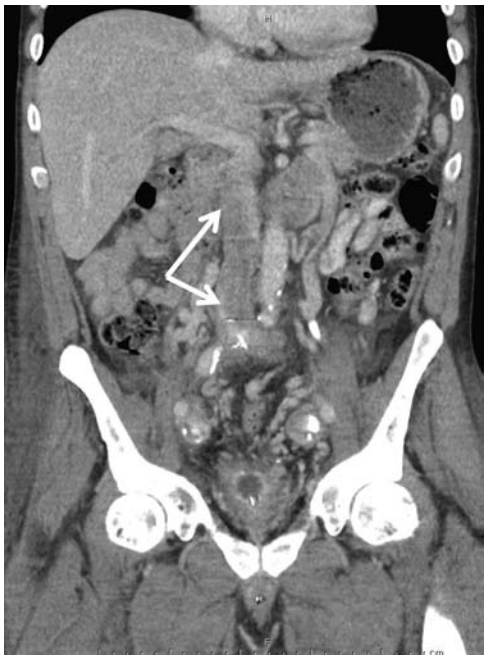


Figure 47.1 Contrast-enhanced computed tomography scan revealing a thrombosed inferior vena cava (arrows), coronal view. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

Figure 47.2 Magnetic resonance imaging scan demonstrating acute thrombus in the inferior vena cava (arrows). (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

47.3 TECHNIQUE OF ENDOVENOUS RECANALIZATION

Successful recanalization of a chronically occluded IV and/or IVC depends on many factors. Experience in managing catheters and guidewires is needed. Selection of the correct access site is one of the most important aspects. For recanalization of an IV occlusion, the contralateral FV approach is not recommended. The steep angle around the IVC bifurcation directs much of the forward energy up into the IVC rather than into the contralateral IV. This makes it difficult to pass balloon catheters and stents across into the contralateral vein. Therefore, most operators use the ipsilateral FV or CFV access and/or access from the right internal jugular vein (RIJV). Contralateral common femoral or mid- to distal-FV access is usually easy, and ultrasound guidance should be used for the initial puncture. The superficial femoral artery is frequently superficial to the vein in the thigh, making access somewhat challenging. The relatively small FV and CFV give extra support to catheters and guidewires as they are advanced through the chronic obstruction. From this standpoint, this way is favored over the RIJV access, in which the large right atrium and IVC do not offer good support and looping of the catheter system can be a problem (arrhythmias and pericardial perforation).

The RIJV approach has its advantages and is favored by many operators. The issue with poor support from the right atrium and IVC can be partially averted by using long introducer sheaths. The CFV often has post-thrombotic changes in it, as well as the inflow vessels, the FV, profunda FV, and the great saphenous vein. These veins can be dilated if RIJV access is used; however, this cannot be easily

achieved when coming from below, such as from the FV. This is particularly true for the profunda FV, which is not easily accessible from a caudal approach. In addition, if the FV access is high, introducer sheaths may be too close to the diseased area to be treated safely with stents or balloon angioplasty.

For the procedure, an introducer sheath needs to be used. Coming from the jugular vein, a 45-cm long introducer sheath will habitually extend to the level of the IVC bifurcation. Having the introducer sheath at that level will, in addition to the support, allow simultaneous pressure measurement in the open IVC above the obstructed segment, through the introducer sheath, and from the catheter which has been advanced distally into the open distal "inflow" vein. This gives the pressure gradient across the obstructed segment before the procedure and following angioplasty and stent placement. If access has been gained from the CFV, FV, or popliteal vein, an introducer of a sufficient length to extend to the distal landing zone should be selected. The long introducer will ease repeat exchange of balloons and catheters when an extended segment of partially recanalized FV is crossed on the way to the distal landing zone (CFV).

A hydrophilic (glide) wire such as the stiff-angled glide wire from Terumo (Terumo Medical Corporation, Somerset, NJ) combined with a 5-Fr angiographic catheter with hydrophilic coating (Glidex; Terumo Medical Corporation, Somerset, NJ) works well to traverse chronically occluded IVs. Often, the fibrotic veins are quite tough to pass through. Spinning the guidewire or rolling it between one's fingers as it is slowly advanced works well. Direct forward force is usually not advised. Performing intermittent contrast injections through the angiographic catheter will offer a picture of where the channels within the vein go, serving as a guiding map. The glide catheter is then advanced over the wire with a spinning forward motion. As soon as the occluded segment has been passed and the catheter has reached the normal (or best distal) venous segment, pressures should be measured on both ends of the obstructed segment to obtain the pressure gradient across the obstruction.

At this point, the glide wire can be exchanged for a stiffer wire. We have preferred a braided guidewire such as the Amplatz Super Stiff guidewire (Medi-Tech, Boston Scientific Corporation, Natick, MA). For the IVs and CFV, pre-dilation is always performed prior to stent delivery. The IVs and the CFVs can be dilated to 16 mm and the common iliac vein (CIV) even up to 18 mm. The IVC can be dilated to the same diameter prior to stent placement (Figures 47.3). Passing the balloon (14–20-mm balloons have large deflated profiles) through the occluded veins can be quite difficult. Therefore, pre-dilation with a smaller-profile balloon such as a 4–8-mm balloon may be needed in order to be able to pass the larger balloons through. If a catheter or balloon still cannot be passed through the vessel, but the wire has been passed, a puncture can be made into the vessel distally and the wire pulled through that puncture site, typically the RIJV and the CFV. By applying tension to both ends, the catheter and balloon can now be pulled through.

When the occluded segments have been pre-dilated, the stents are placed. Balloon-expandable stents are generally used for this purpose. There is a variety of self-expandable stents available, as discussed above, but it is important to select stents with flexibility and adequate radial strength. When placing them, it is important not to leave behind uncovered diseased vein in between stents. In other words, the stents should overlap by a few millimeters.

For recanalization and stenting of IV obstruction without IVC involvement, there has been debate with regards to how far into the IVC the IV stents have to be placed. We place the proximal stent such that it extends barely into the IVC, overriding the contralateral IV by approximately 5 mm. Others advocate placing the stents into the IVC overriding the contralateral IV. Caliste et al. experienced 9.7% (five patients) contralateral thrombosis of the non-stented contralateral iliofemoral vein where stents extended from the treated IV into the IVC, crossing the non-thrombosed contralateral IV, but several of the patients had been non-compliant with the prescribed anticoagulation regimen.[26] It is still unclear whether this causes a higher rate of contralateral IV thrombosis or other related issues such as increased

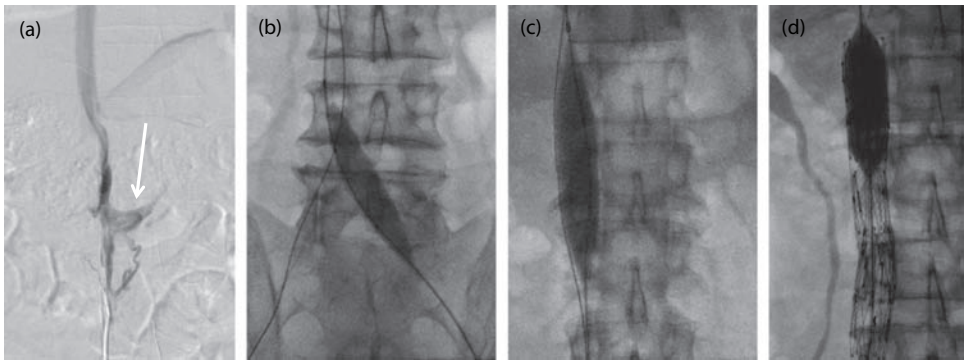


Figure 47.3 Venography demonstrating: **(a)** post-thrombotic obstruction of the inferior vena cava, including the pararenal level (left renal vein; arrow); **(b** and **c)** sequential dilatation of the inferior vena cava and common iliac veins; **(d)** stent placement and angioplasty of the inferior vena cava. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

venous pressure, but we avoid extending the stents fully across the contralateral side because of concern regarding thrombosis of the healthy side.

The placement of stents into the CFV used to be an object of considerable debate; however, this is common practice today and is accepted by most operators. Of the 35 patients in the series from O'Sullivan et al., 12 received an infrainguinal CFV stent, and the patency rates at 1 day, 1 month, and 1 year were 91.3%, 81.7%, and 81.7%, respectively. The authors reported no fractures or mechanical failures in this group.[27] Andrews et al. demonstrated that, in a swine model in which metallic stents were placed across the hip, no fractures were noted.[28] There have been anecdotal reports of fracture in the CFV in humans with Nitinol-type self-expandable stents.

The renal veins are commonly occluded or partially occluded when the IVC occlusion/partial occlusion involves the suprarenal IVC. If stents are placed across the renal vein, one of the concerns is further affecting of the venous drainage from the kidney, which subsequently could lead to a decline in renal function. This has, however, not been reported or been our experience. Raju et al. did not find an indication of impaired renal function that could be attributed to stent placement across the level of the renal veins.[6] When the renal veins are involved in the thrombosed process and have collaterals which they drain by, it seems acceptable to stent across these.

Recanalization of a chronically occluded IVC bifurcation poses a technical challenge (Figure 47.4). Both CIVs are usually involved as well in cases of the IVC occlusion extending to the bifurcation, which is the most frequent situation. This means that the bifurcation has to be reconstructed.[29–31] No bifurcated stents similar to an abdominal aortic endograft are available. There are many solutions for

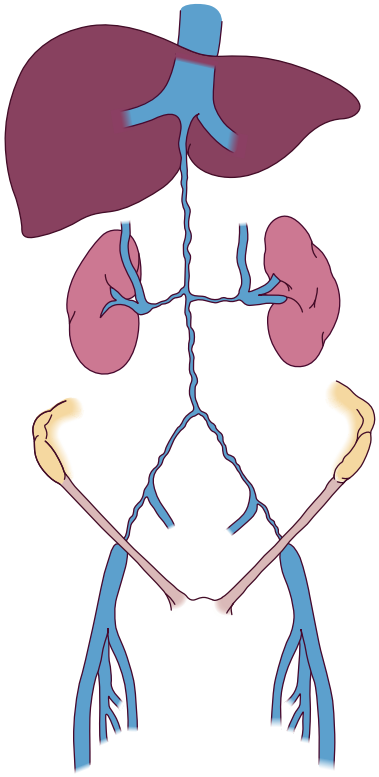


Figure 47.4 Diagrammatic representation of inferior vena cava occlusion. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

reconstructing the bifurcation (Figure 47.5). A combination of the available stents can be used to build it. We prefer to perform a single-barrel recanalization of the IVC using large-diameter stents such as the Wallstent (22–24 mm) (Boston Scientific Corporation, Natick, MA) in combination

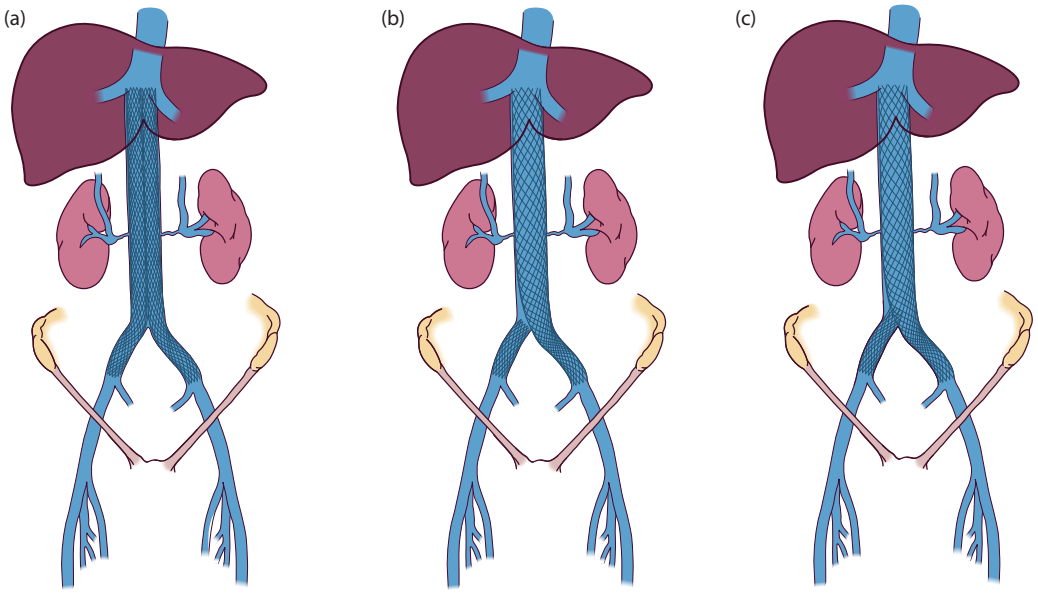


Figure 47.5 Stenting techniques of the inferior vena cava: **(a)** double-barrel technique; **(b)** side butting; and **(c)** side piercing. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

with the Gianturco (20 mm) (Cook, Inc., Bloomington, IN) stents. At the bifurcation, we simultaneously bring stents across the CIVs such that the inferior edges of the CIV stents just touch at the bifurcation, rather than bringing the stent parallel into the IVC (Figure 47.6). The Gianturco stents can also be used to go across the renal or the hepatic veins when expansion of the IVC is needed through the ostium of those veins. A more tightly woven stent can then be used at the edge of the visceral veins, placing the Gianturco just across the ostia. This will still permit the expansion of the IVC in the peri-renal or peri-hepatic segment, but also allow the flow into the IVC. Using the Gianturco stents will also increase the radial force of the distal stents at their weakest point. We have found it helpful to place 15-mm Gianturco stents in each central common IV into the bifurcation to give support to the sometimes competing stents and better open the bifurcation (Figure 47.6). Raju et al. did describe a modification of this method in which they cut a suture holding the distal Gianturco stent together, allowing it to flair.[30]

Raju et al.[6] reported early on their experience using Wallstents for the IVs, forming an inverted Y within the distal portion into the IVC, or a double barrel (double-barrel IVC recanalization) (Figure 47.5a). They have also reported a technique in which one of the stents will then continue up to the proximal healthy segment of the IVC while the shorter stent will end at the side of the longer stent. The blood from the contralateral side will flow through the sidewall and into the longer and parallel IVC stent (Figure 47.5b). This is often referred to as the side butting technique. Finally, instead of having the contralateral stent end at the side of the main stent, the side stent is placed through the side of it and dilated (side-piercing technique) (Figure 47.5c).

Intravascular ultrasound (IVUS) may have been underutilized as a tool in endovascular therapy in the past and at present. This may be due to the relatively high cost of the ultrasound unit and catheters, which are single-use items. Hurst et al.[32] used IVUS in 12 out of 18 patients who had IV stents placed and found that IVUS changed the management in five patients.[4–6] Raju et al. used IVUS as an invaluable diagnostic and intra-operative tool to guide accurate stent placement.[33] The authors thought that venography, even with the injection close to the diseased and treated area, did not provide adequate information about the severity and location of the lesion.

IVUS may be even more important on the venous side than on the arterial side because pressure measurements had not reliably confirmed the hemodynamic significance of narrowed segments. O'Sullivan et al. did not find that intravascular pressure measurements with gradients across obstructed or narrowed segments were useful for the determination of the severity of an obstruction. Instead, these authors made judgments based on the presence or absence of collaterals.[27] Raju et al. found that of 36 patients with documented collaterals on initial venography, the collaterals disappeared following successful recanalization and stenting in 33 patients. The authors did not rely on intravascular pressure measurements, but mainly used IVUS to determine which stenoses were severe and needed stent placement, as discussed above.[4]

Most if not all iliac venous recanalizations can be performed with the patient under conscious sedation and local anesthesia, but for complex IVC recanalization, general anesthesia is more appropriate.[29] Because angioplasty of a chronically occluded IV is often painful, stronger analgesia (fentanyl) in combination with sedatives such as midazolam is used. For IVC recanalization combined with IV recanalization, Propofol anesthesia and frequently general anesthesia are needed. These procedures can be painful and lengthy, lasting up to several hours. For the longer procedures, a urinary catheter should also be considered. In some cases, with poor common femoral inflow, an open surgical procedure such as endophlebectomy is performed in combination with the recanalization procedure.

Generally, it has not been our practice to give antibiotics prophylactically prior to endovascular bare metal stent placement. Stent infections have been rarely reported.[34] We give a single dose of antibiotics if we think there has been a breach in sterile technique and for procedures which are expected to be long, such as IVC recanalization. However, Hartung et al. reported administering antibiotics at the beginning of all procedures.[35]

During the procedure, full anticoagulation with unfractionated heparin is given, with a target activated clotting time of around 220–300 seconds. Immediately following the procedure, a therapeutic dose of low-molecular-weight heparin (LMWH) is given in the post-operative area. The patient is then converted to longer-term blood thinners unless it has been determined that LMWH is needed long term, which is rare. The length of anticoagulant therapy depends on risk factors such as hypercoagulability, suboptimal technical outcome, or poor inflow, which may call for indefinite anticoagulation. The introducer sheaths at the

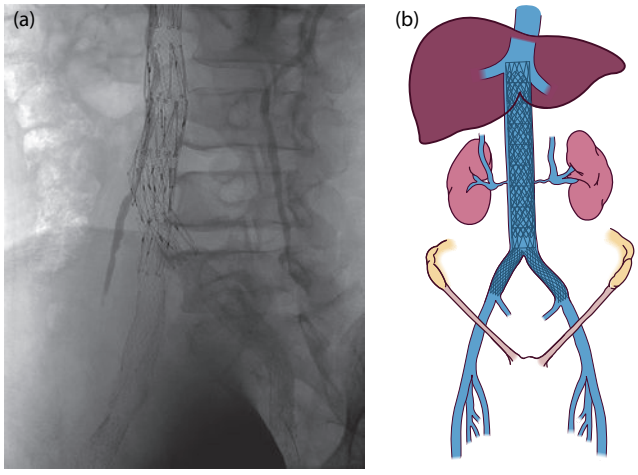


Figure 47.6 **(a)** Radiographic and **(b)** diagrammatic representation of reconstruction of the inferior vena cava. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

access sites can be removed with the patient fully anticoagulated. Bed rest is usually for at least 2–4 hours following the procedure. For jugular vein access alone, the bed rest period can be shorter, but if femoral or popliteal access has been used, a longer period is appropriate, typically 4 hours.

Most patients who undergo conventional IV or IVC recanalization with stent placement can be discharged on the same day. Only patients who have severe post-procedural pain will need to be hospitalized overnight for pain management. Full anticoagulation—usually LMWH followed by oral anticoagulation—is started immediately after the procedure. We have in the past used vitamin K antagonist, but have recently started using the novel anticoagulants. However, if reversible factors were the cause of the thrombosis or if stents were placed for a non-thrombotic vein obstruction and a good endovascular outcome was achieved with good inflow and outflow following stent placement, typically 3 months of fully therapeutic anticoagulation is recommended. This duration is an extension and extrapolation from the literature on coronary artery stenting until it has endothelialized.

Ultrasound can be performed the next day to verify patency, but we do not practice this unless the patient's symptoms indicate a problem. Compression stockings are applied after the procedure.

We used to prescribe a regimen of clopidogrel 75 mg/day for 4–6 weeks and aspirin 81 mg/day indefinitely following the procedure, but we have moved away from that practice due to a lack of evidence.

47.4 STENT SELECTION

Endovascular stents can be divided into two general groups based on their mechanism of expansion: self-expandable and balloon-expandable stents. Balloon-expandable stents will expand and stay at the diameter of the delivery balloon. They are occasionally used when extra radial force is needed, because they tend to have a higher radial force than self-expandable stents. This is beneficial in areas with high recoil force, which is occasionally encountered in the venous system. Balloon-expandable stents can be placed within self-expandable stents where the recoil force or external pressure, such as from the overlying iliac artery, has led to compression of the stent.[29] An example of this is the Palmaz stent (Cordis Corporation, Miami, FL). Because balloon-expandable stents are malleable, they do not re-expand if bent or crushed. Juhan et al.[36] described a case of a Palmaz stent that had been placed in the left common iliac vein. During subsequent pregnancy, the stent became crushed and the treated venous segment thrombosed. Therefore, balloon-expandable stents are only used in locations that are protected from external physical forces, such as in the chest cavity or pelvis, and rarely in the pelvis in women of reproductive age.

Self-expandable stents are made of a flexible metal and delivered through a constraining tube. These stents come in certain diameters, which they will typically not exceed, but will constrain to the vessel diameter. Self-expandable stents will re-expand if compressed or crushed. The benefits of self-expandable over balloon-expandable stents include the availability of longer lengths and better conformation to vessel bends and tortuosity.

The first self-expandable stent in general use was the Gianturco stainless steel stent, which is still commercially available and in clinical practice. This stent is especially indicated for the treatment of venous obstructions because of its large diameter (up to 25 mm) and the long distance between the interstices. The large spaces between the interstices allow inflow from side branches, which the stent crosses, into the stent lumen. This makes it possible to stent across side branches without compromising inflow from those (see the discussion above regarding the renal and hepatic veins). Most other stents, both self-expandable and balloon-expandable, have tighter interstices and thus have the potential to hinder inflow through the sidewalls of the stent.

The Wallstent was one of the first self-expandable stents following the Gianturco stent. It is available in a variety of diameters and lengths. The available diameters that are pertinent to the IVs and the IVC are 12, 14, 16, 18, 20, and 22 mm. Because of its unique design, it will shorten significantly as it is deployed and subsequently dilated. With that comes significant radial force when the stent is first settled in the vein. At the same time, the Wallstent is quite flexible. Pre-dilation to at least the nominated stent diameter will reduce foreshortening when deployed.

Many newer self-expandable stents made of Nitinol have been marketed and been used extensively for IV recanalization. Included in this group are the Smart stent (Cordis Endovascular, Warren, NJ), Protégé stent (ev3, Plymouth, MN), Luminex (Angiomed/Bard, Karlsruhe, Germany), and the Silver stent (Cook, Inc., Bloomington, IN). The Nitinol stents can be placed accurately as they will not foreshorten significantly upon deployment and dilation. On the other hand, these stents deform or compress quite easily and take on a "fish mouth" appearance, with constriction of the lumen, which can cause hemodynamically significant narrowing. There are now several stents on the market that are specifically made for venous applications, and these are in clinical trials or have recently been released to the market. The Zilver Vena stent (Cook, Inc., Bloomington, IN) has been designed as a venous stent with extra radial force.[37] Sinus-XL and the Sinus Venous stent, both from Optimed (Ettlingen, Germany), are venous stents that are available in Europe.[38,39] Lugli and Maleti are working on stents with even more specific venous applications in mind.[40] The VICI VENOUS STENT®, produced by VENITI (St. Louis, MO), is a stent that is approved in Europe and undergoing trial in the United States. This stent was developed specifically for the venous system. Medtronic (Minneapolis, MN) is also working on a stent for venous application which has not entered a trial yet, but may be available in sizes that are large enough for the IVC.

47.5 OUTCOMES

When discussing outcomes of stent placement in the venous system, it is important to make a distinction between stent placement in a previously thrombosed venous segment on the one hand and an obstructed venous segment without previous or current thrombosis on the other. This is particularly important as successful recanalization depends on good inflow, which requires a near-healthy vein distally, typically the CFV, with inflow from the profunda femoral and FVs with some contribution from the great saphenous vein. It has been estimated that up to 88% of patients with IV occlusion will also have post-thrombotic changes in any or all of the following veins: common femoral, deep femoral, femoral, and popliteal and infrapopliteal.

Isolated IV recanalization and stenting has quite a long track record. One of the first large series was by Raju et al.,[4] demonstrating a primary patency rate of 49%, a primary assisted patency rate of 62%, and a secondary patency rate of 76%. In their larger series,[5] in which they reported on patients whose main problem was venous insufficiency, the primary patency rate was 71% and the primary assisted and secondary patency rates were 97% at the 2-year follow-up. The reported primary patency rates by Hurst et al.[32] were 89% at 6 months and 79% at 12 and 18 months. O'Sullivan et al. had a primary patency rate of 93.6% at 1 year.[27]

Kurklinsky et al.[41] studied 89 patients treated for isolated IV recanalization and stenting for post-thrombotic obstruction. No patient had IVC involvement. The primary patency rates at 1 and 3 years were 81% and 71%, respectively, the primary assisted patency rates were 94% and 90%, respectively, and the secondary patency rate was 95%. Of the 17 patients who were found on surveillance ultrasound to have imaging-confirmed narrowing, 11 underwent repeat intervention and did not occlude. The remaining six did occlude the stents; one underwent a failed attempt at opening the stent, three declined re-intervention, and two had successful re-intervention. There were no reported major complications, except for one re-thrombosis within 30 days of the procedure.

Friedrich de Wolf et al.[42] had a quite similar experience with their series of 75 procedures in 63 patients. Endophlebectomy of the CFV was performed in eight of the procedures and arteriovenous fistulas were placed in four of those patients. They reported six hematomas (one requiring surgical intervention) and one common femoral artery puncture.

There is a surprisingly large number of predominantly young male patients presenting with acute IV thrombosis that turn out to be an "atretic" IVC. These cases have been called "absence of the IVC," "IVC atresia," "agenesis of the IVC," or "congenital interruption of the IVC."[21] In most but not all cases, one can identify a cord in the predicted path of the IVC on axial imaging, such as CT or MRI. It is therefore likely that many of those "absent IVCs" are simply chronically thrombosed IVCs which have been asymptomatic and the initial acute event has been silent or masked by other coexisting symptoms. There is a growing literature describing the treatment of such conditions using the same basic technique as for IV chronic obstruction. Raju et al.[6] documented the first large series on this treatment. For IVC recanalization and stenting, they found cumulative primary and primary assisted stent patency rates of 58% and 82%, respectively, at 2 years.

A recent report from the Mayo Clinic presented 66 patients treated for IVC chronic thrombotic obstructions.[31] This retrospective review included all patients treated for chronic thrombosis of the IVC with involvement of the IVs and CFVs from January 2001 to December 2008. Cumulative primary, primary assisted, and secondary patency rates as determined by duplex ultrasound at 36 months were 78%, 91%, and 87%, respectively. In nine patients, an occlusion occurred by the first follow-up (mean 2.4 ± 0.5 months). In five cases, the occluded segments were successfully opened up, none of which required a second re-intervention during the following 12 months. The remaining four patients did not undergo an attempt at re-intervention. Two were asymptomatic, one received a femoral–femoral bypass, and the fourth died soon after follow-up from unrelated causes.[31]

de Graaf et al. treated 40 patients with IVC and IV occlusions. The first 24 patients had parallel self-expandable stents placed inside a single IVC stent, which resulted in competing compromise of one lumen. The last 16 patients had balloon-expandable stents placed within the parallel iliac stents. The primary patency, primary assisted, and secondary patency rates in the first group with unsupported parallel stents were 85%, 85%, and 95%, respectively, at 12 months. For the supported stents, there was a 100% primary patency rate at 134 days.[29]

With regards to clinical outcomes, most of the literature consists of single retrospective cohort case studies. Yin et al.[43] retrospectively evaluated a group of patients with chronic thrombotic IV occlusion who did undergo endovascular recanalization and a stent procedure. They compared this group to a group with similar obstructive disease treated with elastic compression stockings alone. They found that patients with severe post-thrombotic syndrome had significantly greater improvement in their Villalta score if treated with recanalization and stent placement. This was not as convincing (not statistically significant) in patients with moderate post-thrombotic syndrome. Patients with ulcers would see significantly better recurrence-free ulcer healing if they were treated with recanalization and stenting compared to compression stockings alone. No improvement in popliteal vein reflux was noted.[43]

Almost all venous stents will develop some in-stent layering of thrombus. Neglén and Raju found several risk factors associated with in-stent narrowing.[44] The three main factors were presence of thrombotic disease in the stented area prior to stenting, positive thrombophilia test results, and stent extending below the inguinal ligament. The one common factor appears to be thrombosis. Longer stents are usually needed for more thrombosed segments than non-thrombosed segments, which possibly explains the

extension association with the CFV stents. Overall, at 42 months, 15% of limbs had more than 50% diameter reduction, 61% had more than 20% diameter reduction, and only 23% had no in-stent stenosis. It appears that the incidence of in-stent stenosis levels off at 2–3 years.[29]

Neglén et al. found 5-year cumulative ulcer healing of 58% in their patients who did undergo IV stenting of the affected limb. Several of these patients had additional treatments, such as ablation.[45]

47.6 TECHNICAL AND CLINICAL SUCCESS

The technical outcomes as well as patency rates are listed in Table 47.1. Technical success for IV recanalization has been reported to be in the range of 87%–100% of cases.[4,32,41,46] Failures have been attributed to an inability to cross the occluded segment. Raju et al. found that, following successful recanalization and stent placement, collaterals present prior to the procedure will no longer be filled in 92% of patients, and in 47% of patients who had been previously measured, pressure gradient improved.[4]

Recanalization of an occluded IVC seems to be more complicated. Raju et al. found that in all patients with narrowing of the IVC, the success rate was 100%, but when the IVC was occluded, the success rate was 66% (14 of 21 patients). They were unable to identify factors that could help to predict whether or not recanalization would be successful. Considered factors were the length of the occluded segment, amongst other venographic findings.[6]

de Graaf et al. reported successful recanalization in all cases in which they attempted recanalization of the IVC and IVs.[29] Clinical success is difficult to assess, but Raju et al. found that 74% of their patents who underwent IV recanalization and stenting experienced clinical amelioration (free of pain), and 66% had improvements in leg swelling.[5] In a series of 304 patient with venous insufficiency treated for IV stenosis, Raju et al. observed 68% ulcer healing at the 2-year follow-up.[5]

In a similar manner, Hurst et al. noted clinical improvement in 47% of patients treated with iliac stents and angioplasty for iliocaval compression syndrome.[32] Patients with IVC obstruction or occlusion had very significant betterment in symptoms. Swelling disappeared in 51% of patients with swelling prior to procedure, and 74% of patients who indicated pain as a symptom prior to the procedure were pain free at 3.5 years following the procedure. Of the 19 patients with active ulcers, 12 (63%) healed and remained healed at 2 years. Overall, there was a rate of 70% excellent or good clinical outcomes in a group of 97 patients who underwent stent placement including the IVC.[6]

If re-thrombosis is excluded, complications are relatively rare. One could expect bleeding into the perivenous space to be a frequent observation. This actually does not appear to be the case. Hurst et al.[32] reported on a retroperitoneal hematoma treated successfully with blood transfusion without sequel. Nazarian et al.[2] documented two stent fractures, both with Gianturco stents. These were found incidentally in asymptomatic patients. There is one report of an infected stent in the common IV after thrombolysis and stent placement for May–Thurner syndrome.[34]

Recanalization of the IVC appears to be safe. In their study, Raju et al. found no mortality, no clinically apparent bleeding complications, and no negative effects on renal or liver function in patients with stents placed across the hepatic vein or renal vein level. Mild back pain was frequently noted post-procedurally, but this was easily controlled with non-steroidal anti-inflammatory drugs.[6]

Among 66 patients in the Mayo Clinic's experience, only two developed a post-procedural hematoma. In one patient, this was associated with thrombolysis of an occluded stent. The other patient developed a hematoma at a puncture site just following an angioplasty and stent procedure. There were no deaths reported at 30 days and no retroperitoneal hematoma.[31]

Stent migration has been associated with IV and IVC stent procedures. Hartung et al.[35] observed migration of two stents following deployment. One stent had to be snared from the right atrium and surgically removed from the CFV after being pulled there. The other stent migrated into the retrohepatic IVC and was pulled into the infrarenal IVC,

Table 47.1 Technical outcomes and patency rates for iliac vein recanalization and stenting

Author	Number of patients	Technical success	PP at 12 months	Late PP	Late SP success (months)
O'Sullivan et al.[27]	20	–	93.0%	–	–
Nazarian et al.[2]	56	92%	50%	50% at 48 months	75% at 48 months
Blattler and Blattler[47]	14	85.7%	79%	–	–
Neglén and Raju[44]	5	–	–	75% at 36 months	93% at 36 months
Hurst et al.[32]	18	100%	79%	–	–
Hartung et al.[48]	44	95.5%	83.6%	73.2% at 36 months	89.9% at 36 months
Raju et al.[6]	97	100%[a]/66%[b]	–	58% at 24 months	82% at 24 months
Kurklinsky et al.[41]	89	100%	81%	71%	95% at 48 months

Note: PP: primary patency rate; SP: secondary patency rate.
[a] For obstructed inferior vena cava.
[b] For occluded inferior vena cava.

where it was left without sequel. There is a report of stents placed for May–Thurner syndrome, which migrated by almost 1 year following the procedure and were removed from the heart surgically.[49]

47.7 CONCLUSIONS

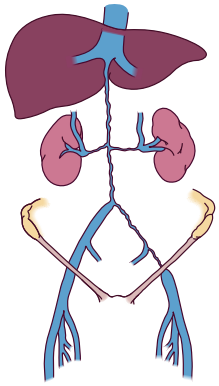
Treatment of chronic IV and IVC occlusions by using endoluminal stents is an established therapeutic alternative for patients with post-thrombotic symptoms. The technical success rate of IV and IVC stenting is good, the patency rate is acceptable, and clinical outcomes are satisfactory. Patency depends to a large extent on adequate inflow into the stented area and the ability to secure good cephalic outflow.

Adjunctive procedures such as the combination of surgical endophlebectomy and intra-operative stenting may expand the number of patients who are offered this type of treatment.[50,51]

Crowner et al. suggested an anatomic classifications system for the IVC and IVs. The obvious intent is to facilitate the comparison of patients and help with the direction of care based on anatomic distribution and outcomes.[52] This classifications system does not take into account inflow from the femoral, profunda femoral, and great saphenous veins, which arguably can have significant influences on the outcome. We suggest a classification that considers the anatomic distribution of venous obstruction as well as the inflow vessels (Table 47.2).

Table 47.2 The Mayo Clinic classification of inferior vena cava obstructions

Inferior vena cava obstruction	A. Suprarenal and infrarenal B. Suprarenal C. Infrarenal D. Suprahepatic
Associated iliofemoral or renal vein obstruction (right=R or left=L)	1. Common iliac vein 2. External iliac vein 3. Common femoral vein 4. Renal vein
Inflow vessel patency	f) Femoral vein p) Profunda femoris vein s) Great saphenous vein



Guidelines 4.19.0 of the American Venous Forum on the endovascular reconstruction of complex iliocaval venous occlusions

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.19.1	We suggest endovascular stents for the reconstruction of complex iliocaval venous occlusions.	2	B

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● = Major primary paper
★ = Major review paper
◆ = Published guideline

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48

Open surgical reconstructions for non-malignant occlusion of large veins

ARJUN JAYARAJ, PETER GLOVICZKI, AND MARK D. FLEMING

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48.1 INTRODUCTION

Catheter-based endovenous reconstructions using pharmacological or mechanical thrombolysis, angioplasty, and stents have become the first line of treatment in patients with venous thrombosis due to non-malignant disease. Open surgical reconstructions of the inferior vena cava (IVC), the iliac vein, and the femoral vein are reserved for those symptomatic patients who are not candidates for endovascular reconstructions or who have failed attempts at venous stenting. In this chapter, we review the patient selection, diagnostic evaluation, techniques, and results of open venous reconstructions for chronic non-malignant occlusion of the iliac and femoral veins and of the IVC. Chapter 54 in this volume discusses venous reconstructions for trauma, Chapter 55 presents venous bypasses in patients with malignant tumors, and Chapters 20 and 45–47 address endovascular reconstruction of the IVC and iliofemoral veins.

48.2 PATIENT SELECTION

Post-thrombotic femoral, iliac, or IVC obstructions have been the most frequent cause for open reconstruction of large veins in patients with non-malignant disease.[1,2] Post-thrombotic syndrome develops in 35% of patients with iliofemoral deep vein thrombosis (DVT) over 5 years (~7% per year).[3] Compression of the left common iliac vein by the overriding right common iliac artery (May–Thurner syndrome [MTS]) has been recognized now as the most frequent cause of left iliofemoral venous thrombosis.[4,5] The incidence of MTS is not precisely known, with estimates ranging from 5% to 24% of patients presenting with lower extremity venous disorder.[5,6] In a recent review, MTS was found in women more frequently than men (72% vs. 28%).[7] Lower extremity DVT is the most common presentation of MTS (77%), and non-thrombotic MTS causing edema and pain was found in 23% of MTS patients. Acute symptoms (73%) were more common than a chronic presentation.[7] Primary compression of the left iliac vein without DVT is an important etiology of symptomatic chronic venous outflow obstruction: in a series of 982 venous stents, 53% of the femoro-iliocaval lesions were of primary and not of post-thrombotic etiology.[8] A study from Northwestern University used computed tomography (CT) to evaluate the frequency of left iliac vein compression in the asymptomatic population. Kibbe et al.[9] reported that 24% of the people treated at an emergency room for other conditions had >50% compression of the left common iliac vein, and 66% had >25% compression. It is likely that some degree of left iliac vein compression is a normal anatomic variant.

Venous obstruction may also develop as a result of iatrogenic or blunt trauma,[10] irradiation, retroperitoneal fibrosis,[11] benign or malignant tumors,[12,13] or compression by cysts, iliac artery aneurysm, fibrous bands, or ligaments.[14] Congenital anomalies, such as membranous occlusion of the suprahepatic IVC, with or without associated thrombosis of hepatic veins (Budd–Chiari syndrome),[15] or hypoplasia of the iliofemoral veins as observed in some patients in Klippel–Trenaunay syndrome,[16] can also cause outflow obstruction. A breakdown by etiology of iliofemoral venous obstructions is presented in Figure 48.1.

Failure of medical management with compression garments and lifestyle modifications in patients with non-malignant venous occlusion are indications for venous

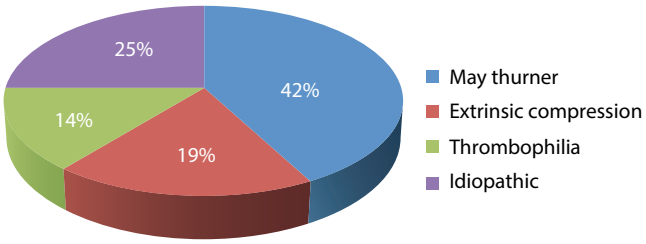

Figure 48.1 Iliofemoral venous occlusion by etiology.

reconstruction. Patients who are not candidates for endovascular reconstruction or those who failed multiple attempts at venous stenting are selected for open reconstruction using autologous or prosthetic bypasses.

48.3 PRE-OPERATIVE EVALUATION

Pre-operative evaluation of the patients should reveal the etiology and functional significance of the deep venous obstruction and the extent and severity of the associated venous incompetence. Notably, in at least two-thirds of patients with venous outflow obstruction, distal reflux due to incompetent valves will contribute to the development of chronic venous insufficiency.

48.3.1 History and physical examination

History and physical examination, complemented by a hand-held Doppler examination, should reveal signs and symptoms typical of venous congestion. Patients with venous occlusion have swelling and develop exercise-induced pain in the thigh or calf, known as venous claudication. This pain is described as a bursting pain in the thigh, and sometimes in the calf, that develops after exercise and is relieved by rest and leg elevation. The swollen leg has a cyanotic hue with distended varicose veins even in the supine position. Bilateral swelling indicates bilateral iliofemoral or caval occlusion or systemic disease. Collateral veins in the suprapubic and abdominal wall usually indicate pelvic venous occlusion. Bleeding from high-pressure varicosities is not infrequent. In some patients, venous congestion results in hyperhidrosis and significant fluid loss through the skin. Associated chronic lymphedema may also develop. Advanced disease presents with stasis skin changes and venous ulcerations. Patients with membranous occlusion of the IVC frequently will have evidence of hepatic failure and portal hypertension as well.[17] For details of the clinical and diagnostic evaluation of the patients with chronic venous insufficiency, the readers are referred to Chapters 13, 14, and 29.

48.3.2 Diagnostic testing

48.3.2.1 ROLE OF NONINVASIVE TESTING: DUPLEX SCANNING, PLETHYSMOGRAPHY, AND VENOUS PRESSURE MEASUREMENT

A complete evaluation to establish the clinical class of venous disease is necessary. Duplex scanning and, in selected cases, plethysmography are used to demonstrate deep venous occlusion and to determine the extent of valvular incompetence and calf muscle pump failure. Outflow plethysmography is useful to confirm functional venous outflow obstruction and to document improvement following treatment (see Chapters 13–14).

The functional or hemodynamic effects of an obstruction can be ascertained by venous pressure measurement. Normal pressure at that level is 2–4 mmHg, while in patients with hemodynamically significant proximal obstruction, it is 6–8 mmHg.[18] However, in the presence of well-developed collateralization, venous pressure may be normal at rest and manifest hemodynamic significance only during exercise. For the purpose of testing, exercise consists of 10 dorsiflexions of the ankle or 20 isometric contractions of the calf muscle, which should increase the pressure by two-fold in the setting of significant obstruction.[18] A pressure difference of at least 5 mmHg between the femoral and the central pressures or a two-fold increase in femoral vein pressure after exercise also indicates a hemodynamically significant lesion.[1,18] Venous pressure measurement following reactive hyperemia is another means of assessing hemodynamic significance. With the transducer in the dorsum of the foot in the supine position, a thigh cuff is inflated to 300 mmHg for 2 minutes and the pressure measured 5 seconds after cuff deflation. An increase in pressure of up to 30 mmHg indicates functional significance.[18] However, in cases of severe post-thrombotic syndrome, the increase in pressure either does not take place or is only very small.

48.3.2.2 CONTRAST PHLEBOGRAPHY, CT VENOGRAPHY, AND MAGNETIC RESONANCE VENOGRAPHY

Detailed contrast phlebography is performed in patients in whom venous reconstruction is being considered (see Chapter 15). CT, magnetic resonance (MR), or contrast venography is performed to define the level of obstruction and evaluate inflow (Figure 48.2a–c).[1,17] Iliocavography and abdominal cavography through a brachial approach may also be necessary in some patients in order to visualize the IVC proximal to the occlusion. Direct femoral access is useful not only for iliocavography, but also for measuring femoral venous pressures. It is also important to exclude any abdominal or pelvic pathology (tumor, cyst, or retroperitoneal fibrosis) with contrast-enhanced CT or MR imaging (see Chapter 16). MR venography has the advantage of avoiding the use of intravenous contrast, but details are less clear than using contrast or CT venography. Three-dimensional CT venography has been used with increasing frequency to document the extent of deep vein obstruction (Figure 48.3).

48.3.2.3 INTRAVASCULAR ULTRASOUND

Intravascular ultrasound is performed frequently today to assess the degree of iliac vein stenosis before stenting and to document results after stenting (see Chapters 45 and 46).[8]

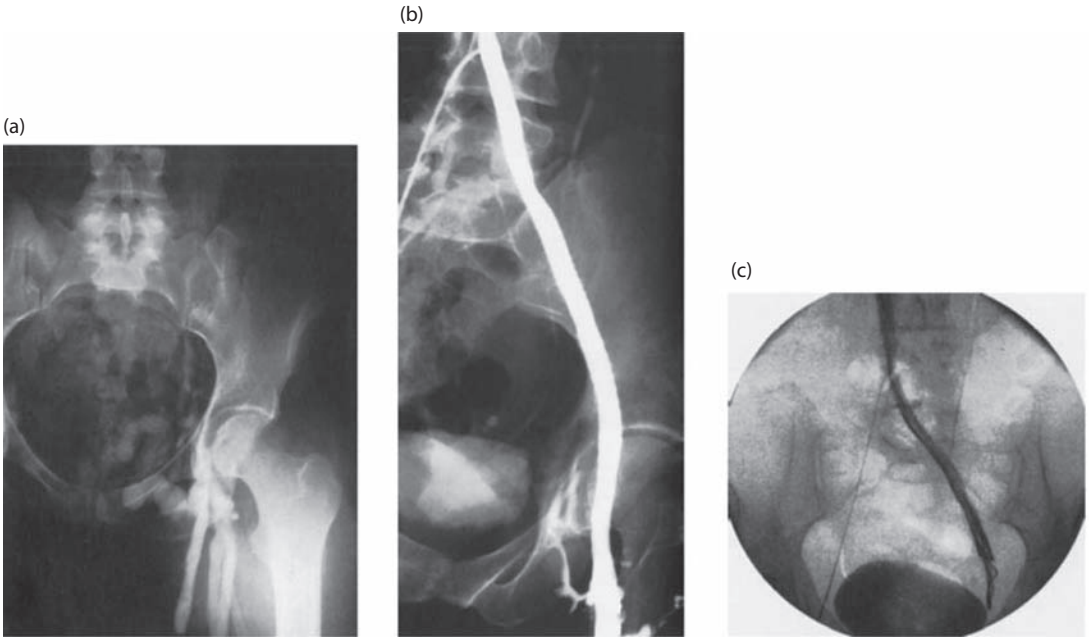

Figure 48.2 **(a)** Ascending venogram of a 36-year-old woman confirms left iliac vein thrombosis. **(b)** Venogram 1.6 years after implantation confirms widely patent left femorocaval expanded polytetrafluoroethylene graft. **(c)** Venogram at 11.7 years after graft placement. The patient has excellent clinical result. (Reproduced with permission from the Mayo Foundation.)

48.4 SURGICAL PROCEDURES

48.4.1 Saphenous vein transposition to the distal femoral or popliteal vein (May–Husni procedure)

Patients with unilateral deep venous outflow obstruction involving the femoral vein can be considered for the May–Husni procedure.

48.4.1.1 TECHNIQUE

The operation is conducted through a vertical incision at the level of the distal thigh. The great saphenous vein (GSV) and distal femoral vein/proximal popliteal vein are exposed through the same incision. After heparinization, a thigh tourniquet is inflated to provide a bloodless field, the distal femoral vein/popliteal vein is opened longitudinally, the old recanalized thrombus is excised, and an end-to-side anastomosis is performed between the GSV and the distal femoral vein/popliteal vein using a running 6–0 monofilament suture (Figure 48.4).

48.4.1.2 RESULTS

A study by AbuRahma and colleagues of 19 patients, with a mean of 66 months of follow-up, demonstrated a 56% cumulative 8-year patency.[19] A recent study from the University of Michigan of 17 patients with a median follow-up of 103 months demonstrated an 82% success rate for near or complete resolution of venous claudication and a 67% success rate for venous ulcer healing. With regards to patency, primary patency was 56%, primary assisted patency was 69%, and secondary patency was 75% for the 16 patients that the authors were able to follow.[20]

48.4.2 Femorofemoral saphenous vein transposition (Palma procedure)

Patients with unilateral iliac vein obstruction and a suitable contralateral saphenous vein are candidates for saphenous vein transposition (Palma procedure) (Figures 48.5a–d and 48.6).

48.4.2.1 TECHNIQUE

During the operation, the contralateral saphenous vein is dissected and divided distally; the vein is then transposed in a subcutaneous tunnel above the pubis to the affected side. If there is a kink in the vein at the saphenofemoral junction after tunneling, sometimes it is necessary to disconnect the saphenous vein with a 2-mm cuff from the common femoral vein and re-anastomose it, after rotating it upwards by 180°. If the vein is less than 5 mm in size or the pressure difference between the two femoral veins is less than 3 mmHg, a femoral arteriovenous fistula (AVF) is added. A saphenous vein of under 4 mm in size should rarely be used because of the low flow volume through the graft and the increasing rate of failure. AV fistula (see below) is performed selectively between the superficial femoral artery and the hood of the saphenous vein, usually using a separate reversed segment of the GSV or a small, externally supported polytetrafluoroethylene (PTFE) graft.

48.4.2.2 RESULTS

Although few large series have been reported, the overall patency of saphenous vein Palma grafts in nine series including 412 operations ranged between 70% and 83% at 3–5 years.[1,2,21–23] Results were better in patients with good

Figure 48.3 Three-dimensional computed tomographic venography confirms occluded left iliac stent with large suprapubic venous collaterals. (Reproduced with permission from the Mayo Foundation.)

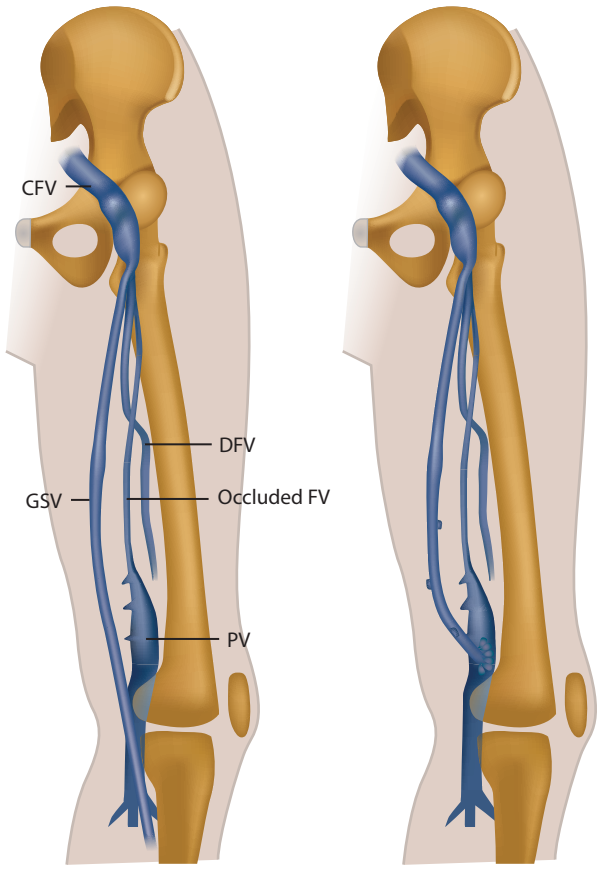

Figure 48.4 May–Husni procedure. CFV: common femoral vein; GSV: great saphenous vein; FV: femoral vein; DFV: deep femoral vein; PV: popliteal vein. (Reproduced with permission from the Mayo Foundation.)

inflow, with no infrainguinal venous disease, and in those with MTS without previous DVT. Gruss and Hiemer[18] reported 71% patency of 20 Palma vein grafts at 5 years. In the Mayo Clinic series,[24] primary and secondary patency rates of 25 saphenous vein Palma grafts at 5 years were 70% and 78%, respectively. Halliday et al.[23] reported a series of 34 patients with saphenous Palma grafts in 1985; 5-year patency was 75%.

48.4.3 Cross-pubic prosthetic bypass

In the absence of a suitable saphenous vein, cross-pubic venous bypass with an expanded PTFE (ePTFE) graft is an acceptable alternative if the patient is not a candidate for in-line reconstruction.[18]

48.4.3.1 TECHNIQUE

An 8- or 10-mm PTFE graft is pulled into the suprapubic tunnel, the ends are anastomosed to the femoral veins bilaterally, and a femoral AVF is added to improve patency (Figure 48.7a–e).

48.4.3.2 RESULTS

Variable patency rates of ePTFE grafts in this location have been reported. Eklöf[27] observed patency in only two of seven grafts at 2 years, while Comerota et al.[25] reported patency in two of three grafts at 40 and 63 months. Sottiurai[26] reported a 100% (19/19) patency rate at follow-up that ranged from 11 to 139 months. Gruss and Hiemer[18] have significant experience with ePTFE; they observed 77% patency at 5 years in 27 PTFE Palma grafts. These authors recommend externally supported ePTFE grafts with AVF for all cross-pubic venous bypasses.

48.4.4 Femoro-iliocaval bypass

Anatomic in-line reconstruction can be performed for unilateral disease when an autologous conduit for suprapubic graft is not available or for bilateral iliac, iliocaval, or IVC occlusion.[27] Extensive venous thrombosis (not infrequently following previous placement of an IVC filter), failure of iliac vein stenting, or iliocaval occlusion caused by tumors or retroperitoneal fibrosis are potential indications. Failure of previous endovascular attempts and occlusion following the placement of multiple stents have also been indications for bypass.

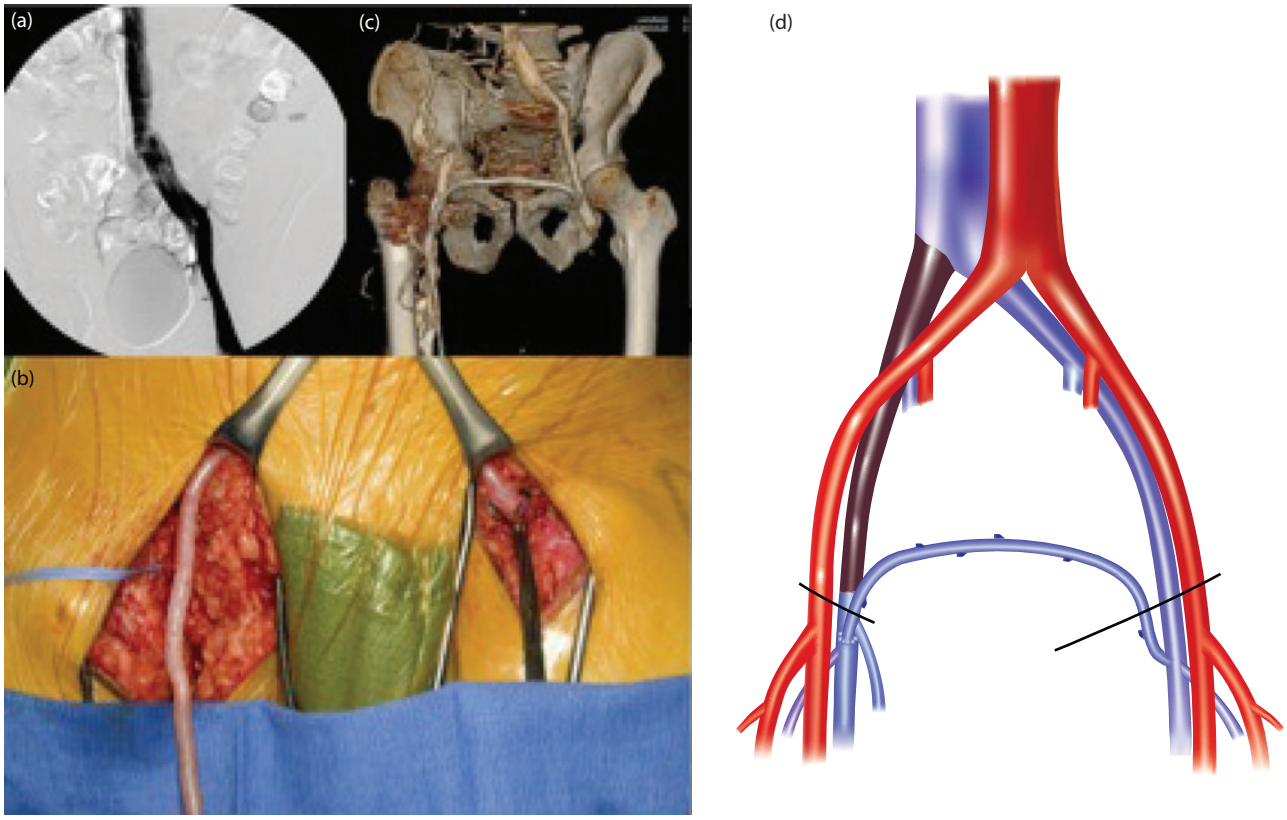

Figure 48.5 Palma procedure. A 38-year-old male with history of post-traumatic deep vein thrombosis had right leg ulcers, swelling, and venous claudication. **(a)** Contrast venogram shows chronic right iliofemoral obstruction. Multiple attempts at endovenous recanalization had failed. **(b)** Right-to-left femoral vein bypass of the left great saphenous vein (Palma procedure) was performed. **(c)** Computed tomographic venogram at 2 months revealed a patent bypass. **(d)** Diagrammatic representation of the open reconstruction **(a–c)**. (Reproduced with permission from the Mayo Foundation.)

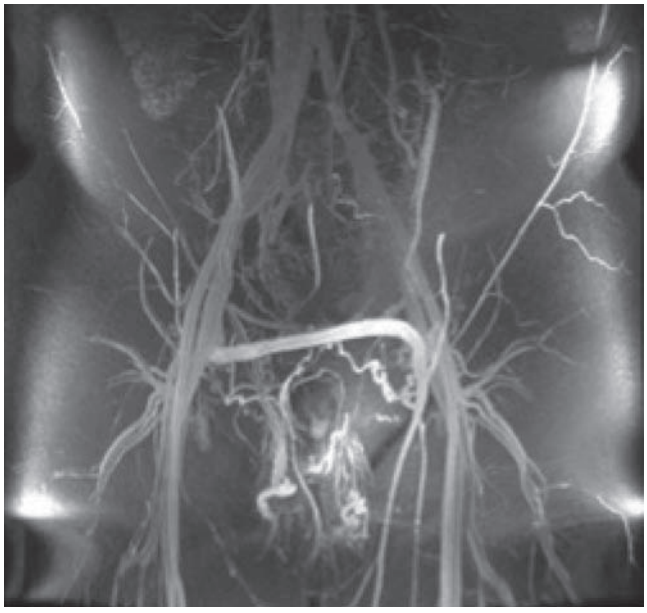

Figure 48.6 Magnetic resonance angiography at 9 months after a Palma procedure performed for left iliac vein occlusion. (Reproduced with permission from the Mayo Foundation.)

48.4.4.1 TECHNIQUE

The femoral vessels are exposed at the groin through a vertical incision. The iliac vein or the distal segment of the IVC is exposed retroperitoneally through an oblique flank incision. The IVC at the level of the renal veins is best exposed through a midline or a right subcostal incision. The infrarenal IVC is reconstructed with a 16–20-mm graft, the iliocaval segment usually with a 14-mm graft, and the femorocaval segment with a 12–14-mm ePTFE graft. Short iliocaval bypass with a significant pressure gradient or reconstruction of the IVC with a straight ePTFE graft in the presence of good inflow can be performed without an AVF, but long iliocaval and all femorocaval PTFE grafts benefit from a femoral AVF. Complex reconstructions with bifurcated bi-iliac or bi-femorocaval grafts can also be performed (Figure 48.8a–f).

48.4.4.2 RESULTS

Only a few centers have reported larger experience with femorocaval or iliocaval bypass. Alimi and colleagues[28] reported the results of eight iliac vein reconstructions with femorocaval or iliocaval bypass grafting for both acute and chronic obstructions. At a mean follow-up of 20 months, seven out of eight grafts were patent. Sottiurai[26] noted

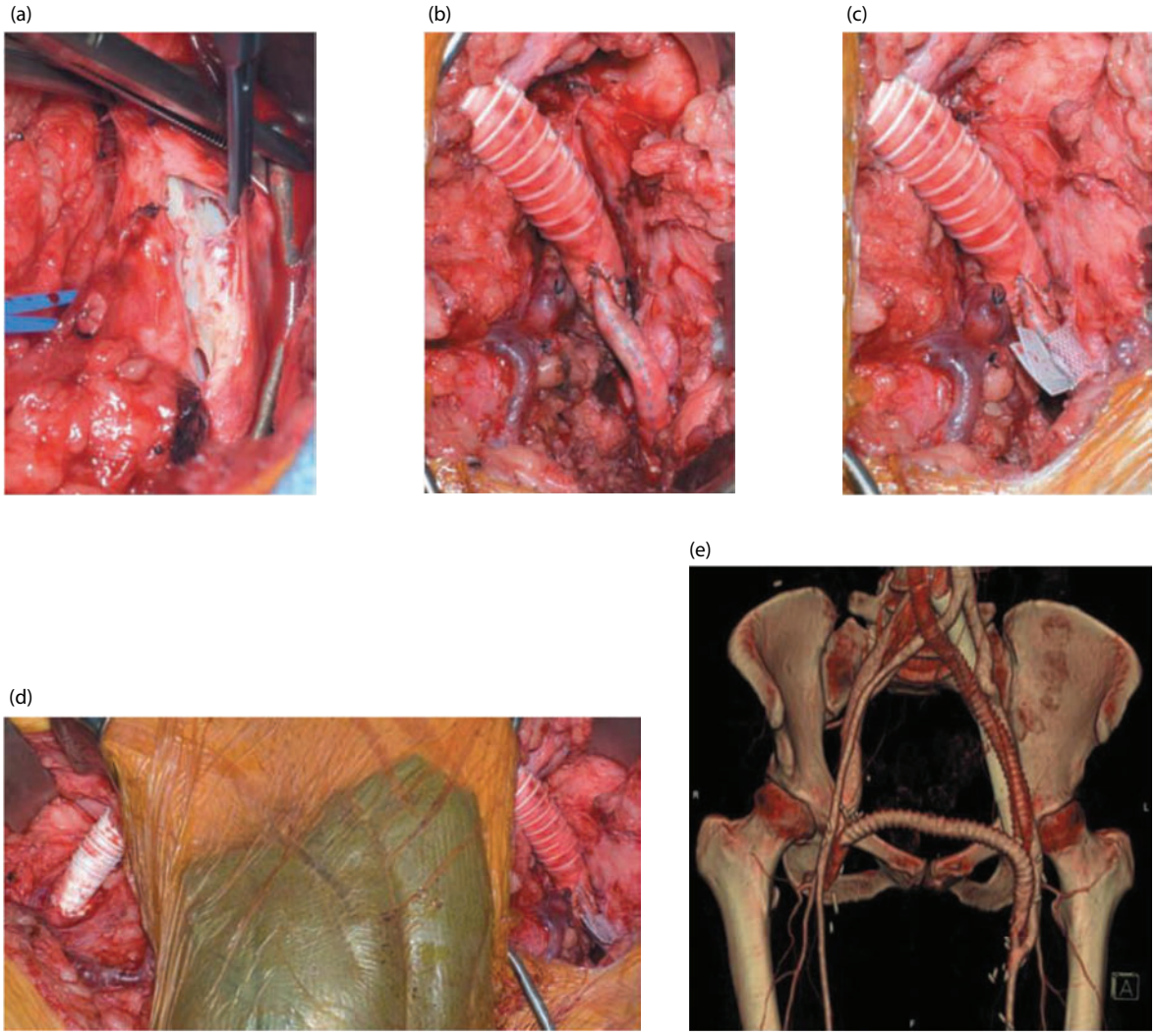

Figure 48.7 **(a)** Partially recanalized femoral vein found after venotomy. Endophlebectomy was performed to remove the organized thrombus and improve inflow into a femorofemoral crossover venous polytetrafluoroethylene (PTFE) bypass. **(b)** A PTFE arteriovenous fistula was performed between the superficial femoral artery and the hood of the cross-femoral PTFE graft. **(c)** A small silastic sheath is placed around the fistula and marked with metal clips for easy identification at reoperation when the fistula is closed. **(d)** Completed left-to-right femoral crossover PTFE graft with an arteriovenous fistula. **(e)** Computed tomographic venography of the cross-femoral PTFE graft with a patent arteriovenous fistula 8 months after surgery. (Reproduced with permission of the Mayo Foundation.)

long-term patency in 16 of 19 ePTFE grafts at a last follow-up ranging from 80 to 113 months following femoro-femorocaval (five), femoroiliac (six), and femorocaval (eight) bypass grafting with the aid of AVF.[26] Ulcer healing was noted in 10 of 13 (77%) patients, and improvements of limb edema were noted in 16 of 19 patients.

Results of the Mayo Clinic series of 52 large vein reconstructions have been reported by Garg et al.[24] All patients underwent surgical treatment for benign iliocaval or femoral venous pathology. The 52 open surgical repairs included 29 femorofemoral (Palma vein: 25; PTFE: 4), 17 femoroiliac IVC (vein: 3; PTFE: 14), and six complex bypasses. Primary and secondary patency rates for femoroiliac and ilio-infrahepatic IVC bypasses were 63% and 86%, and for femoro-infrahepatic IVC bypasses were 31% and 57%, respectively. Complex bypass procedures had 28% and 30% 2-year secondary patency rates. The only factor that significantly affected graft patency in the multivariate analysis was MTS with associated chronic venous thrombosis.[24] Early patency of caval reconstruction performed in patients together with excision of primary or secondary malignant disease is excellent and it is discussed in detail in Chapter 55.

48.4.5 Suprarenal IVC reconstruction

The most common reason to reconstruct the suprarenal IVC for benign disease is membranous occlusion of the IVC, which is frequently associated with occlusion of the hepatic veins (Budd–Chiari syndrome) and consequent

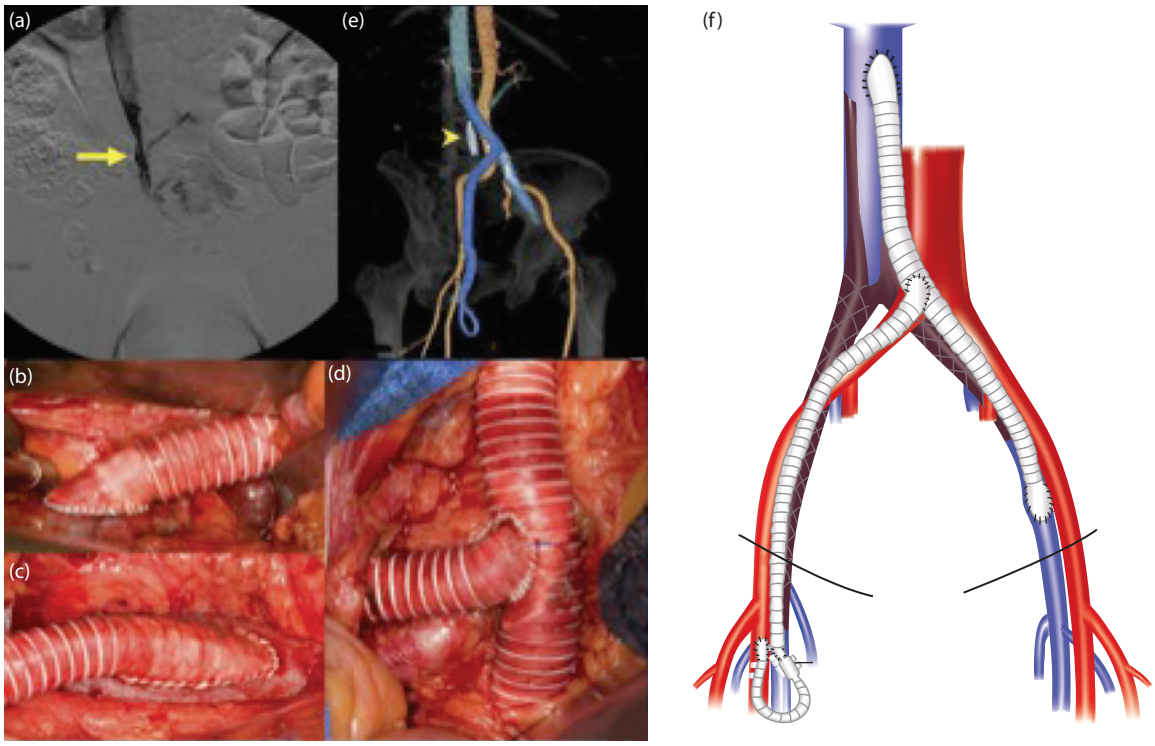

Figure 48.8 Complex venous reconstruction. A 61-year-old male with previous deep vein thrombosis and inferior vena cava (IVC) filter presented with severe bilateral swelling and venous claudication. **(a)** Venogram revealed a partially occluded IVC filter (arrow) and IVC and bilateral iliac and right femoral obstruction, with occluded bilateral venous stents. **(b)** Proximal and **(c)** distal anastomosis of the left external iliac vein (EIV) to the IVC bypass with 14 mm ringed polytetrafluoroethylene (PTFE). **(d)** An interposition PTFE graft to the right femoral vein from the IVC to the left EIV graft was performed. **(e)** Computed tomographic venogram at 2 months revealed patent bypass and previous IVC filter (arrowhead). **(f)** Diagramatic representation of the open reconstruction **(a–e)**. (Reproduced with permission from the Mayo Foundation.)

portal hypertension and liver failure. Occlusion of the suprahepatic IVC usually does not cause significant congestion of lower extremity veins, although leg edema and venous claudication may still develop in affected patients. If percutaneous balloon angioplasty, stenting, or transatrial dilatation of the membranous occlusion fails and portosystemic shunting is not required, cavoatrial bypass using an externally supported PTFE prosthesis is an effective technique to decompress the IVC.

48.4.5.1 TECHNIQUE

The retrohepatic segment of the vena cava and the right atrium are exposed through a right anterolateral thoracotomy, extending the incision across the costal arch such that the peritoneal cavity is entered through the diaphragm. The liver is retracted anteriorly and the paravertebral gutter exposed together with the suprarenal segment of the IVC. The pericardium is opened anterior to the right phrenic nerve and the right atrium is isolated. The IVC is controlled with a partial occlusion clamp above the renal vein and a 16- or 18-mm externally supported ePTFE graft is sutured end-to-side with a running suture of either 5–0 or 6–0 Prolene. The graft is then passed parallel to the IVC up to the right atrium or to the suprahepatic IVC. The central anastomosis is performed after placement of a partial occlusion clamp on the IVC or the right atrium. Before completion of the anastomosis, the graft is de-aired to prevent air embolization. An anterior approach was suggested by Kieffer et al.[29] for replacement of a short segment of the suprahepatic IVC with a ringed ePTFE graft. Tunneling of a long cavoatrial graft in front of the liver or under the left lobe was also reported.

48.4.5.2 RESULTS

The reported clinical success rate with cavoatrial grafts is about 77%, with a peri-operative mortality of 3% and 2-, 5, and 10-year patency rates of 86%, 78%, and 57%, respectively. Wang and associates[15] reported clinical improvement at 1.5 years in 10 of 12 patients who underwent cavoatrial bypass grafting for Budd–Chiari syndrome. Kieffer's group[29] reported the long-term patency in five of six grafts that were placed for membranous occlusion of the vena cava. Victor and coworkers[30] reported patent grafts at 21 months to 6 years after the operation in five patients. Three cavoatrial grafts placed for non-malignant disease were reported by our group: the patient with an ePTFE graft was asymptomatic at 10 years, the long Dacron graft failed at 3 years, and the spiral vein graft occluded within 1 year.[17]

48.5 ADJUNCTS TO IMPROVE GRAFT PATENCY

48.5.1 Arteriovenous fistula

Multiple experiments have confirmed that a distal AVF, first suggested by Kunlin in 1953,[31] improves the patency of grafts placed in the venous system.[32–34] An AVF increases flow and decreases platelet and fibrin deposition in prosthetic grafts placed in the venous system.[17] Prosthetic grafts have significantly higher anti-thrombotic threshold velocities than autologous grafts and require higher flow to maintain patency.

The disadvantages of an AVF include an increased operating time and the inconvenience of a second procedure to ligate the fistula at a later date. A potential side effect is a high cardiac output caused by high fistula flow, which may also defeat the purpose of the operation by increasing femoral venous pressure and thus causing venous outflow obstruction. Experimental work in our laboratory revealed that, in order to avoid venous hypertension, the optimal ratio between the diameters of the fistula and the graft should not exceed 0.3.[34] Elevated intra-operative pressure in the femoral vein after placement of a fistula is a warning sign, and fistula diameter should be decreased by banding the conduit.

Several configurations and locations for a fistula have been suggested.[1,27,35] The authors prefer placement of the venous end of the AVF right onto the hood of the graft at the distal anastomosis, with either a 4-mm vein (GSV or a large tributary thereof) or a 4- or 5-mm ePTFE graft. The arterial anastomosis is usually made to the superficial femoral artery. A small silastic sheet and a 2–0 Prolene suture is loosely tied around the fistula and its end positioned in the subcutaneous tissue, close to the incision, to help with the identification and dissection of the fistula during a second procedure. Percutaneous closure of the fistula with transcatheter embolization or the placement of an endovascular plug is also an option. The use of an AVF is recommended for all prosthetic grafts that are anastomosed to the femoral vein and all longer (>10 cm) iliocaval prosthetic grafts in order to help maintain patency. The fistula is kept open for at least 6 months post-operatively, but in patients without any side effects, it is kept open for as long as possible to help maintain patency. For patients with saphenous vein grafts, take-down of a fistula at 3 months is needed in order to achieve good functional results.

48.5.1.1 THROMBOSIS PROPHYLAXIS

Intravenous heparin (5000 U) is given before cross-clamping, and anticoagulation is maintained during and after the procedure in most patients. Low-dose heparin (500–800 U/hour) can be administered locally through a small polyethylene catheter and continued until complete systemic heparinization is achieved, with twice the normal partial thromboplastin time by 48 post-operative hours. The use of subcutaneous low-molecular-weight heparin to shorten hospitalization is suggested. The catheter is then removed and the patient converted to oral anticoagulation. The use of an intermittent pneumatic compression pump, leg elevation, elastic bandages, and early ambulation are recommended. The patients are fitted with 30–40-mmHg compression stockings before discharge. Warfarin is usually continued indefinitely.

48.6 GRAFT SURVEILLANCE

Direct pressure measurements are carried out before closure in every patient with and without graft flow to document hemodynamic benefit. On the first post-operative day, duplex scanning is performed to confirm patency. Any stenosis or thrombosis should be revised. Post-operatively, duplex surveillance imaging is obtained at 3 and 6 months, and twice yearly thereafter. Outflow plethysmography can also be performed to document hemodynamic improvement following the bypass procedure. Patients with abdominal grafts undergo a CT venogram at 6 months and annually afterwards.

Guidelines 4.20.0 of the American Venous Forum on open surgical reconstructions for non-malignant occlusion of the inferior vena cava and iliofemoral veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.20.1	For symptomatic patients with unilateral iliofemoral venous occlusions who fail attempts at endovascular reconstruction, we recommend open surgical bypass using the saphenous vein as a cross-pubic bypass (Palma procedure).	1	B
4.20.2	For symptomatic patients with iliac vein or inferior vena cava obstruction, we recommend open surgical bypass using externally supported polytetrafluoroethylene prosthesis if endovascular options fail or in whom endovascular intervention is not feasible.	2	B

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● = Key primary paper
★ = Major review article

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49

The management of incompetent perforating veins with open and endoscopic surgery

JEFFREY M. RHODES, MANJU KALRA, AND PETER GLOVICZKI

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49.1 INTRODUCTION

Perforating veins connect the superficial to the deep venous system, either directly to the main axial veins (direct perforators) or indirectly through muscular tributaries or soleal venous sinuses (indirect perforators). Incompetent perforating veins were first linked to chronic venous insufficiency (CVI) and its most severe manifestation, venous ulceration, nearly one and a half centuries ago by John Gay.[1] Since then, interest in their treatment has waxed and waned with the development of each new surgical method or ablative technique. Surgical interruption of these veins to treat and prevent venous ulcers was first suggested by Linton in 1938.[2] Linton's operation was championed over the next several decades by Cockett[3] and Dodd[4] and, through the mid-twentieth century, was considered the gold standard for the surgical treatment of refractory venous ulcers. The classic Linton procedure was ultimately abandoned because of major wound complication rates of up to 24%.[5,6] Although several authors made modifications to Linton's original technique to decrease wound complications, a major change in practice did not occur until the development of subfascial endoscopic perforator surgery (SEPS). It was not until 1985, when Hauer[7] first described a minimally invasive endoscopic approach to perforator vein ablation, that these wound-healing issues were overcome. Using an endoscope inserted subfascially into the superficial posterior compartment through a small incision remote from the area of ulceration and lipodermatosclerosis, the perforating veins could be ligated under direct visualization. In contrast to the Linton procedure, wound complication rates with SEPS, including minor wound problems, are of the order of only 5%.[8] SEPS quickly became the surgical technique of choice for perforator ablation over the next two decades. In the past few years, further minimally invasive, percutaneous techniques of perforator ablation have continued to develop with the emergence of ultrasound-guided catheter ablation of perforating veins and ultrasound-guided foam sclerotherapy, both of which are now being performed in the office setting.[9–11] The development of these minimally invasive surgical techniques has led to increasing interest and much debate about appropriate surgical therapy for the treatment of severe CVI and venous ulcers. However, the efficacy of perforator ablation, regardless of which technique is used, remains intensely debated.

This chapter will review the relevant surgical anatomy of perforating veins, the evidence to support the contribution of incompetent perforating veins to the pathophysiology of chronic venous disorders, and the techniques and results of both open and endoscopic perforator ablation. These data will then serve as the benchmark against which the newer techniques will be compared as they continue to evolve.

49.2 SURGICAL ANATOMY OF PERFORATING VEINS

Important details on the anatomy of the perforating veins are outlined in Chapter 2. A few observations pertinent to the surgical techniques to be discussed need to be mentioned here. Perforating veins are those that connect the superficial venous system to the deep veins. Valves within the calf and thigh perforators prevent blood from refluxing from

the deep system into superficial veins, although in some normal limbs, reversal of flow in the perforators can be demonstrated. The most significant calf perforators, termed the posterior tibial perforators (Cockett perforators), connect the posterior accessory great saphenous vein (GSV; Leonardo's vein) to the paired posterior tibial veins. This observation is extremely important as, although the posterior accessory GSV does connect to the GSV just below the knee, stripping of the GSV will not affect flow through incompetent medial calf perforators. The perforators encountered during SEPS include the upper, middle, and lower posterior tibial perforators and the paratibial and Boyd's perforators, which connect the GSV to the posterior tibial and popliteal veins in the calf.[12]

Certain anatomic considerations specific to the endoscopic interruption of medial calf perforators need to be emphasized. In cadaver dissections, Mozes et al.[12] noted that only 63% of all medial perforators were directly accessible from the superficial posterior compartment. These constitute 32% of the mid-posterior tibial, 84% of the upper posterior tibial, and 43% of the lower paratibial perforating veins; the remaining traverse the inter-muscular septum dividing the deep and superficial compartments, or reside solely within the posterior deep compartment itself.[12] In order to gain access to these, a paratibial fasciotomy must be performed, incising the entire length of the fascia of the posterior deep compartment.

49.3 SIGNIFICANCE OF PERFORATING VEINS

There is a consensus of opinion that venous hypertension in the erect position and during ambulation is the most important factor responsible for the development of skin changes and venous ulceration in CVI. The relationship between venous ulceration and ambulatory venous pressure (AVP) was first described by Beecher et al.[13] in 1936. Subsequent studies have confirmed that AVP has not only diagnostic but also prognostic significance in CVI. Negus and Friedgood[5] described pressures in the supramalleolar network well above 100 mmHg during calf muscle contraction. The importance of incompetent perforators is also supported by the observation that skin changes and venous ulcers almost always develop in the gaiter area of the leg (the area between the distal edge of the soleus muscle and the ankle), where large incompetent medial perforating veins are located.

Evidence is increasing that the majority of patients with venous ulcers have multisystem (superficial, deep, and/or perforator) incompetence, involving at least two of the three venous systems. Incompetent calf perforators in conjunction with superficial or deep reflux have been reported in 56%–73% of limbs with venous ulceration.[8,14] A correlation between the number and size of incompetent perforating veins, as detected by duplex, and the severity of CVI was demonstrated by Labropoulos and coworkers.[14] In patients with advanced disease, more incompetent perforators were found, and their diameters were also larger. In spite of this evidence, the contribution of incompetent perforators to the hemodynamic derangement in limbs with CVI remains a topic of debate. However, functional studies cannot reliably differentiate perforator from deep vein incompetence in most patients, so the task of documenting hemodynamic problems related directly to perforator incompetence, even if confirmed with duplex scanning, remains difficult.

The question that remains at the heart of the debate is not so much of the hemodynamic significance, but rather the relative clinical significance of these perforating veins; specifically, do they independently contribute to the severity of CVI or are they merely a secondary effect of advanced superficial and/or deep incompetence. A statistically significant decrease in perforator incompetence over 12 months was seen in 261 patients in the ESCHAR study[15] following superficial venous reflux ablation alone, although the absolute reduction was only from 51% to 42%. Mendes et al.[16] similarly found reversal of perforator incompetence in 71% of limbs free of deep incompetence treated with superficial surgery alone, while the Edinburgh group[17] found that 72% of limbs with significant deep venous involvement will have persistent perforator incompetence after isolated superficial venous surgery. In a randomized prospective trial that included only patients with superficial and perforator reflux with primary valvular insufficiency, Kianifard et al. found similar results with 78% of patients randomized to correction of superficial reflux only demonstrating perforator incompetence at 1 year compared to a significantly lower 31% who had concomitant SEPS.[18]

49.4 INDICATIONS FOR PERFORATOR INTERRUPTION

The presence of incompetent perforators in patients with advanced CVI (clinical classes 4–6; i.e., lipodermatosclerosis or healed or active ulceration) and low operative risk constitutes a potential indication for surgical intervention. These include patients with isolated perforator incompetence, as well as those with combined superficial, deep, and perforator incompetence. In the last group, combined superficial and perforator reflux ablation is a reasonable approach to providing maximum benefit; however, the procedures may be staged in selected patients with limited perforator involvement, reserving perforator interruption for persistent problems. Patients with varicose veins (C2–C3) should be considered for perforator ligation only if varices recur following treatment of superficial incompetence.

An open ulcer is not a contraindication for SEPS. Contraindications include associated arterial occlusive disease (ankle–brachial index <0.8), infected ulcer, and a non-ambulatory or a medically high-risk patient. Diabetes, renal failure, liver failure, morbid obesity, or ulcers in patients with rheumatoid arthritis or scleroderma are relative contraindications. Presence of deep venous obstruction

at the level of the popliteal vein or higher on pre-operative imaging is also a relative contraindication. Patients with extensive skin changes, circumferential large ulcers, recent deep venous thrombosis, severe lymphedema, or large legs may not be suitable candidates. SEPS has been performed for recurrent disease after previous perforator interruption; however, it is technically more demanding in this situation. Owing to limitations of space in this subfascial compartment, limbs with lateral ulcerations should be managed by open interruption or percutaneous ablation of lateral or posterior perforators where appropriate.

49.5 PRE-OPERATIVE EVALUATION

Pre-operative evaluation includes imaging studies to document superficial, deep, and/or perforator incompetence and to guide the operative intervention. The preferred test is duplex scanning. Ascending and descending phlebography is reserved for patients with underlying occlusive disease or recurrent ulceration after perforator division in whom deep venous reconstruction is being considered. Pre-operative duplex mapping assists the surgeon in identifying all incompetent perforators at the time of operation. Duplex scanning is performed with the patient on a tilted examining table with the affected extremity in a near-upright, non-weight-bearing position. Perforator incompetence is defined by retrograde (outward) flow lasting longer than 0.5 seconds or longer than antegrade flow during the relaxation phase after release of manual compression in a vein that measures at least 3.5 mm in diameter.[19] Duplex scanning has 100% specificity and the highest sensitivity of all diagnostic tests for predicting the sites of incompetent perforating veins.[20] All identified perforators are marked on the skin with a non-erasable marker.

In addition to duplex scanning, a functional study such as strain gauge or air plethysmography is performed before and after surgery to quantitate the degree of incompetence, identify abnormalities in calf muscle pump function, aid in the exclusion of outflow obstruction, and assess the hemodynamic results of surgical intervention.

49.6 OPEN SURGICAL TECHNIQUES

Open surgical techniques of perforating vein ablation are discussed here to serve as a historical background. Linton's initial description of subfascial perforator ligation included long incisions not only medially, but also antero- and postero-laterally. This approach was soon abandoned by Linton owing to the high rate of wound complications.[21] Linton modified the original approach in 1953 to include only the medial incision, through which all medial and posterior perforating veins were ligated. The modified Linton procedure also included stripping of both the great and small saphenous veins and excision of a portion of the deep fascia. The medial incision continued to be placed through the most diseased, lipodermatosclerotic skin, and wound complications remained high. When studied in a prospective manner, the significant wound complication rate was documented at 53%.[20]

In attempts to decrease these wound complications, several authors attempted further modifications, such as extrafascial ligation as proposed by Cockett.[3] This approach can potentially miss perforator branches that occur subfascially but branch extensively on exiting the fascia.[12] Moving the incision further posterolaterally (stocking seam incision) has also been described, but when extensive skin changes are present, this does not solve the problem, and the subfascial dissection is still extensive.[3,22]

DePalma[23] limited wound complications by using parallel incisions along the natural skin lines to create bipedical flaps through which he could access the perforating veins. To decrease wound complications further, a technique of ablating incompetent perforating veins from sites that are remote from diseased skin was first reported by Edwards in 1976.[24] He designed a device, called the phlebotome, which is inserted through a medial incision just distal to the knee, deep into the fascia, and advanced to the level of the medial malleolus. Resistance is felt as perforators are engaged and subsequently disrupted with the leading edge. Other authors have subsequently reported successful application of this device, passed in either the subfascial or extrafascial plane.

Interruption of perforators through stab wounds and hook avulsion is another possibility, and the accuracy of this blind technique will improve if duplex scanning is used for mapping. Suture ligation of perforators without making skin incisions is another reported technique. With the widespread use of ultrasound-guided techniques, some phlebologists will localize perforators and do a small, direct cut-down, thus minimizing the extent of the operation; however, even this can have a higher rate of wound infections compared to SEPS (18% vs. 0%), as reported by Vashist et al.[25]

49.7 ENDOSCOPIC SURGICAL TECHNIQUES

Since its introduction, two main techniques of SEPS have been developed. The first, practiced mostly in Europe, is a refinement of the original work of Hauer,[7] with further development by Bergan et al.,[26] by Pierik et al.,[20] and Wittens.[27] In the early development of the "single-port" technique, available light sources such as mediastinoscopes and bronchoscopes were used. With time, a specially designed instrument was devised which uses a single scope with two channels for the camera and working instruments, which sometimes makes visualization and dissection in the same plane difficult (Figure 49.1). Recent developments in instrumentation for this technique now allow for carbon dioxide (CO_2) insufflation into the subfascial plane.

The second technique—the "two-port" technique—utilizes standard laparoscopic instrumentation and two ports, one for the camera and another for dissection.

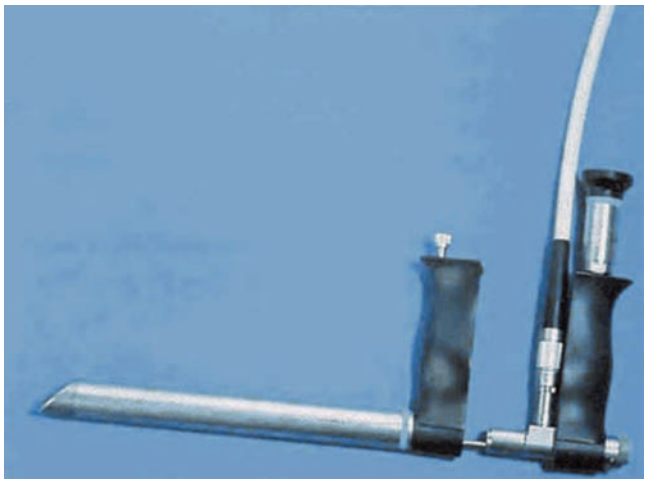
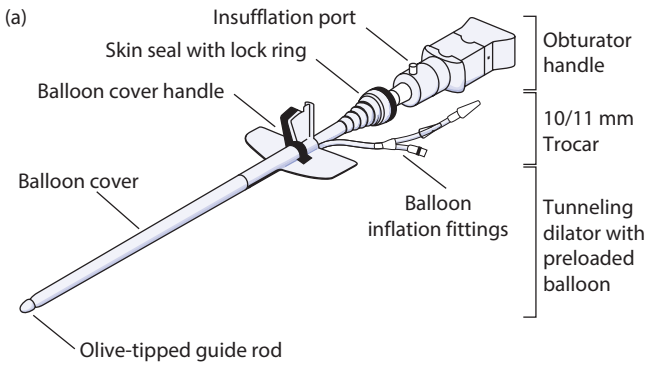


Figure 49.1 Olympus endoscope for subfascial perforating vein interruption. The scope can be used with or without carbon dioxide insufflation. It has an 85-angle field of view, and the outer sheath is either 16 or 22 mm in diameter. The working channel is 6 × 8.5 mm, with a working length of 20 cm. (Reproduced with permission from Springer Science+Business Media: *Atlas of Endoscopic Perforator Vein Surgery*, Subfascial endoscopic perforator surgery: The open technique, 1998, 141–9, Bergan JJ, Ballard JL, Sparks S.)



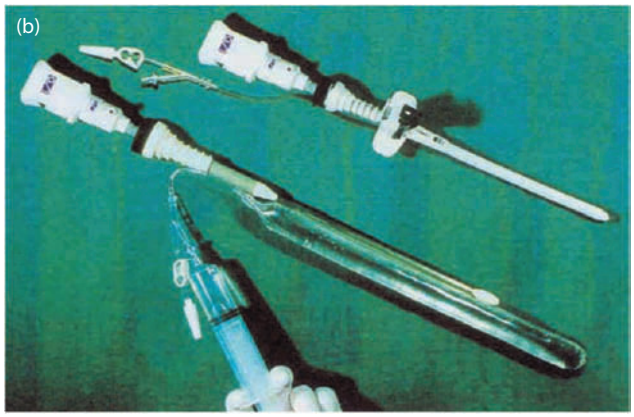


Figure 49.2 **(a)** Components of balloon dissector (General Surgical Innovations, Palo Alto, CA) for the creation of a large subfascial working space. An integral 10-mm endoscopic port is included. **(b)** The balloon dissector device before (top) and after (bottom) balloon cover removal. Note the degree of radial and distal balloon expansion that occurs when fully inflated with saline solution. Balloon inflation is performed with 200–300 mL of saline. The balloon expands both radially and distally with minimal trauma to the surrounding tissue, thus creating a large, bloodless working space. (Reproduced with permission from Springer Science+Business Media: *Atlas of Endoscopic Perforator Vein Surgery*, Endoscopic perforator vein surgery: Creation of a subfascial space, 1998, 153–62, Allen RC et al.)

O'Donnell[28] initially described this approach in the United States, and it was then simultaneously developed by our group at the Mayo Clinic[29] and by Conrad[30] in Australia. To provide a bloodless operative field, the limb is first exsanguinated with an Esmarque bandage, and a pneumatic tourniquet placed on the proximal thigh is then inflated to 300 mmHg. Two 10-mm diameter endoscopic ports are placed in the medial aspect of the calf 10 cm distal to the tibial tuberosity and about 10–12 cm apart, proximal to the diseased skin. It is now routine to perform the procedure with a 5-mm distal port, due to the availability of 5-mm harmonic scalpels and excellent 5-mm instruments (scissors and dissecting instruments). The distal port is placed halfway between the first port and the ankle, for easier dissection. The 10-mm camera withstands the torque better than a 5-mm device and reaches all the way to the medial malleolus. We are now routinely using balloon dissection to widen the subfascial space and facilitate access after port placement (Figure 49.2).[31] CO_2 is insufflated into the subfascial space and pressure is maintained at around 30 mmHg to improve visualization and access to the perforators. Using laparoscopic scissors inserted through the second port, the remaining loose connective tissue between the calf muscles and the superficial fascia is sharply divided.

The subfascial space is widely explored from the medial border of the tibia to the posterior midline and down to the level of the ankle. All perforators encountered are divided with the harmonic scalpel, electrocautery, or sharply between clips (Figure 49.3). A paratibial fasciotomy is next made by incising the fascia of the posterior deep compartment close to the tibia to avoid injury to the posterior tibial vessels and nerve (Figure 49.3b). The Cockett II and Cockett III perforators are located frequently within an intermuscular septum, and this has to be incised before identification and division of the perforators can be accomplished. The medial insertion of the soleus muscle on the tibia may also have to be exposed to visualize proximal paratibial perforators. By rotating the ports cephalad and continuing the dissection up to the level of the knee, the more proximal perforators can also be divided. While the paratibial fasciotomy can aid in distal exposure, reaching the retromalleolar Cockett I perforator endoscopically is usually not possible, and, if incompetent, may require a separate small incision over it to gain direct exposure.

After completion of the endoscopic portion of the procedure, the instruments and ports are removed, the CO_2 is manually expressed from the limb, and the tourniquet

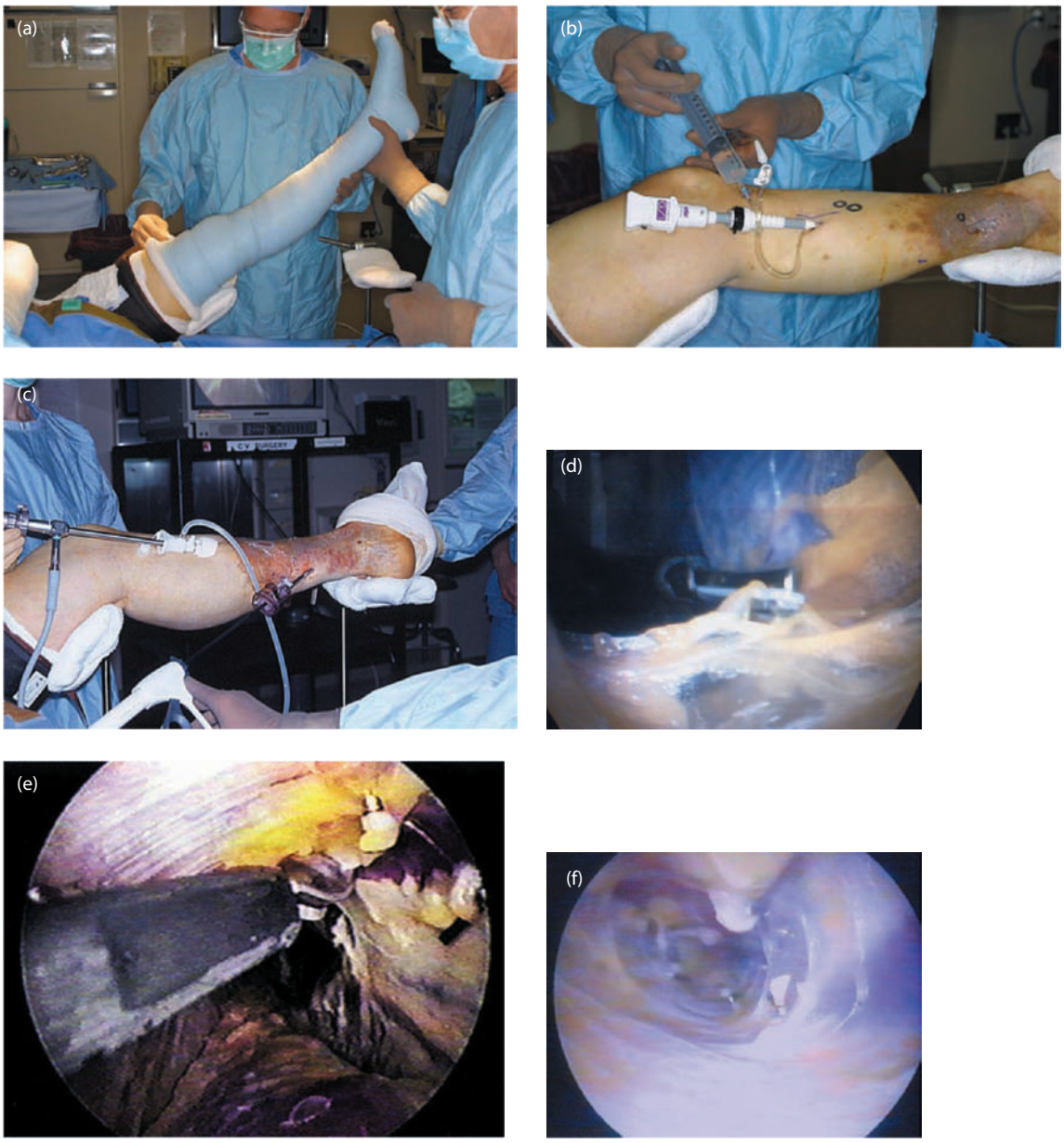


Figure 49.3 **(a)** Endoscopic perforator division is performed in a bloodless field. A pneumatic tourniquet is placed on the thigh and the extremity is exsanguinated with an Esmarque bandage. The tourniquet, inflated to 300 mmHg, is used to create a bloodless field. **(b)** Balloon dissection is used to widen the subfascial space. **(c)** SEPS is performed using two ports: a 10-mm camera port and a 5- or 10-mm distal port inserted under video control. Carbon dioxide is insufflated through the camera port into the subfascial space to a pressure of 30 mmHg to improve visualization and access to perforators. **(d)** The subfascial space is widely explored from the medial border of the tibia to the posterior midline and down to the level of the ankle. Division of the perforator with endoscopic scissors occurs after placement of vascular clips or a harmonic scalpel is placed through the second port. **(e)** A paratibial fasciotomy is routinely performed to identify perforators in the deep posterior compartment. **(f)** Full view of the superficial posterior compartment after clipping and division of the medial perforating veins. ([a,e] With kind permission from Springer Science+Business Media: *Atlas of Endoscopic Perforator Vein Surgery*, Subfascial endoscopic perforator vein surgery with gas insufflation, 1998, 125–38, Gloviczki P et al.; [c,d,f] from Gloviczki P et al. *J Vasc Surg* 1996;23:517–23.)

is deflated. A total of 20 mL of 0.5% marcain solution is instilled into the subfascial space for post-operative pain control. Stab avulsion of varicosities in addition to ablation/stripping of the great and/or small saphenous vein, if incompetent, are performed. The wounds are closed and the limb is elevated and wrapped with an elastic bandage. Elevation is maintained at 30° post-operatively for 3 hours, after which ambulation is permitted.

Unlike the in-hospital stay after an open Linton procedure, this is an outpatient procedure, and patients are discharged the same day. Restrictions are the same as with great saphenous stripping. Patients are allowed to return to work in 10 days to 2 weeks. Proebstle and Herdemann have reported performing SEPS successfully under tumescent local anesthesia alone in 78% of patients.[11]

49.8 ULTRASOUND-GUIDED TECHNIQUES

Although these will be covered in more detail in other chapters, the emerging office-based therapies of endovenous perforator vein ablation and ultrasound-guided sclerotherapy deserve mention here in order to place them in the context of the natural evolution in the treatment of perforator incompetence. These techniques are also now allowing us to examine the effect of the treatment of perforating veins and their tributaries in patients who have already had correction of superficial axial incompetence, thus allowing a more direct cause-and-effect analysis of their treatment. Endovenous perforator ablation arose from the treatment of superficial saphenous reflux with both radiofrequency ablation and endovenous laser ablation of the saphenous veins. The procedure is technically much more demanding because of the short and often tortuous nature of these perforators.[10,11] Lawrence et al. reported their results with radiofrequency perforator ablation alone in patients with active ulcers who had failed intensive wound management and prior correction of superficial reflux. In this refractory population, 90% of ulcers healed after successful perforator closure with a 4% recurrence rate at 1 year, and no ulcer healed without closure of at least one perforating vein.[32] Ultrasound-guided foam sclerotherapy is another office-based procedure for the treatment of perforator incompetence. There are several different agents and techniques for this, including liquid and foam sclerotherapy with sotradecol and polidocinal, as well as the emergence of cyanoacrylate; however, the reader is referred to Chapters 33 and 35 for further details regarding these agents.[9,33,34] Ultrasound-guided foam sclerotherapy in a heterogeneous patient population that, similarly to the UCLA group, had previously been treated for superficial reflux was reported by Kiguchi et al.[33] They demonstrated that in those patients who went on to heal their ulcers after intervention, successful perforator closure was associated with ulcer healing (69% vs. 38% for those who failed to have perforator closure).

49.9 RESULTS OF PERFORATOR ABLATION

49.9.1 Clinical results

The need for perforator interruption remains a subject of debate, as the significance of incompetent perforating veins and their contribution to the severity of CVI remains in question. The controversy relates to whether the incompetent perforating veins are the cause or the effect of the global venous incompetence in the limb and, if they are contributing to the disease process, whether their relative contribution is enough to warrant specific treatment of it. This debate continues because of the lack of direct comparative studies in large enough patient samples to make conclusions, specifically when comparing interventions of isolated perforator incompetence.

In their seminal papers, Linton[2] and Cockett[3] reported the initial clinical benefits of open perforator ligation. Table 49.1 summarizes the results from 10 reports of open perforator ablation in nearly 600 limbs performed since the 1970s. The ulcer healing rate was excellent at 89%.

Table 49.1 Clinical results of open perforator interruption for the treatment of advanced chronic venous disease

First author (year)	No. of limbs treated	No. of limbs with ulcers	Wound complications, *n* (%)	Ulcer healing, *n* (%)	Ulcer recurrence,[b] *n* (%)	Mean follow-up (years)
Silver (1971)[36]	31	19	4 (14)	–	– (10)	1–15
Thurston (1973)[37]	102	0	12 (12)	[a]	11 (13)	3.3
Bowen (1975)[38]	71	8	31 (44)	–	24 (34)	4.5
Burnand (1976)[35]	41	0	–	[a]	24 (55)	–
Negus (1983)[5]	108	108	24 (22)	91 (84)	16 (15)	3.7
Wilkinson (1986)[6]	108	0	26 (24)	[a]	3 (7)	6
Cikrit (1988)[39]	32	30	6 (19)	30 (100)	5 (19)	4
Bradbury (1993)[40]	53	0	–	[a]	14 (26)	5
Pierik (1997)[20]	19	19	10 (53)	17 (90)	0 (0)	1.8
Sato (1999)[41]	29	19	13 (45)	19 (100)	13 (68)	2.9
Total	**594 (100)**	**203 (34)**	**126/497 (25)**	**157/176 (89)**	**110/471 (23)**	–

[a] Only class 5 (healed ulcer) patients admitted in study.
[b] Recurrence calculated where data available and percentage accounts for patients lost to follow-up.

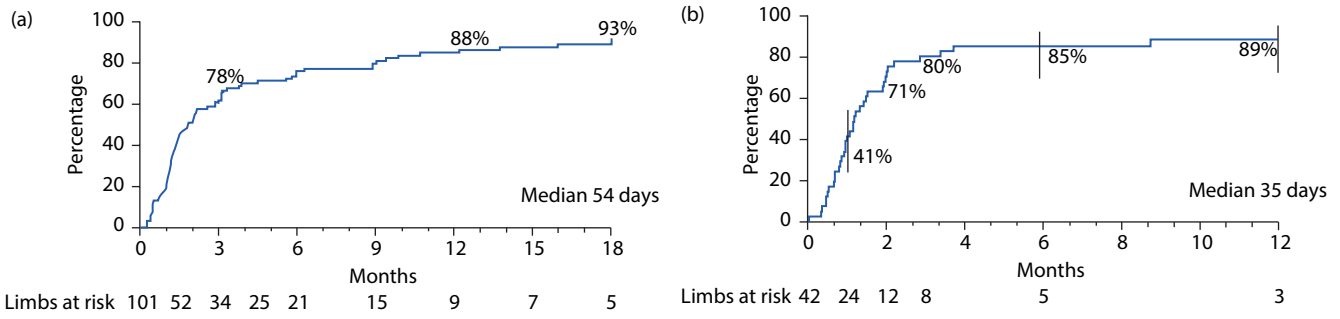


Figure 49.4 **(a)** Cumulative ulcer healing in 101 patients after subfascial endoscopic perforator surgery (SEPS). The 90-day, 1-year, and 1.5-year healing rates are indicated. The standard error is less than 10% at all time points. **(b)** Cumulative ulcer healing in 42 patients after SEPS. The 90-day and 1-year healing rates are indicated. The standard error is less than 10% at all time points. ([a] From Gloviczki P et al. *J Vasc Surg* 1999;29:489–99; [b] from Kalra M et al. *Vasc Endovasc Surg* 2002;36:41–50.)

Ulcer recurrence was 23% over 2–5 years, but most of these reports originated prior to the present-day reporting standards and the patient populations are likely to have been heterogeneous. Burnand et al.[35] brought the utility of open perforator ablation into question with a report of a 55% ulcer recurrence rate in their surgical patients. Although the post-thrombotic subset (Es) rate was 100%, the mere 6% recurrence rate in those patients with primary valvular insufficiency (Ep) was obscured by the high recurrence. Despite the apparent benefit in the Ep subset, both the long recovery period after open perforator ablation combined with a significant wound complication rate of 25% on average led to the abandonment of open perforator ligation, with interest in it now being for historical purposes only. This was solidified by Pierik et al.[20] in their randomized trial comparing open and endoscopic perforator ablation that had to be terminated early because of the high (53%) wound complication rate in the open group compared with 0% in the SEPS group, with no ulcer recurrence in either group over a mean follow-up of 21 months.

With the advent of SEPS, the wound complication rate of perforator ablation and the prolonged recovery period seen with the modified Linton procedure were no longer major concerns, as documented by multiple reports from centers in both Europe and North America.[8,20,26,41,42] These series also documented the safety and efficacy of SEPS, with rapid ulcer healing and early low recurrence rates. With extended follow-up, however, the ulcer recurrence rates seen with SEPS have proven to be similar to those seen historically with open ablation. In reporting late results of their prospective randomized study comparing SEPS with open perforator ligation, Sybrandy et al.[43] noted no significant difference in ulcer recurrence: 22% versus 12%, respectively. The midterm (24-month) results of the North American Subfascial Endoscopic Perforator Surgery (NASEPS) registry, reporting on SEPS performed in 17 U.S. centers, demonstrated an 88% cumulative ulcer healing rate at 1 year (Figure 49.4).[8] The median time to ulcer healing was 54 days. The cumulative rate of ulcer recurrence was significant: 16% at 1 year and 28% at 2 years (Figure 49.5). In the largest series from

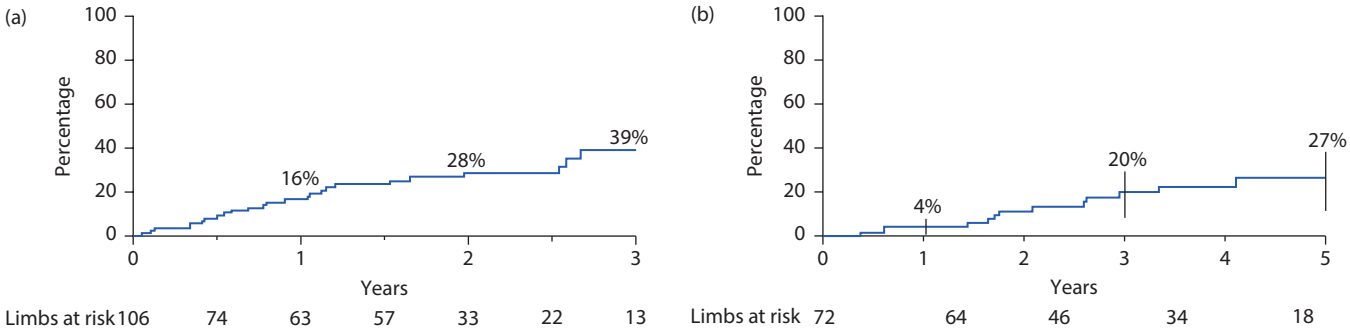


Figure 49.5 **(a)** Cumulative ulcer recurrence in 106 patients after subfascial endoscopic perforator surgery (SEPS). The 1-, 2-, and 3-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points. **(b)** Cumulative ulcer recurrence in 72 patients after SEPS. The 1-, 3-, and 5-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points. ([a] From Gloviczki P et al. *J Vasc Surg* 1999;29:489–99; [b] from Kalra M et al. *Vasc Endovasc Surg* 2002;36:41–50.)

Table 49.2 Clinical results of subfascial endoscopic perforator surgery for the treatment of advanced chronic venous disease

First author (year)	No. of limbs treated	No. of limbs with ulcer[a]	Concomitant saphenous ablation, *n* (%)	Wound complications, *n* (%)	Ulcer healing, *n* (%)	Ulcer recurrence,[c] *n* (%)	Mean follow-up (months)
Jugenheimer (1992)[44]	103	17	97 (94)	3 (3)	16 (94)	0 (0)	27
Pierik (1995)[45]	40	16	4 (10)	3 (8)	16 (100)	1 (2.5)	46
Bergan (1996)[26]	31	15	31 (100)	3 (10)	15 (100)	(0)	–
Wolters (1996)[46]	27	27	0 (0)	2 (7)	26 (96)	2 (8)	12–24
Padberg (1996)[47]	11	0	11 (100)	–	[b]	0 (0)	16
Pierik (1997)[48]	20	20	14 (70)	0 (0)	17 (85)	0 (0)	21
Gloviczki (1999)[8]	146	101	86 (59)	9 (6)	85 (84)	26 (21)	24
Illig (1999)[49]	30	19	–	–	17 (89)	4 (15)	9
Sato (1999)[41]	27	20	17 (63)	2 (7)	18 (90)	5 (28)	8
Nelzen (2001)[42]	149	36	132 (89)	11 (7)	32 (89)	3 (5)	32
Kalra (2002)[50]	103	42	74 (72)	7 (6)	38 (90)	15 (21)	40
Iafrati (2002)[51]	51	29	33 (65)	3 (6)	22 (76)	6 (13)	38
Baron (2004)[52]	98	53	36 (42)	–	53 (100)	0 (0)	–
Van Gent (2006)[53]	94	94	51 (54)	–	78 (83)	21 (22)	29
Vashist (2014)[25]	100	12	74 (74)	8 (8)	12 (12)	–	3
Van Gent (2015)[54]	45	45	–	–	43 (96)	22 (49)	97
Total	**1075 (100)**	**546 (51)**	**660/983 (67)**	**58/780 (7)**	**488/546 (89)**	**109/719 (15)**	–

[a] Only class 6 (active ulcer) patients are included.
[b] Only class 5 (healed ulcer) patients were admitted in this study.
[c] Recurrence calculated for class 5 and 6 limbs only where data are available, and percentage accounts for patients lost to follow-up.

a single institution, Nelzen[42] reported on prospectively collected data from 149 SEPS procedures in 138 patients. During a median follow-up of 32 months, 32 of 36 ulcers healed, more than half (19/36) within 1 month. Three ulcers recurred, one of which subsequently healed during follow-up. Table 49.2 summarizes the data from 16 separate reports in over 1000 limbs during a 12-year period. The ulcer healing rate of 90% is indistinguishable from that seen in open perforator ablation. The crude ulcer recurrence rate is also comparable at 11%, although the follow-up was slightly less in the SEPS series, ranging from just under 1 year to almost 4 years.

TenBrook and colleagues[55] conducted a systematic review and a combined statistical analysis of the reported series on SEPS that included a total of 1140 limbs. They found similar results as listed in Table 49.2, but identified that the presence of a large ulcer (>2 cm), secondary etiology of the venous disease (Es), and the presence of persistent incompetent perforating veins post-operatively were all risk factors for the non-healing of the ulcers. Interestingly, the presence of deep venous incompetence was not an identifiable risk factor for the non-healing of the ulcers or recurrence. Kalra et al.[50] for the Mayo Clinic specifically examined their results in these post-thrombotic patients. Although the 5-year ulcer recurrence rate was significantly higher in this subgroup (Ep 15% vs. Es 56%), these patients still gained clinical benefit as measured by improved venous clinical severity scores, as well as an apparent ease in treating the smaller, superficial ulcers compared with their preoperative state (Figures 49.6 and 49.7). The Dutch SEPS trial was the first of its kind: a randomized multicenter trial

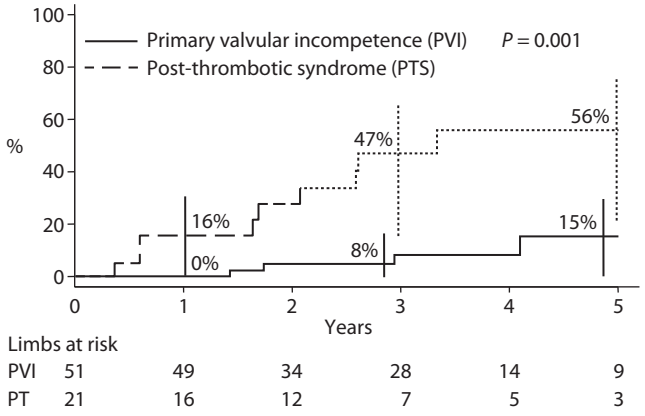


Figure 49.6 Ulcer recurrence based on cause of chronic venous insufficiency. Limbs were separated into primary valvular incompetence ($n = 51$) and post-thrombotic syndrome ($n = 21$). The 1-, 3-, and 5-year recurrence rates are indicated. The dashed line represents a standard error of greater than 10% (primary valvular incompetence versus post-thrombotic syndrome, $P < 0.05$). (From Kalra M et al. *Vasc Endovasc Surg* 2002;36:41–50.)

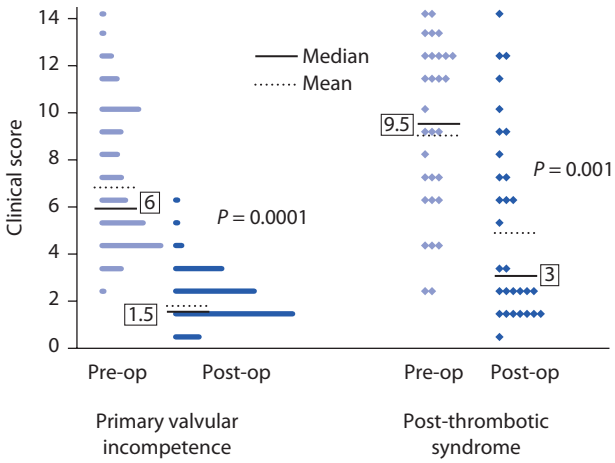


Figure 49.7 Pre-operative and post-operative clinical scores based on the etiology of chronic venous insufficiency. Limbs were separated into primary valvular incompetence ($n = 73$) and limbs with post-thrombotic syndrome ($n = 30$). (From Kalra M et al. *Vasc Endovasc Surg* 2002;36:41–50.)

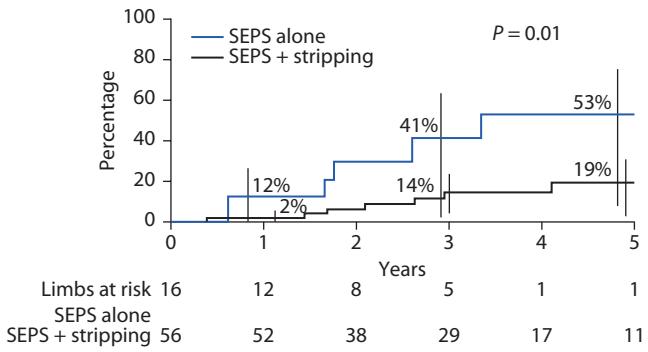


Figure 49.8 Ulcer recurrence based on the extent of venous surgery. Limbs underwent subfascial endoscopic perforator surgery (SEPS) alone ($n = 16$) or SEPS with saphenous vein stripping ($n = 56$). The 1-, 3-, and 5-year recurrence rates are indicated (SEPS alone versus SEPS with saphenous vein stripping, $P < 0.05$). (From Kalra M et al. *Vasc Endovasc Surg* 2002;36:41–50.)

prospectively comparing surgical treatment (SEPS with or without superficial reflux ablation) with medical treatment (ambulatory venous compression) in patients with venous ulcers.[56] The study included 200 patients, 97 randomized to medical treatment and 103 in the surgical group. The ulcer healing rate of 83% and recurrence in the surgical group of 22% at 29 months in this trial are comparable to previously reported results. In the conservative group, ulcers healed in 73% and recurred in 23%. Ulcer size and duration were independent factors that adversely affected ulcer healing and recurrence.[53] On extended follow-up (mean: 97 months) of this same cohort, van Gent et al. reported that the ulcer-free rate was significantly greater in the surgical group (59% vs. 40%), as was the overall ulcer recurrence rate (49% for the surgical group vs. 94% for the conservative group), with the number of incompetent perforators on extended follow-up being a significant risk factor for not being ulcer free.[54] In a *post hoc* analysis of the surgical arm examining only patients with active ulcers at the time of intervention, the presence of missed perforators (two or more missed perforators) was predictive of ulcer recurrence at 27 months, suggesting their importance in the pathophysiology. Interestingly, the identification of new incompetent perforators was not associated with recurrences, making this less clear.[57]

It must be emphasized that the majority (more than two-thirds) of patients reported in the above studies underwent concomitant saphenous vein stripping and branch varicosity avulsion (Table 49.2), making it difficult to ascertain how much clinical improvement can be attributed to SEPS alone. Patients undergoing SEPS and accessory vein avulsion without saphenous stripping have been shown to have significant clinical improvement as measured by Venous Clinical Severity Score.[58] The NASEPS registry demonstrated improved ulcer healing in limbs that underwent SEPS with saphenous vein stripping compared with limbs that underwent SEPS alone, demonstrating 3- and 12-month cumulative ulcer healing rates of 76% and 100% versus 45% and 83%, respectively (Table 49.2).[8] Ulcer recurrence at 3 years was not significantly different between the two groups. Although this is indirect evidence, it does support the clinical benefit of addressing perforator incompetence. We attempted to study this in our analysis of 103 limbs.[50] Ulcer healing was significantly delayed in limbs undergoing SEPS alone compared with limbs that underwent SEPS with superficial reflux ablation: the 90-day cumulative ulcer healing rates were 49% versus 90%, respectively. Cumulative ulcer recurrence at 5 years was also higher in limbs that underwent SEPS alone (53%) than those undergoing SEPS with superficial reflux ablation (19%) (Figure 49.8). However, all limbs in the SEPS-alone group had recurrent or persistent ulcers after previously having undergone saphenous vein ligation and stripping, and there was a relative predominance of Es limbs in this group.

49.9.2 Hemodynamic results

Similarly to the debate over clinical effectiveness, there is ongoing controversy regarding the hemodynamic improvement that can be attributed to perforator interruption. Because perforator incompetence is frequently treated together with ablation of superficial reflux, post-operative hemodynamic measurements reflect the results of a combined operation. Akesson et al.[59] demonstrated a significant reduction in AVP after saphenous stripping in patients with recurrent venous ulcers, but the improvement in mean AVP did not reach significance after further perforator interruption. However, in a classic study using AVP measurements, Schanzer and Pierce[60] documented significant hemodynamic improvements after isolated perforator interruption in 22 patients. These results were confirmed in a 1996 air plethysmographic study by Padberg and colleagues[47] using foot volumetry and duplex scanning. At a

median follow-up of 66 months, in patients with no ulcer recurrence, both expulsion fraction and half-refilling time had improved significantly. We used strain gauge plethysmography to quantitate calf muscle pump function and venous incompetence before and after SEPS (Figures 49.9 and 49.10).[58] We observed significant improvements in both calf muscle pump function and venous incompetence in 31 limbs studied within 6 months of SEPS. Twenty-four of the 31 limbs underwent saphenous stripping in addition to SEPS. Although the seven limbs undergoing SEPS alone had significant clinical benefits, the hemodynamic improvements did not reach statistical significance. Proebstle et al.[61] reported that Ep patients demonstrate significantly better hemodynamic improvements than Es limbs.[61]

Further research into the best pre-operative test with which to determine the hemodynamic effects of incompetent perforators and to help select patients for perforator interruption is clearly justified. As less invasive techniques have evolved, often being performed in the office setting under local anesthetic, we may now have the ability to better delineate the role of these incompetent perforating veins by treating the overall venous incompetence in the leg in a stepwise fashion. At present, the body of literature on these other treatments—percutaneous endovenous perforator ablation and ultrasound-guided sclerotherapy of perforating veins—is limited, and results have focused on technical success rather than clinical and hemodynamic improvements. These topics are discussed in greater depth in other chapters. Masuda et al.[9] reported their clinical results with ultrasound-guided foam sclerotherapy with sodium morrhuate in 80 limbs predominantly with perforator incompetence alone. After treatment, there was a significant improvement in Venous Clinical Severity Score and an 86.5% ulcer healing rate, with a mean time to heal of 36 days. The ulcer recurrence rate was 32% at a mean of 20 months, despite only 15% compliance with compression hose. These results are very similar to those seen in the NASEPS registry (all patients, 28% recurrence at 2 years; SEPS only, 35% recurrence at 2 years).[8] New and recurrent perforators were identified in 33% of limbs and ulcer recurrence was statistically associated with incompetent perforator recurrence, as well as the presence of post-thrombotic syndrome (Es). Based on the available data, it seems likely that the clinical outcome and hemodynamic benefit of perforator vein ligation will be similar, regardless of the method of ablation: open, endoscopic, or endovenous.

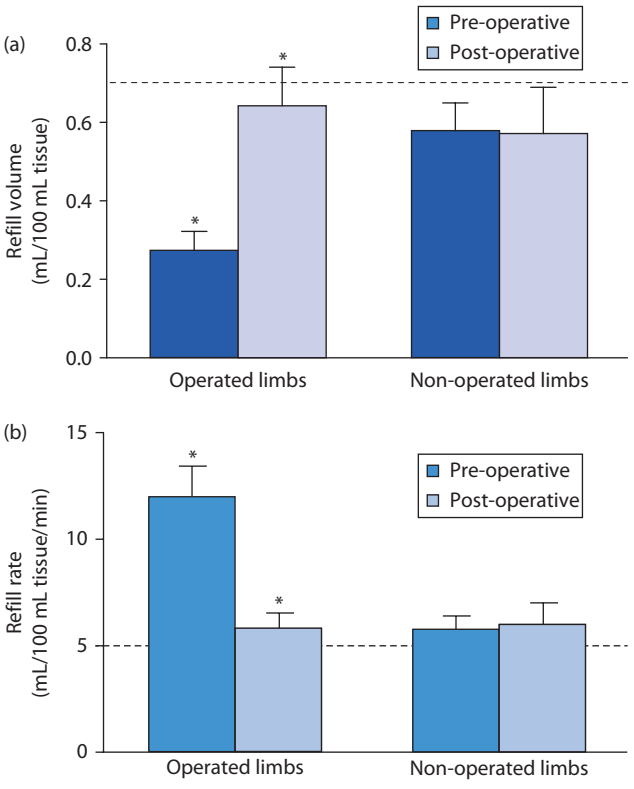


Figure 49.9 **(a)** Calf muscle pump function (refill volume) measured in 28 limbs before and after subfascial endoscopic perforator vein surgery and in 18 contralateral non-operated limbs. *$P < 0.01$; the dashed line indicates normal refill volume ≥0.7/100 mL tissue. **(b)** Venous incompetence as assessed by refill rate after passive drainage both pre- and post-operatively in the operated ($n = 30$) and non-operated contralateral limbs ($n = 20$). *$P < 0.001$; the dashed line indicates normal refill rate ≤5.0/100 mL tissue/minute. ([a] From Rhodes JM et al. *J Vasc Surg* 1998;28:839–47; [b] adapted from Rhodes JM et al. *J Vasc Surg* 1998;28:839–47, with permission.)

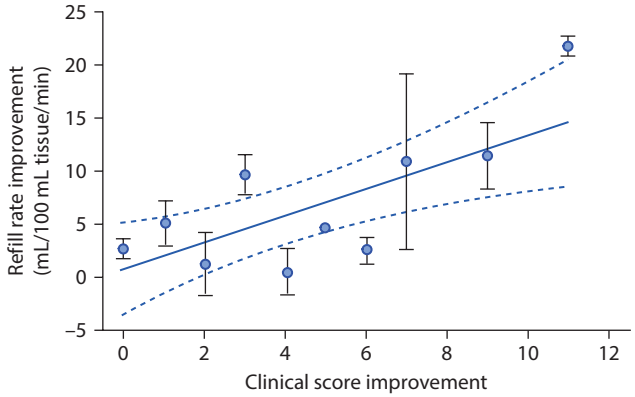


Figure 49.10 Correlation between clinical and hemodynamic improvement measured by refill rate after subfascial endoscopic perforator surgery with or without ablation of superficial reflux ($n = 29$). The mean values ± standard error of the mean and the results of linear regression analysis are depicted with 95% confidence intervals ($r = 0.77$, $P < 0.01$). (Adapted from Rhodes JM et al. *J Vasc Surg* 1998;28:839–47, with permission.)

49.10 CONCLUSIONS

Treatment of perforating vein incompetence in patients with advanced chronic venous disease remains controversial. The debate has continued because of the lack of studies that address the isolated treatment of perforator incompetence.

The use of more radical open perforator ablative techniques is considered to be of historical interest only and is not advised. Treatment of superficial axial reflux is clearly beneficial in patients with advanced CVI. The addition of perforator ablation by SEPS appears to add to the overall hemodynamic and clinical benefit, although the exact degree of benefit remains undetermined. With the emergence of office-based endovenous techniques of perforator ablation allowing us to treat perforator incompetence in an isolated fashion in those refractory patients with advanced CVI, we will hopefully gain further understanding of the relative contributions they have in the disease process.

Guidelines 4.21.0 of the American Venous Forum on the management of incompetent perforating veins with open and endoscopic surgery

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.21.1	For open surgical treatment of incompetent pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath a healed or active ulcer, we suggest against the modified open Linton procedure owing to associated morbidities.	2	C
4.21.2	For those patients who would benefit from pathologic perforator vein ablation, we suggest treatment by percutaneous techniques over subfascial endoscopic perforator surgery.	2	C

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● = Key primary paper
★ = Major review article
◆ = First formal publication of a management guideline

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Radiofrequency and laser treatment of incompetent perforating veins

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50.1 INTRODUCTION

The number of endovenous thermal ablation procedures performed on incompetent perforator veins has dramatically increased in recent years as their role in managing patients with advanced chronic venous insufficiency has gained more credibility. When left untreated, ambulatory venous hypertension can progress to lipodermatosclerosis and ulceration.[1] Although other chapters in this book refer frequently to perforating veins, it is appropriate to summarize here a brief review of the history, anatomy, and physiology of the perforating veins before we discuss diagnostic evaluation, the role of ablation of incompetent perforating veins, the technique of using radiofrequency (RF) and laser in the treatment of incompetent perforating veins, and the indications and timing of treatment, and before we present the best outcomes data.

50.2 HISTORY

The relationship between venous hypertension and venous ulceration was described nearly 100 years ago by Beecher et al. and since then it has been repeatedly validated.[2] Superficial vein, deep vein, and perforator vein incompetence have been demonstrated to independently contribute to lower extremity venous hypertension and severe venous disease.[3,4] The significance of the perforator veins is supported through the findings that venous ulceration most often occurs in the ankle region, known as the "gaiter zone," which sits directly on top of the large posterior tibial perforator veins. It has also been shown that the number and extent of incompetent perforating veins is directly related to the degree of reflux, and that perforator reflux is often associated with superficial venous reflux; and if the reflux is not treated, new perforators may develop.[5–8] It has been suggested that as many as 66% of patients with lower extremity skin changes have perforator reflux in addition to superficial and/or deep reflux.[9,10]

Ligation of perforator veins by open surgery was first reported in 1938 with the Linton procedure, also referred to as the medial subfascial approach.[11] This approach began with a medial incision through the fascia and fat tissues from the medial malleolus to the calf, exposing the perforating veins. Through the work of Cockett and Dodd, this technique was refined and demonstrated to be effective[12,13]; however, it was often complicated by poor incision healing.[14,15] Nearly 50 years after it was first described by Linton, Hauer developed and demonstrated a new perforator ablation technique using an endoscope, avoiding the need for large incisions.[16] This new technique—subfascial endoscopic perforator surgery (SEPS)—was less morbid, could be performed as an outpatient procedure, and resulted in fewer complications.[17,18] Despite these advantages over the Linton procedure, SEPS still required regional or general anesthesia, which hindered its long-term use.[19] The emergence of thermal ablation as a minimally invasive approach to perforator ablation, as well as sclerotherapy of perforators, has raised questions regarding the continued appropriateness of performing the more morbid SEPS procedure.[20]

50.3 ANATOMY AND PHYSIOLOGY

Lower extremity perforating veins connect the deep and superficial venous systems (see Chapter 2) and their names are based on their anatomic location and distance from the base of the foot (Figure 50.1). The role of perforating

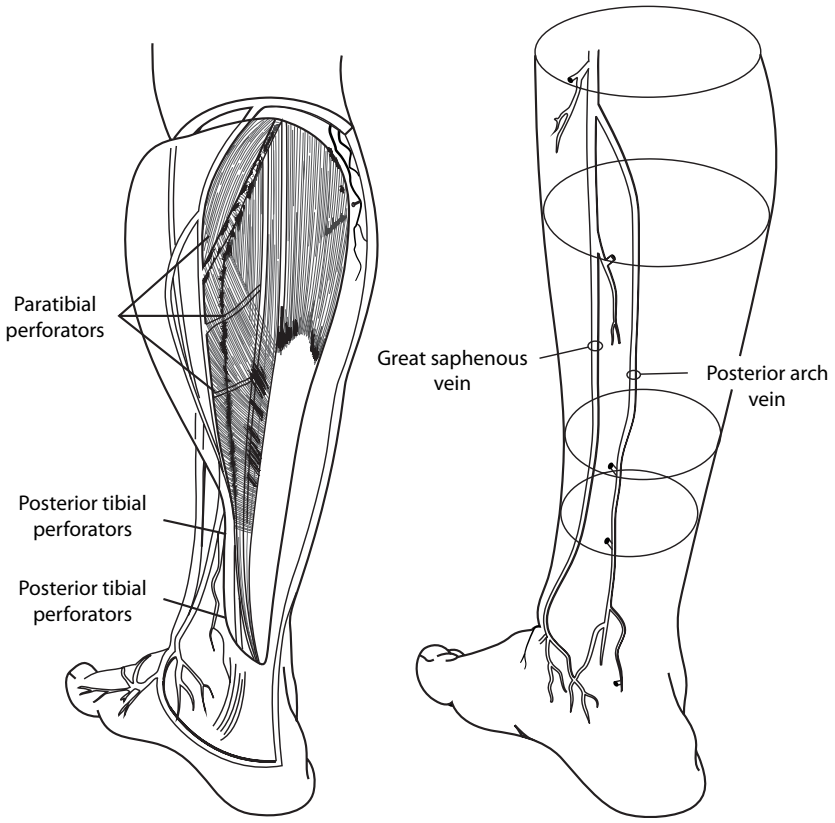

Figure 50.1 The locations of lower extremity perforator veins. (With permission of the Mayo Foundation.)

veins is to direct flow to the deep venous system. There are valves within the perforator veins that both direct flow from superficial to deep and prevent flow reversal from deep to superficial. Damage to these valves causes venous reflux and "ambulatory superficial venous hypertension." The perforating veins that are most frequently involved with reflux and therefore routinely treated with thermal ablation are those located in the medial calf, called the posterior tibial perforator veins (previously referred to as Cockett's perforators). These perforating veins connect the posterior arch vein to the posterior tibial veins. Incompetent perforator veins have been strongly correlated with both nonhealing and recurrent venous ulcers.[21–23] The goal of RF and laser ablation (thermal ablation) is to close incompetent pathologic perforator veins in order to reduce venous hypertension and promote wound healing.

50.4 DIAGNOSIS AND PRE-OPERATIVE EVALUATION

Duplex ultrasound has become the gold standard for evaluating lower extremity venous reflux and has the highest specificity and sensitivity of the available imaging modalities.[24]

Duplex ultrasound of the deep, superficial, and perforator veins must be completed in order to evaluate the degree of venous incompetence and guide management. Duplex ultrasound evaluation is performed with the patient in an upright or standing position with color Doppler or pulsed-wave Doppler using a linear 7.5–10-MHz transducer to directly visualize flow directionality. Venous reflux is characterized by antegrade flow followed by retrograde flow after compression of the vein from deep muscle pumps. Examination begins at the saphenofemoral junction, where the common femoral vein can be investigated for reflux and obstruction, commonly using the Valsalva maneuver. Next, the great saphenous vein can be traced along its course, including any accessory or tributary veins. After the proximal deep and superficial veins have been evaluated, the saphenopopliteal junction, popliteal vein, and small saphenous vein can be imaged before moving distally to evaluate the posterior tibial perforator veins for reflux. As outlined in the Society for Vascular Surgery (SVS)/American Venous Forum (AVF) guidelines for treating lower extremity venous disease, the criteria for incompetence of the deep system are defined as having a maximum vein diameter >3.5 mm with reflux >1 second, and for superficial and perforator veins incompetence are defined as having a maximum vein diameter >3.5 mm with reflux >500 ms.[25]

Following evaluation and documentation of the extent of reflux present, superficial veins should be treated prior to perforator veins. An algorithm for management of patients with superficial and perforator reflux has been previously described in the literature and validated prospectively (Figure 50.2).[22] Prior to initial incision, the surgeon verifies incompetent veins that were identified by an independent vascular laboratory specialist pre-operatively and marks the vein course on the skin.

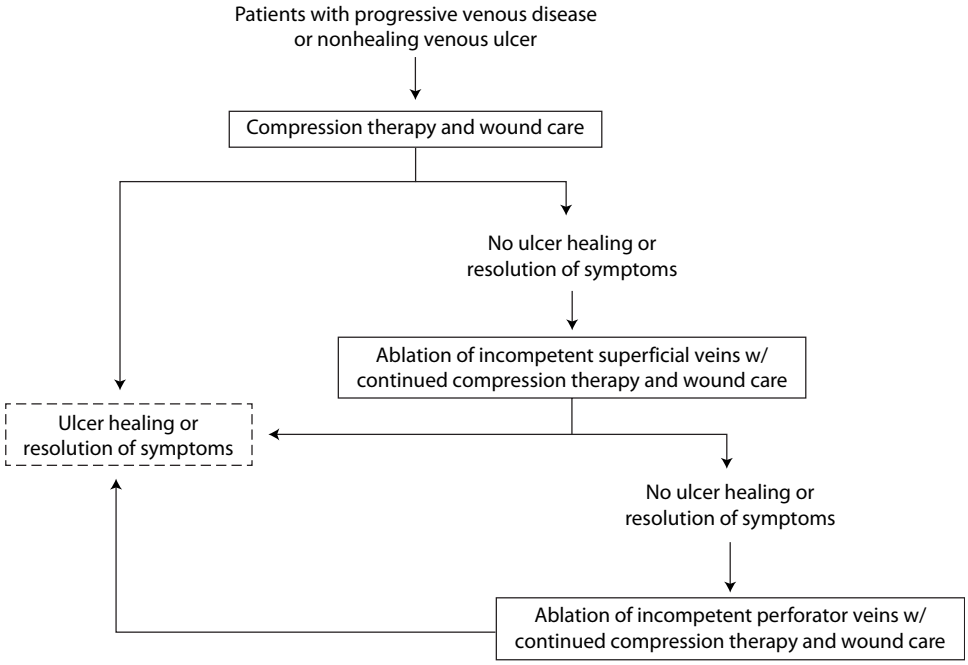

Figure 50.2 Algorithm for the management of symptomatic patients with lower extremity venous incompetence. Based on the Society for Vascular Surgery (SVS)/American Venous Forum (AVF) guidelines, endovenous ablation of incompetent perforator veins should only be pursued in patients with C4b, 5, and 6 disease, when appropriate.

50.5 TECHNIQUE

Treatment of incompetent perforating veins with RF and laser catheters is technically difficult (59%–90% success rate) and often has a steep learning curve, so ablation success is associated with surgeon experience and volume. Perforator ablation's technical challenges are in part due to the difficulty of cannulating the perforating veins, as they are frequently deep, tortuous, and located under or near damaged and ulcerated skin.[26] The higher-velocity flow associated with short perforator veins results in reduced thrombosis, in comparison to superficial vein ablation. Factors that have been associated with technical failure are anticoagulation, obesity, and venous pulsatility.[27,28] While immediate technical success of thermal ablation can be determined by 48–72 hours post-procedure using duplex ultrasound, it is often difficult to determine at a later date whether new incompetent perforators developed or whether recanalization has occurred.[26]

50.5.1 RF ablation

After the patient is placed in the reversed Trendelenburg position, a portable duplex ultrasound scanner is used to identify the incompetent perforating vein(s) prior to the procedure and the veins are marked. The duplex transducer, covered by a sterile sleeve, is used to identify the incompetent perforator veins. To puncture the skin, a no. 11 blade is applied, or sometimes the stylet from the ClosureRFS catheter (Covidien Ltd, Dublin, Ireland) is used to puncture the skin. The stylet is advanced at a 45° angle under ultrasound guidance, with the transducer being used to confirm the position of the catheter tip. The stylet is advanced to the level of the fascia and the perforator vein is punctured and then confirmed by aspiration of blood. The stylet is removed and the catheter position is again verified using ultrasound (Figure 50.3). Before ablation, the area directly surrounding the catheter is injected with anesthetic solution to the level of the fascia. After placing the patient in the

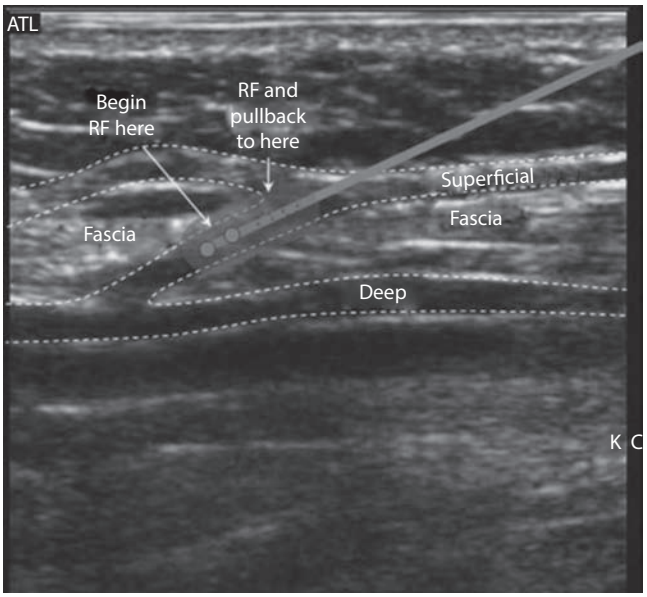

Figure 50.3 Duplex ultrasound used to confirm the position of the radiofrequency (RF) catheter tip within the perforating vein.

Trendelenburg position, the catheter is maintained in the vein and treated at 0°, 90°, 180°, and 270° with RF energy (<400 Ω and at 85°C) for one treatment in each quadrant (total duration = 4 minutes). Duplex ultrasound confirms closure of the vein. Immediately after the procedure, the ultrasound can yield a false occlusion appearance, due to the infiltration of the area by local anesthetic solution. To assess perforator closure, a duplex ultrasound is performed at 48–72 hours post-ablation.

50.5.2 Laser

Following vein identification, confirmation, and preparation as described above, the vein is punctured using a 21-gauge needle, confirmed with aspiration of blood. The laser fiber (810-, 980-, or 1470-nm wavelengths, most commonly) is introduced into the perforator vein through the needle and tumescent anesthesia is injected along the course of the catheter, around the perforator vein. Energy is delivered through the fiber tip (50 J/5 mm). The laser fiber is slowly withdrawn to treat the entire length of the perforator vein. Following treatment of the vein segment, pressure is applied directly over the perforator vein. As with RF treatment, post-procedure duplex ultrasound can be performed immediately following treatment, although results may vary depending on the amount of tumescent solution used. The technical results of the intra-operative duplex should always be verified by duplex ultrasound imaging 48–72 hours post-procedure.

50.6 INDICATIONS AND TIMING OF TREATMENT

The SVS/AVF consensus guidelines for venous disease recommend perforator treatment only for patients with active or healed venous ulcers.[25] Randomized trials examined the impact of incompetent superficial vein ablation in addition to compression therapy and confirmed that ablation was beneficial in ulcer healing, and significantly reduced ulcer recurrence.[29,30] The utility of incompetent perforator vein ablation as an adjunct to compression therapy and superficial vein ablation has only been studied by single institutions. The authors reported the effect on the acceleration of ulcer healing, prevention of ulcer recurrence, and progression of venous hypertension and associated symptoms.[31,32] Currently, there is no level 1 evidence directly supporting perforator ablation for patients with healed or active venous ulcers; however, the reports have suggested that these procedures may be of interest not only in patients with venous ulcers, but also with progressive lipodermatosclerosis and hyperpigmentation. At this time, the guidelines recommend against perforator ablation for patients with reticular veins or telangiectasia, varicose veins, and/or venous edema.[25]

50.7 OUTCOMES

The technical success of both RF and laser ablation ranges from 71% to 100% in recent studies. A proposed learning curve associated with perforator ablation has been described by van den Bos and colleagues, who found that technical failures occurred when the first patients were treated and outcomes significantly improved after an initial learning curve.[33] One institution reported the learning curve of a single surgeon to be a 4-year period: technical success was 56% initially, increasing to 79% 3 years later. These data show that perforator ablation is difficult and that improved success was directly related to the number of procedures performed.[22] Based on recent evidence, the success of thermal ablation with RF does not differ from reported results using laser (Table 50.1). Although most studies

Table 50.1 Technical success of radiofrequency and laser ablation of incompetent perforating veins in studies conducted between January 1, 2009, and January 1, 2014, which included the primary endpoints and data included above

First author (year)	Treatment modality (wavelength)	Number of patients/ procedures	Mean follow-up (months)	Method and timing of confirming treatment success	Overall success rate (%)
Harlander-Locke (2012)[31]	RF	20/28	25	DUS, 48–72 hours	96
Harlander-Locke (2012)[32]	RF	88/140	12	DUS, 48–72 hours	82
Dumantepe (2012)[34]	EVLT (1470 nm)	13/23	14	DUS 12 months	87
Lawrence (2011)[22]	RF	45/51	13	DUS, 48–72 hours	71
Corcos (2011)[35]	EVLT (808 nm)	303/534	18	DUS, mean 28 months	72
Hissink (2010)[36]	EVLT (810 nm)	28/33	3	DUS, 3 months	78
Marrocco (2010)[37]	RF	24	5	DUS, 1–7 days	100
Marsh (2010)[38]	RF	53	14	DUS, mean 14 months	82
van den Bos (2009)[33]	RF	12/14	3	DUS, 3 months	64
Hingorani (2009)[27]	RF	38/48	2	DUS, 3–7 days	88
Bacon (2009)[28]	RF	37	60	DUS, 5 years	81

Note: RF: radiofrequency; EVLT: endovenous laser therapy; DUS: duplex ultrasound.

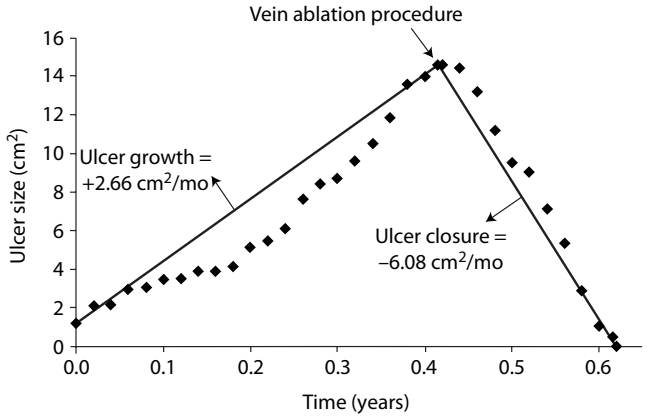

Figure 50.4 Tracking ulcer size on a single patient during a period of compression therapy, treatment, and a follow-up period, during which the patient's ulcer heals.

assessed post-procedure success within the first week using duplex ultrasound, several studies reported assessment months or even years after the initial procedure and may be biased by reporting primarily long-term successful patients. In patients with recanalization or initial technical failure, repeat RF or laser procedures were completed with nearly 100% closure rates.

Many studies assessing ulcer healing utilize absolute ulcer healing as a primary endpoint. While this endpoint captures the desired result of each incompetent perforator ablation in CEAP C6 patients, it falls short of quantitatively determining the direct impact of perforator ablation, particularly in patients who have had prior superficial venous treatment. Many studies are now including planimetry to track ulcer area (and volume) (Figure 50.4). This information provides surgeons and wound care clinicians with feedback regarding the impact of each vein treatment and may aid surgeons in determining which patients may benefit the most from incompetent perforator vein ablation.

Differences between study results examining perforator ablation outcomes may be due to the inaccurate identification of competent versus incompetent perforators, inappropriate sequencing of the treatment of chronic venous insufficiency, poor technique in performing perforator ablation, inadequate measurement of ulcer area and volume, and inadequate compression and/or wound care. Unanswered questions that remain include determination of the role in ulcer healing and ulcer recurrence of proximal iliac or inferior vena cava stenosis or occlusion.

50.7.1 Radiofrequency

Technical success rates achieved in the last 5 years using RF range from 64% to 100% using ablation confirmation with duplex ultrasound (Table 50.1). The higher closure rates reported in more recent studies may reflect improved technique based on increasing experience. van den Bos and colleagues reported successful ablation of perforator veins of up to 7 mm in size, validating the effectiveness of the RF ablation of large incompetent perforator veins.[33]

In patients with healed venous ulcers, a recent study reported a 5% ulcer recurrence rate when all incompetent perforators were closed. In one case with recurrence, a new incompetent perforator vein was identified under the ulcer in the "gaiter" zone. This ulcer healed after treatment with RF.[31] Other series have reported ulcer recurrence rates that range from 0% to 16%. Following perforator ablation in patients with healed venous ulcers, Marrocco and colleagues reported recurrence in 4% of them. However, in patients with active venous ulcers, recurrence occurred in 16% of patients, despite persistent venous occlusion.[37] Absolute ulcer healing rates ranged from 63% to 100%, and >80% for the majority of authors using RF for incompetent perforator ablation (Table 50.2).

Complications that occur with RF and laser catheters are similar and include skin burn, analgesia, paresthesia, nerve injury, and thrombophlebitis. Complication rates were typically less than 10%, but ranged up to 14%.

50.7.2 Laser

Technical success using laser catheters ranged from 72% to 87% in studies reported within the last 5 years. Technical success varied depending on the wavelength of laser catheter used, with the highest success rates associated with higher wavelengths (~1470 nm) (Table 50.1).[34] This recent evidence contrasts with earlier studies that reported that laser wavelength had no long-term effects on outcomes.[40] The impact of laser ablation on ulcer healing is directly related to the technical success of the ablation procedure, with ulcer healing rates reported in the last 5 years being lower than with RF (Table 50.2). Abdul-Haqq et al. stated that patients who underwent superficial and perforator ablation healed "faster" than those who underwent superficial vein ablation only.[39] In addition to technical outcomes, Dumantepe and colleagues noticed significant improvement in patient Venous Clinical Severity Score quality of life scores after perforator ablation.[34]

The most common complication associated with laser treatment is paresthesia, which occurs in under 10% of procedures. Shepherd et al. have reported pain scores associated with laser and RF ablation and found that there was no significant difference between RF and laser. However, patients undergoing laser ablation experienced more pain during the procedure, as well as during the 10-day postoperative period.[41]

50.8 CONCLUSIONS

Current evidence supports both RF and laser as excellent tools for closing incompetent perforator veins, with nearly identical technical success and complication rates reported. A combination of compression and thermal ablation of incompetent superficial and perforating veins can result in the healing of open venous ulcers and in the prevention

Table 50.2 Impact of radiofrequency and laser ablation of incompetent perforating veins on ulcer healing and ulcer recurrence in patients with active venous ulcers in studies conducted between January 1, 2009, and January 1, 2014, which included the primary endpoints and data included above

First author (year)	Treatment modality (wavelength)	Number of patients/procedures	Mean follow-up (months)	Outcomes (%)	
				Ulcer healing	Ulcer recurrence
Abdul-Haqq (2013)[39]	EVLT (810 nm)	17	2.5	71	0
Harlander-Locke (2012)[31]	RF	20/28	25	–	5
Harlander-Locke (2012)[32]	RF	88/140	12	76	–
Dumantepe (2012)[34]	EVLT (1470 nm)	13/23	14	80	–
Lawrence (2011)[22]	RF	45/51	13	90	4
Hissink (2010)[36]	EVLT (810 nm)	28/33	3	80	–
Marrocco (2010)[37]	RF	24	5	84	16
Marsh (2010)[38]	RF	53	14	100	0
Hingorani (2009)[27]	RF	38/48	2	63	–

Note: RF: radiofrequency; EVLT: endovenous laser therapy.

Guidelines 4.22.0 of the American Venous Forum on the radiofrequency and laser treatment of incompetent perforating veins[a]

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.22.1	In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins in addition to standard compressive therapy to aid in ulcer healing and to prevent recurrence.	2	C
4.22.2	In a patient with skin changes at risk of venous leg ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. Treatment of the incompetent perforating veins can be performed simultaneously or staged.	2	C
4.22.3	In a patient with isolated pathologic perforator veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed, regardless of the status of the deep veins, we suggest ablation of the "pathologic" perforating veins in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.22.4	For those patients who would benefit from pathologic perforator vein ablation, we suggest treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin.	2	C

[a] Based on the recommendation of the Guidelines of the Society for Vascular Surgery and the American Venous Forum.[25]

of recurrences. Thermal ablation of incompetent perforator veins is technically challenging because of anatomical variations and heavily scarred skin in the area of incompetent perforator veins. After healing of a venous ulcer, it is a crucial to determine whether there is still "ambulatory venous hypertension." If an ulcer is not healing with optimal compression therapy or has healed in a compliant patient but with progressive lipodermatosclerosis or hyperpigmentation, there is likely to be a mechanical cause, often a persistent incompetent perforator, which can be treated with endovenous thermal ablation.

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● = Major primary paper
★ = Major review paper

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Local treatment of venous ulcers

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51.1 INTRODUCTION

Prevalent in 1%–1.5% of the population, venous ulcers are associated with significant disability and socioeconomic impact.[1] Since at least 50% of venous ulcers recur within 10 years, they are marked by an insidious component of chronicity, which compounds their economic impact. Venous ulcers are also painful and affect both the working and retired generations, but increase in incidence with age. The economic cost of treating venous ulcers approaches 1% of the health care budget of Western European countries, which in the U.K. is estimated to cost £300–400 million per year.[2] Although most patients with venous ulcers are treated on an outpatient basis and are infrequently hospitalized except for complications, the direct cost of treating venous ulcers in the United States has been calculated to average $2500 per month. The direct cost of this care is related to: (1) personnel (i.e., reimbursement of physicians, nurses, and home health aids); (2) wound care treatments; (3) medications; (4) specialized wound dressings; and finally (5) compression garments.

Compression either by multilayer bandages or by custom-fitted elastic compression stockings is one of the essential components for promoting ulcer healing.[3] In a systematic review of the effect of compression bandaging on the healing of ulcers, a Cochrane review demonstrated that high levels of compression with a multilayered system are most effective and are associated with an ulcer healing rate of 60%–80%.[4] There are other modalities, however, which, when applied to the venous wound, may have an additive effect on ulcer healing. They will be reviewed in this chapter. Since Chapter 31 has addressed compression bandaging, this chapter will focus on local wound care for venous ulcers and, in particular, the role of wound dressings.

51.1.1 Why is local wound care important?

Any additional treatment modality which could improve the proportion of wounds healed as well as the healing time of venous ulcers would provide not only important benefits to the patient—a shorter period of pain and wound care with an improved quality of life—but also have a profound socioeconomic impact. There are a myriad of wound dressing products available for the care of chronic wounds, and claims for their efficacy in the healing of venous ulcers sometimes ascribe miraculous results to their use. Currently, the putative benefits of these modalities may not be clearly defined for clinicians, so their adoption for wound care treatment should be validated by carefully designed clinical studies defining their benefit compared to standard care. This chapter will encompass not only what are the usual (customary) elements of local wound care for venous ulcers, but also what are the "cutting-edge" developments in this area and, most importantly, what is their real value. Recommendations for both of these areas will be derived from systematic reviews of randomized controlled trials (RCTs) wherever possible.

51.1.2 The importance of level 1 evidence

The majority of wound treatment studies of venous ulcers can be classified as providing low-quality evidence derived from case series (Table 51.1). RCTs provide a higher level of evidence to recommend therapy. These trials have the greatest statistical power and can scientifically validate a new treatment modality (Table 51.1). Moreover, Centers for Medicare and Medicaid Services (CMS) and other third-party payers are greatly influenced by well-designed RCTs on whether to reimburse for a specific treatment. However, RCTs are not always available to

Table 51.1 Basis for comparative studies

Level	Study type	Strength
Large RCT	Low risk of error	Great
Small RCT	High risk of error	Moderate
Non-RCT	Contemporaneous control	Weak
Non-RCT	Historical control	Weak
Uncontrolled case series	–	Weak

RCT: randomized controlled trial.

assist in critical treatment recommendations. Recently, the Society for Vascular Surgery (SVS) and American Venous Forum (AVF) have completed an exhaustive review of the literature concerning the care of venous ulcers to support their updated guidelines, published in 2015.[5] These guidelines integrate the best available evidence as well as expert opinion from a diverse group of experts in the field and will be employed to support the recommendations in this chapter. The first section of this chapter will review what is the usual or customary care of venous ulcers, whereas the second part will examine recent RCTs on not only newer wound dressings for venous ulcers, but also other elements of local wound care. There are several potential positive benefits of a dressing or any modality which accelerates wound healing: shorter period of pain, drainage, and disability related to the open wound for the patient, as well as a reduced cost of the total treatment.

51.1.3 The biology of wound healing

A chronic venous ulcer can be defined as a wound that has "failed to proceed through the orderly and timely series of events which should occur to produce a durable structural and cosmetic closure."[6] Chapter 31 has discussed the microcirculatory and subcellular pathophysiology of venous ulcers. Although the mechanisms may be different for each type of chronic wound, the biology is basically similar. The biologic phases of wound healing have traditionally been divided into three progressive segments: the inflammatory phase, the proliferative phase, and the maturational phase. Chronic wounds, such as a venous ulcer, appear to be stuck in the inflammatory phase. In a non-randomized evaluation of various cytokine levels and venous ulcer healing in patients undergoing compression therapy, it was determined that untreated ulcers typically display high levels of pro-inflammatory cytokines, including several interleukins, tumor necrosis factor-α, and interferon-γ. After 4 weeks of compression therapy, the levels of pro-inflammatory cytokines decreased significantly and the wounds began to heal. After compression, levels of transforming growth factor-β1 increased significantly as the ulcers improved. When specific cytokine levels were related to the percentage of healing, it was found that those with higher levels of pro-inflammatory cytokines, including interleukin-1 and interferon-γ, healed significantly better than those with lower levels of these cytokines before compression.[6]

From a practical standpoint, it is important to understand that the typical venous ulcer is heavily exudative and the fluid created by the wound is laden with matrix metalloproteinases and pro-inflammatory cytokines that are harmful to the normal tissue surrounding the wound bed. The etiology of this is initially venous hypertension, but in some cases the situation may be exacerbated by overgrowth of colonizing bacteria that further increase inflammation and exudate. Wound dressings and the application strategy must be designed to minimize contact of the inflammatory exudate with the surrounding tissue. Compression, debridement and elimination of bacteria from the wound bed will act together to reduce the inflammatory conditions, reducing exudate and allowing healing to commence.

51.2 WOUND DRESSINGS

Over the last several decades, there has been a major transformation in the type of dressing used for wounds. In the past, it was common practice to leave a wound as dry as possible, where the function of the wound dressing became simply to keep infections out and reduce trauma to the wound. However, Winter[7] and associates' ground-breaking experiments carried out in both a porcine wound model and human volunteers demonstrated that the healing rate of wounds was markedly increased if an occlusive dressing was employed. These investigators observed a 40% increase in epithelialization rate in wounds treated with occlusive dressings over those treated with dry, non-occlusive dressings. While slow to occur in certain quarters, the shift to semi-occlusive or occlusive dressings in wound therapy has been characterized succinctly by Falanga[8] as "the composition and properties of a dressing itself now play a major role in modifying the micro environment of the wound." Semi-occlusive/occlusive wound dressings provide both a warm and moist wound environment by reducing heat loss and water evaporation. In addition, a new class of dressings—the biologic dressing—has emerged. This dressing type is based on the principle of stimulating or providing important protein substrates, growth factors, or other key mediators that are necessary to promote wound healing.

51.2.1 Classification of wound dressing types

Figure 51.1 demonstrates a convenient general classification of wound dressing types: passive, interactive, and active dressings.[7] These types are further subdivided into four classes: (1) non-occlusive; (2) semi-occlusive; (3) occlusive that are based on evaporative water loss; and finally (4) biologic.

The basic principles of wound care recognize that no single wound dressing may be ideal for all wounds and the type of dressing that is employed may change as wound healing and other local wound factors progress. Non-occlusive dressings such as topical antibiotics covered with dry gauze simply protect the wound from trauma and potential infection and are classified as passive dressings. By contrast, the interactive types of wound dressings—semi-occlusive or

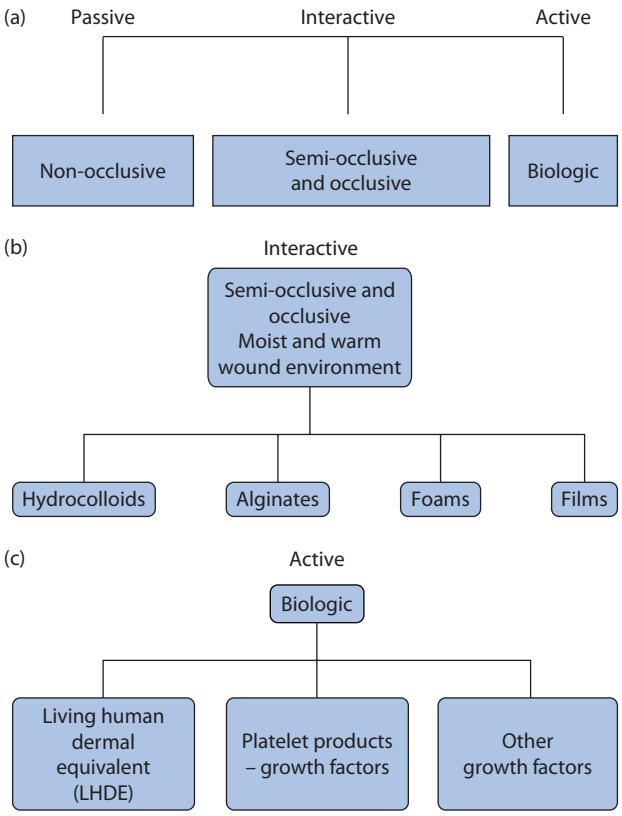

Figure 51.1 **(a)** Overall classification of wound dressings. **(b)** Interactive or semi-occlusive/occlusive dressing types are subdivided into four types dependent on the unique properties of each subtype. **(c)** Biologic wound dressings are subdivided into living human dermal equivalent or human skin equivalent, platelet products, and other growth factors. (Reproduced from Winter CD. *Nature* 1962;193:293–4.)

occlusive dressings—maintain a moist, warm wound environment and, dependent on the dressing's properties, help to control the amount and composition of wound exudate.[7]

The old standby dressing—"saline wet-to-dry gauze dressing"—functions as a semi-occlusive dressing when wet. Saline wet-to-dry dressings have been the subject of considerable criticism, but this dressing is still the most widely used form of wound dressing in certain areas of medicine. This dressing can facilitate healing in a moist environment if the gauze is kept wet, but when the gauze is dried out, the dressing assumes a non-occlusive characteristic. When these sponges are moist, they may be marginally occlusive, thereby permitting some water vapor loss, but as the gauze sponges dry, they probably promote vapor and heat loss from the wound by evaporative cooling. It is a commonly held tenet that removal of the gauze dressing serves to debride the wound, so that many physicians employ this dressing for this specific purpose. Unfortunately, ulcers associated with venous insufficiency are typically highly exudative and produce sufficient drainage to prevent a wet-to-dry dressing from drying, eliminating the potential benefit of this method. Worse, the exudate rapidly overwhelms the absorptive capacity of the dressing, requiring frequent dressing changes to avoid tissue maceration and damage of surrounding tissue from the inflammatory exudate components. For these reasons, gauze or saline wet-to-dry dressings are rarely recommended for venous ulcers, particularly in patients being treated at home.

51.2.2 Common types of semi-occlusive/occlusive dressings

This class of dressings (Figure 51.1b) will be discussed briefly based on the dressing properties and mechanisms of action, as shown in Table 51.2.

51.2.2.1 HYDROCOLLOIDS

Hydrocolloid dressings are composed of two layers: an inner hydrocolloid layer and an outer water-impermeable layer, which usually contains pure polyurethane.[9] While maintaining a moist, warm environment, this dressing also has properties of debridement and absorption of wound drainage. They have greater absorptive capabilities than gauze or film dressings, but less than foams or alginates. Hydrocolloid dressings are less permeable than film dressings. Some common examples of this wound dressing are DuoDerm (Convatec, Princeton, NJ), Comfeel (Coloplast, Peterborough, U.K.), and Signadress (Convatec, Princeton, NJ). They may be particularly useful later in the treatment phase of a venous ulcer when, after the exudate is controlled, the wound is healing and becomes less exudative. It may serve as a useful wound cover for patients with small ulcers using compression stockings for their method of compression.

51.2.2.2 HYDROGELS

Hydrogel dressings are semi-transparent, non-adherent hydrogels which are customarily constructed in sheets, but can be supplied in other forms, such as a gel. Although primarily designed to donate moisture to dry wounds, these dressings have a moderate absorptive capacity owing to their composition of insoluble polymers with hydrophilic substitutes.[10] Like other occlusive dressings, a particular advantage of hydrogel dressings is promoting debridement by inducing autolysis. An example of this dressing type is Tegagel (3M, Bracknell, U.K.). They are not typically recommended for venous ulcers due to their limited absorptive capacity.

51.2.2.3 FILM

Film dressings are composed of a transparent and adherent polyurethane which permits transmission of water vapor, oxygen, and carbon dioxide from the wound. While this dressing protects and insulates the wound, it also provides autolytic debridement of the eschar.[11] There are several drawbacks to the film dressings: (1) their lack of significant absorption capabilities; and (2) pooling of drainage under the dressing with resultant maceration of the surrounding skin. Examples of this type of dressing are Opsite (Smith & Nephew Healthcare Ltd, Hull, U.K.) and Tegaderm (3M, Bracknell, U.K.).

Table 51.2 Individual dressing types in non-occlusive/semi-occlusive dressing classes

Subtype	Composition	General properties	Capacity for wound fluid absorption	Commercial example
Non-occlusive				
Wound dressing pads	Gauze	Protects wound; dry → adheres to wound	Limited	Dry sterile dressing
Tulle gras	Woven fabric Impregnated with paraffin	Protects wound; less adherent	None	
Non-adherent	Various synthetic; configured in pores	Protects wound; permits drainage	None	Tegapore polyamide Mepitel silicone Adaptic synthetic
Semi-occlusive/occlusive				
Film	Transparent and adherent polyurethane	Transmits H_2O, O_2, and CO_2; protects and insulates	None	Tegaderm Opsite
Hydrocolloid	Water-impermeable outer layer → polyurethane; hydrocolloid inner layer	Less permeable than films; protects and insulates	Moderate	DuoDerm, Comfeel
Hydrogels	Semi-transparent, non-adherent hydrogels → insoluble polymers with hydrophilic subtitles	Protection	Moderate	Tegagel
Foam	Silastic or polyurethane foam sheets or liquids; hydrophobic layer	Permeable to gases and H_2O prevents penetration of liquid	Moderate	Allevyn
Alginate	Derived from brown seaweed	Insoluble alginate converted to soluble salt → hydrophilic gel	Greatest	Sorbsan

Source: Adapted from O'Donnell TF Jr. et al. *J Vasc Surg* 2014;60:3S–59S; Falanga V. *J Invest Dermatol* 1993;100:721–5.

51.2.2.4 FOAM

Foam dressings have the potential for absorbing considerable quantities of wound exudate and are typically a composite of two materials: silastic and polyurethane foam. The hydrophobic properties of the dressing's outer layer prevent penetration of liquid, but the dressing is permeable to gases and water vapor.[12] Allevyn (Smith & Nephew Healthcare Ltd, Hull, U.K.) is an example of this dressing type.

51.2.2.5 ALGINATES

Sodium alginate derived from brown seaweed is the major component of this dressing. Alginates' great absorptive capabilities as well as their use in infected wounds are their chief advantages.[13] Sorbsan (Pharma-Plast Ltd, Alexandria, Egypt) is an example of this dressing type.

51.2.3 Biologic dressings

A variety of therapies have been developed to apply to venous ulcers as active therapies in order to stimulate acceleration of healing in addition to standard care. These strategies include a diverse group of Food and Drug Administration (FDA)-approved products which may be characterized as: (1) living cellular constructs; (2) platelet products, either autologous or recombinant (DNA technology); (3) collagen matrix products; and (4) tissue products derived from amniotic membrane (Figure 51.1c).

Currently, there is only one type of living cellular construct approved in the United States for the treatment of venous leg ulcers (VLUs). This product, Apligraf (Organogenesis, Canton, MA), is composed of keratinocytes (cells occupying the outer layer of the skin or epidermis) as well as fibroblasts (the dermis) on a bovine type I collagen matrix.[14] The keratinocytes are derived from cultured neonatal foreskin cells and differentiate to simulate the anatomy of human skin. Blood vessels, melanocytes, hair follicles, and sweat glands, however, are not present in this skin substitute.

Although living cellular therapies provide temporary epithelial coverage of the wound, their main mechanism of action is through the secretion and stimulation of wound growth factors and cytokines. Endogenous cells migrate into the wound to promote healing. Clinical studies with Apligraf have shown that the cells from the construct do not persist for longer than 4–6 weeks, so reapplication at routine intervals is recommended in order to maximize the healing potential.[15]

Platelet-derived products have been developed for the treatment of venous ulcers and are clinically available.

These typically require a specific process in the clinic to obtain blood from the patient, followed by processing to separate the platelets and the application of a procedure to release the contents of the platelets to create the platelet releasate for application to the wound bed and stimulation of healing.

Multiple collagen matrix products are available for use in venous ulcers, being sourced from a variety of animal tissues. These products are believed to provide the collagen substrate and, in some cases, active growth factors to stimulate accelerated ingrowth of cells in order to granulate and close the wound. Oasis (Smith and Nephew Healthcare Ltd, Hull, U.K.) is an example of this type of therapy.

Recently, amniotic membrane tissues have been developed for use in numerous medical conditions, including chronic wounds. In theory, these membranes contain progenitor cells, growth factors and other proteins that are believed to be beneficial for wound healing. Epifix (MiMedx Group, Inc., Marietta, GA) is an example of this type of therapy.

51.3 STANDARD OR USUAL CARE IN THE MANAGEMENT OF VENOUS ULCERS

To determine what is the customary care provided for venous ulcers, authoritative texts or clinical guidelines provide some information. To better define the elements of care supported by a higher level of evidence, the following sources were employed: in 2006, O'Donnell and Lau published a review of all RCTs published since 1997 that described the treatment of venous ulcers by wound dressings, as well as other chronic wounds.[16] This start date was chosen because it coincided with the completion (end date) of a previous systematic review conducted by the National Health Services Health Technology Assessment Survey (NHS-TAS).[17] Only RCTs were assessed because these level 1 trials characteristically have the most extensive description of the background care compared with other, less rigorous study designs. The control arm of the RCT was designated as the "usual care group." The SVS/AVF guidelines for the care of venous ulcers were used as well, as this document contains a review of the literature on the relevant areas up to 2014.[5]

51.4 CURRENT RECOMMENDATIONS FOR LOCAL CARE OF THE WOUND

51.4.1 Wound bed preparation

The SVS/AVF guidelines, as well as most other recent guidelines on the care of venous ulcers, have defined the following key elements of wound bed preparation: (1) debridement of the non-vital tissue from the wound, which provides a nidus for bacterial infection; (2) cleansing the wound; (3) controlling bacterial colonization with wound care, while treating true wound infection aggressively with antibiotics; (4) providing optimal moisture and temperature balance, usually by the wound dressing; (5) optimizing general nutrition; and (6) employing mechanical measures that favorably alter local hemodynamics (discussed in other chapters).[5]

51.4.2 Wound debridement (surgical and non-surgical)

To accomplish surgical wound debridement, the use of a scalpel is most expeditious. Surgical debridement requires some degree of skill to differentiate between normal and abnormal tissue—the detritus of cells and devitalized tissues which are located predominantly on the surface and margins of the wound. Debridement of necrotic tissue is generally performed to reduce the potential for delayed wound healing by the accumulation of these breakdown products as well as gross bacterial infection, which in itself leads to persistent inflammation.

Although protocols for the management of VLUs usually recommend wound debridement to remove non-viable tissue and to reduce bacterial burden, there is a lack of robust evidence that routine wound debridement accelerates wound healing. Williams et al.[18] have shown in a concurrent controlled prospective cohort study of 45 patients that debridement of a venous ulcer is an independent factor which promotes wound healing. A four-fold greater proportion of ulcers in the debrided group achieved complete healing than in the control group. Cardinal et al.[19] reviewed the relationship of debridement with ulcer healing in two prospective RCTs of topical wound treatments on 366 VLUs and 310 diabetic foot ulcers. VLUs treated at a clinic visit with debridement had a significantly higher median wound surface area reduction in the week after debridement than did those for which debridement was not performed. However, debridement frequency per patient did not statistically correlate with rates of wound closure.

Recommendations to debride non-viable or necrotic tissue from the wound bed are supported by established principles of the management of all wounds.[20,21] However, the frequency and methods of debridement are not well studied and have not been well established as they relate to the incidence of wound closure.[22]

No method of debridement has been proved to be superior to surgical methods. However, in some cases, patients may not have ready access to a clinician who is trained to perform surgical debridement, or this method may be less desirable because of comorbid patient conditions or pain considerations. Hydrosurgical debridement was found in some studies to shorten the procedural time of debridement, but may be associated with significant additional cost.[23,24] Enzymatic debridement, which does not require a trained clinician for application, has been found in several studies to remove non-viable tissue from VLU wound beds, but there is no evidence that this method provides a benefit over surgical debridement.[25,26] In clinical trials, larval therapy along with compression has been shown to be an effective method of debridement. However, the use of larval therapy did not increase the rate of healing of necrotic tissue

or slough in leg ulcers compared with ulcers treated with hydrogel and compression.[27,28]

51.4.3 Wound cleansing

Although there is little evidence that the routine use of a wound cleanser results in improvement of VLU outcomes measures, most patients with VLUs present with significant wound exudate and other debris in and around the wound area that must be cleansed routinely before dressing application. Numerous cleansing solutions have been described in this role with reasonable success.[29] It appears that the main selection factor is to avoid routine use of a cleanser that would result in toxicity to the viable tissue in the wound bed.[30]

51.4.4 Antimicrobials and bacterial control

The management of the bacterial involvement in chronic VLUs is controversial, with limited high-quality research and contradictory results in the studies available for review. Although there is general agreement among experts that wounds with obvious signs of clinical infection should be treated with systemic antibiotics, there is no consensus on the management of wounds colonized by bacteria or bacterial biofilms without signs of systemic infection.[5] The definition of a critically colonized wound is not universally standardized and may vary by the virulence of the colonizing bacteria.

Although there is a lack of clinical studies evaluating the specific treatment of infected VLUs, the available evidence supports systemic antibiotic treatment of patients with clinical evidence of infection and ulcers containing $>1 \times 10^6$ colony-forming unit (CFU)/g of bacteria on quantitative culture.[31] Aggressive mechanical debridement of infected VLUs whenever possible is also suggested, although there is a lack of high-quality evidence indicating that debridement improves results in the treatment of infected or heavily colonized ulcers.

The NHS-HTA (National Health Services-Health Technology Assessment) performed a systematic review of both systemic and topical antimicrobials, which included RCTs of two systemic antibiotics and seven topical antibiotics for venous ulcers.[32] Neither of the two RCTs of systemic antibiotics showed improvement in ulcer healing. There has been a great deal of enthusiasm for silver-based wound dressings because of their purported activity against a wide range of bacteria. Three RCTs using this type of dressing focused on the primary endpoint of complete wound healing. While an activated charcoal dressing impregnated with silver showed an early advantage in terms of reduction of wound size, as did another RCT in which silver sulfadiazine was used, neither trial showed superiority of wound healing over the control group at the end of the trial. A Cochrane review on the use of topical silver for infected VLUs concluded that there is insufficient evidence to recommend the use of silver-containing dressings or topical agents for the treatment of infected or contaminated chronic wounds.[33]

In the only prospective RCT of topical antibiotics, which examined the treatment of non-infected VLUs, Michaels et al.[34] randomized 213 patients with VLUs to silver-releasing dressings compared with non-silver-releasing dressings. No significant differences in ulcer healing or other quality of life measures were identified in the silver dressing group. Given the increased cost of silver-containing dressings, routine use of topical antimicrobial dressings for the treatment of VLUs is not supported.[35,36]

51.4.5 Management of pain

A frequent problem with venous ulcers is the complication of pain, which may be worsened with dressing changes or certain treatments such as debridement. A Cochrane review presented a meta-analysis of six trials, which showed a significant advantage of a eutectic mixture of a local anesthetic (lidocaine–prilocaine) cream compared to placebo in the reduction of pain at the time of wound debridement.[37]

51.4.6 Compression bandaging

Finally, compression bandaging and/or elastic stockings, as demonstrated in Chapter 31, are the essential elements to favorably modify local hemodynamics and eliminate the inflammatory effect of chronic venous hypertension.[4]

51.5 SELECTION OF A WOUND DRESSING FOR VENOUS ULCERS

The type of dressing chosen for a venous ulcer will depend on many factors, a number of which are related to the wound: (1) wound drainage; (2) potential infection (i.e., bacterial burden); (3) eschar formation; and (4) the amount and type of granulation tissue present. Other important considerations are the patient's acceptance of the dressing and the pain relief or exacerbation provided by the dressing. Finally, the choice of a wound dressing is also influenced by the complexity of the application process of the dressing, its cost, and the frequency of dressing applications.

A basic principle of wound dressings is that no dressing truly fits all wound types. Dressing types may be changed as the character of the wound changes. The optimal dressing for a large, heavily exudative wound with extensive periulcer inflammation is likely to be different from a small, granulating wound that is progressing towards closure. Most VLUs produce large amounts of exudate. As noted above, this fluid contains high concentrations of proteases and inflammatory cytokines that may damage surrounding healthy skin.[6] Removal of wound drainage from the wound bed will reduce the inflammatory environment that prohibits wound healing. We recommend the use of dressings that will manage the wound exudate and maintain a moist wound bed. Primary dressings with high absorptive capabilities, including foams, alginates, and other specialty dressings, are often selected for the primary coverage layer for heavily exudative VLUs.[35]

At each visit, the wound must be carefully evaluated to determine its status and the factors affecting its healing process. Measurement of wound size at each visit is important to determine the progress with the current treatment plan. Wounds making significant progress using a specific treatment plan may usually continue with this plan until progress slows or ceases. It has been reported that wounds that close by 30%–40% over 4 weeks of treatment have a high rate of complete closure within 12 weeks of treatment. Wounds that do not achieve this percentage of closure at 4 weeks were completely healed in <20% of cases after 12 weeks of treatment.[38] For recalcitrant wounds, complete re-evaluation of the etiology of the wound should be performed, considering the potential for associated arterial insufficiency, vasculitis, or other confounding variables that would delay healing. In addition, it should be confirmed that the patient is compliant with sufficient compression to eliminate venous hypertension and that other components of wound bed preparation have been addressed. If these are correct and wound improvement remains slow, adjuvant wound therapies should be considered.[5]

51.6 ADJUVANT WOUND THERAPIES

51.6.1 Split-thickness skin grafting

There is currently insufficient information to recommend the use of autologous skin grafting as a primary therapy for VLUs. Studies in this area have biases, small sample sizes, and indirect comparators. A Cochrane review on skin grafting for VLUs also found that the available evidence did not support a definitive recommendation.[39] Although definitive evidence is lacking, some clinicians consider skin grafting in slow-responding wounds or for patients with large soft tissue deficits that are able to granulate well in order to provide a clean, healthy bed to support graft take. In a non-randomized study of 111 patients, Jankunas[40] demonstrated improved healing and durability with skin grafting compared with conservative therapy for large venous wounds that were present for longer than 6 months, but only 65% of cases were judged to have good take of the split-thickness skin graft.

51.6.2 Living cellular therapies

Apligraf, an allogeneic bilayer cellular therapy, was approved by the FDA for the treatment of VLUs in 1998. The product is recommended only after appropriate wound bed preparation is performed, including complete removal of non-viable tissue and eschar from the wound bed. It is also recommended that the level of bacteria in the wound bed be evaluated and controlled prior to living cellular treatment.[5] The efficacy of Apligraf was studied in an RCT of 245 patients with VLUs treated with standard of care compared with standard of care plus the application of Apligraf.[41] VLUs had been present for at least 6 weeks and had not responded well to the initial use of compression and the other aspects of standard care. Subsequent research has identified improved outcomes for recalcitrant VLUs (>1 year duration or large surface area). In these difficult-to-heal ulcers, closure occurred in 47% of Apligraf-treated ulcers after 6 months compared to 19% of patients treated with standard of care ($P < 0.01$).[42] Given that the applied cells do not persist for long periods of time, reapplication is recommended at 1–3–week intervals if needed to continue to support wound healing.[5] No other living cellular therapies have demonstrated benefit for the treatment of VLUs in prospective RCTs.

51.6.3 Tissue matrices and other biologic therapies

Numerous tissue constructs are available for use in chronic wounds that employ either human tissue (amniotic membrane or cryopreserved skin) or animal tissue (bladder, fetal bovine skin, or others). Some are reported to contain active growth factors or other attributes that might be beneficial to the healing of VLUs.[43] Of the multitude of such products currently marketed, only porcine small intestinal submucosa (SIS; Oasis, Healthpoint, Ft. Worth, TX) has prospective RCT data supporting its use in accelerating VLU closure.[44] In this randomized trial, 120 patients were allocated to standard VLU care with compression and wound bed preparation compared to standard care plus weekly application of SIS. At 12 weeks, a significantly higher incidence of closure occurred in SIS-treated patients (55%) compared to standard care (34%).

51.6.4 Negative pressure wound therapy

This mechanical method of wound care induces a local sub-atmospheric pressure on the wound. The putative advantages of this technique are increased growth factor production, control of wound exudates, removal of bacteria, and increased blood flow.[45] There is currently not enough information to support the primary use of negative pressure wound therapy for VLUs. Evidence supports positive effects of its use for wound healing in general. Tissue granulation, area and volume reduction, and reductions in bioburden have all been reported. Clinical studies have reported accelerated healing of diabetic foot ulcers treated with negative pressure wound therapy, but no robust randomized studies have been reported using this modality for the treatment of VLUs.

51.6.5 Physical measures

Various techniques such as laser, therapeutic ultrasound, electrotherapy, and electromagnetic therapy have been explored in a limited number of small, poorly designed RCTs.[5,46] One small study showed a slight advantage for limbs treated with laser and infrared light, but its sample size limits firm conclusions. Of seven RCTs on therapeutic ultrasound and three on electromagnetic therapy, no clear-cut superiority was observed for either modality.

Guidelines 4.23.0 of the American Venous Forum of the local treatment of venous ulcers

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.23.1	For wound cleansing, we suggest that venous leg ulcers be cleansed initially and at each dressing change with a neutral, non-irritating, non-toxic solution, performed with a minimum of chemical or mechanical trauma.	2	C
4.23.2	We recommend that venous leg ulcers receive thorough debridement at their initial evaluation to remove obvious necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells.	1	B
4.23.3	We suggest maintenance debridement to maintain the appearance and readiness of the wound bed for healing and suggest choosing one or more from several debridement methods, including sharp, enzymatic, mechanical, biologic, and autolytic.	2	B
4.23.4	We recommend local anesthesia (topical or local injection) to minimize the discomfort associated with surgical ulcer debridement. In selected cases, regional block or general anesthesia may be required.	1	B
4.23.5	We recommend surgical debridement for venous leg ulcers with slough, non-viable tissue, or eschar. Serial wound assessment will determine the need for repeated debridement.	1	B
4.23.6	We suggest hydrosurgical debridement as an alternative to standard surgical debridement.	2	B
4.23.7	We suggest against ultrasonic debridement over surgical debridement.	2	C
4.23.8	We suggest against enzymatic debridement over surgical debridement, with the exception of when no clinician trained in surgical debridement is available.	2	C
4.23.9	We suggest larval therapy for ulcers as an alternative to surgical debridement.	2	B
4.23.10	We recommend systemic Gram-positive antibiotic treatment for cellulitis surrounding the ulcer.	1	B
4.23.11	We suggest against systemic antimicrobial treatment of venous leg ulcer colonization or biofilm without clinical evidence of infection.	2	C
4.23.12	We suggest antimicrobial therapy for ulcers with clinical evidence of infection and $>1 \times 10^6$ CFU/g of tissue, or at lower levels of colony-forming units per gram of tissue in the presence of virulent or difficult-to-eradicate bacteria (such as β-hemolytic streptococci, *Pseudomonas*, and resistant staphylococcal species). We suggest a combination of mechanical disruption and antibiotic therapy as most successful in eradicating venous leg ulcer infection.	2	C
4.23.13	We recommend oral systemic antibiotics, guided by sensitivities performed on wound culture, for ulcers with clinical evidence of infection. The duration of antibiotic therapy should be limited to 2 weeks unless wound infection persists.	1	C
4.23.14	We suggest against the use of topical antimicrobial agents for the treatment of infected ulcers.	2	C
4.23.15	We suggest a topical dressing that will manage ulcer exudate and maintain a moist, warm wound bed.	2	C

(*Continued*)

Guidelines 4.23.0 of the American Venous Forum of the local treatment of venous ulcers

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.23.16	We suggest selection of a primary wound dressing that absorbs wound exudate produced by the ulcer (alginates and foams) and protects the skin around the ulcer.	2	B
4.23.17	We suggest against the routine use of topical antimicrobial-containing dressings in the absence of infection.	2	A
4.23.18	We suggest lubricants underneath compression to reduce the dermatitis that commonly affects peri-ulcer skin. If severe dermatitis is associated, we suggest topical steroids.	2	C
4.23.19	We suggest against use of anti-inflammatory therapies for the treatment of venous leg ulcers.	2	C
4.23.20	We recommend adjuvant wound therapy options for non-healing ulcers after standard therapy for 4–6 weeks.	1	B
4.23.21	We suggest against split-thickness skin grafting as the primary therapy of venous ulcers, but suggest it for large ulcers without signs of healing for 4–6 weeks.	2	B
4.23.22	We suggest the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) in non-healing ulcers after standard therapy for 4–6 weeks.	2	A
4.23.23	We suggest a trial of compression and wound moisture control before cellular therapy.	2	C
4.23.24	Before using a bi-layered cellular graft, we recommend wound bed preparation, including complete removal of slough, debris, and any necrotic tissue. We also recommend additional evaluation and management of increased bioburden levels.	1	C
4.23.25	We suggest reapplication of cellular therapy as long as the ulcer continues to respond.	2	C
4.23.26	We suggest porcine small intestinal submucosal tissue constructs for the treatment of non-healing ulcers after standard therapy for 4–6 weeks.	2	B
4.23.27	We suggest against routine primary use of negative pressure wound therapy for venous leg ulcers.	2	C
4.23.28	We suggest against electrical stimulation therapy for venous leg ulcers.	2	C
4.23.29	We suggest against routine ultrasound therapy for venous leg ulcers.	2	B

Source: Adapted from O'Donnell TF Jr. et al. *J Vasc Surg* 2014;60:3S–59S.

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Guidelines for the treatment of chronic venous disease in patients with venous ulcers

THOMAS F. O'DONNELL JR. AND MARC A. PASSMAN

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52.1 INTRODUCTION

Venous leg ulcers (VLUs) are a major health care problem due to their prevalence of approximately 1.0%–1.5% of the population and significant potential socioeconomic impact with a need for significant resource utilization, as well as their potential for prolonged disability. Since approximately 50% of VLUs may recur within 10 years, they are marked by a dominant component of chronicity, which extends the need for repetitive care and compounds their economic impact. In addition to the direct cost of treating an open VLU, which averaged nearly $16,000/year overall in a recent study, the indirect burden of the lost wages of the patient as well as those of their family members is significant.[1]

While there are various treatment protocols for VLUs, they differ in efficacy, quality, and cost. A more uniform method of treatment for VLUs based on clinical evidence for efficacy may improve therapeutic effectiveness, increase healing rates, decrease potential recurrence, and possibly reduce cost.[2–5] However, widespread implementation of VLU guidelines has been a challenge, highlighting the need for a consensus guideline for VLU management.[6] Recognizing this gap, in 2014, the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) published a comprehensive set of clinical practice guidelines for the management of VLUs addressing the management of VLUs at all levels of care based on the strength and quality of supporting evidence guiding specific recommendations.[7] This chapter summarizes the current SVS/AVF clinical practice guidelines for the management of VLUs.

52.2 METHODOLOGY

A joint SVS/AVF Venous Ulcer Guidelines Committee was organized in 2012 with a sub-committee structure covering the important areas required for the comprehensive document: diagnosis, compression, surgery/endovascular, wound care, ancillary, and prevention. The overall committee developed a series of key clinical questions to guide the overall approach for the guideline document. All guidelines were developed by building on existing guidelines with a complimentary literature search by the section sub-committee and the development of *de novo* guidelines for identified gaps in current guideline recommendations. The need for a systematic and meta-analytical review was determined. Based on several key questions, the surgery/endovascular and compression sections were selected for *de novo* development of specific guideline recommendations, and an independent group of researchers was commissioned to conduct two systematic reviews to evaluate the effectiveness of different compression strategies and endovascular and open surgical approaches.[8,9]

Through a systematic process, the committee developed guidelines based on the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) system (Table 52.1).[10,11] Using the GRADE system, the strength of the recommendation or the extent to which one can be confident that adherence to the recommendation will do more good than harm was divided into: [1] strong (we recommend), favoring benefit over harm; and [2] weak (we suggest), with benefits closely balanced by the risk.[12] The "quality of evidence" or the extent to which confidence in an estimate of affect is sufficient to support a particular recommendation was graded as [A], [B], or [C] using standard evidenced-based methodological criteria. When there were no comparable alternatives to a recommendation or evidence was lacking but was supported by the best opinion of a panel of experts, the recommendation was labeled as [BEST PRACTICE]. An independent review of

Table 52.1 Grading of Recommendation Assessment, Development, and Evaluation (GRADE) recommendations based on level of evidence

Grade	Description of recommendation	Benefit vs. risk	Methodological quality of supporting evidence	Implications
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Randomized controlled trials without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Randomized controlled trials with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low-quality or very-low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher-quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	Randomized controlled trials without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	Randomized controlled trials with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2C	Weak recommendation, low-quality or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; risks, benefits, and burdens may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be reasonable

Source: Adapted from Guyatt G et al. *Chest* 2006;129:174–81.

GRADE assignments made by the Venous Ulcer Guideline Committee was also performed by independent epidemiologists to corroborate the proper strength of evidence and quality of evidence for each guideline. The final document was reviewed by the entire committee for concurrence. An additional independent review was obtained from selected reviewers representing multiple medical specialties vested in venous ulcer management. The final document was then reviewed and approved by the SVS Document Oversight Committee and approved by the Executive Committees of the SVS and AVF. The VLU Guidelines were endorsed before publication by the American College of Phlebology and Union Internationale de Phlebologie, and they were endorsed post-publication by the American College of Wound Healing and Tissue Repair.

52.3 PRACTICE GUIDELINES

52.3.1 Definition of venous ulcer, venous anatomy, and pathophysiology

GUIDELINE 1.1: VENOUS LEG ULCER DEFINITION

We suggest use of a standard definition of venous ulcer as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension. [BEST PRACTICE]

GUIDELINE 2.1: VENOUS ANATOMY NOMENCLATURE

We recommend use of the International Consensus Committee on Venous Anatomical Terminology for standardized venous anatomy nomenclature. [BEST PRACTICE]

GUIDELINE 2.2: VENOUS LEG ULCER PATHOPHYSIOLOGY

We recommend a basic practical knowledge of venous physiology and venous leg ulcer pathophysiology for all practitioners caring for venous leg ulcers. [BEST PRACTICE]

For use of VLU guidelines, a standard definition of VLUs, use of consensus anatomic terminology, and an understanding of pathophysiology are critically important. VLU was defined as "an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension." While VLUs usually occur in direct relation to venous pathophysiology, they can also occur as mixed ulcers, representing other contributing etiologies, such as arterial ischemia, scarred tissue of the gaiter area, hypersensitive skin, lymphedema, autoimmune disease, local trauma, infection, etc.

Anatomically, veins of the lower extremities are divided into superficial, deep, and perforating venous systems. However, there has been variability in nomenclature for specific veins in the leg within each system. For practitioners caring for patients with VLUs, correct standardized venous nomenclature should be used as defined by the 2002 International Consensus Committee on Venous Anatomical Terminology and updated in 2005.[13,14] Furthermore, while recognizing that venous hypertension is the result of reflux and/or obstruction as a focal phenomenon in the distal extremity or as a central mechanism, additional biochemical factors due to activation of the inflammatory cascade can also play a role. Understanding the complex pathophysiology of VLUs is also important for effective implementation of treatment strategies.

52.3.2 Clinical evaluation

GUIDELINE 3.1: CLINICAL EVALUATION

We recommend that for all patients with suspected leg ulcers fitting the definition of venous leg ulcer, clinical evaluation for evidence of chronic venous disease be performed. [BEST PRACTICE]

GUIDELINE 3.2: NON-VENOUS CAUSES LEG ULCERS

We recommend identification of medical conditions that affect ulcer healing and other non-venous causes of ulcers. [BEST PRACTICE]

GUIDELINE 3.3: WOUND DOCUMENTATION

We recommend serial venous leg ulcer wound measurement and documentation. [BEST PRACTICE]

GUIDELINE 3.4: WOUND CULTURE

We suggest against routine culture of venous leg ulcers and to only obtain wound cultures when clinical evidence of infection is present. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 3.5: WOUND BIOPSY

We recommend wound biopsy for venous leg ulcers that do not improve with standard wound and compression therapy after 4–6 weeks of treatment and for all ulcers with atypical features. [GRADE: 1; LEVEL OF EVIDENCE: C]

GUIDELINE 3.6: LABORATORY EVALUATION

We suggest laboratory evaluation for thrombophilia for patients with a history of recurrent venous thrombosis and chronic recurrent venous leg ulcers. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 3.7: ARTERIAL TESTING

We recommend arterial pulse examination and measurement of Ankle–Brachial Index on all patients with venous leg ulcer. [GRADE: 1; LEVEL OF EVIDENCE: B]

GUIDELINE 3.8: MICROCIRCULATION ASSESSMENT

We suggest against routine microcirculation assessment of venous leg ulcers, but suggest selective consideration as an adjunctive assessment for the monitoring of advanced wound therapy. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 3.9: VENOUS DUPLEX ULTRASOUND

We recommend comprehensive venous duplex ultrasound examination of the lower extremity in all patients with suspected venous leg ulcer. [GRADE: 1; LEVEL OF EVIDENCE: B]

GUIDELINE 3.10: VENOUS PLETHYSMOGRAPHY

We suggest selective use of venous plethysmography in the evaluation of patients with suspected venous leg ulcer if venous duplex ultrasound does not provided definitive diagnostic information. [GRADE: 2; LEVEL OF EVIDENCE: B]

GUIDELINE 3.11: VENOUS IMAGING

We suggest selective computed tomography venography, magnetic resonance venography,

contrast venography, and/or intravascular ultrasound in patients with suspected venous leg ulceration if additional advanced venous diagnosis is required for thrombotic or non-thrombotic iliac vein obstruction, or for operative planning prior to open or endovenous venous interventions. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 3.12: VENOUS DISEASE CLASSIFICATION

We recommend that all patients with venous leg ulcer should be classified based on venous disease classification assessment including clinical CEAP, revised Venous Clinical Severity Score, and venous disease-specific quality of life assessment. [BEST PRACTICE]

GUIDELINE 3.13: VENOUS PROCEDURAL OUTCOME ASSESSMENT

We recommend venous procedural outcome assessment, including reporting of anatomic success, venous hemodynamic success, procedure-related minor and major complications, and impact on venous leg ulcer healing. [BEST PRACTICE]

For a leg ulcer to be classified as a VLU, there needs to be clinical manifestations consistent with venous disease. Clinical evaluation should differentiate primary, secondary, or congenital venous problems and establish the presence or absence of venous reflux, obstruction, or both. A thorough medical history should be performed to identify venous symptoms, risk factors for venous disease, the presence of other systemic diseases associated with leg wounds, and other possible associated medical factors that may contribute to non-healing leg wounds. Physical examination should identify signs of venous disease and include: inspection for telangiectasia, varicose veins, edema, chronic venous skin changes (skin discoloration, inflammation, eczema, hyperpigmentation, malleolar flair, corona phlebectatica, atrophie blanche, and lipodermatosclerosis), healed ulcer, and active ulcer; palpation for varicosity, palpable venous cord, tenderness, induration, edema, and pulses; auscultation for bruit and reflux; and evaluation of ankle mobility. Differentiation of VLUs from non-VLUs is important prior to the initiation of therapy by identifying other medical conditions that can cause leg ulcers and affect ulcer healing.

VLU wound measurement and documentation is important as a baseline and for determining the effect of subsequent treatment measures on healing parameters. Documentation should include the number and positions of ulcers on the leg. Wound measurements should be made for each VLU, including area, perimeter, and depth, with additional descriptors of wound edge parameters, wound base quality, drainage, and infection. Adjuncts for the standardization of ulcer documentation, including wound planimetry, digital photography, and digital planimetry software, are recommended.

There is no evidence to support routine microbiology surface cultures of VLUs in the absence of clinical signs of infection, as these wounds are usually colonized by multiple microorganisms. For patients with VLUs that develop associated clinical signs of infection, microbiology cultures can be obtained from the wound surface or wound drainage using validated quantitative bacteriology swab methods. Deep wound tissue cultures should be reserved for wounds colonized by multiple microorganisms when the bacterial pathogen is not clear from surface cultures, biofilm infections, or for recurrent or persistent infection despite appropriate antimicrobial therapy. When VLUs do not respond to standard wound and compression therapy, additional contributing factors should be considered along with tissue biopsy within 4–6 weeks of non-responsiveness to standard treatment. The biopsy should be obtained from several sites, including the wound edge and central provisional matrix.

Because adequate arterial perfusion is needed for improved healing, it is important to confirm the presence or absence of underlying peripheral arterial disease (PAD). Evaluation should include the identification of possible PAD risk factors, symptoms and signs of PAD, and comprehensive arterial examination. Lower extremity Ankle–Brachial Index (ABI) should be determined in all patients, and for ABI $\leq$0.90, referral should be made to a vascular specialist for further arterial evaluation and possible revascularization consideration prior to VLU compression or operative therapy.

By definition, for a leg ulcer to be a VLU, there needs to be objectively documented evidence of venous disease. Ultrasound assessment needs to include evaluation for both obstructive and reflux patterns of venous disease. Venous duplex ultrasound not only provides diagnostic utility, but also identifies patterns of venous disease that may have therapeutic implications. Additional venous plethysmography (strain gauge, air, or photoplethysmography), which provides additional venous limb physiologic parameters regarding global venous reflux, outflow obstruction, and calf muscle pump function, has shown a good correlation with venous duplex ultrasound. This additional examination should be reserved for equivocal venous duplex ultrasound examination, recalcitrant or recurrent VLU, or if additional venous physiologic testing is required for diagnostic or therapeutic reasons. When venous outflow obstruction is suspected, additional contrast imaging with computed tomography venography or magnetic resonance venography may also be indicated. While screening computed tomography venography and magnetic resonance venography may provide additional information regarding potential venous outflow obstruction, diagnosis should be confirmed by contrast venography and intravascular ultrasound.

Because accurate classification of venous disease is critically important for standardization of venous disease severity and assessment of treatment effectiveness, classification systems for reporting venous disease severity should be used, including CEAP and Venous Clinical Severity Score, in all patients with VLU.[15–17] In addition, for patients with post-thrombotic syndrome, Villalta score should also be used. Additional evidence supports the inclusion of venous disease-specific quality of life more than generic quality of life as complementary to these other venous assessment tools. For all patients with VLUs who require venous endovascular or operative intervention, outcome assessment should be performed in order to determine the success of the procedure over time.

52.3.3 Wound

Local treatment of the wounds and the SVS/AVF Guidelines 4.1–4.26 on the evidence of efficacy for different local treatments of venous ulcers are discussed in great detail in the preceding chapter of this book, and so readers are invited to consult Chapter 51 on this topic.

52.3.4 Compression

GUIDELINE 5.1: COMPRESSION—ULCER HEALING

In a patient with a venous leg ulcer, we recommend compression therapy over no compression therapy to increase venous leg ulcer healing rate. [GRADE: 1; LEVEL OF EVIDENCE: A]

GUIDELINE 5.2: COMPRESSION—ULCER RECURRENCE

In a patient with a healed venous leg ulcer, we suggest compression therapy to decrease the risk of ulcer recurrence. [GRADE: 2; LEVEL OF EVIDENCE: B]

GUIDELINE 5.3: MULTI-COMPONENT COMPRESSION BANDAGE

We suggest the use of a multi-component compression bandage over single-component bandages for the treatment of venous leg ulcers. [GRADE: 2; LEVEL OF EVIDENCE: B]

GUIDELINE 5.4: COMPRESSION—ARTERIAL INSUFFICIENCY

In a patient with a venous leg ulcer and underlying arterial disease, we do not suggest compression bandages or stockings if the Ankle–Brachial Index is 0.5 or less or if absolute ankle pressure is less than 60 mmHg. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 5.5: INTERMITTENT PNEUMATIC COMPRESSION

We suggest using intermittent pneumatic compression when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy. [GRADE: 2; LEVEL OF EVIDENCE: C]

For the treatment of VLU, compression is critical to providing hemodynamic improvement of the dysfunctional venous pumping function. The preponderance of evidence suggests that VLUs heal more quickly with compression therapy versus no compression, and multi-component is preferred over single-component dressings. Once the VLU is healed, there is additional evidence supporting the effect of compression on ulcer recurrence.

For patients with VLU and concomitant PAD, use of standard compression has been shown to be safe if ABI is ≥0.80. Modified compression bandages or compression stockings with lower pressure ratings can be used for ankle systolic pressures of ≥60 mmHg, digital pressures of ≥30 mmHg, or ABI of ≥0.50 with close monitoring, but only after consultation with a vascular specialist. Use of ankle perfusion pressures of 60 mmHg or greater rather than ABI of ≤0.5 as a cut-off for compression is preferred, since this correlates better with tissue perfusion pressure, and any sustained external compression pressure should never exceed this cutoff perfusion pressure.

Intermittent pneumatic compression has shown promise for decreasing VLU healing times in patients who had previously failed conservative treatment, but further studies are needed in order to fully evaluate the benefit of intermittent pneumatic compression as a primary therapy.

52.3.5 Operative/endovascular treatment

GUIDELINE 6.1: SUPERFICIAL VENOUS REFLUX AND ACTIVE VENOUS LEG ULCER—ULCER HEALING

In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we suggest ablation of the incompetent veins in addition to standard compressive therapy to improve ulcer healing. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.2: SUPERFICIAL VENOUS REFLUX AND ACTIVE VENOUS LEG ULCER—PREVENT RECURRENCE

In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux

directed to the bed of the ulcer, we recommend ablation of the incompetent veins in addition to standard compressive therapy to prevent recurrence. [GRADE: 1; LEVEL OF EVIDENCE: B]

GUIDELINE 6.3: SUPERFICIAL VENOUS REFLUX AND HEALED VENOUS LEG ULCER

In a patient with a healed venous leg ulcer (C5) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we recommend ablation of the incompetent veins in addition to standard compressive therapy to prevent recurrence. [GRADE: 1; LEVEL OF EVIDENCE: C]

GUIDELINE 6.4: SUPERFICIAL VENOUS REFLUX WITH SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B)

In a patient with skin changes at risk for venous leg ulcer (C4b) and incompetent superficial veins that have axial reflux directed to the bed of the affected skin, we suggest ablation of the incompetent superficial veins in addition to standard compressive therapy to prevent ulceration. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.5: COMBINED SUPERFICIAL/ PERFORATOR VENOUS REFLUX WITH OR WITHOUT DEEP VENOUS REFLUX AND ACTIVE VENOUS LEG ULCER

In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins, in addition to standard compressive therapy to aid in ulcer healing and prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.6: COMBINED SUPERFICIAL AND PERFORATOR VENOUS REFLUX WITH OR WITHOUT DEEP VENOUS DISEASE AND SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B) OR HEALED VENOUS ULCER (C5)

In a patient with skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. [GRADE: 2; LEVEL OF EVIDENCE: C]

Treatment of the incompetent perforating veins can be performed simultaneously with correction of axial reflux or can be staged with re-evaluation of perforator veins for persistent incompetence after correction of axial reflux. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.7: PATHOLOGIC PERFORATOR VENOUS REFLUX IN THE ABSENCE OF SUPERFICIAL VENOUS DISEASE, WITH OR WITHOUT DEEP VENOUS REFLUX, AND A HEALED OR ACTIVE VENOUS ULCER

In a patient with isolated pathologic perforator veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed, regardless of the status of the deep veins, we suggest ablation of the "pathologic" perforating veins, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.8: TREATMENT ALTERNATIVES FOR PATHOLOGIC PERFORATOR VEINS

For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin. [GRADE: 1; LEVEL OF EVIDENCE: C]

GUIDELINE 6.9: INFRAINGUINAL DEEP VENOUS OBSTRUCTION AND SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B), HEALED VENOUS LEG ULCER (C5), OR ACTIVE (C6) VENOUS LEG ULCER

In a patient with infrainguinal deep venous obstruction and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest autogenous venous bypass or endophlebectomy in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.10: DEEP VEIN REFLUX WITH SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B), HEALED VENOUS LEG ULCER (C5) OR ACTIVE VENOUS LEG ULCER (C6)—LIGATION

In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6),

we suggest against deep vein ligation of the femoral or popliteal veins as a routine treatment. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.11: DEEP VENOUS REFLUX WITH SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B), HEALED VENOUS LEG ULCER (C5), OR ACTIVE VENOUS LEG ULCER (C6)—PRIMARY VALVE REPAIR

In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest individual valve repair for those who have axial reflux with structurally preserved deep venous valves, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.12: DEEP VEIN REFLUX WITH SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B), HEALED VENOUS LEG ULCER (C5), OR ACTIVE VENOUS LEG ULCER (C6)—VALVE TRANSPOSITION OR TRANSPLANTATION

In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest valve transposition or transplantation for those with an absence of structurally preserved axial deep venous valve(s) when competent outflow venous pathways are anatomically appropriate for surgical anastomosis, in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.13: DEEP VEIN REFLUX WITH SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B), HEALED VENOUS LEG ULCER (C5), OR ACTIVE VENOUS LEG ULCER (C6)—AUTOGENOUS VALVE SUBSTITUTE

In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest consideration of autogenous valve substitutes by surgeons experienced in these techniques to facilitate ulcer healing and to prevent recurrence in those with no other option available, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.14: PROXIMAL CHRONIC TOTAL VENOUS OCCLUSION/SEVERE STENOSIS WITH SKIN CHANGES AT RISK FOR VENOUS LEG ULCER (C4B), HEALED VENOUS LEG ULCER (C5), OR ACTIVE VENOUS LEG ULCER (C6)—ENDOVASCULAR REPAIR

In a patient with inferior vena cava and/or iliac vein chronic total occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, which is associated with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend venous angioplasty and stent recanalization, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE: 1; LEVEL OF EVIDENCE: C]

GUIDELINE 6.15: PROXIMAL CHRONIC VENOUS OCCLUSION/SEVERE STENOSIS (BILATERAL) WITH RECALCITRANT VENOUS ULCER—OPEN REPAIR

In a patient with inferior vena cava and/or iliac vein chronic occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, which is associated with a recalcitrant venous leg ulcer, and who have failed endovascular treatment, we suggest open surgical bypass using an externally supported expanded polytetrafluoroethylene (ePTFE) graft in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.16: UNILATERAL ILIOFEMORAL VENOUS OCCLUSION/SEVERE STENOSIS WITH RECALCITRANT VENOUS ULCER—OPEN REPAIR

In a patient with unilateral iliofemoral venous occlusion/severe stenosis with recalcitrant venous leg ulcer who failed attempts at endovascular reconstruction, we suggest open surgical bypass using the saphenous vein as a cross-pubic bypass (Palma procedure) to aid in venous ulcer healing and to prevent recurrence. A synthetic graft is an alternative in the absence of autogenous tissue. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 6.17: PROXIMAL CHRONIC TOTAL VENOUS OCCLUSION/SEVERE STENOSIS (BILATERAL OR UNILATERAL) WITH RECALCITRANT VENOUS ULCER—ADJUNCTIVE ARTERIOVENOUS FISTULA

For those patients who would benefit from an open venous bypass, we suggest the addition of an adjunctive arteriovenous fistula (4–6 mm in size) as an adjunct to improve inflow into autologous or prosthetic crossover bypasses when the inflow is judged to be poor to aid in venous leg ulcer healing and to prevent recurrence. [GRADE: 2; LEVEL OF EVIDENCE: C]

For operative/endovascular management, guidelines are categorized anatomically as superficial venous disease, perforator venous disease, deep infrainguinal venous disease, and iliocaval (outflow) disease, and cover both open surgical or endovascular techniques. Furthermore, the separate pathologies of primary degenerative reflux disease and inflammatory thrombotic disease provide different challenges. Because of these complexities, operative/endovascular management was one of the two major areas chosen for a dedicated systematic review and meta-analysis for several additional reasons: (1) the recent development of less invasive endovascular techniques, such as endovenous ablation and iliac vein stenting; and (2) the lack of content in this area in previous guidelines, which in addition were not specialist oriented. In general, the quality of the evidence available to support recommendations for operative and endovascular management is mostly limited to level C evidence, due to an absence of comparative prospective randomized controlled trials of treatment techniques, with the exception of superficial venous treatments. The strength of the clinical recommendations for operative and endovascular management was increased by the concurrence of results from individual large case series and the expert opinion of the Venous Ulcer Guideline Committee.

For superficial venous disease, the commissioned systematic review and meta-analysis concluded that the available evidence fails to provide unequivocal support for surgical or endovascular techniques in terms of promoting the healing of VLU, but treatment of superficial venous incompetence can prevent VLU recurrence. Furthermore, although the systematic review and meta-analysis showed no statistical advantage of superficial ablation and compression over compression alone to promote ulcer healing, with the advent of minimally invasive thermal ablation, the low morbidity of an outpatient procedure under local/tumescent anesthesia shifts the benefit-to-harm ratio in favor of intervention. The evidence for the benefits of ablation and compression for lowering recurrence rates is an extrapolation of randomized controlled trials, which compared open ligation and stripping with compression to compression alone, such as the ESCHAR trial.[18] These randomized controlled trials showed no difference between the two techniques with regard to efficacy.[19] Ablation can also be carried out in a slow-to-heal ulcer with the goal of recurrence prevention and the potential benefit of improving time to healing with significant cost savings and better quality of life.

The treatment of perforators is based on the role of a pathologic perforator, which shunts abnormal deep flow to superficial high-volume flow, with resultant ambulatory hypertension in the lower medial and lateral calf. Duplex criteria of flow reversal (outward flow) greater than 500 ms and a perforator diameter of >3.5 mm further define this entity. A recent case series using direct radiofrequency ablation to treat perforators associated with "recalcitrant" venous ulcers showed an initial 58% success of perforator closure, while 12% required additional treatment.[20] The overall final perforator closure rate was 71%. Most importantly, in those whose perforators were closed, 90% of the venous ulcers healed. While subfascial endoscopic perforator surgery (SEPS) advanced a less invasive approach of perforators than the open approach popularized by Linton and subsequently expanded the treatment of perforator disease, the technical demands of SEPS affected outcomes. The Dutch SEPS trial demonstrated that optimal results were based on experience and were volume dependent; an appreciable proportion of perforators were missed in that trial, as over 50% had at least one missed perforator.[21] The above guideline promotes direct percutaneous techniques with ultrasound-guided sclerotherapy or thermal ablation, which can be done under local anesthesia. Lawrence et al.'s series demonstrated that these techniques have a steep learning curve and are much more demanding than ablation of the saphenous vein.[20] The evidence for a direct thermal approach to ablating perforators is based on a few case series in peer-reviewed journals. These case series are limited by small patient populations, short follow-up, and a focus on surrogate outcomes (occlusion of the perforator) rather than clinical or functional outcomes. Moreover, most of these series were carried out in patients with mild disease and not in patients with C4b–C6 disease. Sclerotherapy of incompetent perforating veins (ICPVs), by either liquid or foam, shows promise, but requires greater evidence.

Over time, a certain proportion of patients may fail conservative therapies and interventional treatment of superficial venous disease, so treatment of deep venous reflux may be required. The type of procedure is dictated by the anatomical findings on imaging, particularly the presence and condition of the venous valves. For patients with intact valve structures, valvuloplasty is the best option. In the absence of intact valve structures that can be repaired, vein valve transplant, usually from the axillary vein to the popliteal vein segment, has been associated with venous ulcer healing in long-term observational case series. These procedures should be carried out by surgeons who are experienced with the various techniques.

There is an increasing recognition of obstruction—either post-thrombotic or compression—as a cause of advanced chronic venous disease. For outflow obstruction, a percutaneous solution with an excellent patency favors this approach when possible. There is a paradox between the strength of this recommendation (GRADE: 1) and the lower quality of evidence (C). The expert panel felt that there was strong clinical experience with a high volume of positive case series, but there are no level 1 randomized controlled trials, which accounted for the low quality of evidence assignment.

52.3.6 Ancillary therapy

GUIDELINE 7.1: NUTRITION ASSESSMENT AND MANAGEMENT

We recommend that nutrition assessment be performed in any patient with a venous leg ulcer who has evidence of malnutrition and that nutritional

supplementation be provided if malnutrition is identified. [BEST PRACTICE]

GUIDELINE 7.2: SYSTEMIC DRUG THERAPY

For long-standing or large venous leg ulcers, we recommend treatment with either pentoxifylline or micronized purified flavonoid fraction used in combination with compression therapy. [GRADE: 1; LEVEL OF EVIDENCE: B]

GUIDELINE 7.3: PHYSIOTHERAPY

We suggest supervised active exercise to improve muscle pump function and reduce pain and edema in patients with venous leg ulcers. [GRADE: 2; LEVEL OF EVIDENCE: B]

GUIDELINE 7.4: MANUAL LYMPHATIC DRAINAGE

We suggest against adjunctive lymphatic drainage for healing of chronic venous leg ulcers. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 7.5: BALNEOTHERAPY

We suggest balneotherapy to improve skin trophic changes and quality of life in patients with advance venous disease. [GRADE: 2; LEVEL OF EVIDENCE: B]

GUIDELINE 7.6: ULTRAVIOLET LIGHT

We suggest against using ultraviolet light for the treatment of venous leg ulcers. [GRADE: 2; LEVEL OF EVIDENCE: C]

In addition to specific treatments for VLUs, such as wound care, compression therapy, or operative/endovascular interventions as described in prior guidelines, some specific complementary measures have been used to improve ulcer healing, including nutritional supplementation, systemic drug therapy, physiotherapy, lymphatic massage, and balneotherapy. Pharmacologic therapy with micronized purified flavonoid fraction (MPFF or Daflon; not Food and Drug Administration approved in the United States) and pentoxifylline, which is directed at reducing leukocyte interaction with the microcirculation, has shown improved VLU healing in multiple randomized controlled trials. The later drug has a strong level of recommendation and high-quality evidence supporting its use, but has the side effect of diarrhea, which can limit its continued use. Physiotherapy and exercise to improve mobility of the Achilles tendon with associated improvement in calf muscle pump function has been shown to improve the surrogate outcomes of increased ejection fraction and reduced residual volume fraction (RVF) as assessed by air plethysmography. While balneotherapy has shown some benefit, evidence has been equivocal for manual lymphatic drainage and ultraviolet light therapy.

52.3.7 Primary prevention

GUIDELINE 8.1: PRIMARY PREVENTION—CLINICAL CEAP C3–C4 PRIMARY VENOUS DISEASE

In patients with clinical CEAP C3–C4 disease due to primary valvular reflux, we recommend 20–30 mmHg compression, knee or thigh high. [GRADE: 2; LEVEL OF EVIDENCE: C]

GUIDELINE 8.2: PRIMARY PREVENTION—CLINICAL CEAP C1–C4 POST-THROMBOTIC VENOUS DISEASE

In patients with clinical CEAP C1–C4 disease related to prior deep vein thrombosis, we recommend compression, 30–40 mmHg, knee or thigh high. [GRADE: 1; LEVEL OF EVIDENCE: B]

GUIDELINE 8.3. PRIMARY PREVENTION—ACUTE DEEP VEIN THROMBOSIS TREATMENT

As post-thrombotic syndrome is a common preceding event for venous leg ulcers, we recommend current evidence-based therapies for acute deep vein thrombosis treatment. [GRADE: 1; LEVEL OF EVIDENCE: B]

We suggest use of low-molecular-weight heparin over vitamin K antagonist therapy of 3 months' duration to decrease post-thrombotic syndrome [GRADE: 2; LEVEL OF EVIDENCE: B]

We suggest catheter-directed thrombolysis in low-bleeding risk patients with iliofemoral deep vein thrombosis of <14 days' duration [GRADE: 2; LEVEL OF EVIDENCE: B]

GUIDELINE 8.4: PRIMARY PREVENTION—EDUCATION MEASURES

In patients with C1–C4 disease, we suggest patient and family education, regular exercise, leg elevation when at rest, careful skin care, weight control, and appropriately fitting foot wear. [BEST PRACTICE]

GUIDELINE 8.5: PRIMARY PREVENTION—OPERATIVE THERAPY

In patients with asymptomatic C1–C2 disease from either primary or secondary causes, we suggest against prophylactic interventional therapies to prevent venous leg ulcer. [GRADE: 2; LEVEL OF EVIDENCE: C]

Ambulatory venous hypertension promotes the development of VLU. Meaningful ways to prevent VLUs in patients who are at risk are effective, but are limited by a

lack of provider knowledge of diagnosis and treatment and patient compliance with the primary means of prevention, which is compression. Equally important for prevention of VLUs in patients with deep vein thrombosis is adherence to evidence-based guidelines for the prevention of deep vein thrombosis recurrence. Venous reflux related to post-thrombotic syndrome is associated with more severe symptoms than that related to primary valvular reflux. As a result, after deep vein thrombosis, patients with CEAP C1–C4 disease may progress to a more advanced CEAP clinical class, and therefore have an increased risk of VLU. Several studies have shown that the use of elastic compression stockings (30–40 mmHg) will reduce progression to CEAP C5–C6 disease.

52.4 FUTURE CONSIDERATIONS

While publication of a set of guidelines is important, their implementation in the clinical setting and monitoring of use are essential to wider adoption. While evidence supporting various recommendations in any guideline can change over time, or new therapies may prove to be effective, there can be significant lag between the publication of well-conducted randomized controlled trials and their adoption into guideline recommendations. Therefore, guidelines have to be dynamic and capable of frequent updating in order to maintain their clinical value. The SVS/AVF clinical practice guidelines for the management of VLUs have provided a solid foundation to build upon as future evidence and therapies become available.

REFERENCES

● = Key primary paper
★ = Major review article
◆ = Guideline

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PART 5

Special Venous Problems

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Surgical and endovenous treatment of superior vena cava syndrome

MANJU KALRA, HARALDUR BJARNASON, AND PETER GLOVICZKI

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53.1 INTRODUCTION

Obstruction of the superior vena cava (SVC) or innominate veins occurs most frequently in patients with metastatic malignant disease. Non-malignant causes are increasing, however, because of the more frequent use of central venous lines and catheters and the widespread use of pacemakers. Signs and symptoms of venous congestion of the head, neck, and upper extremities are determined by the duration, progression, and extent of the venous occlusive disease, and by the amount of collateral venous circulation that develops. Mortality is high in patients with metastatic malignant disease, and usually occurs at 6–12 months after the onset of symptoms.

In this chapter, we will review the etiology of SVC syndrome and discuss the clinical presentation, preoperative evaluation, and surgical/endovascular treatment of these patients.

53.2 ETIOLOGY

Obstruction of the SVC caused by a syphilitic aortic aneurysm was first described in 1757 by William Hunter.[1] The most frequent etiology of SVC syndrome today is metastatic malignant disease. In a review of multiple large series in 1984, 85% of 1986 patients with SVC syndrome had metastatic pulmonary or mediastinal malignancy.[2] The most frequent tumor was metastatic adenocarcinoma of the lung. SVC syndrome is the presenting symptom in 10% of patients who are eventually diagnosed with small-cell lung carcinoma (SCLC) and in 1.7% of those with non-small-cell lung carcinoma (NSCLC).[3]

Benign causes of SVC syndrome include fibrosing mediastinitis or granulomatous fungal diseases such as histoplasmosis. Previous radiation treatment to the mediastinum or retrosternal goiter are additional etiologies. Central venous lines and catheters used for hemodynamic monitoring, parenteral alimentation, or drug administration have become more frequent causes of SVC, innominate veins, or subclavian vein thrombosis.[4] Over 5 million central venous catheters and 170,000 pacemakers are now implanted annually in the United States and are associated with upper extremity or central vein deep vein thrombosis in 7%–33% of patients.[5,6] SVC syndrome reportedly occurs in 1%–3% of patients with central venous catheters and 0.2%–3.3% of patients with implanted pacemakers.[7] In the past, mediastinal fibrosis constituted up to 80% of cases of benign SVC syndrome,[8] but recent data attribute up to 74% of new cases to indwelling catheters or wires.[7,9] In patients on chronic hemodialysis, repeated episodes of infection in long-standing, large-caliber central venous catheters predispose them to central venous thrombosis. In addition, central venous stenoses have been reported in 11% of patients with threatened upper limb arteriovenous fistulae, with intimal hyperplasia secondary to turbulent flow being the underlying physiology.[10] However, malignancy still remains the etiology in 60% of cases.[7] SVC thrombosis can also be associated with thrombophilia, caused by deficiencies in circulating natural anticoagulants (antithrombin, protein S, and protein C) or factor V Leiden mutation.

53.3 CLINICAL PRESENTATION

The most frequent symptom of SVC syndrome is the feeling of fullness in the head and neck, which is more severe when the patient bends over or lies flat in bed. These patients can sleep only by elevating the head on multiple pillows. Headache, dizziness, visual symptoms, or occasional blackout spells may result from cerebral venous hypertension and can be incapacitating (Table 53.1).[11] Additional symptoms may include mental confusion, dyspnea, orthopnea, or cough. Swelling of the face and eyelids is evident and the patient notes the need for larger-sized shirts because of enlargement of the neck (Figure 53.1). Ecchymosis and dilated jugular veins accompany cyanosis of the upper body. Extensive venous collaterals of the chest will frequently develop. Mild to moderate upper extremity swelling may occur, but the primary symptoms in these patients are localized to the head and neck. In patients with end-stage renal disease, asymptomatic SVC occlusion may be unmasked upon creation of an arteriovenous fistula with rapid development of arm swelling and neck engorgement.

Table 53.1 Signs and symptoms of superior vena cava syndrome of benign etiology in 70 patients

Signs and symptoms	No. of patients (%)
Symptoms	
Feeling of fullness in the head or neck	61 (87)
Dyspnea on exertion or orthopnea	39 (56)
Headache	27 (39)
Dizziness or syncope	25 (36)
Visual problems	11 (25)
Cough	10 (22)
Nocturnal oxygen requirement	3 (16)
Protein losing enteropathy	1 (2)
Signs	
Head and neck swelling	65 (93)
Large chest wall venous collaterals	40 (57)
Facial cyanosis	24 (34)
Arm swelling	23 (33)
Pleural effusion	2 (3)

Source: Parish JM et al. Etiologic considerations in superior vena cava syndrome. *Mayo Clin Proc* 1981;56(7):407–13.

53.4 DIAGNOSTIC EVALUATION

A detailed clinical history with physical examination can usually establish the diagnosis of SVC syndrome. Routine laboratory tests, chest roentgenogram (chest X-ray), and contrast-enhanced computed tomography (CT) (arterial and venous phases) of the chest are performed in all patients to exclude underlying malignant disease. In a study by Parish et al. from 1981, abnormalities on chest X-ray were identified in 84% of patients.[8] CT imaging accurately depicts the location and extent of the obstruction and also distinguishes various types of benign and malignant mediastinal disease. The extent of venous collateral formation is also well demonstrated. These collateral pathways include: (1) the azygos–hemiazygos pathway; (2) the internal mammary pathway; (3) the lateral thoracic–thoracoepigastric pathway; and (4) the vertebral pathway and small mediastinal veins. Less commonly, unusual shunts, including hepatic parenchymal as an intense focal enhancement in the medial segment of the left lobe of the liver, and pulmonary pathways are identified on CT scan. The presence of these chest collateral venous pathways on CT venography carries a 96% sensitivity and 92% specificity for diagnosing SVC syndrome.[12] An additional advantage includes the ability to perform CT-guided biopsy and aid in the diagnosis of mediastinal masses.[12] Magnetic resonance venography is also suitable for defining anatomy, although patients with pacemakers are not candidates for this test. Patency of at least one internal jugular vein should be confirmed with duplex scanning in those patients who are candidates for surgical reconstruction.

Evaluation of patients who are being considered for endovascular or open surgical treatment is continued with bilateral upper extremity venography. Based on the extent of venous occlusion, as defined by bilateral upper extremity venography, Stanford and Doty classified patients with SVC syndrome into four types (Figure 53.2a–d).[13] Bronchoscopy, mediastinoscopy, thoracoscopy, thoracotomy, or median sternotomy may be necessary in some patients to provide tissue diagnosis or occasionally to attempt resection of a localized tumor causing SVC occlusion.

53.5 CONSERVATIVE THERAPY

Conservative measures are used first in every patient to relieve symptoms of venous congestion. These include elevation of the head during the night on pillows, modifications of daily activities by avoiding bending over, and avoidance of wearing constricting garments or tight collars. Patients frequently need diuretics to decrease venous edema, and anticoagulation with heparin and warfarin are used to protect the venous collateral circulation. Thrombolytic treatment should be considered in patients with acute or subacute SVC thrombosis causing SVC syndrome, although this may be contraindicated in patients in the end stages of metastatic malignant disease.

Symptoms of SVC syndrome associated with metastatic malignant disease frequently improve following irradiation or chemotherapy, and these constituted the mainstay of treatment in these patients before endovascular treatments became available. Chen et al.[14] treated 42 patients with malignant SVC syndrome using external beam radiotherapy and/or chemotherapy. Symptoms of SVC syndrome resolved in 80% of the patients who underwent radiotherapy, with a mean interval of 4 weeks. A similar benefit of radiation

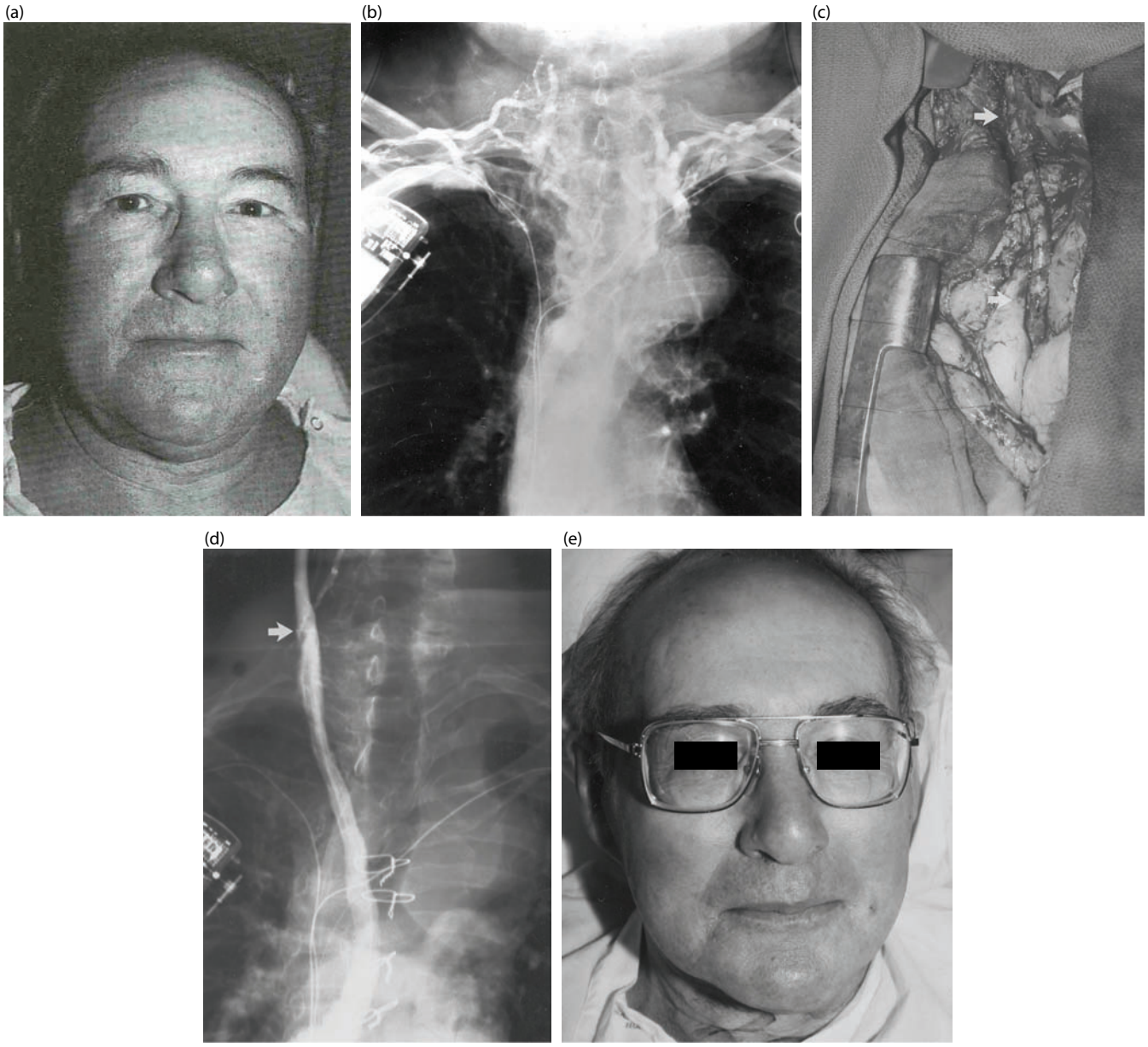

Figure 53.1 **(a)** Severe symptomatic superior vena cava (SVC) syndrome in a 69-year-old man. **(b)** Bilateral upper extremity venogram confirms thrombosis of the SVC and both innominate **(a)** veins following the placement of pacemaker lines bilaterally. **(c)** Right internal jugular vein–right atrial appendage spiral saphenous vein graft. Arrows indicate anastomoses. **(d)** Post-operative venogram confirms graft patency (denoted by arrow). **(e)** The patient 5 days after spiral vein graft placement. The clinical result is excellent 8 years after the operation.

or chemotherapy has been noted by others as well.[15] Since external compression by the tumor is the usual pathomechanism of caval occlusion in these patients, endovascular treatment, as discussed later, using stents is the best technique to alleviate symptoms. A systematic Cochrane review by Rowell and Gleeson evaluated two randomized and 44 non-randomized studies on the treatment of SVC syndrome in patients with bronchial malignancy. Chemotherapy and/or radiotherapy relieved symptoms of SVC occlusion in 77% and 60% of patients with SCLC and NSCLC, respectively. Endovascular treatment with stenting, however, relieved symptoms in 95% patients and much more rapidly.[3]

53.6 INDICATIONS FOR TREATMENT

Patients with SVC syndrome can have severe, frequently incapacitating symptoms, which cannot be alleviated by conservative measures, including medical measures as well as chemoradiation in malignant cases. Up to a quarter of malignant cases could be resistant to radio-chemotherapy, and those who are sensitive could take up to 3 weeks to obtain symptomatic relief.[3] Further treatment options include endovenous or surgical intervention, depending upon the etiology and anatomy of the SVC lesion. Traditionally, endovenous treatment has been the unequivocal first choice

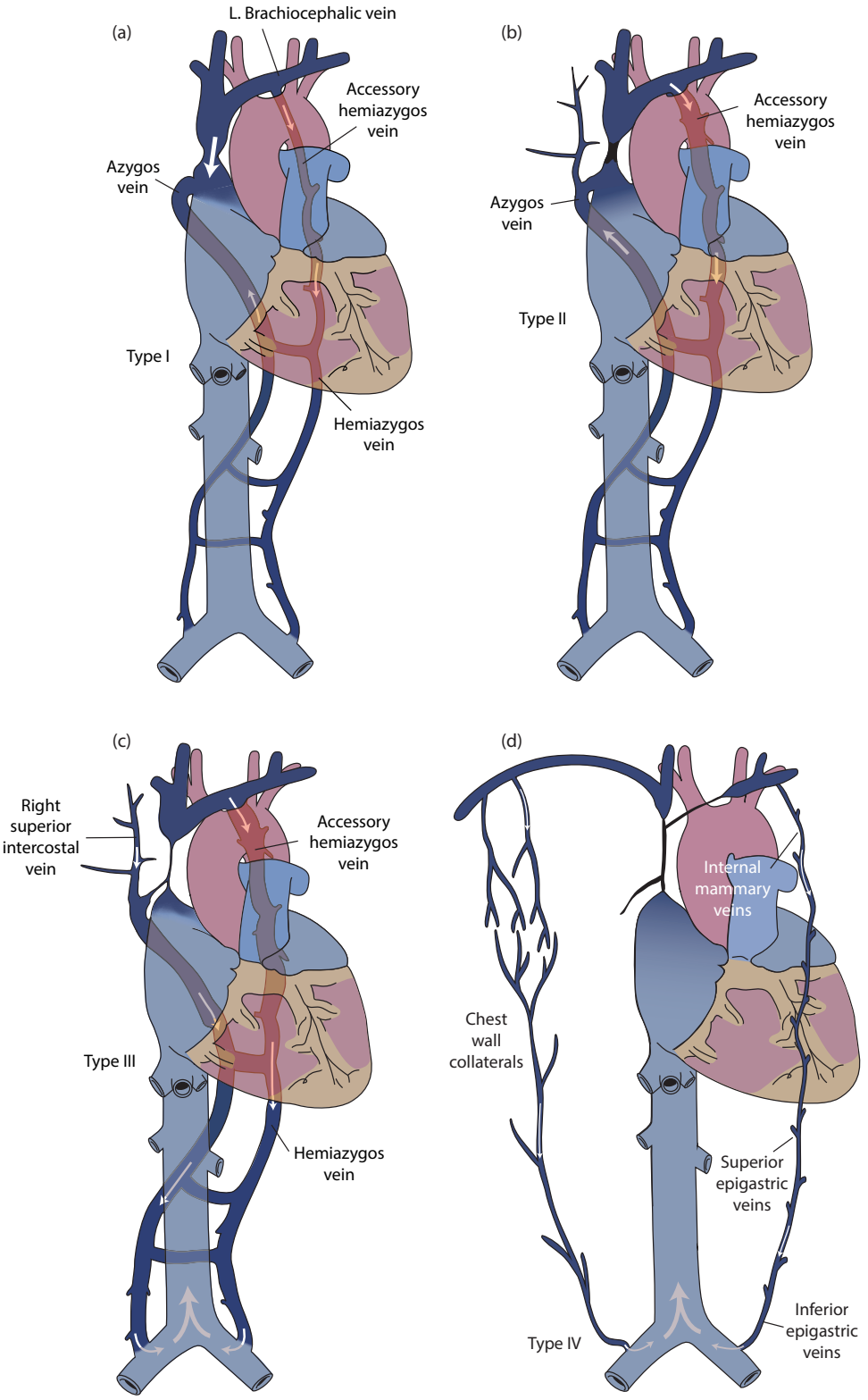

Figure 53.2 Venographic classification of superior vena cava (SVC) syndrome according to Stanford and Doty. **(a)** Type I. High-grade SVC stenosis with still normal direction of blood flow through the SVC and azygos veins. Increased collateral circulation through hemiazygos and accessory hemiazygos veins. **(b)** Type II. Greater than 90% stenosis or occlusion of the SVC, but patent azygos vein with normal direction of blood flow. **(c)** Type III. Occlusion of the SVC with retrograde flow in both the azygos and hemiazygos veins. **(d)** Type IV. Extensive occlusion of the SVC and innominate and azygos veins with chest wall and epigastric venous collaterals. (From Alimi YS et al. Reconstruction of the superior vena cava: Benefits of postoperative surveillance and secondary endovascular interventions. *J Vasc Surg* 1998;27(2):287–99; 300–1.)

for patients with malignant SVC obstruction because of their limited life expectancy. Patients with benign disease have been treated with surgical replacement/bypass of the occluded SVC because of their longer life expectancy and therefore need for a durable reconstruction. For more than two decades, studies of the endovascular treatment of non-malignant SVC syndrome were limited to case reports and small series with short follow-up periods,[16–21] in spite of the fact that the first reported endovenous treatment was for SVC occlusion of benign etiology.[22] In recent years, however, much experience has been gained in this field, and today, most patients with benign SVC syndrome would be considered for endovenous treatment first.[11,23] Indications for surgical treatment, however, are better defined because experience dates back many years and long-term results are good. At present, surgical reconstruction is reserved for patients with extensive chronic venous thrombosis not anatomically suitable for endovascular treatment and those with less extensive disease who have not benefited from endovascular attempts. We have performed reconstruction of the SVC for obstruction caused by granulomatous and idiopathic mediastinal fibrosis, central venous catheters, pacemaker electrodes, or ventriculoatrial shunts and in patients with antithrombin deficiency or idiopathic venous thrombosis.[4,11,24–26] The indications for reconstruction of the SVC in patients with benign disease were similar in the reports by Doty et al.[27] and Moore.[28]

Surgical reconstruction of the SVC has also been performed in patients with different types and stages of malignant disease.[29–32] However, endovascular techniques should clearly be the treatment of choice in these patients, and surgical reconstruction should be contemplated almost exclusively only when the tumor is resectable. Patients with a malignant tumor should undergo reconstruction through a median sternotomy only if their life expectancy is greater than 1 year. This group of patients may include those with lymphoma, thymoma, or metastatic medullary carcinoma of the thyroid gland. Extra-anatomic subcutaneous bypass between the jugular vein and the femoral vein using a composite saphenous vein graft is an alternative if symptoms are severe and endovascular techniques fail or are not possible.[33]

53.7 ENDOVENOUS TREATMENT

The first percutaneous treatment with angioplasty in an adult was performed in 1986 by Sherry et al.[22] for an SVC lesion caused by a pacemaker wire. There has been tremendous progress in the endovenous treatment of SVC syndrome since then, with increasing technical and clinical success. This achievement served patients with malignant disease well in terms of rapid symptomatic relief; however, long-term results of stents placed in young patients for benign lesions are still not well known, and re-thrombosis or intimal hyperplasia can be significant. In spite of this, endovascular treatment is now accepted as the first-line treatment in benign as well as malignant cases.[3,11]

Treatment modalities include percutaneous transluminal balloon angioplasty (PTA), stenting, and thrombolysis performed alone or in combination. Following early interventions with angioplasty alone, it soon became evident that this resulted in early restenosis due to the elastic/fibrotic nature of many SVC lesions with or without external compression from mediastinal masses. The earliest stents deployed were Gianturco Z-stents, as they were the only ones available in larger diameters. They are self-expanding stents with hooks for fixation to prevent migration and have the advantages of ease of placement, rigidity, and lack of shortening. The large stent interstices, however, are worrisome for allowing tumor ingrowth. Palmaz (Cordis Corp., Miami, FL) balloon-expandable stents are ideally suited for short, focal fibrotic/compressive lesions because of their precise deployment and good radial force (Figure 53.3). Disadvantages include poor flexibility and availability only in short lengths. In recent years, other self-expanding stents like Wallstents (Boston Scientific Corp., Natick, MA), Smart stents (Cordis Endovascular, Warren, NJ), Protégé stents (ev3, Plymouth, MN), E*Luminexx (Bard GmbH/Angiomed, Karlsruhe, Germany), Sinus-XL (OptiMed Medizinische Instrumente GmbH, Ettlingen, Germany), and Zilver Vena (Cook Medical, Inc., Bloomington, IN) stents have been used more frequently for longer SVC stenoses because of their flexibility and availability in multiple sizes. Occasional reports of covered stents are also available for extravasation during the procedure and potentially to control tumor ingrowth, providing better freedom from the need for reintervention.[34,35] In recent years, we have used covered stents electively as well in selected cases with the impression that they are associated with a lower incidence of intimal hyperplasia (unpublished data). Thrombolysis may be performed alone for acute SVC thrombosis related to indwelling catheters or prior

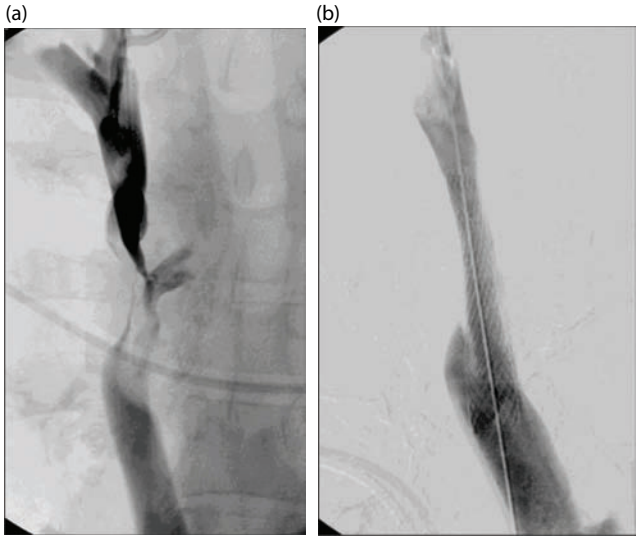

Figure 53.3 **(a)** Venogram showing type II superior vena cava obstruction due to mediastinal fibrosis in a 31-year-old man. Successful placement of a Palmaz stent resulted in immediate resolution of symptoms. **(b)** The patient has since undergone balloon dilatation for in-stent stenosis 11 months later and remains asymptomatic.

to angioplasty/stenting to resolve the thrombosis and reveal the underlying stenotic lesion for definitive treatment.

The technique of endovenous repair involves ultrasound-guided percutaneous venous access of the common femoral vein and placement of 6–10-Fr sheaths followed by crossing the stenotic/occlusive lesion with hydrophilic guidewires and catheters. The right internal jugular/arm vein can be an alternative or additional venous access site in patients with short focal lesions or if the lesion cannot be crossed from the femoral approach, respectively. Access of a hemodialysis arteriovenous fistula, if present, is a viable option. Long sheaths extending to the site of a long occlusion can be helpful in providing the necessary support to cross the lesion. Once wire access across the lesion is obtained, primary PTA using standard 10–16-mm angioplasty balloons is performed, followed by stenting. Choice of stent is tailored to the etiology, degree, length, and tortuosity of the SVC stenosis. Venous stenoses can be very resistant, often requiring angioplasty with high-pressure balloons (e.g., Mustang [Boston Scientific Inc., USA] or ATLAS [Bard Peripheral Vasc Inc., AZ, USA]). Perforation can occur during this process, and if minor—manifesting as a mild perivenous blush without hemodynamic changes—can be managed successfully with prolonged balloon inflation. Placement of a covered stent is required to control larger, more significant perforations, especially if associated with hemodynamic instability.[36] Rarely, SVC rupture can result in pericardial tamponade. Rapid diagnosis and immediate ultrasound-guided pericardial drainage is necessary.[37]

Thrombolysis may be performed alone for acute SVC thrombosis related to indwelling catheters or prior to angioplasty/stenting to resolve the thrombosis and reveal the underlying stenotic lesion for definitive treatment. If thrombolysis is determined to be appropriate prior to PTA or stenting, a suitable-length catheter with side holes is placed across the lesion for catheter-directed lytic therapy. Successful catheter-directed thrombolysis as well as pharmacomechanical thrombectomy have been reported not only in various catheter-related thromboses, but also in malignant SVC occlusions.[38] For details of thrombolytic therapy, refer to Chapters 24 and 25. The need for post-procedure anticoagulation is also individualized based on the cause of SVC syndrome. The majority of patients, especially those with malignancy and catheter-related thrombosis, receive oral anticoagulation at least for a few months until the stent is lined with pseudointima and the risk of re-thrombosis decreases. Patients with mediastinal fibrosis are often treated with antiplatelet therapy alone. Both re-thrombosis following the cessation of anticoagulation as well as excellent results without have been reported.[39,40]

53.8 SURGICAL TREATMENT

53.8.1 Selection of graft

For replacement of the SVC or the innominate vein in patients with benign disease, autogenous spiral saphenous vein graft is our first choice. This graft was described in animal experiments by Chiu et al.[41] in 1974, and Doty and Baker[42] used it first in patients. Our technique of preparing and implanting the spiral graft has been described previously in detail.[4,11] The saphenous vein is harvested, opened longitudinally, the valves are excised, and the vein is wrapped around a 32- or 36-Fr polyethylene chest tube. The edges of the vein are then approximated with running 6–0 monofilament polypropylene sutures (Figure 53.4). More recently, we have used non-penetrating vascular clips (US Surgical, Inc., Mansfield, MA) for this purpose, with good results. The vein is continuously irrigated during the phase of preparation with heparinized papaverine solution to preserve the integrity of endothelial cells and to prevent desiccation. Spiral saphenous vein graft is a relatively non-thrombogenic autologous tissue. Disadvantages include the additional incision and the time (60–90 minutes) needed to prepare the graft. In addition, the length of the graft is limited by the availability of an adequate-length segment of saphenous vein. The saphenous veins may also be used as panel grafts.

The femoral vein, or the femoropopliteal vein, was one of the first conduits used to reconstruct the SVC.[43] It has been used with success because of its excellent suitability in terms of size and length.[44,45] It is an excellent graft; however, if the patient has underlying thrombotic abnormalities, removal of a deep leg vein may result in at least moderate lower extremity post-thrombotic syndrome. For this reason, in young patients who undergo SVC reconstruction for benign disease, the femoral vein has been only our second choice for graft following spiral saphenous vein graft.

Of the available prosthetic materials, externally supported expanded polytetrafluoroethylene (ePTFE) is almost exclusively used for large vein reconstruction because of its low thrombogenicity. Short, large-diameter (10–14-mm) grafts have excellent long-term patency because flow through the innominate vein usually exceeds 1000 mL/minute. If the peripheral anastomosis is performed with the subclavian vein, venous inflow is significantly less, and the addition of an arteriovenous fistula is usually required in the arm to ensure graft patency. For an internal jugular–atrial appendage bypass, a large-diameter (12-mm) PTFE graft is a suitable alternative if the spiral saphenous vein is not possible. An arteriovenous fistula with direct flow into the graft has not been performed for jugular grafts. An externally supported prosthetic graft is a good choice in patients with a tight mediastinum and usually for all patients with malignancy, because recurrent tumor is more likely to compress and occlude a vein graft.

Iliocaval allografts can be considered in those patients who receive immunosuppressive treatment for the protection of a transplanted organ. Cryopreserved femoral vein grafts are potential alternatives, as are grafts prepared from autogenous or bovine pericardium.

53.8.2 Surgical technique

The operation is performed through a median sternotomy. If the internal jugular vein is used for inflow, the

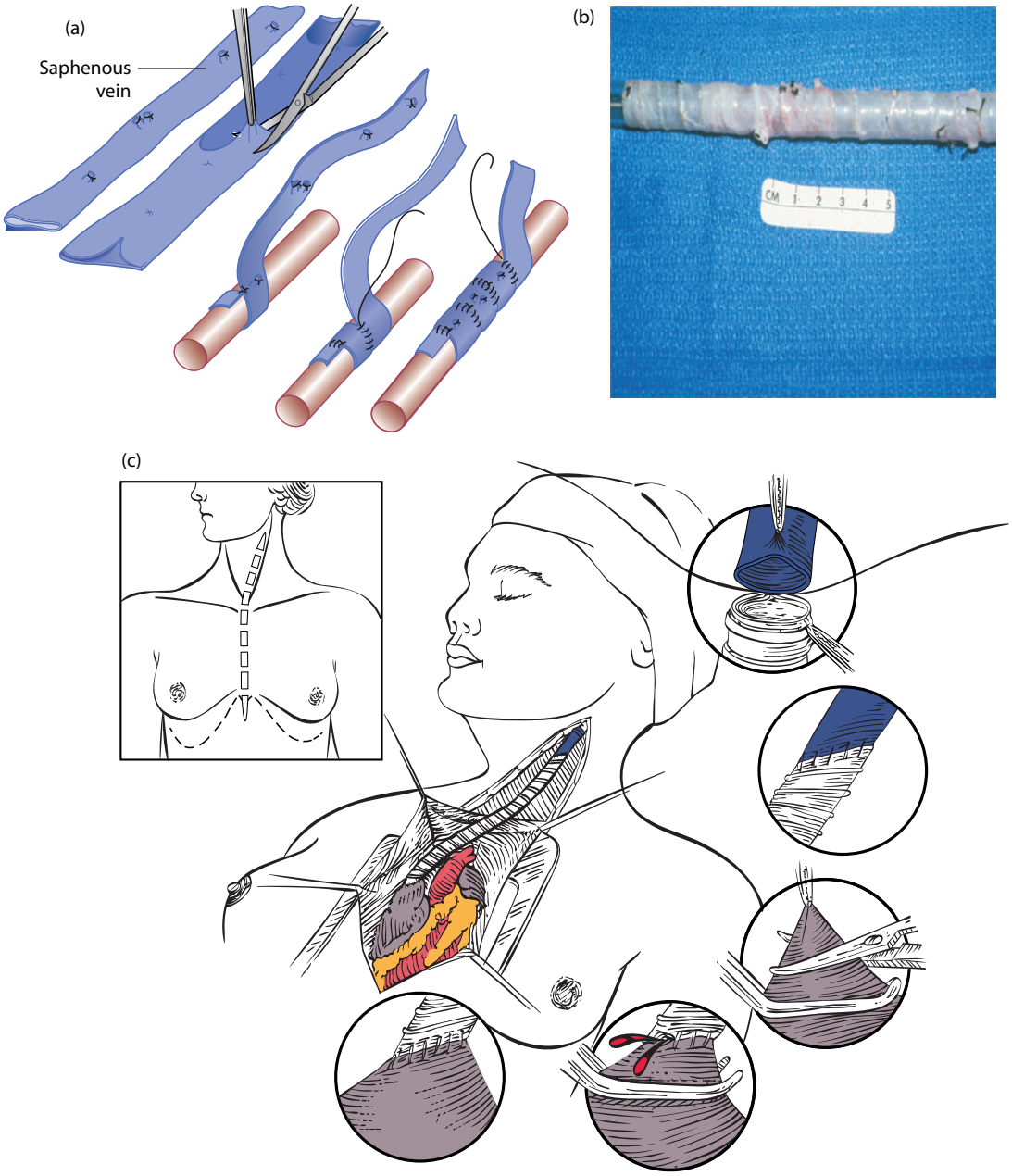

Figure 53.4 **(a)** Technique for a spiral saphenous vein graft. The saphenous vein is opened longitudinally, the valves are excised, the vein is wrapped around an argyle chest tube, and the vein edges are approximated with sutures. **(b)** A 15-cm long spiral saphenous vein graft ready for implantation. **(c)** Technique of left internal jugular–right atrial spiral vein graft implantation. Spiral vein graft prepared using non-penetrating vascular clips. (From Gloviczki PG, Pairolero PC. Venous reconstruction for obstruction and valvular incompetence. In: Goldstone J, ed. *Perspectives in Vascular Surgery*. St. Louis, MO: Quality Medical Publishing, 1988, 75–93.)

midline incision is extended obliquely into the neck along the anterior border of the sternocleidomastoid muscle on the appropriate side. The mediastinum is exposed, and biopsy of the mediastinal mass or resection of the tumor is performed before caval reconstruction.

Once biopsy or tumor resection is done, the pericardial sac is opened to expose the right atrial appendage, which is used most frequently for the central anastomosis. A side-biting Satinsky clamp is placed on the right atrial appendage, which is opened longitudinally. Some trabecular muscle is excised to improve inflow, and an end-to-side anastomosis with the vein graft is performed with a running 5–0 monofilament suture (Figure 53.4). If not involved in the fibrosing process, a patent SVC central to the occlusion can also be used for this purpose. The peripheral anastomosis of the graft is performed with the internal jugular or innominate vein in an end-to-side or, preferably, an end-to-end fashion.

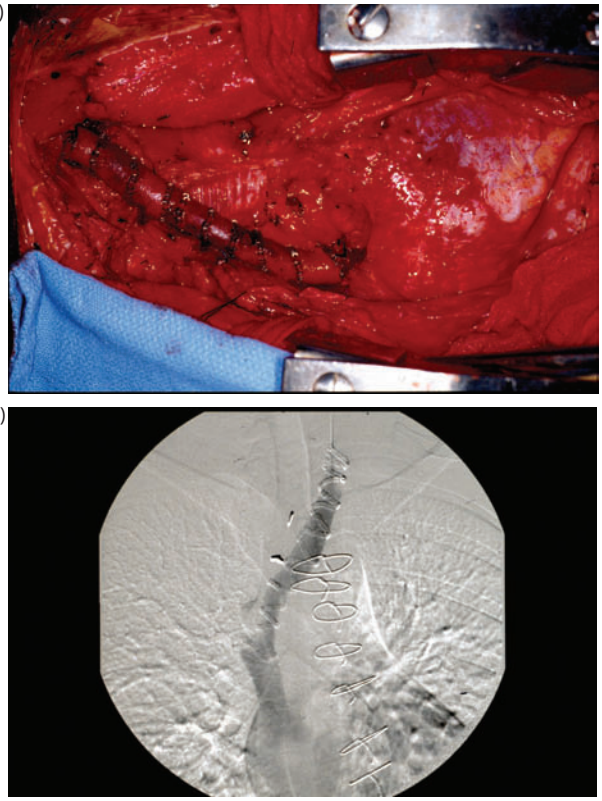

Figure 53.5 **(a)** Non-penetrating vascular clips used for the preparation of a spiral vein graft. **(b)** Post-operative venogram demonstrating the patent left internal jugular–right atrial appendage bypass graft. The graft is patent and the patient is asymptomatic 3 years later.

Although we have performed bifurcated spiral vein grafts or bifurcated prosthetic grafts in a few patients, a single straight graft from the internal jugular or innominate vein (Figures 53.5 through 53.7) is our current operative choice for SVC reconstruction. Because collateral circulation in the head and neck is almost always adequate, unilateral reconstruction is sufficient to relieve symptoms in most patients. When only part of the circumference of the SVC is invaded by the tumor, resection and caval patch angioplasty using a prosthetic patch, bovine pericardium, or autogenous material, such as saphenous vein or pericardium, is also a viable option.

Post-operative anticoagulation is started 24 hours later with heparin, and the patient is discharged on an oral anticoagulation regimen. Patients with spiral or femoral vein grafts who have no underlying coagulation abnormalities are maintained on warfarin (Coumadin) for 3 months only. Those with underlying coagulation disorders and most patients with ePTFE grafts continue lifelong anticoagulation therapy.

53.9 RESULTS

53.9.1 Results of endovenous treatment

Initial attempts at treating SVC syndrome by endovascular means employed PTA alone, with early restenosis caused by elastic recoil or compression from surrounding fibrosis. The earliest reports of SVC stenting in 1986/1987 were in patients with malignant SVC occlusion and were presented independently by Charnsangavej et al.[17] and Rosch et al.,[18]

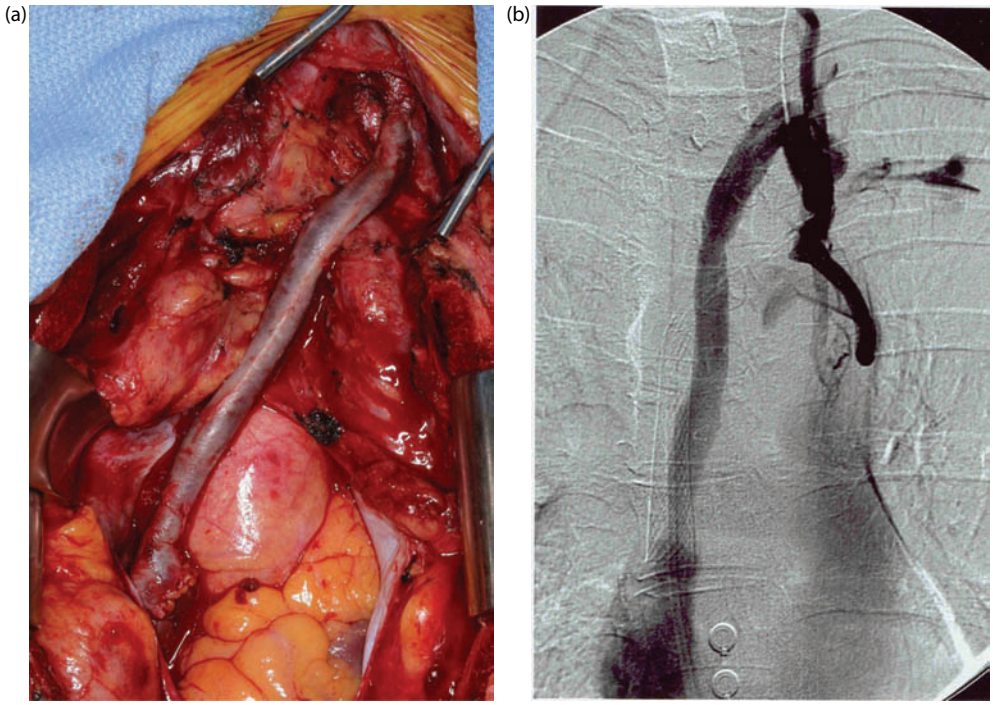

Figure 53.6 **(a)** Left innominate vein–right atrial appendage bypass graft using the femoral vein. **(b)** Venogram 3 months after surgery confirms the graft to be widely patent.

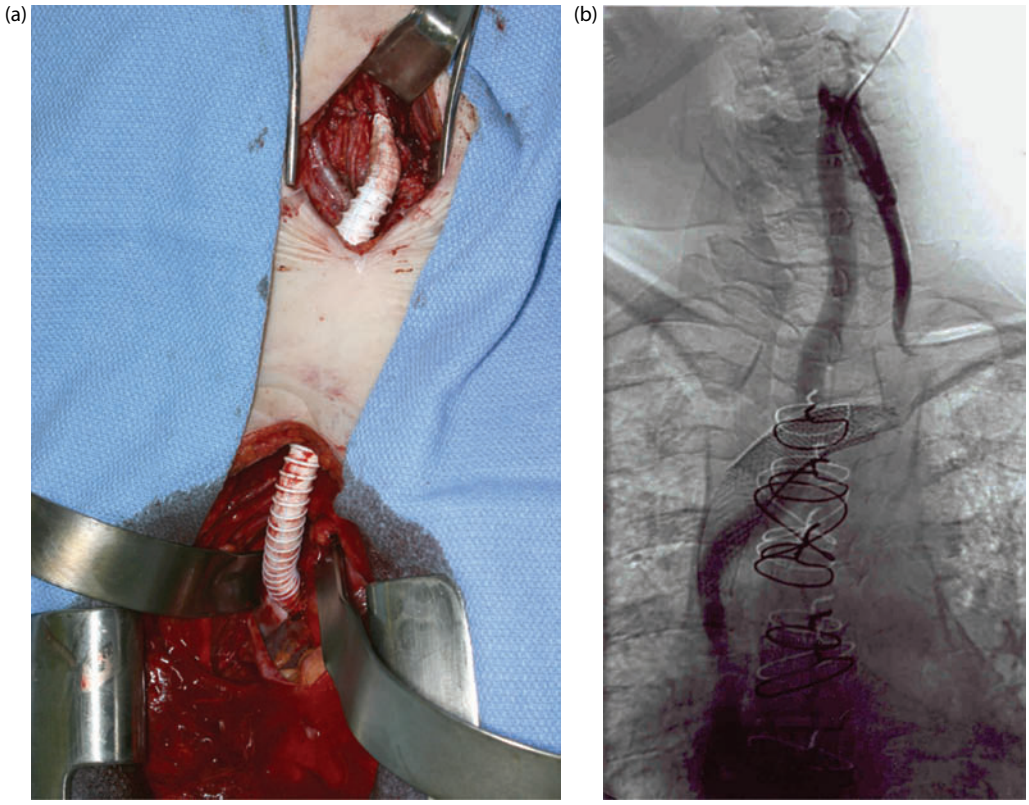

Figure 53.7 **(a)** Left internal jugular vein–atrial appendage externally supported expanded polytetrafluoroethylene graft. **(b)** Widely patent graft at 13 months after the operation.

resulting in prompt relief of symptoms that lasted until death at 3 weeks to 6 months. With endovascular stenting, clinical response is "immediate" relief of headache, with edema of the face and arm resolving within 24–72 hours. Early experience was with Gianturco Z-stents, which were subsequently modified by Rosch et al.[18] to create a multibody design that minimized stent migration. In the early 1990s, occasional cases of stent deployment for pacemaker wire-induced thrombosis were reported, but repeated interventions were required to maintain patency in the short term.[17,18,40]

In 1997, Nicholson et al.[46] reported the largest study up to that time of endovenous intervention in the SVC in 75 patients with malignant SVC syndrome. Symptomatic relief was achieved in all patients within 48 hours and 90% remained symptom free until death. The authors compared SVC stenting with palliative radiation for symptomatic SVC syndrome and concluded that radiation provided durable relief from symptoms in only 12% of patients. In a later study by Garcia Monaco et al.,[47] dramatic symptomatic improvement was seen in 91% of 40 patients following SVC stenting, and this was maintained in 83% during the course of the disease. Greillier et al.[48] reported that there was complete resolution of symptoms more frequently in stented than in unstented patients with lung cancer (75% vs. 25%), as well as a lower relapse rate and a longer time to relapse. Based on these and similar results reported in several smaller series, endovenous treatment became the unequivocal first-line treatment for malignant SVC syndrome, and also provided an opportunity for endovenous biopsy during the procedure.[49–52]

Kee et al. reported the results of treatment with thrombolysis, PTA, and stents in 27 patients with benign SVC syndrome. Four (15%) patients had complete lysis, whereas in 21 (77.8%) patients, thrombolysis revealed underlying significant stenosis, which was treated by stenting.[53] However, a Cochrane review concluded that thrombolysis when added to stenting resulted in increased morbidity.[3] Qanadli et al.[16] reported 12 patients treated with Wallstents; one symptomatic recurrence occurred at 2 months over a mean follow-up of 11 months. In a contemporary series, Sheikh et al.[9] treated 19 patients with benign SVC obstruction, with symptomatic relief in all, secondary interventions in three over a mean follow-up of 28 months, and one death from complications of anticoagulation.

Studies reporting on the treatment of benign SVC syndrome are scarce in the literature. We have reported our results of successful endovenous treatment of SVC syndrome of benign etiology in 28 of 32 patients in whom it was attempted, 19 with catheter-related thrombosis and nine with mediastinal fibrosis.[11] Six patients underwent PTA and 22 underwent stenting; five procedures (two PTAs and three stents) were preceded by thrombolysis. Over a mean follow-up of 1.8 years (range 0–6.3 years), primary patency rates at 1 and 3 years were 70% and 44%, and assisted primary and secondary patency rates were 96% and 96%, respectively

(Figure 53.8). These were not significantly different from the patency of surgical reconstruction of the SVC at our institution. We did, however, notice that the need for re-intervention persisted at least out to the mid-term, unlike in surgical patients' grafts, in whom stenoses requiring intervention occurred mostly in the first 1–2 years, following which there was maintained, durable graft patency (Figure 53.9).[11]

Most studies have emphasized the need for customizing treatment with a combination of thrombolysis, angioplasty, and stenting to achieve an initial technical success rate of 90%–100% and secondary patency rates of up to 85% at 1 year in small numbers of patients.[21,38,53,54] Barshes et al. reported 100% technical success and 96% symptomatic relief following stenting in 40 patients with malignant and 16 patients with benign SVC syndrome, with primary patency rates of 64% and 76% at 1 year, respectively, and symptom-free survival ranging from 1 to 34 months.[55] However, to date, prospective, randomized data comparing stent types or treatment modalities do not exist. Oudkerk et al. reported on comparing Gianturco Z-stents and Wallstents and found the latter to be more prone to re-occlusion, presumably because of a closer weave and greater surface area of metal.[56] In a study of 84 patients with malignant SVC syndrome, Dinkel et al. found that bilateral Wallstent placement was technically feasible, but was associated with a greater incidence of re-occlusion.[57]

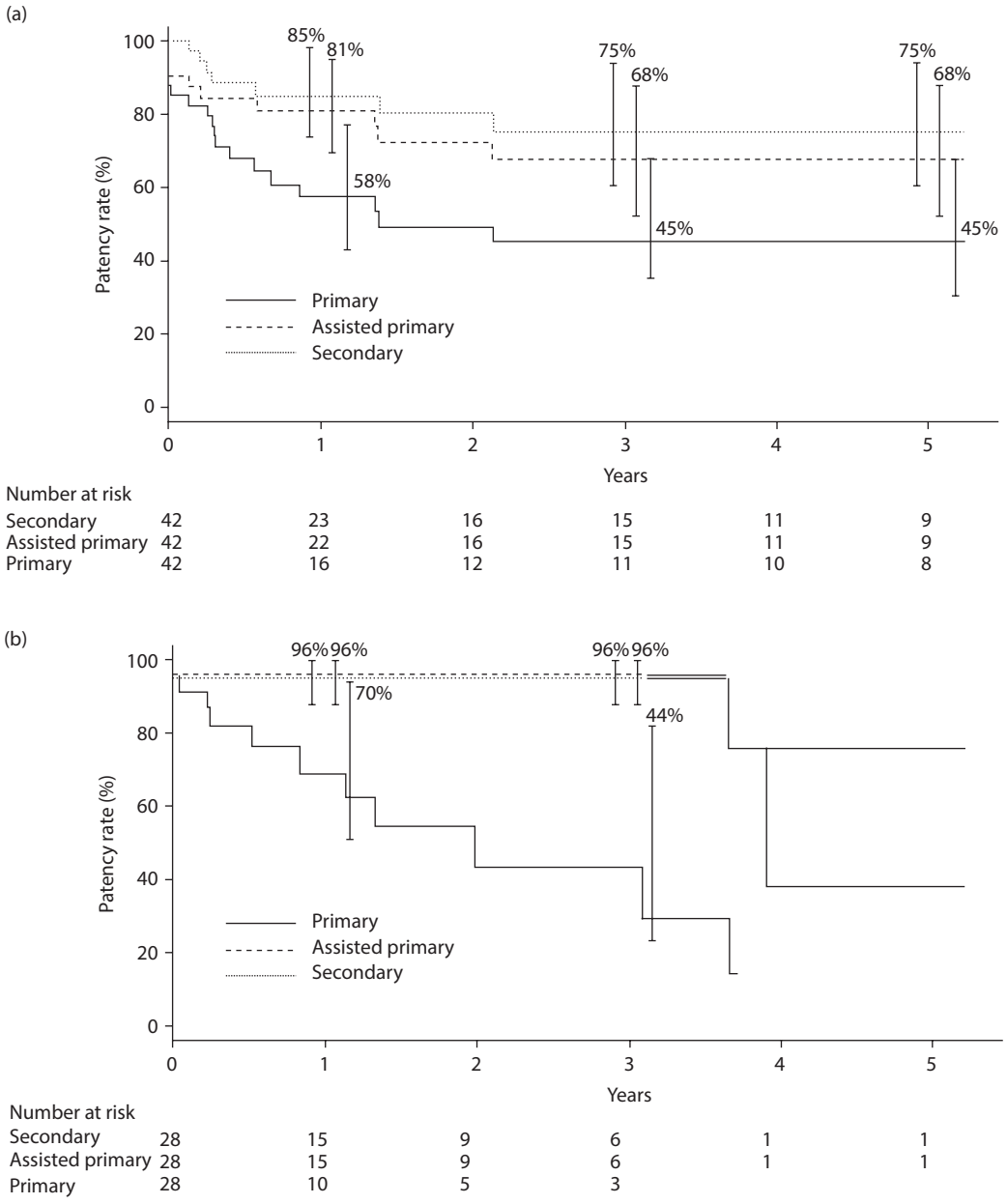

Figure 53.8 **(a)** Cumulative primary, assisted primary, and secondary patency rates at 1, 3, and 5 years of open surgical reconstruction ($n = 42$). Solid bars represent standard error margin (SEM) < 10%. **(b)** Cumulative primary, assisted primary, and secondary patency rates at 1 and 3 years of endovascular repair ($n = 28$). Solid bars represent SEM < 10%. (From Rizvi AZ et al. Benign superior vena cava syndrome: Stenting is now the first line of treatment. *J Vasc Surg* 2008;47(2):372–80.)

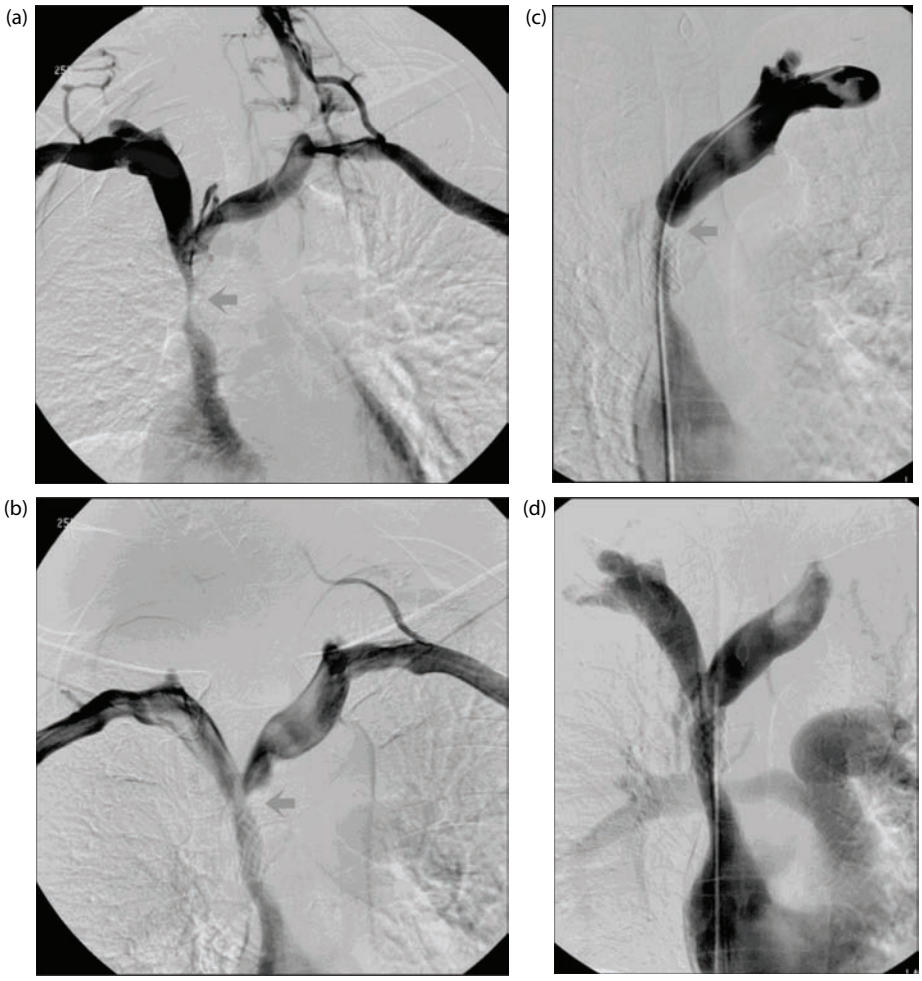

Figure 53.9 **(a)** Venogram showing type II superior vena cava obstruction (arrow) due to mediastinal fibrosis in a 38-year-old man. Successful placement of a Palmaz stent resulted in immediate resolution of symptoms. **(b)** Venogram 14 months after stent placement shows high-grade stenosis of the left innominate vein proximal to the stent (arrow). This was successfully treated with balloon angioplasty. **(c)** Venogram 8 months later shows recurrence of stenosis (arrow). **(d)** Venogram following balloon angioplasty of stenosis of the left innominate vein and stent shows a widely patent stent. Patient underwent two further balloon angioplasties over the next 10 months to maintain patency.

Occlusion of stents because of protrusion of tumor between stent struts in patients with malignancy, as well as intimal hyperplasia, fibrosis, and extrinsic compression from mediastinitis, are real concerns following endovenous treatment. Restenosis is almost always associated with recurrence of symptoms and necessitates repeat interventions, especially in patients with benign SVC syndrome. Other risks of endovenous treatment include access site complications, bleeding related to thrombolysis/anticoagulation, stent migration, and cardiac tamponade from intrapericardial hemorrhage. The latter occurs infrequently and has been reported after both PTA and stenting, and management entails urgent ultrasound-guided pericardiocentesis. We encountered this complication during repeat PTA in two patients.

There have been significant further advances in endovascular therapy for SVC syndrome over the last decade. Technical success rates now approach 100%. Maleux et al. reported stenting in 78 patients with malignant SVC syndrome (large-bore Nitinol SE [Zilver, Cook Medical, Inc., Bloomington, IN]), with a 100% technical success rate and 89% primary patency at 12 months. However, only 30% of patients were alive at 12 months.[58] Fagedet et al. reported the need for re-intervention in 22% of 164 patients following stenting with Wallstents and Mesotherm (CR Bard, Inc., Billerica, MA).[59] Recanalization of total occlusions with large-caliber stents (>16 mm) was associated with a higher incidence of vena cava rupture, cardiac tamponade, and pulmonary edema.[59] However, now that large-diameter stents specifically designed to treat SVC lesions (Nitinol Sinus-XL SE [OptiMed, Ettlingen, Germany]) have been developed, Mokry et al. have since reported successful stenting with 20–24-mm Sinus-XL stents in 23 patients with malignant SVC syndrome without any procedural complications.[60] Concerns of restenosis and symptomatic recurrence rates as high as 40% have prompted the use of covered stents. Gwon et al. described better cumulative patency with covered than uncovered stents (94% vs. 48%

at 12 months; $P = 0.038$); however, there was no survival benefit.[34] Over the last decade, we have adopted the selective practice of covered stents for the SVC, and placed them in 13 out of 44 patients with benign SVC syndrome (unpublished data). Although not statistically significant, we have noticed a decreased need for re-intervention at 1 year in the group with covered stents (15%) versus those with uncovered stents (39%) in spite of an equal incidence of symptom recurrence: 40% versus 34%. It is too early to draw conclusions, but this preliminary experience mirrors the findings reported by Gwon et al.[34]

53.9.2 Results of surgical treatment

Reconstruction of the occluded SVC or innominate vein gives the most gratifying results of venous bypasses. The patency rate is very good, since the mean flow through the graft is usually high (mean 1440 mL/minute, range 750–2000 mL/minute).[61] Shorter grafts placed entirely within the mediastinum have a better chance of long-term patency than those with an anastomosis in the neck. Doty et al.[27] reported on the long-term results in nine patients who underwent spiral vein grafting for SVC syndrome caused by benign disease. Seven out of nine grafts remained patent during follow-up that extended from 1 to 15 years, and all but one of the patients became asymptomatic. Their larger experience consisting of 16 spiral saphenous vein grafts for benign SVC syndrome reported in 1999 documented 88% long-term graft patency and excellent clinical results at a mean follow-up of 10.9 years.[62] Similar results have been reported from our institution in the past with no operative mortality, 80% graft patency at 5 years (90% in vein grafts), and 79% symptom relief.[26]

We have reported our results on the evolving treatment of benign SVC syndrome by endovascular means and compared them with surgical reconstruction, which has been the mainstay over the years.[11] Forty-two patients underwent 22 spiral saphenous vein grafts, six reversed femoral vein grafts, 13 ePTFE grafts, and one patient received an iliocaval allograft. The grafts originated from the internal jugular vein in 15 patients, the subclavian vein in one patient, and the innominate vein in 26 patients; they were anastomosed centrally to the SVC in 12 patients and the right atrial appendage in 30 patients. No early deaths or pulmonary thromboembolism occurred. Six patients had early reoperation for graft thrombosis, thrombectomy of four ePTFE grafts, and thrombectomy and revision of side limbs of two bifurcated spiral saphenous vein grafts. All grafts, except one limb of a bifurcated graft, were patent at the time of discharge. The 30-day primary, assisted primary, and secondary patency rates were 93%, 98%, and 100%, respectively. During a mean follow-up of 4.1 years (range 0.1–17.5 years), primary and secondary patency rates of all the grafts at 5 years were 45% and 75%, respectively. Of the different graft types, spiral saphenous vein grafts performed well, with 86% secondary patency at 5 years, 19 of the 22 grafts patent at last follow-up, and good to excellent clinical results.

Results with ePTFE grafts implanted into the mediastinum in some series have shown excellent patency. Dartevelle et al.[30] observed continued patency in 20 of 22 ePTFE grafts at a mean follow-up of 23 months. Moore[28] observed no graft occlusion at a mean follow-up of 30 months among 10 patients who underwent large central vein reconstruction. In eight of these 10 patients, an additional arteriovenous fistula in the arm was used to increase flow and maintain patency. Magnan et al.[29] reported on 10 patients who underwent reconstruction of the SVC using ePTFE grafts. Nine of the 10 patients had malignancy. Although early mortality was high, with only two survivors during the follow-up period, no patient developed recurrent symptoms of SVC syndrome.[29] When reviewing other series from the literature, however, we found that the patency of ePTFE grafts at 2 years was approximately 70%. In our experience, some thrombus formation occurs even in patent ePTFE grafts. Thrombosis occurs much more in patients in whom the distal anastomosis is performed with the internal jugular or the subclavian veins, and results appear much better in patients with innominate or SVC interposition grafts. Similarly to our experience, Shintani et al.[63] noted a greater incidence of occlusion in bifurcated than in straight grafts. Although spiral vein grafts continue to be our first choice for SVC replacement, short, large-diameter ePTFE is an excellent alternative for SVC replacement and cryopreserved vein grafts. Success with femoral vein grafting as an arterial conduit has resurrected this autologous graft for large vein reconstructions as well.[45] Recent reports demonstrating good early results indicate that, when available, autologous femoropopliteal vein grafts show promise for the replacement of large central veins. All six femoral vein grafts performed by us have remained patent. Still, the morbidity of harvesting a deep vein in patients with thrombotic potential and venous thrombosis elsewhere in the body is not well known. Two of our six patients who underwent SVC reconstruction using the femoral vein have mild but persistent swelling and venous claudication. Nonetheless, it is a good conduit in patients with an unavailable or inadequate saphenous vein.

Post-operative follow-up is important, but unfortunately, duplex scans provide only indirect evidence regarding the patency of an intrathoracic graft. Therefore, contrast or magnetic resonance venography are used, and they are performed before discharge and again at 3–6 months after surgery. In our experience, most graft stenoses presented within 1–2 years after implantation and were invariably associated with recurrence of symptoms (Figure 53.10). The need for re-intervention occurred mostly during this time period with durable patency thereafter, unlike the continuing need for re-intervention following endovascular treatment, especially in patients with benign disease (Figure 53.11).[11] Endovascular therapy, however, remains an invaluable adjunctive measure for the treatment of graft stenoses and to improve long-term graft patency.[24,26] Relief from symptoms was equally good following endovascular and open surgical reconstruction (Figure 53.12).

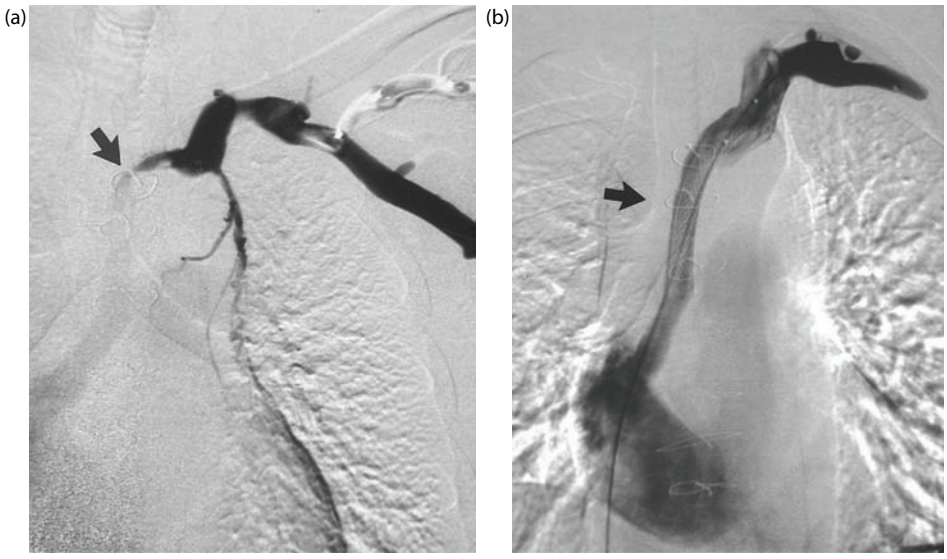

Figure 53.10 **(a)** Venogram 10 months after placement of a left innominate vein–right atrial appendage spiral vein graft reveals severe stenosis at the proximal anastomosis (arrow). **(b)** Successful reconstruction with placement of a Wallstent. (From Alimi YS et al. Reconstruction of the superior vena cava: Benefits of postoperative surveillance and secondary endovascular interventions. *J Vasc Surg* 1998;27(2):287–99; 300–1.) 2008

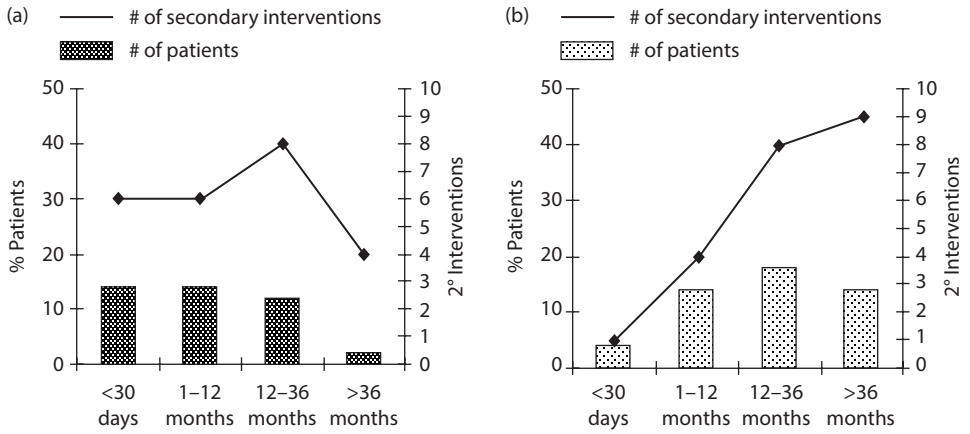

Figure 53.11 Treatment of benign superior vena cava syndrome. Secondary interventions required to maintain patency in **(a)** the open surgical group ($n = 42$) and **(b)** the endovascular group ($n = 28$). The bars represent the percentage of patients in each group and the line graphs represent the total numbers of interventions. (From Rizvi AZ et al. Benign superior vena cava syndrome: Stenting is now the first line of treatment. *J Vasc Surg* 2008;47(2):372–80.)

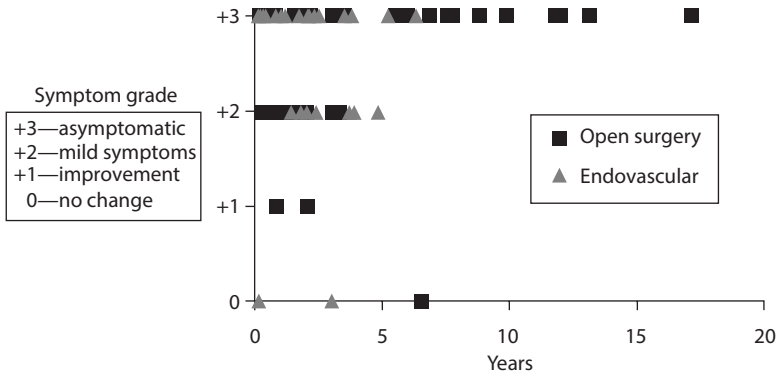

Figure 53.12 Grading of symptom relief at last clinical follow-up in patients undergoing open surgical reconstruction ($n = 42$) or endovascular repair ($n = 28$). (From Rizvi AZ et al. Benign superior vena cava syndrome: Stenting is now the first line of treatment. *J Vasc Surg* 2008;47(2):372–80.)

53.10 CONCLUSIONS

The incidence of SVC syndrome is increasing with the growing use of indwelling catheters and pacemakers. The techniques of endovascular treatment have been refined and experience with their use has increased. Endovascular treatment is now an appropriate primary intervention in patients with SVC syndrome of both malignant and benign etiology. It is less invasive and has lower morbidity than open surgical reconstruction, with equal efficacy and patency in the mid-term, albeit at the cost of multiple secondary interventions. Covered stents may prove to have a decreased need for re-intervention; however, it is too early in the experience to draw conclusions. Endovascular therapy does not adversely affect the feasibility or patency of subsequent open surgical reconstruction and is also a helpful adjunct to prolonging the patency of the grafts used for SVC replacement. Open surgical treatment of SVC syndrome with spiral vein grafts, prosthetic grafts or autologous femoral vein grafts is effective, provides long-term relief, and remains an excellent option in patients who are not suitable for or who fail endovascular treatment.

Guidelines 5.1.0 of the American Venous Forum on the surgical and endovenous treatment of superior vena cava syndrome

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.1.1	In patients with malignant superior vena cava obstruction, we recommend stenting as the primary therapy, unless the malignancy can be excised.	1	A
5.1.2	In patients with superior vena cava syndrome due to non-malignant etiology, we recommend endovascular treatment as the initial therapy.	1	B
5.1.3	We recommend open surgical reconstruction of the superior vena cava with spiral vein graft, autologous femoral vein, or expanded polytetrafluoroethylene graft if the patient is not suitable or fails endovascular therapy.	1	B

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● = Key primary paper
★ = Major review article

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Management of traumatic injuries of large veins

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54.1 INTRODUCTION

Trauma is the fifth leading cause of all civilian deaths in the United States, and the leading cause of death for the population aged 1–44 years.[1] Injuries to young persons aged 25–44 years account for approximately 70% of the total costs of injuries yearly.[2] Similarly, in military trauma, the average age of wounded soldiers is 22 years.[3] Approximately 30% of all soldiers injured in the Global War on Terrorism (GWOT) had some form of vascular injury. The true incidence of venous injuries is underreported in most series. In the GWOT Vascular Trauma Database, only 85 patients were documented as having sustained 106 named venous injuries compared with over 200 arterial injuries over the same 5-year period.[4]

Historically, venous disease reporting and management had lagged behind arterial disease. The first successful lateral repair of a lacerated femoral vein is reported to have been performed by Schede in 1882.[3] In addition, Goodman is also reported to have performed one of the first wartime venous repairs in 1918.[4] However, ligation of venous injuries was the accepted standard of care during World War I. In an attempt to improve limb salvage, Makins in 1919 recommended ligation of the uninjured vein when an arterial injury was treated by ligation.[5] It was not until the work by Hughes and Rich et al. in 1955 and 1970, respectively, that it was shown that repair of military venous injuries could be performed safely.[6,7]

Most venous injuries occur in combination with arterial injuries. Isolated venous injuries occur much less commonly. Quan et al.[4] reported only 25% of patients with extremity vascular trauma who had isolated venous injuries.[4] This current report is similar to historical reports on the incidence of venous injuries occurring during wartime. Despite dramatic differences in the magnitude of injury, reports on civilian vascular trauma show that the majority (75%) of venous injuries also occur in association with arterial injuries.[6–9]

54.2 ETIOLOGY

The majority of injuries occurring in the United States do so during motor vehicle accidents. Injuries resulting from the use of firearms are the second leading cause of injury death in the United States, but this is the leading cause of vascular injury. Penetrating injury from gunshot wounds is also the leading cause of venous injury. Venous injuries from other causes occur much less frequently, including stab wounds (1%–28%), blunt trauma (1%–23%), and shotguns (1%–17%). Nonetheless, iatrogenic venous injury occurs during various surgeries with unknown prevalence. Annually, over 1 million total joint replacement surgeries are done in the United States according to the Centers for Disease Control and Prevention (CDC). Arterial injury occurs at a rate of 0.15%–0.2%. It is likely that venous injuries occur more frequently, but are underreported in the literature. In addition, Oktar[10] and Mandolfino et al.[11] reported on venous injuries and their management during radical cancer surgery. Oktar[10] reported that the most common sites of venous trauma were the iliac and femoral veins. Primary repair was possible in 76.6% of these injuries. This was accomplished via lateral venorrhaphy or end-to-end anastomosis. The rest of the injuries were managed with interposition graft, patch venoplasty, or venous ligation. On the other hand, Mandolfino et al.[11] reported that venous injury in radical cancer surgery carries high morbidity and mortality, mainly due to massive bleeding. They concluded that rapid vascular control and venous repair would improve early and late outcomes.

Historically, the majority of military vascular injuries result from penetrating trauma caused by projectiles that

are generated by explosive devices.[3,7,9] The type of explosive devices has changed over time from mortars and shells to the present-day improvised explosive devices (IEDs). Numerous reports on the conflicts in Iraq and Afghanistan have stated that up to 70% of patients are wounded by IEDs, 20% by high-velocity rifles, and 10% by blunt traumatic injury.[3,12]

54.3 DISTRIBUTION OF INJURIES

A review of the recent literature shows that nearly 90% of civilian venous trauma occurs in the extremities, with a near equal distribution between the upper and lower extremities.[2] Gaspar and Trieman[13] documented the incidence of civilian venous injuries as 17% femoral vein, 15% inferior vena cava (IVC), 15% internal jugular vein, 14% brachial vein, and 8% popliteal vein. In a report from Louisiana State University, Smith et al.[14] reported 25% of venous injuries involved the iliac veins, 45% involved the femoral vein, 20% involved the popliteal vein, and 10% involved the basilic vein.

Owing to the use of truncal body armor and ballistic helmets, truncal injuries are unusual in military vascular trauma. A review of military injuries reveals that injuries to the head and neck accounted for 31% of overall injuries, with the trunk accounting for 14%, lower extremities accounting for 26%, and upper extremities accounting for 30%. Injuries to the superficial femoral vein accounted for the largest percentage of venous injuries (37%) during the Vietnam conflict. Injuries to the popliteal vein occurred in 29.3% and injuries to the common femoral vein (CFV) occurred in 5%. Upper extremity venous injuries were less common, with brachial vein injuries accounting for 14% and axillary vein injuries accounting for 5%.

54.4 DIAGNOSIS

Diagnosis of injuries to major extremity venous structures may not be obvious on initial presentation. The presence of an associated long bone fracture or nerve injury should increase suspicion of a major venous injury. Patients may present with non-expanding hematomas or simply slow, continuous hemorrhage from a missile track. More commonly, major extremity venous injuries are diagnosed during exploration for an associated arterial injury. Lacerations or transections of injured veins are easily recognized but often overlooked. These injuries may simply be managed in the process of exposing and managing an arterial injury.

Recognition of injured venous structures in patients with non-life- or non-limb-threatening trauma can be more of a challenge. Ultrasonography is the initial technique of choice for the detection and evaluation of venous thromboses associated with trauma. The loss of spontaneous venous flow, respiratory variation, and compressibility confirm venous thrombosis. Gagne et al.[15] reported that color-flow duplex ultrasonography detected seven of eight (88%) venous injuries in 37 civilian patients with penetrating proximity extremity trauma. In military conflict, we find the use of ultrasonography extremely limited owing to the presence of large soft-tissue defects or external fixators. For this reason, either conventional venography or late-phase analysis of 64-slice computed tomography (CT) angiography is utilized for venous imaging. Both of these techniques, however, may be non-diagnostic because of artifacts created by retained missiles or fragments.

54.5 TREATMENT

To ligate or not to ligate… This dilemma in venous injury management has been the subject of controversy in the trauma and vascular literature alike.

54.5.1 Ligation

The most common method of managing venous injuries is ligation. This is true for both non-axial and major axial veins such as the common femoral, femoral, or popliteal veins. Several reports exist on the results of venous ligation after civilian trauma.[12,16,17] This method of management is the most expedient and appropriate for venous injuries associated with other multisystem life-threatening injuries. In more controlled circumstances, however, the ligation of venous injuries remains controversial regarding the short- and long-term effects of ligating the main venous outflow to the extremity, namely the iliac, common femoral, and popliteal veins. The immediate effects of venous ligation include not only venous hypertension and increased compartment pressures, but also diminished arterial inflow. This was demonstrated in several animal studies by Hobson et al.[18] and Wright et al.[19] Most reports agree that the immediate side effects of venous ligation can be minimized by the liberal use of fasciotomy, appropriate fluid resuscitation, and post-operative limb elevation. Long-term side effects of iliac, common femoral, or popliteal venous ligation have generally shown a higher incidence of edema and chronic venous insufficiency after ligation compared with venous repair[20,21]; however, this has not been found by all investigations.[22,23] Ligation was the principal method of management of military venous injuries up to and through the Korean War. Not until Hughes[6] and Spencer and Grewe[24] began to explore the possibilities of arterial repair did they begin to attempt repair of military venous injuries. In the wars in Iraq and Afghanistan, ligation of venous injuries continued to be the most common method of managing the majority of axial and non-axial venous injuries.

The physiologic effects of axillary, femoral, or popliteal vein ligation might be extrapolated from reports on the harvest of the axillary or femoropopliteal veins for vascular reconstruction. Raju et al.[25] found only transient mild upper extremity swelling in less than 2% of patients undergoing axillary vein valve transfer for the treatment of popliteal vein reflux. The ligation and excision of the femoropopliteal vein for arterial reconstruction was first reported by Clagett et al.[26] Their group, as well as Wells et al., reported finding that less than a third of patients had lower extremity edema,

and no patient had major chronic venous changes or venous claudication.[26,27] They found that fasciotomy was performed in 20.7% of limbs in response to the development of severe venous hypertension after complete deep vein harvest below the adductor hiatus. In contrast, the authors found that fasciotomies were not required in patients undergoing subtotal deep vein harvest ending above the adductor hiatus. In addition, a fasciotomy was performed in 76.0% of limbs undergoing concurrent ipsilateral great saphenous vein and deep vein harvest, compared with 11.7% of patients undergoing deep vein harvest alone.[28] These observations show that elective harvest of the femoropopliteal vein conduit is possible and that the associated morbidity is acceptable. They may not, however, accurately reflect the physiologic situation of the acutely injured extremity with large soft-tissue injury and acute interruption of extremity lymphatics, in addition to compromised venous drainage. It is also important to note that multiple studies have reported on the importance of maintaining the profunda femoris venous flow in cases of femoropopliteal venous harvesting. The profunda femoris vein becomes the primary outflow for the lower extremity via collateralization to the distal popliteal/calf veins. This has to be taken into account in trauma situations, as the profunda femoris vein might also be injured with extensive lower extremity trauma. In these cases, ligation of the femoral vein might have a deleterious effect on maintaining the limb's survival. We would recommend maintaining either femoral or profunda femoris outflow unless it is a limb versus life situation.

54.5.2 Primary repair

In 1955, Hughes[6] reported the successful repair of 13 venous injuries occurring in patients with concomitant arterial injury. Stimulated by this experience, Rich et al.[9,21,29,30] investigated the utility of venous repair during the Vietnam War. Following these results, repair of traumatic venous injuries in civilian trauma has also been reported by several centers over the last 30 years.[14,16,31] Simple lateral suture repair is the most common method of managing civilian venous trauma,[14,23] with 76%–93% patency in short-term follow-up. Reports from the Korean and Vietnam Wars have shown that lateral venorrhaphy was used in 85% of venous repairs.[7] Similarly, lateral venorrhaphy has been employed most often for the management of venous injuries during the wars in Iraq and Afghanistan.[4]

Venous repair should be considered when dealing with major outflow veins of the lower extremity, such as the iliac, common femoral, or popliteal veins. After debridement of the injured venous segment back to the normal vein, the surgeon should then assess whether an end-to-end repair can be performed. This is usually achievable after mobilization of the proximal and distal venous segments. Reports from civilian institutions have shown that end-to-end venous repairs of the femoral vein have been very successful, with patency rates of up to 74% in the early post-operative period. Hughes[6] reported the first use of end-to-end anastomosis for the management of military venous trauma in 1955. In more recent conflicts, end-to-end repair of major venous injuries has been documented rarely in injured United States service personnel.[4]

In case of vena cava, mesenteric, or iliac venous trauma, primary repair can usually be accomplished via lateral venorrhaphy or patch venoplasty. Patching can be done utilizing an autologous venous or a synthetic polytetrafluoroethylene patch repair.

54.5.3 Interposition grafting

When there is a large segmental loss of the common femoral or popliteal vein, interposition grafting is the procedure of choice. The great saphenous vein is an excellent conduit for the majority of interposition grafts and should be harvested from the uninjured or contralateral lower extremity. When performing interposition grafting in the venous system, the vein is used in a non-reversed fashion. In civilian trauma series, interposition grafting accounts for 11%–42% of venous repairs according to several recent reports.[16,23] Long-term patency of interposition grafts, however, have been somewhat disappointing, with 30-day patency rates reported in the range of 40%–75%. The largest military experience with vein graft interposition for the repair of venous injuries has been reported by Rich et al.[9,21,29,30] During the Vietnam War, 4% of patients with venous injuries underwent surgery for major venous injuries. In recent military conflicts, use of this technique has rarely been reported.

Prosthetic conduits have been used for traumatic vascular reconstruction when the great saphenous vein is of inadequate size, poor quality, or is needed for venous outflow in the multiply injured patient.[32] These conduits have performed well over the short term. Interposition grafting using expanded polytetrafluoroethylene (ePTFE) bypasses has led to diminished venous hypertension and the ability to evacuate the patient to a facility where reconstruction using autologous conduits can be performed. Reports regarding the long-term patency of these conduits in the venous system have been less impressive than in terms of the short-term patency. Borman et al. found that roughly 100% of these grafts used for civilian venous injuries were thrombosed at post-operative follow-up.[33] However, other reports[34] have demonstrated better longer-term patency rates of ePTFE grafts for venous reconstruction, which ranged between 45% and 80% at an average follow-up of 16–24 months. In recent conflicts, ePTFE interposition grafts have been used as temporary shunts in the venous system and have facilitated the rapid evacuation of many patients back to the United States. Experience has shown that these prosthetic venous reconstructions have limited the effects of venous hypertension, thereby facilitating extremity wound management.

Spiral and panel grafts are rarely used for the management of venous injuries.[33–35] In 1997, surgeons from the University of Medicine and Dentistry of New Jersey published their experience with the use of complex venous

repairs for the management of civilian venous trauma.[15] These authors found that only 8% of patients received spiral vein grafts and 11% received panel grafts in the iliac, common femoral, or popliteal veins. The patency of these complex repairs is significantly lower than when simpler techniques are used. Nearly 50% of these repairs will be thrombosed in the early post-operative period. The use of panel or spiral grafts for military injuries has not been reported.

54.5.4 Temporary shunting followed by repair

The use of temporary shunts has been advocated by several civilian trauma groups for the management of critically ill patients who are deemed too ill for prolonged surgery and vascular repair. These groups advocate for the use of intravenous as well as intra-arterial shunts.[36,37] Basic science investigations have shown that shunts are effective and maintain patency without the use of systemic anticoagulation in the short term.[38] Recently, military vascular surgeons have revisited the use of intravascular shunts for the management of venous and arterial injuries. Rasmussen et al.[12,39,40] reported their series of 126 vascular injuries treated with intravascular shunting in Iraq. In this series, the authors reported a high degree of short-term patency in a small subset of proximal venous injuries treated with silastic shunt interposition.

In an unstable patient with a vena cava injury that requires repair, utilization of atrial–caval shunts to temporize the patient's injury until it can be repaired should be considered.[41]

54.5.5 Endovascular repair

Over the past 10–15 years, many reports have emerged supporting the utilization of endovascular techniques in the management of venous trauma, which ranges from endovascular assistance for open repair to complex endovascular reconstructive techniques. Tillman et al.[42] reported on the utilization of low-pressure, high-compliance elastomeric balloons for the control of iliac venous flow while performing primary repair of a pelvic venous injury. Burket,[43] Azizzadeh et al.,[44] and Anaya-Ayala et al.[45] have all reported the utilization of aortic endografts for the repair of vena caval tears. Watarida et al.[46] reported using a fenestrated endograft for the repair of a juxtahepatic IVC injury.

Similarly, management of injury to major veins within the chest and abdomen is usually dictated by the patient's hemodynamic status. Generally speaking, in an unstable patient, an IVC injury below the renal veins can be managed with ligation since the azygos and hemiazygos systems can usually provide adequate collateral venous drainage for the abdominopelvic region. If repair is warranted for the IVC, surgical repair can be accomplished by lateral venorrhaphy or polytetrafluoroethylene patch repair. In an unstable patient who will need the injury repaired, utilization of atrial–caval shunts to temporize the patient's injury until it can be repaired has been reported.[39,41] Injury to the portal vein and the superior mesenteric vein carries a high mortality risk. Ligation can be done to either structure if needed. Nonetheless, most surgeons would recommend a second-look operation in order to assess the viability of the liver and the bowel, respectively.[44,47] Repair is usually done by lateral venorrhaphy or vein patch venoplasty.

54.6 OUTCOME

It is important to understand that hemodynamically significant venous injury might not be very common, but the problem lies in their outcomes. Oderich et al.[48] reported that despite a rigorous and aggressive management strategy, iatrogenic abdominal and pelvic venous injuries can be devastating. This group reported that complications occurred in almost 70% of patients and carried a mortality rate of 18%. The key to managing these injuries is early recognition and expeditious management of the injury. The goal is to utilize the technology at hand to facilitate the best outcome possible for each individual patient. Long-term follow-up of traumatic venous injuries ranging from 6 to 20 years after the initial management has been reported. These studies have shown patency rates for simple repairs in the range of 67%–100% in long-term follow-up.[29,30,49] In recent conflicts, we have found that six out of 39 (15%) vein repairs thrombosed in the post-operative period. Two patients developed phlegmasia, both as a result of a CFV ligation.

Morbidity from complications of venous repairs, such as pulmonary emboli or deep venous thrombosis, has been cited as a reason to avoid these techniques when managing venous trauma. Numerous reports from both military and civilian trauma centers, however, have not found a high incidence of venous thromboembolic complications (0%–1%) in patients managed by venous repair.[24,32] Quan et al.[4] presented an extensive report on their military experience with venous injuries. They reported three of their patients experiencing post-operative venous thrombosis after primary repair of major lower extremity veins and two patients experiencing the same after interposition grafting. Three patients developed pulmonary embolism after saphenofemoral vein repair with an interposition vein graft. Two patients developed pulmonary embolism after ligation of an injured vein, one patient from a brachial vein ligation and the other from an iliac vein ligation. In this study, the authors found no significant difference with regard to pulmonary emboli when comparing ligation with venous repair (3.1% vs. 2.5%, P = non-significant).

54.7 CONCLUSIONS

The management of traumatic venous injuries should be performed with consideration for the overall physiologic status of the patient. For patients with multisystem injury

and who are hemodynamically unstable, ligation of the venous injury—even if caval, iliac, common femoral, or popliteal—would be prudent. In stable trauma patients with single-system injuries, however, major venous injuries should be repaired if possible. Specifically, the axillary, subclavian, common iliac, external iliac, common femoral, and popliteal veins and the vena cava should be repaired. Even short-term patency of these veins in the acute trauma patient will help to avoid massive swelling distal to these injuries in the extremities and the possibility of developing a compartment syndrome. To date, there is no evidence that repair of venous injuries leads to a higher incidence of venous thromboembolic events. If repair of these injured veins is not safe or possible, ligation is the obvious alternative and should be accomplished. In these cases, the surgeon should expect massive extremity swelling in the acute setting and manage it accordingly. Fasciotomies should be performed on the involved extremity, accompanied by elevation. If repairing the venous injury is decided, choosing an open repair versus an endovascular repair is based on the type of injury and the comfort level of the surgeon with endovascular techniques. There are no data comparing the outcomes of open versus endovascular repair of traumatic venous injuries. The safest method should be the approach of choice.

After reviewing the literature, we believe that developing a grading system to unify the classification of reported venous injuries in the literature should occur. Based on our literature review, we recommend a four-tier grading system to classify all venous injuries and to guide their management. Further studies to validate this grading system would be needed. Our grading recommendations are proposed as such:

Grade I: puncture injury—management is pressure or suture repair
Grade II: laceration in hemodynamically stable patients—management is lateral venorrhaphy or consideration of endovascular management
Grade III: transection in hemodynamically stable patients—management is end-to-end anastomosis or interposition graft
Grade IV: in a hemodynamically unstable patient, management is bypass versus ligation

Guidelines 5.2.0 of the American Venous Forum on the management of traumatic injuries of large veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.2.1	For the management of a grade I puncture injury, we recommend pressure or suture repair.	1	B
5.2.2	For the management of a grade II injury (a laceration in a hemodynamically stable patient), we recommend lateral venorrhaphy or consideration of endovascular treatment.	1	B
5.2.3	For the management of a grade III injury (a transection of a large vein in a hemodynamically stable patient), we recommend end-to-end anastomosis or interposition graft.	1	B
5.2.4	For the management of grade IV large vein injury in a hemodynamically unstable patient, we recommend bypass versus ligation.	1	B

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● = Key primary paper
★ = Major review article

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Primary and secondary tumors of the inferior vena cava and the iliac veins

THOMAS C. BOWER AND BERNARDO C. MENDES

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55.1 INTRODUCTION

The majority of tumors which involve the inferior vena cava (IVC) or iliac veins are malignant. Early diagnosis is uncommon, and for this reason, patients with these malignancies present at an advanced stage and have a poor prognosis. While some gains have been made in neoadjuvant therapies to treat sarcomas and select adenocarcinomas, surgery remains the mainstay of treatment. The technical feasibility of aggressive surgical resection and IVC or iliac vein reconstruction in select patients has been firmly established by data from multiple centers around the world.[1–4] Moreover, recent series have shown overall and disease-free survival to be better in patients who undergo surgical resection with major venous replacement in comparison to non-operative therapies. Tumor types, clinical presentation, patient evaluation and selection, principles of management, and surgical techniques used to replace major veins will be reviewed in this chapter.

55.2 DEFINITION AND TUMOR TYPES

IVC and iliac vein tumors are divided into two types: primary and secondary. Tumors may involve the infrarenal, suprarenal, and suprahepatic segments, with the suprarenal segment further subdivided into an infrahepatic and retrohepatic portion. Some surgeons arbitrarily call the region around the renal vein–caval confluence the pararenal IVC segment.

Primary tumors originate from smooth muscle cells in the vein wall and exhibit intraluminal, extraluminal, or both mechanisms of growth. Termed primary venous leiomyosarcoma (PVL), these tumors are nodular or polypoid in appearance, firmly attached to the vein wall, but pathologically have less intratumor hemorrhage or necrosis as compared to other sarcomas. The most common location of PVL is the IVC, with the suprarenal segment involved most often. PVL is hard to distinguish from other retroperitoneal sarcomas if it is large and invades through the IVC wall. Distant metastases to the lung, liver, or bone are present in more than half of patients when diagnosis is made. These tumors are more prevalent in women than men and occur over a wide age range, with a mean age of 54.4 years reported by Mingoli and associates.[5] Median survival without surgical resection is measured in months.[5,6]

Secondary tumors are more common than PVL (Figure 55.1). The most common secondary tumor with IVC involvement is renal cell cancer (RCC) with tumor thrombus. This thrombus may grow within the IVC toward the right heart and is classified by its upper extent. The level of involvement carries implications for surgical treatment.[7] Level I thrombus is located within 2 cm of the renal vein; level II thrombus extends into the suprarenal IVC but is below the hepatic veins; level III thrombus extends across the hepatic veins but remains infradiaphragmatic; and level IV thrombus represents right heart involvement. Tumor thrombus is present in 4%–15% of patients, originates in the right kidney more often than the left, and is more frequent in cancers over 4.5 cm in diameter.[8–10] The majority of patients with tumor thrombus have it near the IVC–renal vein confluence. In another 30%–40% of patients, the thrombus

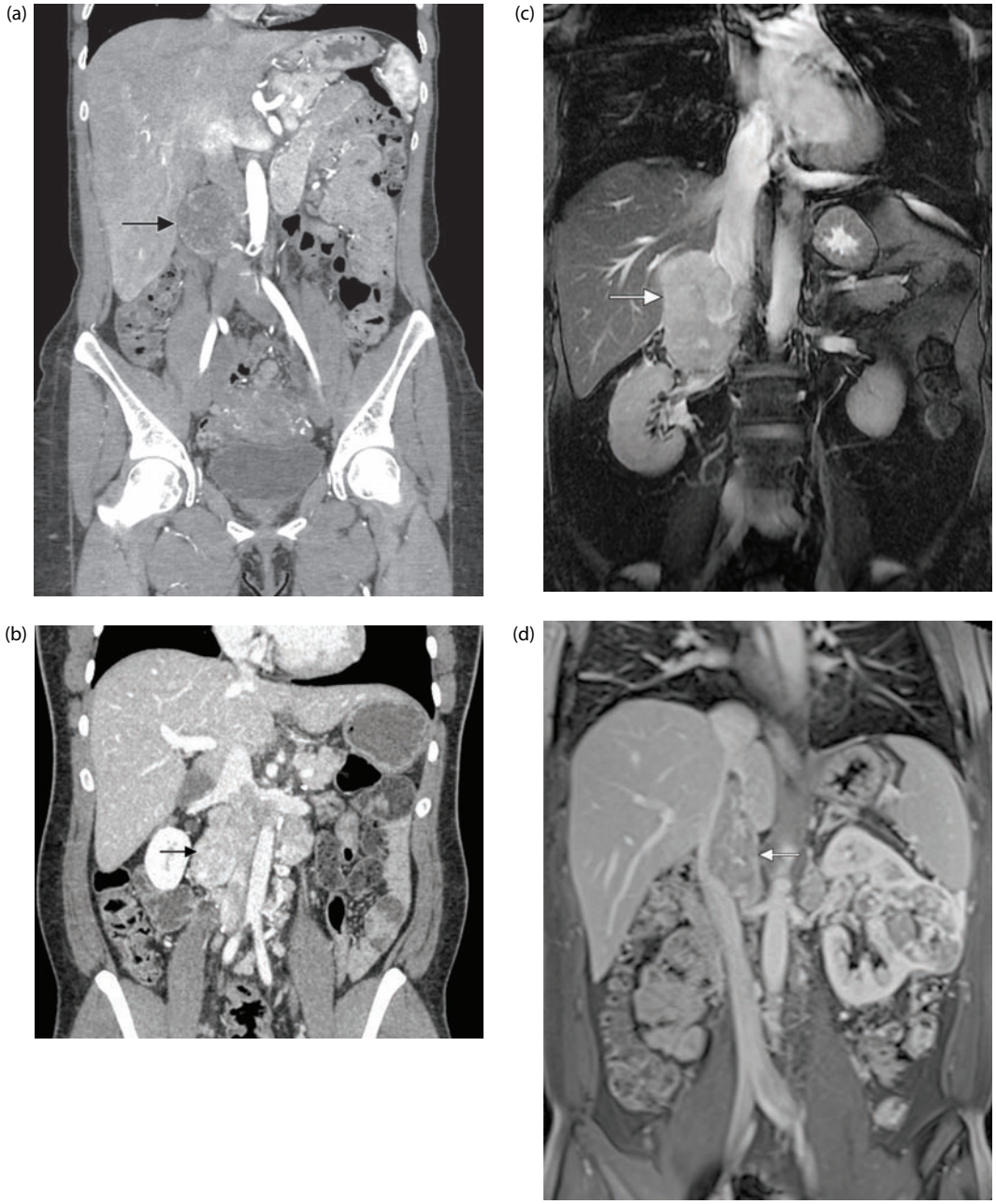

Figure 55.1 Coronal images of four different tumors (shown by arrows) involving the pararenal inferior vena cava (IVC). In **(a)** the lesion is circumscribed, causing indentation of the IVC, and was successfully resected without violation of the vena cava and proved to be a teratoma. **(b)** shows a paraganglioma involving the pararenal vena cava with nodal involvement along the aorta, extending into the iliac arteries and upper sacrum. This patient needed IVC resection and replacement. **(c)** proved to be a retroperitoneal sarcoma, and **(d)** represents tumor thrombus from a left renal carcinoma.

extends into the suprarenal segment, while the remaining 5%–10% of patients have right heart involvement, usually of the atrium.[7,8] Adrenocortical cancers and uterine sarcomas may also exhibit growth of tumor thrombus into the IVC or iliac vein.

Retroperitoneal sarcoma is the most common secondary tumor to extrinsically compress and invade the infrarenal IVC or iliac veins.[11,12] Approximately a third of these malignancies invade the IVC and exhibit both intraluminal and extraluminal growth, which makes them pathologically indistinguishable from PVL.[8,9] Germ cell tumors or teratoma of the inter aortocaval and paracaval lymph nodes may adhere to the veins, especially following cytoreductive chemotherapy or radiation. The age range of patients with malignancies which secondarily involve the IVC or iliac veins is between the fifth and eighth decades of life. Prognosis in this group of patients is also poor without surgery, with survival measured in months.

55.3 CLINICAL PRESENTATION

Patients with IVC or iliac vein malignancies present with symptoms and signs related to the tumor or its metastases, but rarely due to venous obstruction. Only 3% of patients with PVLs reported by Mingoli et al.[5] were asymptomatic at the time of diagnosis, while the others had multiple symptoms or signs. Abdominal pain was noted in at least two-thirds of the 144 patients in this series, a palpable abdominal mass was present in nearly 50%, lower limb edema was present in 39%, weight loss was present in 31%, and Budd–Chiari syndrome was present in 22%. Fever, anorexia, malaise, weakness, nocturnal sweating, vomiting, dyspnea, or other non-specific symptoms were noted in less than 15%. Others have reported rare findings such as consumption coagulopathy or red blood cell abnormalities.[5] Symptoms were present in a majority of the 102 patients with IVC graft replacement for primary and secondary tumors from the most recently presented Mayo Clinic data, with pain noted in 59%.[13] Weight loss, fatigue, or nausea occurred in a quarter of the patients, lower extremity edema affected 10%, and only one patient had a lower extremity deep vein thrombosis. Nearly 30% of the patients were asymptomatic but had a mass discovered on physical examination or by an imaging study. The widespread use and availability of computed tomography (CT) and magnetic resonance imaging (MRI) may enable earlier detection of such tumors.

Symptomatic IVC obstruction occurs from acute thrombosis when venous collaterals are poorly developed or when the venous hypertension caused by progressive IVC or iliac vein obstruction exceeds the capacity of the collaterals. Outflow obstruction by tumor thrombus in the right heart may cause arrhythmias, syncope, pulmonary hypertension, or right heart failure.[8,9] Hepatic vein obstruction causes hepatomegaly and may lead to the development of ascites or jaundice (Budd–Chiari syndrome). Frank liver failure is rare. Patients with suprarenal IVC occlusion may present with back or right upper quadrant abdominal pain, biliary tract symptoms, nausea, vomiting, renal dysfunction, or lower extremity edema. Nephrotic syndrome is unusual, and dialysis-dependent renal failure is uncommon because of collateral venous drainage from the left kidney, unless the patient has outflow obstruction from a solitary right kidney. Symptoms associated with infrarenal IVC or iliac vein tumor involvement include back, abdominal, or lower extremity pain; dysesthesias or weakness if there is invasion of the lumbosacral plexus, nerve roots, or psoas muscle; a palpable mass; or lower extremity edema.[9,13] Deep vein thrombosis is unusual with IVC malignancies, but more common in the rare patient with PVL of the iliac or peripheral veins.[6,8,9,14]

55.4 EVALUATION

Treatment for patients with IVC or iliac vein tumors involves medical, radiation, and surgical oncologists as appropriate to determine the tumor type, direct the evaluation, determine if resection is possible, and provide input regarding the need for chemotherapy or radiation therapy. If operation is possible, vascular, hepatobiliary, urologic, and cardiothoracic surgeons may be needed as part of a multidisciplinary team, depending on the type and location of the tumor and whether there is vascular involvement. CT or MRI are the procedures of choice to determine the extent of the tumor and the presence of regional or distant metastases. Venous phase imaging defines the severity of venous obstruction and the status of venous collaterals. MRI is the study of choice by many urologists to define the upper extent of intracaval tumor thrombus and to differentiate bland from tumor thrombus in the infrarenal cava.[15] However, some patients are intolerant of MRI and so need multi-detector CT imaging. A study of 41 patients by Guzzo et al. showed that pre-operative CT findings correlate with the intraoperative pathologic findings in 84% of this group, and the level of tumor thrombus was accurately demonstrated in 96% of patients.[16] Two small studies showed the accuracy of CT to be between 75% and 100%, and that of MRI to be between 75% and 88%.[17,18] MRI criteria have been studied for the prediction of IVC wall invasion in patients with RCC and tumor thrombus. An abnormal signal along the caval wall on gadolinium imaging, an IVC diameter of 40 mm or more, level III or IV thrombus, or the combination of an 18-mm IVC diameter and a renal vein ostium diameter of 14 mm predict vein wall invasion with as high as 90% sensitivity.[19] Psutka and colleagues from the Mayo Clinic recently created a multivariable model to predict the likelihood of vena cava wall invasion by RCC tumor thrombus and the need for IVC resection and complex venous reconstruction based on pre-operative radiographic imaging.[20] A blinded analysis was conducted by two radiologists of a number of anatomic factors measured from scans of 172 patients treated for RCC and level I–IV tumor thrombus during a 10-year period ending in 2010. There was strong interobserver concordance. Based on multivariable analysis of 38 patients who required IVC resection and a patch or prosthetic interposition graft, the authors found a nearly five-fold increase in IVC wall invasion if the IVC was occluded at the renal vein–caval ostium; a more than four-fold chance of invasion if the anterior–posterior diameter of the IVC at the renal vein ostium was 24 mm or greater; and an over three-fold risk of caval invasion if the tumor involved the right kidney.[20]

Venacavography is rarely used anymore unless the pathology of a CT- or ultrasound-guided biopsy of an intracaval mass is equivocal, treatment is dependent on the differentiation between tumor thrombus and bland thrombus, or if a positive biopsy would necessitate pre-operative adjuvant therapy. Transvenous biopsy may allow for better sampling.

Ultrasonography provides an accurate assessment of peripheral vein obstruction and can be used to determine the patency of the iliac veins or the IVC if CT or MRI are unclear in this regard. The authors routinely image the lower extremity deep veins to exclude occult deep vein thrombosis

in patients with pelvic tumors and iliac vein involvement. However, central vein assessment by ultrasonography is hampered by bowel gas or tumor distortion of the veins.[8,9] Pre-operative or intra-operative transesophageal echocardiography is sometimes used to corroborate the proximal extent of tumor thrombus if it is near the right atrium.[7]

If the tumor is localized and resection is felt to be possible, the next step is a thorough medical evaluation to assess the medical risk of the operation. A comprehensive cardiopulmonary evaluation is needed, particularly if the tumor involves the liver, retrohepatic IVC by direct invasion or from tumor thrombus, or if there is tumor thrombus in the right heart. Transthoracic, transesophageal, or stress echocardiography may be necessary, as well as pulmonary function tests and a resting arterial blood gas. Of equal importance is the assessment of patient performance status as proposed by the Eastern Cooperative Oncology Group (ECOG).[1] A performance score of 0 represents a fully active patient with no limitations in daily function, whereas a score of 4 indicates that the patient is bedridden and unable to perform self-care. Patients with performance status scores of 0 or 1 have the best chance of retaining postoperative functional capacity in our experience. We have done major tumor resections and IVC reconstructions in a handful of patients with performance status scores of 2, but recovery time is prolonged and few had improvements in performance. Patients with scores of 3 or 4 are not offered operation.[1,8,9,21]

55.5 TREATMENT APPROACH AND TYPES OF RECONSTRUCTION

Most patients with IVC tumors have advanced local or metastatic disease when diagnosis is made, so operation is not an option for treatment. Our surgical group does not consider operation for patients with diffuse metastases, a large central tumor in the mesentery that involves multiple large veins or arteries, poor cardiopulmonary function, or physical debility. However, we aggressively treat patients with localized tumors, good performance status, and few medical comorbidities, even if there is IVC or iliac vein involvement.[1,3,4,8,9,22–29]

Critical steps in pre-operative planning include choice of incision for optimal exposure to remove the tumor and control the major veins, the need for venous replacement and choice of patch or conduit, and whether hemodynamic support with veno-venous bypass or cardiopulmonary bypass is necessary. Consideration must be given to the tumor type, its extent, and the level of IVC involvement; whether liver or bowel will be resected en bloc with the tumor; the degree of caval obstruction; and the status and location of collateral veins.

In addition to the aforementioned issues, choice of incision is critical. Body habitus, location of the tumor and facility for control of the IVC or iliac veins weigh into this decision. A midline abdominal incision works well to expose the infrarenal or infrahepatic IVC for patients with narrow costal margins and those with enlarged subcutaneous abdominal wall venous collaterals. A bilateral subcostal incision works well for patients with wide costal margins who need exposure of the infra- or retro-hepatic IVC to remove large retroperitoneal sarcomas and to perform a hepatectomy or a nephrectomy. A median sternotomy can be added to a subcostal incision or extended from a midline incision in patients with large RCCs and level III or IV tumor thrombus in whom cardiopulmonary bypass may be needed. This is an important maneuver, as the liver is often engorged by the venous obstruction, which makes intra-abdominal mobilization of the liver and control of the suprahepatic IVC difficult and fraught with bleeding. Lastly, some patients with narrow costal margins and large tumors that need major liver resection and retrohepatic IVC replacement may be best approached through a right eighth or ninth interspace thoracoabdominal incision.[8] A radial or circumferential diaphragmatic incision facilitates exposure of the upper IVC in the latter case.

Surgical treatment of secondary tumors of the iliac veins is also dependent on the extent of tumor, but adjacent arterial and nerve involvement must be anticipated.[30–32] Long segment chronic occlusions of the iliac veins rarely require replacement, unless collateral veins are sacrificed in the course of resection. If the iliac vein is patent but requires segmental resection and replacement, the authors prefer externally supported polytetrafluoroethylene (PTFE) grafts, provided there is no violation of the bowel or genitourinary tract and the remaining iliac vein is healthy. If there is contamination of the field, spiral or panel saphenous vein grafts or cryopreserved aorta, iliac artery, or vein grafts can be used, depending on the native iliac vein size and the length of the defect. Venous reconstruction should follow arterial reconstruction when both vessels are resected.

55.6 IVC RESECTION WITHOUT REPLACEMENT

The decision to replace the IVC during tumor resection is controversial, but depends on whether or not the patient has problems from the caval obstruction, such as lower extremity edema or deterioration of renal function.[1,5,8,9,14] The IVC can be resected en bloc with the tumor with little venous morbidity in patients with chronic IVC occlusion and well-developed venous collaterals that are not interrupted by the operation.[2] Patients with rapid thrombosis of the IVC and/or lower extremity edema who have not had time to develop venous collaterals are best treated with graft replacement.[1,8,9]

Our preference has always been to reconstruct the suprarenal IVC because of the potential for acute kidney failure and lower extremity edema from resection only.[1,8,9,27] The ability to predict which patients will develop renal failure if the suprarenal IVC is not replaced is difficult, even if the paravertebral, lumbar, epigastric, adrenal, and gonadal venous pathways are patent.[8,9] While some surgeons do not

reconstruct the remnant left renal vein if the gonadal, adrenal, and lumbar veins are intact, our preference has been to reconstruct the renal veins by re-implantation or a short interposition graft (Figures 55.2 and 55.3). Direct outflow from the renal vein into the IVC should be preserved if the patient develops intra-operative anuria or has low urine output.[1,3]

55.7 RCC WITH IVC TUMOR THROMBUS

RCC with intraluminal tumor thrombus is the most common malignancy to involve the IVC. In most cases, the thrombus is removed en bloc with the kidney, except for some patients with very large cancers and bulky thrombus that extends high into the retrohepatic vena cava.[7–10] Early ligation of the renal artery may shrink the thrombus and "simplify" operation when the proximal extent of the tumor is near the hepatic veins or right atrium.[10,33] This may allow for IVC clamping above or immediately below the hepatic veins and obviate the need for cardiopulmonary bypass or total vascular isolation (TVI) of the liver. Intra-operative transesophageal echocardiography is useful to guide clamp position. Some patients with large cancers are best served by transection of the renal vein at the caval confluence and removal of the kidney before extracting the tumor thrombus.

Renal artery embolization has been described as a method to reduce tumor vascularity in large cancers in order to shrink the tumor thrombus. The Cleveland Clinic group compared the results of 135 patients who had pre-operative embolization, radical nephrectomy, and IVC tumor thrombectomy to 90 patients who did not have embolization.[34] There was no benefit with this technique. The embolized group had a higher mortality (13% vs. 3%) and a five-fold higher risk of peri-operative death by multivariable analysis. Treated individuals required more transfusions and had a higher post-operative complication rate (43% vs. 29%). Importantly, the level of tumor thrombus did not decrease. At the Mayo Clinic, renal artery embolization is reserved for palliation of symptomatic and inoperable RCC. Most blood loss during radical nephrectomy comes from disruption of dilated peri-renal and retroperitoneal veins, and these are not decompressed with renal artery embolization. Rather, retroperitoneal bleeding is reduced once the IVC has been cleared of thrombus and blood flow has been restored.

The majority of patients have tumor thrombus confined to the infrahepatic IVC, and this segment is isolated after the caudate lobe veins have been divided.[7] Clamping at this level rarely causes hemodynamic compromise. Patients with thrombus in the retrohepatic IVC extending to the hepatic veins benefit from TVI of the liver, which enables removal of the thrombus in a bloodless field. Occasionally, a replaced left hepatic artery or dilated lumbar veins may cause troublesome back-bleeding during TVI. Mobilization of the retrohepatic IVC on its right lateral side allows for ligation of these rare veins. Quite often, there is one or more dilated lumbar veins immediately posterior to the renal vein–caval confluence, which causes troublesome bleeding if not controlled before making the cavotomy. If such a lumbar vein cannot be easily ligated or clipped, control can be achieved with digital pressure posterior to the IVC or, more often, directly over the origin of the vein from within the IVC after the thrombus is mobilized. There initially is some blood loss with the latter. A few patients with level III thrombus require veno-venous bypass during TVI to support hemodynamics, but usually intravenous volume loading obviates this need.[7]

When tumor thrombus involves the right heart, cardiopulmonary bypass, hypothermia, and/or circulatory arrest may be necessary. Deep hypothermia increases the risk of coagulopathy. The liver is often congested in these patients, and mobilization of it to access the IVC is best done during low flow with the patient on bypass to avoid capsular tears.[7–9]

The IVC is closed primarily unless tumor adherence or wall invasion requires partial or circumferential resection. We patch the IVC if 50% of its wall circumference requires resection. Graft replacement is necessary if tumor is adherent to more than 50% of the caval wall. Zini et al. found a nearly six-fold increased risk of death from RCC among 32 patients who had incomplete removal of the tumor based on multivariable analysis controlling for tumor size, stage, and thrombus level.[19]

Some patients need interruption of the IVC because of adherent or chronic occlusive bland thrombus which forms caudal to the renal veins in order to reduce the risk of pulmonary emboli. The Mayo Clinic urology group reported 40 caval interruptions among 160 cases treated for level II, III, or IV tumor thrombus over a 24-year period.[35] The IVC was interrupted by either ligation, oversewing, or placement of a Greenfield filter. Post-operative venous-related disability, according to the American Venous Forum International Consensus Committee, was minimal in 60% of patients. No patient had class III disabilities. The aforementioned operative techniques also apply to other cancers which exhibit intracaval tumor extension.

55.8 IVC REPLACEMENT

The authors believe the IVC should be replaced if it is partially obstructed and a majority of its circumference requires resection to provide clear tumor margins.[1,4,8,9] Large-diameter externally supported PTFE grafts (20 mm) work well, and patency rates exceed 90% in more than 100 patients operated on at our institution to date (Figure 55.3). The UCLA group favors PTFE grafts as well, but uses smaller-diameter grafts because of the theoretical increase in blood flow velocities across the graft.[3] Aortic or venous homografts or cryopreserved allografts have been successfully implanted (Figure 55.2).[8,36] There may be an advantage to using prosthetic or autogenous grafts with higher radial and tensile strengths to withstand compression by the viscera. One of our patients with a femoral vein panel

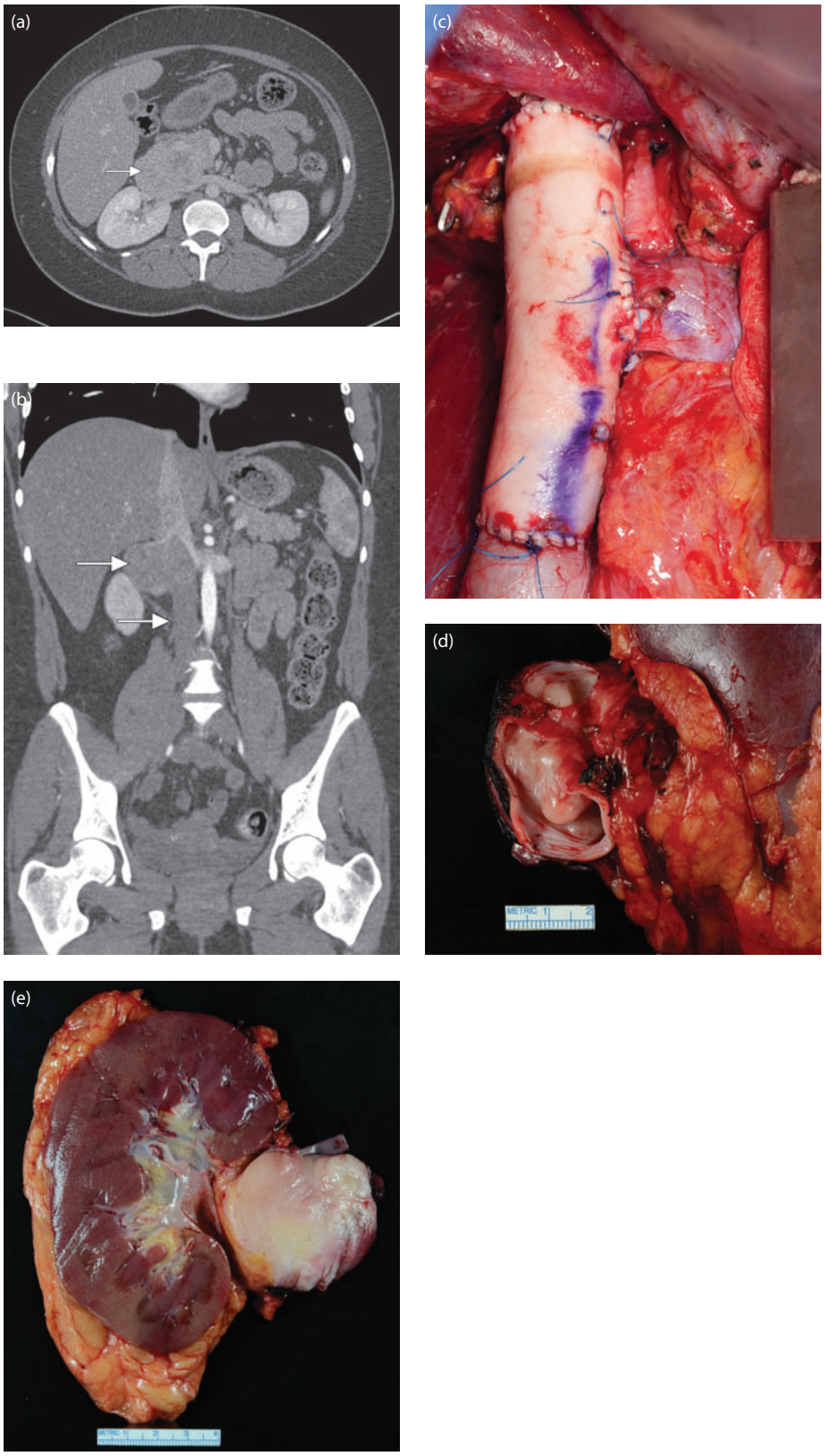

Figure 55.2 Cross-sectional **(a)** and coronal **(b)** images of a patient with a primary inferior vena cava (IVC) leiomyosarcoma involving portions of the suprarenal and infrarenal vena cava (arrows). The patient was reconstructed with a cryospreserved aortic allograft because part of the serosa of the duodenum required resection with the tumor. The left renal vein was re-implanted onto the caval graft **(c)**. Two images of the pathologic specimen are shown **(d** and **e)**. The tumor had nodular infiltration of the IVC. The bi-valve specimen shows significant infiltration of the renal vein, extending into the hilum of the kidney, as was seen on the computed tomography scan.

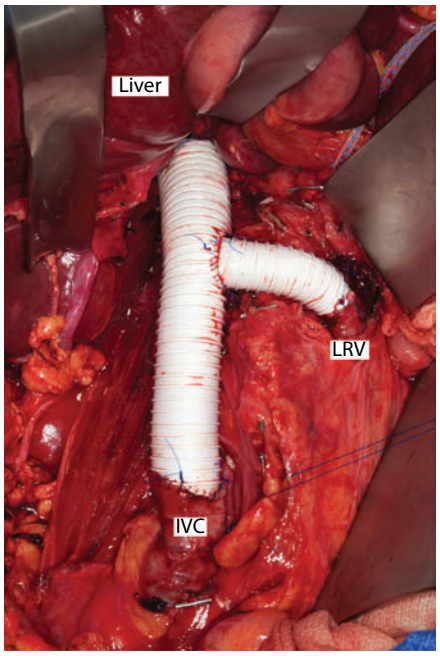

Figure 55.3 Graft replacement of the infrahepatic and infrarenal inferior vena cava (IVC) with a separate interposition graft to reconstruct the remnant left renal vein (LRV) following a right radical nephrectomy and tumor thrombectomy for renal cell cancer. The IVC reconstruction was prompted by tumor invasion into these segments and part of the left renal vein.

graft, which was placed because of bowel contamination, developed a stenosis at the upper caval anastomosis which required balloon angioplasty. Perhaps a spiral vein or homograft would have provided better radial force to resist visceral compression. Another patient required a stent to treat an anastomotic stenosis because of the lack of ring support in a PTFE graft. Our current practice is to leave the PTFE graft rings immediately at the anastomoses. Placement of an arteriovenous fistula to enhance graft patency is not necessary in our opinion.

55.9 RETROHEPATIC IVC REPLACEMENT IN CONJUNCTION WITH MAJOR LIVER RESECTION

A number of centers, including our own, have reported successful liver resection and retrohepatic IVC replacement for cancers or sarcomas.[1–4,22,24–27,29,36,37] Operations can be done *in situ* or with *ex situ* techniques. We believe *in situ* resection and IVC replacement has broader applicability and versatility and similar efficacy as *ex situ* resection and IVC replacement.[4]

The technique of combined liver resection and retrohepatic IVC replacement has been refined over the years.[4] Important steps include TVI, selective use of veno-venous bypass to maintain hemodynamics, a secure position for the upper caval cross-clamp, and early ligation of the lobar vasculature prior to parenchymal division. Intra-operative ultrasonography is used to exclude occult intraparenchymal metastases and to determine tumor proximity to major vascular structures, particularly the planned remnant hepatic vein. The infrahepatic IVC and the vessels in the gastrohepatic ligament are isolated before the liver is mobilized. The suprahepatic IVC is dissected free in either an infradiaphragmatic or immediate extrapericardial supradiaphragmatic location. Hepatic resection is performed using the CUSA device (Valley Lab, Boulder, CO) with periodic inflow vascular occlusion to the liver. Patients with polycystic liver disease or who need reoperation benefit from ischemic preconditioning because resection planes can be bloody. Before TVI begins, the suprahepatic IVC is temporarily cross-clamped to assess hemodynamic response. If systolic blood pressure cannot be kept over 100 mmHg with intravenous fluid, veno-venous bypass is performed via a cannula in the infrarenal IVC, a large-bore jugular vein catheter, and extracorporeal circulation via a roller pump. This technique is rarely necessary, but is advantageous for some old patients with underlying cardiopulmonary dysfunction.[1] Only 1000–2000 U of heparin is given before the IVC is cross-clamped, unless there has been significant blood loss during the liver resection, from which the patient may be auto-anticoagulated. Whether or not veno-venous bypass is used, once the surgeon is ready to complete en bloc tumor resection, the clamp sequence is infrahepatic IVC, portal triad, followed by the suprahepatic IVC. The upper caval anastomosis is performed during TVI and often includes the remnant hepatic vein(s). The anastomosis is tested and flushed with the patient in the head down position and the lungs inflated to 30 mmHg to avoid air embolism and to wash out acid metabolites from the liver. The clamp is transferred onto the graft. Graft position and length are marked during maximum inspiration and expiration, as the tendency is to cut the graft too long. A redundant or twisted graft will compromise hepatic vein and IVC blood flow. The lower anastomosis is fashioned end-to-end to the IVC. The graft is circumferentially wrapped with omentum to avoid contact with the bowel. The technical steps of the operation are outlined in Figure 55.4.

The major limitation to *in situ* liver resection and caval reconstruction is the warm hepatic ischemia time. Our last reported mean liver ischemia time was 18 minutes, but it can be unpredictable.[4] We have used cardiopulmonary bypass and hypothermic circulatory arrest to reconstruct two patients with PVL of the retrohepatic IVC because of an engorged liver, tumor involvement of the hepatic veins, and concern about warm ischemic injury (Figure 55.5). *Ex situ* hepatic resection and autotransplantation of the hepatic remnant have been successfully used at other centers because of the unpredictability of hepatic ischemia time.[28,37] Isolated hypothermic liver resection with protective liver perfusion allows time to perform difficult vascular reconstructions.[4,28,37] However, operative time is longer, there are often more vascular anastomoses which increase the potential for technical failure with subsequent mortality or liver

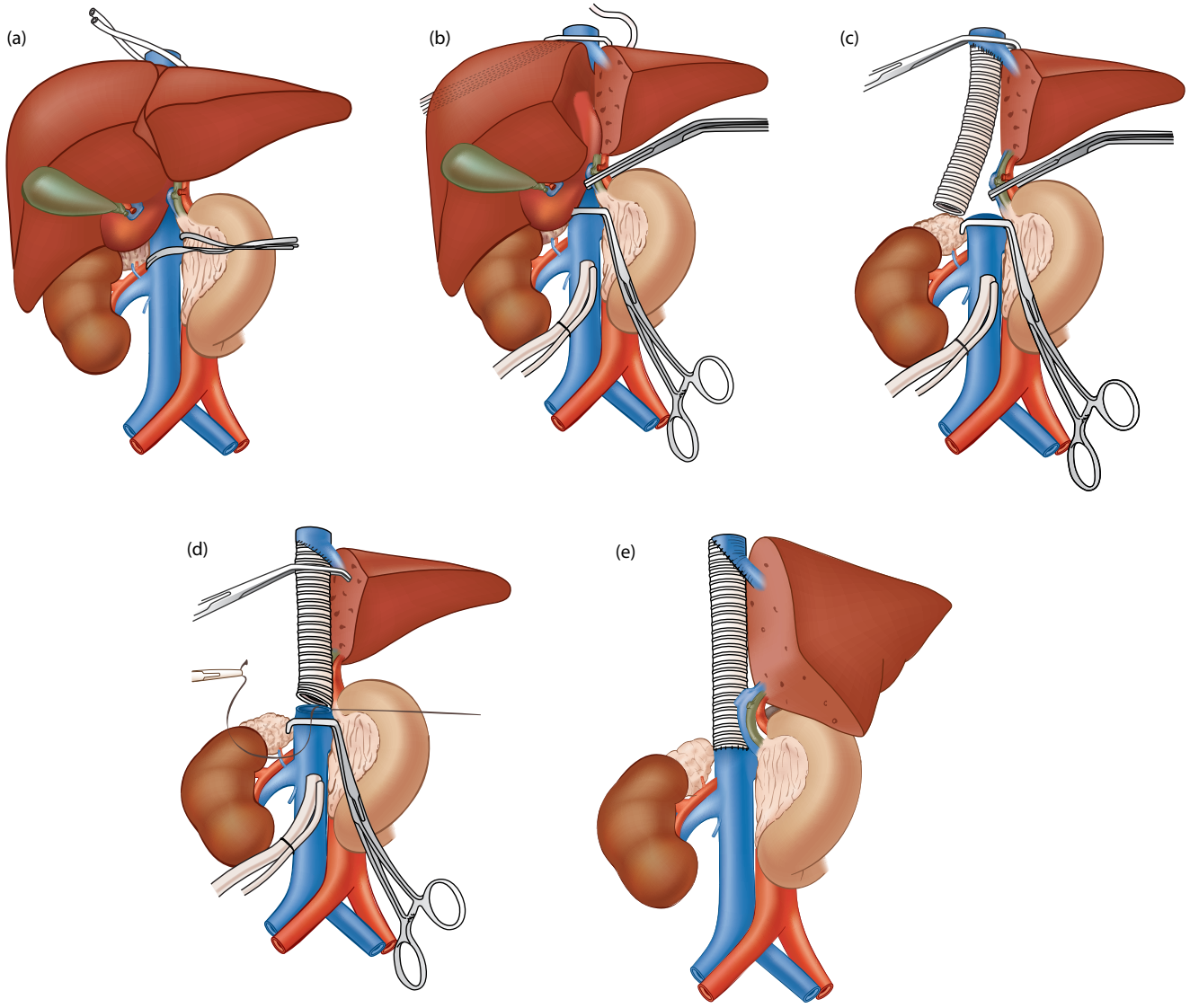

Figure 55.4 Key steps in the performance of retrohepatic inferior vena cava (IVC) replacement and liver resection. **(a)** Early isolation of the suprahepatic and infrahepatic IVC. **(b)** Vascular isolation of the liver just prior to completion of tumor and IVC resection. **(c)** Upper caval anastomosis performed with vascular isolation of the liver. Some patients require veno-venous bypass to maintain stable hemodynamics. **(d)** Blood flow is re-established through the liver and the lower caval anastomosis is completed. **(e)** Completed graft reconstruction with reattachment of the ligaments of the liver to avoid torsion of the hepatic venous outflow.

failure, and there is a real but low risk of salvage orthotopic liver transplantation.[17,18,27]

The accrued data from a number of centers have now firmly established the technical feasibility of these major operations.[1–4,22,24–27,29,36,37] The addition of other ischemic protective factors in order to preserve hepatic function, more detailed patient selection factors, and better neoadjuvant therapies may enhance the applicability and utility of these operations in the future.[4]

Liver function tests (LFTs) remain abnormal over the first several post-operative days, depending on the length of warm ischemia time. Generally, LFTs return to baseline within 7–10 days.[1,4,8,9] If the LFTs remain elevated beyond what is expected, ultrasound or CT imaging of the IVC graft and the remnant hepatic and portal veins is necessary. Some patients remain auto-anticoagulated for 24–48 hours after the operation. Subcutaneous heparin is begun once the surgeon feels that the risk of hemorrhage is low and as long as the platelet counts are in the normal range. Warfarin is begun prior to hospital dismissal, with a goal international normalized ratio of between 2 and 3. Anticoagulation is continued for at least 6 months as long as imaging studies show the IVC graft to be widely patent. Thereafter, patients with suprarenal IVC grafts are switched to aspirin only, because of the high blood flow volume.[1,4,8,9] Most patients with infrarenal grafts are anticoagulated lifelong. Other groups only use aspirin regardless of the location of the graft.[3]

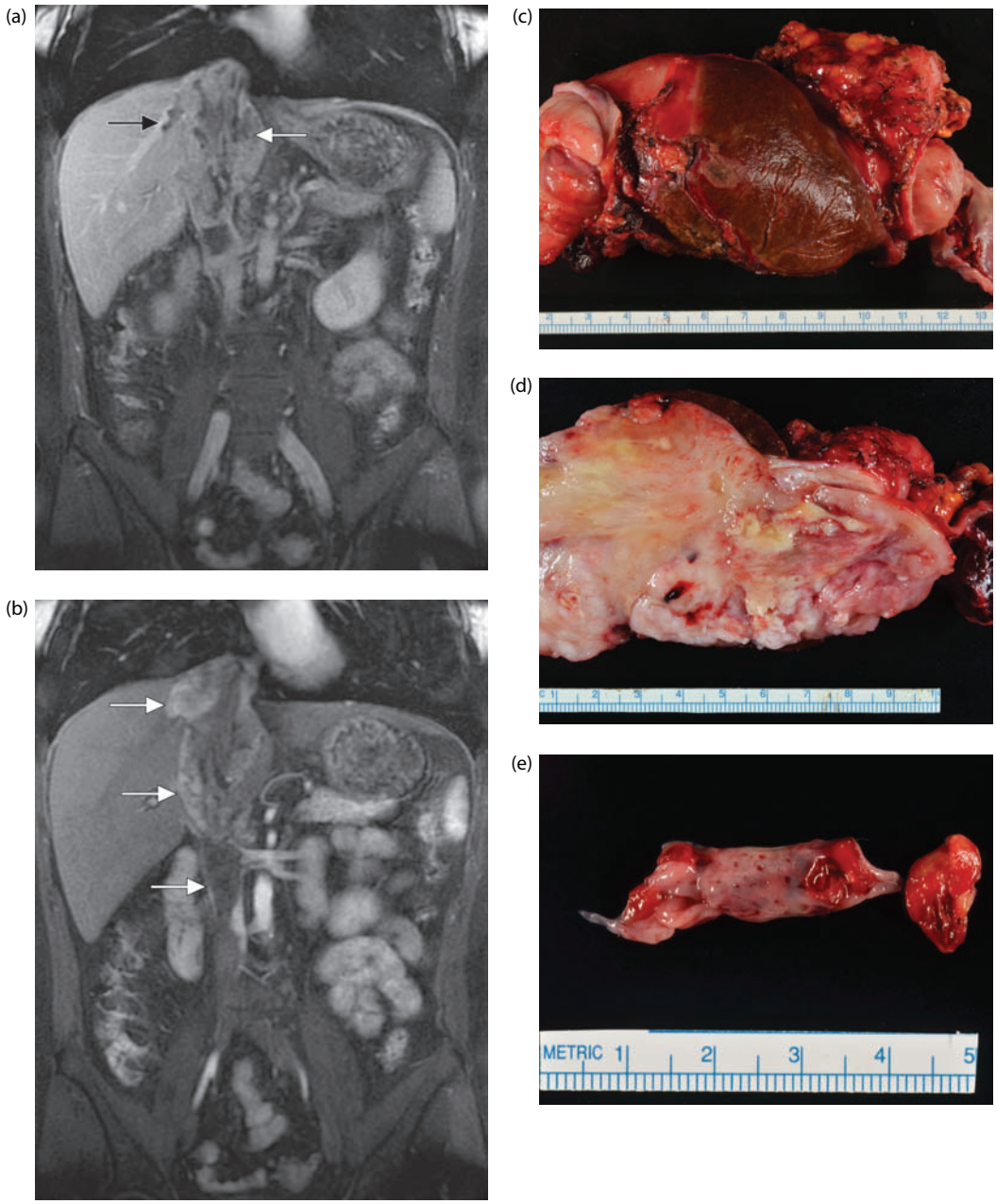

Figure 55.5 Coronal images **(a** and **b)** show a primary inferior vena cava (IVC) leiomyosarcoma involving the retrohepatic vena cava (white arrows show extent of tumor and bland thrombus). Thrombus was noted in the right hepatic vein **(a**, black arrow**)**. The patient proved to have thrombus extending into the left and middle hepatic veins as well. **(b)** shows bland thrombus extending below the left renal vein–caval confluence into the infrarenal segment (lower white arrow). Anterior **(c)** and posterior **(d)** views of the pathologic specimens show invasion of the IVC with nodular components. The patient was treated with cardiopulmonary bypass and a period of circulatory arrest to enable removal of thrombus from the hepatic veins **(e)**. (*Continued*)

55.10 MANAGEMENT OF THE ILIAC VEINS DURING TUMOR RESECTION

Management of the iliac veins during sacral resection or hemipelvectomies is challenging. Often, the anterior stage of the sacral resection is done first. If resection extends above the L5 vertebral body, the lower aorta and IVC require mobilization. There may be one to three small vein branches at the iliac vein–caval confluence and a moderate-size posterior branch near the right common iliac vein–caval confluence which can be thin walled or broad based. Simple ligation of these branches is ineffective, and suture ligation is needed. Isolation of the common and external iliac arteries and veins is done before dissection of the internal iliac artery and vein branches. Ligation of as many internal iliac artery and vein branches as possible reduces blood loss

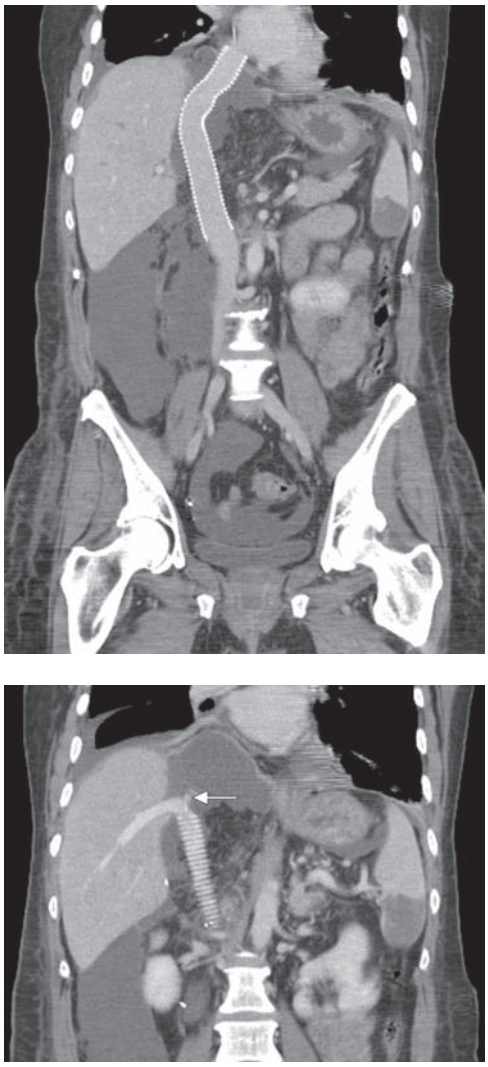

Figure 55.5 (Continued) The right hepatic and left and middle hepatic veins were re-implanted as two cuffs. Postoperative computed tomography venography shows a widely patent IVC graft extending from the cavoatrial junction to the left renal vein–caval confluence **(f)** and a patent re-implanted right hepatic vein **(g**, white arrow**)**. The last image is in partial profile as there is no filling defect within the IVC, nor any residual tumor mass.

during the bone resection. The internal iliac artery branches are ligated first to minimize distention of the internal iliac vein branches. Patients with high sacral resection may benefit from preservation of the anterior division branches of the internal iliac artery. We prefer to control but not ligate the main internal iliac vein trunk until the more caudal and posterior branches are isolated, ligated, and divided. This prevents distention of the distal branches. Some of these may be broad or thin walled and will cause troublesome bleeding if inadvertently injured. Short or broad-based vein branches along the pelvic sidewall are best oversewn or suture-ligated. Patch angioplasty of the external or common iliac veins is preferred over graft replacement if possible. If graft replacement is necessary, 12- or 14-mm diameter PTFE conduits work well. Replacement of both common iliac veins is rarely done if they are encased by tumor, and this is certainly not done if there is intraluminal tumor thrombus because the likelihood of occult distant metastasis is high. Similar to prosthetic IVC grafts, those in the pelvis are covered by omentum, adjacent soft tissue, or bovine pericardium.

55.11 OUTCOMES

Patient outcome is dictated by tumor type and stage, the IVC or iliac vein segment that requires resection or replacement, the need for concomitant major liver resection or cardiopulmonary bypass, and patient performance status and comorbidities.[2,3,21,24–27,38] Moreover, an experienced surgical, anesthesia, and critical care team is invaluable for good outcomes.

Although there is a recent and growing literature supporting IVC reconstruction for malignancy in select patients, comparison of outcomes remains difficult for two primary reasons. First, most studies include patients with a variety of cancers or sarcomas at different stages of disease. Second, outcome analysis compares those who have circumferential IVC resection and graft replacement to patients with primary or patch closure of the IVC. The hemodynamic and physiologic stresses of partial resection of the IVC wall with patch angioplasty or removal of the infrarenal segment do not approach the same levels of stresses and technical challenges as retrohepatic IVC replacement in conjunction with major liver resection or cardiopulmonary bypass and circulatory arrest to remove tumor thrombus. For example, the Keiffer et al. study noted a mortality rate of 20%, which on first glance is high. However, the tumors were very large, and 14 of the 22 patients (63%) had involvement of the retrohepatic or suprahepatic IVC, with cardiac extension or involvement of the hepatic veins in five patients. Thirteen patients needed a graft to reconstruct the IVC.[26] In contrast, the Brigham and Women's Group and the Italian series by Illuminati et al. laudably report no mortality. In the former study, 20 patients were treated for PVL, but only five required prosthetic graft replacement of the IVC. Additionally, there was just one patient who had tumor involvement above the hepatic veins and another that needed partial liver resection. Two patients had concomitant arterial replacement: the aorta in one and the iliac artery in the other.[25] The majority of tumors in the Illuminati et al. series involved the infrarenal IVC, though all 11 patients had graft replacement.[24] Table 55.1 lists the larger, more contemporary series with respect to primary or secondary malignancies, the segment of IVC treated, the number of patients who needed grafts placed, and perioperative mortality. Major morbidity with these operations ranges between 11% and 33%. Prosthetic graft patency is excellent, ranging from 85% to 100% over a follow-up ranging from 18 months to nearly 4 years.[1,3,4,22,24–27]

More recent data within the last 3 years warrant mention. A 2012 report from Quinones-Baldrich and colleagues[3] included 47 patients who had tumor excision and either primary closure,[11] patch angioplasty,[9] or segmental

Table 55.1 Contemporary results of inferior vena cava resection with graft replacement for malignant disease

First author	Year	*n*	Type	*n*	Location			Graft	Mortality *n* (%)
					IR	SR	SH		
Kieffer	2006	22	PVL	22	3	13	4	13	4 (20)
Ito	2007	20	PVL	20	6	13	1	5	0
Kuehnl	2007	35	Secondary	20	5	7	14	13	2 (6)
			PVL	6					
Illuminati	2008	11	PVL	11	8	3	0	11	0
Quinones-Baldrich	2012	47	Secondary	17	25	14	8	27	0
			PVL	30					
Hemming	2013	38	Secondary	38	0	38	3	38	5 (13)
Benkirane	2014	26	Secondary	26				26	1 (4)
Bower[a]	2014	102	Secondary	69	28	14	1	102	2 (2)
			PVL	33					

Note: PVL: primary venous leiomyosarcoma; IR: infrarenal; SR: suprarenal; SH: suprahepatic.
[a] 59 other patients had multiple IVC segments replaced.

resection and graft replacement[27] of the IVC between 1990 and 2011. The majority of tumors were sarcomas (77%), of which 30 were PVL. The 27 patients who needed grafts had multiple segments replaced in addition to hepatic or renal vein revascularization. Eighteen (67%) had replacement of more than one caval segment. Eight of these 18 patients had replacement of all IVC segments combined with renal and hepatic vein re-implantation, six others had replacement of the pararenal/suprarenal IVC, with seven renal veins re-implanted, and four had the infrarenal/pararenal segment replaced, for which four renal veins were re-implanted. The remaining nine patients had infrarenal IVC grafts. Impressively, there was no mortality in this series. Major morbidity was 10.6% and included bowel obstruction, temporary acute renal failure, reoperation for bleeding, chylous ascites, and graft thrombosis in one each. Cumulative 5-year survival for the series was 45%.[3]

Hemming and associates published their series of 60 patients who underwent IVC resection specifically for hepatic tumors.[2] Cholangiocarcinoma (43%) and hepatocellular carcinoma (27%) were most common. Thirty-eight patients needed graft replacement, 14 had patch angioplasty, and the remaining eight had the IVC closed primarily. There were five peri-operative deaths (8%), three from liver failure, one from pulmonary hemorrhage, and the other from pulmonary embolism. An additional nine patients developed significant liver dysfunction but survived. Kaplan–Meier estimates of survival at 1 and 5 years were 89% and 35%, respectively. The authors concluded that despite the risk of surgery, the risk of death and major adverse events is balanced by the possible survival benefit in patients who have no other curative options.

Benkirane and colleagues from Lille, France, in 2014 reported the outcomes of 26 patients who had prosthetic graft replacement of the IVC in conjunction with radical nephrectomy for RCC with tumor thrombus.[38] During the 11-year study period through to 2011, 820 patients had radical nephrectomy for RCC. The general approach cited was to use a graft to reconstruct the infrahepatic IVC if there was tumor invasion, but not to place a graft if there was tumor involvement of the retro- or supra-hepatic segments. Six of the 26 patients required cardiopulmonary bypass to remove the tumor thrombus from the heart. Sixteen patients (61.5%) had histologic invasion of the IVC wall. Over a median follow-up of 28 months, graft thrombosis occurred in five patients (19%) during the first year, despite the use of large-diameter grafts (19-mm PTFE) and the routine use of anticoagulation with warfarin. No specific cause was given for the graft failures. This thrombosis rate is higher than that reported in other series. Overall patient survival was 64% at 3 years.

The updated Mayo Clinic experience was presented at the Vascular Annual Meeting in June 2014, although publication of the data is pending.[21] When published, this study will represent the largest experience of segmental IVC resection and graft replacement for malignancy, with 102 patients treated over a 25-year period. A number of patients had renal or hepatic vein revascularization. Patients with primary venorrhaphy and nearly 200 patients with patch angioplasty were excluded from analysis. Importantly, 90% of patients had good or excellent ECOG performance status prior to operation. A third of the patients (32%) had PVL, a quarter had renal cell or adrenocortical carcinoma, and nearly 20% had retroperitoneal sarcomas. Reconstruction was done with externally supported PTFE grafts in all but two patients. There were two early deaths (2%) and 15 patients sustained major adverse events. Six patients developed graft occlusion, most of them late, with a 5-year graft patency of 92%. The longest patency of a graft is 18 years. Overall survival was 51% at 5 years and 30% at 10 years. The risk of local or regional recurrence was low, with cause of death by distant metastases in most patients.[21]

The operative mortality and morbidity rates for patients with RCC and intracaval tumor thrombus are the lowest at high-volume centers, and have improved over time. At the Mayo Clinic, more than 300 radical nephrectomies are performed each year, and approximately 10%–15% have

IVC thrombus. A report from this institution by Blute et al. analyzed the impact of volume and time period on operative mortality.[7] The mortality rate was 8.1% for 86 patients with RCC and tumor thrombus treated between 1970 and 1989, but risk of death fell to 3.8% for the 105 patients treated between 1990 and 2000. Complication rates were higher if the IVC thrombus was level III or IV. The need for cardiopulmonary bypass to remove tumor thrombus conferred higher mortality and complication rates than if veno-venous bypass could be used.[9]

Survival for patients with IVC leiomyosarcoma is best with curative resection. Although a dated review by Mingoli et al. showed little difference in survival between curative and non-curative resection for PVL,[39] publications from a number of centers in the last decade have shown improvement in survival with aggressive surgical treatment. The Kieffer et al. report found mean 3- and 5-year actuarial survival rates to be 52% and 34.8%, respectively.[26] Ito et al. found a mean disease-free survival of 21 months, but a median overall survival of 71 months for 19 patients who had complete resection.[25] The cumulative disease-free survival rate in the Illuminati et al. study was 44% at 5 years.[24]

Survival rates for patients with secondary IVC malignancies have also improved in the last 10 years. In the last series published from the Mayo Clinic group in 2000, overall survival was 89.3% at 1 year, 80.3% at 2 years, and 75% at 3 years.[1] Survival was better for patients with infrarenal IVC resection and replacement (mean survival of 3.1 years), but poorer for those who needed retrohepatic or multilevel IVC replacements (2.88 vs. 2.26 years, respectively). Certainly, type of tumor played a role in outcome. This same group reported another analysis focused on 19 patients who had retrohepatic IVC replacement combined with major liver resection. Operative mortality was low. The overall survival of 21% at 5 years and the median overall survival of 38 months seem poor, but without surgery, survival would have been limited to only a few months. The subset of patients with cholangiocarcinoma did best, with a survival rate of 69% at 3 years.[4] The 1-, 3-, and 5-year survival rates reported by the group from Munich, Germany, were 76%, 32%, and 21%, respectively. Incomplete resection and cardiopulmonary risk had a negative impact on survival.[27] Four out of 12 patients operated on by the University of Miami group died of recurrent disease over a median follow-up of 24 months.[22]

The greatest survival benefit of surgery for patients with primary or secondary malignancies which involve the IVC is patients with RCC and IVC tumor thrombus.[7,40–42] Five-year survival rates for patients with venous involvement and no metastases range from 40% to 65%, but fall significantly to only 6% to 28% if metastases are present at operation.[42] Five-year cancer-specific survival rates are best if there is no nodal or metastatic disease,[7] but survival worsens if performance status is poor or if there is lymph node involvement, distant metastases, and/or sarcomatoid features.[40]

There is a clear need for better adjuvant therapies if disease control or survival are to improve, and some advances have been made. Patients with sarcoma are at high risk of local recurrence if the tumor is large or high grade or an R0 resection is not achieved. Radiation combined with wide local tumor excision has improved local recurrence rates in this group if an R0 resection is anticipated. The combination of external beam radiation therapy (45–50 Gy) with an intraoperative focused radiation boost of 10–20 Gy has shown improvement in local control of disease. This approach provides a more favorable therapeutic ratio of radiation for tumor control and fewer local complications to adjacent nerves, blood vessels, bone, and soft tissue.[43] Targeted molecular therapies with tyrosine kinase inhibitors such as sunitinib are being applied to patients with large RCCs to reduce size and thereby enable success of resection. Data regarding the impact of these agents for patients with RCC and tumor thrombus are evolving, but at present, these approaches do not seem to reduce the extent of tumor thrombus.[44]

Few studies have assessed quality of life after operation. In reports from the Mayo Clinic, over 80% of select patients operated on for malignant disease of the IVC are able to maintain an excellent performance status after operation.[1,4]

Guidelines 5.3.0 of the American Venous Forum on primary and secondary tumors of the inferior vena cava and iliac veins

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.3.1	For patients with invasion of the wall of the inferior vena cava by primary or secondary tumors, we recommend caval replacement if the vein was patent before surgery and if the collateral circulation appears inadequate following caval resection. Repair with externally supported polytetrafluoroethylene graft is safe, effective, and durable.	1	B
5.3.2	For inferior vena cava tumor thrombus—usually a renal cell carcinoma—that extends into the right heart, we recommend removal with cardiopulmonary bypass, with or without hypothermic circulatory arrest.	1	B

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● = Key primary paper
★ = Major review article

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56

Arteriovenous malformations: Evaluation and treatment

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56.1 INTRODUCTION

Arteriovenous malformation (AVM) is a congenital vascular malformation (CVM) in which an anatomic defect results in shunting of arterial blood to the venous system to varying degrees.[1–3] The arteriovenous (AV) communications allow the shunting of high-velocity, low-resistance flow from the arterial vasculature into the venous system.[4–6]

This unique condition of "AV shunting" between the arterial and venous systems causes altered cardiovascular hemodynamics centrally, peripherally, and locally, thus making the AVM the most hemodynamically complex type of CVM.[7–9]

The hemodynamic alterations to the arterial, venous, and lymphatic systems affect the entire cardiovascular system and may produce cardiac failure, peripheral arterial insufficiency (e.g., gangrene), chronic venous insufficiency, and lymphatic overload due to venous hypertension. These lesions also have local effects on the surrounding tissues and organs and are associated with significant morbidity and high recurrence rates following treatment.[4,5] The AVM is considered to be the most virulent of all CVMs.[10,11]

56.2 INCIDENCE AND EPIDEMIOLOGY

Epidemiologic data reported in the medical literature often misrepresent the true incidence and prevalence of the CVMs based on name-based classifications. Before the International Society for the Study of Vascular Anomalies (ISSVA) and Hamburg CVM Classification systems were established, much confusion remained with limited reliability of data regarding AVM incidence and prevalence.[5,12,13]

Data reported by Tasnadi (1993) show the overall incidence of CVMs to be 1.2%.[14] The CVMs are a group of various birth defects involving the vascular system that present at birth over 90% of the time, with a male–female ratio of 1:1.[1,4,12]

The incidence and prevalence of cerebrospinal AVMs were reported in a systematic review.[15] The incidence of AVMs was found to be approximately 1 per 100,000 per year in unselected populations, and the point prevalence in adults was approximately 18 per 100,000. In the United States, 1 per 250,000 people has a cerebrospinal AVMs, appearing in the age range of 20–40 years, with a male–female ratio of 1:1 or 1:2.[15]

Peripheral AVMs were reported to be the least common CVMs, representing approximately 10%–15% (range of 5%–10% to 15%–20%) of all clinically significant CVM lesions.[4,16]

Among all CVMs as defined by the Hamburg Classification (Table 56.1),[5,13] the AVM is a much more rare condition than venous malformations (VMs)[17,18] or lymphatic malformations (LMs).[19,20] The majority of CVMs are either VMs or LMs, and the VMs represent approximately two-thirds of all CVMs.[21]

Among the AVMs, the "extratruncular" AVM (formerly angiomatous AVM) lesions comprise most AVM cases.[4] The "truncular" AVM lesions are extremely rare and occur as a result of direct communication between an artery and a vein; for example, between the pelvic vessels or the femoral

Table 56.1 Hamburg Classification of congenital vascular malformations

Primary classification[a]

- Arterial malformation
- Venous malformation
- Arteriovenous malformation
- Lymphatic malformation
- Capillary/microvascular malformation
- Combined vascular malformation: hemolymphatic malformation

Embryological sub-classification[b]

Extratruncular forms (former "angioma")[c]

- Diffuse, infiltrating
  - Limited, localized

Truncular forms[c]

- Obstruction and/or stenosis
  - Aplasia, hypoplasia, hyperplasia
  - Membrane, congenital spur
- Dilatation
  - Localized (aneurysm)
  - Diffuse (ectasia)

[a] Modified based on the consensus on congenital vascular malformations through the international workshop in Hamburg, Germany, in 1988 and Seoul, Korea, in 1995.

[b] Developmental arrest at the different stages of embryonal life: earlier stage—extratruncular form; latter stage—truncular form.

[c] Both forms may exist together, may be combined with various other malformations (e.g., capillary, arterial, arteriovenous shunting, venous, hemolymphatic and/or lymphatic), and/or may exist with hemangioma.

artery and vein. They are genuine fistulous lesions without a nidus such as a patent ductus arteriosus or pulmonary AV fistula.[4]

The vast majority of AVMs exist alone as independent lesions, but infrequently occur with a VM and/or LM, making its diagnosis and management more difficult. These mixed CVMs, newly classified as hemolymphatic malformations, often become a clinician's nightmare (e.g., Parkes–Weber syndrome [PWS]). Their management is quite confusing and the treatment results are often disappointing (e.g., microshunting AVM).[22,23] To date, no racial, demographic, or environmental risk factors for AVMs have been identified.[4]

56.3 ETIOLOGY AND PATHOPHYSIOLOGY

There has been significant progress to explain the growth tendency of extratruncular AVM lesions based on gene mutations occurring in tissues. Several gene mutations have been shown to be responsible for the defective development during embryogenesis resulting in high-flow AV shunts through dysplastic vessels.[4,6,24–27]

Although further studies are required in order to better understand these mechanisms, identification of the causative genes in several defects has already allowed a more precise diagnosis. Some mutations have been found to be responsible for a number of rare inheritable vascular malformations, such as Osler–Weber–Rendu syndrome (hereditary hemorrhagic telangiectasia), blue rubber bleb nevus syndrome (Bean's syndrome), RASA1 mutations, PTEN mutations, etc.[24–27] For example, hereditary hemorrhagic telangiectasia is an autosomal dominant condition caused by loss-of-function mutations in the genes encoding activin receptor-like kinase-1 (ACVRL1) and endoglin (ENG), both transforming growth factor-β vascular growth factors.

The majority of AVM lesions develop progressively over time, particularly in the brain, lungs, and liver, and are eventually diagnosed in patients when they are adults. A high percentage of the angio-architecture of the AVM is an AV fistula, and positive results have been reported in patients treated with angiogenesis inhibitors, such as bevacizumab. RASA1 mutations are responsible for another autosomal dominant condition of combined capillary malformations (CMs) and AVMs. The most common sites for AVMs among affected family members are the brain, spine, face, and extremities. Intracranial AVMs can be typical arteriolovenular malformations or pial AV or arteriolovenous fistulae.

PWS is associated with the RASA1 mutation. The AVMs in these patients generally present as "micro-shunting" lesions initially, remaining as diffuse small vessel lesions in the muscles and subcutaneous tissues of the limbs. Together with other vascular malformation components (VMs and LMs), it often results in marked tissue overgrowth of the affected muscle, bone, and subcutaneous fat. However, individuals with PWS without multiple additional CM lesions generally do not carry RASA1 mutations.

PTEN mutations are responsible for the focal tissue overgrowth in hamartomas that frequently contain AVMs. These mutations represent syndromes of tissue overgrowth (e.g., Cowden and Bannayan–Riley–Ruvalcaba syndromes). Multiple AVM lesions are common, often affecting the muscles of the limbs, paraspinal muscles, and the dura mater of the brain. The angio-architecture is usually arteriolovenous and exhibits aggressive behavior that is difficult to control by embolization.[4,6]

Further research on the genetic mechanisms of CVM/AVM formation is required for better understanding of the morphogenesis and biology of both extratruncular and truncular AVM lesions.

56.3.1 Abnormal endothelial cell turnover rate among the AVMs

The endothelial cell turnover rate (ECTR) is an endothelial cell characteristic that differentiates vascular malformations from hemangiomas, with the latter having higher rates. The ECTR has been found to be significantly greater in AVMs than in normal blood vessels. The mean Ki-67 index is higher for AVM vessels than control vessels, with an approximately seven-fold increase in the number of non-resting endothelial cells.[4,6] The Ki-67 protein presents during all active phases of the cell cycle except resting phase

(G0). Therefore, non-resting endothelial cells can be identified by use of immunohistochemistry for the Ki-67 antigen.

Increased expression of stromal cell-derived factor-1 (SDF-1) was also found in the AVM nidus that suggests that endothelial progenitor cells (EPCs) may play a role in maintaining active vascular remodeling within the AVM nidus, whereas SDF-1 expression is rarely identified in normal vessels.[4,6,28,29]

In addition, mRNA expression of the factors that recruit the EPCs vascular endothelial growth factor, SDF-1α, hepatocyte growth factor, and hypoxia-inducible factor-1 have been found to be different in Schobinger stages II and III of the AVMs. Increased expression of EPCs and growth factors among higher-staged AVMs suggests EPCs as a promoting factor for the evolution of AVMs, stimulating their recruitment for neovascularization.[28,29]

The research on the ECTR over the last 10 years has brought substantial improvement to our molecular vision of AVMs, together with the role of EPCs.[4,6]

56.3.2 The different genetic expression of EPC activity

Despite the early work of Mulliken et al. indicating that vascular malformations do not grow by cellular proliferation, more recent data demonstrate the importance of cellular proliferation and the upregulation of matrix metalloproteinases, especially in symptomatic AVMs.[4,30] This new finding may lead to the development of new strategies of pharmacotherapy for treating symptomatic AVMs.[4,30]

56.3.3 The sporadic and familial/syndrome-based AVMs[4,6,24–27]

The "sporadic" type of AVMs without documented genetic mutations may be explained by underlying genetic abnormalities in the future. Nevertheless, the familial/syndrome-based AVMs behave differently from the majority of AVMs belonging to the sporadic type. AVMs in patients with RASA1 mutation generally remain relatively stable with minimal progression, although symptomatology varies based on the anatomical location of the AVM lesion, as those of the central nervous system can produce significant mass effect and hemorrhage.

The AVM lesion among PWS patients often shows a slow progression when compared to the sporadic type of AVM occurring in the lower limb. The amputation rate is more frequent with sporadic AVMs in the lower limb, even though they usually present with a smaller size lesions.

Bleeding of visceral AVM lesions in patients with hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome) is more frequent than in the sporadic type of visceral AVM. However, the need for intestinal resection to control bleeding is exceedingly rare. On the other hand, surgical resection to control intestinal bleeding has been reported to be higher in patients with sporadic-type AVM.

The AVMs caused by PTEN mutations are known to be the most aggressive type of AVMs, not only recurring rapidly following the embolization or resection, but also with a tendency to develop new lesions at different sites.

56.3.4 Hemodynamic consequences of AV shunting

AVMs are a unique, complex vascular conditions bypassing the normal capillary system and resulting in a "short circuit" of the normal circulation between the arterial and venous–lymphatic systems. The pivotal function of the capillary system is no longer present to maintain the delicate balance between the two hemodynamically different systems.[1–4,6,31,32] When the capillary system is no longer present, the balance between these three uniquely different hemodynamic components of the circulatory system—arteries, veins, and lymphatics—is profoundly disrupted.

This abnormal connection between the high- and low-pressure systems forces these two circulatory systems to respond in a compensatory manner to minimize hemodynamic effects. Depending on the location and/or degree (e.g., size and flow) of the fistulous connection, the arterial and venous systems produce responses that occur in two distinct phases: the compensation period and the decompensation period.[4,6]

During the compensation period, increased heart pump function can assist the failing arterial system by low peripheral resistance through the AV fistula and so maintain arterial flow as before, preventing peripheral tissue ischemia. However, increased heart pumping results in increased load on the venous as well as lymphatic system, and subsequently on the heart itself. Initially, the normal venous system is able to respond to this increased pressure and volume produced by the AV fistula together with the lymphatic system. However, the lymphatic system has limited capacity to assist the failing venous system due to its unique lymphodynamic mechanism based on autoregulated peristaltic circulation. Once these compensatory mechanisms involving the arterial, venous, and lymphatic systems and the heart reach their maximum capacity, the decompensation period begins.

The arterial system can no longer maintain adequate arterial blood flow to the peripheral tissues distal to the AV fistula, resulting in tissue ischemia. The venous system distal to the AVM lesion is also no longer able to maintain normal valvular function and allows retrograde blood flow. Continuous reflux further impedes normal antegrade venous flow from the peripheral tissues, resulting in severe venous hypertension and chronic venous insufficiency.

Hence, the hemodynamics of the AVM affect every vascular component of AV communication, resulting in local, peripheral, and central effects. Proper management of the various pathophysiologic effects of the AVM on the entire vascular system requires precise information regarding the close relationship between three pairs of proximal, distal, and collateral arteries and veins at the different stages of the condition.[1–4,6]

56.4 CLASSIFICATION

A consensus workshop held in Hamburg in 1988 attempted to develop a logical classification system of CVMs, as the old, traditional nosology-based classification (e.g., Klippel–Trenaunay syndrome) failed to provide appropriate differentiation of anatomic, pathophysiologic, and clinical presentations among the various CVMs.[4,5,13,33,34]

The group first described the morphological differences between lesions involving the main vessel trunks, often with a direct communication ("truncular" form) and lesions occurring peripherally as separate defects (AV angiomas).[4,5] In order to avoid the confusing term of "angioma" (c.f. hemangioma), Belov et al. reintroduced an old embryologic term—"extratruncular"—for these "angiomatous" AVM lesions based on their distinctively different morphology from "truncular defects."[4,5,13,33,34]

The morphological difference between these two groups was further categorized according to its embryological mechanism by Belov et al. as an outcome of the developmental arrest of the vascular system during two different stages of angiogenesis. Defective development occurring in the "earlier" stage would produce primitive vascular structures in the form of a "reticular network," while those defects occurring in the "later" stage of vascular trunk formation would produce normal, mature vascular structures.[5,34–36]

Subsequent CVM classifications as the basis of the contemporary approach to precise evaluation, diagnosis, and therapeutic implementation were refined and later became the "modified" Hamburg Classification (Table 56.1).[4,5,13,34]

Based on the Hamburg Consensus, Mulliken et al. also introduced another new classification for vascular anomalies to differentiate the hemangiomas as vascular tumors from the vascular malformations, and further classified vascular malformations using flow characteristics: fast-flow and slow-flow lesions. This new classification was later adopted as the ISSVA Classification (Table 56.2).[4,5,12]

In addition, two other classifications were adopted for the AVM, namely the Schobinger Classification and the Arteriographic Classification, to improve AVM management.[4,6,37,38]

The Schobinger Classification of AVMs (Table 56.3) is important for defining the level of clinical progression in AVM diagnosis and treatment. It provides a more accurate assessment of the AVM lesions at different clinical stages and serves as a practical guideline in their management based on the patient's clinical status.

The Arteriographic Classification of AVMs (Table 56.4) is utilized exclusively to classify the "extratruncular" AVM lesions located in the torso and extremities based on the arteriographic morphology of the "nidus." These radiological findings of the "nidus" represent the primitive reticular networks of dysplastic minute vessels which failed to mature into normal "capillary" vessels.[4,6,38]

The nidus lesions are classified into three types: type I (AV fistulae), type II (arteriolovenous fistulae), and type IIIa and IIIb (arteriolovenulous fistulae). This classification is helpful not only for the better management of extratruncular AVM lesions, but also for predicting outcomes of endovascular treatment.

Table 56.2 International Society for the Study of Vascular Anomalies (ISSVA) classification of congenital vascular malformations and vascular tumors

Vascular malformations

- Fast-flow lesions:
  - Arterial malformation
  - Arteriovenous malformation
  - Arteriovenous fistula
- Slow-flow lesions:
  - Capillary malformation (port wine stain, telangiectasia, angiokeratoma)
  - Venous malformation
  - Lymphatic malformation
  - Combined vascular malformation (CVM, CLM, CLVM, CAVM, CLAVM)

Vascular tumors:

- Infantile hemangioma
- Congenital hemangioma
- Other

Note: CVM: capillary malformation + venous malformation; CLM: capillary malformation + lymphatic malformation; CLVM: capillary malformation + lymphatic malformation + venous malformation; CAVM: capillary malformation + arteriovenous malformation; CLAVM: capillary malformation + lymphatic malformation + arteriovenous malformation.

Table 56.3 Schobinger classification of arteriovenous malformations

Stage I—quiescence: Pink–bluish stain, warmth, and arteriovenous shunting are revealed by Doppler scanning. The arteriovenous malformation mimics a capillary malformation or involuting hemangioma.

Stage II—expansion: Stage I plus enlargement, pulsations, thrill, bruit, and tortuous/tense veins.

Stage III—destruction: Stage II plus dystrophic skin changes, ulceration, bleeding, and tissue necrosis. Bony lytic lesions may occur.

Stage IV—decompensation: Stage III plus congestive cardiac failure with increased cardiac output and left ventricle hypertrophy.

56.4.1 Clinical implementation of the embryological concept[4,5,13,34]

AVMs are further classified into two subtypes with different embryological characteristics—extratruncular and truncular lesions—based on the embryological stage at which the developmental arrest occurred (Table 56.1).

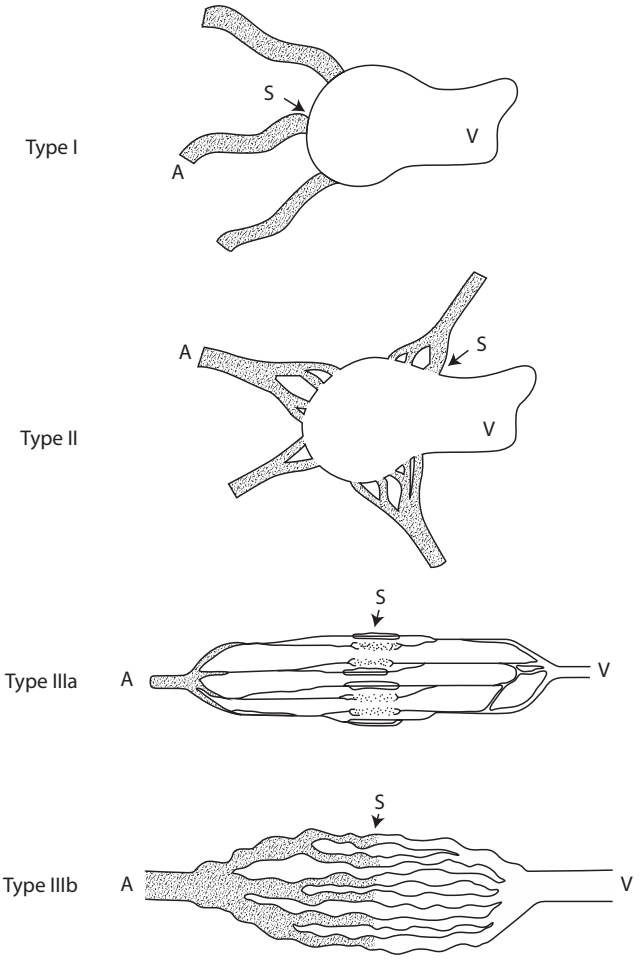
An extratruncular lesion is an embryonal tissue remnant of the primitive capillary network that is the result

Table 56.4 Arteriographic Classification of arteriovenous malformations

Type I (arteriovenous fistulae): At most three separate arteries shunted to a single draining vein

Type II (arteriolovenous fistulae): Multiple arterioles shunted into a single draining vein

Type IIIa and IIIb (arteriolovenulous fistulae): Multiple shunts between the arterioles and venules



of developmental arrest occurring during an "early stage" of embryogenesis. This type of the endothelial cell/lesion therefore retains the characteristics of mesenchymal cells, maintaining its ability and potential to proliferate, making its clinical and biological behavior unpredictable.[35,36]

Stimulation of an extratruncular lesion by various intrinsic (e.g., menarche or pregnancy) and extrinsic (e.g., trauma or surgery) stimuli results in lesion recurrence or progression. The potential for further proliferation underscores the importance of a well-planned treatment regimen.

Stimulation of a dormant extratruncular lesion during treatment often leads to an erratic response with explosive growth, worsening the clinical picture. An infiltrating extratruncular lesion is far more complicated than a truncular lesion because of its embryologic characteristics. Therefore, this extratruncular lesion carries a higher risk of progression and has more destructive potential.

In contrast, a truncular lesion, which is the result of developmental arrest occurring during a "late stage" of embryogenesis, no longer has the potential to proliferate (e.g., pulmonary AV fistula). However, a truncular lesion is hemodynamically more significant than its extratruncular counterpart, owing to its unique high-flow "fistulous" state with no nidus in the capillary beds to limit blood flow. These types of fistulous lesions have a direct connection between the arterial and venous systems, resulting in significant hemodynamic effects centrally, peripherally, and locally (briefly, on the entire cardiovascular system) with varying degrees of severity.

56.4.2 AV fistula versus AVM[4,5,12]

Due to the sub-classification of the AVM into AV fistula and AVM by ISSVA Classification 12, many mistakenly identify AVMs as "non-fistulous" lesions (Table 56.2). All AVM lesions are "fistulous" whether they have a "nidus" or not. In other words, there is no such AVM lesion *without* a fistulous connection between the artery and vein to allow free "high-flow" shunting. Due to the unique embryological nature of AVMs as a consequence of defective development, there are no "non-fistulous" AVMs. All AVMs are "fistulous" by nature.

The "AV fistula" lesion defined by the ISSVA Classification is equivalent to the "truncular" AVM lesion with no nidus (e.g., ductus botalli or pulmonary AVM) defined by the Hamburg Classification. The "AVM" defined by the ISSVA Classification is equivalent to the "extratruncular" AVM lesion with nidus defined by the Hamburg Classification.

56.4.3 "Nidus" versus "non-nidus" AVM[4–6]

The term of "nidus" is a clinical radiological term used to describe the clusters of small-sized AV connections—fistulae—filled with contrast on arteriography (Table 56.4).[4–6] "Nidus" is therefore not a histological term, nor an anatomic or pathologic term, but a descriptive term of a conglomerate of blood vessels constituting the AVM.

A "nidus" is a characteristic of an "extratruncular" AVM lesion, always being present in an extratruncular lesion, and only present in "extratruncular" AVM lesions. A "nidus" often appears as a net of pulsating, dysplastic, tortuous vessels between the artery and vein. The "nidus" remains a "diffuse, multiple small fistulous" entity, in contrast to the truncular lesion, which is a large, individual AV fistula. In contrast, truncular AVM lesions have a direct connection between the artery and vein.

56.5 EVALUATION

56.5.1 General overview

Progression of an AVM invariably produces symptoms (pain, ulceration, and bleeding) and tissue ischemia when increased shunting results in arterial steal and venous hypertension, both reducing tissue perfusion.[1–4]

The clinical manifestations of AVMs are dependent on their anatomical location: cardiac failure for centrally located lesions and arterial and venous insufficiency associated with local venous hypertension in peripherally located lesions. In addition, local effects of AVMs may include ulceration and gangrene.[1–4] Therefore, a complete systematic evaluation is required after a thorough history and physical examination, followed by noninvasive diagnostic imaging in order to distinguish AVMs from other CVMs.

Although most AVMs occur as single lesions, the evaluation of an AVM should be started as an evaluation of a CVM, followed by a more specific evaluation and confirmation of an AVM. The evaluation should follow basic differential diagnoses among the various CVMs.

The investigations should rule out the co-presence of other CVMs as well, since AVMs may exist combined with other CVMs, like VMs and LMs (e.g., PWS).[1–4]

Appropriate differential diagnosis, therefore, should be made initially with various combinations of noninvasive to less invasive tests and more specific diagnostic procedures, followed by further precise and detailed assessment of the AVM as a whole (Table 56.5).[4,6]

In addition to the assessment of the primary AVM lesion, evaluation of its secondary impact on the non-vascular organ systems, especially the musculoskeletal system, is also warranted. Early detection of vascular–bone syndrome with long-bone length discrepancy is essential for appropriate management.[39,40]

Among the noninvasive tests, duplex ultrasound sonography (DUS) remains the first choice in the initial clinical assessment and subsequent follow-up. DUS readily differentiates the AVM, with its unique finding of pulsatile flow, from VMs and LMs. In addition, B-mode and Doppler findings of multiple vascular channels with a honeycomb appearance are characteristic of an AVM and are absent in vascular tumors.[4,6,41]

Magnetic resonance imaging (MRI) remains the major diagnostic study for the entire group of CVMs, including the AVMs, since MRI is able to provide basic information on lesion extent, severity, and anatomic relationship with the surrounding tissues, structures, and organs. However, standard MRI is usually not able to precisely demonstrate the nidus and is limited in terms of demonstrating the presence of dilated fast-flow vascular channels.[4,6,42]

Transarterial lung perfusion scintigraphy (TLPS)[5] has a unique role in determining the degree of shunting through an extremity AVM. It can detect and assess a micro-AV shunting lesion. These types of malformations are notoriously difficult to detect with conventional arteriography alone. Such micro-AVM lesions are often missed with conventional arteriography and frequently occur in the combined form of CVM (e.g., PWS).[2,6,8]

In addition, TLPS can also provide quantitative measurements of the shunting status during therapy; TLPS may replace the substantial role of traditional arteriography as a follow-up assessment tool for extremity AVMs.[2,6,8]

Table 56.5 Lists of diagnostic tests for arteriovenous malformations

Noninvasive to minimally invasive tests for initial studies:

- Duplex ultrasonography (arterial and venous)[25]
- Whole body blood pool scintigraphy[26]
- Transarterial lung perfusion scintigraphy[5]
- Magnetic resonance imaging of T1 and T2 images and magnetic resonance angiography[27]
- Computed tomography (CT) and CT angiography with contrast enhancement, and/or three-dimensional CT[28]

Invasive tests for the confirmation of the final diagnosis[a]:

- Selective and super-selective arteriography
- Percutaneous direct puncture arteriography
- Standard direct puncture phlebography

[a] Confirmation of the final diagnosis should be made to create a road map for the proper treatment.

56.6 TREATMENT STRATEGY

56.6.1 General principle

Treatment of AVMs, either extratruncular or truncular, should take priority over all other CVMs because of the potential for the development of life- and/or limb-threatening conditions.[1,4,32]

The main goal of the treatment of all "extratruncular" AVM lesions should be to eliminate the "nidus." Incomplete surgical resection or simple occlusion and/or ligation of feeding arteries, leaving the nidus intact, is inadequate treatment, resulting in stimulation of the lesion and causing its recurrence from the development of new feeding vessels.

Early aggressive control of the nidus is required to prevent recurrence and produce eventual deterioration and eradication of the AVM lesion. This is often difficult due to the high likelihood of recurrence following a conventional approach with currently available treatment modalities.

A "controlled" aggressive approach should be exercised in the treatment of AVMs only when the benefit exceeds the associated morbidity of the proposed treatment.[4,32] The temptation to initially intervene radically in an AVM must be tempered with a realistic assessment of the long-term goal of the treatment plan.

To achieve this goal, the treatment strategy should be based on a consensus reached by the many different specialists involved in the patient's care (e.g., vascular surgeon, orthopedic surgeon, plastic surgeon, head and neck surgeon, interventional radiologist, and physiatrist). The final decision for treatment, as well as selection of the treatment modalities, should be made via a multidisciplinary team approach based on the various indications outlined above.[2,4,7,32]

The new approach to the treatment of AVMs as a multidisciplinary team has resulted in significant improvements in diagnosis and treatment, with substantial reductions in morbidity, mortality, and recurrence rates through the full integration of the latest treatment modalities.[7,10,32]

Table 56.6 Indications for the treatment of arteriovenous malformations

- Hemorrhage
- High-output heart failure
- Secondary arterial ischemic complications
- Secondary complications of chronic venous hypertension
- Lesions located at a life-threatening region (e.g., proximity to the airway) or located in an area threatening vital functions (e.g., seeing, eating, hearing, or breathing)
- Disabling pain
- Functional impairment
- Cosmetically severe deformity
- Vascular–bone syndrome: abnormal long-bone growth with leg length discrepancy[19,20]
- Lesions located in an area with potentially high risk of complication (e.g., hemarthrosis)

For advanced diagnosis and treatment of AVMs, a fully integrated specialty team is required in order to provide maximum coordination among the various CVM-related specialists, utilizing the full spectrum of endovascular treatments in addition to traditional surgical treatment.

After assessment of the extent and severity of the AVM has been performed, indications for treatment are determined based on its urgency. These indication criteria were formulated based on the "extratruncular" lesions, since the absolute majority are of the extratruncular type, while the truncular AVM lesions are extremely rare (Table 56.6).[2,4]

Among the criteria, the latter five indications are common conditions that clinicians will encounter, but the first five indications are relatively rare, often reflecting conditions with a high risk of morbidity as well as mortality.

The role of careful assessment and diagnosis in the development of a treatment strategy that maximizes the risk–benefit ratio is critical and cannot be overemphasized, in which the ultimate goal of treatment must be clearly defined with realistic expectations.

56.7 TREATMENT MODALITY

56.7.1 Endovascular embolosclerotherapy

56.7.1.1 GENERAL OVERVIEW

Endovascular embolosclerotherapy with embolization and sclerotherapy modalities have major roles in the "surgically inaccessible" lesion, in addition to a new role to supplement the surgical therapy of a "surgically accessible" lesion.[1,23]

Endovascular therapy is now the "preferred" therapeutic option in the majority of "extratruncular" AVM lesions, and embolosclerotherapy alone is the treatment of choice as an independent therapy for surgically "inaccessible" lesions (Figure 56.1), especially for the "diffuse infiltrating" type with extension beyond the deep fascia, involving muscle, tendon and bone, with prohibitive surgical risks.[1,2,4,7,16,23,43]

Nevertheless, many new associated problems have been reported, which include both acute complications (e.g., tissue necrosis, vein thrombosis, pulmonary embolism, nerve damage, and cardiopulmonary arrest) and various chronic complications (e.g., muscle/tendon contraction), in addition to their related morbidity.[4]

Therefore, careful assessment of the potential risk of collateral damage is critical in the selection of any embolic agent and sclerosing agent. Every effort should be made to minimize collateral damage to the surrounding tissues—nerve, vessel, cartilage, skin, and soft tissue.

Embolosclerotherapy should be performed in multiple sessions whenever possible, using the minimal effective amount of agent during each session in order to minimize the associated risk of complications (e.g., ethanol).

The preferred treatment modality should be selected based on a careful risk–benefit analysis in which the associated morbidity is justified, such as in the case of the treatment of a life-threatening or limb-threatening condition (e.g., hemorrhage or high cardiac output failure).

For primary control of the AVM lesion, absolute ethanol, Onyx, N-butyl cyanoacrylate (nBCA), contour particles, and/or venous coils can be utilized in various combinations,[42–46] simultaneously or in multiple stages. The use of nBCA or Onyx alone, however, is generally inadequate to provide long-term control of the AVM.[4,10,44,45]

All of these agents can be grouped into two different categories—embolic agents and liquid agents—based on their chemical properties. All "embolic" agents (e.g., coils) have a limited function in terms of producing mechanical occlusion of the vessel lumen and do not have the ability to penetrate the lesion nidus. In contrast, liquid agents (e.g., ethanol) do have this critical ability to penetrate and treat the lesion nidus. These liquid agents are ideally suited for the treatment of extratruncular AVM lesions.[4,46,47]

Liquid agents are further classified to two different groups: sclerosants and polymerizing agents. nBCA and Onyx are the two most commonly used polymerizing agents.

Among the many sclerosing agents, ethanol is by far the most commonly used and most effective agent, especially for AVM lesions, while the rest of the sclerosing agents (e.g., sodium tetradecol sulfate, polidocanol, and bleomycin) are primarily used in the treatment of low-flow venous and lymphatic lesions.[4,23]

Absolute ethanol still remains the sclerosing agent of choice for the treatment of extratruncular AVM lesions, especially in situations in which the lesion is surgically unresectable, such as in the diffuse infiltrating type.[4,48,49]

56.7.1.2 N-BUTYL CYANOACRYLATE[4,23,44]

nBCA is a free-flowing adhesive liquid that polymerizes on contact with any ionic solution. Following the immediate mechanical effect to occlude the vessel lumen, nBCA causes an acute inflammatory response to the heat generated during the polymerization process, and then a chronic inflammatory response to its chemical effect.

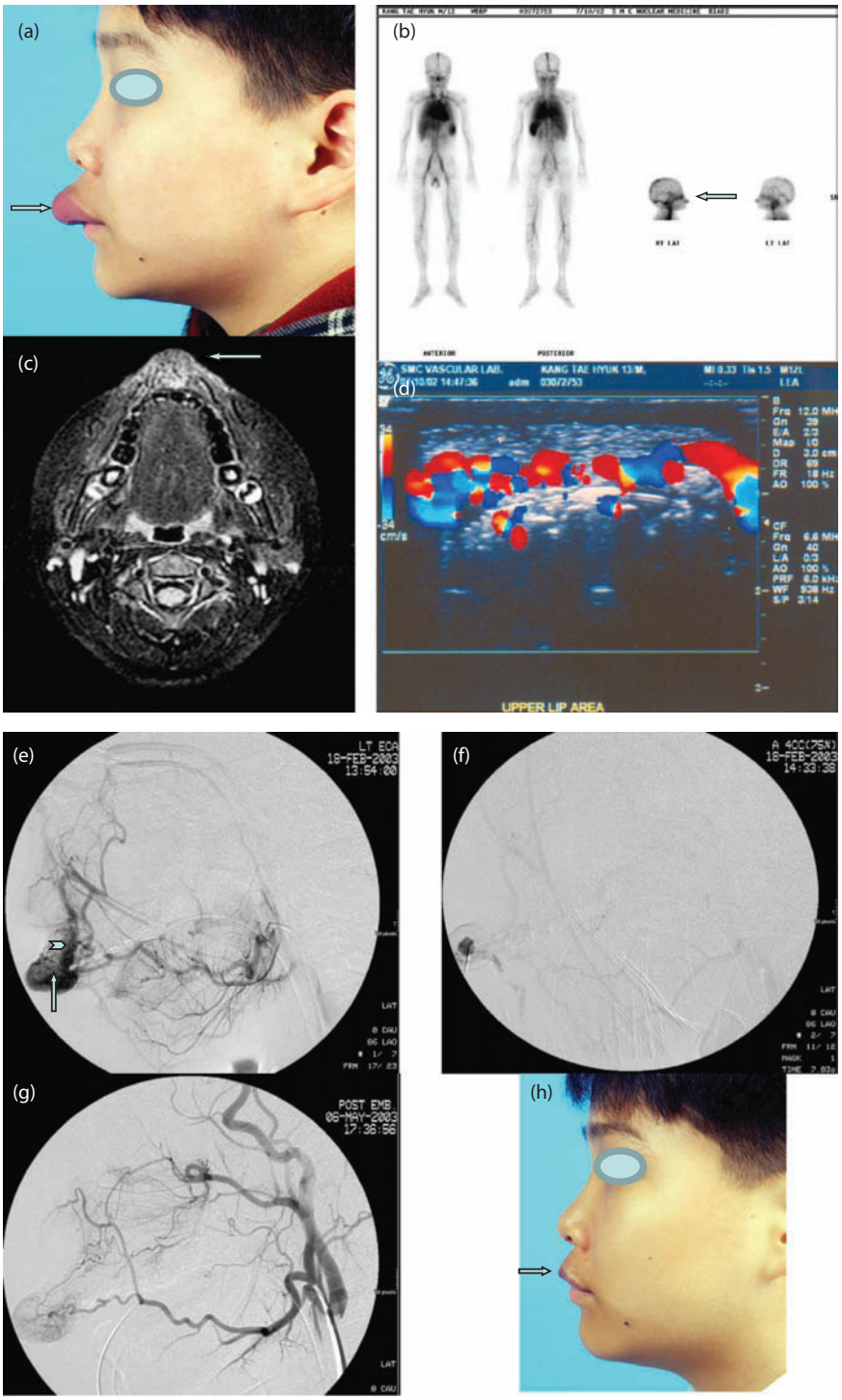


Figure 56.1 Surgically "inaccessible" extratruncular arteriovenous malformation (AVM) lesions treated with multisession embolosclerotherapies as independent therapies. **(a)** Clinical appearance of AVM lesion affecting the upper lip (arrow) with painful swelling. **(b)** Whole-body blood pool scintigraphy findings of AVM lesion localized to the upper lip (arrow); this test can provide qualitative as well as quantitative measurement for the follow-up assessment. **(c)** T2-weighted magnetic resonance imaging finding of infiltrating extratruncular AVM lesion (arrow) throughout the entire upper lip. **(d)** Duplex scan findings of hemodynamically very active AVM lesion affecting the entire upper lip. **(e)** Pre-treatment arteriographic findings of an upper lip AVM lesion (arrow) with localized nidus and its extensive collaterals as well as its venous drainage (arrow head). **(f)** Angiographic finding of initial ethanol sclerotherapy via the direct puncture percutaneous approach; 4.0 mL of 75% ethanol was used to control the nidus. **(g)** Arteriographic finding of a completely controlled AVM lesion following two sessions of endovascular treatment. **(h)** Clinical appearance of the upper lip with completely restored normal contour following successful ethanol sclerotherapy as an independent treatment.

nBCA has been used as a single-agent therapy with acceptable results in limited specific situations (e.g., inoperable pelvic AVMs). It should not be used as a single-agent therapy in the vast majority of AVM lesions requiring therapy for significant symptoms. Furthermore, nBCA appears to be "resorbed" over time, resulting in AVM recurrence.

Many consider nBCA to be "palliative at best," and its long-term effects as a foreign body and its effect on the AVM lesion remain controversial when used as a single-agent therapy.

56.7.1.3 ONYX[4,45]

Onyx is a new, "less adhesive" liquid polymerizing embolic agent consisting of ethylene copolymer and vinyl alcohol dissolved in dimethyl sulfoxide.

Onyx has several advantages over glue (nBCA) for the embolization of AVMs. It is less adhesive and polymerizes more slowly than glue. The microcatheters are rarely glued into the nidus and consequently make intranidal injection more controllable, resulting in a much more satisfactory result. In addition, Onyx carries a much lower risk of pulmonary embolism compared to the other emboloagents.

In some patients, however, onyx embolization results in extensive arterial occlusion without penetration of the nidus of the extratruncular AVM lesions, and so its effectiveness may be variable.

Onyx is not curative and remains a palliative or preoperative embolic agent like nBCA for the treatment of peripheral AVM lesions.

There is a concern regarding neovascular stimulation following extensive Onyx embolization of large AVMs. It is believed that Onyx treatment leads to the development of new collaterals, producing a "massive network of small arteries/arterioles" that is impossible to embolize by any means.

56.7.1.4 COILS[2,4,7,10,23,50]

Coils are designed to focally occlude larger vessels, rather than penetrating into the lesion nidus. The mechanism of action of coil embolization is limited to the vessels in which it is placed.[2,4,50]

Therefore, coil embolotherapy itself produces only a mechanical effect to occlude the flow and induce thrombosis. Coils do not have any direct effect on the endothelium and do not prevent recanalization of the lesion nidus. Subsequent regeneration or recovery of the endothelium will result in recurrence of the lesion. Hence, additional permanent therapy is often required to control the nidus completely, either with absolute ethanol or surgical excision if feasible, combined with nBCA.

Coil embolotherapy as an independent therapy is never clinically appropriate for extratruncular AVM lesions. However, coil embolotherapy is the most effective method to convert a high-flow lesion to a lower-flow lesion, which is essential for the treatment of the large, multifistulous AVM lesions that are often associated with a prohibitively high risk of complications related to extremely fast-shunting blood flow and volume.[2,4,50]

Therefore, a new endovascular approach utilizing initial coil embolization has been developed in which control of the high-flow lesion is achieved with the use of coils, followed by the administration of liquid endovascular agents (e.g., ethanol). Preliminary conversion of a high-flow state to a reduced/lower-flow state would make the lesion more amenable to ethanol sclerotherapy or nBCA glue embolotherapy for subsequent surgical excision with a reduced risk of complication and morbidity.

Hence, coils are typically used as secondary devices on the venous side of the lesion to slow down the outflow in order to enable subsequent injection of absolute ethanol so as to bring about permanent occlusion of the AVM (Figure 56.2).

In contrast, coils are appropriate and very effective for treating "truncular-type fistulous AVM lesions" as the primary treatment. Unlike the extratruncular lesions, the truncular AVM lesions lack the ability to proliferate, so coils can be used as an effective treatment modality, together with other mechanical occlusive devices (e.g., the Amplatz device).

These truncular lesions often require many coils for successful occlusion of the fistula (lesion) in order to control the associated hemodynamic sequelae (cardiac failure, arterial insufficiency, and venous insufficiency).

56.7.1.5 ABSOLUTE ETHANOL[46–51]

Absolute ethanol is a powerful sclerosant with curative potential to denude the endothelial cell from the vascular wall, precipitate its protoplasm, and fracture the vascular wall to the level of the internal elastic lamina. The thrombotic process progressively occludes the vascular lumen from the vascular wall, permanently eliminating the "chemotactic cellular factor" and "angiogenesis factor" since the endothelial cell is completely destroyed.[4]

However, ethanol sclerotherapy carries a significant risk of cardiopulmonary complications, warranting appropriate measures to be taken during its administration, including close monitoring with a Swan–Ganz catheter under the general anesthesia.[49,51]

Pulmonary hypertension is a potentially fatal complication that is caused by pulmonary arterial spasm when a significant amount of ethanol reaches the pulmonary circulation. The pulmonary hypertension can lead acute right heart failure and progress to cardiopulmonary arrest.

Prompt recognition and immediate cessation of ethanol therapy in addition to the appropriate control of pulmonary spasm with the various vasodilators is absolutely necessary to prevent further progression to cardiopulmonary arrest.[4,49,51] Increased pulmonary artery pressure is the earliest indication of the development of potentially fatal pulmonary hypertension.

A total dose of ethanol of 1 mL/kg of body weight is generally accepted as the maximum volume that can be safely administered during a procedure in order to prevent pulmonary hypertension.

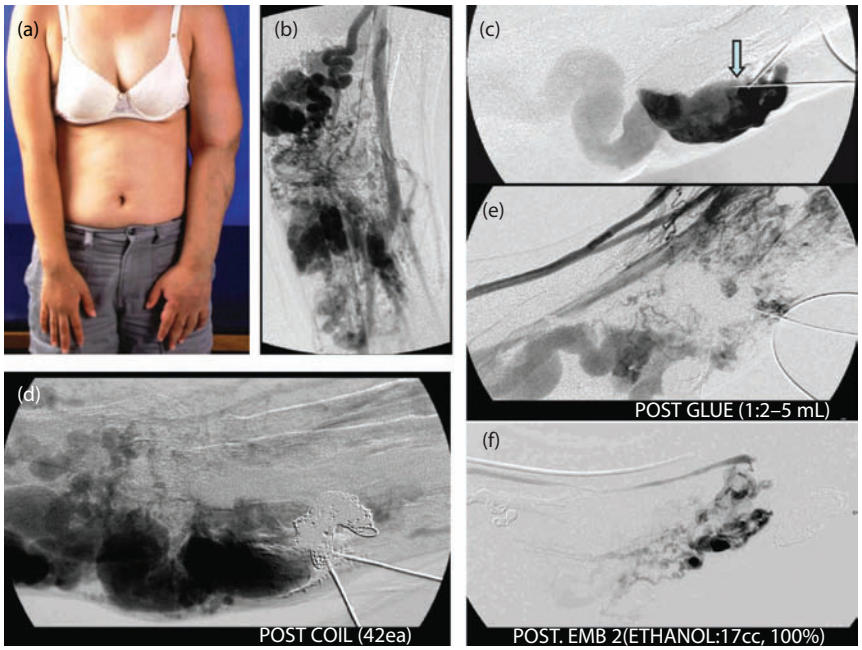


Figure 56.2 Multistage embolosclerotherapy of multifistulous arteriovenous malformation (AVM) lesions to control massive high flow. **(a)** Clinical appearance of the left upper extremity affected by AVM lesions along the elbow and forearm region as the cause of massive recurrent bleedings. **(b)** Arteriographic findings of extensive AVM lesions in the "multifistulous high-flow" condition; the feeding arteries are severely dilated and tortuous and the draining veins are also massively dilated. These findings suggest that the lesion has extremely high flow, increasing the risk of the therapy. **(c)** Angiographic finding of a massively dilated vein by a high-flow fistulous connection (arrow) allowing massive shunting from the artery. This condition is extremely difficult to manage with a conventional one-stage approach; it often requires a multistage approach to control/lower the flow with coils and/or glue first before the final treatment with ethanol. **(d)** Angiographic finding of initial coil embolotherapy right at the junction of the arteriovenous connection, making an artificial dam to control the flow. **(e)** Angiographic finding of subsequent N-butyl cyanoacrylate glue embolotherapy to convert the flow to the lowest possible level before final treatment with ethanol. **(f)** Angiographic finding of the final stage of endovascular treatment on the "multifistulous" AVM with 17 mL of 100% ethanol.

Further limiting ethanol administration to 0.14 mL/kg ideal body weight every 10 minutes is recommended when using large volumes of ethanol to treat large lesions in order to obviate the need of a pulmonary artery catheter, as advocated by Shin et al.[4,49,51]

The safe use of ethanol in AVM sclerotherapy requires precise delivery into the lesion with the use of microcatheters. Proximal injection of ethanol into a feeding artery would cause severe tissue necrosis.

Special precaution should be exercised in order to minimize the increased risk of skin necrosis, especially when ethanol is delivered via an arterial puncture. The minimally effective amount and concentration of ethanol should be administered whenever possible to reduce the risk of complications. Absolute ethanol may be diluted to 60% when used to treat superficial AVM lesions with a high risk of skin necrosis and AVM lesions in close proximity to nerves.

Administration of smaller volumes in divided doses also minimizes the risk of surrounding tissue injury. The residual ethanol within the lesion may be drained before the removal of catheters, especially when swelling/reaction is severe. Light compression may be applied for 5–10 minutes after the removal of catheters following the completion of therapy.

Compression may be applied to the draining vein during the ethanol injection in order to prevent early and premature drainage of ethanol from the lesion and to prolong the exposure time to the endothelium in order to maximize its effect. A great deal of caution should be exercised in order to avoid unnecessary collateral damage.

A combination of the three delivery routes should be utilized to reach the "nidus" of the AVM lesion: transarterial, transvenous, and direct puncture. These approaches should be utilized simultaneously in order to maximize the efficacy of the treatment. The percutaneous direct puncture approach to the lesion, however, is generally preferred and carries minimal risk.

The transarterial approach carries a higher risk of complications; therefore, its use should be limited to situations in which the direct puncture approach is not possible owing to small lesion size (e.g., facial AVMs). In these situations, the transarterial delivery of glue would be a safer approach if indicated and would limit the high risk of skin necrosis.

With the transvenous approach, coil embolization can be performed on the large, high-flow draining vein first, if present, before ethanol is injected.

56.7.2 Surgical/excisional therapy[2,4,7,10,23,32,43]

Surgical excision has long been the gold standard for the treatment of "extratruncular" AVMs and still remains the most ideal treatment to produce a "cure." However, unless the lesion is well localized, allowing minimal morbidity with total surgical excision, total surgical removal often carries prohibitively high morbidity and complication rates (e.g., massive operative blood loss and functional loss). Indeed, surgical therapy alone often results in *incomplete* control of the lesion owing to the high morbidity associated with complete radical surgical resection to prevent recurrence.[2,4,7]

The traditional role of surgical resection has been changed with the development of endovascular therapy over the last decades. A new endovascular embolosclerotherapy was introduced as an adjunct to open surgical therapy.[2,4,7,23,43]

Pre-operative embolosclerotherapy results in a significant improvement in the safety and effectiveness of subsequent surgical therapy, producing reduced morbidity and complications associated with surgical resection (e.g., intra-operative bleeding). Post-operative supplemental therapy also results in improved overall efficacy of surgical therapy. When implemented for the treatment of residual lesions after surgery, such post-operative embolosclerotherapy has also been shown to be as effective as pre-operative embolosclerotherapy.

nBCA glue is primarily used pre-operatively in surgically excisable lesions for this purpose. The glue-filled lesion can be safely dissected for surgical removal with minimal collateral damage.[2,4,10]

Embolosclerotherapy is now fully integrated with conventional surgical therapy for the treatment of "surgically accessible" AVM lesions, resulting in improved outcomes compared with lesions treated by surgical therapy alone, especially among marginally accessible lesions (Figure 56.3).

Unfortunately, however, most of the currently available treatments still carry a significant risk of complication and morbidity. Careful planning, from diagnosis and treatment to long-term follow-up assessment, is critical for successful AVM management.[2,4]

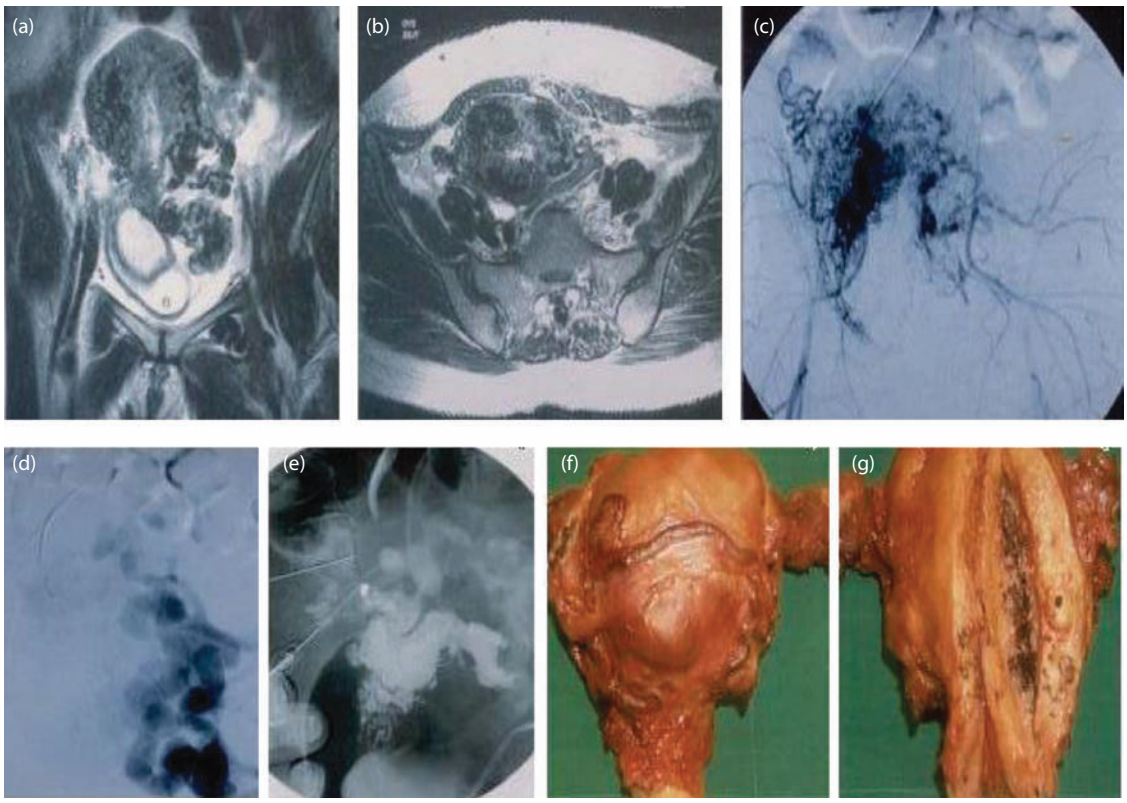


Figure 56.3 Surgically "accessible" extratruncular arteriovenous malformation (AVM) lesion treated with a combined approach with multisession pre-operative endovascular treatment and subsequent surgical excisions. **(a and b)** T2-weighted magnetic resonance imaging (MRI) findings of a pelvic AVM extensively affecting the uterus and para-adnexal soft tissues; this is a life-threatening lesion causing hemorrhagic shock, requiring emergency measures to control massive recurrent uterine bleeding. **(c)** Arteriographic findings of massively infiltrating extratruncular AVM lesions affecting the para-adnexal tissue and uterus. **(d)** Angiographic finding of massively dilated pelvic veins as the venous drainage route for the extensive pelvic AVM lesions. **(e)** Angiographic findings of N-butyl cyanoacrylate glue-filled pelvic AVM lesions; this pre-operative embolotherapy reduces/eliminates the risk of massive intra-operative bleeding during the subsequent surgical excision of the lesions. **(f)** Surgical specimen findings of the uterus. **(g)** The inner lumen of the transected uterus also shows glue-filled lesions infiltrating all along the endometrium as well as the uterine muscle structures, which is compatible with the MRI findings.

Periodic follow-up evaluation and assessment of treatment results should be made based on duplex scan, whole-body blood pool scintigraphy, TLPS, computed tomography, and/or MRI in the majority of cases. This is especially important during therapy requiring multiple treatment sessions. For evaluation of the majority of AVMs, arteriography has been the gold standard for the confirmation of treatment results at its completion.[2,4]

56.8 CONCLUSIONS

A multidisciplinary team approach is required to achieve effective control of AVM lesions with fully integrated endovascular therapy and surgical therapy. Endovascular therapy is preferred in the surgically "inaccessible" lesion, whereas surgical therapy combined with supplemental endovascular therapy is the best option for the surgically "accessible" lesion.

An early aggressive approach to all AVM lesions is required in general in order to reduce the consequences of any hemodynamic impact. A calculated approach is warranted based on a careful assessment of the risks and benefits associated with the treatment, unless the treatment is indicated for a life-threatening or limb-threatening condition (e.g., hemorrhage or high cardiac output failure).

Guidelines 5.4.0 of the American Venous Forum on arteriovenous malformations: evaluation and treatment

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.4.1	For symptomatic arteriovenous malformations, we recommend endovascular treatment with embolization or sclerotherapy. We recommend it for both definitive treatment of surgically "inaccessible" lesions and for initial therapy of surgically "accessible" lesions.	1	B

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● = Seminal primary article
★ = Key review paper
◆ = First formal publication of a management guideline

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The management of venous malformations

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57.1 INTRODUCTION

Congenital vascular malformations (CVMs) are rare, localized, or diffused abnormalities of vasculogenesis and angiogenesis that arise by embryologic dysmorphogenesis without increased endothelial proliferation, which leads to true structural and/or functional anomalies of the vascular system.[1,2] Most clinicians—from primary care doctors to subspecialists (including vascular surgeons)—consider the management of CVMs to be a difficult task reserved for referral centers with specialized expertise in this area. The main reason why expertise for vascular malformation management is centralized to major centers is the low frequency at which they occur, the confusing nomenclature and the lack of a uniform classification system that traditionally characterized the majority of the literature discussing CVMs, as well as the absence of established guidelines in the past for their management. Some malformations were initially described according to their appearance (nevus flammeus, port wine stain, stork bite, etc.).[3] Other descriptions relied on pathology of the abnormality (angioma simplex, hemangioma cavernosum and recemosum, or glomangioma).[4] Consequently, a significant number of CVM patients have been discouraged by the lack of correct diagnosis and proper treatment, despite numerous visits to different clinics.

The current chapter will deal with the diagnosis and management of low-flow vascular malformations (LFVMs) that are considered to be predominantly venous. With an estimated incidence of 0.8%–1%, predominantly venous malformations are the most common type and they comprise approximately two-thirds of all CVMs.[5] The evaluation and treatment of high-flow vascular malformations (HFVMs) with clinically significant arteriovenous shunting is described in Chapter 56.

57.2 CLASSIFICATION

As mentioned earlier, historically, numerous attempts have been made to properly classify CVMs based on anatomic, clinical, and/or embryologic criteria, and no real consensus existed regarding the nomenclature and management of these lesions. Based on a classification of "vascular birthmarks" initially proposed by Mulliken and Glowacki in 1982,[1] the International Society for the Study of Vascular Anomalies (ISSVA) introduced a classification system in which all vascular anomalies were divided into two categories: vascular malformations and vascular tumors. The differentiation of vascular anomalies into tumors and CVMs permitted more effective communication between different medical specialists. Unfortunately, the eponym-based terminology which characterized the ISSVA classification, as well as the lack of clinical applicability of this classification with regards to pre-treatment planning, was believed by many to be a major limitation for widespread acceptance and utilization of this system. To address the ISSVA classification limitations, the authors of "Hamburg" and subsequently the "Modified Hamburg Classification" developed a classification system by incorporating CVM flow characteristics (i.e., arterial, venous, and capillary) and defining CVMs based on the stage of developmental arrest during embryogenesis into truncular and extratruncular lesions, which is important for treatment selection and prognosis of treatment outcomes, as extratruncular lesions are associated with significantly higher recurrence rates and resistance to therapy, presumably because of their preserved mesenchymal characteristics of independent growth potential.[6] The "Modified Hamburg Classification" system has been considered to be "a more clinician-friendly classification for CVM management," as outlined in the 2009 Consensus

Document for the treatment of venous malformations of the International Union of Phlebology (IUP).[7]

Despite these efforts, many physicians still did not understand the difference between CVMs and vascular neoplastic lesions, and archaic terms such as "cavernous hemangioma," "port wine stains," "angel kiss," etc., were still frequently used by some specialists to describe CVMs. The growing recognition of the need for more efficient communication among practitioners and the need for a clinically applicable classification system informed the creation of a unified classification system by a group of authors commissioned by the IUP to foster comprehensive management of CVMs. The authors used both the ISSVA and "Modified Hamburg Classification" systems as the basis for the development of a new Integrated Classification System for the management of CVMs.[8] Malformations were categorized according to hemodynamic characteristics either as high flow or low flow, with further subdivision into anatomic subgroups designated by the predominant vascular element (arterial, venous, capillary, or lymphatic). In this scheme, venous, lymphatic, and capillary malformations are all low-flow lesions. Arterial malformations are considered high-flow lesions. Malformations are further classified either as extratruncular or truncular. Extratruncular lesions are categorized as diffuse/infiltrating or localized, whereas truncular lesions are categorized as obstruction/narrowing or dilatation (Table 57.1). In addition, vascular malformations usually occur alone, but there are also complex combined CVMs that are typically associated with various extravascular anomalies. A detailed description of these syndromes is beyond the scope of this chapter, but the reader is referred to an excellent review by Garzon and colleagues.[9] The relatively recently introduced concept of the multidisciplinary team approach, characterized by full integration of the expertise of different medical specialists, mandates the use of a unified classification system as an initial step in a multistep algorithm for the management of CVMs.[8]

57.3 ETIOLOGY

Although the etiology of CVMs remains to be elucidated, data from relatively recent studies suggest that the pathophysiologic mechanisms responsible for the formation of CVMs are caused by dysfunctions in the signaling process(es) responsible for the regulation of the proliferation, differentiation, maturation, adhesion, and apoptosis of vascular cells during the development of the vascular system.[10] Vessel development occurs in two different ways: vasculogenesis and angiogenesis.[11] The exact mechanisms through which these processes occur remain largely unknown and have just recently begun to be unveiled. Vasculogenesis refers to the process by which endothelial cells are differentiated *de novo* from mesodermal precursors. It occurs only during embryonic development. In angiogenesis, new vessels are formed from pre-existing ones by budding (sprouting), splitting (intussusception), and fusion (intercalated growth). These new vessels that are formed by angiogenesis (the so-called juvenile system) evolve into mature vessels by the processes of maturation and remodeling.[12] These complex processes involve several receptor tyrosine kinases. Some of these receptors and their ligands have been identified (i.e., vascular endothelial growth factors and Tie1 and Tie2).[13]

Several specific genetic abnormalities affecting some of these receptors in families with malformations have been identified. The study of these mutations has not only improved the understanding of the molecular pathogenesis of vascular malformations, but also facilitated the definition of each subtype into more specific clinical entities. For example, genetic analysis of families with autosomal dominantly inherited cutaneous venous malformations revealed mutations on the gene encoding for the kinase domain of the endothelial cell receptor Tie2 (also known as TEK) located at the *VMCM1* locus on 9p2.[14,15] This receptor has been associated with three ligands: angiopoietins 1, 2, and 4. It is theorized that mutations of this gene produce increased

Table 57.1 Integrated classification system of congenital vascular malformations[a]

Congenital vascular malformations					
Low flow			**High flow**		
Venous	Extratruncular	Diffuse/infiltrating Localized	Arterial	Extratruncular	Diffuse/infiltrating Localized
	Truncular	Obstruction/narrowing Dilatation		Truncular	Obstruction/narrowing Dilatation
Lymphatic	Extratruncular	Diffuse/infiltrating Localized	Arteriovenous	Extratruncular	Diffuse/infiltrating Localized
	Truncular	Obstruction/narrowing Dilatation		Truncular	Obstruction/narrowing Dilatation
Capillary					

Note: Syndrome associated malformations can be both low and/or high flow vascular malformations.

[a] International Union of Phlebology and International Union of Angiology endorsed.

phosphorylation of TEK and inhibition of apoptosis, resulting in abnormal remodeling with uncontrolled sprouting and branching of the capillaries and small veins, but not the larger veins and arteries.[16] Glomovenous malformations, when familial, have an autosomal dominant mode of inheritance, with incomplete penetrance. Thirty mutations have been identified in 86 families affecting the glomulin gene on chromosome 1p21–22.[14] Glomulin expression is limited to vascular smooth muscle cells and it is believed that, when lacking, abnormal differentiation towards the "glomus cell" phenotype occurs.[17] Many other genetic abnormalities have been discovered in families affected by CVMs.

Recently, genetic studies have identified high-susceptibility genetic loci associated with a development of truncular venous malformations found within the *HLA* locus on chromosome 6p21.32.[18] In particular, the number of copy number variations due to either deletion or duplication was found to be associated with an increased probability of developing truncular lesions. The region contains 211 known genes. Data from more recent genetic studies showed that regulatory genes of vasculogenesis and angiogenesis (*TIE-2*/*PDGFB*) play important roles in the development of extratruncular venous malformations.[19] In 2013, Rössler et al. performed an immunohistochemical analysis for cluster of differentiation-31 (CD31), D2–40, GLUT-1, and Ki67 in order to differentiate hemangiomas from LFVMs.[20] In addition to this, the authors analyzed the expression levels of β1, β2, and β3 adrenoreceptor mRNAs utilizing quantitative real-time polymerase chain reaction. Data from this study showed that all LFVMs showed CD31-positive immunostaining of endothelial cells and negative GLUT-1 staining. Immunostaining for Ki67 was positive in proliferative hemangioma endothelial cells (confirming their growth potential) and negative in venous malformation, which can serve as basis for the molecular differentiation and diagnosis of these two lesions. More importantly, venous malformations did not demonstrate significant expression levels of all three subtypes of β-adrenoreceptor mRNAs.[20] This was the first study to provide the genetic evidence of distinctions between hemangiomas and venous malformations based on β-adrenoreceptor subtype mRNA levels and provided valuable data that can potentially reveal the mechanism by which β-blocker medications are reasonable treatment options for certain types of hemangiomas but *not* for venous malformations.

57.4 CLINICAL PRESENTATION

The clinical presentation and course of CVMs are highly variable (in both their extent and severity), depending upon location, size, organ involved, and morphology of the lesion. They are rarely asymptomatic, although some lesions remain quiescent for many years. Their appearance and growth may be caused by trauma, infection, and/or the effects of hormones (during puberty, pregnancy, and menopause), or lesions may occur spontaneously in the absence of triggering factors. It seems likely that antecedent trauma can disturb a previously stable collateral system and unmask a lesion. Although progesterone receptors are identified in venous malformations, the exact mechanism that causes the appearance and progression of a lesion when hormonal levels change remains to be elucidated.[21]

Table 57.2 Incidence of physical changes in 82 affected extremities

Change	No.	Percentage
Color changes	57	69.5
Erythema	33	–
Cyanosis	24	–
Venous varices	49	59.7
Edema	46	56.0
Increased length	20	24.3
Deformity	9	11.0
Ulceration	8	9.8
Pulse deficit	3	3.6
Bleeding	3	3.6

Source: Adapted from Szilagyi DE et al. *Arch Surg* 1976;111:423–9.

Patients most often seek medical attention for pain, hemorrhage, cosmesis, palpable mass, limb edema, varicosities, thrombophlebitis, and/or other complications of venous hypertension (Table 57.2). In addition, some of patients have a significant reduction in daily functional capacity and quality of life. Venous malformations are typically bluish, soft and easily compressible, non-pulsatile masses that can enlarge in size when the affected extremity is dependent or after Valsalva maneuver. There is no increase in local skin temperature or thrill when the malformation is palpated, and there is no bruit present on auscultation. In patients with very large venous malformations, the affected limb may be warmer than the uninvolved limb, and patients may complain of increased girth and heaviness from increased venous volume. Young adolescents may develop scoliosis and limb-length discrepancies. The finding of lateral leg varicosities, capillary malformations, unilateral limb osteomuscular hypertrophy, or other venous abnormalities in a young person should alert the examiner to the possibility of Klippel–Trenaunay syndrome (KTS; see below). Pelvic malformations are complex and can produce rectal pain, sexual dysfunction, massive uterine bleeding, and ureteral outlet obstruction with hydronephrosis.

57.5 EVALUATION

The most important initial step in the management of congenital vascular anomalies is to differentiate CVMs from hemangiomas, as the clinical course and long-term consequences are distinctly different (Table 57.3). CVMs are present at birth and exhibit normal endothelial cell structure, function, and turnover.[1] They grow proportionately with the child and do not regress over time. In contrast, hemangiomas are true neoplastic disorders and pathohistologically demonstrate an increased endothelial cellular turnover

Table 57.3 Characteristics of vascular birthmarks

Type	Hemangioma	Malformation
Clinical	Usually nothing seen at birth; 30% present as red	All present at birth; may not be evident
Clinical	Rapid post-natal proliferation and slow involution	Commensurate growth; may expand as a result of trauma, sepsis, or hormonal modulation
Clinical	Female-to-male ratio of 3:1	Female-to-male ratio of 1:1
Cellular	Plump endothelium, increased turnover	Flat endothelium, slow turnover
Cellular	Increased mast cells	Normal mast cell count
Cellular	Multi-laminated basement membrane	Normal thin basement membrane
Cellular	Capillary tubule formation *in vitro*	Poor endothelial growth *in vitro*
Hematologic	Primary platelet trapping: thrombocytopenia (Kasabach–Merritt syndrome)	Primary stasis (venous); localized consumptive coagulopathy
Radiologic	Angiographic findings: well-circumscribed, intense lobular–parenchymal staining with equatorial vessels	Angiographic findings: diffuse, no parenchyma
Radiologic	–	Low flow: phleboliths, ectatic channels
Radiologic	–	High flow: enlarged, tortuous arteries with arteriovenous shunting
Skeletal	Infrequent "mass effect" on adjacent bone; skeletal hypertrophy rare	Low flow: distortion, hypertrophy, or hypoplasia High flow: destruction, distortion, or hypertrophy

Source: Mulliken JB, Young AE eds. *Vascular Birthmarks: Hemangiomas and Malformations*. Philadelphia, PA: W.B. Saunders Co., 1988, 35, with permission.

rate.[2] Hemangiomas usually manifest during the first several weeks of life, proliferate rapidly, with disproportionate growth relative to the child, and then slowly involute over a period of years.

The second step in the diagnostic algorithm, which follows initial differentiation between CVMs and hemangiomas (as well as other vascular neoplasms), is hemodynamic assessment of the lesion, which leads to differentiation between LFVMs and HFVMs.[22] Plain radiographs, computed tomography (CT), angiography, venography, duplex ultrasonography, and magnetic resonance imaging (MRI) are techniques that were traditionally used for this purpose, as clinical evaluation often underestimated the involvement of deep structures (i.e., muscles, bones, joints, or abdominal viscera) and frequently was not sufficient to differentiate HFVMs from LFVMs. Plain films can demonstrate soft tissue and bony hypertrophy, limb-length discrepancy, and phleboliths. Contrast-enhanced CT can identify the location of the venous malformation, bony involvement, vessel ectasia, and aneurysm formation. The true extent of the lesion into the soft tissue, is underestimated on non-contrast CT as only contrast-enhanced vessels opacify.

Duplex ultrasonography is a portable, noninvasive imaging technique that provides both functional and anatomic data in the evaluation of venous malformations. It is particularly helpful in defining the flow characteristics within the anomaly, thus aiding in differentiating between pure venous, arterial, and mixed malformations. On duplex ultrasonography, venous malformations demonstrate monophasic, biphasic, and no detectable flow in 78%, 6%, and 16% of cases, respectively, while the duplex ultrasonography of HFVMs is characterized by multidirectional blood flow, rapid arteriovenous shunting, and high-amplitude arterial waveforms with spectral broadening.[23] On grayscale ultrasonography, venous malformations appear as hypoechoic or heterogeneous lesions, with anechoic structures visible in <50% of cases.[23] In some cases, flow in venous malformations is only detectible on ultrasonography with compression and release of the malformation.

Although the above-described ultrasonography imaging is useful for confirming a diagnosis, as it is rapid and easy to perform, it is frequently inadequate for demonstrating the extent of the lesion and its relationship with the surrounding anatomic structures. Thus, MRI became the imaging modality of choice in the evaluation of the CVMs.[24] High-flow lesions have a significantly different appearance on MRI than venous malformations. They typically demonstrate low-signal regions ("flow voids") that can be observed on T1- and T2-weighted images. In contrast to this, venous malformations are visualized as high T2-weighted signals (Figure 57.1). The absence of feeding artery dilatation and draining is also indicative of venous malformations. As numerous particulars can interfere with the above-mentioned observations, distinguishing between HFVMs and LFVMs using MRI can be challenging in some more complex cases. For instance, a blood vessel that courses within an imaging plane can give an intraluminal signal on MRI despite fast flow, which can be a falsely positive finding for a venous malformation.[22]

The relatively recently introduced dynamic contrast-enhanced MRI (dceMRI) more accurately assesses the flow within the lesion, since it yields more information with

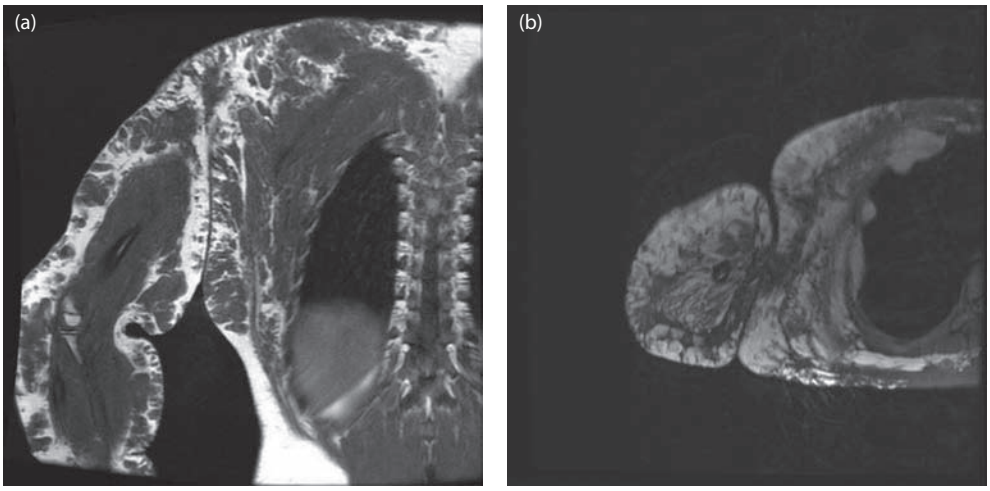

Figure 57.1 Coronal **(a)** and axial **(b)** T2-weighted magnetic resonance imaging demonstrates extensive low-flow venous malformation affecting the right hand, arm, shoulder, chest, and upper back in a 9-year-old patient.

regards to the hemodynamic characteristics of CVMs by utilizing time-resolved imaging of contrast kinetics and the time-resolved echo-shared angiographic technique, where images are acquired sequentially every few seconds. These techniques have an additional advantage of being able to delineate dominant or multiple feeding vessels, which can be useful for treatment planning. Data from our study showed a dceMRI accuracy of 83.8% with regards to differentiating HFVMs and LFVMs.[25] The data also showed that the specificity and sensitivity for the diagnosis of LFVM were 78.6% and 85.2%, respectively.[25] This leaves a relatively small number of inconclusive cases where dceMRI is not definitive for assessing flow characteristics and when suspicion of arterial flow cannot be excluded based on dceMRI findings. In this subgroup of patients, an appropriate diagnostic workup includes a venography. Venography allows precise evaluation of draining veins and is used to evaluate the extent of a lesion for pre-treatment planning (Figure 57.2). In some patients, angiography can be utilized to provide an opportunity to intervene. Based on data from our analysis, we recommend using dceMRI as the diagnostic modality of choice for making an accurate hemodynamic and anatomic diagnosis and for pre-treatment planning, as dceMRI allows a significant number of patients to be spared the expense, risk, and inconvenience of a catheter-based diagnostic study, as well as a delayed or erroneous diagnosis.[25]

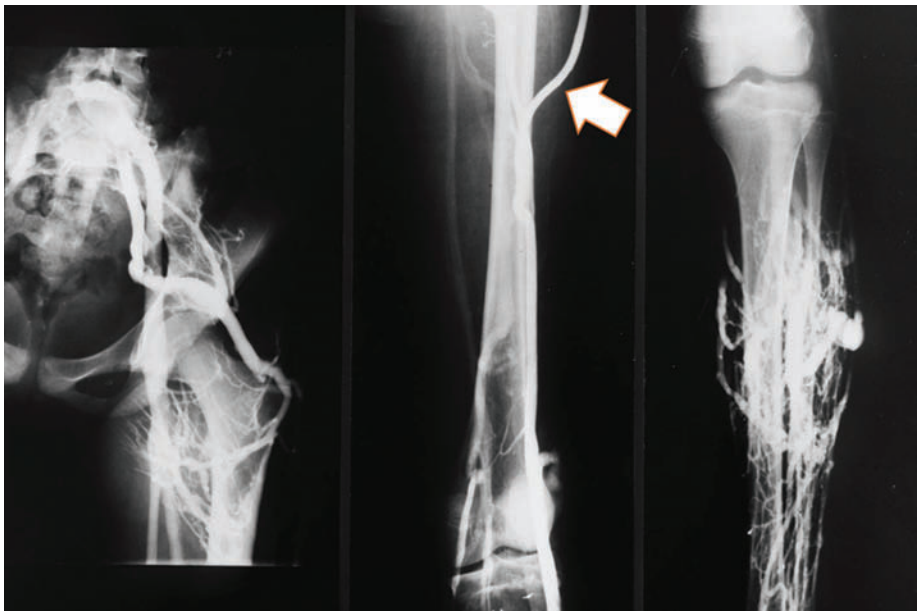

Figure 57.2 Venography demonstrates a large lateral embryonic vein (arrow) in a patient with Klippel–Trenaunay syndrome. Venography is not only used for diagnosis, but also for the assessment of the patency of the deep venous system and for the communicating pattern between the malformation and the deep venous system, which is important for pre-operative planning. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

Figure 57.3 Pathognomonic lower extremity hypertrophy, capillary malformations, and lateral varicosities affecting the right lower extremity in a male patient with Klippel–Trenaunay syndrome. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

57.5.1 Klippel–Trenaunay syndrome

The most common syndrome associated with venous malformations is KTS. This is a rare, sporadic syndrome characterized by the clinical triad of: (1) capillary malformations; (2) soft tissue and bone hypertrophy or, occasionally, hypotrophy of usually one lower limb; and (3) an atypical, mostly lateral varicosity with or without deep venous anomalies (Figure 57.3). It can also include lymphatic anomalies. It is important to differentiate KTS from Parkes–Weber syndrome on the basis that the latter has associated arteriovenous communications and KTS has none. Readers are referred to an exceptional review of the extensive experience at the Mayo Clinic in managing these syndromes published by Gloviczki and Driscoll.[26]

57.6 TREATMENT

Evaluation with a plan toward intervention in patients with venous malformations is best done by a multidisciplinary vascular malformation team. Prior to treatment planning, every effort should be exerted to rule out the arterial component. This differentiation is of critical value in the management of CVMs, as the treatment options for HFVMs and venous malformations are significantly different and the presence of an arterial component represents an absolute contraindication to sclerotherapy due to the increased risk of distal embolic events.[22] Pre-treatment planning should routinely incorporate the evaluation of the patency of the deep and superficial venous system due to the high prevalence of deep venous system anomalies in venous malformation patients. In a study of 392 patients, Eifert et al. documented aplastic or hypoplastic deep venous trunks in 8% of CVM patients.[27] The prevalence of deep venous anomalies is even higher (18%) in the subgroup of patients with KTS.[28] This assessment needs to be included in the treatment planning since venous blood flow from the affected extremity may depend on the malformed vessels, and obliteration or exclusion of the malformation from the circulation carries the risk of the impairment of venous return from the affected extremity. Surgical resection of dilated superficial varicosities in a patient with an absent or hypoplastic deep venous system is disastrous. The remaining venous collateral system is not adequate to drain the limb, and massive lower extremity swelling and ulceration can develop.

The treatment of venous malformations is frequently characterized by multiple treatment sessions utilizing the treatment modality that is the most appropriate for the location, extent, and morphology of the lesion. The need for multiple treatment sessions should be discussed with a patient prior to the initiation of treatment to increase the patient's compliance with the therapy. The possibility of recurrence following the treatment (especially in patients with extratruncular lesions) should also be discussed with the patient prior to starting the treatment in order to minimize the patient's frustration in case of recurrence. Goals of the treatment should be preset with each patient individually, and successful accomplishment of the preset goals marks the completion of treatment, as treatments are frequently palliative and goal oriented, especially in extensive lesions.

If asymptomatic, venous malformation should be treated conservatively (with external compression where appropriate). Patients with venous malformations should be placed in compressive stockings and sleeves early on to offset the long-term complications of venous stasis. Only patients who are symptomatic or have complications of their venous malformation are considered candidates for therapeutic intervention, given the potential for additional morbidity related to any intervention.

Traditionally, surgical resection was effectively used for encapsulated and small lesions. However, in patients with diffuse and multifocal lesions, the surgical approach is relatively contraindicated, as damage to surrounding anatomic structures and massive hemorrhage may ensue. In 2016, Malgor et al. retrospectively evaluated the long-term outcomes of open surgical treatment in 49 patients (53 limbs) with KTS.[29] Great saphenous vein stripping and lateral embryonic vein, small saphenous vein, and accessory saphenous vein surgical removal were performed in 17 (32%), 15 (28%), 10 (19%), and nine (17%) lower extremities, respectively. Data from this study showed that two patients developed deep vein thrombosis, one had a pulmonary embolism (PE), and one patient had peroneal nerve palsy. Kaplan–Meier analysis demonstrated that freedom from

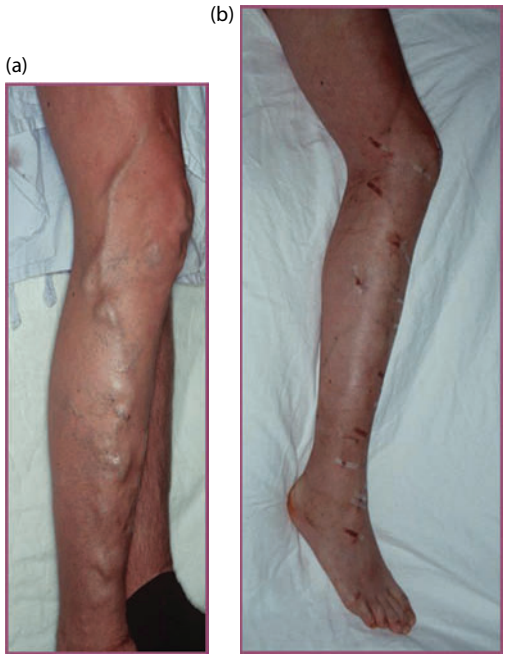

Figure 57.4 **(a)** Large lateral embryonic vein in Klippel–Trenaunay syndrome. **(b)** Intra-operative photograph demonstrates incisions of a mini-phlebectomy and skin closure with Steristrips following surgical removal of the lateral embryonic vein and congenital varicosities. (From Noel AA et al. Surgical treatment of venous malformations in Klippel-Trenaunay syndrome. *J Vasc Surg* 2000;32:840–7.)

disabling pain at 1, 3, and 5 years was 95%, 77%, and 59%, respectively.[29] Respective rates for freedom from secondary procedures were 86%, 78%, and 74%. In addition, at the last follow-up visit, the venous clinical severity score had decreased from 9.4 ± 3.27 to 6.0 ± 3.20 ($P < 0.001$). Data from this study showed that the surgical approach in patients with KTS is safe and durable (Figure 57.4).[29]

Treatment of the lateral embryonic vein deserves special consideration, since the hemodynamic alterations associated with blood stasis in these frequently valveless veins not only causes symptoms, but is also associated with a high risk of venous thromboembolic events. It has to be emphasized that there is inconsistent terminology that characterizes the majority of the literature discussing persistent embryonic veins. The persistent lateral (marginal) embryonic vein and the persistent sciatic vein are the only two persistent embryonic veins found in KTS patients. The lateral marginal vein is a superficial vein, although from an anatomical standpoint, the term "superficial" is a misnomer, since this vein frequently penetrates the deep fascia and involves muscles of the deep compartment of the lower extremity. The persistent sciatic vein is part of the deep venous system. The specific indications for treatment are based on symptom severity and the status of the deep venous system. In symptomatic patients (i.e., hemorrhage, debilitating pain, and/or functional disability) with patent deep veins, treatment of the lateral embryonic vein is indicated for the elimination of altered hemodynamics without compromising lower extremity blood return. This also applies to a subgroup of patients with hypoplasia of the deep veins: in this case, treatment of the lateral marginal vein will lead to spontaneous dilation of the deep veins, and therefore hypoplasia of deep veins is not a contraindication for treatment.[8] By contrast, aplasia of the deep veins does represent a contraindication for intervention, as the lateral embryonic vein serves as a major draining vein of the affected limb in these cases. All patients with a lateral marginal vein should undergo a complete hypercoagulability workup (including measurement of D-dimer and fibrinogen) and should be anticoagulated appropriately with a weight-adjusted dose (100 U/kg/day) of low-molecular-weight heparin peri-procedurally.[8] Traditionally, as mentioned above, surgical resection is preferred to endovascular treatment modalities as it is safe and durable and due to the superficial location of this vein and the fact that endovenous treatment modalities are associated with a risk of skin damage. In addition to this, in a small series of patients, Frasier et al. documented that the majority of KTS patients treated with radiofrequency ablation required retreatment due to recanalization of the treated vein.[30]

Definitive cure is possible in patients with limited, superficial lesions that are amenable to complete surgical excision. In reviewing the literature, only 20%–30% of patients with vascular malformations are candidates for complete excision. The largest surgical series were published in 1976, 1983, 1990, and 1992, comprising fewer than 100 patients. Szilagyi et al. reported on 18 patients with vascular malformations treated surgically.[31] A total of 55% of patients reported improvement in their symptoms following excision, 11% were unchanged, and fully a third were worse after surgery than before.[30] In 1992, Scott et al. reported the Northwestern experience in 15 patients with vascular malformations treated surgically.[32] Five patients were lost to follow-up. Assuming those patients did well and did not seek further intervention, two-thirds of those undergoing excision improved. A total of 13% were unchanged and 20% were worse after surgical excision.[31] If complete excision of the malformation is not possible, some authors suggest isolation of the lesion as an alternative. Skeletonization of lesions by ligation of all vessels feeding and draining the lesion is conceptually appealing, but more difficult in practice. Even minor collateral inflow can compensate over time and result in recurrence. Proximal ligation or embolization of major feeding vessels results in temporary improvements of symptoms. Recurrence of the lesion occurs as collaterals restore inflow to the vascular mass. Occlusion of the main feeding trunk surgically or through endovascular means precludes further interventional approaches and should be avoided.

Sclerotherapy has been used as an effective alternative to surgery in the treatment of venous malformations. Traditionally, the most widely used sclerosant was ethanol. Ethanol sclerotherapy, although effective, is associated with limitations and major complications (local and systemic), including severe pain requiring general anesthesia, ethanol toxicity, and localized tissue necrosis.[33] In a study of 87

patients with venous malformations who received 98 sessions of ethanol sclerotherapy, Lee et al. reported outstanding results, with 95% initial success and no recurrence in 71 patients at a mean follow-up of 24 months.[34] Data from this study also documented complications in 26.7% of patients which ranged from mild to severe. There were nine cases with ischemic bullae, five with nerve palsy, four cases of transient pulmonary pressure elevation, two with tissue necrosis and tissue fibrosis, one with deep vein thrombosis, and one with PE. Of the five nerve palsies, one (affecting the peroneal nerve) was irreversible.[33] Other studies also reported major side effects following ethanol sclerotherapy, including cardiac arrest and episodes of transient bradycardia.[35] Ethanol sclerotherapy can also result in transmural vessel necrosis, massive swelling (sometimes resulting in compartment syndrome), central nervous system depression, hypertension, and pulmonary vasospasm.[36] Burrows and Mason reported good to excellent results after serial sclerotherapy in 75%–90% of patients with LFVMs and showed that ethanol injections should be avoided close to major nerves or cutaneous lesions.[37] There was a 12% complication rate per session and 28% complication rate per patient in this series, with at least some skin necrosis occurring in 10%–15%.[36]

Since liquid sclerosing agents become diluted by intralesional blood, the use of sclerosants in microfoam form significantly improves the procedure for venous malformations, as the foam bubbles displace intralesional blood and prevent the sclerosant from becoming diluted. Following intravascular foam injection (with or without ultrasound or fluoroscopic guidance) sclerosants induce irreversible chemical damage to the vascular endothelial lining by the disruption of cell membranes. The response to the subendothelial collagen exposure leads to vasospasm, platelet aggregation, and subsequent endofibrosis that obliterates the vessel.[38] Foam bubbles achieve maximal exposure between the sclerosing agent and the endothelial lining of the malformation and the echogenicity of the bubbles makes them visible on ultrasonography, making the procedure more effective and easier to perform. For these reasons, foam treatments, in contrast to liquid sclerotherapy, can be performed on an ambulatory basis under local anesthesia. In a prospective randomized clinical trial, Yamaki et al. compared the efficacy of ultrasound-guided foam sclerotherapy with ultrasound-guided liquid sclerotherapy in the treatment of 89 symptomatic venous malformations.[39] Data from this study showed that the amount of sclerosant required to treat the lesion was significantly smaller in patients who were treated with foam sclerotherapy. These properties of sclerosant in the form of microfoam make it possible to use smaller doses in small increments, which reduces the risk of side effects and toxicity.

Foam can be produced with different techniques that result in differences in bubble size, foam stability, and reabsorption rates. The most widely accepted method for producing stable foam is the "Tessari method," first described in 2001.[40] The choice of foamed sclerosant is typically physician dependent. Currently, the majority of venous malformations are treated with 0.5%–1% sodium tetradecyl sulfate or 1% polidocanol. Alternative sclerosants such as bleomycin or doxycycline may be used in special circumstances, including venous malformations located on the hands and in lesions with a lymphatic component. At our institution, we currently use ultrasound- or fluoroscopically guided polidocanol foam sclerotherapy as the first line of treatment for venous malformations in the majority of patients.

The first large study of patients treated by foam sclerotherapy was published by Cabrera et al.[41] This study included 50 patients (35 with venous malformations and 15 with KTS). Sclerotherapy was performed by ultrasound-guided injection of 0.25%–4% polidocanol microfoam. Data from this study showed that the treatment was beneficial in 46 (92%) patients. Total disappearance of treated malformation, reduction in size of more than 50%, and reduction in size of less than 50% were documented in 158, 15, and 13 patients, respectively. In a subgroup of patient who presented with pain ($n = 39$), 25 experienced total relief, and the pain was significantly reduced in the remaining 14 patients. There were no major adverse events. Skin necrosis developed in three patients and four patients developed skin hyperpigmentation that was transient. Data from another perspective study that included 14 LFVM patients (eight with KTS) treated with 1% or 2% polidocanol demonstrated that the use of polidocanol foam sclerotherapy was effective and showed no major complications, no downtime, and no need for general or regional anesthesia.[42]

Relatively recently, we evaluated the efficacy and safety of the above-described treatment algorithm implemented by our multidisciplinary CVM team in a large series ($n = 136$) of CVM patients.[43] There were 105 (77.2%) LFVMs. In total, 47.1% and 14.0% of CVMs were located in the lower and upper extremities, respectively; this was followed by the head and neck (19.9%), trunk (5.1%), and pelvis (2.9%). A total of 11% of CVMs were diffuse, affecting two or more of the above-mentioned anatomic locations. Twenty-three (21.9%) LFVMs were managed conservatively, 38 (36.2%) were treated with sclerotherapy (sodium tetradecyl sulfate, polidocanol, doxycycline, and/or ethanol), 18 (17.1%) were surgically resected, and eight (7.6%) were managed with a combination of modalities. Foam sclerotherapy (sodium tetradecyl sulfate or polidocanol) was used in 31 (29.5%) lesions and ethanol in seven (6.7%) lesions. One (0.95%) patient was treated with doxycycline. Our data showed that conservative treatment was indicated for patients with minimal and tolerable symptoms and uncomplicated lesions. We documented significant improvements in symptoms and the attainment of patient and physician predetermined goals of therapy in approximately 88% of LFVM patients. In a subsequent study, we also analyzed the morphology of LFVMs to identify the lesion characteristics that affect the outcomes of treatment.[44] Data from our analysis demonstrated that symptomatic, diffuse, extensive LFVMs and LFVMs that involve multiple tissue planes and vital structures are best treated with foam sclerotherapy. LFVMs that are characterized by microcystic, septated vessels do not

respond to sclerotherapy, and these lesions are best treated with surgical resection. Primary surgical resection is also the treatment of choice for localized, microcystic, and superficial LFVMs.[43] As mentioned earlier, treatment of extensive lesions was palliative and goal oriented.

Similarly to our findings, based on data from a retrospective review of 33 patients with venous malformations, the group from Birmingham Children's Hospital proposed conservative management for patients with tolerable symptoms, reserving primary resection for localized and well-circumscribed lesions and sclerotherapy for vascular malformations involving vital structures.[45] Data from this study showed that 3% sodium tetradecyl sulfate sclerotherapy (performed in 12 patients) was associated with a 75% benefit and improvement in symptoms. The three patients who did not benefit from sclerotherapy had malformations infiltrating the knee joint. The cumulative complication rate for sclerotherapy and surgery was 15%. Of those who had sclerotherapy, three patients (25%) developed terminal necrosis of the distal phalanx, skin necrosis, and acute renal failure (due to the administration of a large dose of sclerosant) treated by dialysis. In a subgroup of patients who had surgery, minor complications such as wound dehiscence and skin necrosis occurred in two patients (11%).[44]

The initial determination of whether sclerotherapy can be performed safely must be made on clinical grounds for each patient and each lesion by an experienced practitioner with the knowledge of the venous malformation extent, communicating pattern, hemodynamics, and the feasibility of other treatment modalities. In properly selected patients, sclerotherapy is technically feasible and the risk of severe side effects can be minimized by utilizing several techniques that limit venous outflow during the delivery of the sclerosant. A tourniquet or manual compression can be applied downstream of the venous outflow to minimize the risk of passage of the sclerosant into the systemic circulation, to help contain sclerosant within the lesion, and to ensure maximal contact between the sclerosing agent and the endothelial lining of the malformation.

In the most challenging cases, in which the anatomy of the venous drainage is complex, multimodal (selective) treatment of the venous malformations, including preoperative embolization of the draining vein followed by sclerotherapy of the venous malformation, can be effectively utilized. In a study of 201 patients, Jin et al. showed that embolization of the draining vein followed by sclerotherapy of the lesion was beneficial in 196 (97.5%) patients.[46] Among the responders, complete resolution of symptoms, significant improvement (to nearly normal), and marked improvement were documented in 56 (28.6%), 42 (21.4%), and 62 (31.6%) patients, respectively. After a total of 592 treatment sessions, the authors documented no major complications (defined as side effects requiring further therapy, permanent adverse sequelae, or death). Minor complications were sclerosant specific and included tissue necrosis, peripheral nerve palsy, blistering, skin pigmentation, fever, and gastrointestinal irritation, which were documented in 6 (1.0%), 5 (0.8%), 5 (0.8%), 10 (1.7%), 35 (5.9%), and 76 (12.8%) cases, respectively. All complications were self-limiting and were characterized by spontaneous resolution.[45]

57.7 SUMMARY

Over the last two decades, there has been significant progress in the understanding of the molecular and genetic mechanisms responsible for the etiology and pathophysiology of venous malformations and of the management of these lesions. Data from numerous studies provide strong evidence that experienced providers working in the context of a coordinated and structured multidisciplinary vascular malformation team offer safe and efficient management of patients with CVMs. The diagnostic algorithm that is utilized to distinguish vascular tumors from CVMs and venous malformations from HFVMs is clinically applicable for making an accurate diagnosis and for pre-treatment planning in the majority of patients. A systematic evaluation of venous malformation is based on the characteristics of the blood flow, delineates the anatomic extent of involvement, and determines the presence of associated extravascular anomalies. For most asymptomatic venous malformations, observation alone is the best strategy. For others, external compression alone is sufficient treatment. Patients with symptomatic venous malformations are best treated with foam sclerotherapy and/or primary surgical resection, dependent upon the lesion's location, extent, and morphologic characteristics. This treatment pathway results in favorable outcomes with reasonable complication rates in this frequently challenging group of patients.

Guidelines 5.5.0 of the American Venous Forum on the management of venous malformations

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.5.1	For symptomatic venous malformations not responding to compression treatment, we suggest foam sclerotherapy over sclerotherapy with alcohol.	2	C
5.5.2	For surgically accessible and localized symptomatic venous malformations, we suggest surgical excision as an alternative to sclerotherapy.	2	C

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● = Key primary papers
★ = Major Review articles

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The management of venous aneurysms

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58.1 INTRODUCTION

Venous aneurysms are rare abnormalities. Sir William Osler first described a venous aneurysm in 1913.[1] Since then, venous aneurysms have been reported to occur in virtually every major vein. Despite numerous case reports and small single-center series, our current knowledge about this uncommon vascular abnormality remains limited. Most of the recommendations regarding the management of venous aneurysms are supported only by anecdotal and retrospective experience.

The terminology used to describe vein dilatations is often used without precise definitions. Not infrequently, the terms "phlebectasia," "venous aneurysm," and "varix" are used as synonyms. In this chapter, we will use the term "aneurysm" for any significant venous dilatation, whether saccular or fusiform. The term "phlebectasia" is used to describe a fusiform, diffuse dilatation. The association of a dilatation with tortuosity is called a "varix."

Aneurysmal dilatation of veins is often observed in association with either high-flow states or congenital venous malformations.[2] Following the creation of an arteriovenous fistula, venous dilation occurs to accommodate the high shear forces. Eventually, venous aneurysms form. Such aneurysms are associated with arteriovenous fistula access for chronic hemodialysis and with trauma. Occasionally, venous aneurysms form proximal to a partial venous obstruction, presumably as a result of increased pressure.[3] Multiple venous aneurysms are also found in association with vascular malformations that do not have arteriovenous shunting. Phlebectasia with venous aneurysms is associated with "genuine diffuse phlebectasia" and the Klippel–Trenaunay syndrome. Genuine diffuse phlebectasia is a rare disease characterized by diffuse venous enlargement of any extremity (usually upper) that is present at birth and progresses with age.[4] Pathologic specimens reveal smooth muscle atrophy and loss of elastin fibers. A related disease, Klippel–Trenaunay syndrome, is characterized by abnormalities of the deep venous system, including ectasia, hypoplasia, aberrant vessels (i.e., lateral veins), and venous aneurysms.[5] As these venous malformations form during embryologic development, multiple abnormalities exist simultaneously, including multiple venous aneurysms (Figure 58.1).

Solitary venous aneurysms (those not associated with high-flow states, trauma, inflammation, or congenital malformations) are uncommon, and they are the focus of this chapter. It appears that the most common site that is affected by venous aneurysms is the popliteal vein, followed by the saphenous and superficial extremity veins. Other venous aneurysms occur in the jugular vein, portal vein, azygous vein, superior vena cava (SVC), mediastinal veins, inferior vena cava (IVC), axillary vein, facial vein, and parotid vein.[6]

58.2 ETIOLOGY

The pathogenesis of venous aneurysms is unknown. The histologic findings in reported cases vary from normal to marked medial disruption and inflammation. With increased flow, "arterialization" of the venous outflow occurs with early hypertrophy of the vein wall followed by dilation and sclerosis (calcification). Venous remodeling, termed "endophlebohypertrophy" and "endophlebosclerosis," may be important factors in the development of venous aneurysms.[7] In a study of the popliteal vein, Lev and Saphir[7,8] found that endophlebohypertrophy begins at birth

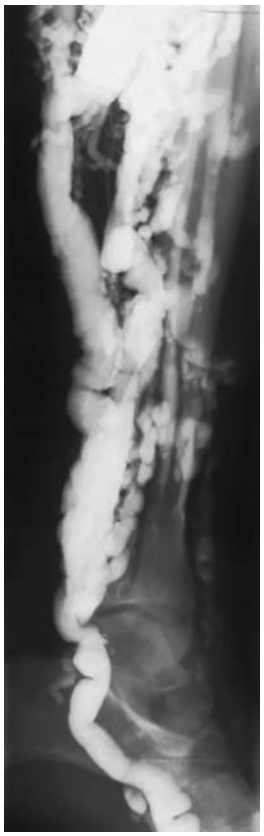

Figure 58.1 Lower extremity venogram of a patient with diffuse phlebectasia.

and is associated with areas of stress (entry of tributaries and adjacent to the artery). Endophlebosclerosis (thinning) increases with age and occurs immediately adjacent to the artery. Lev and Saphir believe that thinning of the vein wall occurs where the vein and artery are opposed. This finding suggests that an external force (rather than an intraluminal force) could alter venous histology.

The pathogenesis of venous aneurysms found in association with major vascular malformations is somewhat easier to understand. During embryologic development, the major vascular and lymphatic spaces coalesce and separate to form the arterial, venous, and lymphatic components of the circulatory system. Arteriovenous malformations are formed by abnormal communications between the artery and vein. Cystic hygromas occur when there is a failure of the lymph sacs to completely separate from the venous system. The failure of the jugular venolymphatic to completely mature may explain the high incidence of cervical and thoracic venous aneurysms with cystic hygromas.[9] On occasion, a persistent jugular sac may be misinterpreted as a venous aneurysm.[10] The etiology of a solitary peripheral venous aneurysm is the most difficult to understand. The very localized nature of these lesions suggests a specific abnormality in the vein wall. Similar to arterial aneurysms, the media of the vein wall is thinned with loss of smooth muscle.[11] The reason for the frequent occurrence of venous aneurysms in the popliteal vein is unknown, but may be related to the findings of Lev and Saphir.[7,8]

58.3 POPLITEAL ANEURYSMS

The popliteal vein is believed to be the most common site of venous aneurysms, with at least 208 cases reported in the literature.[12,13] The true prevalence of popliteal venous aneurysms and the frequency with which they cause symptoms are impossible to estimate. In a comprehensive review of the world literature, Bergqvist et al.[12] found that, in most of the reported cases, the popliteal aneurysms were discovered in patients with chest symptoms suggestive of pulmonary embolism (PE; 46/105), followed by patients complaining of local symptoms in the popliteal fossa (38/105). With the recent widespread use of ultrasound (US) and other imaging modalities, it is possible that most popliteal venous aneurysms today are found incidentally. Four cases of fatal PE in patients have been published. Rupture has never been reported. Bilaterality can occur but is uncommon. Very often, associated symptoms of venous insufficiency are present.

The diagnosis can be accurately made with duplex ultrasonography. Operative plans can be made with US alone, but most surgeons prefer the details of venography. Computed tomography (CT) venograms and magnetic resonance (MR) venograms have virtually replaced ascending phlebography in our (and most) practices. A recent report suggested a potential association between popliteal venous aneurysms and May–Thurner syndrome.[14] Nevertheless, other authors have analyzed CT and MR scans of patients with popliteal venous aneurysms and have not observed evidence of left iliac vein compression by the right common iliac artery.[15]

Given their frequent association with PE, most authors agree that popliteal venous aneurysms should undergo surgical treatment once the diagnosis is made. Anticoagulation alone has been used with fatal outcomes. This has been reported in the literature in at least five cases.[13,16,17] On the other hand, fatal PE has never been reported after surgical therapy. The size of the aneurysm does not appear to correlate with the risk of thromboembolism.[18] Contrary to this traditional approach of mandatory surgical repair, a recent series suggests that incidentally found popliteal venous aneurysms can be treated with anticoagulation or with observation alone. In this single-institution series, imaging reports were queried for "dilated, ectatic, or aneurismal popliteal veins." After finding an average dilation of the popliteal vein of 2 cm, a retrospective chart review revealed no PE or PE-related deaths in four patients who were anticoagulated and 13 patients who received no treatment at all after a mean follow-up of 34 months.[15] Because of the retrospective nature of this image report-driven review and the small diameter of the popliteal dilations observed, we believe that this provoking approach should be used with caution. Given the paucity of data and the lack of solid scientific evidence, an individual approach to each patient appears prudent. We favor operative repair for patients

Figure 58.2 Popliteal vein aneurysm exposed through a posterior approach. The sural nerve is observed lateral to the venous aneurysm and the popliteal artery has been encircled with vessel loops medially.

Figure 58.3 Lower extremity venogram showing a saphenous vein aneurysm in a patient with varicose veins.

presenting with venous thromboembolism and in those with large or thrombus-filled aneurysms. Only in selected patients with small, incidentally found aneurysms with high surgical risk are anticoagulation or observation used.

The short-term results of surgical treatment at our institution[2,11] and those reported in the literature are excellent. Aneurysmectomy with lateral venography or patch angioplasty repair, resection with end-to-end anastomosis, or bypass (using the non-reversed great saphenous vein, internal jugular vein, saphenous panel composite, or spiral vein) appear to have similar results. The long-term patency rates of venous repairs remain poorly defined. Reported rates in the literature vary from 40% to 90%,[17] but very few studies report patency rates after 12 months. Some have suggested that even short-term patency may facilitate the development of collateral venous channels.[19] Most aneurysms can be approached posteriorly (Figure 58.2), and peri-operative intravenous anticoagulation has been routinely used and frequently continued via the oral route for 1–3 months post-operatively.

58.4 OTHER VENOUS ANEURYSMS OF THE EXTREMITIES

Venous aneurysms of the extremities can develop in the superficial or in the deep venous systems. Most superficial venous aneurysms of the extremities present as soft, blue, compressible masses with few symptoms. Aneurysms of the saphenous vein are often associated with varicosities (Figure 58.3). It is not uncommon for those aneurysms located in the upper thigh to be misdiagnosed as reducible inguinal or femoral hernias. If the aneurysm is located in the superficial venous system, engorgement causing expansion during inspiration (upper extremities) or expiration (lower extremities) is typical.

The risk of PE due to aneurysms in the superficial veins of the lower extremity is low and very likely null for those in the upper extremities. For these reasons, most superficial venous aneurysms should be treated only if symptoms occur (cosmesis, pain, or thrombosis). In the majority of cases, excision of the aneurysmal segment alone is the best management option. In cases in which there is evidence of thrombosis or occlusion of the deep system, excision with reconstruction may be necessary.[20,21]

Deep venous aneurysms of the extremities usually present as asymptomatic soft masses or are discovered incidentally during imaging studies performed for other reasons. Location determines surgical repair of venous aneurysms of the extremities. Venous aneurysms of the brachial or axillary veins (Figure 58.4) are not associated with PE and should be treated only if symptoms occur (cosmetic or thrombosis). Iliac aneurysms (Figure 58.5) are rare. Most patients with external iliac vein aneurysms are female and many are young and involved in athletic activities.[22] Because iliac venous aneurysms appear to be associated with thromboembolic events in the majority of the reported cases,[2,3,23] they should be treated surgically. The same applies to femoral vein aneurysms. As with popliteal aneurysms, tangential excision with lateral venography or resection with reconstruction are viable options. Jayaraj and Meissner described a novel technique involving the use of a stapler over a balloon mandrel to resect iliac venous aneurysms.[24]

Figure 58.4 Venogram showing a large left axillary vein aneurysm.

Figure 58.5 Large left external iliac vein aneurysm (arrow) discovered incidentally in an asymptomatic patient undergoing a computed tomography scan of the pelvis.

58.5 CERVICAL AND FACIAL VENOUS ANEURYSMS

Venous dilatations have been described in the facial vein,[25,26] over the parotid gland,[27] and in the jugular system. Jugular aneurysms can be saccular or—more commonly—fusiform. The latter condition is more often seen in children and has been named "jugular phlebectasia." Gruber recognized it in 1875 and Harris in 1928. It has also been described as venoma, venous cyst, venous aneurysm, and congenital venous cyst.[28] Most cases are deemed idiopathic, but various theories of pathogenesis related to venous wall defects and increased intrathoracic venous pressure[29] have been proposed. In a review of the English literature published in 2001, Paleri and Gopalakrishnan[29] found 31 cases of pediatric internal jugular phlebectasia. We found over 100 additional cases of jugular aneurysms in children and adults. Typically, a unilateral soft mass in the neck is discovered. It enlarges on straining, crying, coughing, and Valsalva maneuver. The mass is almost always asymptomatic, although some patients have described the feeling of constriction, sensation of chocking and giddiness, bluish discoloration of the neck, discomfort during physical activity, coughing, swallowing, and cessation of voice during reading or speaking out loud.[30] In a single instance, an aneurysm of the internal jugular vein was discovered when the patient was being ventilated with positive pressure following an operative procedure.[31] Phlebectasia occurs more commonly on the right internal jugular vein and bilaterality is uncommon. Duplex US is the diagnostic method of choice and should be used to differentiate jugular phlebectasia from other neck masses in childhood, especially from the other two conditions that enlarge on Valsalva maneuver: superior mediastinal tumor or cyst and laryngocele.

The management of jugular phlebectasia is controversial, especially in asymptomatic cases. Spontaneous rupture has never been described, although massive bleeding during tonsillectomy occurred in one instance.[32] The risk of thromboembolic complications appears to be very low. Spontaneous thrombosis has been reported in only six cases, all of them adults with external jugular vein aneurysms. No instances of PE associated with jugular phlebectasia have been described. For these reasons, most authors strongly recommend conservative treatment.[21,28,29,33] Others follow a more aggressive approach with liberal surgical repair.[34] The arguments for surgical repair are fear of enlargement, fear of future misdiagnosis or rupture, potential for thromboembolic complications, and cosmetic and psychological considerations.[34,35] If surgical management is entertained, a choice is made between simply ligating the ectatic jugular vein versus the use of reconstructive techniques to maintain patency. Jugular vein ligation can result in head and neck edema.[34,35] Three out of 32 cases undergoing surgical repair for jugular phlebectasia in a single institution developed head and cerebral edema, causing intracranial hypertension, craniofacial edema, and even a stroke in one instance.[34] The group reporting these cases cautions about ligating the right jugular vein and suggests that temporary pre-operative internal jugular vein occlusion facilitates the development of collateral circulation between the intracranial and the extracranial veins.[35]

58.6 THORACIC ANEURYSMS

Thoracic aneurysms can arise from the SVC, the azygos vein system, or the innominate and subclavian veins.

58.6.1 SVC aneurysms

We found 30 reports of SVC aneurysms. Most aneurysms were found incidentally in asymptomatic patients undergoing imaging studies for other reasons or in patients with mild symptoms such as cough, dyspnea, and chest discomfort. In five cases, the SVC aneurysm coexisted with subclavian,

innominate, and azygos venous aneurysms. An association of SVC aneurysms and neck hygroma has been described. Fifteen patients underwent surgical management: 10 with excision or aneurysmorrhaphy, one aneurysm was wrapped in cellophane, one case was aborted, and in three cases the operation was performed for diagnostic purposes. Among the patients who underwent surgery, one patient died of intra-operative PE while his aneurysm was being palpated. All other surgically managed patients apparently did well, although the reported follow-up period was usually very short. On the other hand, half of the patients reported in the literature did not undergo surgical treatment. One patient died from PE while undergoing diagnostic SVC venography and one patient experienced contained rupture but survived and did not require surgery. As with the surgically treated cohort, the follow-up period was often short or not reported, although some authors documented 4[36] and 14[37] years of follow-up.

Based on the collective experience obtained from this review, some observations can be made. Surgical repair for fear of hemorrhage appears unjustified, since only two cases of aneurysm rupture exist and, in both, the rupture was contained. One was treated surgically and the other one did well with observation alone. No cases of free rupture with hemodynamic collapse have ever been reported. Although thrombus was observed within several aneurysms on imaging studies or in surgical specimens, no cases of documented spontaneous PE or, more importantly, spontaneous fatal PE have been reported. On the other hand, PE has occurred with catastrophic consequences during venography and during surgery as well. It seems that a prudent approach to SVC aneurysms is justified, with non-invasive imaging follow-up using MR venography and dynamic CT scans. In patients with progressive enlargement, severe symptoms, presence of thrombus, or evidence of PE, operative intervention should be considered. Pasic et al.[38] recommend the use of cardiopulmonary bypass during the excision of SVC aneurysms.

58.6.2 Azygos vein aneurysms

Thirty-eight cases of azygos and hemiazygos vein aneurysms were found in the literature. In 15 cases, associated anatomic and hemodynamic abnormalities were found. These abnormalities include cirrhosis and portal hypertension, pulmonary sequestration, IVC obstruction, azygos continuation syndrome (congenital anomaly consistent with failure of the right supracardinal vein to anastomose with the hepatic vein, resulting in drainage of blood from the distal IVC through the azygos vein into the SVC), Ehlers–Danlos syndrome, and lung cancer. There were three reported cases of false aneurysms occurring after chest trauma. In the remaining 20 cases, no evidence of increased flow or obstruction was found and thus the aneurysms were considered idiopathic. Most aneurysms were discovered incidentally in asymptomatic patients or in patients complaining of mild chest discomfort, dyspnea, or cough. Chest radiographs showed mediastinal enlargement and non-specific findings. In cases published prior to the widespread use of dynamic CT and MR, diagnosis was often made at thoracotomy after imaging studies suggested the presence of a posterior mediastinal mass. In most recent reports, the diagnosis was made based on imaging studies. Dynamic CT shows slight enhancement in the arterial phase and homogeneous enhancement in the late phase (Figure 58.6).[39–41] Respiratory and postural maneuvers induce changes in the size of the contrast-enhancing mass. Gadolinium injection during MR causes homogeneous enhancement of the aneurysm.[42] Transesophageal echocardiogram shows an anechoic mediastinal mass.[43] The aneurysm may compress the right main stem bronchus or the SVC. Thrombus has been documented in only two cases,[40] although no instances of PE have been reported. Rupture has never been reported.

Management strategies in the 38 reported cases varied from observation alone and aneurysm excision via a right lateral thoracotomy to placement of a stent graft from the right hepatic vein to the azygos vein in a case of azygos continuation syndrome in a patient with Ehlers–Danlos syndrome. Given the very low incidence of thrombosis and the fact that no reported cases of PE or rupture exist, a conservative approach with imaging follow-up appears more reasonable for most patients with no symptoms. If obstruction of the right bronchus or SVC exists, if symptoms are present, or if follow-up studies show enlargement or thrombosis, surgical or interventional treatment may be indicated. Podbielski et al.[44] and others[45] suggest that azygos vein aneurysms are ideal for video-assisted thoracoscopic excision. Alternatively, experienced endovascular specialists can consider the creation of azygo-systemic shunts, as described by D'Souza et al.,[46] after careful definition of the suitable anatomy.

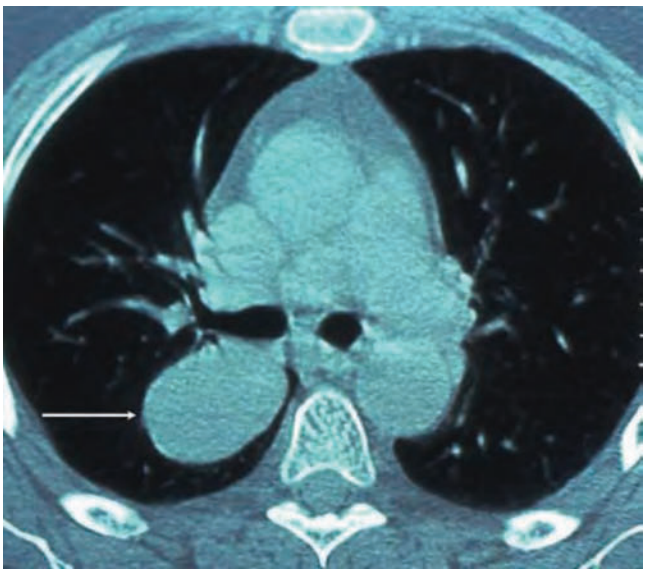

Figure 58.6 Azygos vein aneurysm (arrow). (Courtesy of Dr. Francis J. Podbielski.)

58.6.3 Other thoracic aneurysms

Reports of a total of 19 aneurysms of the subclavian and innominate veins have been published. Coexisting venous aneurysms were found in the SVC (five cases), azygos vein (one case), and jugular vein (one case). In one report of right innominate vein aneurysm, cystic hygroma was present. The majority of these aneurysms are saccular, asymptomatic, and occur in females. No thromboembolic complications have been reported. In one case mentioned above,[47] a 24-year-old woman with an anomalous persistent left SVC experienced spontaneous, contained rupture. This patient was managed expectantly and the aneurysm thrombosed and was eventually absorbed with a satisfactory outcome. These reports suggest that subclavian and innominate aneurysms should be managed conservatively unless symptoms or complications occur.

58.7 ABDOMINAL VENOUS ANEURYSMS

Most reports of abdominal venous aneurysms are in the portal venous system (Figure 58.7). We found 115 cases of portal system aneurysms. Although more than 25 cases were classified as idiopathic or congenital, the majority of portal aneurysms are associated with liver cirrhosis and portal hypertension. Pancreatitis has also been linked to the development of splenic and superior mesenteric aneurysms, presumably due to severe local inflammation. Most aneurysms are found in the extrahepatic segment of the portal vein, but aneurysms have been reported in the intrahepatic portal segment (25 cases), the superior mesenteric vein (17 cases), and the splenic vein (10 cases). Given the widespread use of high-definition imaging modalities, the majority of portal aneurysms described in the recent past have been found incidentally on abdominal US, MR, or CT scan studies performed for other reasons. In one case, a portal aneurysm was discovered *in utero*.[48] Small portal aneurysms are usually asymptomatic. Larger aneurysms can cause abdominal discomfort or compression of adjacent structures, provoking jaundice (common bile duct), dyspepsia (duodenum), and even portal hypertension (as in one aneurysm of the superior mesenteric vein causing obstruction of the portal vein with no evidence of liver disease). Not infrequently, portal vein aneurysms are discovered during workup for upper gastrointestinal bleeding in patients with portal hypertension.

Figure 58.7 Large aneurysm of the portal vein discovered incidentally in an asymptomatic patient.

The natural history of these aneurysms has not been defined. Most reports describe the imaging characteristics of the aneurysms at the time of diagnosis, but only a few have followed up these aneurysms prospectively. Spontaneous thrombosis has been reported in at least a dozen cases and rupture in at least four. The more common occurrence of gastrointestinal bleeding is usually caused by portal hypertension and is not a consequence of the aneurysm itself. From this review of the literature, it appears prudent to perform repeat imaging studies on asymptomatic patients with portal aneurysms. Aneurysm expansion appears to be rare in the absence of portal hypertension. In one case, the size of a splenic vein aneurysm changed along with the size of the spleen in a patient with leukemia, and regression occurred with resolution of splenomegaly. If gastrointestinal bleeding occurs, portosystemic shunts to alleviate portal hypertension should be considered. Patients presenting with thrombosis or symptoms related to the compression of adjacent structures should be considered for aneurysm repair, and those caused by portal hypertension should be considered for portal decompression.[49] Successful thrombectomy and aneurysmorrhaphy have been reported at 10-year follow-up.[50] Others have obtained good results with resection alone. Alternatively, some authors have reported good outcomes with observation in cases of thrombosed aneurysms.[51] Advocates of surgical repair argue that, although aneurysm thrombosis has been managed successfully without intervention, cavernous transformation of the porta hepatis, portal hypertension with potential variceal bleeding, and mesenteric venous infarction can be prevented with a more aggressive approach. This suggests that surgical intervention can be selectively applied to average-risk and low-risk patients and that observation can be used in elderly, high-risk subjects.

58.8 IVC ANEURYSMS

We reviewed 25 cases of aneurysms of the IVC. In the majority of published cases, no symptoms were present and the aneurysm was discovered incidentally. Thrombosis was reported in eight cases, rupture in one,[1] and PE in two, one of which was fatal. One aneurysm was discovered during evaluation for penile bleeding.[1] Modern imaging techniques usually allow for the diagnosis of these uncommon aneurysms. In cases of thrombosed IVC aneurysms, diagnosis may be difficult and the aneurysm can be confused with retroperitoneal tumors, renal carcinoma, lymphadenopathy,

and IVC tumors. In one report, an IVC aneurysm coexisted with a retroperitoneal ganglioneuroma. Some authors have classified IVC aneurysms depending on their anatomic location.[52] As with other venous aneurysms, the limited number of cases makes their natural history unclear and thus management recommendations are difficult to make. Since thrombosis, rupture, and embolism have been described, low-risk patients should be considered for operative repair. Simple resection, resection with primary repair, patch angioplasty repair, or caval replacement have been described. Patients who cannot undergo surgical treatment can be considered for filter placement in the suprarenal segment of the IVC for the prevention of PE.

58.9 CONCLUSIONS

Venous aneurysms are uncommon. The presentation and management of these abnormalities depend on their location. Aneurysms of the deep veins in the lower extremities carry a significant risk of thrombosis and embolism, and repair should be carried out once the diagnosis is made. Aneurysms of the lower extremity superficial system and those in the upper extremities—whether superficial or deep—are rarely associated with thromboembolism, and repair is only indicated for cosmetic reasons or if thrombosis occurs. Aneurysms of the neck and face often present as visible, soft masses that change in size with respiration and straining. In children, jugular phlebectasia should be included in the differential diagnosis of neck masses that enlarge during the Valsalva maneuver. The management of this condition remains controversial.

Thoracic aneurysms are rarely associated with thromboembolism or hemorrhage and can be managed conservatively. When enlargement or complications occur, traditional surgical repair, thoracoscopic excision, and endovascular techniques are viable alternatives. Venous aneurysms in the abdomen are most frequently discovered incidentally during imaging examinations. Management should be individualized with surgical treatment for low-risk patients and expectant management for asymptomatic patients who are poor candidates for surgery.

58.10 SUMMARY

- Venous aneurysms of the lower extremity deep system carry a significant risk for thromboembolic complications and should be repaired.
- Venous aneurysms of the superficial venous system in the upper and lower extremities and those in the deep system in the upper extremities are rarely associated with embolism or rupture and can be managed conservatively unless cosmetic reasons or complications occur.
- Jugular phlebectasia carries a low risk for thromboembolism. Surgical management is indicated only for cosmetic and psychological reasons.
- Thoracic venous aneurysms are infrequently associated with rupture or thromboembolic complications and can be observed in most cases.
- Abdominal venous aneurysms have been linked with complications such as rupture and embolism. Repair should be considered in patients who are fit for surgery.

Guidelines 5.6.0 of the American Venous Forum on the management of venous aneurysms

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.6.1	We recommend surgical repair of even asymptomatic deep lower extremity venous aneurysms because of the risk of thromboembolic complications.	1	B
5.6.2	For aneurysms of superficial veins of the arm or leg or of deep veins of the arm, we suggest observation unless cosmetic reasons or complications warrant repair.	2	B
5.6.3	For jugular vein aneurysms, we suggest observation unless cosmetic reasons or psychological reasons warrant surgical repair.	2	C
5.6.4	For abdominal venous aneurysms, we suggest repair because of the risk of rupture and thromboembolism.	2	C
5.6.5	Thoracic venous aneurysms are infrequently associated with rupture or thromboembolic complications and can be observed in most cases.	2	C

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● = Key primary paper
★ = Major review article

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Management of pelvic congestion syndrome and perineal varicosities

JOHN V. WHITE, LEWIS B. SCHWARTZ, AND CONNIE RYJEWSKI

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Nearly 9 million women in the United States awaken each day to worsening chronic pelvic pain. Chronic pelvic pain is defined as intermittent or constant pelvic pain of unknown etiology that is present for 6 months or longer and refractory to conventional therapies. It is a major health problem in the United States, affecting approximately 15% of all women between the ages of 18 and 50 years and adding nearly $2 billion of cost to the health care system without significant patient benefit. Affected persons experience more physical limitations, fatigue, and depression, often leading to lost time from the workplace.[1] In the absence of an identified cause despite a complete gynecological evaluation, including bimanual examination, pelvic ultrasonography, and laparoscopy, more than 80% are likely to be suffering from pelvic congestion syndrome (PCS).

PCS represents a constellation of symptoms associated with pelvic venous flow abnormalities that cause chronic pelvic pain (Table 59.1). It is widespread, affecting an estimated 6–7 million women in the United States, but has been poorly defined until recently. It is now recognized that PCS stems from reflux into the pelvic veins, which leads either to the development of pelvic varicosities or, through alternative venous pathways, to recurrent varicose veins of the legs. As with varicose veins of the legs, pelvic venous congestion is generally a gravity-dependent abnormality and causes similar symptoms of aching, throbbing, or stinging pain when the person is standing or sitting for prolonged periods of time. The syndrome does not reduce the quantity of life of those afflicted, but does have a significantly negative impact upon quality of life. The goals of helping patients with PCS are to reduce or eliminate the symptoms and, when possible, to treat the underlying causes. To do this, the vascular specialist must have a clear understanding of the pelvic venous anatomy, the mechanisms of normal and abnormal venous flow, and the symptoms associated with flow abnormalities.

59.1 RELEVANT PELVIC VENOUS ANATOMY

As the site of reproduction, the female pelvis has a rich, complex, and interconnected venous drainage system capable of accommodating a nearly 60% increase in blood volume and flow during pregnancy.[2] The reproductive complex is positioned in the pelvis amidst the venous drainage pathways of both the other pelvic viscera and the lower extremities and shares interconnections with each.

The uterus has an extraordinary venous system (Figure 59.1). The veins within the endometrium and myometrium form an extensive interconnected network that dilates through the course of the menstrual cycle.[3] The veins of the outer myometrium and the perimetrium have multiple interconnections with the vaginal veins to form a functional anastomotic network.[4] The fundic portion of the uterus drains into the ovarian venous plexus.[5] The remainder of the uterus drains into uterine veins that flow into the internal iliac veins. The uterine and ovarian veins are generally of a similar diameter, which suggests that there is no preferential venous drainage pathway with venous blood capable of moving freely through them.[6]

Each ovarian vein forms from the confluence of the small veins of the pampiniform plexus within the broad ligament (Figure 59.1). The usually single, thin-walled ovarian vein

Table 59.1 Symptoms of pelvic venous congestion syndromes

Symptom	Gravitational ovarian reflux	Nutcracker syndrome	May–Thurner syndrome
Pelvic pain with prolonged standing	+++	+++	+++
Pelvic pain with prolonged sitting	++	+	++
Pelvic pain when supine	–	++	–
Dyspareunia	++	++	–
Post-coital pelvic pain	+++	++	–
Dysmenorrhea/dysmenorrhagia	++	++	+/–
Left flank pain	–	+++	–
Intermittent hematuria	–	+++	–
Left leg edema	–	–	+++

Note: +++: most common; ++: common; +: less common; +/– may or may not be present; –: usually absent.

is generally between 5 and 7 mm in diameter as measured on computed tomography (CT) scan.[7,8] The left gonadal vein rises from the pelvis to join the left renal vein and the right ovarian vein rises to enter the inferior vena cava directly, usually just below the level of the right renal vein. Each ovarian vein has a single valve present just prior to its termination.

The remainder of the pelvic structures and the upper portion of the leg drain through branches of the internal iliac vein, forming another significant anastomotic network that connects with the reproductive complex. The superior and inferior gluteal veins collect blood not only from the three gluteal muscles, but also from the superior posterior thigh. The small veins that drain the superior portion of the biceps femoris of the posterior thigh may flow either into the lateral circumflex femoral vein, a tributary of the deep femoral vein, or into the gluteal veins that flow into the internal iliac vein. These pathways link the posterolateral thigh with the pelvis and may become a reflux pathway causing recurrent varicose veins.

The obturator veins of the lateral pelvis are also interconnected with the femoral venous system. The small veins that

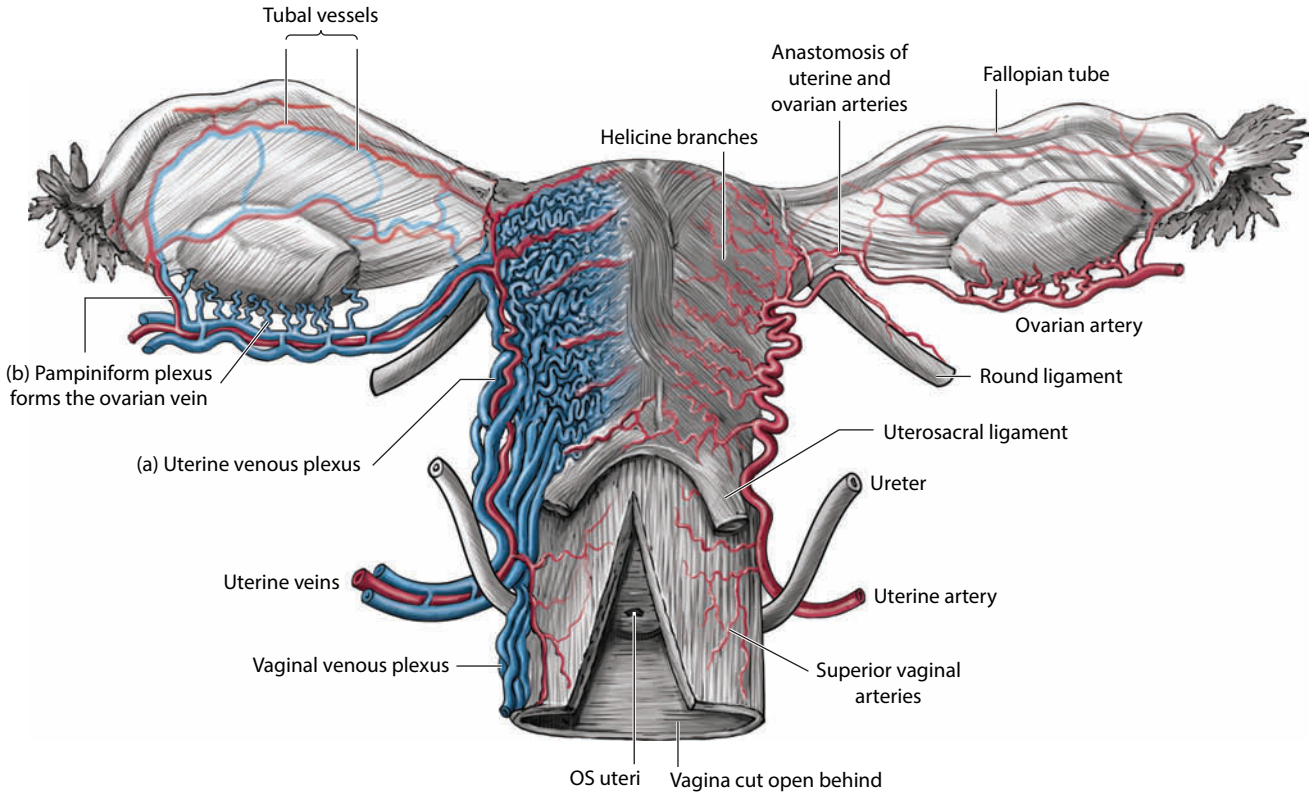

Figure 59.1 The major venous drainage pathways of the female reproductive system. **(a)** The uterus has venous lakes within the myometrium and the perimetrium that communicate with and drain through both the uterine veins and the pampiniform plexus. **(b)** The pampiniform plexus coalesces to form the ovarian vein. With the exception of a single ovarian vein valve, this system is valveless and free flowing.

collect blood from the adductor muscle groups may flow into the medial circumflex vein of the deep femoral venous system or into the obturator veins that coalesce with the small veins draining the bladder, traverse the pelvic floor, and empty into the internal iliac vein. These pathways link the anteromedial thigh with the pelvis.

Finally, the perineum also has a dual venous drainage pathway that directly connects the pelvis with the anterior aspect of the lower extremity. The skin of the perineum and the vulva drain through the superficial dorsal vein into the external pudendal vein, which courses laterally and empties into the great saphenous vein at the level of the saphenofemoral junction. The deeper layers of the perineum and the vulva drain through the deep dorsal vein into the internal pudendal vein that merges with the inferior rectal vein and carries blood into the internal iliac vein. There is an anastomotic network that connects the internal and external pudendal veins, establishing another connection between the reproductive structures and the perineum.

Unlike the lower extremity, the veins of the pelvis have few valves to restrict the direction of venous outflow. In a cadaver study of 200 gonadal veins, single bicuspid valves were noted in 62% of left-sided veins and 48% of right-sided veins. The ovarian vein valve is located just prior to its termination point.[9] However, there are no valves within the uterine veins. The internal iliac veins also share this paucity of valves. LePage and colleagues studied 79 internal iliac venous systems in 42 cadavers. The common iliac vein was formed by the confluence of the external iliac vein with single internal iliac veins in 73% and dual internal iliac veins in 27%. Valves were identified in only 10.1% of the main trunks of the internal iliac veins and in only 9.1% of the secondary branches.[10] In the absence of valves, the rich anastomotic networks allow blood to flow in alternative directions during periods of relative venous overload, such as that which may occur during pregnancy or in the setting of venous reflux.

59.2 MECHANISMS OF PELVIC VENOUS FLOW

The mechanisms that propel blood through the pelvic venous system are as yet undefined. The paucity of valves within the pelvic venous system suggests that the lower extremity unidirectional stepwise rise in venous blood from the tibial veins to the common femoral vein valve propelled by muscle contraction does not occur. Indeed, the venous return from the pelvis is able to take the path of least resistance. While generally coursing in a cephalad direction, pelvic venous blood may travel through any of the many anastomotic channels detailed above during its return to the heart. It is most likely that the branches of the internal iliac vein that collect blood from the muscles of the pelvis and superior portions of the leg are driven by contractions of these muscles during ambulation in a manner similar to that of the lower extremity. This force of movement assists in the transport of venous blood from the other pelvic structures. Once this venous blood travels through the internal iliac vein into the common iliac vein, it maintains a straight course to the right atrium.

The mechanism that drives the ovarian vein remains enigmatic. The ovarian veins carry blood upward against gravity for a distance of 20–40 cm without intrinsic motility or surrounding muscle or other contractile structures. Despite this singular upward trajectory without a clear pumping mechanism, flow rates within the ovarian veins exceed those of the uterine veins.[4]

The plurality of pelvic venous drainage and the effective venous pumps ensure that the many physiologic changes that occur during reproduction, from dramatic increases in the volume of blood passing through the pelvis to compression of venous structures by the gravid uterus, can be accommodated without interruption of the pelvic circulation. It is these same mechanisms, when overloaded, which can cause the symptoms and signs of pelvic venous congestion.

59.3 MECHANISMS OF ALTERED PELVIC VENOUS FLOW

As with varicose veins of the lower extremity, all of the underlying mechanisms of pelvic venous congestion are not yet well defined. The largely valveless system of veins within the pelvis generally adheres to the tenets of venous physiology, with flow moving in a cephalad direction from smaller veins to larger veins on the ipsilateral side. In the setting of pelvic venous congestion, each of these tenets may be compromised to preserve pelvic venous drainage. There are permissive elements, such as the intrinsic structural weakness of vein valve cusps or increases in vein diameter rendering vein valves incompetent, which often combine with driving forces to cause the development of pelvic varicose veins and generate the symptoms of PCS. In addition to gravity, some of the driving forces that move excessive venous blood into the pelvis have been defined. These include pregnancy, left renal compression, and left common iliac vein compression. Identifying and controlling these mechanisms when possible are important steps in the treatment of patients with pelvic venous congestion syndrome.

Pregnancy is a well-recognized cause of pelvic and lower extremity varicose veins. There is a significant increase in arterial inflow to the pelvis during pregnancy. To achieve this, there is an increase in absolute blood volume by nearly 50% over the course of the pregnancy and an increase in pulse rate, stroke volume, and cardiac output and thus an increase in pelvic venous return.[2] As the gravid uterus enlarges, it is capable of compressing or distorting pelvic veins, thereby altering venous outflow patterns. To maintain venous outflow, there is increased flow through many of the anastomotic networks associated with the uterus and ovaries. There is also an increase in the diameter of the major veins of the pelvis and the legs. The increase in ovarian vein diameter may render valves of the ovarian veins, internal iliac veins, and superficial veins of the legs incompetent. In an abdominal CT study of 110 women who had previously been pregnant compared to 41 who had

not, the investigators noted ovarian vein reflux in 44% of uniparous or multiparous women, but only in 5% of women who had not been pregnant.[7] The diameter of the left ovarian vein was also greater in those with reflux compared to those without (8.3 ± 2.1 mm vs. 4.9 ± 1.3 mm, $P < 0.0001$). Similar findings of diameter increases and valvular incompetency have been noted in the great saphenous veins during pregnancy.[11] As the gravid further compromises pelvic venous return, flow may be forced through anastomotic channels that connect the pelvic veins to the lower extremity veins, manifesting as vaginal, labial, or anteromedial or posterolateral upper thigh varicose veins. In many women, these changes are reversible after delivery, but up to 28% may develop chronic varicose veins after a single pregnancy, and the incidence rises with each subsequent pregnancy.[12,13]

The most common form of PCS is gravitational reflux through the left ovarian vein due to lack of a competent ovarian vein valve (Figure 59.2). As noted previously, the single bicuspid ostial valve may be congenitally absent or may become incompetent due to structural weakness of the valve or dilation of the ovarian vein. Regardless of the cause of valvular malfunction, gravity will cause reflux in the ovarian vein when the patient is in the sitting or standing positions. Since the kidneys receive approximately 25% of the cardiac output, the volume of blood refluxing into and traversing the pelvic collaterals can be quite significant. The patients will often experience pelvic symptoms that progress over the course of the day and are relieved by lying supine to reduce the effects of gravity.

Reflux through the left ovarian vein can be compounded when the left renal vein is compressed between the aorta and the superior mesenteric artery (nutcracker syndrome) (Figure 59.3). As pressures in the renal vein rise, the ostium of the left ovarian vein may dilate and the single ostial valve in the left ovarian vein may be rendered incompetent, if not already so as a result of prior pregnancies. Blood exiting

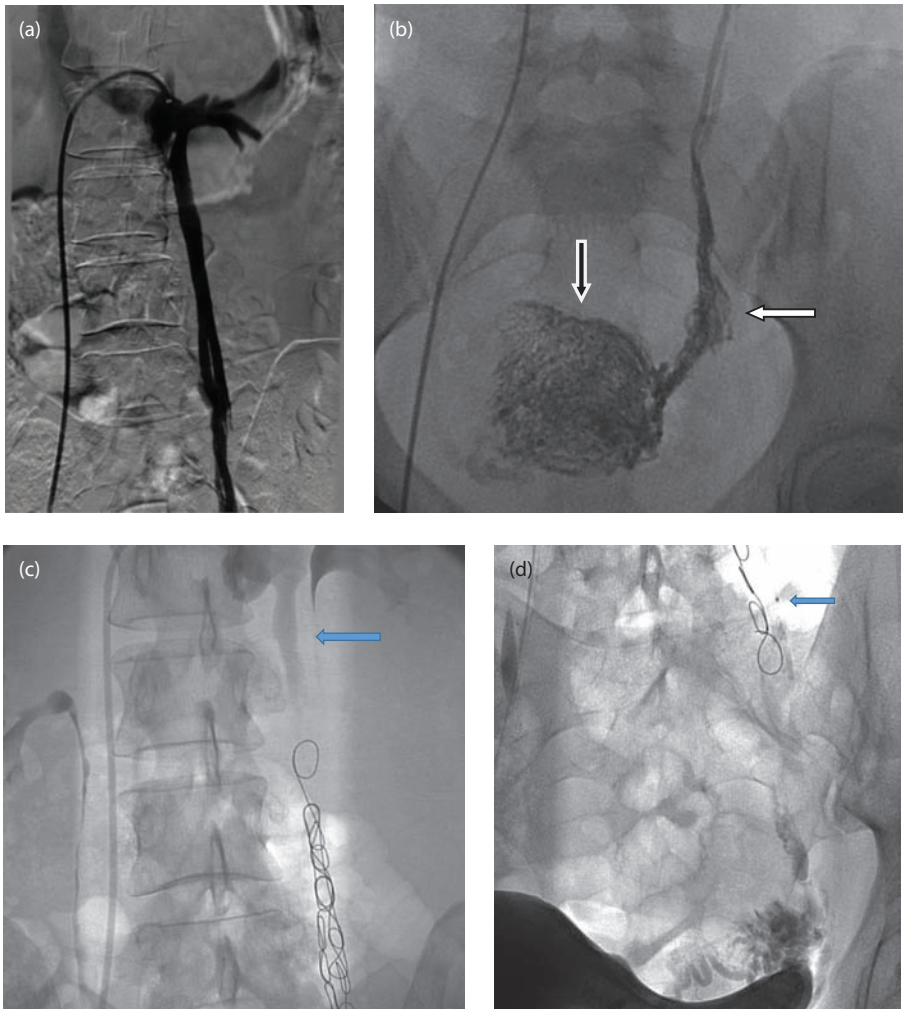

Figure 59.2 Gravitational reflux down the left ovarian vein. **(a)** The left ovarian vein develops reflux after the valve at its junction with the left renal vein. **(b)** The reflux in the left ovarian vein forces blood through pampiniform plexus (white arrow) and small perimetrial veins of the uterus (black arrow), and then through the uterine vein into the right internal and common iliac veins. The reflux is most easily demonstrated with the patient in reverse Trendelenburg position. **(c)** Reflux in the ovarian vein (arrow) can be eradicated by coil occlusion of this vessel. **(d)** Foam sclerotherapy using iodinated contrast and a sclerosant can be delivered through a microcatheter (arrow) to close more distal varicosities.

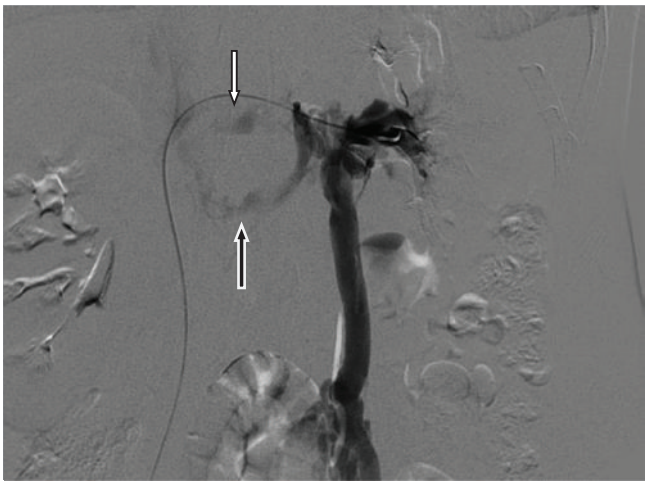

Figure 59.3 Nutcracker syndrome is a driving force for the development of pelvic varicose veins. This patient had both anterior and posterior compression of her circumaortic left renal vein, as noted by the arrows. This compression forces the development of collateral venous drainage pathways, such as the ovarian vein.

the left renal vein from the kidney will reflux down the left ovarian vein into the pampiniform plexus. From there, it may travel into the perimetrial and myometrial veins of the uterus and exit either through the left or right uterine veins into the internal iliac vein and return to the heart through the iliocaval conduit. If the ovarian vein reflux develops rapidly, there may be no symptoms of left flank pain or intermittent microscopic hematuria, but progressive symptoms of pelvic congestion.

Compression of the left common iliac vein by the right common iliac artery (May–Thurner syndrome) may also be a mechanism of pelvic venous congestion (Figure 59.4). This form of extrinsic compression of the left common iliac vein is well recognized as a cause of left common iliac venous thrombosis and/or chronic intermittent left leg edema. In the setting of decreased outflow from the left common iliac vein, venous outflow from the left leg may be preserved through reversal of flow in the left internal iliac vein. Venous return coursing through the left external iliac vein may descend through the internal iliac vein across the pelvis through the anastomotic channels and return to the right atrium through the right iliocaval system. With such flow alterations, the patient may not experience any left leg symptoms, but may develop signs and symptoms of PCS. Correction of the common iliac vein stenosis may reduce the pelvic venous flow abnormality and improve deep venous outflow from the leg.[14]

The course of refluxing blood that is most frequently generated by these mechanisms is retrograde flow in the left ovarian vein that refluxes through the pampiniform plexus, across the uterus through the perimetrial and myometrial veins, exiting through the right uterine vein or the right pampiniform plexus, with systemic return via the right iliac or ovarian veins. The cross-pelvic flow may overload

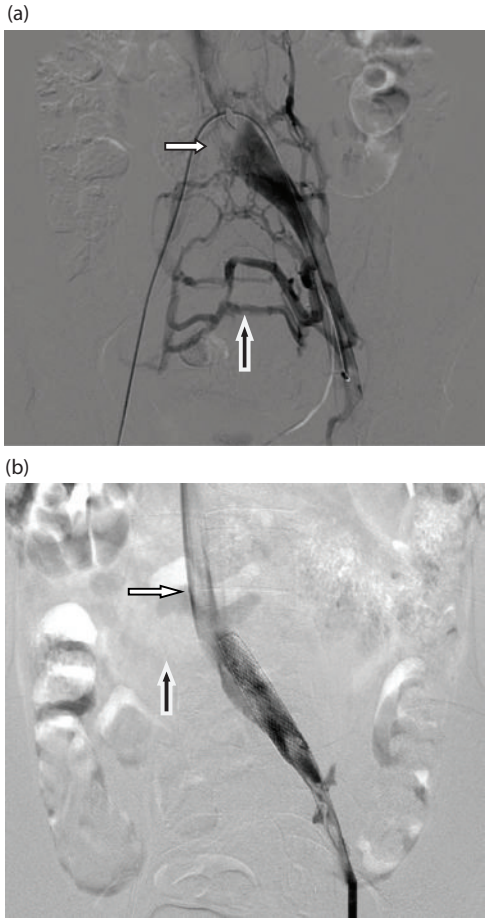

Figure 59.4 May–Thurner syndrome. **(a)** Compression of the left common iliac vein by the right common iliac artery (white arrow) forces left leg venous outflow down the left internal iliac vein and across the pelvis through small collateral veins (black arrow), to return to the heart through the right iliac venous system. **(b)** Treatment of May–Thurner syndrome by placement of a left common iliac vein stent normalizes pelvic venous flow (white arrow) with the cephalad movement of the venous outflow from the left leg and the elimination of cross-pelvic flow (black arrow).

the right side of the pelvis and generate varicosities of the right pampiniform plexus, causing right pelvic pain, or descend through the anastomotic networks shared with the lower extremity and cause varicose veins of the upper thigh (Figure 59.5).

59.4 SYMPTOMS

There are several distinct etiologies of pelvic pain, including the veins, the end organs associated with venous engorgement, and the underlying driving mechanisms, which often make the diagnosis challenging (Table 59.1). Aching, throbbing, and stinging are the most common descriptors of pelvic pain associated with varicosities of the pampiniform plexus. When a woman with this form of abnormal pelvic venous flow is standing for any period of time, she will likely

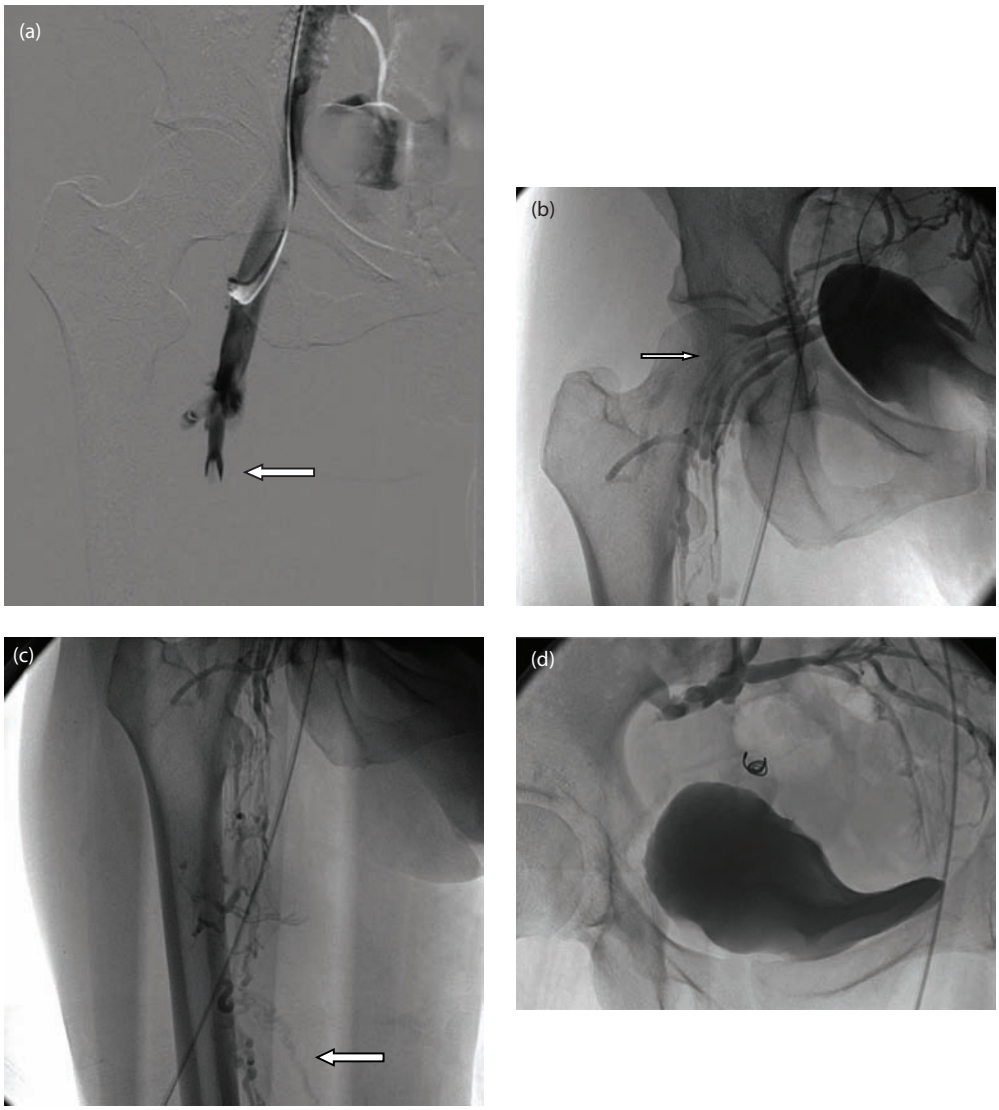

Figure 59.5 Pelvic venous flow causing recurrent lower extremity varicose veins. **(a)** Descending venography demonstrates no significant reflux down the right leg due to a competent valve in the femoral vein (arrow). **(b)** Reflux through the superior gluteal vein branch of the internal iliac vein into the deep femoral vein branches (arrow). **(c)** Reflux from the deep femoral vein into superficial varicose veins (arrow). **(d)** Eradication of reflux into the right leg by coil occlusion of the pelvic venous tributary.

experience progressive pelvic discomfort as the pelvic varicosities engorge. That the pelvic pain is associated with distention of the pelvic varicosities has been confirmed. In a single-blind crossover study, 12 women with PCS and pelvic varicose veins were treated with intravenous administration of dihydroergotamine (DHE). In six of the women, 1 mg of the medication was given during pelvic venography, causing a mean diameter reduction of 35% of the pelvic varicose veins. In the other six women, either intravenous DHE or placebo was given during presentation for pelvic pain, and the pain scales were recorded before and after the injection and for the subsequent 5 days. They were then treated with the alternative agent during the next episode of pelvic pain and the pain scale recordings noted. Pain was statistically significantly reduced after DHE compared with placebo ($P < 0.05$).[15] These data strongly link congestion of pelvic varicose veins with pelvic pain.

The sites of greatest venous engorgement are likely the locations of greatest discomfort. If the greatest engorgement is in the region of either the left or right pampiniform plexus or the uterus, the epicenter of pain is usually in these locations. If pelvic varicose veins reflux freely into the vulvar vein, then the pain experienced by the patient is in the labia and perineum. If there is reflux into the veins of the leg, the patient will generally manifest with symptoms of lower extremity varicose veins. Dyspareunia, a very common complaint amongst those with PCS, may be multifactorial in origin, resulting from engorgement of pelvic and uterine varicosities and mechanical trauma during and especially after coitus.

The end organs associated pelvic varicose veins can also cause symptoms. There is often stasis within the pelvic veins in patients with PCS causing a rise in pelvic temperatures and being an additional source of discomfort in the area of the left ovary.[16] Retrograde flow into and congestion of the perimetrial and myometrial veins can cause edema of the uterine walls, which can cause uterine aching and increasingly heavy menses associated with greater discomfort.

Pain can also stem from the underlying mechanisms of altered pelvic venous flow. Nutcracker syndrome often initially presents with left flank pain and intermittent hematuria. As venous congestion of the left kidney persists, the left ovarian vein valve becomes incompetent. The patient will complain of both pelvic and flank pain. Once reflux in the ovarian vein is able to accommodate venous outflow from the left kidney, the left flank pain resolves and the patient experiences only the discomfort of pelvic venous congestion. Similarly, May–Thurner syndrome may also cause intermittent left leg swelling and aching from reduced left lower extremity venous outflow obstruction. As the left internal iliac vein enlarges to accommodate flow from the left leg, the symptoms of aching and swelling may resolve, with only pelvic congestion remaining.

Patients who experience chronic pelvic pain also frequently suffer from depression.[1] While this is not a somatic symptom that vascular surgeons can directly address, it is no less important. Patients who have suffered for a significant length of time with chronic pelvic pain and who have been given no diagnosis despite numerous tests and procedures and for whom many therapies have been tried without benefit may, over the course of time, become despondent and depressed. A comprehensive therapeutic plan will require not only the eradication of pelvic congestion and its causes, but also treatment of the psychological well-being of the patient.

59.5 DIAGNOSIS

The diagnosis of PCS begins with the exclusion of other pelvic problems. As such, there should be a complete gynecologic evaluation with urogynecologic or gastrointestinal assessment as indicated. In the absence of other causes of chronic pelvic discomfort, a pelvic venous flow abnormality should be suspected and the patient appropriately evaluated for this.

A detailed history to identify factors associated with pelvic venous congestion should be obtained (Table 59.2). Women often report that their pelvic pain was first manifest during pregnancy or in the early postpartum period. It typically presents shortly after awakening, escalates over the course of the day and, by evening, can be incapacitating. Post-coital pain, often for prolonged periods of time, is also characteristic of PCS. Gross or microscopic hematuria and dysuria are well described and most often associated with nutcracker syndrome.[17] More painful menses and/or increasing menstrual flow are common complaints of those with uterine venous congestion. Complaints of heaviness and/or edema of the left lower extremity should raise suspicion of May–Thurner syndrome, with or without deep venous thrombosis. Lastly, patients with pelvic congestion that depressurizes via the internal or superficial external pudendal veins may complain of vulvar varicosities and/or varicose saphenous or deep femoral vein tributaries in the thigh. On aggregate, this information is of significant value for establishing a comprehensive diagnostic plan.

Table 59.2 Pertinent history

Aching, stinging, or throbbing pain in the left or right lower quadrant over the ovary
Radiation of pain either across the midline or down the left leg with prolonged standing
Progression over the course of the day
Worsening of pain just prior to onset of the menstrual cycle
Associated symptoms such as left flank pain or left leg swelling with prolonged standing
Coital/post-coital pain
Some relief when lying supine
Lack of strongly positive response to prior treatments, including hormonal manipulation

Although physical examination is often remarkably normal with pelvic examination findings limited to mild left ovarian tenderness, there are some findings that can strongly suggest pelvic flow disorders. These findings include the presence of labial, vaginal, or suprapubic varicose veins, chronic or intermittent left leg edema with left groin varicosities, or the recurrence of thigh varicose veins prior to the appearance of calf varicose veins (Figure 59.1).

59.5.1 Pelvic ultrasonography

Most patients with PCS have already undergone pelvic sonography with negative ovarian and uterine findings. In this instance, a repeat study specifically dedicated to pelvic venous anatomy and emptying may be helpful. The examination is aided by using transabdominal 5-MHz and transvaginal probes after a thorough fast. Optimally, the test should be performed in the standing or reverse Trendelenburg position, although intermittent use of the Valsalva maneuver while supine can also be effective. The usefulness of endoscopic ultrasonography has recently been suggested.[18]

Sonographic findings suggestive of PCS include ovarian vein dilation >4 mm with sluggish (<3 cm/second) or retrograde (craniocaudad) flow, dilated and tortuous pelvic veins >6 mm in diameter, and dilated arcuate veins within the myometrial or pampiniform plexuses that communicate with the iliac venous system.[19–21] Interestingly, an association of PCS with polycystic ovary disease has been consistently observed.[20]

59.5.2 CT and/or magnetic resonance venography

Along with clinical complaints and findings, CT and/or magnetic resonance (MR) venography can assist with the establishment of a diagnosis of PCS. These scans can be most useful in severe cases, when pelvic varices are present even when the patient is supine.[19] CT venography is optimized by using either iopromide or iohexol injected intravenously at a rapid rate (~3 mL/second), while contrast MR venography typically employs gadolinium.

On cross-sectional CT and MR images, pelvic varices appear as dilated and tortuous parauterine tubular structures, which may extend laterally in the broad ligament or inferiorly to communicate with the paravaginal venous plexus. As suggested by Coakley and colleagues, the CT/MR criteria for establishing a diagnosis of pelvic varices include: (1) at least four ipsilateral tortuous parauterine veins of varying caliber, at least one of which measures >4 mm in maximum diameter; or (2) an ovarian vein diameter of >8 mm.[22] While these criteria can confirm the presence of pelvic varicose veins, their sensitivity is low since venous diameter is often minimal in the supine position and reflux through an ovarian vein of smaller diameter may be significant.[23] Additional important findings can include compression of the left renal vein beneath the superior mesenteric artery (nutcracker syndrome; Figure 59.2) or compression of the left iliac vein beneath the right common iliac artery (May–Thurner syndrome).

MR venography has greater resolution for assessing reflux compared to CT venography. Duplex sonography, MR venography, and conventional venography were compared in a prospective study of 23 women with chronic pelvic pain. Asciutto and colleagues evaluated the ability of each modality to determine pelvic venous anatomy and patterns of reflux in the ovarian vein. MR venography correlated well with venography for visualization of anatomy, correctly demonstrating the ovarian veins in 88%, internal iliac veins in 100%, and pelvic floor veins in 91% of cases. Unfortunately, despite the high levels of sensitivity for the detection of pelvic venous anatomy, there was a significantly lower correlation with reflux and congestion within these same veins. Reflux was correctly identified by MR venography in only 67% of ovarian veins, 38% of internal iliac veins, and 42% of pelvic floor veins. MR venography, therefore, may be of value if conventional venography fails to clearly define the pelvic venous anatomy and the presence of pelvic varicose veins.[24]

59.5.3 Contrast venography

Conventional contrast venography remains the gold standard for establishing a diagnosis of PCS. Although the optimal technique is a matter of some controversy, the procedure is best performed via jugular or femoral vein access with the patient in at least 20° reverse Trendelenburg position ("tilt-table venography") with separate selective injections of the left renal vein, bilateral gonadal veins, bilateral common femoral/external iliac veins, and bilateral internal iliac (hypogastric) veins.[25] Contrast should be injected by hand rather than by a power injector to prevent false-positive reflux due to the high pressure of the injected contrast (Figure 59.2).

Venographic criteria suggestive of a diagnosis of PCS include: (1) reflux in the ovarian vein; (2) uterine venous engorgement; (3) congestion of the ovarian plexus; (4) filling of pelvic veins across the midline; and/or (5) filling of vulvovaginal thigh varicosities.[19] Brisk and extensive filling of collateral lumbar veins can also be indicative of the syndrome (Figure 59.3). Although the absolute diameter of the ovarian vein has been used as a criterion for pelvic venous congestion syndrome, it is now recognized that PCS is a disorder of venous flow, independent of venous diameter.[8] The diagnosis is most firmly established in the presence of free reflux in the left ovarian vein, cross-pelvic flow through smaller collateral veins, and drainage of the left pelvis through the right internal iliac vein.[26] If labial or vaginal varicose veins are present but renal and pelvic venography fail to identify the presence of reflux or large pelvic varicose veins, direct stick venography through an accessible external varicose may be of value.

59.6 RECOMMENDED DIAGNOSTIC APPROACH

An algorithm for the diagnostic management of patients with suspected PCS as the cause of either pelvic pain or recurrent lower extremity varicose veins is presented in Figure 59.6. An aggressive approach to the diagnosis of the cause of chronic pelvic pain must be taken to reduce the morbidity associated with this problem. Patients with chronic pelvic pain who have a normal bimanual pelvic examination and an unremarkable gynecologic laparoscopic evaluation should be evaluated with tilt-table venography, since this is the only test of pelvic venous flow that can be performed in a gravity-dependent manner. If a pelvic venous flow abnormality is identified, then a causative mechanism should be sought. A transverse linear defect in either the left renal vein or the left common iliac vein suggests nutcracker syndrome and May–Thurner syndrome, respectively. Both of these anatomic abnormalities are best evaluated with CT venography, since pressure gradients may be minimal in the setting of brisk reflux in the left ovarian or internal iliac veins. If recurrent thigh varicose veins are the indication for venographic evaluation, careful imaging of the internal iliac venous branches is required. Once all information regarding PCS is obtained, then a comprehensive treatment plan can be developed.

59.7 TREATMENT

Once symptomatic PCS has been identified, treatment should be undertaken, with the goals of treatment being a

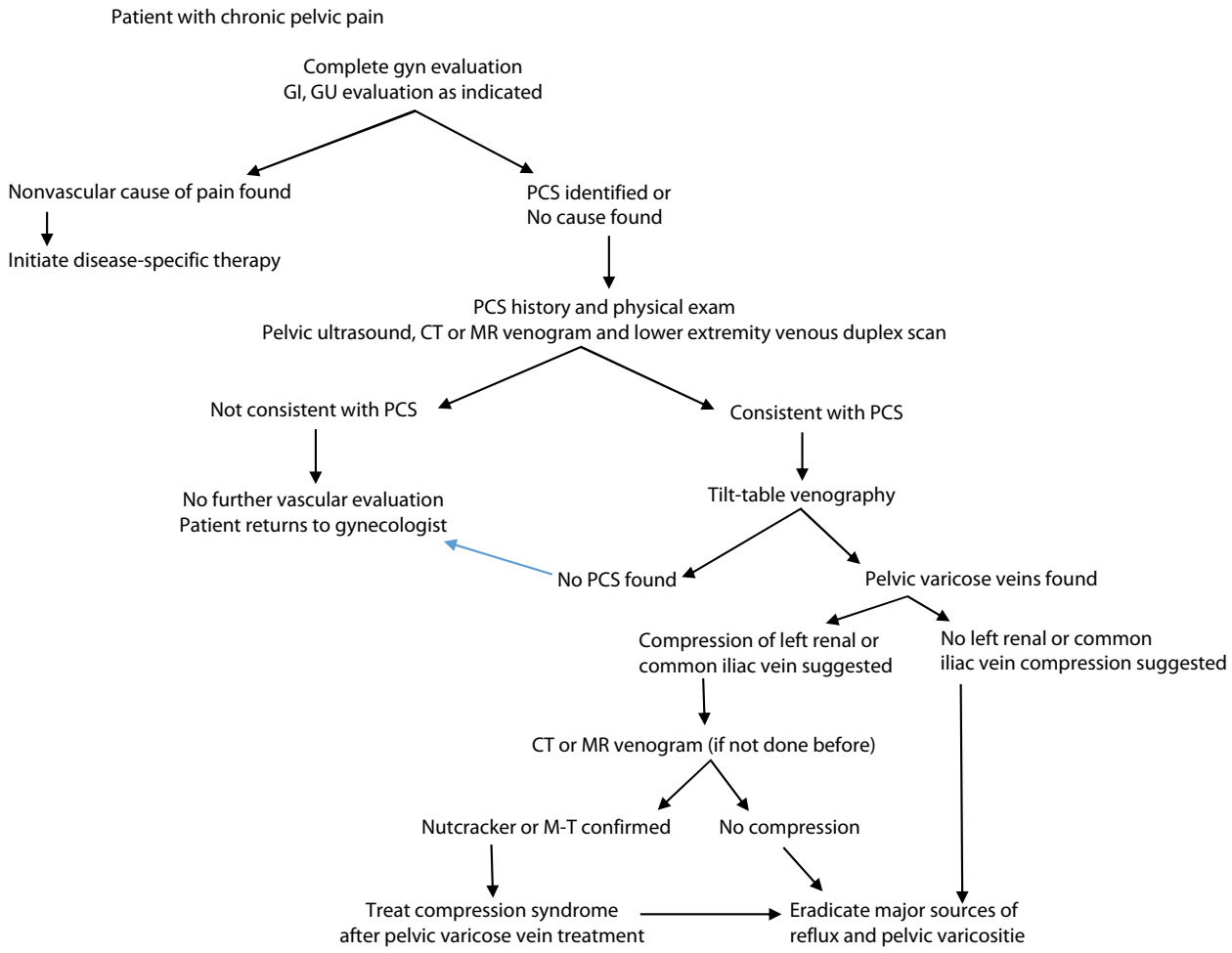

Figure 59.6 Diagnostic algorithm for the diagnosis of pelvic congestion syndrome. GI: Gastrointestinal; GU: genitourinary; PCS: pelvic congestion syndrome; CT: computed tomography; MR: magnetic resonance; M-T: May-Thurner.

reduction or elimination of the pelvic venous flow abnormalities that produce the patient's symptoms and, when possible, control of the underlying causes of the pelvic varicose veins. Only if eradication of the clinically relevant varicose veins and the reflux pathways in the pelvis are not possible should other therapeutic strategies be considered. Many treatments have been proposed over the decades since PCS has been recognized, ranging from pharmacotherapy to open surgery.

In a randomized prospective study of 47 women with PCS, goserelin, a gonadotrophin-releasing hormone antagonist, was compared to medroxyprogesterone acetate (MPA) for the control of symptoms. While goserelin was found to be better than MPA, both reduced but did not eliminate pelvic pain. Goserelin has the added negative effect of significantly decreasing libido in more than 30% of patients receiving the medication.[27] Similar studies have been performed with Implanon and other hormonal treatments, achieving similar results.[28] Overall, such pharmacological treatments have little effect upon the symptoms of lower extremity varicose veins, suggesting the limited value of these hormonal manipulations in terms of controlling abnormal venous flow for extended periods of time. Therefore, other more definitive therapies are required.

The most effective and expeditious treatment of pelvic venous flow abnormalities is transvenous coil occlusion of the ovarian vein with or without sclerotherapy of pelvic varicosities. This can be accomplished most effectively through endovascular approaches with coil occlusion and/or sclerotherapy of the problematic veins, with a high likelihood of both technical and clinical success. In 127 consecutive patients who presented with symptoms of chronic pelvic pain and venographically proven pelvic varicose veins, ovarian vein reflux was interrupted with coils and incompetent internal iliac veins were occluded in 85% of cases. Of these patients, 83% reported significant improvement, 13% had no change, and 4% developed worse pain. Followed for a mean period of 45 months, the patients reported less pelvic pain, with a decrease in pain scores from a pretreatment level of 7.6 ± 1.8 to 2.9 ± 2.8 after coil occlusion of the offending veins ($P < 0.0001$).[29] Similar results have been achieved with conventional and foam sclerotherapy to eradicate problematic pelvic varicosities (Figure 59.5d). Gandini and colleagues have treated a total of 64 patients

with significant reflux in the ovarian vein and symptomatic pelvic varicosities with conventional or foam sclerotherapy and demonstrated a technical success rate of 100% and significant symptom relief for at least 1 year.[30,31] Occlusion of these refluxing and symptomatic varicosities causes no clinically significant alterations in the menstrual cycle.[23]

For those with recurrent varicose veins, especially of the thigh or perineum, eradication of pelvic reflux can also be of significant value (Figure 59.5). Asciutto and colleagues noted on pelvic venography that 62% of women with pelvic venous insufficiency had flow from the pelvis into lower extremity varicose veins.[32] In a study of 86 women with lower extremity varicose veins and PCS, coil occlusion of the refluxing pelvic veins without additional therapy resulted in improvement in lower extremity varicose veins in 51% of cases.[33]

Perineal and vulvar reflux can contribute to recurrent varicose veins. During pregnancy, these veins can enlarge and become quite symptomatic, sometimes posing a problem for vaginal delivery because of congestion. Therefore, if noted early in pregnancy, the woman should be encouraged to wear a perineal compression garment until after delivery. These varicosities can then be treated through a direct stick approach, which is effective for the eradication of these veins if they persist after control of pelvic reflux.

Overall, endovascular treatment has a reported technical success rate of more than 99%, with a low complication rate of less than 3%, a clinical improvement rate of more than 90%, and a varicose vein recurrence rate of 13% over 5 years.[34]

As with varicose veins of the leg, open or minimally invasive surgery to ligate the ovarian veins has been of value in the treatment of women with PCS. Surgical ligation to eradicate ovarian vein reflux and to occlude other major refluxing or varicose veins is also an effective therapy with significant improvement in patient symptoms and excellent short- and mid-term results.[35] When minimally invasive techniques are utilized, Trendelenburg positioning with legs in stirrups and pneumoperitoneum can frequently decompress the pelvic varicose veins, making them difficult to identify. Therefore, when the patient has largely left-sided reflux and varicosities, placing the patient in a right lateral decubitus position with the table tilted to the same extent as used for venography enables the surgeon to more readily identify and address the venous targets seen on the preoperative study.

Hysterectomy and bilateral oophorectomy, with ligation or removal of the large pelvic varicose veins, have long been utilized as treatments of pelvic pain. In a study of 36 women with PCS and intractable pelvic pain undergoing hysterectomy and bilateral oophorectomy, 67% were subsequently pain free.[36] Given the limited effectiveness of this major procedure, this treatment should be avoided in women of child-bearing potential unless other gynecologic issues require it or all other treatments have failed to improve symptoms.

Whether an endovascular, minimally invasive, or open approach is used in the treatment of PCS, normalization of pelvic flow patterns should be the goal. There are multiple interventions to treat nutcracker syndrome, including placement of a stent into the left renal vein, surgically transposing the left renal vein onto the more distal inferior vena cava, or creating a bypass between the left renal vein and the inferior vena cava to enhance renal vein outflow.[17] Care must be taken to size stents appropriately since the diameter of the left renal vein may increase when venous outflow through the left ovarian vein is terminated. For patients with pelvic venous congestion due to May–Thurner syndrome, the best option is stent placement in the left common iliac vein.[37] When treatment is successful, cephalad flow, cross-pelvic collateral flow, and venous return through the contralateral venous tree should be reduced or eliminated (Figure 59.4b). Complete treatment should reduce the likelihood of early recurrence.

59.8 OUTCOMES

The outcomes of the treatment of pelvic venous congestion syndrome when history, physical examination, and venographic findings are in concert are excellent. In a systematic review of the literature, of 866 women who underwent endovascular treatment of pelvic vein reflux, the technical success rate was 99.8%.[34] Complete or significant improvement in more than 90% of patients has been reported in most recent studies.[29,38,39] Similar results have been established with minimally invasive therapy.[35] The recurrence rate is estimated to be 13% at 5 years.[34] However, there are few large studies with well-defined pelvic venous flow abnormalities to document the specific outcomes and recurrence rates for each subgroup.

59.9 COMPLICATIONS

Each type of therapy has its specific complications. Hormonal manipulation is often associated with increased risks of deep vein thrombosis, hirsutism, decreased libido, and fluctuating emotional status. Coil embolization of the ovarian vein, internal iliac vein, and large pelvic varicosities is complicated by coil migration in approximately 1.5% of patients, with the most common site of coil lodgment being the lung.[34] Removal of a coil from the lung or other pelvic veins is generally not necessary. Other complications that are typical of venous endovascular intervention, such as cannulation site problems, are seen in a very small number of patients. No mortality has been reported. Similarly, very few patients undergoing minimally invasive ligation of pelvic varicosities will experience complications that are typical of this approach, such as port placement problems and bleeding. Stent migration has been noted in up to 5% of patients treated for nutcracker or May–Thurner syndromes.[40]

Guidelines 5.7.0 of the American Venous Forum on the management of pelvic venous congestion and perineal varicosities

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.7.1	We recommend pelvic ultrasonography for the initial evaluation of patients with suspected pelvic varicose veins. Ultrasound will confirm pelvic varicose veins and may determine their etiology. We recommend computed tomographic venography or magnetic resonance venography for further evaluation.	1	B
5.7.2	We recommend selective contrast pelvic venography in reversed Trendelenburg position to confirm the diagnosis and etiology of pelvic and perineal varicose veins, to delineate the anatomy, and to plan endovenous treatment.	1	B
5.7.3	We recommend endovenous ablation of the refluxing ovarian vein with coil embolization, with or without liquid or foam sclerotherapy.	1	B
5.7.4	We recommend an open surgical approach to ligate the refluxing symptomatic ovarian vein if endovascular treatment fails or is not possible.	1	B
5.7.5	We suggest liquid or foam sclerotherapy for the treatment of perineal and vulvar varicosities.	2	B

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● = Key primary papers
★ = Major reviews

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60

The management of nutcracker syndrome

YOUNG ERBEN AND PETER GLOVICZKI

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60.1 INTRODUCTION

Nutcracker syndrome (NS) is a rare entity first described by Grant in 1937. The first patient was reported in 1950 by El-Sadr and Mina.[1,2] The nutcracker phenomenon denotes compression of the left renal vein (LRV) between the aorta and the superior mesenteric artery (SMA), resembling the cracking of a nut between the jaws of a nutcracker (Figure 60.1). NS has been attributed to those patients who present with a nutcracker phenomenon and with signs or symptoms of LRV congestion.[3] Rarely, the LRV is compressed between the aorta and the vertebral column, causing a "posterior" NS (Figure 60.2).[4]

In this chapter, we review the clinical presentation and evaluation of patients with NS. We also discuss treatment options, including observation and medical management and open surgical, endovascular, and hybrid interventions. Based on currently available evidence, we suggest clinical practice guidelines for the management of this rare and challenging disease.

60.2 CLINICAL PRESENTATION

Patients most frequently present with hematuria and left flank pain or pelvic pain. Other manifestations of renal venous congestion include abdominal pain, microscopic hematuria, and proteinuria. Females are more frequently affected than males, and the mean age of diagnosis is usually in the second and third decades of life.[5,6] Coincidental cases in siblings have been reported and a low body mass index has been shown to correlate with NS.[7,8] Males may present with left-sided varicocele. The symptoms of NS can be quite incapacitating in many patients.

Differential diagnoses include renal calculi, glomerulonephritis, endometriosis, vascular malformation of the renal pelvis, primary varicocele, pelvic congestion due to isolated ovarian or pelvic vein incompetence, and musculoskeletal problems causing back or flank pain.[9–12] Those patients in whom symptoms are debilitating and imaging studies do demonstrate compression of the LRV should be recommended for operative management.[13,14]

60.3 DIAGNOSTIC EVALUATION

There is usually considerable delay in the diagnosis of NS because of its rarity.[15–17] LRV compression can be confirmed with cross-sectional imaging studies such as computed tomography venography (CTV) and magnetic resonance venography (MRV) (Figure 60.3). Furthermore, on the sagittal view of CTV/MRV, an acute angle of <39° between the SMA and the aorta is a clue to the diagnosis of NS. Duplex ultrasound scanning (US) and contrast venography are also utilized for the diagnosis of NS.[18,19] Lately, intravascular ultrasound (IVUS) has been frequently used as an adjunct to confirm hemodynamically significant compression of the LRV.[4]

On US, a ratio of ≥5 of the diameter of the LRV at the point of compression and lateral to it and of the peak systolic velocities measured in the same area are considered diagnostic of NS (Figure 60.4).[17,20,21] On contrast venography, a pressure gradient of ≥2 mmHg at the two sides of the compression measured during contrast venography is also considered diagnostic of NS (Figure 60.5).[22–24]

60.4 TREATMENT

60.4.1 Medical therapy

The goal of observation and medical management of the pain is to encourage weight gain and an increase of retroperitoneal

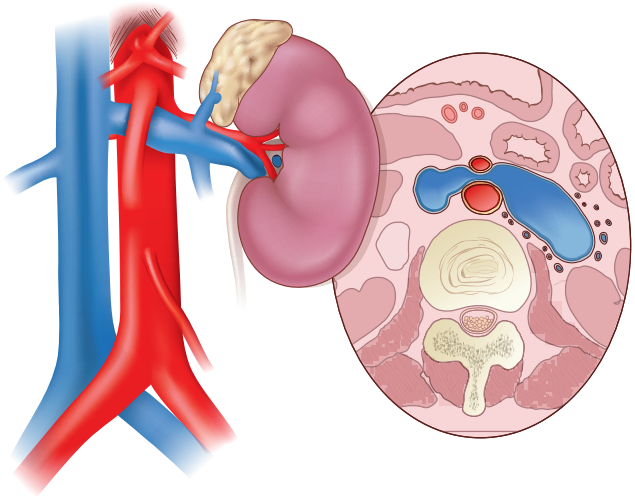

Figure 60.1 Anterior nutcracker syndrome with extrinsic compression of the left renal vein between the aorta and the superior mesenteric artery. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

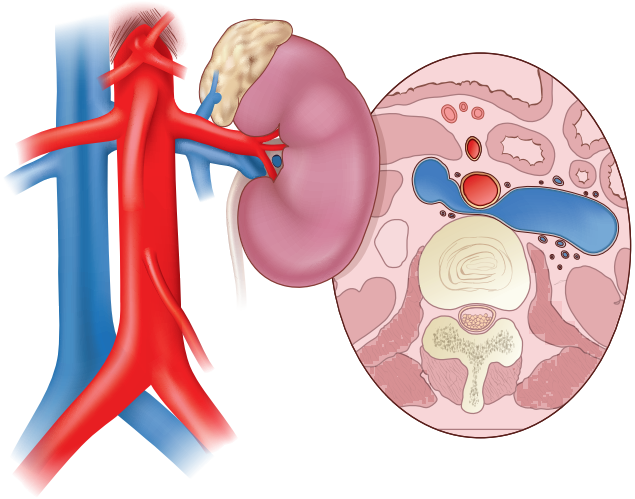

Figure 60.2 Posterior nutcracker syndrome with extrinsic compression of the left renal vein between the aorta and the spine. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

fat. This may result in decreasing tension on the LRV and improve venous outflow. Observation and medical management have been successful in about 30% of the patients in our experience.[21] It is important to consider conservative management of young patients to delay any intervention if possible.

60.4.2 Open surgical treatment

The goal of open surgical treatment is to remove the compression on the LRV in the nutcracker position. The most successful operation so far has been distal transposition of the LRV into the inferior vena cava (IVC). Other surgical techniques to decompress the LRV congestion include

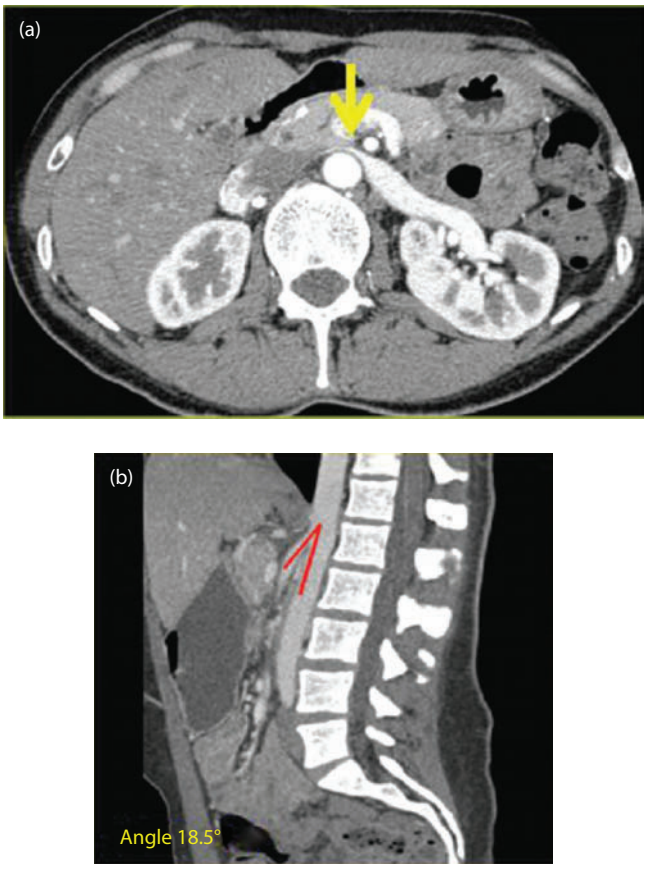

Figure 60.3 Axial and sagittal cuts of a computed tomographic venography demonstrating **(a)** compression of the left renal vein and **(b)** the acute angle of the superior mesenteric artery to the aorta. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

re-implantation of the proximal ovarian vein into the IVC, LRV to IVC saphenous vein bypass graft, auto-transplantation of the kidney into the pelvis, and SMA bypass with resection of the compressing SMA segment.[25,26] Occasionally, nephrectomy was performed for definitive therapy.[6]

In our experience,[9] the intervention of choice has been the distal transposition of the LRV (Figure 60.6). This operation is performed transperitoneally through a small (<15-cm) midline laparotomy. Once the retroperitoneum is opened inferior to the transverse mesocolon, the LRV is completely mobilized, ligating the left adrenal and the gonadal veins. After intravenous heparinization to maintain an activated clotting time of >200 ms, a side-biting clamp is applied on the IVC across the LRV confluence. The LRV is transected and re-anastomosed to the lateral aspect of the IVC in a more distal area. To achieve a tension-free anastomosis, some of these patients also undergo adjunctive procedures to decrease the tension, enlarge the renal vein and improve its outflow. These techniques include great saphenous vein (GSV) patch, GSV cuff, and both a cuff and a patch (Figure 60.7).

Laparoscopic techniques of LRV transposition have also been reported with excellent technical success. However,

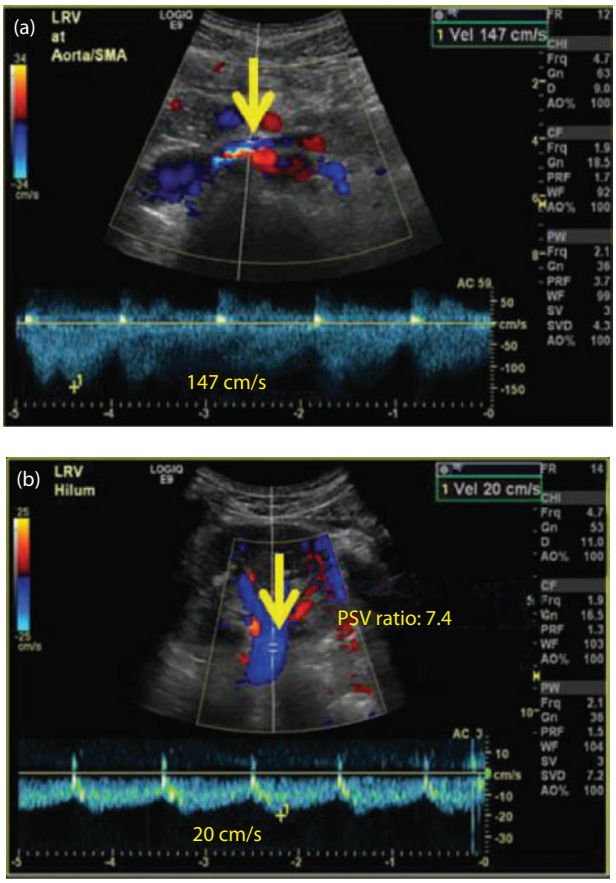

Figure 60.4 **(a)** Peak systolic velocity (PSV) measurements at the narrowest point and hilum of the left renal vein and **(b)** the PSV ratio. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

these require experience in laparoscopic suturing techniques and vascular laparoscopic surgery.[23]

60.4.3 Endovascular therapy

Primary stenting has been suggested in the literature and it has gained popularity in the recent years. It usually involves access of the right femoral vein with an initial 5-Fr sheath, followed by a venogram of the IVC and LRV using a pigtail and/or a cobra catheter (Cook, Bloomington, IN). Then, renocaval pressures are measured and intravenous heparin is given to all patients to maintain an activated clotting time of >200 ms. The 5-Fr sheath is exchanged with an 8–10-Fr sheath to accommodate the stent delivery system and subsequently a self-expanding Wallstent (Boston Scientific, Marlborough, MA) or a SMART stent (Cordis, Fremont, CA). Finally, completion venography is performed prior to sheath retrieval. In recent series, an intra-operative IVUS was used to complement the findings of a two-dimensional venography.

60.4.4 Hybrid procedure

Our group introduced a hybrid approach to decrease the risk of restenosis due to persistent compression on the

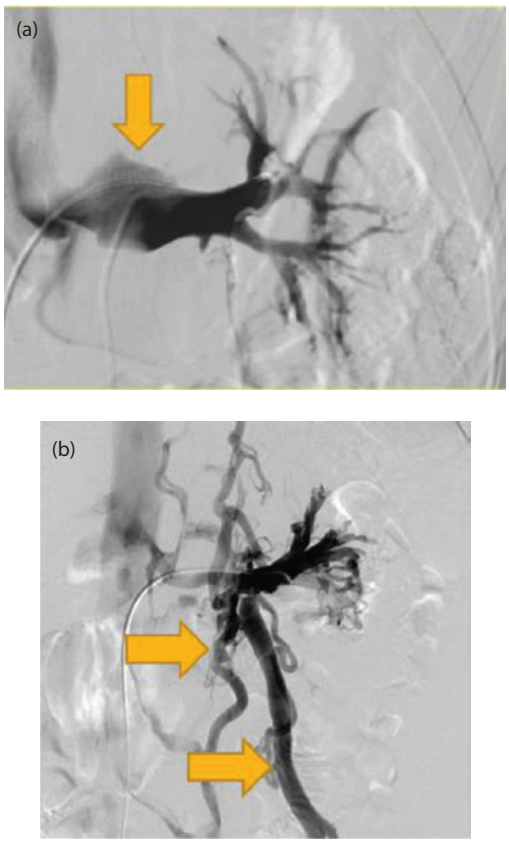

Figure 60.5 Venogram of a left renal vein demonstrating **(a)** narrowing between the aorta and superior mesenteric artery and **(b)** multiple engorged tributaries. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

transposed LRV by the SMA or the small bowel, and also to prevent the most disastrous potential complication of the stent: migration.[27] This approach includes the distal transposition of the LRV followed by immediate placement of a Wallstent. Using interrupted 5–0 polypropylene sutures, the stent is then transfixed to the LRV to avoid any

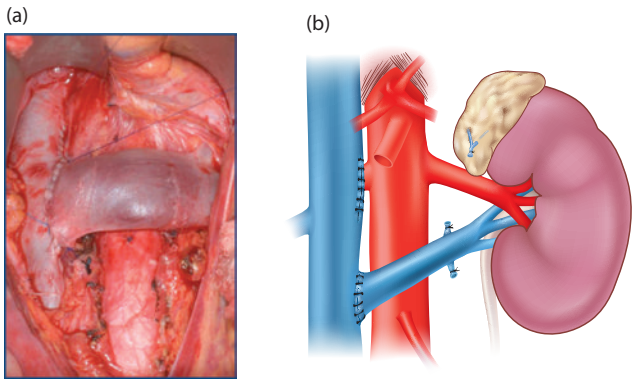

Figure 60.6 **(a)** Intra-operative photograph of a left renal vein transposition and **(b)** drawing of a left renal vein transposition. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

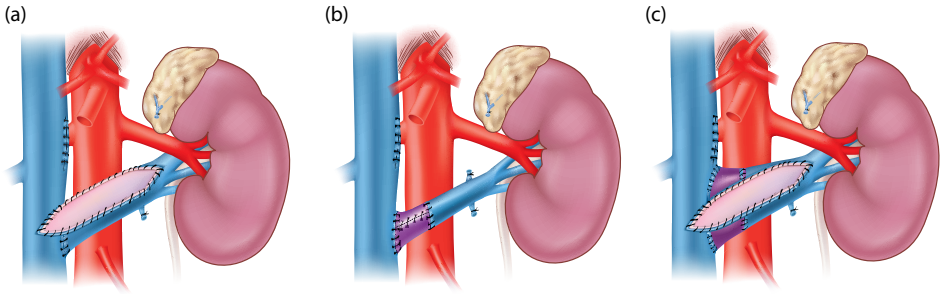

Figure 60.7 Adjuncts to left renal vein transposition to enlarge the renal vein (patch) or decrease tension caused by the abdominal aorta and lack of retroperitoneal fat: **(a)** vein patch, **(b)** vein cuff, and **(c)** vein patch and cuff. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

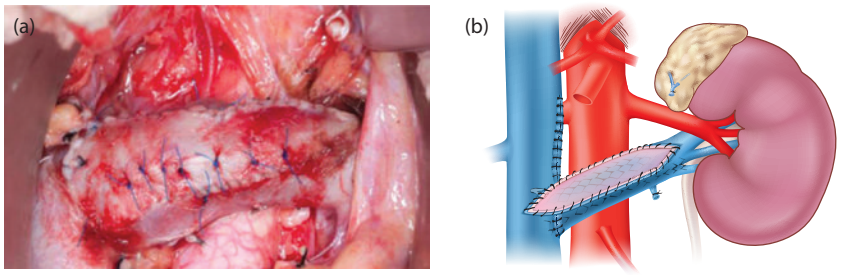

Figure 60.8 **(a)** Intra-operative photograph of the hybrid repair of left renal vein compression using a great saphenous vein patch and Wallstent (Boston Scientific, Marlborough, MA); **(b)** diagrammatic representation of what is shown in **(a)**. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.)

migration and dislodgement. If the renal vein is too small, a vein patch is used to enlarge the vein to accept a 12- or 14-mm Wallstent (Figure 60.8).[28–31] Patients are usually discharged on low-molecular-weight heparin and warfarin and maintained on oral anticoagulation for a period of 3 months until the first post-operative visit. If improvement of symptoms and patency of the LRV are confirmed, the next visit is set-up for 6 months later, or whenever the patient demonstrates any recurrence of symptoms.

60.5 RESULTS

In the Mayo experience that included 37 patients with a mean age of 27 years,[9] there were no early major complications, renal failure, or mortality. Three patients with recurrent symptoms required re-intervention within 30 days: one with open revision (patch angioplasty using GSV) due to stenosis of the implanted left gonadal vein and two with endovascular angioplasty with stenting of the transposed LRV.

During a follow-up of 36.8 ± 52.6 months, eight additional patients needed re-interventions: seven due to stenosis and one due to occlusion. Endovascular procedures were performed in six cases and open surgery was performed in two cases. Subsequently, these patients required additional endovascular interventions (stenting) due to either primary stenosis or in-stent stenosis, resulting in primary and secondary patency rates of 74% and 100%, respectively, at 24 months (Figures 60.9 and 60.10). Freedom from re-intervention at 24 months was 68%. Symptoms resolved in 87% of patients. Hohenfellner et al.[32] reported a similar rate of re-interventions after open surgery. Therefore, we recently changed our strategy for the treatment of NS patients and evaluated the efficacy of the hybrid technique of LRV transposition with immediate stenting. In this procedure, the stent is transfixed prior to closure to avoid its dislodgement/migration.[27] The long-term results will be followed closely to determine whether this technique will become our treatment of choice for NS patients.

Several reports of smaller series of the open treatment of NS have been published to date, with outcomes similar to our experience. In 2002, Hohenfellner et al.[32] followed eight patients after LRV transposition for over 5 years, with symptom improvement in 88% of patients. In 2009, Wang et al.[33] also demonstrated good results after LRV transposition, with resolution of symptoms in 86% of the patients. Most recently, a systematic review of all published series and case reports was analyzed by Orczyk et al.[5] Based on this collective experience, LRV transposition remains the recommended approach for the treatment of NS.

Chen et al.[34] followed 61 patients for over 5 years after primary stenting and reported excellent outcomes. Improvement of symptoms was noted in 95% of patients. However, four stent migrations were noted: one into a small tributary of the LRV, another into the IVC, the third into the right atrium, and the fourth into a collateral of the LRV.

The efficacy of endovascular treatment with LRV stenting using a self-expanding SMART Nitinol stent was studied by Wang et al.[35] in a series of 30 patients. Improvement

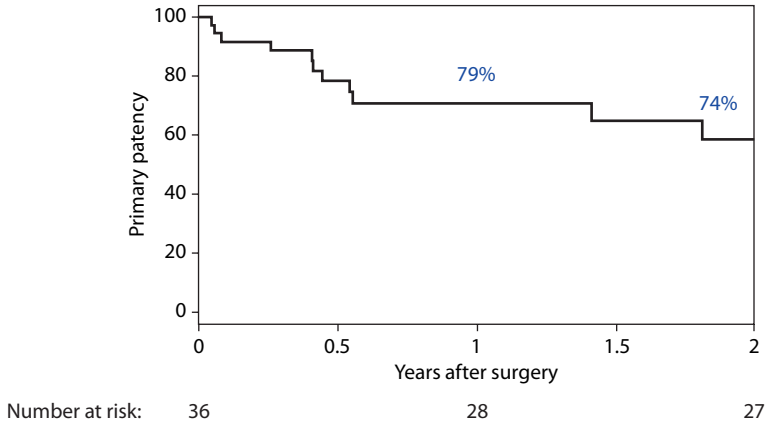

Figure 60.9 Primary patency of the transposed/reconstructed left renal vein or gonadal vein in 36 patients.

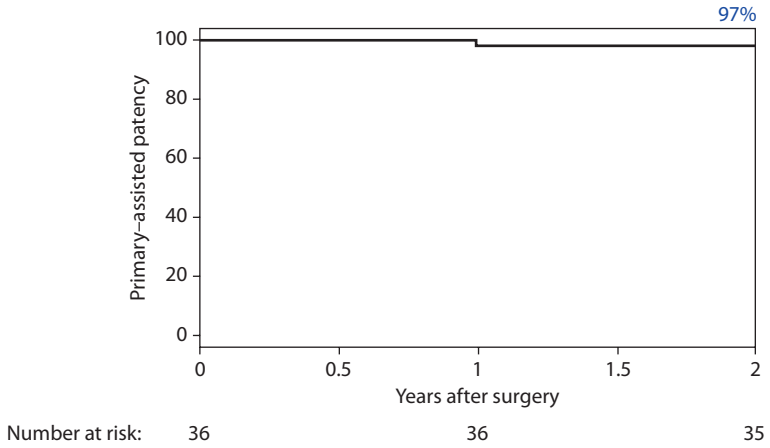

Figure 60.10 Primary assisted patency of the transposed/reconstructed left renal vein or gonadal vein in 36 patients.

of symptoms without the need for re-intervention occurred in 93% of patients during a follow-up period of a median of 30 months and ranging from 12 and 80 months.

In our experience, stenting has been used primarily as a bail-out procedure in patients with recurrent symptoms after initial open operative management of LRV compression. When stenting was used, we had two in-stent restenoses within 30 days, one stent thrombosis, and one stent migration that needed removal of the stent from the IVC and replacement with a larger stent placed into the LRV. All of the stents that were utilized were Wallstents.

Stent migration can be a serious complication in this frequently very young patient population.[28,34,36] Stent dislodgement into the right atrium may require median sternotomy for stent removal.[30] The hybrid procedure eliminates stent migration, but long-term follow-up is needed to assess the durability of this procedure.

60.6 CONCLUSION

LRV transposition remains a safe and effective treatment of patients with NS. Open reconstruction should be tailored

Guidelines 5.8.0 of the American Venous Forum on the management of nutcracker syndrome

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.8.1	We suggest open surgical intervention, such as left renal vein transposition, as the primary treatment of nutcracker syndrome.	2	B
5.8.2	We suggest left renal vein stenting for the treatment of nutcracker syndrome in those patients who are not candidates for open surgery or who failed open surgical treatment.	2	C

to the patient's anatomy, and the placement of adjuncts may improve outflow. Although stenting seems to improve patency, the safety and durability of the currently available stents need to be established. In the United States, the currently used stents have a low but definite possibility of migration. A hybrid approach eliminates this complication.

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PART 6

Lymphedema

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Lymphedema: Pathophysiology, classification, and clinical evaluation

THOM W. ROOKE AND CINDY L. FELTY

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61.1 INTRODUCTION

The CEAP (Clinical, Etiology, Anatomy, and Pathophysiology) classification has proven valuable for classifying venous disorders.[1] A logical extension is to consider using it to classify lymphedema and lymphatic disorders.[2–4] Indeed, given the similarities between the venous and lymphatic systems, it is somewhat surprising that this approach to classification has not already been widely embraced. This chapter will therefore discuss the classification of lymphedema in terms of the CEAP categories (Clinical, Etiology, Anatomy, and Pathophysiology).

61.2 CLINICAL

The purpose of the lymphatic system is to remove interstitial fluid from the periphery and return it to the circulation.[5] When protein-rich interstitial fluid is not removed because of lymphatic abnormalities, the result is lymphedema.[6]

In the acute form, lymphedema resembles most other types of edema (such as that seen with congestive heart failure, venous disease, etc.). In the early stages of lymphedema, the swelling may be occult, although objective testing might reveal subclinical abnormalities involving the lymph vessels. As the condition becomes more overt, clinically significant edema develops. At first, the swelling is "reducible" with overnight rest, elastic compression, or topical pressure ("pitting"). Over time (often a year or more), the pressure of high-protein interstitial fluid alters the cutaneous/subcutaneous tissues; this produces fibrosis, cellular proliferation, inflammation, and other changes.[7] The result is progressive hardening and induration of the skin, which can be appreciated by inspection and palpation. These skin changes may include "peau d'orange" thickening and wrinkling. Lymphedema can often be appreciated by eliciting the "Stemmer sign," which involves the inability to pinch the skin at the base of lymphedematous toes (Figure 61.1).[8] In chronic lymphedema, the skin gradually loses its ability to "pit" under pressure, and eventually the swelling becomes non-reducible even with prolonged limb elevation, wrapping, etc.[9]

Over time, the appearance of the limb may change further. Along with continued skin thickening, there may be lichenification and the development of verrucous lesions.[10] As these lesions proliferate and coalesce, the limb may acquire a cobblestone, irregular appearance. In its most extreme manifestations, this is referred to as "elephantiasis," because the affected limb begins to resemble the leg of an elephant.[11]

Although commonly occurring in patients with chronic venous disease or other vasculocutaneous abnormalities, there is also an increased tendency for traumatic or erosive skin damage in patients with lymphedema, which can produce non-healing lesions.[12] Patients may "weep" clear fluid through the skin; sometimes, the trauma needed to produce this is so minimal that the weeping seems to be spontaneous.[13] In the worst cases, copious fluid production may soak patients' stockings and/or fill their shoes or boots.

Limbs affected by lymphedema are susceptible to episodes of cellulitis or lymphangitis, usually caused by Gram-positive cocci such as *Streptococcus*.[14] A crucial part of the clinical evaluation entails a search for occult infections or potential sites of infection. In some cases, a documented history of recurrent cellulitis will lead to intermittent or continuous prophylactic treatment with appropriate antibiotics.[15]

Figure 61.1 Positive Stemmer's sign (a failure by the assessor to pick up or pinch a fold of skin at the base of the toe). (From Gasbarro V, Michelini S, Tsolaki E et al., *BMC Geriatr* 2010;10(Suppl. 1):A58.)

Figure 61.2 Myxedema can produce swelling and skin changes that resemble lymphedema. (From Smeltzer DM, Stickler GB, and Schirger A. *Pediatrics* 1985;76:206–18.)

Lymphedema can produce a variety of other symptoms, and these should be sought and documented as part of the clinical evaluation.[16] Although pain is relatively uncommon in patients with lymphedema, its presence can be debilitating.[17] Many patients complain of heaviness due to their limb swelling and experience subsequent limitations in mobility; these impairments should be documented.[18] Paresthesias and abnormal temperature sensations (typically "coldness") are common and annoying.[19] Some "symptoms" are striking; for example, the patient whose limb is so large that he or she cannot wear pants. This limitation obviously has significant implications for employment, social interactions, etc.[20]

The combination of increased limb size, skin changes, weeping transudation, recurrent lymphangitis, and symptoms such as pain and limited mobility may cause disability in the most seriously affected individuals. It is essential that the clinician assess and document the degree of this disability, which may range from minimal to severe and debilitating.[21]

A final note of caution: there are many disease entities that mimic lymphedema. Myxedema (associated with thyroid dysfunction) can produce swelling and skin changes that resemble classic lymphedema (Figure 61.2).[22] Another common "lookalike" is lipedema, which is caused by genetically determined excessive subcutaneous fat deposits.[23] The edema associated with prolonged limb dependency (e.g., the dependency that follows traumatic spinal cord injury that is severe enough to confine a patient to a wheelchair) may be erroneously assumed to be some type of post-traumatic lymphedema. Factitial edema, caused by the application of tourniquets or other methods, is rare but is occasionally seen (Figure 61.3).[24] Other conditions may also imitate lymphedema.

61.3 ETIOLOGY

Lymphedema is traditionally divided into two mayor categories: primary and secondary.[25] Even this simple classification is not as straightforward as one might think. Primary lymphedema may be further subdivided into several categories. Congenital lymphedema typically develops within 2 years of birth.[26] Some of the congenital forms are genetic and thought to be autosomal dominant (e.g., Noone–Milroy syndrome),[27,28] while others follow non-dominant or more obscure genetic patterns. Still other types of congenital lymphedema may be associated with specific hereditary syndromes. These include chromosomal abnormalities such as Turner's syndrome,[29] Klinefelter's syndrome, and trisomy 21, 13, or 18. Other congenital syndromes associated with lymphedema include Klippel–Trenaunay–Weber syndrome, Proteus' syndrome, yellow nail syndrome,[30] Maffucci's syndrome,[31] neurofibromatosis, and many others.

Approximately 10% of all cases of primary lymphedema are "congenital." However, when one considers the various entities associated with "congenital" lymphedema, it is sometimes difficult to know whether the swelling is truly primary or secondary to occult pathology. For example,

Figure 61.3 Factitial edema to the right thigh from tourniquet.

is primary lymphedema merely associated with Turner's syndrome, or does Turner's syndrome somehow cause secondary lymphedema in some patients? As more is learned about the underlying etiologies of primary lymphedema, it is possible that many forms of "primary lymphedema" will someday be explained as "secondary" to some other process.

In addition to the congenital variety, there are two other forms of lymphedema that are thought to be "primary." The first and most common (accounting for roughly 80% of all forms of primary lymphedema) has been termed lymphedema praecox by Allen.[27] This entity is defined as lymphedema occurring spontaneously between the ages of 2 and 25 years; it is called "spontaneous," but there are often minor events that trigger the onset, such as an insect bite, burn, etc. Although sporadic cases are most common, a few forms (i.e., Meige's disease) are hereditary.

Lymphedema tarda accounts for roughly 10% of all primary lymphedemas.[32] By arbitrary definition, it has its onset in those over 35 years of age.

Secondary lymphedema is caused by inflammation or obstruction of the lymph vessels. Some of the most common causes include the following:

- *Cancer*: In particular, (1) lymphoma, (2) cancer of the prostate, breast, or cervix, and (3) melanoma are frequent producers of lymphedema. However, any metastatic cancer may be responsible.
- *Trauma*: The most common type of trauma producing lymphedema is iatrogenic trauma. Radiation therapy, inadvertent disruption of lymphatics during surgical operations, lymph node resection, and other invasive therapies may damage the lymphatics and produce lymphedema. Non-iatrogenic forms of trauma, such as blunt or penetration injuries or burns, can also damage the lymphatics.
- *Infection/inflammation*: As noted earlier, cellulitis and lymphangitis are common in patients with preexisting lymphedema and may further damage lymph vessels. In some cases, an otherwise normal limb may develop lymphedema after a single initial episode of infection. Other inflammatory triggers include insect bites, rheumatoid or psoriatic arthritis,[33] and a host of inflammatory conditions. Even diseases thought to be only minimally associated with inflammation, such as chronic venous disease or lipedema, may be complicated by the eventual appearance of true lymphedema.
- *Filarial disease*: By far the most common cause of lymphedema worldwide is filarial disease,[34] caused by agents such as *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. The World Health Organization estimates that the number of people affected worldwide by this problem may approach 100 million.

61.4 ANATOMY

The anatomy of the lymphatic system is complex and underappreciated. An excellent review can be found in Browse.[35]

When discussing lymphatic anatomy, especially the anatomy of the limb lymph vessels, there are several ways to divide the proverbial pie. For example, lymphatics can be classified as superficial or deep, with the superficial system typically being more important than the deep. A distinction can also be made between distal lymph vessels (located below the inguinal region) as opposed to proximal or truncal vessels, which include the iliacs, lumbars, cisterna chili, and thoracic duct. Similar, although more complicated divisions exist for the lymphatics of the upper extremity. In addition, a systematic approach to lymphatic anatomy must address the various nodes through which the lymph vessels pass. An understanding of basic lymph node anatomy (e.g., recognizing that the efferent vessels leaving a node are normally larger and more tortuous than the afferent vessels entering one) is essential, but beyond the scope of this short chapter. Additional information on lymphatic anatomy can be obtained elsewhere.[35]

Some authors have chosen to characterize lymphatics not just in terms of their location (superficial versus deep, proximal versus distal, etc.), but also in terms of their lymphangiographic appearance.[32]

Lymphatic abnormalities can be divided into four anatomical categories: aplasia, (no lymph vessels present), hypoplasia (less than a normal amount of lymph vessels present), numerical hyperplasia (more lymph vessels than normal), and lymphangiectasia (numerous lymph vessels, many of which are dilated and tortuous). Although this is strictly an anatomical classification (since it is based entirely

on the lymphangiographic appearance), it nonetheless has some pathophysiological and functional implications. In addition, some authorities[36] question the significance of these categories (e.g., is mild lymphatic hyperplasia a primary problem of lymph vessels or does it reflect a response to occult early proximal obstruction?).

61.5 PATHOPHYSIOLOGY

There are three major categories of lymphatic pathophysiological abnormalities, all of which can be further subdivided. These include obstruction, reflux, and overproduction of lymph fluid.

- *Obstruction*: This is the most common mechanism by which lymphedema is produced, accounting for nearly all cases of secondary lymphedema and most cases of primary lymphedema. With primary disease, the obstruction may be distal (hypoplasia or aplasia), proximal (upper limb or higher), or a combination of proximal and distal involvement. In cases of secondary obliteration by cancer, trauma, radiation therapy, filarial, etc., the obstruction may be located anywhere along the lymphatic pathway.
- *Reflux*: A significant number of patients with primary lymphedema (perhaps as many as 10%) are thought to have chronic reflux.[37] This includes patients with congenital lymphatic hyperplasia, which, in its most extreme form, is sometimes known as "megalymphatic" disease.
- *Overproduction*: A less common or obvious cause of lymphedema is the overproduction of interstitial/lymphatic fluid.[38] Acutely, this can be seen with almost anything that increases capillary permeability and leads to an increase in interstitial fluid production. Ambient heat, trauma, inflammation, and many other conditions are thought to produce lymphedema via this mechanism. Most of these underlying conditions resolve in time, and along with them so does the lymphedema.

It is thought that chronic states of lymph fluid overproduction may exist. While a chronically "leaky lymphatic" syndrome has been postulated, it is difficult to prove its existence at this time. One exception is the lymphedematous change seen in patients with chronic arteriovenous fistula of the periphery. Although it is hard to rule out the possibility that some of these patients actually have occult obstruction of their lymphatics, it is reasonable to speculate that these high blood flow states are accompanied by increased interstitial fluid production, which subsequently leads to lymphedema.

61.6 CEAP-L FOR LYMPHEDEMA

As noted earlier, it seems obvious to classify lymphedema using a similar system to that utilized for classifying venous disease. Indeed, Gasbarro and Cataldi[2] have proposed modifying the existing CEAP system so that it is applicable to lymphatic diseases. Highlights of their work include:

- *Clinical classification*: This ranges from C_0 to C_4 (C_0, normal; C_1, reversible edema; C_2, fixed edema; C_3, healed ulcer; C_4, open ulcer). Perhaps in recognition that ulcers are somewhat atypical for lymphedema, the authors have created a clinical subcategory addressing the production of fluid through the skin (S_0, none; S_1, minimal or "droplets"; S_2, "wet"). It seems to us that exudate status could be substituted for ulceration status.
- *Lymphangitis*: The authors propose a subcategory describing the patient's history of lymphangitis (L_0, no episodes; L_1, one to three episodes; L_2, more than three episodes).
- *Symptoms*: Patients can be classified as to whether they have no symptoms (asymptomatic) or specific symptoms such as pain, cramps, heavy or cold sensations, etc. (symptomatic). These patients may need to be reclassified after treatment if their symptoms are altered by effective therapy.
- *Disability*: The clinical status of patients can be further categorized according to their disability (D_0, none; D_1, needs minimal help for activities of daily living; D_2, needs regular daily help for activities of daily living; D_3, needs continuous and complete help for activity of daily living). The patient's need for support devices to control swelling could also be included as an "sd+" or "sd–" in the subscript; for example, D_{2sd+} or D_{2sd-}.
- *Skin morphology*: A final clinical subcategory includes an assessment of skin morphology (S_0, normal; S_1, edema; S_2, fibrosis).

Other clinical classification schemes also exist. Beninson[39] suggests a strategy based on four elements: inspection, palpation, effect of leg elevation, and function. Beninson creates four categories ranging from grade 1 (normal inspection, normal skin with pitting edema on palpation, complete reduction of leg swelling with leg elevation, and normal function) to grade 4 (yellow, hyperpigmented, weeping keratotic, lichenified, papule-covered skin on inspection; palpation revealing thick, non-pitting skin; no reduction in edema with leg elevation; and serious functional loss with movement impairment). Numerous other clinical classification schemes are possible:

- *Etiology*: Gasbarro and Cataldi[2] suggest dividing lymphedema into congenital forms, which include the primary forms and secondary forms. It seems logical to expand this to include separate categories for congenital, praecox, and tarda forms of primary lymphedema.
- *Anatomy*: This is perhaps the most difficult characteristic of lymphedema to classify. Strategies for dividing the lymphatic system into superficial, deep, lateral, medial, or other components have been suggested, with

complex schemes that name the involved deep segments according to their nearby blood vessels or other structures. In addition, relatively complicated approaches for identifying the involved node groups have been outlined. Separate strategies for describing lower extremities versus upper extremities or the trunk also exist.

- *Pathophysiology*: A relatively simple way to describe the pathophysiology of lymphedema has been proposed (P_a, agenesis/hypoplasia; P_o, obstruction; P_h, hyperplasia; P_r, reflux; P_{ov}, overproduction).[40] Additional refinements to this scheme are possible.

Finally, the authors have proposed a "gravity" score in which they assign points to various components of the CEAP score and derive an overall "severity" grade for the patient. For example, points might be assigned to the clinical grade, extent of disease, disability, and symptomatology; these can be totaled to give an overall severity score. The utility of this scoring system remains undetermined.

In conclusion, a "CEAP"-type approach to lymphedema could provide all of the information necessary for accurate and complete classification of the various lymphatic disorders. It would therefore appear that a universal "CEAP-L" system is ripe for development. At this time, proposals have been made to do this, but more input/consensus is needed in order to optimize the final product. It is our opinion that an international consensus committee approach, akin to that used to create the current CEAP system for venous disease,[41] is needed to create a similar scheme for the classification of lymphatic disorders.

Guidelines 6.1.0 of the American Venous Forum on lymphedema: pathophysiology, classification, and clinical evaluation

No.	Guideline	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
6.1.1	Lymphedema is divided into two major categories: primary and secondary. Primary lymphedema may be further subdivided into three categories: • Congenital lymphedema (10%) develops within 2 years of birth. Some of the congenital forms are hereditary. • Lymphedema praecox (80%) occurs between the ages of 2 and 25 years. Although sporadic cases are most common, a few forms are hereditary. • Lymphedema tarda (10%) has its onset in those over 35 years of age. Secondary lymphedema is caused by inflammation or obstruction of the lymph vessels. Some of the most common causes include filariasis, cancer, trauma (mostly iatrogenic), and infection/inflammation.	B
6.1.2	Lymphatic abnormalities can be divided into four anatomical categories: aplasia, hypoplasia, numerical hyperplasia, and hyperplasia.	B
6.1.3	There are three major categories of lymphatic pathophysiological abnormalities: obstruction, reflux, and overproduction of lymph fluid.	B

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● = Key primary paper
★ = Major review article

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62

Lymphoscintigraphy, lymphangiography, magnetic resonance imaging

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62.1 INTRODUCTION

Imaging of the lymphatic system was revolutionized in the 1950s by the pioneering work of Kinmonth,[1] who described a practical technique of direct cannulation of pedal lymphatic vessels and injection of radio-opaque contrast material to visualize pelvic and leg lymph vessels and lymph nodes. His systematic review and classification of contrast lymphangiograms provided the basis of our understanding of the lymphatic anatomy in patients with lymphedema.[2] However, with the development of isotope lymphoscintigraphy, a less invasive imaging technique, the role of contrast lymphangiography has largely diminished in the evaluation of patients with lymphedema. Nevertheless, there remain several situations in which contrast lymphography has distinct advantages, and, when required, the anatomic resolution of this technique is unparalleled. Later in this chapter, we will discuss current indications for, and techniques of, contrast lymphangiography. Additionally, we will discuss the role of computed tomography and magnetic resonance lymphangiography (MRL) in today's practice.

62.2 LYMPHOSCINTIGRAPHY

Lymphoscintigraphy, broadly described as an assessment of the lymphatic clearance of injected radioactive particles, was also developed in the 1950s. Because it is less invasive, easier to perform, and associated with fewer complications, lymphoscintigraphy has largely replaced contrast lymphangiography in the evaluation of the lymphatic system. With newer imaging equipment and modern radiolabeled tracers, normal and pathologic lymphatic function can be accurately determined, and a great deal of anatomic information can also be obtained. Recently, lymphoscintigraphic techniques have been most commonly employed for the delineation of lymphatic drainage and potential nodal metastasis from a variety of neoplastic lesions. Magnetic resonance lymphangiography is a new' and also promising' imaging modality of the lymphatic system.

62.2.1 History of lymphoscintigraphy

Sherman and Ter-Pogossian[3] first reported the transport of radioactive colloids by the lymphatic system in 1953. They utilized colloidal gold (^{198}Au) in experiments, hoping to deliver tumoricidal doses of β-irradiation to regional lymph nodes as a treatment for metastatic cancer. Sherman and Ter-Pogossian performed autoradiographs of the regional lymph nodes, demonstrating the potential of this technique for lymphatic imaging.

In the same year, Jepson et al.[4] demonstrated the feasibility of using plasma protein radiolabeled with ^{131}I in the evaluation of lymphatic transport. They found slower clearance of interstitial protein via the lymphatic system than crystalloid ^{131}I via the capillary network. In 1957, Taylor et al.[5] showed delayed transport of radiolabeled protein from the subcutaneous injection site in patients with lymphedema compared with normal subjects. Although many lessons regarding the physical properties and rate of lymphatic transport of colloidal materials were gleaned from these early studies, it became evident that high-energy irradiation emitters are not appropriate for use in diagnostic imaging. The development of technetium 99m (^{99m}Tc)-labeled radiocolloids and macromolecules, however, has made lymphoscintigraphy a safe and practical technique.

62.2.2 Technique of lymphoscintigraphy

Selection of an appropriate radiolabeled macromolecule or colloidal material is key to high-quality imaging. Characteristics such as particle size and surface charge affect the biokinetic behavior of subcutaneously injected materials. Particles greater than 10 nm in diameter are transported by the lymphatics, whereas smaller particles are transported via the capillary network. Lymphatic transport time is directly related to particle size, and particles of over 100 nm in size are transported very slowly. The optimal size for the delineation of lymphatic vessels and nodes in extremity lymphoscintigraphy is between 10 and 40 nm.[6] The initial experience at the Mayo Clinic was with ^{99m}Tc–antimony trisulfide colloid, but for the past decade this compound has not been available in the United States. Currently, filtered ^{99m}Tc–sulfur colloid (Tc-fSC) is the radiopharmaceutical most commonly used for lymphoscintigraphy in the United States. When Tc-fSC is passed through a 0.1-mm filter, it yields a stable particle with a mean diameter of 38 nm, and 90% of the particles are less than 50 nm.[7] Clinical and research studies have demonstrated that Tc-fSC produces similar results to previously used agents.[8]

Exercise is known to influence the rate of lymphatic transport and therefore must be standardized during the performance of lymphoscintigraphy.[9] Patients are comfortably positioned supine on the imaging table. For studies of the lower extremities, the feet are attached to a foot ergometer and the patient is instructed in its use. For upper extremity studies, the patients are given a squeezable ball which is compressed during the study.

For studies of a lymphedematous extremity, subcutaneous injection of the radiolabeled tracer utilizing a tuberculin syringe and 27-gauge needle is performed into the web space between the second and third digits of the hand or foot. A topical anesthetic is often applied to the skin 15–20 minutes prior to injection. The volume of the injection is kept between 0.1 and 0.2 mL, which is associated with a brief period of discomfort at the injection site but is otherwise tolerated extremely well. We use 15–18 MBq (400–500 mCi) of Tc-fSC. Over 3 hours, 10%–20% of the injected activity is transported from the injection site using these compounds.

A γ-camera with a large field of view is positioned immediately following injection of the tracer to include the groin region in the upper field of view. An all-purpose collimator is used, and a 20% window is placed symmetrically around the 140-keV photopeak of the ^{99m}Tc isotope. Dynamic anterior images are obtained every 5 minutes during the first hour (Figure 62.1). Exercise using the foot ergometer or plastic ball begins immediately following injection of the tracer compound. The patient is requested to exercise for 5 minutes initially and then for 1 minute out of every 5 for the remainder of the first hour while dynamic images are obtained.

Total body images over 20 minutes are obtained after 1 and 3 hours following the injection (Figure 62.2). Patients are encouraged to ambulate between these images, although the degree of exercise is no longer standardized at this point in the study. In selected patients with delayed lymphatic transport, total body images may also be obtained at 6 and 24 hours to further delineate the degree of lymphatic obstruction.

62.2.3 Mapping of lymphatic drainage in neoplastic disease

The primary focus of this chapter is on the evaluation of the extremity with lymphedema. However, injection of Tc-fSC to detect nodal drainage from the area of a tumor has become the primary clinical application of lymphoscintigraphic techniques. The potential for detection and treatment of lymph nodes draining a neoplasm was appreciated in the earliest days of lymphoscintigraphy and later confirmed in the 1970s.[10,11] The clinical application of lymphoscintigraphy to identify and assist in sentinel node biopsy grew rapidly in the 1990s.[12–15] Lymphatic mapping is being commonly utilized in a growing number of cancers, including those affecting the skin, breast, head and neck, vulva, and penis.[15–19]

The sentinel lymph node is the first lymph node that filters lymph draining from the tumor site. Lymphatic drainage varies greatly in each individual. Lymphoscintigraphy maps the drainage pattern in each patient. The Tc-fSC particles injected adjacent to the tumor site are trapped in the sentinel node. Pre-operative lymphoscintigraphy is valuable for identifying lymphatic drainage and sentinel node location. A hand-held γ-probe is then used intra-operatively to identify the lymph nodes where radioactivity has accumulated. Tracer injections in the dermis, subcutaneous tissue, and peri-tumor locations have all been used with reasonable results. Most reports have agreed that a combination of radioactive tracer with a visible dye (isosulfan blue) yields the best results. Investigators have reported the identification of a sentinel node in well over 90% of patients. The utility and long-term impact of sentinel node mapping and examination in the management of melanoma and breast cancer are well established, but are beyond the scope of this chapter.[20–23]

62.2.4 Interpretation of lymphoscintigraphy

Before any diagnostic information is derived from a lymphoscintigraphic study, the images can be used to ensure proper injection technique. The liver should not be visualized over the first 10–15 minutes of the study and should only be faintly visible after 1 hour. Early visualization of the liver without activity in the regional or abdominal lymph nodes is suggestive of intravenous injection of the tracer compound, which may cloud interpretation of the study. Once proper technique is confirmed, lymphatic function can be assessed quantitatively by the appearance of radioactivity in the regional lymph nodes during dynamic imaging, or qualitatively using the visual scintigraphic images. A combination of these techniques employs the visual images

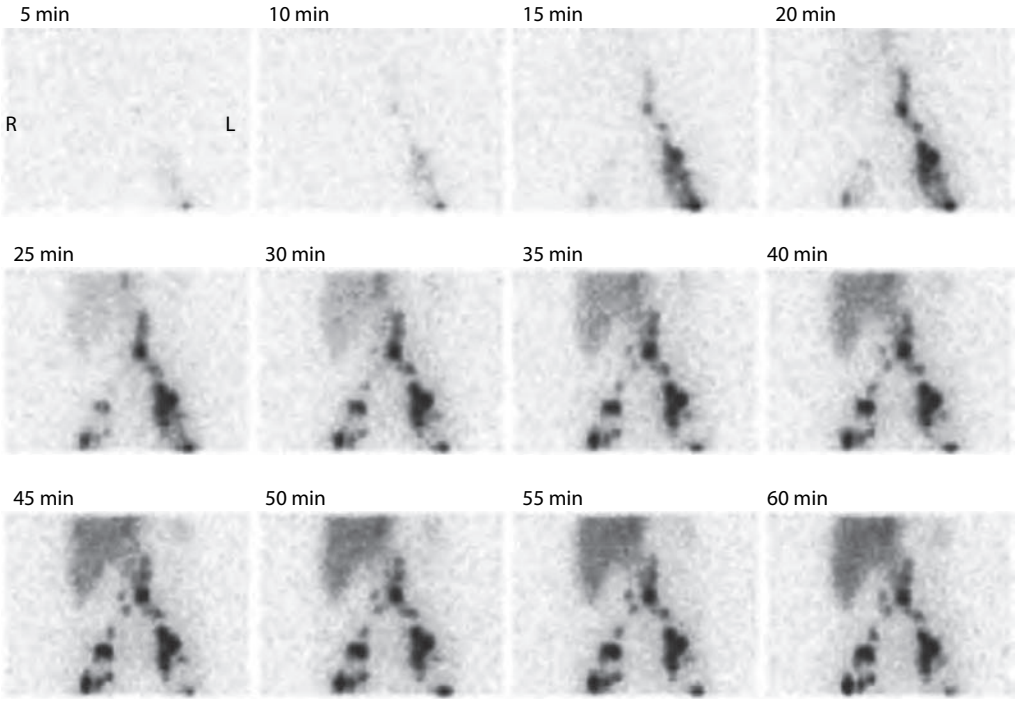

Figure 62.1 Dynamic anterior images obtained every 5 minutes for 60 minutes following tracer injection in both feet. This 57-year-old man with intermittent bilateral leg swelling had prompt, normal lymphatic transport, with activity appearing in the groin nodes within 15 minutes.

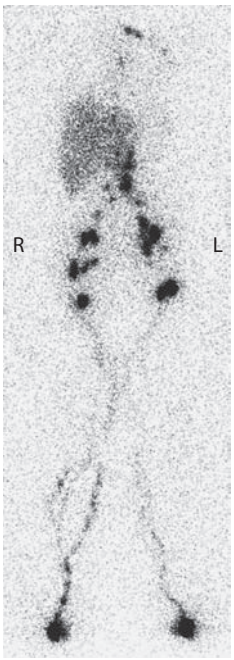

Figure 62.2 Anterior total body lymphoscintigram 1 hour after injection of tracer. This 54-year-old woman was admitted with a 19-year history of bilateral lower extremity swelling. Lymph vessels, nodes, and transport kinetics appear normal. There are several collateral lymph channels in the right popliteal region. The activity in the left supraclavicular region is within the thoracic duct. (With permission from Mayo Foundation and Research.)

to derive a lymphatic transport index, a modification of the scoring system initially described by Kleinhans et al.[24]

The transport index is a scoring system for the lymphoscintigraphic images that can range from near 0 in normal scans to a maximum of 45 in scans demonstrating the absence of lymphatic transport. The components of the score and criteria for scoring the studies are depicted in Figure 62.3. By examining the images, information on the appearance of tracer in the regional nodes, the location and number of lymphatic channels and nodes, and the distribution pattern of tracer can be scored and tabulated. This semi-quantitative score is most useful for comparing serial scans in an individual patient, or for comparison of lymphatic function between patients.

A prospective evaluation of 386 extremities using the transport index demonstrated that asymptomatic extremities ($n = 79$) had an average transport index of 2.6, while lymphedematous extremities ($n = 124$) had a mean index of 23.8.[25] In this series, a transport index of greater than 5 was highly suggestive of lymphedema (sensitivity, 80%; specificity, 94%). Unfortunately, the transport index was unable to distinguish those extremities with primary lymphedema from those with secondary lymphedema. This is not surprising, since the lymphatic anatomy in the end stages of these disorders can be quite similar. However, lymphoscintigraphy allowed exclusion of lymphatic pathology as a cause of extremity swelling in a third of patients.

Several reports have noted the accuracy of lymphoscintigraphy using a variety of tracer compounds and

Patient's initials _____

Clinic number _____ Date _____

Lymphoscintigraphy

Date evaluation

_____ Arms _____ Legs

	1 hour		3 hour		6 hour		24 hour	
Image	R	L	R	L	R	L	R	L
Lymph transport kinetics: 0 = no delay, 1 = rapid, 3 = low-grade delay, 5 = extreme delay, 9 = no transport								
Distribution pattern: 0 = normal, 2 = focal abnormal tracer, 3 = partial dermal, 5 = diffuse dermal, 9 = no transport								
Lymph node appearance time: Minutes								
Assessment of lymph nodes: 0 = clearly seen, 3 = faint, 5 = hardly seen, 9 = no visualization								
Assessment of lymph vessels: 0 = clearly seen, 3 = faint, 5 = hardly seen, 9 = no visualization								
Abnormal sites of tracer accumulation (describe)								

Figure 62.3 Evaluation form for the calculation of lymphatic transport index.

interpretation methods. Stewart et al.[26] reported very high sensitivity and specificity rates using visual interpretation of lymphoscintigraphic images alone. These findings are supported by others.[27,28] However, some authors have recommended the use of time–activity curves obtained with dynamic imaging over the regional lymph nodes for the analysis of lymphatic function.[29–31] Weissleder and Weissleder[9] reported an improvement in sensitivity of the examination when quantitative clearance data were used. Experience with quantitative analysis of regional lymph node tracer accumulation has demonstrated a great deal of variability in normal extremities, making interpretation of these data difficult.[32] Therefore, we have come to rely heavily on the visual interpretation of the lymphoscintigraphic images for a given study and use the semi-quantitative transport index as described above to compare serial examinations or studies in different patients.

62.2.5 Lymphoscintigraphic patterns in normal and swollen extremities

In normal lymphoscintigrams, the areas of highest tracer activity usually remain at the injection site. As mentioned previously, only 10%–20% of the injected activity is normally transported from the injection site over the period of the study. In the case of the lower extremity, this intense area of activity overshadows any anatomic detail in the area of the foot. Gradual ascent of the tracer from the foot occurs, and, with normal transit, activity is detected in the inguinal lymph nodes on the dynamic images at between 15 and 60 minutes from the time of injection. Appearance of significant activity in the groin in less than 15 minutes indicates rapid transport, and absence of activity after 1 hour is suggestive of delayed lymphatic transport (Figure 62.4). On the total body images, several lymphatic channels may be seen in the area of the calf, but in the thigh, the lymphatics run close together on the medial aspect. Separate activity in each of the channels is seldom seen. With normal transit times, the inguinal nodes should be clearly visualized by 1 hour following injection, and faint visualization of the para-aortic nodes, liver, and bladder may be seen (Figure 62.2). On the 3-hour image, the uptake in the pelvic and abdominal nodes and liver should be intense (Figure 62.5), and occasionally the area of the distal thoracic duct in the left supraclavicular fossa will be visible.

In lymphedematous extremities, several lymphoscintigraphic patterns may be observed either alone or in combination.[33] These can be broadly classified as follows:

1. Delay or absence of lymphatic transport from the injection site. Little or no activity is detected in the regional lymph nodes by 1 hour following injection. In extreme circumstances, no transport of activity from the foot can be detected.
2. Collateral channels or a cutaneous pattern consistent with dermal backflow may be seen in the extremity. These finding are suggestive of obstruction of lymphatic vessels in the extremity, with lymphatic flow either

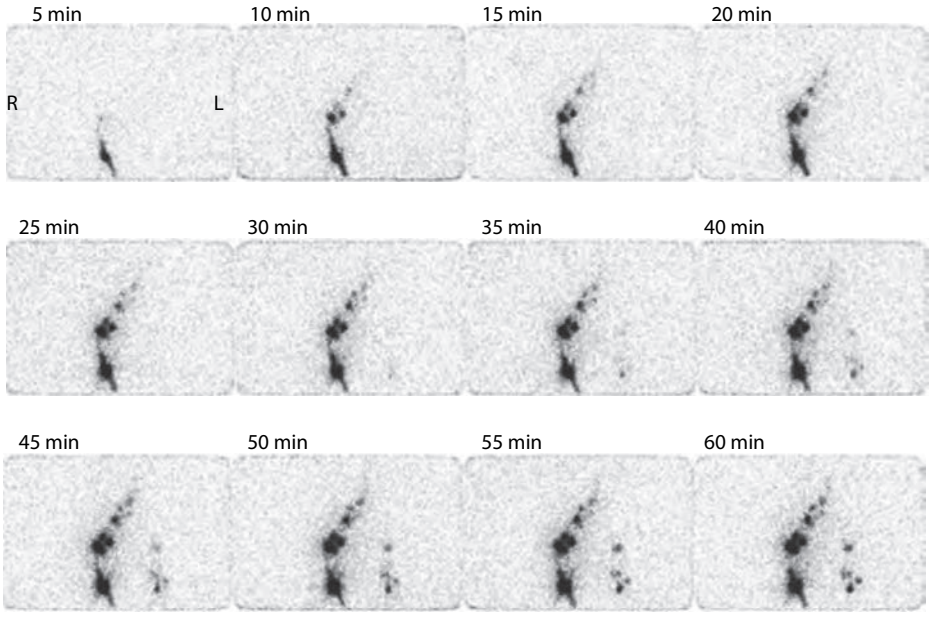

Figure 62.4 Dynamic anterior images obtained every 5 minutes for 60 minutes following tracer injection in both feet. Normal lymphatic transport and image pattern of the inguinal nodes on the right, no visualization of the lymphatics on the left. This 26-year-old woman had primary lymphedema of the left leg.

finding new channels around the obstruction or backfilling the rich dermal lymphatic network (Figure 62.6).

3. Reduced, faint, or no uptake in the lymph nodes of the groin, pelvis, or para-aortic regions, indicating a localized area of lymphatic obstruction at the level of the regional lymph nodes (Figure 62.6). Although this pattern may be seen in primary lymphedema, it is more suggestive of secondary disease following lymph node dissection or radiation for neoplastic disease.
4. Abnormal tracer accumulation suggestive of extravasation, lymphocele, or lymphangiectasia (Figure 62.7).

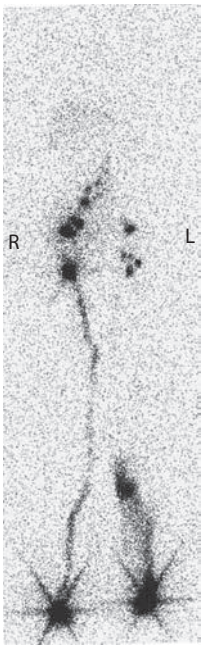

Figure 62.5 Anterior total body image 3 hours after injection in a 75-year-old man with a 5-year history of left leg swelling (primary lymphedema). There is a localized area of dermal distribution in the left calf with a diminished number of lymph nodes in the left inguinal region.

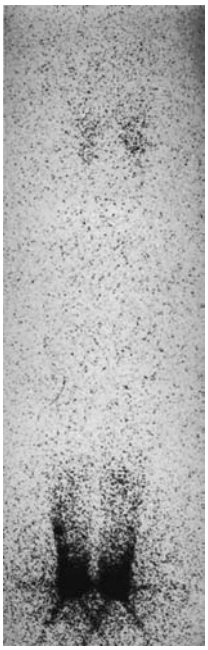

Figure 62.6 Anterior total body image 6 hours after injection in a 25-year-old woman with congenital primary lymphedema of both lower extremities and intestinal lymphangiectasias. Note the absence of lymph vessels and minimal lymph node activity at 6 hours, with only mild dermal backflow visible in the distal calves.

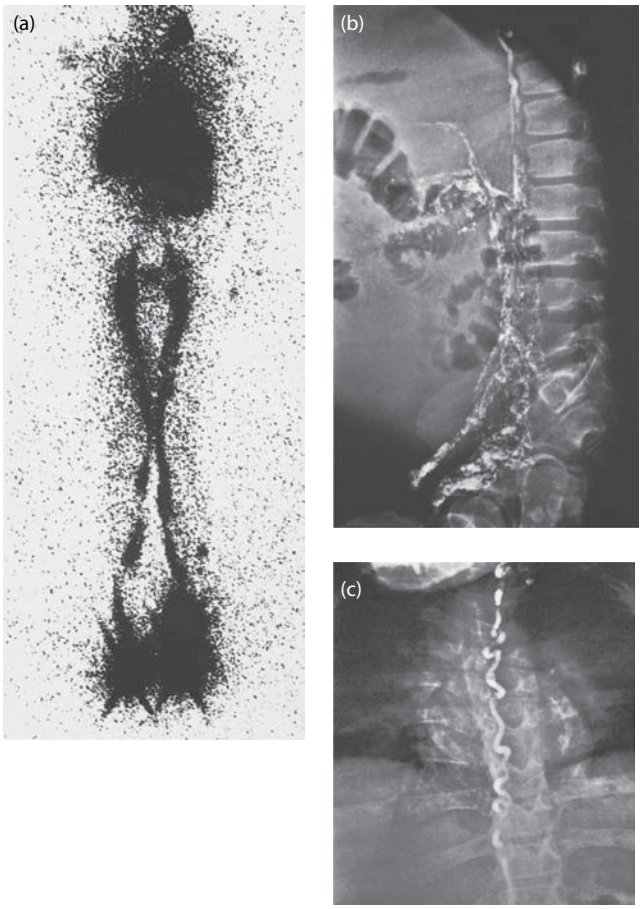

Figure 62.7 **(a)** Lymphoscintigram of an 18-year-old man with lymphangiectasia, protein-losing enteropathy, and chylous ascites. Note the large leg lymphatics and reflux of colloid into the mesenteric lymph vessels, filling almost the entire abdominal cavity. **(b)** Lymphangiogram of the same patient reveals reflux of dye into the dilated mesenteric lymphatics. **(c)** Note the extremely dilated and tortuous but patent thoracic duct. (From Gloviczki P, and Wahner HW. *Vascular Surgery*. Philadelphia, PA: W.B. Saunders, 1995, 1899–920.)

These types of accumulation can be seen in a wide variety of lymphatic pathologies, ranging from direct trauma to the lymphatic vessels following surgery to extravasation of lymphatic fluid into body cavities (chylous ascites or chylothorax) or reflux of chyle to the skin (lymphorrhea). Scintigraphic findings in these disorders rarely yield enough anatomic detail to pinpoint the site of lymphatic leak, however, and contrast lymphangiography may be helpful in this regard.

Lymphoscintigraphy can be used to monitor the effects of therapeutic intervention or the progression of lymphedema over time. In one study, over 80% of extremities demonstrated an improvement in lymphoscintigraphic findings following a regimen of complex physical therapy and compression.[34] Similarly, alterations in lymph flow with the application of either hot or cold compresses can be measured with lymphoscintigraphy.[35] The Mayo Clinic transport index (Figure 62.3) has correlated well with the degree of symptoms on repeated examination in several patients.

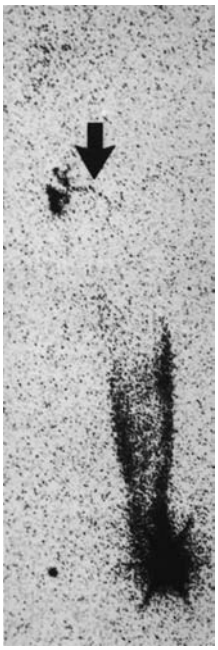

Figure 62.8 A 52-year-old man with secondary lymphedema of the left lower extremity who underwent suprapubic lymphatic grafting 5 years previously. The arrow indicates a patent lymphatic graft. Note that injection of the colloid was made into the left foot and that the suprapubic graft fills the right inguinal lymph nodes.

Lymphoscintigraphy has become quite useful in the evaluation of patients who are being considered for direct lymphatic reconstruction. In the ideal patient (secondary lymphedema due to obstruction at the groin or axillary level), lymphoscintigraphy can identify dilated lymphatics in the involved extremity with sufficient accuracy to proceed with surgical exploration on the basis of these findings.[32] In addition, this study is suitable for following the effectiveness of some lymphatic reconstructions. While patency of lymphovenous anastomoses cannot be directly demonstrated,[36] the study can image patent suprapubic or axillary lymphatic grafts placed for unilateral lymphatic obstruction (Figure 62.8).[24]

Lymphoscintigraphic findings in extremities with venous disease vary depending on the duration and extent of venous pathology. Early in the course of venous disease, before extensive edema formation or the development of lipodermatosclerosis, the lymphatic system is normal and the lymphoscintigraphic appearance will reflect this. An increase in lymphatic transport (rapid transit) develops as capillary filtration and edema in the extremity increases. This was noted in early studies of lymphatic flow with ^{131}I-labeled albumin[37] and has been confirmed in both animal models[38] and humans.[26] The increase in lymphatic transport occurs as a homeostatic mechanism in which the lymphatic system

attempts to reduce the increased tissue fluid. Others have demonstrated a decrease in lymphatic transport associated with venous pathology.[9,31,39] Lymphatic vessels are damaged in areas of the extensive lipodermatosclerosis that accompanies advanced venous disease, leading to delayed lymphatic transport and exacerbation of edema in the extremity. In a prospective series in which 31 patients had evidence of deep venous insufficiency, four of these (13%) had rapid transport, nine (29%) had normal lymphatic transport, and 18 (58%) had delayed transport.[25]

62.2.6 Summary

Lymphoscintigraphy has become the test of choice in patients with suspected lymphedema. Unlike contrast lymphangiography, it is noninvasive, well tolerated, and associated with very few complications. When necessary, it can be repeated serially to follow the clinical course of lymphatic function. Although initially developed as a functional study, newer imaging techniques and equipment can yield a great deal of anatomic information, which in certain cases may be sufficient for direct surgical intervention on the lymphatic system. While diagnostic accuracy through utilizing several methods of interpretation has been reported, we have come to rely largely on visual interpretation of scintigraphic images. When necessary, a simple scoring system can be applied to derive a lymphatic transport index, which can then be used to compare individual scintigraphic studies with one another. Most recently, lymphoscintigraphy has begun to be used frequently for the mapping of lymphatic drainage and sentinel node localization in a variety of neoplasms.

62.3 LYMPHANGIOGRAPHY

In 1943, Servelle performed the first contrast lymph angiogram. Nearly a decade later, Kinmonth[1] described the basic technique of the subcutaneous injection of a vital dye for the identification of superficial dorsal foot lymphatics for cannulation and direct injection of contrast material. Almost 50 years later, there have been modifications only to the injected contrast agents and the radiographic filming of the examination.

The continued development and refinement of cross-sectional imaging techniques (computed tomography, magnetic resonance imaging, and ultrasonography) and isotope lymphoscintigraphy have led to a reduced need for diagnostic lymphangiography.

Although lymphangiography is a time-consuming and technically challenging radiologic procedure, it provides a highly detailed examination of both the lymphatic vessels and nodes. It provides the detail required for percutaneous embolization in leakage situations.

62.3.1 Technique of lymphangiography

Lymphangiography is an outpatient procedure. The patient is instructed not to eat or drink 8 hours prior to the examination. Medications and clear liquids are permitted. Conscious sedation may be given if the patient is anxious or unable to remain quiet for at least 60 minutes. The patient is placed supine on a padded radiographic fluoroscopic table. Patients with respiratory disease may not be able to tolerate the procedure due to the importance of patient positioning.

The lymphatic channels must first be visualized so that they can then be cannulated during lymphangiography. The blue dyes used for the opacification of lymphatic channels is isosulfan blue (Lymphazurin 1%; Hirsch Industries). Lymph vessels are identified as thin-walled in contrast to the thicker walls of nearby veins. A total of 90% of isosulfan blue is excreted via the biliary tract and the remaining 10% is excreted in the urine. The urine can be discolored for a few days. In patients with allergies to blue dyes, fluorescein can be used to localize the lymph vessels, but is less intense than the traditional blue dyes.

In this initial phase, the skin between each toe is cleaned with alcohol, and 0.5 mL of lidocaine is injected intracutaneously in each web.[40] This is followed by an injection of 0.5 mL of isosulfan blue (Lymphazurin 1%). Some authors have mixed the solutions for a single injection in each web. The patient is then instructed to actively flex and extend the toes and ankles until optimal visualization has occurred. The hair on the dorsum of the foot is shaved if necessary.

The site for blue dye injection to visualize the deep lymphatics of the leg is the sole of the foot, close to the abductor hallicus muscle. For lymphangiography of the arm, the dorsum of the hand, between the fingers, is injected, and for cervical lymphangiography, the site of injection is behind the ears. Striking blue streaks through the skin are visualized lymphatic channels. They may be difficult to identify in dark-skinned patients. Sterile drapes are placed around both feet, providing a large working surface for the examiners. A large lymphatic channel on the dorsum of the foot that is oriented in a direction which will accept easy cannulation and subsequent tubing fixation is selected for cannulation. This channel is often located on the mid-dorsum of the foot, but occasionally a more proximal channel near the ankle is optimal.

Using a cut-down technique, lidocaine 1% without epinephrine is generously injected into the subcutaneous tissues surrounding the blue lymphatic channel. The purpose of this liberal local anesthetic injection is to obtain a pain-free environment, as well as to facilitate the delicate procedure of removal of perilymphatic adipose and other tissue. Lidocaine may also have an antispasmodic effect on small lymphatic channels.

A 2-cm vertical or transverse incision is made over the lymph vessel and blunt dissection is performed until the channel is located. A thin 3 × 1 cm malleable metallic wedge is then slipped under the vessel, which is further cleaned of any adjacent fat or fibrous tissue. At both the proximal and distal ends of the exposed vessel, a 5–0 silk tie is gently positioned for further use. Next, the proximal tie (toward the ankle) is taped with a Steristrip. This tie is put under slight tension in order to distend the lymph vessel. The more distal

tie can be used as a repair for leaks, but the needle must pass through the tie.

We use a 30-gauge lymphangiography needle based on the diameter of the visualized lymphatic vessel. The needle tip is held nearly parallel to the lymphatic channel for cannulation. The needle can be gently test injected with sterile saline to check position. Once in position, a Steristrip is used to secure the needle or the dorsum of the foot. The proximal tie is then released to allow flow; it can be moved just proximal to the bevel of the needle and tightened for a better seal. The tubing of the needle can be draped between the appropriate toes and then taped to the skin.

A Harvard infusion pump apparatus (Bard Medsystems) is used to inject the heated contrast material at 0.10–0.15 mL per minute for a total of 5–7 mL per leg, without leakage. The iodinated contrast material used for lymphangiography is Lipiodol (iodinated ethyl esters of fatty acids of poppy seed oil; Guerbet LLC). Almost 90% of the contrast material is retained by the lymph nodes and the remainder flows into the thoracic duct entering the pulmonary bed. In patients with diminished pulmonary function, this may lead to further pulmonary compromise.

If unsuccessful on one side, overfilling of the infused side using 10–12 mL can cross-fill at the bilateral para-aortic lymph node level. After 1–2 mL of injection, brief fluoroscopy or a radiograph is taken to confirm lymphatic filling. Patients can experience leg cramping as contrast material ascends in the lower leg. After the injection, both incisions are washed with sterile saline. Single or double vertical mattress polypropylene sutures are used to close the incision. Antimicrobial ointment and a small dressing are applied. Sutures should be removed in 10 days.

The standard series of radiographs obtained immediately after the procedure (for vessel evaluation) and at 24 hours (for node architecture and location) include:

- Pelvic: Anteroposterior, lateral, and both obliques
- Lumbosacral spine: Anteroposterior, lateral, and both obliques
- Chest: Posteroanterior and lateral

Radiographic spot films are useful to identify sites of extravasation in the trunk, chest, or limbs. Early, frequent fluoroscopic observation can assist in the localization of leaks. Frequently, immediate post-lymphangiogram computed tomography (CT) is obtained to document the site of leak, detect subtle leaks not identified on fluoroscopy or plain film, and provide detailed anatomy to assist the interventional radiologist or surgeon prior to further management. Delayed 24-hour CT may also be useful in difficult cases. Extremity films are also taken if the test is being performed for lymphedema.

The ultrasound-guided intranodal lymphangiogram technique is being used in some facilities to identify lymphatics for thoracic duct embolization.[41] Inguinal nodes are injected with Lipiodol using a 25-gauge needle with the tip positioned in the transitional zone between the cortex and hilum of the node. This technique can also be used in pediatric patients. We choose to do pedal lymphangiography with our team's experience of over 40 years.

62.3.2 Interpretation of lymphangiography

Complete evaluation of a lymphangiogram includes interpretation of the channel (immediate) and nodal (after 24 hours) phases of the study, as well as any spot films and CT scans taken (Figure 62.9). The lymphatic channels are evaluated for size, number, leak, obstruction, or metastatic involvement. The lymph nodes are individually evaluated for size, number, contour, and internal architecture.

Lipiodol usually clears from the lymphatic vessels within 3–4 hours. Delayed emptying occurs in proximal obstruction. Extravasation into the perilymphatic tissues can occur in lymphatic obstruction or with too rapid infusion rates.

The appearance of the lymph nodes depends on: (1) the degree of opacification and (2) histology. Contrast material is located within the sinuses. A normal lymph node appears

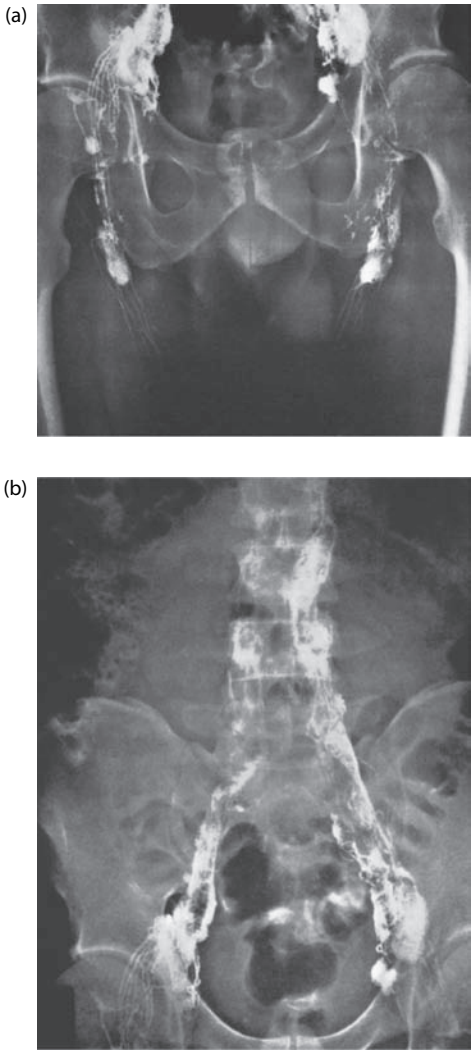

Figure 62.9 **(a and b)** Normal lymphatic anatomy demonstrated by bipedal contrast lymphangiography.

as a sharply defined round or oval density with a fine, homogeneous, and granular appearance. From the hilus of the node, efferent lymphatic channels emanate centrally.

62.3.3 Complications of lymphangiography

Lymphangiography is relatively safe as long as patients are carefully selected and standard precautions are taken.[41,42] Complications are classified as follows:

- Idiosyncratic reactions to blue dyes or Lipiodol
- Pulmonary complications
- Central nervous system embolization of oily contrast
- Local wound complications
- Accidental intravenous injection of Lipiodol
- Post-lymphography pyrexia
- Progression of lymphedema

Mild or anaphylactic reactions to either the blue dyes or Lipiodol are rare (less than 1%). Life support measures, however, must be available in the procedure room. Delayed reactions within a few hours can also occur. Weg and Harkleroad[43] have detected modest decreases in total lung diffusion and capillary volume after lymphangiography in patients without pre-existing lung disease.

The severity of pulmonary complications is related to pre-existing pulmonary disease and larger volumes (>20 mL) of Lipiodol. Extremely rare cases of hemoptysis, pulmonary infarction, and respiratory distress syndrome have been reported.[44,45] Pulmonary embolization of Lipiodol has been reported by Bron et al.[46] in 55% of patients. However, clinically significant pulmonary complications were observed by Hessel et al.[47] in only 0.4% of patients. If lymphangiography must be performed in patients with pulmonary disease, a single-extremity study using 4–5 mL of Lipiodol can be offered. The overall mortality rate reported by Hessel et al.[47] was 0.01%.

Clouse et al.[48] have described mild to moderate fevers in 5% of patients in their series of 108 procedures. Worsening of the chronic obstructive lymphedema after contrast lymphangiography has also been reported.[33]

62.3.4 Indications for lymphangiography

The current uses of lymphangiography are small in number. Lymphoscintigraphy is our examination of choice for routine evaluation of lymphedema. Contrast lymphangiography is rarely and selectively used for the diagnosis of lymphedema (Figure 62.10a and b).[33] It can be useful in those patients who are candidates for microvascular lymphatic reconstruction or for percutaneous thoracic duct embolization of leaks in patients with chylothorax, chylous ascites, and lymphatic fistula.[49] Direct lymphangiography has been noted to be a therapeutic option for lymphatic leakage in some instances.[50] It is very helpful in the evaluation of patients with lymphangiectasia and reflux of chyle. The details of the extent and location of the dilated ducts are much better delineated with contrast lymphangiography

Figure 62.10 **(a)** Lymphoscintigram of a 43-year-old woman with left lower extremity lymphedema following hysterectomy and bilateral iliac node dissection for cervical cancer. A dermal pattern is seen on the left with no visualization of the inguinal nodes. Transport was mildly delayed in the clinically asymptomatic right limb. Note the lack of visualization of iliac nodes bilaterally. **(b)** Contrast lymphangiography in the same patient confirms the lymphoscintigraphic findings. Few small lymph vessels and two small nodes are seen only in the thigh. (From Gloviczki P and Wahner HW. *Vascular Surgery*. Philadelphia, PA: W.B. Saunders, 1995, 1899–920.)

than with lymphoscintigraphy (Figure 62.7). Obstruction of the thoracic duct and localization of pelvic, abdominal, or thoracic lymphatic fistulae are best studied by lymphangiography.

62.3.5 Contraindications for lymphangiography

Careful selection of patients and routine precautions are key to the success of this invasive procedure. Patients with a prior history of significant contrast reactions, pulmonary disease, or intracardiac or intrapulmonary shunts should be excluded. Lymphangiography should not be performed in patients undergoing pulmonary radiation therapy. It should not be performed in patients with possible extensive lymphatic obstruction (e.g., bulky pelvic or retroperitoneal adenopathy).

62.4 MAGNETIC RESONANCE LYMPHANGIOGRAPHY

Lymphatic evaluation with MRL is garnering increased interest due to its ability to visualize both lymphatic

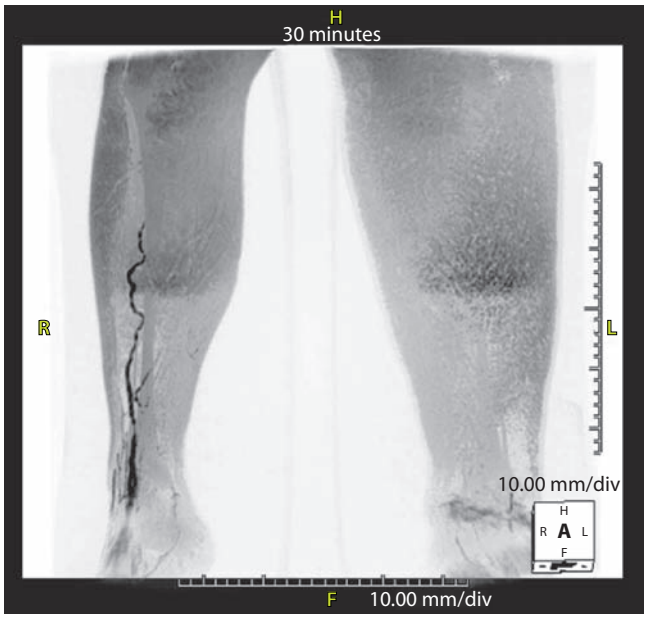

Figure 62.11 Bipedal injection of gadopentetate dimeglumine at 30 minutes. Magnetic resonance imaging shows a swollen edematous left lower extremity with hesitation of contrast at the ankle. Mild ectasia of the right lower extremity lymphatics without obstruction can be seen. Note the faint peripheral outline of veins in the right extremity. Multiple follow-up imaging sessions are required.

channels and lymph nodes. Magnetic resonance has long been used to evaluate the lymph node involvement in malignancies such as prostate, cervical, and breast cancer. MRL with intradermal contrast has the potential to define sentinel nodes and differentiate between metastatic and non-metastatic nodes.[51–53] MRL plays an important role in patients with lymphatic malformations in terms of delineating the extent and exact location of malformation involvement, both for diagnostic and procedure planning purposes. Lymphangiectasia and lymphedema are evolving indications, and MRL is not currently a mainstay of evaluation for these patients.[54–57]

The role of MRL in patients with chylothorax or chylous ascites is in flux and is a source of ongoing investigation. At many institutions, MRL is performed to evaluate the cisterna chyli prior to a planned thoracic duct embolization procedure. We have not found this to be necessary in our experience, as it is expensive and often not predictive of lymphangiography findings. A Japanese study, however, was able to identify the entire thoracic duct in 72% of cases by using respiratory gating.[58] Identification of the exact site of leakage on MRL is challenging and not routinely done in our practice. Some investigators have had success identifying leakage from inguinal lymphatics.[59]

The MRL technique depends on the indication and body part being imaged. Most investigators report using 3D gradient echo and T2 sequences. Intradermal contrast injection can be used to visualize lymphatic channels and evaluate patterns of enhancement in lymph nodes and the kinetics of lymph flow.[58,60] Using both axial and off-axial evaluation of lymphatic channels in conjunction with magnetic resonance venography can help differentiate lymphatics from veins (Figure 62.11).[61]

62.5 CONCLUSIONS

Lymphoscintigraphy has become the test of choice in patients with suspected lymphedema. Since lymphoscintigraphy is noninvasive and well tolerated, it can be repeated serially to follow the clinical course of patients with lymphatic dysfunction. Newer lymphoscintigraphy imaging techniques and equipment can provide sufficient anatomic information for direct surgical intervention on the lymphatic system, especially for directing sentinel node biopsy. The authors rely largely on qualitative interpretation of scintigraphic images. A simple scoring system to derive a lymphatic transport index can be employed to compare scintigraphic studies and to document responses to treatment.

Contrast lymphangiography should be used very selectively in patients with lymphedema. However, it does provide useful information in the evaluation of patients with lymphangiectasia or abdominal or thoracic lymphatic fistulae, or in patients with anomalies of the thoracic duct.

Guidelines 6.2.0 of the American Venous Forum on lymphoscintigraphy and lymphangiography

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
6.2.1	We recommend lymphoscintigraphy and not contrast lymphangiography for the initial evaluation of patients with lymphedema.	1	B
6.2.2	We recommend lymphoscintigraphy, using visual interpretation of the images with a semi-quantitative scoring index, to document response to the treatment of lymphedema.	2	B

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● = Seminal primary article
★ = Key review paper
◆ = First formal publication of a management guideline

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63

Lymphedema: Physical and medical therapy

STEVEN M. DEAN

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63.1 INTRODUCTION

Within the introduction of the 2013 Consensus Document of the International Society of Lymphology, an enlightening encapsulating statement regarding lymphedema therapy exists: "Most members are frustrated by the reality that *no* treatment method has really undergone a satisfactory meta-analysis" (let alone rigorous, randomized, stratified, long-term, controlled study).[1] Unfortunately, the quality of lymphedema therapy studies is relatively poor from a design, reporting, and systematic review standpoint. For example, a dearth of double-blinded therapy trials exists in which blinding patients or the persons administering their compressive-based therapy is obviously difficult to impossible. Moreover, many studies have failed to document whether outcome assessors were blinded. Even in observational lymphedema treatment studies, a significant quality issue is a failure of addressing the comparability of the exposed and unexposed groups in the design or analysis. Many trials are suspect due to sample sizes. As a result, a *definitive* consensus addressing which patients benefit from which therapy is absent and underlies the varying treatment guidelines. Thus, an understandable degree of discontent and skepticism exists within the health care field regarding the management of lymphedema. Despite these trial inadequacies, more than 160 mainstream publications are available to assist in formulating a set of general recommendations for the treatment of the patient with lymphedema. It should be recognized that the preponderance of studies that address the treatment of secondary lymphedema are related to breast cancer. Regrettably, relatively few studies have evaluated the clinical effectiveness and potential side effects of treatments for cancer or other secondary types of lower limb lymphedema.

Unfortunately, lymphedema is not curable and can be associated with significant morbidity, including chronic disability related to its functional, cosmetic, and emotional consequences. However, it can be improved by early identification and instituting prompt treatment. Without therapy, lymphedema will inevitably progress and disabling complications, such as irreversible scleroindurative pachydermitis, may ensue and inhibit activities of daily living.[2] The benefit of the early diagnosis and treatment of breast cancer-associated lymphedema was confirmed in a case–control study of 196 subjects. By incorporating pre- and post-operative limb volume measurements, early compression therapy was associated with objectively documented and sustained volume reductions in the setting of subclinical upper extremity lymphedema.[3]

The primary goals of lymphedema therapy include reducing limb girth, alleviating symptoms, and preventing progression. Secondary goals include reducing the risk of infection, decreasing physical disability and psychological sequelae, and stimulating the development of collateral lymph drainage pathways.

The non-operative therapy of lymphedema can be divided into three distinct modalities: (1) physiotherapeutic techniques provide the foundation for lymphedema therapy, which is often initially instituted in the setting of a specific lymphedema program under the auspices of specially trained lymphedema therapists; (2) various pharmacotherapies can provide adjunctive benefit in a chronic lymphedema management program; and lastly (3) minimization of risk factors and preventative measures (primary and secondary) are increasingly recognized components of multimodality lymphedema therapy.

63.2 PHYSIOTHERAPY TECHNIQUES

Varying combinations of manual therapy are the predominantly utilized interventions to treat both primary and

secondary lymphedema. Novel compression devices that actively treat lymphedema as well as maintain reduced limb volumes are continually being developed.

63.2.1 Complex decongestive therapy (complex lymphedema therapy)

A multifaceted management approach termed complex decongestive therapy (CDT) is considered the international therapeutic "gold standard" for lymphedema by many societies and lymphedema experts.[1,4–7] By incorporating an empirically derived integral lymphatic massage known as manual lymphatic drainage (MLD) with compression bandaging and exercises, CDT decreases and controls swelling in the lymphedematous limb and restores its function. In addition to removing excess interstitial fluid from the limb, CDT softens associated fibrotic induration and mobilizes excess protein as well. The MLD component of CDT is purported to redirect and enhance the flow of lymph through the uninvolved initial cutaneous lymphatics, as well as to augment the dilation and contractility of the larger lymphatic conduits. Initial gentle massage of the contralateral (healthy) trunk and limb creates a watershed pathway for lymphatic flow from the subsequently manipulated affected extremity. The massage begins at the base of the lymphedematous limb and progresses to the distal segment. Figure 63.1 provides an excellent illustration of the correct sequence of truncal–limb MLD.[6] Table 63.1 lists the components of the two-phase CDT program composed of a treatment phase (phase I) followed by a maintenance phase (phase II).

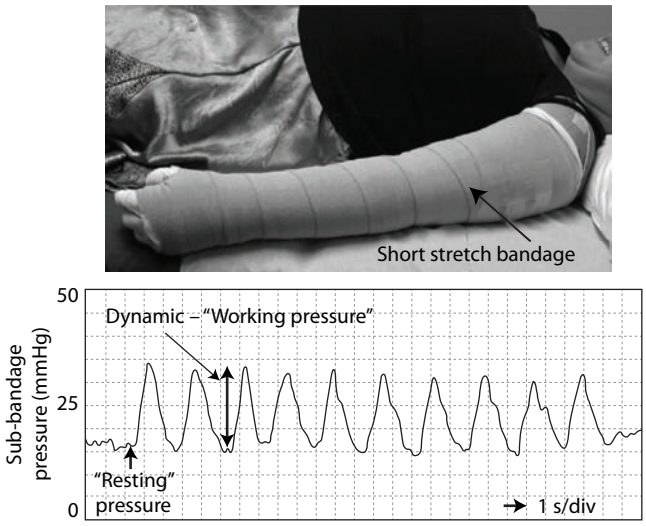

Figure 63.1 Short-stretch compression bandaging as a component of lymphedema care. Short-stretch compression bandaging serves to sustain the reduced volume, and also acts as an external inelastic covering that facilitates lymph movement via the dynamic pressures developed during limb movements and muscle contractions. The "working pressure" that is the stimulus for lymph propulsion is the difference between the peak dynamic pressure and the "resting pressure" when the muscle is relaxed. In this example, the patient is squeezing a rubber ball at a rate of about once every 2.5 seconds while the sub-bandage pressure is recorded. (Reprinted with permission from Mayrovitz HN. *Lymphat Res Biol* 2009;7(2):101–8.)

Table 63.1 Components of a two-phase complex decongestive therapy program composed of a treatment phase (phase I) followed by a maintenance phase (phase II)

Phase I (reduction)—treatment is provided in an office or clinic setting two to five times per week over a 2–4-week time interval and consists of the following components:

1. Meticulous skin and nail care
2. Manual lymphatic drainage for 30–60 minutes
3. Multilayer, short-stretch (low-stretch) compression bandaging with foam or layers of fabric padding of the involved limbs
4. Lymphedema directed exercises to assist lymph movement
5. Gradient compression garments to maintain the reduced limb volume

Phase II (maintenance)—treatment is focused on maintaining and optimizing the results achieved in the reduction phase. The patient and/or their caregivers assume responsibility for the long-term daily home-based treatment.

The efficacy of CDT was supported by a contemporary comprehensive review of nine primary research articles and five systematic reviews published from 2009 to 2014 in which the authors gave this modality the highest evidence for best clinical practice.[4] Limb volume reductions from a low of 3% to a high of 66% were documented in a 2015 lymphedema literature review that included seven studies on CDT.[8] Both upper and lower extremity lymphedema responds to CDT, as evidenced by a study involving 299 patients where average volume reductions of 59% and 68% were observed in the upper and lower extremities, respectively.[9] CDT yields the greatest volume reduction within the first 5 days of its initiation, with improvement continuing at a lesser degree in the next several weeks until progress plateaus. Although this manifold technique appears effective at decreasing lymphedema, the comparative roles of the individual components of CDT and the features that influence its effectiveness are not yet definitively understood.

A legitimate criticism of CDT is that it is physically demanding, inconvenient, potentially uncomfortable, and time consuming, especially the MLD and compression bandaging components. Consequently, effective and compliant long-term maintenance of phase II (self-care) CDT is challenging. For example, a study of 299 patients with upper or lower extremity lymphedema illustrated that at least 90% of the volume decrement was maintained over a 9-month period when patients were compliant with phase II CDT. However, non-compliant patients lost 33% of their initial reduction.[9]

Several relative contraindications to participating in CDT exist that are primarily related to the MLD component. These include moderate to severe heart failure, active cellulitis, active cancer, and acute deep venous thrombosis. However, these exclusions are primarily based upon theoretical concerns, and a paucity of supportive data exists to support them. For instance, a retrospective comparison of secondary lymphedema patients with and without locoregional cancer documented that a safe and effective limb volume reduction was possible in both groups with CDT.[10] However, it did take longer to achieve a volume reduction in the presence of locoregional cancer. The authors concluded, "Manipulative therapy of lymphedema (LE) should not be withheld because of persistent or recurrent disease in the draining anatomic bed." No study has unequivocally demonstrated that the MLD component of CDT disseminates and accelerates active cancer.

63.2.2 MLD unbundled

The technique and salutary effects of MLD have been described above. Although MLD was not envisioned to be a standalone therapy for lymphedema, it has been investigated in this setting. In a recent randomized trial of 67 women who underwent breast cancer surgery, subjects were assigned to either a 6-month course of MLD (initiated on post-operative day 2) or no MLD.[11] At 6-month follow-up, no increase in arm volume transpired in the treated women. However, the untreated cohort experienced significant increases in limb volume ($P = 0.0033$). Didem et al. conducted a randomized trial involving post-surgical upper extremity lymphedema where the intervention cohort ($n = 27$) received standard CDT (including MLD) and the control group ($n = 26$) had standard therapy without MLD.[12] An arm volume reduction of 36% occurred in the control group without MLD, whereas a 56% volume reduction was achieved in the standard CDT (with MLD) group ($P < 0.05$).

In contrast, a randomized study of 42 women with mild or early-onset breast surgery-related lymphedema identified that MLD did not yield a further volume reduction when compared to compression alone.[13] In a comprehensive review article, Leal et al. documented that MLD is *not* an effective standalone therapy for lymphedema, as compression bandaging is required in combination with MLD to attain optimal volume reduction.[14] These discordant results probably reflect study protocols that differed in how lymphedema was defined, measured, and treated.

Lastly, a 2015 Cochrane database review on MLD for breast cancer lymphedema concluded that the modality is safe and *may* offer additional benefit to compression bandaging for volume reduction.[15] Subgroup analyses showed that subjects with mild to moderate breast cancer related lymphedema (BCRL) were better responders to MLD than were moderate to severe participants. Results were contradictory for range of motion and inconclusive for quality of life.

63.2.3 Compression bandaging

In addition to MLD, CDT incorporates the application of external compression in the initial management of lymphedema via repetitively applied short-stretch (or low-stretch) bandages and padding material. Consequently, a multilayered compartment is created that applies pressure during muscular contraction that enhances lymphatic contractility and flow (Figure 63.2). Additionally, a reduction in the pathological increased ultrafiltration ultimately improves fluid reabsorption. Variable pressure can be created by inserting different-strength foam pads in order to selectively apply pressure in more dysfunctional regions. During intensive reduction periods, the wraps are placed after MLD and are donned constantly, except for during bathing. Note that traditional long-stretch (or high-stretch) elastic bandages are not utilized. With daily intensive phase I CDT, limb volume reduction will ultimately reach a nadir. Consequently, the maintenance phase of therapy begins where the patient is fitted with an elastic or inelastic compression garment to use during waking hours. Some patients will need nocturnal compression as well. Compression garments must be properly fitted and ideally replaced every 3–6 months.

The effectiveness of multilayered short-stretch bandaging was confirmed in a randomized controlled trial of 54 upper and 29 lower extremity lymphedema patients.[16] Over a 24-week period, subjects were randomized to either multilayered bandaging followed by compression garments

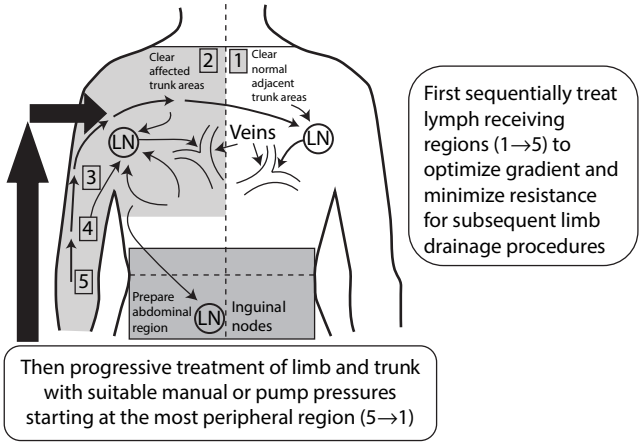

Figure 63.2 Schematized depiction of effective truncal–limb treatment. Normal flow pathways are reduced or absent. Truncal clearance reduces truncal tissue pressure and pressures within lymphatic vessels linking nodes to the venous system in ipsilateral and contralateral quadrants and augments normal lymphatic vessel pumping actions prior to attempting limb drainage therapy. Treatment-related lymph flow is thus optimized. The numbers show the sequential order in which applied therapeutic decongestion or clearance is most appropriate and effective. The main emphasis is on preparing the truncal regions prior to treating the affected limb. LN: lymph node. (Reprinted with permission from Mayrovitz HN. *Lymphat Res Biol* 2009;7(2):101–8.)

versus compression garments alone. The multilayered short-stretch bandaging and compression garment regimen was twice as effective at reducing volume as compared to standalone compression garment use. An experimental, controlled comparative study of 29 patients investigated the loss of pressure and volume under short-stretch bandages applied to normal and lymphedematous lower extremities. A volume decrease within the lymphedematous legs was observed in the following 24 hours after application of a new bandage (–290 mL). The volume reduction was associated with a significant loss of bandage pressure from initial values of over 60 mmHg by 37% and 48% in normal and lymphedematous limbs, respectively.[17]

63.2.4 Elastic compression garments

Elastic compression garment utilization provides the foundation of the maintenance phase (phase II) of lymphedema management. Strict compliance with daily compression stockings is the key to maintaining limb size and volume. Measured elastic two-way stretch compression garments are constructed in a graduated fashion whereby greater pressures are generated distally than proximally, which promotes fluid mobilization. In addition to improving lymphovenous flow, compression garments act as a skin protector and are most commonly worn during daytime hours only.

Compression stockings and sleeves are available in progressive compression classes that provide anywhere from 20–30 to 50–60 mmHg of pressure. Although 30–40 mmHg and rarely 50–60 mmHg of pressure are recommended for advanced lower extremity fibrotic lymphedema, patient comorbid diseases (e.g., morbid obesity, arthritis, or neurological impairment) with attendant lack of dexterity may obviate donning and doffing of these tight stockings; thus, a lighter-compression (20–30 mmHg) garment may provide a less effective yet viable compromise. A pressure of only 20–30 mmHg is typically adequate for upper extremity lymphedema.

Although most patients can undergo fitting with a prefabricated garment, a custom-made stocking may be required for the difficult-to-fit patient with severe, misshapen lymphedema. Multiple manufacturers exist that can provide these garments with a variety of pressures, as well as differing color and fabric options. Ideally, these stockings should be replaced every 3–6 months or when they become ill-fitting.

63.2.5 Non-elastic compression devices

Obesity, physical impairments, poor manual dexterity, discomfort, and/or time constraints are often cited explanations for poor adherence with multilayered wraps or gradient compression stockings and sleeves.[18] Alternatively, the contorted shape of a large, lobular lymphedematous lower extremity can obviate correct fitting with a gradient compression stocking. In such scenarios, Velcro-secured inelastic gradient compression devices that are adjustable and allow variable, tailored compression at multiple levels are an option for maintenance therapy. These wraps allow one to change the circumference diameter by up to 20%. For instance, they can be gradually tightened as the limb reduces, thus improving patient outcomes. Additionally, they offer enhanced ease of donning and doffing, as well as greater comfort. Such products include ReadyWraps (Solaris), FarrowWraps (Farrow Medical), Juxta-Fit (CircAid® Medical Products), and CompreFit (BiaCare). Similar products marketed for nocturnal compression include the ReidSleeve (Peninsula Medical), Tribute NightWare garment (Solaris), and JoViPak (BSN Medical) garments. Both patients and their therapists find these compression alternatives to wrapping very helpful in relevant patients. However, high-quality studies that address compliance and efficacy are needed, and reimbursement for these relatively expensive compression devices can be problematic. For instance, Medicare does not cover these wraps for patients without wounds.

63.2.6 Pneumatic compression pumps

Although CDT represents the standard of care for lymphedema, the multimodal components are both labor and time intensive. Additionally, protracted clinic-based phase I or II CDT is very expensive and a finite number of annual insurance-approved visits exists. Moreover, it is unlikely that a patient's or a caregiver's phase II CDT or "self-care" will consistently yield an equivalent volume reduction as that achieved during professionally administered phase I CDT. Thus, a home-based appliance such as a pneumatic compression pump (PCP) can be a valuable adjunct for maintaining the volume reduction achieved from the preceding active treatment phase. Although a PCP involves an initial purchasing cost, its clinical effectiveness may result in enduring reductions in the use of health care services.

The presumed mechanisms of action of PCP include decreasing capillary filtration, reducing venous reflux, mimicking the calf muscle pump with attendant contraction around the peripheral lymphatics, and mobilizing tissue fluid to regions with normal lymphatic function.[19,20] The typical PCP sequentially inflates a series of air-filled chambers in a distal to proximal direction. Three categories of PCPs exist. The first (code 0650) is a simple and rarely used single-chamber device that delivers non-calibrated, non-gradient, static compression to the entire limb. In contrast, the most advanced PCPs (code 0652) are composed of a calibrated gradient compressor that provides adjustable control on at least three outflow ports and is always paired with multi-chambered garments. Thus, treatment can be customized to address individual patient needs. A novel and more advanced PCP includes garments that treat the core body areas (abdomen and/or chest) and use lower pressure profiles and treatment sequences intended to replicate the technique of MLD.[21]

Multiple studies have documented the efficacy of PCPs for successfully treating lymphedema, either alone or as an adjunct to other modalities such as CDT.[21–25] In a detailed contemporary review of lymphedema therapy, the authors

Table 63.2 Contemporary summary of 21 reviews on the effectiveness of various lymphatic physiotherapies

- There is agreement among reviews that complex decongestive therapy (CDT) is effective at reducing lymphatic volume. However, the most effective components of CDT cannot be identified based on the current level of evidence. It appears that ongoing therapy is required to maintain the initial reductions achieved by an intensive period of CDT.
- The documented effect of manual lymphatic drainage (MLD) on lymphedema is inconsistent. MLD seems to be beneficial when used with compression therapy, but the available evidence does not support its use as a standalone treatment.
- Volume reductions have been achieved with the use of pneumatic compression pumps, with greater reductions demonstrated when the use of pumps was combined with other treatments (e.g., MLD or compression garments).
- Significant volume reductions have been demonstrated with compression bandages and garments in combined treatment programs, but the volume-reducing contribution of compression therapy alone is not well understood.

Source: Adapted from Finnane A, Janda M, and Hayes SC. *Am J Phys Med Rehabil* 2015;94(6):483–98.

noted that prior PCP studies have used highly variable pumping parameters, including pressures from 40 to 150 mmHg, treatment durations from 20 minutes to 6 hours/day, and treatment frequencies from one to three times/day applied anywhere from once weekly to daily.[8] Volume reductions of 7%–45% were achieved. The authors concluded that greater volume reductions ensued when PCPs were combined with other therapies such as MLD and/or compression garments. Similar to CDT, the majority of publications on the efficacy of PCPs involved treatment of upper extremity breast cancer-related lymphedema, whereas information on their effectiveness for lower extremity lymphedema is limited. However, the largest prospective study to date ($n = 196$) involving only subjects with lower extremity lymphedema demonstrated significant limb volume reductions with improved quality of life and no adverse effects with the use of an advanced PCP.[26]

Long-standing and largely theoretical concerns exist that PCPs may actually accelerate lymphedema progression to more advanced stages with worsening cutaneous fibrosis, especially in the setting of high pumping pressures. Nonetheless, in a recently published study of 18 patients with unilateral lower extremity lymphedema, a PCP pressure of 100–120 mmHg was applied on a daily basis for 3 years.[20] No complications ensued and the tissue elasticity actually increased with a concurrent reduction in limb volume. Other purported complications ascribed to high-pressure PCPs, such as genital lymphedema or a thigh ring, did not occur.

In a 2014 retrospective analysis of de-identified health claims data (2007–2013), the impact of PCPs on 1065 patients with cancer-related lymphedema was assessed. PCP utilization was correlated with decreases in rates of hospitalizations (from 45% to 32%, $P < 0.0001$), outpatient hospital visits (from 95% to 90%, $P < 0.0001$), cellulitis diagnoses (from 28% to 22%, $P = 0.003$), and physical therapy use (from 50% to 41%, $P < 0.0001$). The average baseline health care costs were high ($53,422), but significantly diminished in the year after PCP attainment (–$11,833, $P < 0.0001$).[27]

Future research is needed in order to definitively clarify the optimal PCP pressure, frequency, duration, and most effective device.

Table 63.2 is an up-to-date summary of the effectiveness of various physiotherapy modalities.[8]

63.3 PHARMACOTHERAPY

To date, there are no *curative* pharmacologic interventions for lymphedema, and use of medications is controversial. Nonetheless, several classes of drugs may yield some benefit.

63.3.1 Diuretic management

Diuretic therapy was formerly included in treatment program regimens,[28] but is not recommended in more recent literature.[29] It has been suggested that long-term diuretics are potentially injurious because the transfer of large protein molecules is unaffected by the subsequent fluid reduction; consequently, an increased interstitial protein concentration could osmotically increase additional lymph accumulation.[30] However, no corroborative evidence-based data support this contention. In patients with concurrent increased hydrostatic pressure from the post-thrombotic syndrome or "phlebolymphedema," low-dose thiazide diuresis may play a beneficial adjunctive role in lymphedema management.[5] Regardless, high-dose diuretic therapy is unlikely to reduce the swelling of significantly fibrotic lymphedema. Long-term diuresis in the setting of chronic lymphedema is appropriate when prescribed for a concurrent medical condition (hypertension, chronic heart failure, cirrhosis, etc.).

63.3.2 Benzopyrones

A warfarin-like α-benzopyrone (coumarin/5,6-benzo-[α]-pyrone) with proteolytic and vasoconstrictive properties was initially reported to reduce lymphedema by degrading elevated proteins.[31] Conversely, a well-designed and larger crossover study of 140 women documented no difference between coumarin (200 mg twice daily) and placebo in the endpoints of arm volume reduction and symptom relief at 6 and 12 months.[32] Moreover, serological evidence of hepatotoxicity was found in 6% of patients who received coumarin. Although the drug has not been

approved for use in the United States. and is banned in Australia and France, reviews of this botanical are continuously published.

Two groups of γ-benzopyrones exist, known as flavonoids and flavones. Flavonoids are plant pigments that are believed to enhance lymph motoricity, whereas flavones act as capillary stabilizers to decrease macromolecule leakage. Contemporary evidence does not support the use of γ-benzopyrones (including oxerutin, Daflon and Cyclo 3 Fort) in treating the swelling or discomfort associated with lymphedema because of the poor quality of representative trials.[33]

In a trial of healthy volunteers, patients underwent baseline upper extremity lymphoscintigraphy and then used a combination of horse chestnut seed extract, butcher's broom, and *Ginkgo biloba* (horse chestnut seed complex) twice daily.[34] Follow-up lymphoscintigraphy displayed a significant increase in the percentage of lymphatic drainage activity when baseline and follow-up studies were compared. However, the study was unblended with potential for bias.

Selenium is thought to have beneficial effects that may inhibit soft tissue infection in the setting of lymphedema. Two Cochrane database reviews assessed the efficacy of selenium in reducing recurrent infection in the setting of lymphedema. Because of the quality of the studies and associated lack of conclusive beneficial evidence, using selenium to prevent infection or for volume reduction cannot be recommended.[35,36]

In conclusion, the 2004 Cochrane database review of both α- and γ-benzopyrones determined that the poor quality of representative trials obviated any conclusions about the effectiveness of these medications to reduce limb volume, discomfort, and pain.[35]

63.3.3 Antibiotics for soft tissue infection

Despite meticulous skin care, chronic and/or recurrent limb cellulitis may complicate lymphedema. Furthermore, previous studies have demonstrated positive bacterial isolates in deep tissues, tissue fluid, and lymph from limbs of more than 60% of asymptomatic lymphedema patients.[37] Antibiotic therapy with effective *Streptococcus* A coverage should be promptly administered when local signs and/or systemic manifestations (e.g., prodromes) of acute soft tissue infection occur. Timely treatment of soft tissue infection may minimize additional lymphatic vessel damage. Attendant intertriginous tinea pedis should be aggressively treated as well. Long-term antibiotic prophylaxis with medications such as penicillin or erythromycin have been shown to be effective in patients with recurrent soft tissue infection, such as cellulitis, erysipelas, and/or dermatolymphangioadenitis.[37,38] In one study, patients with lymphedema were randomized to placebo or penicillin.[37] The group receiving penicillin had a statistically lower recurrence rate of dermatolymphangioadenitis ($P < 0.002$) with a decreased prevalence of Gram-positive cocci and Gram-negative bacilli isolates in the deep tissues and lymph of the extremities. No resistance to penicillin and other tested antibiotics developed in isolates from the skin surface, deep tissues, and lymph. A 2014 systematic review and meta-analysis of antibiotic prophylaxis included five randomized controlled trials ($n = 535$), with 260 patients in the intervention arm and 275 in the comparator group.[38] Forty-four patients (8%) receiving antibiotic prophylaxis and 97 patients (18%) in the placebo group had an episode of cellulitis. Antibiotic prophylaxis administered for up to 18 months significantly reduced the number of episodes of recurrent cellulitis, with a risk ratio of 0.46 (95% CI: 0.26–0.79). None of the studies reported severe adverse effects due to the antibiotics. Thus, antibiotic prophylaxis can reduce the rate of recurrent cellulitis. Future research should attempt to categorize the ideal type, dosage, duration, and initiation (after the first, second, or third infection episode) of antibiotics for prophylaxis, as well as identifying which specific patient subtype (lymphedema patient) is most likely to derive benefit.

63.4 MINIMIZATION OF RISK FACTORS AND PREVENTATIVE MEASURES

63.4.1 Obesity

Obesity is a common and underappreciated cause of secondary lower extremity lymphedema in the United States. Although the link between obesity and lower extremity lymphedema has not been well described in the medical literature, a 2008 publication of approximately 15,000 patients from 17 wound centers across the United States documented a staggering 74% prevalence of lymphedema in morbidly obese patients.[39] It is improbable that a dramatic reduction in leg swelling will occur until a morbidly obese patient with lymphedema loses considerable weight. Bariatric surgery may be required. Obtaining properly fitting gradient compression stockings for the large, lobular, and often-distorted lymphedematous extremities of the morbidly obese patient can be challenging. Equally difficult is the application and removal of a gradient compression garment in a patient with large legs and abdominal pannus. Although short-stretch bandages are somewhat easier to apply than compression garments, multiple layers are required in large limbs and they often quickly unravel with minimal activity. Thus, the previously referenced adjustable, inelastic compression devices can be a helpful treatment adjunct in this population. The critical importance of weight reduction in an obese lymphedema patient cannot be overstated.

63.4.2 Chronic venous insufficiency

Lymphedema due to chronic venous insufficiency or "phlebolymphedema" represents another frequent yet grossly underappreciated risk factor for secondary lymphedema. Although it is usually stated that cancer (with

associated surgery) is the dominant cause of secondary lymphedema in Western countries, others have stated that phlebolymphedema is actually the most common secondary cause of lymphedema.[40] There appears to be a particularly morbid relationship between obesity, chronic venous insufficiency, and lymphedema. In a study of 21 patients with stage III lower extremity lymphedema (elephantiasis) with an average body mass index of 55.8, 71% of the patients had concurrent chronic venous insufficiency.[41] Consequently, it is critical for the clinician to recognize that lower extremity phlebolymphedema is common and that, in some cases, a remedial venous procedure(s) may be possible. Correcting superficial axial venous reflux and/or recanalizing chronic iliocaval obstruction may significantly reduce venous hypertension, thus treating associated secondary lymphedema. Equally important is attempting to maintain an ideal body weight in the phlebolymphedema patient in order to reduce combined lymphovenous hypertension and avoid progression to elephantiasis.

63.4.3 Exercise

Although participating in sports and/or exercise has traditionally been discouraged in the patient with lymphedema, contemporary data suggest that both exercise and even modest weight training (both machine and free-weight use) benefit the affected limb, as well as the patient's cardiovascular health.[42–45] For example, benefits and safety were documented in a randomized controlled trial of 141 breast cancer survivors with stable upper extremity lymphedema who underwent a regimen of biweekly progressive weight lifting over 1 year.[44] The percentage of women with an increase of 5% or more in limb swelling was comparable in the weight-lifting group (11%) and the control group (12%). When compared with the controls, the weight-lifting group had greater improvements in severity of lymphedema symptoms ($P = 0.03$) and upper and lower body strength ($P < 0.001$ for both comparisons), as well as a lower incidence of lymphedema exacerbations as objectively assessed by a certified lymphedema specialist (14% vs. 29%, $P = 0.04$). Moreover, there were no serious adverse events related to the intervention.

The National Lymphedema Network (NLN) position paper on exercise and lymphedema recommends that some type of compression garment be worn by patients with confirmed lymphedema during exercise.[7] Additionally, the NLN states that an individualized decision should be made on whether or not to don compression garments during exercise in patients that are only "at risk" for lymphedema. Table 63.3 outlines the NLN's recommended modifications of aerobic and resistance exercise in individuals with lymphedema.

The beneficial effects of exercise in lymphedema include: (1) improving flow of interstitial fluid into the lymphatics; (2) stretching exercises reduce the potential for local fibrosis; (3) aerobic exercises increase sympathetic tone, which subsequently augments smooth muscle contraction within the lymph vessels; and (4) resistive exercises increase the functional capacity of individual muscles, thus increasing the threshold for overuse or fatigue. Exercise programs should be undertaken gradually to allow for progressive increase of muscle and local environmental capacity, so as not to overwhelm the lymphatic vessels that are at risk.

Table 63.3 National Lymphedema Network recommended modifications of aerobic and resistance exercise in individuals with lymphedema

1. Allowing adequate rest intervals between sets
2. Avoiding weights that wrap tightly around an extremity or clothing that causes constriction
3. Wearing compression sleeves or bandages during exercise
4. Maintaining hydration
5. Avoiding extreme heat or overheating
6. Exercising in a circuit that alters the type of exercise and body part within the exercise session

Source: National Lymphedema Network. NLN position paper: Exercise for lymphedema patients. http://www.lymphnet.org/pdfDocs/nlnexercise.pdf (updated November 2013).[7]

63.4.4 Skin care

Regular evaluation of skin integrity is imperative and any observable scaling and/or cracking should be promptly addressed in order to minimize risk for cellulitis or dermatolymphangioadenitis. After washing the affected extremity with soap and water, the skin, while still moist, should be treated with an alcohol-free/bland moisturizer in order to maintain a strong, protective skin barrier. Direct and protracted extreme temperatures on the skin should be avoided, as sunburn can induce an inflammatory response with an associated increase in interstitial lymphedema. Sunscreens should be routinely used when a limb is at risk.

The nails and cuticles should be assiduously inspected and kept in good repair. Ingrown toenails should be quickly treated. Regular self-examinations for tinea pedis are paramount, as this infection affects the majority of patients with severe lymphedema due to the opportunistic environment of moisture trapped between swollen toes. Prompt identification and treatment of tinea pedis can potentially obviate resultant intertriginous fissures and colonization, as both provide a nidus for soft tissue infection.

An electric razor instead of a safety razor, depilatories, or abrasive mitts should be used to remove hair.

63.4.5 Avoid "extremes" (temperature, constriction, exercise, etc.)

A useful tactic in advising a patient with "occult" post-surgical lymphedema who is at risk of developing clinically

manifest lymphedema or one who is at risk of exacerbating established lymphedema is to avoid "extremes." Temperature extremes, whether hot or cold, can increase the lymphatic load.[46] When possible and appropriate, wearing light, loose, non-constricting clothing is recommended in order to dissipate heat, moisture, and perspiration, as well as avoiding compressing of the delicate superficial lymphatic vessels. Exercise overuse may also increase the lymphatic preload, which can lead to worsening swelling in the setting of lymphatic outflow obstruction. The NLN position paper on excessive exercise notes that a "sudden increase in an individual's usual exercise duration or intensity may trigger or worsen lymphedema.[7] It is likely that a program of slowly progressive exercise for the affected body part will decrease the potential for common daily activities to result in overuse." While most activities in moderation are not problematic, it is likely that abrupt or sizeable challenges to the lymphatic system can be associated with the appearance and/or exacerbation of lymphedema.

Table 63.4 Summary of lymphedema risk reduction practices

I. Skin care—avoid trauma/injury to reduce infection risk
- Keep extremity clean and dry.
- Apply moisturizer daily to prevent chapping/chafing of skin.
- Attention to nail care; do not cut cuticles.
- Protect exposed skin with sunscreen and insect repellent.
- Use care with razors to avoid nicks and skin irritation.
- If possible, avoid punctures such as injections and blood draws.
- Wear gloves while doing activities that may cause skin injury (e.g., washing dishes, gardening, working with tools, or using chemicals such as detergent).
- If scratches/punctures to skin occur, wash with soap and water, apply antibiotics, and observe for signs of infection (i.e., redness).
- If rash, itching, redness, pain, increased skin temperature, increased swelling, fever or flu-like symptoms occur, contact your physician immediately for early treatment of possible infection.

II. Activity/lifestyle
- Gradually build up the duration and intensity of any activity or exercise. Review the National Lymphedema Network exercise position paper.
- Take frequent rest periods during activity to allow for limb recovery.
- Monitor the extremity during and after activity for any change in size, shape, tissue, texture, soreness, heaviness, or firmness.
- Maintain optimal weight. Obesity is known to be a major lymphedema risk factor.

III. Avoid limb constriction
- If possible, avoid having blood pressure taken on the at-risk extremity, especially repetitive pumping.
- Wear non-constrictive jewelry and clothing.
- Avoid carrying a heavy bag or purse over the at-risk or lymphedematous extremity.

IV. Compression garments
- Should be well-fitting.
- Support the at-risk limb with a compression garment for strenuous activity (i.e., weight lifting, prolonged standing, and running), except in patients with open wounds or with poor circulation in the at-risk limb.
- Patients with lymphedema should consider wearing a well-fitting compression garment for air travel. The National Lymphedema Network cannot specifically recommend compression garments for prophylaxis in at-risk patients.

V. Extremes of temperature
- Individuals should use common sense and proceed cautiously when using heat therapy. Observe if there is swelling in the at-risk limb or increased swelling in the lymphedematous limb and cease use of heat, such as a hot-tub or sauna.
- Avoid exposure to extreme cold, which can be associated with rebound swelling, or chapping of skin.
- Avoid prolonged (greater than 15 minutes) exposure to heat, particularly hot-tubs and saunas.

VI. Additional practices specific to lower extremity lymphedema
- Avoid prolonged standing, sitting, or crossing legs to reduce stagnation of fluid in the dependent extremity.
- Wear proper, well-fitting footwear and hosiery.
- Support the at-risk limb with a compression garment for strenuous activity, except in patients with open wounds or with poor circulation in the at-risk limb.

Source: National Lymphedema Network. NLN position paper: Summary of lymphedema risk reduction practices http://www.lymphnet.org/pdfDocs/nlnriskreduction_summary.pdf (revised May 2012).

63.4.6 Periodic limb elevation

Simple elevation (especially bed rest) of a lymphedematous limb often reduces swelling, particularly in stage I of lymphedema. If swelling is effectively attenuated by this intervention, the effect should be maintained by wearing appropriate compression garments.

Table 63.4 lists relevant lymphedema risk reduction practices from the NLN.[46] However, the following admonition appears at the end of this paper: "Given that there is little evidence-based literature regarding many of these practices, the majority of the recommendations must at this time be based on the knowledge of pathophysiology and decades of clinical experience by experts in the field."

63.5 SUMMARY

A variety of physical treatments are available to reduce the volume within a lymphedematous extremity. The efficacy of CDT has been supported by numerous randomized controlled trials, yet the relative contributions of the separate modalities that impact its efficacy remain cryptic. Patient compliance is important to maintain the volume loss achieved with phase I CDT. Less robust yet increasingly viable and contemporary data support the clinical utility and cost benefit achieved by the use of PCPs. Recognizing and minimizing lymphedema risk factors such as obesity and chronic venous insufficiency is paramount, and appropriate preventative measures should be undertaken, including

Guidelines 6.3.0 of the American Venous Forum on lymphedema: physical and medical therapy

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
6.3.1	To reduce lymphedema, we recommend multimodal complex decongestive therapy that includes manual lymphatic drainage, multilayer short-stretch bandaging, remedial exercise, skin care, and instruction in long-term management.	1	B
6.3.2	To reduce lymphedema, we recommend short-stretch bandages that remain in place for >22 hours per day.	1	B
6.3.3	To reduce lymphedema, we recommend treatment daily, a minimum of 5 days per week, and for this to continue until normal anatomy or a volumetric plateau is established.	1	B
6.3.4	To reduce lymphedema, we suggest compression pumps in some patients.	2	B
6.3.5	For maintenance of lymphedema, we recommend an appropriately fitting compression garment.	1	A
6.3.6	For maintenance of lymphedema in patients with advanced (stage II and III) disease, we recommend using short-stretch bandages during the night. Alternative compression devices may substitute for short-stretch bandages.	1	B
6.3.7	For remedial exercises, we recommend wearing compression garment or bandages.	1	C
6.3.8	For cellulitis or lymphangitis, we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci. Examples include cephalexin, penicillin, clindamycin, and erythromycin.	1	A
6.3.9	For prophylaxis of cellulitis in patients with more than three episodes of infection, we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci, at full strength for 1 week per month. Examples include cephalexin, penicillin, clindamycin, and erythromycin.	1	A
6.3.10	For patients with lymphedema, we recommend risk factor modifications by decreasing obesity, treating chronic venous insufficiency, and promoting skin care and exercise.	1	C

skin care and exercise. The use of various pharmacotherapies as adjuncts in the lymphedema patient is less defined, but can be considered. Without equivocation, more critically derived long-term and comparative data are needed in order to definitively ascertain what constitutes the most effective noninvasive acute and maintenance treatment for both upper and lower extremity lymphedema at various stages.

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● = Key primary paper
★ = Major review article
◆ = First formal publication of a management guideline

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64

Principles of the surgical treatment of chronic lymphedema

YAZAN AL-AJAM, ANITA T. MOHAN, AND MICHEL SAINT-CYR

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64.1 INTRODUCTION

Congenital or acquired obstructions of lymph vessels or the lymph-conducting elements of lymph nodes result in impaired lymphatic transport. Primary or secondary valvular incompetence also decreases normal lymphatic transport capacity. Protein-rich extracellular fluid accumulates and chronic lymphedema develops when the collateral lymphatic circulation becomes insufficient and when all compensatory mechanisms, including the tissue macrophage activity and drainage through spontaneous lymphovenous anastomoses (LVAs), have been exhausted. When the transport of excess tissue fluid containing lymphocytes, different plasma proteins, immunoglobulins, and cytokines is impaired, chronic inflammatory changes in the subcutaneous tissue and skin also occur.

Physical therapy in the form of decongestive lymphatic therapy—compression garments, intermittent pneumatic compression pumps, and massage therapy—are currently the first line of treatment in patients with chronic lymphedema. A variety of surgical techniques to treat patients with this disabling condition have also been attempted. The large number of individual techniques of physiologic and excisional operations that are practiced worldwide today is testimony to the difficulty of this problem.

Excisional operations remove the excess tissue to decrease the volume of the extremity.[1–3] The basic principles of excisional operations are used during the debulking of excess subcutaneous tissue with the minimally invasive technique of liposuction.[4,5] Physiologic operations (Figure 64.1) have been aimed at restoring lymphatic transport capacity with LVAs, lymphatic grafting, enteromesenteric bridge operations, or vascularized lymph node transfers (VLNTs).[6–26] Lymphatic valvular incompetence has been treated by ligation and excision of retroperitoneal lymphatics, with or without LVAs.[27]

64.2 PRE-OPERATIVE DIAGNOSTIC EVALUATION

Imaging studies are used selectively, depending on the age of the patient, the presentation of the disease, and whether surgical treatment is planned or not. Computed tomography is important to exclude underlying malignancy, and magnetic resonance imaging is used in patients with suspected vascular malformations or soft tissue tumors. Magnetic resonance imaging to confirm the presence of lymphedematous tissue in the subcutaneous space is also helpful. Duplex scanning of leg veins excludes venous occlusion or valvular incompetence. Ultrasound scanning can also be useful in evaluating subcutaneous tissue thickness and to assess response to treatment. Lymphoscintigraphy is used now most frequently as the main diagnostic tool to evaluate the lymphatic system. The study involves interstitial injections of small amounts of radiolabeled antimony trisulfide colloid (technetium 99m-labeled Sb_2S_3 colloid) or human serum albumin into the interdigital space. A dual-headed γ-counter is used to image movement of the colloid throughout the lymphatic system, delineating the anatomy of lymphatic flow. Presence of obstruction, reflux from incompetent valves, and distribution of collaterals are assessed. The semi-quantitative transport index of Kleinhans et al.[18] can be used to document the severity of the edema. The sensitivity of the semi-quantitative interpretation is excellent (92%), with a specificity of close to 100% for the diagnosis of lymphedema. It remains the test of choice in differentiating lymphedema from edema of other origins.

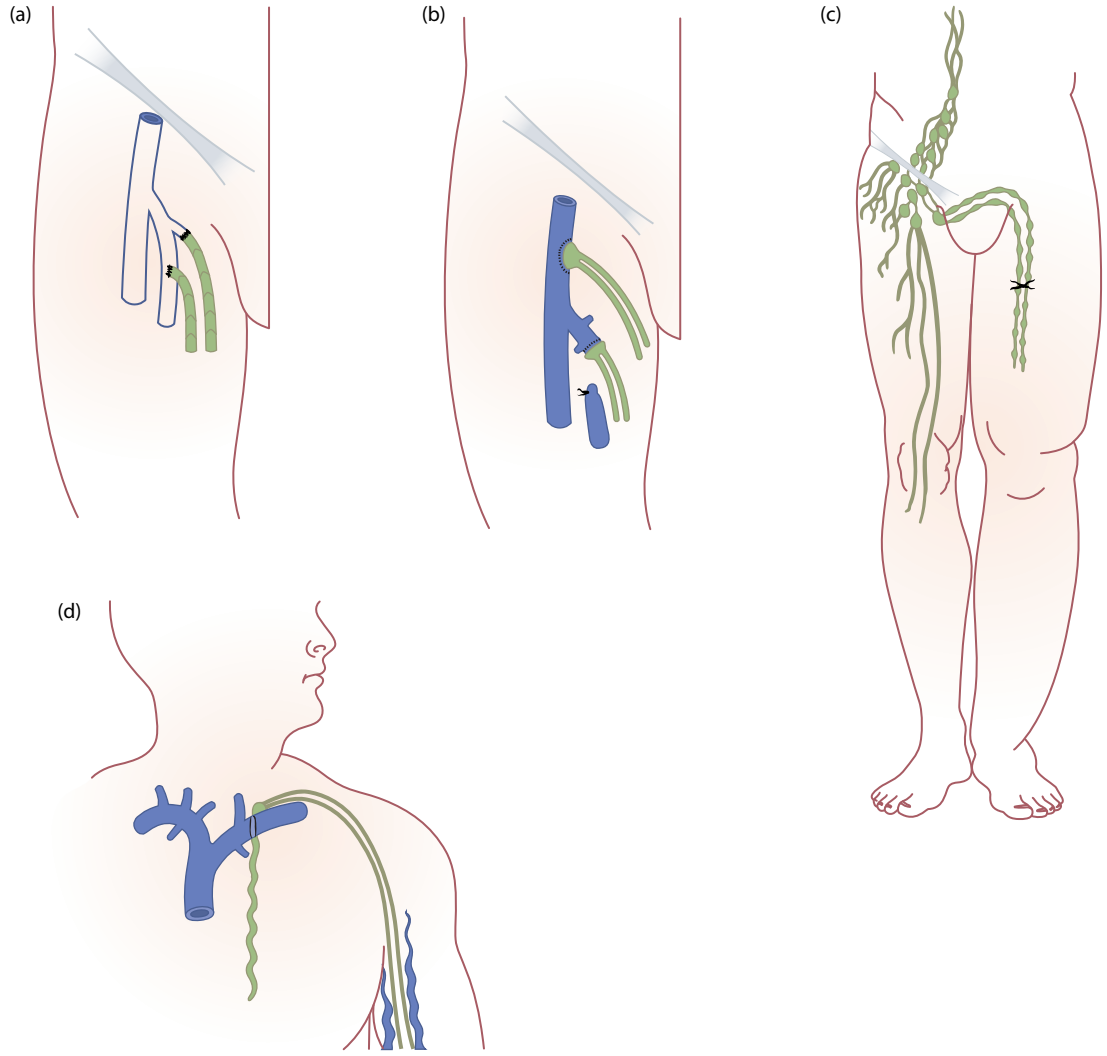

Figure 64.1 Reconstruction for lymphatic obstruction in secondary lymphedema. **(a)** End-to-end and end-to-side lymph node–vein anastomosis. **(b)** End-to-end and end-to-side lymph vessel–vein anastomosis. **(c)** Cross-femoral lymph vessel transposition for secondary lymphedema of the left lower extremity. **(d)** Treatment of post-mastectomy lymphedema with transplantation of two lymph channels from the lower to the upper extremity.

At our institution, lymphatic mapping is performed in the operating room prior to induction but under monitored sedation. Once lymphatic ducts are identified, the general anesthetic can be administered and the lymph node reconstruction procedure can be performed for mapping 0.1–0.2 mL of indocyanine green (ICG) in the webspace immediately prior to lymphatic surgery. Lymphatic ducts are visualized using laser-assisted ICG fluorescence angiography. Visualization takes place immediately post-injection to avoid the "haze" that can obscure accurate visualization of lymphatics. We have found this noninvasive, non-radioactive method of assessing superficial lymphatic function invaluable in identifying lymphatics immediately preoperatively (Figure 64.2). It is possible to identify lymphatic channels and make an assessment of functionality to identify channels that fill up by using the "stroke test" on skin following ICG injection.

64.3 SURGICAL TREATMENT INDICATIONS

Potential indications for surgical intervention are: (1) impaired function and movement of the involved extremity owing to its large size and weight in patients unresponsive to medical management; (2) recurrent episodes of cellulitis and lymphangitis; (3) intractable pain; (4) lymphangiosarcoma; and (5) cosmesis (patient unwilling to undergo more conservative treatment and even willing to proceed with experimental operations). Operations for lymphedema are divided into two major groups: excisional and lymphatic reconstruction.

Controversy as to the exact timing of surgery remains. Improved results are expected when surgery is performed in the early stages of lymphedema, especially in lymphatic reconstruction. However, most patients present with a

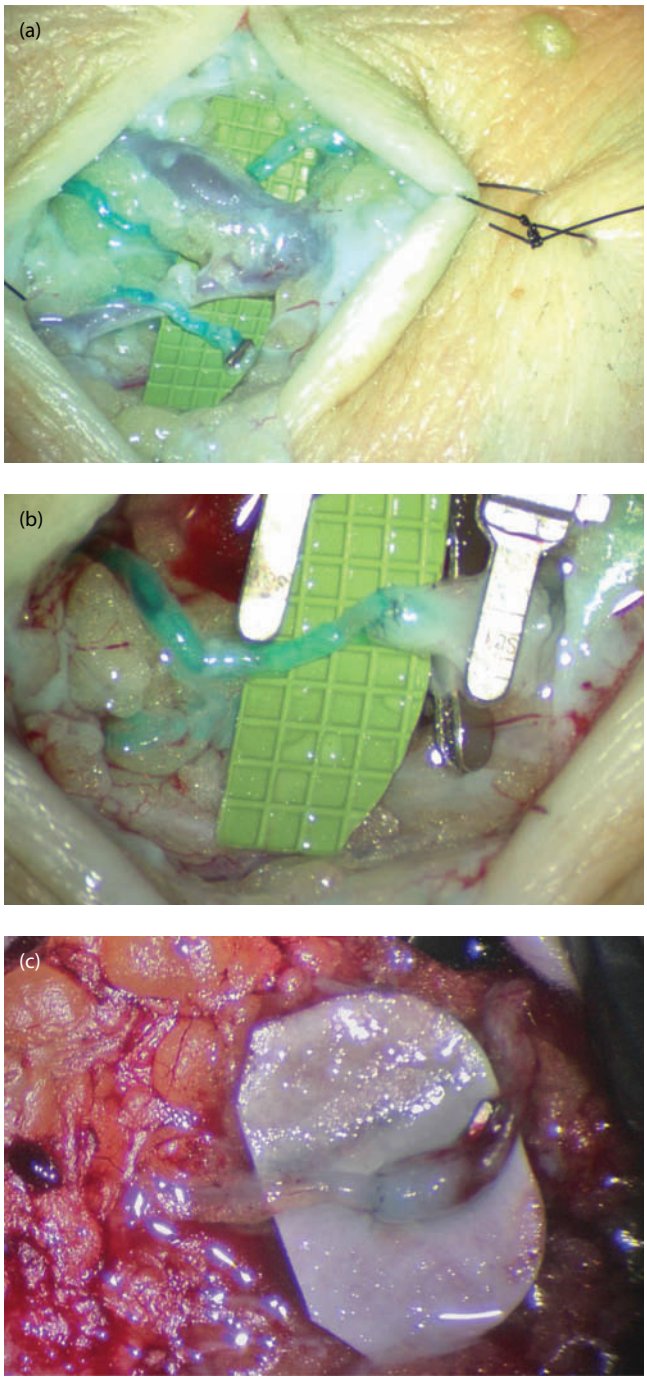

Figure 64.2 Lymphovenous anastomosis performed in the upper extremity. **(a)** Three lymphatic vessels dissected and identification of a superficial vein with a side branch appropriate for anastomosis; **(b)** end-to-end repair of lymphovenous anastomosis; **(c)** second case example demonstrating patent end-to-end lymphovenous anastomosis.

long-standing history, where chronic lymph damage and associated fibrosis significantly reduce the chance of successful lymphatic reconstruction. In such cases, excisional surgery may be more effective. As with all surgical interventions, patient selection is key, and life-long compliance with physical therapy following surgery is critical. Patients should be managed within a multidisciplinary team setting and surgery performed by experienced microsurgeons in specialized centers where such procedures are routinely performed.

64.4 EXCISIONAL OPERATIONS

Excisional procedures usually involve staged removal of the lymphedematous subcutaneous tissue of the leg. If the skin itself is diseased and has to be resected, coverage with skin grafting is necessary. The most radical excisional operation—the Charles procedure—includes total skin and subcutaneous tissue excision of the lower extremity from the tibial tuberosity to the malleoli. The skin grafts are unfortunately difficult to manage with frequent localized sloughing (especially in areas of recurrent cellulitis), excessive scarring, hyperkeratosis, and dermatitis.

The modified Homans operations (Servelle's excisional operation, Miller's staged subcutaneous excision, and Pflug's staged excisional operations) involve localized excision of the fibrosed edematous subcutaneous tissue.[1,2] Moderately thick flaps (1–1.5 cm) are elevated anteriorly and posteriorly to the midsagittal plane in the calf and/or thigh. Excess subcutaneous tissue above the deep fascia together with the overlying redundant skin are excised and the wound is closed, usually in one layer only. Since not all edematous tissue is excised, most of these are palliative procedures and the results are directly related to the amount of subcutaneous tissue excised. The patients are susceptible to recurrences and should continue to wear elastic compression stockings. The results of most of these procedures are good as far as volume reduction is concerned. However, prolonged hospitalization, poor wound healing, long surgical scars, sensory nerve loss, and residual edema of the foot and ankle can be problems. These frequent complications preclude such procedures short of disabling lymphedema not responding to medical measures. Results reported by the group at the University of California, Los Angeles, have been most satisfactory.[1]

Segmental excision of lymphedematous tissue must be performed with attention to preserve adequate blood supply to the skin in order to minimize healing complications. Salgado et al.[3] reported good results in 15 patients treated with debulking surgery combined with microsurgical preservation of perforating skin vessels from the posterior tibial and peroneal arteries. The average overall lymphedema reduction at a mean of 13 months was 52%. There were no cases of wound breakdown or skin flap necrosis. Complications consisted of cellulitis in three patients and seroma and hematoma in one patient.[3] Lee et al. reported a satisfactory response in 28 out of 33 lower limbs at 12-month follow-up. However, only 18 patients with good compliance to continued compression therapy maintained good results at 24 months. Two wound complications occurred: delayed healing and wound infection.[28]

64.5 SUCTION-ASSISTED PROTEIN LIPECTOMY

In long-standing chronic lymphedema, it is the predominance of fat (and not fluid) that results in swelling, which cannot be reduced with physiologic lymphovenous operations, massage, or compression treatment. This forms the rationale behind suction-assisted protein lipectomy (SALP) to reduce limb volume. This is a far less invasive debulking method, carries fewer risks, is quicker to perform than open excision, and is becoming the most commonly performed debulking operation. The procedure is performed under general anesthetic with a surgical tourniquet. Excess proteinaceous fatty tissue is aspirated using a power-assisted liposuction cannula. Granzow et al. reported excellent results, with reductions in volume in four legs of 86% and of 111% in six arms.[25] Brorson and colleagues have advocated this technique and reported on the largest prospective series of SALP: 104 upper limb and 41 lower limb SALPs were followed up for up to 15 years and 8 years, respectively. Mean reduction was greater than 100% in both studies.[29,30] SALP has also been shown to reduce the incidence of severe cellulitis.[25] When performed correctly, SALP is a safe procedure and has been shown not to further damage the lymphatic flow.[4]

SALP has been combined with lymphatic reconstructions, such as LVA,[25] at some centers. At our institution, liposuction is offered in cases where lymphovenous bypass did not work, may not work because of the presence of considerable scarring, and if the patient is not a candidate for lymph node transfer. Following LVA surgery, we wait 6–12 months to determine if there has been no significant improvement, and if the patient has maximized all conservative measures, SALP is considered at that time. The patient must understand the limitations of SALP treatment and, since SALP does not address the underlying cause of the lymphedema, the importance of compliance with compression garments to prevent re-accumulation of excess fluid cannot be overemphasized.

64.6 LYMPHATIC RECONSTRUCTIONS

Developments in microvascular techniques have allowed surgical attempts at direct lymphatic reconstructions, bypassing the level of lymphatic flow obstruction by:

- Directly connecting the lymphatic vessels to the venous system (LVA)
- Interposing vein grafts between lymphatics and the venous system
- Connecting two lymphatic systems together (lymphaticolymphatic anastomosis)
- Importing lymph nodes into the diseased area (VLNTs)

Ideally, such reconstructions should be performed in the early stages of lymphedema, prior to the onset of fatty deposition and fibrosis, and are performed in patients who have proximal obstruction with preserved lymphatics distally. Technically, these operations require supermicrosurgical expertise using high-power magnification as most lymphatics range from 0.1 to 0.6 mm in diameter, and should only be performed by highly experienced microsurgeons in specialized centers.

Efforts to increase lymph transport by implanting a piece of omentum or a segment of ileum (mesenteric bridge operations) into the affected areas in order to promote neolympholymphatic communication have had reported success in small groups of patients.[31–33] Very few surgeons, however, have personal experience with such procedures.

64.6.1 Lymphovenous anastomosis

The rationale for this operation is based on the observation that, in patients with chronic lymphedema, spontaneous LVAs could be demonstrated by lymphangiography. The procedure, first described in the 1970s,[34] involves connecting multiple lymphatic vessels directly to the venous system using microsurgical anastomoses, allowing excess lymph to bypass areas of obstruction or low flow and drain directly into the venous system (Figure 64.3).

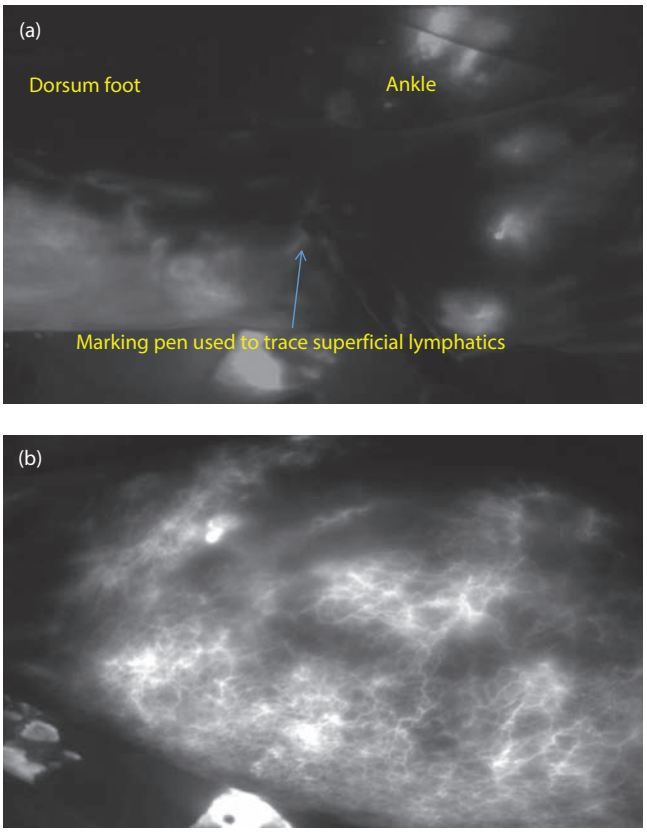

Figure 64.3 Pre-operative laser-assisted indocyanine green (ICG) fluorescence angiography following injection of ICG into the webspaces of the left foot. **(a)** Marking pen used to map and mark out superficial lymphatics and sites for lymphovenous anastomosis. **(b)** Left lower leg demonstrating the plexus of dermal lymphatics following ICG injection and used to identify high-density lymphatic channels and their functionality by stroking the skin and visualizing channels that fill up in the lower leg.

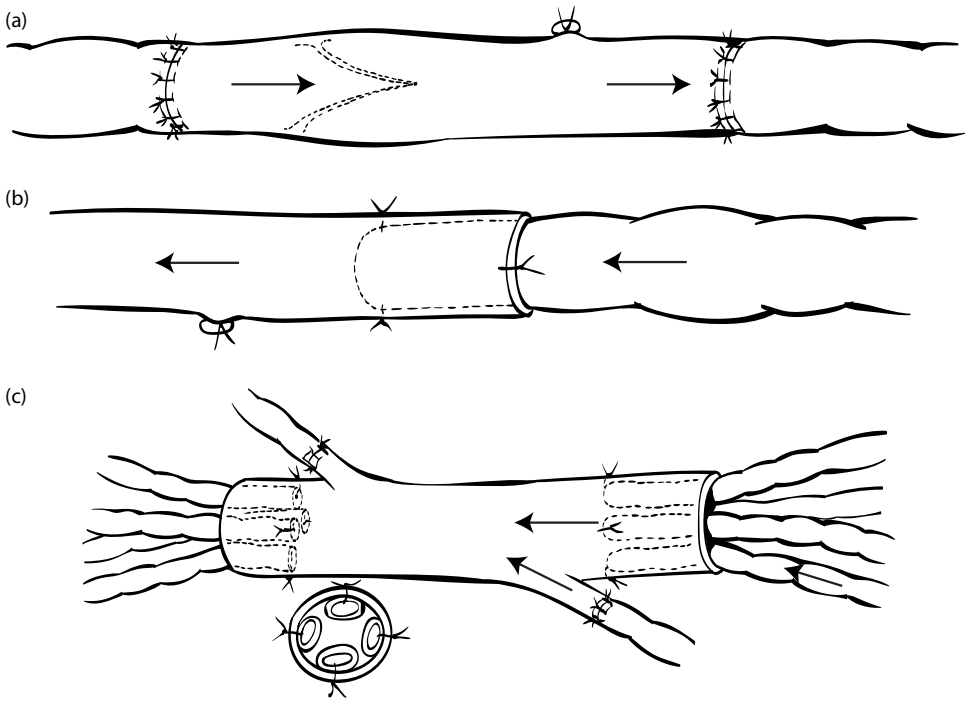

Figure 64.4 Techniques of lymphatic reconstruction according to Campisi et al.[23] with **(a)** interposition vein graft or **(b)** lymphovenous anastomosis. **(c)** Technique of invagination of multiple lymphatics into an interposition vein graft (lymphatic–venous–lymphatic anastomosis). (By permission of the Mayo Foundation.)

Direct reconstructions of the lymphatic system must be initiated early in the course of the lymphedema, prior to the development of subcutaneous fibrosis and lymphatic vessel sclerosis. Venous hypertension is a contraindication due to backflow into the lymphatic system and impaired drainage. In cases of venous disease in which direct LVA cannot be performed, an interposition vein graft can be used to bypass the obstruction and drain directly into a vein (Figure 64.4b) or a vein can be used as a conduit to connect lymphatics above and below the level of obstruction (Figure 64.4a and 64.4b). Valves in veins ensure correct directional flow of lymph. An ideal candidate is a patient with a proximal pelvic lymphatic obstruction with dilated infrainguinal lymph vessels. Lymphatic mapping with ICG is performed as described earlier, and the patient is counseled that if no appropriate lymphatics are found, the procedure will be abandoned. Lymphatic ducts are chosen based on the presence of dynamic lymphatic flow and distal–proximal directionality. Following lymphatic mapping, intradermal injection of 0.1 mL of lymphazurin blue (repeated if necessary) at the level of the webspaces is administered to stain lymphatics and to aid in their identification. Lymphatic ducts are visualized and dissected. In the upper extremity, microsurgical end-to-end anastomoses are performed in subdermal veins; in the leg, they are performed usually between lymph vessels of the superficial medial lymphatic bundle and tributaries of the saphenous or deep femoral vein (Figure 64.3a). These can also be carried out with an invagination of lymph vessels into the saphenous or femoral veins. Anastomoses between groin lymph nodes and adjacent veins can also be performed in an end-to-end fashion with the transected saphenous vein or an end-to-side fashion with the femoral or saphenous veins (Figure 64.3b). Flow of blue-stained lymph into the vein indicates patency of anastomosis (Figure 64.5).

In animal experiments, Gloviczki et al. obtained objective evidence of late patency. Anastomoses using normal femoral lymph vessels and a tributary of the femoral vein in dogs yielded a patency rate of 50% at 3–8 months after

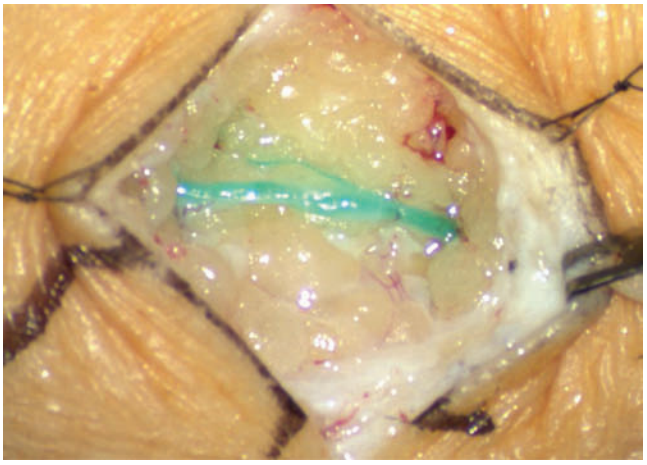

Figure 64.5 Flow of blue-stained lymph into the vein indicates patency of anastomosis; patient received an intradermal injection of lymphazurin blue (0.1 mL) dorsally at the level of the webspaces in the hand after pre-operative mapping with laser-assisted indocyanine green fluorescence angiography before the commencement of surgery.

surgery by cinelymphangiography.[19] The effectiveness of this operation is more difficult to prove in humans, and results have been inconsistent between studies, with no currently available means to study lymph vessel patency. In 14 patients who underwent LVA at the Mayo Clinic, only five limbs maintained the initial improvement at an average of 46 months after surgery.[10] Improvement occurred in four of the seven patients with secondary lymphedema and in only one of seven patients with primary lymphedema. Lymphoscintigraphy can provide only indirect evidence of improved lymph transport and cannot document the patency of the anastomosis. Post-operative lymphangiography would be the only way to confirm anastomosis patency. This is not practical as the procedure is invasive and progression of lymphedema after such studies has been reported.

Experience in large numbers of patients operated on in Australia, Asia, and Europe suggests clinical improvement can be achieved with lymphatic drainage procedures.[7–9,11–16] In the series reported by O'Brien and Shafiroff[6] in Australia, 73% of the patients had subjective improvement and 42% experienced long-term improvement. Chang et al. reported similar findings in a prospective study of 100 patients undergoing LVA (89 upper and 11 lower extremities) with a mean reduction of 42% at 1 year. Lower extremities fared less favorably than upper limbs, although this may be attributable to more advanced disease.[35]

In filariasis, lymphatics are frequently enlarged and lymph flow is high. Lymphovenous reconstructions appear effective in patients with filariasis. Jamal[8] reported success in India in 90% of patients who underwent lymph node venous shunts constructed in the inguinal area.

Campisi and colleagues[11–13,23] in Italy have the largest experience with lymphatic microsurgery. His team reported results in 665 patients with obstructive lymphedema using microsurgical LVA, with subjective improvement in 87% of the patients.[11,12] A total of 446 patients were available for long-term follow-up, and volume reduction was observed in 69% with discontinuation of conservative measures in 85%, and an 87% reduction in the incidence of cellulitis after microsurgery.[13] The authors concluded that microsurgical reconstruction early in the course of lymphedema is more effective, since the intrinsic contractility of the lymphatics is still maintained. Chances of normalization of the lymph circulation are better before significant chronic inflammatory changes in the subcutaneous tissue develop.

Significant improvement at a mean of 3.3 years after LVA was also confirmed in eight out of 13 operated patients by Koshima et al.[15] from Japan. Another group from Japan suggested that LVA can *prevent* the development of lymphedema in patients who undergo pelvic lymphadenectomy for cancer.[16] However, Vignes et al.[17] failed to confirm the therapeutic benefit of LVAs in a group of 13 patients, 10 with primary and three with secondary lymphedema. Global assessment of clinical outcome was very good or good in five patients and intermediate in another five; however, the operation failed to improve the volume of lower limbs and did not reduce the frequency of erysipelas.

64.6.2 Lymphaticolymphatic Bypass

The concept of lymphatic grafting is attractive in that the problems inherent to LVAs (such as venous hypertension causing a reversal of flow into the lymphatic circuit) can be avoided. In addition, the patency of lymphaticolymphatic anastomoses should in theory be better than the patency of a blood-filled system. This technique, pioneered by Baumeister and colleagues,[18,20,21] has been offered to patients with unilateral secondary lymphedema of the lower extremities or to patients with post-mastectomy lymphedema of the arm. It is important to document normal lymphatics in the donor leg with lymphoscintigraphy before considering surgery.

In post-mastectomy lymphedema, autotransplantation of two or three lymph vessels from the major lymphatic bundle from the medial aspect of the thigh to the arm is performed. The distal anastomosis is performed on the proximal arm with epifascial and subfascial lymph vessels in an end-to-end fashion. The proximal anastomosis is best performed in the neck to one of the larger cervical descending lymphatic vessels.

The procedure for lower extremity reconstruction is a transposition of two or three normal lymphatic trunks in the thigh to the diseased limb with a lymphaticolymphatic anastomosis in the groin (cross-femoral grafting). In a report of 55 patients undergoing such procedures, 80% were noted by Baumeister and Siuda[21] to have improvement (volume reduction) after a mean follow-up of 3 years. Objective documentation of flow through the lymphatic graft can be obtained with lymphoscintigraphy. In a recent study from the Mayo group, eight patients with primary or secondary lymphedema of the lower limb were investigated before and for 8 years after autologous lymph vessel transplantation. In all eight patients, lymphatic function, measured by semiquantitative lymphoscintigraphy, significantly ($P < 0.01$) improved after microsurgical treatment.[22]

64.6.3 Vascularized lymph node transfers

Therapeutic transplantation of non-vascularized lymph nodes to areas of lymphedema has been largely experimental, with little clinical experience in humans, and animal studies have been on the whole rather disappointing.[36–38] With advances in supermicrosurgical techniques, research interest has shifted toward the use of VLNTs. This promising novel procedure aims to import vascularized lymph nodes into sites affected by lymphedema. Surgery involves transplanting a vascularized tissue flap containing lymph nodes and surrounding fat from a donor site (superficial inguinal, thorax, supraclavicular, and submental nodes) and microanastomosing the arterial and venous (but not lymphatic) blood supply using microsurgical techniques (Figure 64.6). The exact mechanism of action is subject to debate: one theory claims that lymphangiogenesis occurs, with recanalization of the lymphatic vessels between the transferred lymph node and recipient site.[39] Another theory postulates that the vascularized lymph node acts as a pump,

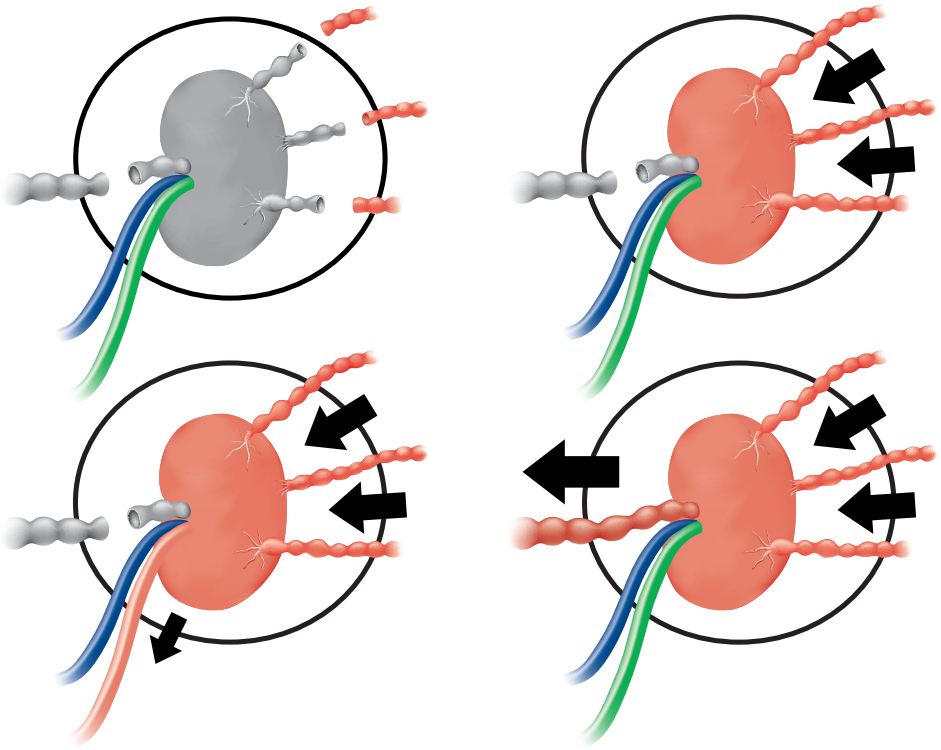

Figure 64.6 Schematic illustration of vascularized lymph node transfer immediately after surgery (top left), recanalization of the lymphatic vessels between the recipient and transferred lymph nodes (top right), and the efferent lymph fluid by means of lymphovenous communication within the node (bottom left) or through the efferent lymphatic vessel from the node (bottom right). (Adapted from Ito R and Suami H. *Plast Reconstr Surg* 2014;134:548–56.)

absorbing lymph fluid from the surrounding tissues and ejecting it into the venous circulation.[40,41]

Depending on which theory is applied, recipient sites can include the dorsum of the lower arm or the distal part of the leg in the "pump" theory, or the axilla and the groin in the lymphangiogenesis model, although a combination of both factors is said to play a part in lymphedema reduction. Studies have shown objective and subjective improvements in symptoms and improvements in skin infections, including erysipelas and lymphangitis, following VLNT.[40–46] In a series of 24 women following breast cancer treatment with upper limb lymphedema and groin to axilla VLNT, Becker et al. showed return to normal girth in 10 patients and improvement in 12 at a mean follow-up of 8.3 years. Five of 16 lymphoscintigraphies performed during the study demonstrated activity in transplanted nodes.[42] Lin and colleagues showed a mean volume reduction of 51% at 56 months in 13 upper extremities, but this time with VLNTs to the wrist instead of the axilla. Lymphoscintigraphy showed more rapid movement of lymph, suggesting improved lymphatic clearance.[40] VLNTs are not without potential complications: Vignes et al. failed to demonstrate volume improvement in 26 patients treated with VLNT and observed a high complication rate (38%), including lymphedema of donor site, lymphocele, and donor site pain.[47] Saaristo et al. combined the harvest of free abdominal tissue for autologous breast reconstruction with inguinal lymph nodes for VLNT as a single procedure. A significant reduction in lymphedema was reported in seven out of nine patients, with three out of nine not needing to wear compression garments or undergo physiotherapy.[48] In some patients, improvement in lymphedema following axillary VLNT was seen in the immediate post-operative period, with similar results reported after autologous flap reconstruction alone.[49] It is postulated in such cases that release of scar tissue at the time of surgery may account for improved lymphatic flow.

A combination of debulking and reconstructive approaches has the potential to address both soft tissue excess and lymphedema. Granzow et al.[25] have combined SAPL with VLNT as a staged procedure in upper limbs, with patients requiring compression only in the evening and at night. They advocate debulking with SAPL to reduce limb volume where lymphedema is long-standing, followed by VLNT (favored in upper limbs) or LVA, a combination they now offer at their institution.

In a systematic meta-analysis of the efficacy and safety of 27 studies of 22 lymphovenous procedures versus five VLNTs, Basta and colleagues[50] reported comparable results in terms of quantitative and subjective improvements between the techniques, with higher complication rates reported in VLNT. However, the authors acknowledged the heterogeneity of the patient population, assessment modalities, and inconsistent reporting of complications as major limiting factors.

The myriad of surgical procedures described highlights the difficulty in treating this chronic condition. Heterogeneity in study design and outcome measures, duration of follow-up, and reporting of complications make it difficult to draw comparisons and conclusions about the various treatment options. Long-term patency rates associated with documented clinical improvement need to be reported in larger numbers of patients who are operated on in more than one center before recommendations for routine surgical treatments, or combinations of treatments, can be made.

Guidelines 6.4.0 of the American Venous Forum on the principles of the surgical treatment of chronic lymphedema

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
6.4.1	All interventions for chronic lymphedema should be preceded by at least 6 months of non-operative compression treatment.	1	C
6.4.2	We suggest excisional operations or liposuction only to patients with late-stage non-pitting lymphedema who fail conservative measures.	2	C
6.4.3	We suggest microsurgical lymphatic reconstructions in centers of excellence for selected patients with secondary lymphedema if performed early in the course of the disease.	2	C

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● = Key primary paper
★ = Major review article

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65

Medical and open surgical management of chylous disorders

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65.1 INTRODUCTION

Chylous disorders develop because of abnormal circulation of chyle, the lipid- and protein-rich lymph fluid collected by the mesenteric lymphatic system. They are uncommon but serious and frequently life-threatening conditions. Primary developmental abnormalities of the lymph vessels (lymphangiectasia, atresia, or hypoplasia)[1] or secondary causes (iatrogenic injury, surgery, trauma, or tumor)[2,3] lead to the accumulation of chyle in the body cavities, and disruption of the lymphatics causes chylous effusions such as chylothorax, chylous ascites, chyloperitoneum, or chylopericardium. Chylous reflux is the term used to describe retrograde flow in the incompetent lymphatic system secondary to lymphangiectasia and loss of lymphatic valve function. In this chapter, we will focus on the medical, open surgical, and endovascular treatment of chylous disorders; lymphedema is discussed in Chapters 61–64. Since these conditions occur rarely, the literature is sparse and consists of case reports and observational series.

65.2 INCIDENCE

The incidence of chylous effusions is not well defined due to the rarity of the disease. A German prospective nationwide epidemiological study reported an incidence of 1:24,000 for congenital chylothorax.[4] However, the majority of the quoted incidences are from retrospective observational studies. Post-operative chylous ascites developed in 1.1% of 1103 cancer patients undergoing abdominal surgery; the incidence increased to 7.4% when retroperitoneal, esophageal, gastric, or cytoreductive surgeries were performed. Among patients undergoing surgery for gynecologic malignancies, post-operative chylous ascites occurred in 0.17%–2.0%.[5] The incidence of chylous effusions after laparoscopic lymphadenectomy was 0.9%. Para-aortic lymphadenectomy carries an increased risk of developing chylous ascites compared with pelvic lymphadenectomy (0.32% vs. 0.08% and 4.08% vs. 0.35%); the median number of removed para-aortic lymph nodes was higher in patients with chylous ascites than in those who do not have this complication (26 vs. 17, $P = 0.001$).

The incidence of post-operative chylothorax was 0.42% among 11,315 patients undergoing general thoracic surgical procedures at the Mayo Clinic[6]; it was 1.4% in 2838 patients operated on by Dr. Cerfolio after pulmonary resection and complete thoracic mediastinal lymph node dissection.[7] In patients with primary lung cancer, chylothorax developed in 2.3% (37/1580) of patients after lobectomy or greater resection with simultaneous systematic mediastinal lymph node dissection. Several studies focused on post-esophagectomy chylothorax, with a quoted incidence of less than 4.0%. The reported incidence of chyle leak after neck dissection varies from 0.6% to 6.2%.

65.3 ETIOLOGY

Primary chylous disorders are fortunately rare and they are usually caused by congenital lymphangiectasia.[1,2,8] The pathogenesis of these disorders is poorly understood. Molecular studies suggest members of the vascular endothelial growth factor (VEGF) and angiopoietin

families collaborate during lymphatic development and that the absence of angiopoietin 2 may result in chylous disorders[9]; mutations in the VEGF-C/VEGFR-3 axis are a central mechanism in the etiopathogenesis of inherited lymphedema.[10] Lymphatic dilatation (megalymphatics) may develop without proximal occlusion, although associated agenesis or obstruction of the thoracic duct (TD) has also been documented.[11,12]

Mayo Clinic data showed that among 35 patients with primary chylous disorders treated between 1976 and 2000, the etiology was primary lymphangiectasia in 66%, yellow nail syndrome in 11%, lymphangioleiomyomatosis in 9%, and other etiologies in 18%[13]; when including a group of 24 patients treated surgically between 1988 and 2015, primary lymphangiectasia was seen in 58% of patients, and the etiology was secondary in 42% of patients due to surgery (50%) or underlying disease (50%).[14] Malignancies invading the TD or lymphatic system in the thoracic or abdominal course, such as lymphoma or esophageal or lung cancer, can be associated with chylous effusions, with or without surgical resection. Lymphangioleiomyomatosis, a slowly progressive systemic disease characterized by smooth muscle cell infiltration of the lung and lymphatics, can also cause chylous effusions.

Browse et al.[15] identified three possible mechanisms of ascites formation: (1) congenital lymphangiectasia caused by congenital valvular incompetence and dilatation of the mesenteric or retroperitoneal lymphatics, or both; (2) congenital obstruction or agenesis of the TD; and (3) obstruction localized to mesenteric lymph nodes and vessels. Surgery-related chylous ascites occurs after extensive retroperitoneal lymph node dissection, abdominal surgery, or abdominal aortic surgery. Other causes include tuberculosis, nephrotic syndrome, cirrhosis, malignancies, or radiotherapy. Blunt abdominal trauma can cause chylous ascites due to rupture of the lymphatic vessels.

The etiology of a chylous pleural effusion can be spontaneous or traumatic. A spontaneous chylothorax may be congenital, infectious, neoplastic, or due to other conditions such as lymphangioleiomyomatosis, superior vena cava thrombosis, sarcoidosis, amyloidosis, and cirrhosis, and can cause obstruction of the TD or lymphatic disruption. For congenital chylothorax, integrin α9 missense mutation, as well as immune response and lymphangiogenesis, have been implicated, especially in in the pathogenesis of fetal chylothorax.[16] Chylothorax may also result from lymphangiectasia with or without TD obstruction (Figure 65.1).

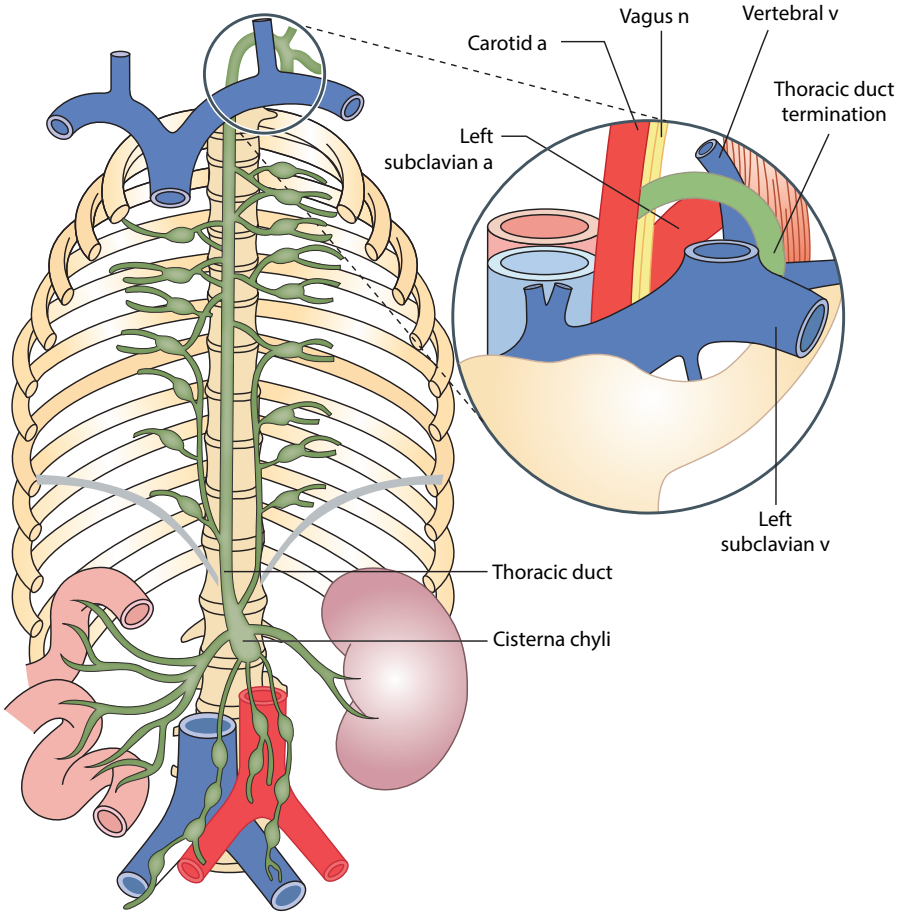

Figure 65.1 Cervical and thoracoabdominal anatomy of the thoracic duct. (Reprinted from *Rutherford's Vascular Surgery*, 6th Ed, Gloviczki P and Noel AA, Surgical treatment of chronic lymphedema and primary chylous disorders, 2428–45, Copyright 2005, with permission from Elsevier.)

Infectious causes include tuberculosis lymphadenosis, mediastinitis and ascending lymphangitis. Currently, the most common causes of traumatic chylothorax are surgery and tumors. Idiopathic causes of chylothorax include Down's syndrome and Noonan's syndrome; however, the mechanisms are unclear. Bilateral chylothoraces are more common in yellow nail syndrome. Chylous ascites can also cross the diaphragm and accumulate in the pleural space, causing chylothorax.

65.4 PRESENTATION

Symptoms of chylous effusions relate to fluid accumulation. The typical sign of lymphangiectasia and chylous reflux is, however, leakage of milky fluid due to disruption of the dilated lymphatics. Rupture of the distended lymph vessels or lymphatic cysts may manifest in protein-losing enteropathy (malabsorption associated with chyle leaking into the lumen of the bowel),[8,11] chylous ascites,[17] chylothorax,[2,18] chyloptysis (chyle in the sputum due to reflux into the lungs and tracheobronchial tree),[19] chyluria, chylometrorrhagia, or chylocutaneous fistula, with or without lymphedema of the limbs or genitalia.[1,20]

In cases of congenital chylous disorders, symptoms develop at a young age. Most patients are in their early teens at the onset of severe symptoms, although occasionally older patients may also present with chylous effusions without underlying malignancy or a history of trauma.

The most common findings associated with chylous ascites are abdominal distension, nausea, vomiting, and milky or creamy peritoneal fluid obtained with an abdominal tap. For chylous effusions secondary to trauma including surgery, a latent period of 2–10 days usually occurs between trauma and the onset of symptoms if the injury is not a major one. Han et al. reported the occurrence of chylous ascites at a mean of 30 days after resection of gynecological malignancies and retroperitoneal lymphadenectomy.[5] Patients with chylothorax can be asymptomatic depending on the volume and location of the leak; however, progressive abdominal pain, dyspnea, cough, and chest discomfort may develop over time.

The mean age of 35 patients—15 males and 20 females—treated surgically for primary chylous disorders at the Mayo Clinic was 29 years, and ranged from 1 day to 81 years.[13] The patients presented with lower limb edema (54%), dyspnea (49%), scrotal or labial edema (43%), and abdominal distension (37%). Among 24 surgical cases operated on for chylous effusions, 50% were females; the mean age was 50 years, ranging from 19 years to 78 years. Chylous ascites was present in 92% of the patients, chylothorax in 58%, and both in 54%; one patient had chylopericardium.[14]

Loss of chyle can also result in malnourishment due to depletion in lipids, protein, calcium, and cholesterol. Significant loss of lymphocytes and immunoglobulins will cause severe compromise of the immune system and these patients are susceptible to infections.

65.5 EVALUATION

History and physical examination are most important and will frequently reveal the diagnosis. Chest X-ray studies may show a pleural effusion. Paracentesis or thoracentesis is necessary to verify the presence of chyle, which is milky fluid that is rich in albumin and lipids. Diagnostic criteria include a milky appearance, separation into a creamy layer on standing, odorless, specific gravity >1.012, and triglyceride levels >110 mg/dL.[21,22] Approximately half of chylothorax presented with milky fluid; patients who are fasting or those with congenital chylothorax produce little or no chyle.[23] Maldonado et al.[24] reported that 14% (10/74) of chylothoraces may have triglyceride levels <110 mg/dL and two patients had triglyceride levels <50 mg/dL. The presence of chylomicrons and lymphocytes at levels that are higher than the corresponding plasma values will also distinguish chyle from "pseudochylous collections" due to cellular degeneration from bacterial infection or neoplasms.[25]

For fetuses and newborns, fluid obtained from the chest or abdomen with triglycerides above 1.2 mmol/L and more than 1000 cells/mL with a predominance of lymphocytes, protein levels above 2.5 g/dL, and lactate dehydrogenase above 110 IU/L confirm the diagnosis of chylous effusions.[26] Magnetic resonance imaging (MRI) is required for suspected lymphatic malformations of the soft tissue and viscera when the fluid is characterized as lymph.

Pre-operative evaluation of patients with chylous effusions includes computed tomography (CT) or MRI to exclude chest or abdominal malignancy, followed by lymphoscintigraphy and lymphangiography. The benefits of lymphoscintigraphy, lymphangiography, and MRI are discussed in detail in Chapter 62. The dilated lymphatics (megalymphatics and lymphangioleiomyomatosis) are better seen with MRI. The radioactive colloid will reflux to the affected limb from the pelvis (Figure 65.2a). Although lymphoscintigraphy is our initial diagnostic test, pedal lymphangiography performed with lipid-soluble contrast will confirm the diagnosis, localize the dilated retroperitoneal lymphatics, and frequently confirm the sites of the lymphatic leak.

65.6 CONSERVATIVE MANAGEMENT

Management of a chylous effusion depends on the underlying cause; conservative therapy should be the first-line treatment option unless there is a life-threatening condition caused by a high volume of chyle leak occurring. The goals of conservative management of chylous effusions are relief of symptoms by drainage of the chylous fluid from the chest or abdominal cavity, decrease on chyle production through nutritional measures with or without medical treatment, and prevention or treatment of malnutrition and immunodeficiency. In some instances, treatment of the underlying causes can also improve chylous effusions.

Medical treatment should be initiated when diet or nutritional measures prove ineffective, or should serve as an adjunctive method to nutritional management. Therapeutic

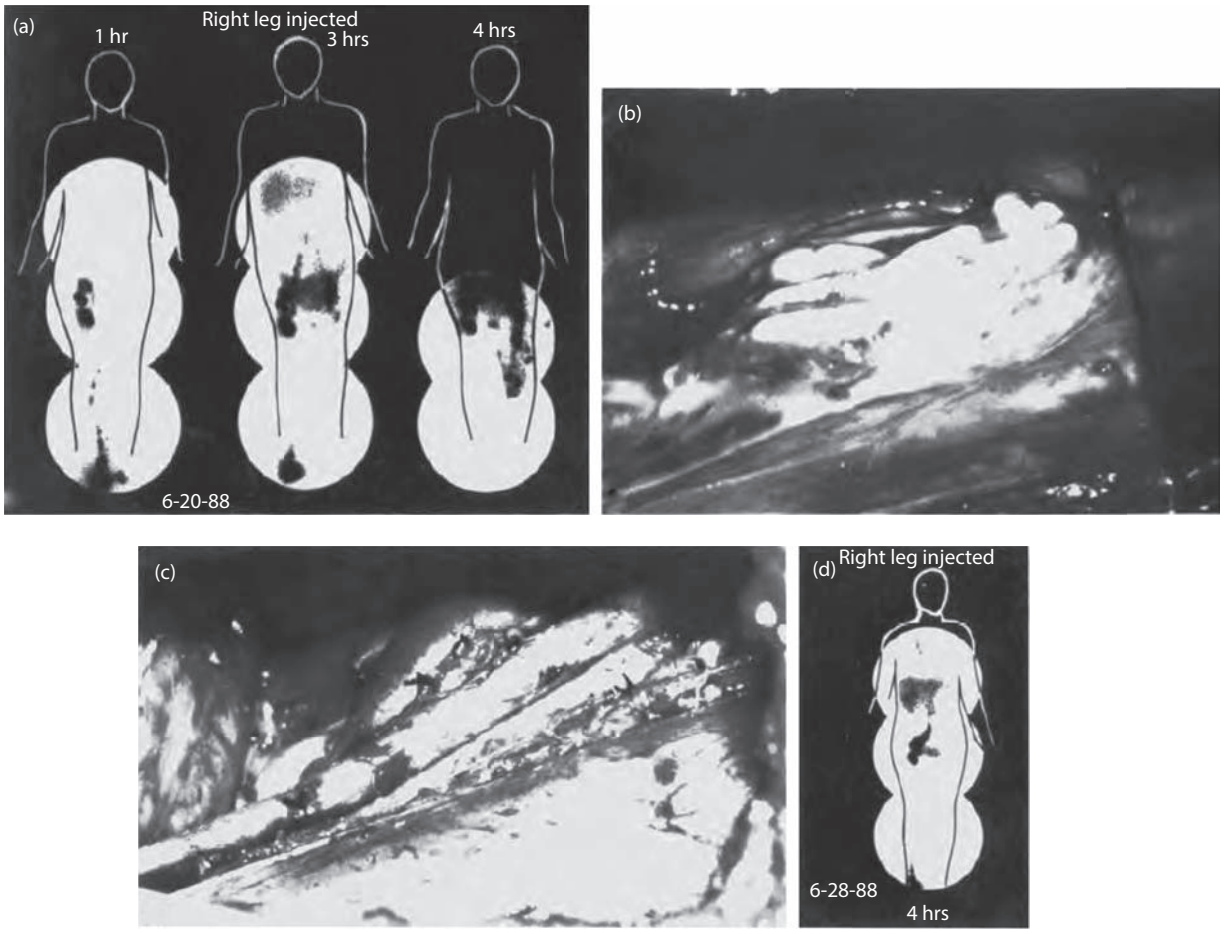

Figure 65.2 **(a)** Right lower extremity lymphoscintigraphy in a 16-year-old girl with lymphangiectasia and severe reflux into the genitalia and left lower extremity. Injection of the isotope into the right foot reveals reflux into the pelvis at 3 hours and into the left lower extremity at 4 hours. **(b)** Intra-operative photograph reveals dilated incompetent retroperitoneal lymphatics in the left iliac fossa containing chyle. **(c)** Radical excision and ligation of the lymph vessels were performed. In addition, two lymphovenous anastomoses were also performed between two dilated lymphatics and two lumbar veins. **(d)** Post-operative lymphoscintigram performed in a similar fashion reveals no evidence of reflux at 4 hours. The patient has no significant reflux 4 years after surgery. (From Gloviczki P et al. *J Vasc Surg* 1989;9:683–9.)

paracentesis or thoracentesis is indicated in patients with severe dyspnea and/or abdominal discomfort. If the chyle flow rate is <500 mL for chylothorax, conservative measures can be applied, and spontaneous closure of the leak may occur in 28%–90% of the patients. Conservative management is effective, particularly for post-operative chylous ascites, with success rates ranging from 71% to 100%.

65.6.1 Nutritional management

Chyle production should be decreased by the avoidance of food ingestion and the institution of parenteral nutrition (PN). Adequate fluid and electrolyte replacement is also important. A medium-chain triglyceride (MCT; a triglyceride with fewer than 12 carbon atoms) diet can be used in selected patients, as these triglycerides are directly absorbed into the portal circulation, bypassing the lymphatic tree. A MCT-rich regime can be delivered as enteral nutrition (EN), or orally with MCT supplements, depending on the patient's nutritional status and tolerance of an oral diet. At present, there is no consensus as to which approach is better regarding a PN, MCT-rich EN, or fat-free MCT-supplemented oral diet.

Nutritional management is used in conjunction with medical therapy, paracentesis, or thoracentesis in order to control symptomatic ascites or pleural effusions. Although these are only palliative measures, many patients may be controlled adequately. If not, surgical intervention is considered to provide long-term improvement.

65.6.2 Medical treatment

Somatostatin and its analogs have been used with beneficial effects as a result of improvements in electrolyte abnormalities, often reducing fluid and electrolyte support. The mechanism of action has been attributed to an increase in splanchnic arteriolar resistance with a resultant reduction in blood and lymphatic flow,[27] or a decrease in gastrointestinal

motility with a consequent decrease in the volume of gastric, pancreatic, and biliary secretions, which in turn decrease lymphatic flow; alternatively, the lymphatic vessels may have somatostatin receptors, and their stimulation can result in decreased lymphatic flow. Compared with somatostatin, octreotide has a longer half-life, greater potency, and allows for subcutaneous administration. Somatostatin and octreotide have shown effectiveness in the management of chylous ascites, chylothorax, and chylous fistulae following neck dissection.

Diuretics are frequently needed to decrease chyle production, and furosemide and aldactone are used in high doses in severe cases. Etilefrine, a sympathomimetic drug that causes smooth muscle contraction of the TD, has helped in the management of post-operative chylous disorders, but has not been used for primary chylous effusions.

Sirolimus, an inhibitor of the mammalian target of rapamycin, was reported to improve chylous effusions in patients with lymphangioleiomyomatosis (LAM). In patients treated with pleurodesis, pleural irrigation with agents such as tetracycline, minocycline, bleomycin, OK-432, povidone iodine, and talc is effective at inducing pleurodesis.

65.7 OPEN SURGICAL TREATMENTS

Open surgical treatment today is reserved for those who are not responsive to conservative management and who are not candidates for, or failed, endovascular treatment. Minimally invasive endovascular techniques with percutaneous sclerotherapy and embolization of the TD have been used with increasing frequency for the treatment of chylous problems, primarily in the chest.

65.7.1 Chylous reflux

In patients with lymphedema and reflux of chyle to the genitalia and the limbs, excision, ligation, and sclerotherapy of the incompetent retroperitoneal lymph vessels is performed, with or without lymphovenous reconstruction (LVR) with lymphovenous anastomosis (LVA) or lymphatic bypass grafting.[12] The patients are fed with 60 g of butter or 16 oz. of whipping cream 4 hours before the procedure. The lymphatics are approached retroperitoneally through a flank incision. The fatty meal allows ready visualization of the retroperitoneal lymphatics during exploration. Careful ligation of the lymph vessels should be done in order to avoid further lymphatic avulsion and leaking (Figure 65.2a–d). Adjunctive sclerotherapy of the dilated lymphatics is carried out to increase the efficacy of the operation. We inject tetracycline solution—500–1000 mg diluted in 20 mL of normal saline—directly into the dilated retroperitoneal lymph vessels to provoke obstructive lymphangitis. LVA can also be done, although reflux of blood into the incompetent lymphatics may be a problem. This procedure is technically demanding and requires microscope enhancement to complete the anastomosis. Although reflux of blood into the dilated and incompetent lymphatics can occur, a competent valve on the venous side using a saphenous vein graft will avoid reflux and increase the chance of successful lymphatic drainage.[13]

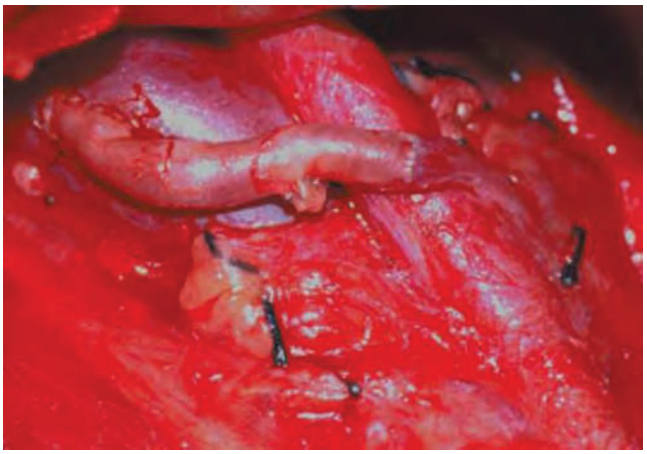

Figure 65.3 Lymphovenous anastomosis using a saphenous vein graft between a large retroperitoneal lymph vessel (end-to-end) and the right common iliac vein (end-to-side). The competent valve in the vein prevents reflux of blood into the dilated and incompetent lymph vessel.

Servelle published excellent and durable results from ligation and excision of the dilated refluxing lymphatics in 55 patients.[20] In a series of 19 patients who underwent ligation of the retroperitoneal lymphatics for chylous reflux to the limbs and genitalia (antireflux procedure) by Kinmonth,[1] permanent cure was achieved in five patients and alleviation of symptoms, frequently after several operations, occurred in 12 patients. No improvement or failure was noted in two cases.

In 35 patients with primary chylous disorders we treated over a 24-year period,[28] 10 patients underwent resection of retroperitoneal lymphatics with or without sclerotherapy of lymphatics, four had LVA or saphenous vein interposition grafts (Figure 65.3), four had peritoneovenous shunts (PVSs), and one patient had a hysterectomy for periuterine lymphangiectasia. All patients improved initially, but five had recurrence of some symptoms at a mean of 25 months (range 1–43 months). In three patients with leg swelling, post-operative lymphoscintigraphy confirmed improved lymphatic transport and diminished reflux.

65.7.2 Chylous ascites

Preparation of the patient for surgery is the same as is used for retroperitoneal lymphatic ligation. Four hours after a fatty meal is ingested, abdominal exploration will confirm dilated and ruptured lymphatics, which can be oversewn, ligated, or clipped. Chylous cysts, when found, should be excised. The most involved segments of the short bowel can be resected in patients who have severe protein-losing enteropathy. Success of the exploration is improved if a well-defined abdominal fistula because of a ruptured lymphatic vessel or cyst is identified. Ligation of leaking lymphatics

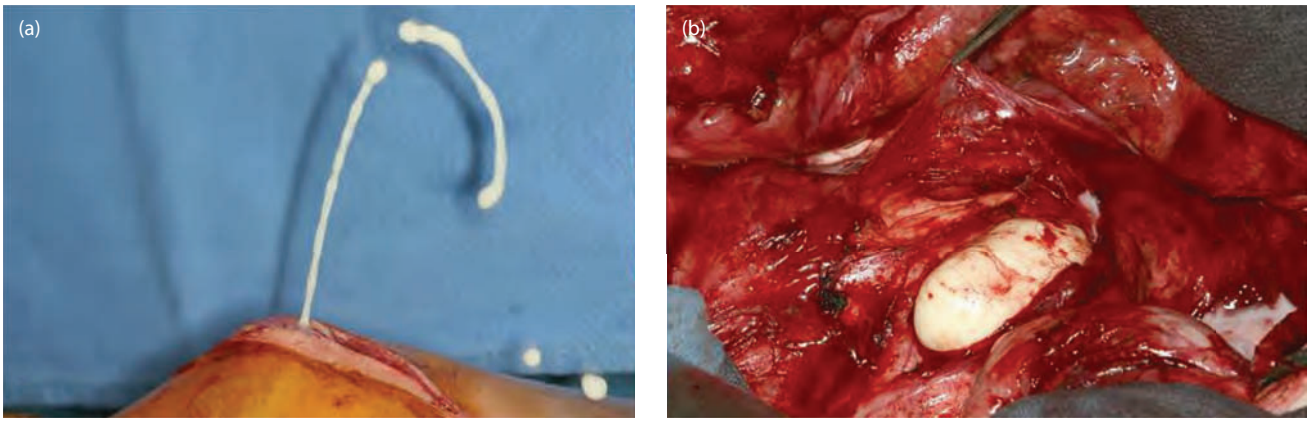

Figure 65.4 **(a)** Chylous ascites in a 62-year-old woman due to primary lymphangectasia. A total of 6500 mL of chylous fluid was removed. **(b)** The ruptured mesenteric lymphatics and many dilated retroperitoneal lymphatics from the left renal vein to the iliac bifurcation were ligated and oversewn; dilated retroperitoneal and pelvic lymphatics were sclerosed and lymphatic cysts were excised.

and sclerotherapy of the lymph vessels will help to diminish lymphatic leak (Figure 65.4). However, if the mesenteric lymphatic trunks are fibrosed, aplastic, or hypoplastic and if diffuse exudation of the chyle is the main source of the ascites, the prognosis is poor and recurrence is frequent. In these patients, control of the chylous ascites can be attempted with a PVS.

Browse et al.[17] reported on a series of 45 patients with chylous ascites. The age at presentation ranged from 1 to 80 (median 12) years; 23 patients were aged 15 years or younger. Thirty-five patients had an abnormality of the lymphatics (primary chylous ascites); in 10, the ascites was secondary to other conditions, principally non-Hodgkin's lymphoma (six patients). Other associated lymphatic abnormalities were present in 36 patients, with lymphedema of the leg being the most common (26 patients). All patients were initially treated conservatively with dietary manipulation, with best results in patients with leaking small bowel lymphatics. Surgery (fistula closure, bowel resection, or insertion of a PVS) was performed in 30 patients. Closure of a retroperitoneal or mesenteric fistula, when present, was the most successful operation, curing seven of the 12 patients.[17] In those patients who develop chylous ascites due to iatrogenic trauma, frequently after aortic reconstructions, a short period of conservative management is justified. If chylous ascites re-accumulates, reoperation with ligation of the fistula is the most effective treatment.

In a retrospective single-center study, Campisi et al.[29] reported on the surgical results of primary chylous ascites in 12 patients with a mean follow-up of 5 years (range 3–7 years). They found that laparoscopy was advantageous for confirming the diagnosis, draining the ascites, and evaluating the extension of dysplasia. Carbon dioxide laser was also used as an adjunct for "welding" lymphatic vessels with a low degree of dilatation in 75% of the patients. Eight patients had no relapse of ascites, three had mild recurrence (one of which was treated effectively with a PVS), and one patient died 1 year after surgery from an unrelated cause.

Results with PVSs have been mixed; patency is usually judged by recurrence of ascites. In a study by Browse et al.,[2] the nine PVS placements all occluded within 3–6 months of insertion. We reported previously on using the LeVeen shunt (Becton Dickinson, Franklin Lakes, NJ) in three patients with good results, although one patient developed symptomatic superior vena cava syndrome due to thrombosis around the shunt.[13] Our experience[14] showed that LeVeen shunts provided temporary clinical benefit at the expense of repeat replacement of non-functioning shunts (Figure 65.5). The only currently available peritoneovenous (PV) shunt—the Denver shunt—had a poor performance in our experience for the treatment of chylous ascites. There are few scattered case reports on the Denver shunt in the management of chylous ascites, with inconsistent results.[30,31] The effectiveness of the Denver shunt in the management of chylous ascites continues to be controversial.

When possible, lymphovenous reconstruction in the form of lymphovenous anastomosis or a vein interposition graft between a mesenteric or retroperitoneal lymphatic and the inferior vena cava or one of the iliac veins can also be performed to help drain the chyle into the venous system.

65.7.3 Chylothorax

Bender et al. summarized reports on the surgical management of chylothoraces between 1981 and 2009; surgical therapy was successful in 67%–100% of the cases.[32] In chylothorax caused by chylous ascites, chylothorax improves when the chylous ascites is controlled.

Cerfolio et al.[6] from the Mayo Clinic reported on 47 patients in whom chylothorax developed after thoracic operations. Non-operative therapy was successful in a third of the patients, but 32 patients required ligation of the TD, and two were treated with mechanical pleurodesis and fibrin

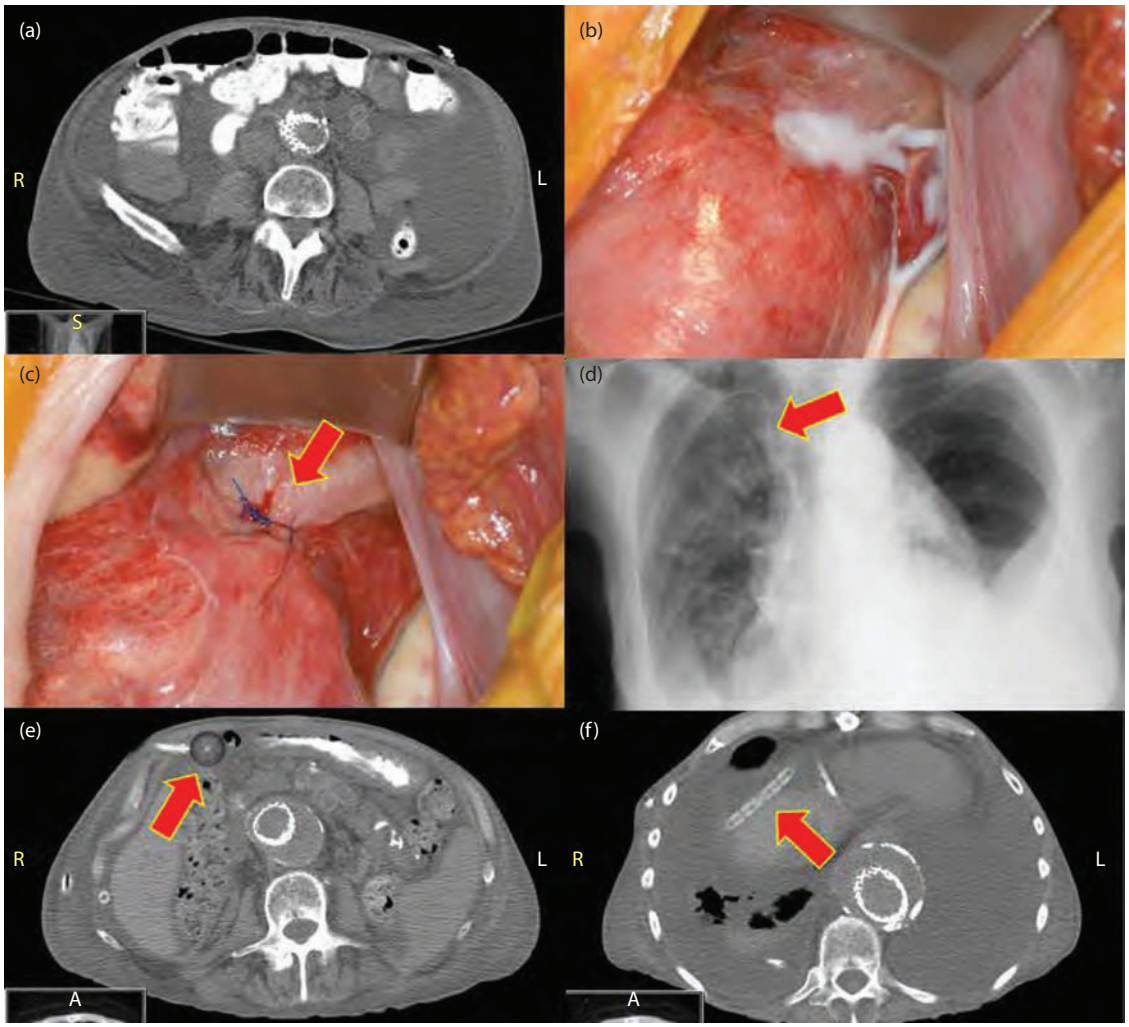

Figure 65.5 **(a)** A 77-year-old male with chylous ascites after type III thoracoabdominal aortic aneurysm repair. **(b)** Lymphatic leaks at the base of mesentery. **(c)** Oversewing of the leaks (arrow) and placement of a LeVeen shunt. **(d)** Post-operative chest X-ray showing peritoneal caval LeVeen shunt in place (arrow). (**e** and **f**) Post-operative computed tomography scan showing valve cage (**e**; arrow) and tube (**f**; arrow) of the LeVeen shunt. During the operation, 6000 mL of chylous ascites was aspirated.

glue. Surgery was successful in 31 of the 34 patients (91%). The authors recommended early reoperation and ligation of the TD when drainage was more than 1000 mL/day. Schild et al.[23] reviewed publications on chylothorax published between 1995 and 2013 and recommended surgical treatment if: (1) more than 1000–1500 mL of chyle is drained every day (>100 mL/kg body weight in children); (2) drain output is up to 1000 mL/day for 5 treatment days (100 mL/year of age in children); (3) a chyle leak (100 mL/day) persists for more than 2 weeks; (4) drain output remains unchanged over 1–2 weeks; or (5) clinical deterioration such as malnutrition or metabolic problems occurs. Early surgical treatment is recommended in young patients with high-volume chyle leaks and in children with body weight below 4 kg. In patients with chylothorax after esophagectomy, a delay of 2–4 weeks is recommended to avoid putting the anastomoses at risk.[23] Takuwa and colleagues[33] suggested surgical treatment for chylothorax that developed after mediastinal lymph node dissection and resection of primary lung cancer if the drainage exceeds 500 mL during the first 24 hours of the initiation of a low-fat diet.

Pre-operative lymphangiography may localize the site of the chylous fistula or document occlusion of the TD. Thoracentesis is diagnostic but rarely therapeutic, as chyle from the TD or large intercostal, mediastinal, or diaphragmatic collaterals will re-accumulate. Although percutaneous or tube pleurodesis may be effective in other forms of non-malignant chylothorax, it is less effective for primary chylothorax. Surgical pleurodesis, either with video-assisted thoracoscopy (VATS) or with open thoracotomy with excision of the parietal pleura is the optimal treatment.[17,18] After a fatty meal, thoracotomy or VATS is performed and the lymphatics oversewn or clipped. This is followed by pleurodesis.

Multiple case reports have been published illustrating the role of thoracoscopic TD ligation in the treatment of

chylothorax.[3,34,35] A summary paper from Kumar et al. in 2004 reported a total of 21 cases of VATS surgery for the treatment of chylothorax ($n = 16$), chylopericardium ($n = 4$), and cervical chylous leak ($n = 1$).[34] Ligation of the TD far above the diaphragm may be more successful than clipping of the duct near the diaphragm. In addition, if extensive fibrosis is present and the TD is not easily identified, VATS may be used to ligate the mass of tissue between the azygos vein and the aorta with good success. One specific advantage of VATS for the treatment of chylothorax is that magnification of the thoracic structures can facilitate ligation. Because of the efficacy, low expense, and low morbidity of VATS, early reoperation is recommended to avoid a lengthy conservative course with concomitant loss of chyle and a long hospital stay. Early intervention with VATS is recommended for most patients with a high-output fistula (>1000 mL/24 hours), although some authors recommend at least a 1-week trial of conservative therapy. If the chylous output remains greater than 200 mL/24 hours after 1 week, VATS intervention is considered.[3,34]

Silk et al.[36] and Engum and colleagues[37] reported on using pleuroperitoneal shunts in children with good results. More recently, Slater and Rothenberg reported on the largest case series using VATS with tissue sealer (5-mm LigaSure®, Covidien Energy, Boulder, CO; 3-mm, Justright Surgical, Boulder, CO) and/or sutures, along with JustRight™, mechanical pleurodesis and the administration of fibrin glue for the management of chylothorax. Twenty-one patients aged from 3 weeks to 5 years were treated and all procedures were performed in the right chest with three ports. Technical success was 90%; two patients who failed to respond had successful thoracoscopic pleurectomy and chemical pleurodesis.[35]

If the upper TD is occluded on lymphangiography resulting in reflux of chyle into the pleural or peritoneal cavity, TD–azygos vein anastomosis can be attempted to reconstruct the duct and improve lymphatic transport. Through a right posterolateral thoracotomy, an anastomosis between the lower TD and the azygos vein is performed in an end-to-end fashion with 8–0 or 10–0 non-absorbable interrupted sutures and magnification using loupes or the operating microscope (Figure 65.6a–c). Kinmonth,[1] who performed this operation in several patients, suggested that the anastomosis alone is not effective for decompressing the TD; ligation of the abnormal mediastinal lymphatics and oversewing of the sites of the lymphatic leak are also necessary. Browse et al.[17] reported on three patients who underwent TD–azygos vein anastomosis, but all shunts occluded by 1 year after intervention. In the series of Browse et al., a total of 20 patients were treated for primary or secondary chylothorax. The authors suggest initial conservative treatment, but abandoned it if the fluid loss exceeded 1.5 L/day for more than 5–7 days in an adult or more than 100 mL/day in a child. Open pleurectomy was the most successful treatment for preventing re-accumulation of the effusion. Twelve of 20 patients were alive and free from an effusion at 3–22 years after treatment.

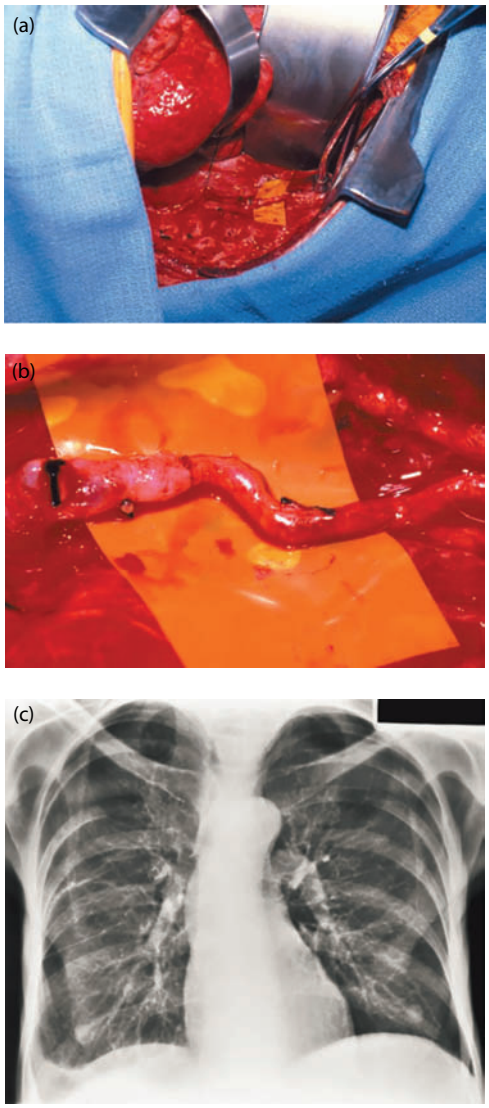

Figure 65.6 **(a** and **b)** Thoracic duct–azygos vein anastomosis performed through a right posterolateral thoracotomy in an end-to-end fashion with interrupted 8–0 Prolene sutures. **(c)** Chest radiograph 2 years later confirms absence of chylothorax. (Reprinted from *Rutherford's Vascular Surgery,* 6th Ed, Gloviczki P and Noel AA, Surgical treatment of chronic lymphedema and primary chylous disorders, 2428–45, Copyright 2005, with permission from Elsevier.)

In an earlier Mayo Clinic study, eight procedures for chylothorax included thoracotomy with decortication and pleurodesis (four patients), ligation of the TD (three patients), and resection of a TD cyst (one patient), with excellent early results in all patients.[13] The most recent study showed that among four patients treated with TD reconstructions with TD–azygos vein ($n = 3$) or TD–internal jugular vein anastomosis ($n = 1$) for chylothorax ($n = 3$) and chylopericardium ($n = 1$), no early deaths occurred. No patients required thoracentesis or paracentesis during follow-up, and clinical benefit was achieved in all patients.[14]

65.8 ENDOVASCULAR TREATMENT

Percutaneous TD embolization (TDE) to treat chylothorax due to a leaking TD was first described by Cope in 1998[38]; case reports[39–44] and a few larger series have also been reported since.[45–49] TDE is performed in patients with traumatic or non-traumatic chylous effusions who are not responsive to conservative management.[43,46–49] Because of its low morbidity and good clinical outcomes, TDE has gained favor over traditional TD ligation.[46–49] Although minimally invasive in nature, TDE is a technically demanding procedure.

65.8.1 Techniques

Patients with chylous effusion undergo a diagnostic pedal lymphangiography first to delineate the lymphatic anatomy and identify the site of lymphatic leak. The procedure is performed using lipid-soluble contrast and a standard technique as described in Chapter 62. To decrease the procedural time of pedal lymphangiography, Nadolski and Itkin demonstrated that ultrasound-guided intranodal lymphangiogram allowed for a quicker visualization and catheterization for TDE.[42] Others also reported success with ultrasound-guided percutaneous lymphangiogram using lipid- or water-soluble contrast.[44]

For TDE, the Mayo Clinic technique was described in detail by Kurklinsky et al.[41] Ultrasound is used to aid a percutaneous transhepatic approach. A 22-gauge, 20-cm Chiba needle (Remington Medical, Inc., Alpharetta, GA) is inserted into the cisterna chyli under fluoroscopic guidance using a bulls-eye approach in the right anterior oblique position and slightly caudal to cranial orientation. A Nitrex wire (ev3 Endovascular, Inc., Plymouth, MN) is advanced into the TD, followed by a 3-Fr dilator. Omnipaque 300 (GE Healthcare, Princeton, NJ) is injected and digital subtraction angiography is performed to identify the lymphatic leak (Figures 65.7 and 65.8). The 3-Fr dilator is exchanged for a TurboTracker microcatheter (Boston Scientific, Natick, MA), which, along with a 0.018-inch GoldGlide wire (Terumo, Somerset, NJ), is used to traverse the transection and to cannulate the TD in the upper chest above the leak (Figure 65.9). Then, 3- and 4-mm Nester coils (Cook, Bloomington, IN) can be used for embolization, deploying them above, across, and below the site of the lymphatic leak. The TurboTracker is then exchanged for a Rebar microcatheter (ev3 Neurovascular, Irvine, CA), a requirement for use of dimethyl sulfoxide, and Onyx-34 glue (ev3 Endovascular, Inc.) can be injected into

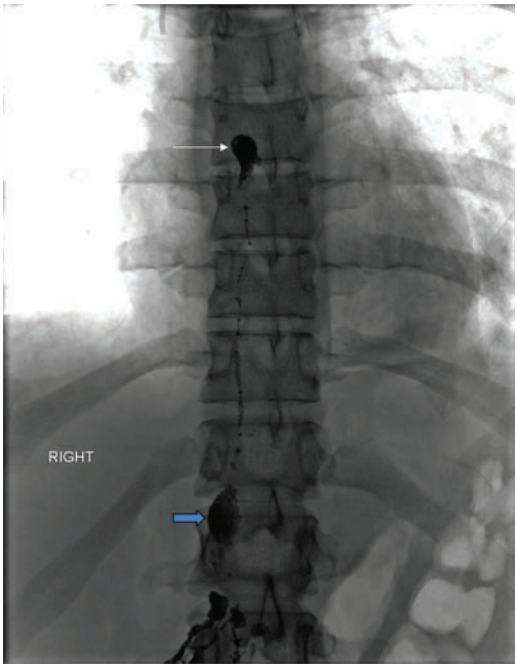

Figure 65.7 Lymphangiogram: this initial image shows a large cisterna chyli (thick arrow) and extravasation in the mid-chest (thin arrow). (From Kurklinsky AK, McEachen JC, and Friese JL. *Vasc Med* 2011;16:284–7. With permission.)

Figure 65.8 Intervention: after successful puncture of the cisterna chyli (black arrow points towards the access needle), thoracic duct lymphangiogram shows an area of extravasation at the thoracic duct transection site (white arrow). (From Kurklinsky AK, McEachen JC, and Friese JL. *Vasc Med* 2011;16:284–7. With permission.)

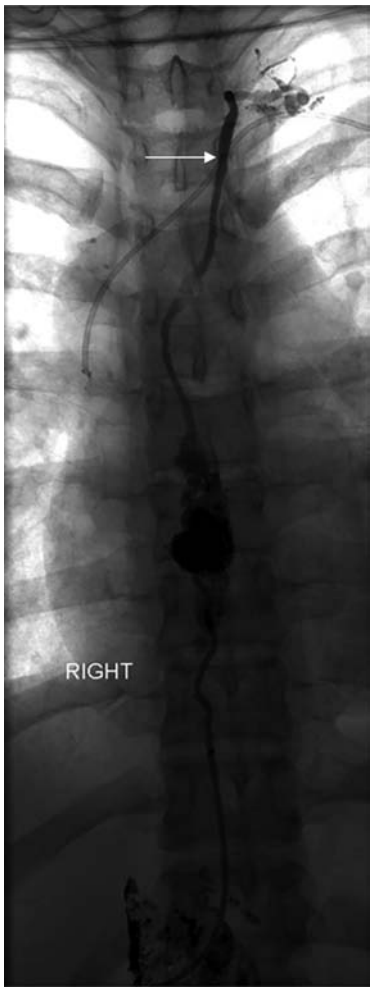

Figure 65.9 Intervention: the microcatheter was successfully advanced cephalad (white arrow) across the transected portion of the thoracic duct. (From Kurklinsky AK, McEachen JC, and Friese JL. *Vasc Med* 2011;16:284–7. With permission.)

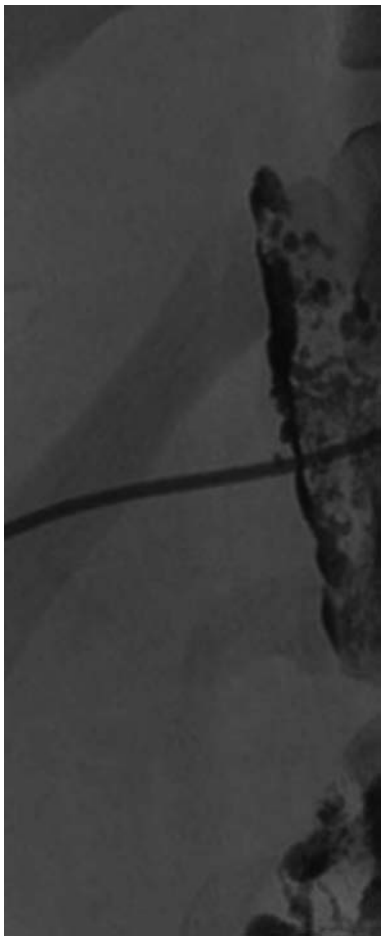

Figure 65.10 Intervention: coils are placed above and below the area of transection in the thoracic duct. Final contrast injection shows no further contrast extravasation at the thoracic duct transection site. (From Kurklinsky AK, McEachen JC, and Friese JL. *Vasc Med* 2011;16:284–7. With permission.)

the inferior TD above the level of the cisterna while slowly pulling the catheter back into the cisterna to completely occlude the TD (Figure 65.10). The catheter is then removed and the procedure is completed. Glue and coils are the most frequently used embolic agents for TDE.[39–41,43,45,46,48,49]

In a patient in which catheterization of the TD cannot be performed, occlusion of the TD below the diaphragm can be attempted by a mechanical needle disruption technique also called thoracic duct disruption (TDD), as reported by Cope and Kaiser[45] and Itkin et al.[46] If conventional percutaneous transhepatic catheterization of the cisterna chyli fails, TDE can also be performed via catheterization of the TD and the cisterna chyli in a retrograde fashion from the subclavian vein, as has been reported by Mittleider et al.[40]

65.8.2 Results

In 42 patients with traumatic or non-traumatic chyle leaks, Cope and Kaiser reported a partial response or cure rate of 74% after TDE and TDD; there was no morbidity or mortality.[45] In a large series of 109 patients with traumatic TD injury (chylothorax: 106, cervical lymphocele: 2, chylopericardium: 1), TDE or TDD was performed with an overall success rate of 71% (77/109). Lymphangiogram was successful in 108 of 109 patients; catheterization of the TD was achieved in 73 patients (67%), 71 of whom underwent TDE, and resolution of the chyle leak was observed in 64 patients (90%) after TDE. TDD below the diaphragm was successful in 13 of 18 patients (72%). The minor complication rate was 3%.[46]

In a single-center retrospective study, 169 patients with traumatic or non-traumatic chylous effusion underwent TDE. The technical success rate was 63%. Chronic diarrhea (12%) and lower-extremity swelling (8%) were described as side effects of the interventions.[47] The same group also reported on outcomes after TDE for 34 patients with non-traumatic chylous effusion. TDE was technically successful in 24 patients (71%); of these, the clinical success rate was 68% ($n = 16$). TDE was most successful in cases of TD occlusion (75%) and extravasation of chyle seen on lymphangiogram (50%).[48]

In another series of 105 patients undergoing 120 consecutive TDEs or TDDs, the technical success rate was 79%. TDE had a clinical success rate of 72% and TDD had a success rate of 55% ($P = 0.13$). The clinical success rate in patients with traumatic chylous effusions was higher than in patients with non-traumatic chylous effusions (62% vs. 13%, $P < 0.05$). The minor complication rate was 6.7%.[49]

Results in patients with chylous ascites or abdominal lymphatic leaks treated with embolization or sclerotherapy have been inferior to those reported with chylothorax. Embolization of the cisterna chyli was reported in a patient with chylous ascites, with short-term success.[40] Treatment of chylous or non-chylous ascites after surgery for gynecologic malignancy can be attempted with sclerotherapy using doxycycline and ethanol or embolization. Failure of endovascular therapy in these patients can be followed by successful open surgery to oversew the lymphatic leak identified by pre-operative lymphangiography.[50] Dinc and colleagues reported successful treatment of post-surgical chylous ascites using ultrasound-guided intranodal lymphangiogram along with CT-guided transabdominal embolization with N-butyl cyanoacrylate glue and percutaneous N-butyl cyanoacrylate glue and coil embolization by direct catheterization of the leaking lymphatics through the chylous collection.[44]

65.9 CONCLUSIONS

- Chylous disorders are fortunately rare. The underlying abnormality of primary chylous disorders is congenital lymphangiectasia, with or without occlusion or atresia of the TD or obstruction localized to mesenteric lymph nodes and vessels.
- CT or MRI is helpful for identifying secondary chylous effusions that develop in patients with malignancies, most frequently lymphoma, and in those who undergo surgical resection for primary or recurrent malignant tumors.
- Medical management of chylous effusions includes diet, PN, somatostatin, paracentesis, or thoracentesis.
- If medical treatment fails, percutaneous embolization using coils and glue should be attempted for the treatment of persistent chylous effusions; embolization is safe and effective, especially in patients with chylothorax. The etiology of the chylous effusion and successful imaging of the site of the leak with pre-operative lymphangiography help to predict the success of endovascular interventions.
- Percutaneous embolization should be considered in patients with chylous effusions over open surgery. For chylothorax, pleurodesis and ligation of the leaking lymphatics or the TD using VATS is frequently effective. In selected patients with chylothorax, a TD–azygos vein anastomosis or pleuroperitoneal shunt may be considered as surgical options.
- Ligation of the incompetent retroperitoneal lymphatics and oversewing ruptured lymphatics can produce long-term improvement in lymphangiectasia and lymphatic reflux. Chylous ascites can be treated with ligation of the mesenteric or retroperitoneal lymphatic fistula.
- The role of PVSs in the treatment of chylous ascites remains controversial because of the high rate of early thrombosis of the only currently available shunt.

Guidelines 6.5.0 of the American Venous Forum on the management of chylous disorders

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
6.5.1	For the primary treatment of chylous effusions and fistulas due to reflux, we recommend first a low-fat or medium-chain triglyceride diet, followed by drug therapy that may include somatostatin and its analogs, diuretics, and sympathomimetic drugs to enhance thoracic duct contractions. This is followed by percutaneous aspirations of chylous fluid by thoracentesis or paracentesis.	1	B
6.5.2	In patients with chylous effusions, we suggest percutaneous embolization using coils or glue as the first line of treatment once conservative management fails.	2	B
6.5.3	If endovascular treatment is not possible or fails, we suggest open surgery for the treatment of chylous effusions and symptomatic lymphangiectasia. These procedures include ligation of lymphatic fistulas, excision of dilated lymphatics, sclerotherapy, video-assisted thoracoscopy with pleurodesis and ligation of the thoracic duct, lymphatic reconstruction, or, as a last resort, placement of a peritoneovenous shunt.	2	C

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● = Key primary paper
★ = Major review article
◆ = First formal publication of a management guideline

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PART 7

Issues in Venous Disease

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Outcome assessment in acute venous disease

PATRICK H. CARPENTIER AND PETER GLOVICZKI

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In 1960, Barritt and Jordan were the first to publish the results of a controlled trial using heparin and a vitamin K antagonist (VKA) for the treatment of patients with pulmonary embolism.[1] The study was halted after enrollment of only 35 patients because of the high mortality of untreated patients in the control group. Although the poor methodology of this pioneer study was criticized by many,[2,3] it was clear that the trial opened the way for both anticoagulation therapy of venous thromboembolism (VTE) and objective assessment of the treatment of acute venous disease.

Since then, hundreds of clinical trials have been performed in acute VTE patients,[4] dealing with the prophylactic and therapeutic use of antithrombotic agents, the diagnostic evaluation of deep vein thrombosis (DVT) and pulmonary embolism (PE), interventional treatments for iliofemoral DVT, and the indications for and results of vena cava filters. The common issues of outcome assessment in these studies will be briefly reviewed in this chapter.

66.1 KEY POINTS IN THE OUTCOME ASSESSMENT OF ACUTE VENOUS DISEASE

As in any disease, the goal of the medical management in acute venous disease (i.e., VTE) is to improve the survival and the quality of life that are endangered or hampered by the disease; in addition, treatment should decrease complications and recurrence of disease, have as few side effects as possible, and achieve all of this at the lowest cost possible. In acute venous disease, the following criteria of successful outcomes are particularly important:

1. Safety criteria are as essential as efficacy. The hemorrhagic complications of antithrombotic treatments are frequently severe. Each year, major bleeding complications occur in 1.3%–3.8% patients who take VKAs,[5] while the complication rate is approximately a third lower in patients on direct oral anticoagulants.[6]
2. The acute onset of the most important complications makes event-related criteria more relevant than quality of life evaluation scales in most instances.
3. Time course specificity is not limited to the acuteness of episodes and recurrences:
   - The preventive effect of antithrombotic drugs on recurrence is restricted to the treatment duration; many recurrences are delayed rather than avoided, and follow-up should include the post-therapy time period.[7,8]
   - Long-term complications are not rare and can be disabling (post-thrombotic syndrome [PTS]) or even life-threatening (pulmonary hypertension), and have to be taken into account in the benefit over risk balance evaluation.

66.2 MORTALITY

In the United States, at the turn of the century PE was responsible for at least 45,000 deaths.[9] Reduction of this excessive mortality remains the main goal of the prevention and treatment of VTE disease. Reduction of PE-related mortality is the main efficacy criterion for thrombolytic therapy in massive PE or PE with right ventricular dysfunction,[10] vena cava filter implantation,[11,12] and for prevention trials of VTE in high-risk patients.[13] Death can also occur due to bleeding complications of antithrombotic therapy. In addition, death is not uncommon in the months following an episode of PE or DVT, mostly due to the complications of associated conditions.[14,15] Therefore, PE-related death, but also death due to any cause, is a meaningful outcome in VTE because it reflects the benefit of treatment and because

antithrombotic drugs may alter the course of some of these associated conditions, such as cancer[16] and cardiovascular events.[17]

66.3 NON-FATAL VTE EVENTS

Thrombi in the deep veins of the lower limbs of asymptomatic patients who are at high risk for VTE are frequently detected.[18] Similarly, in patients with DVT but no respiratory symptoms, ventilation perfusion lung scans or helical computed tomography scans will show asymptomatic PE in up to 40% for proximal DVT[19] and 13% for distal DVT.[20] These silent DVTs or PEs are often used as surrogate endpoints in Phase II prophylactic or therapeutic trials in patients with or at risk of VTE. They are conceptually and statistically highly related to clinical outcomes and allow decrease of the sample size needed to prove the hypothesis of the study (Table 66.1). However, silent DVTs or PEs do not have the same significance as the clinical occurrence or recurrence of objectively confirmed DVT and PE, which is the only valid endpoint for Phase III prophylactic or therapeutic trials or for the evaluation of diagnostic strategies. In such trials, the combination of occurrence or recurrence of clinical PE/DVT is most often chosen as the combined endpoint of efficacy (Table 66.2).

66.4 BLEEDING

Bleeding is a serious side effect of antithrombotic drugs. Systemic thrombolytic therapy for PE can lead to severe bleeding complications in up to 14% of patients[10]; anti-vitamin K anticoagulants also have a high rate of bleeding complications.[5] Heparin, even in a prophylactic dosage, causes significant bleeding hazards,[13] and on the whole, a bleeding complication is considered more serious than a recurrent thromboembolic event.[7] Bleeding complications can include minor bleeding from the site of a venipuncture to massive cerebral hemorrhage and death. Evaluation of risk of bleeding has improved considerably because of the introduction of standardized criteria. The criteria of the European Agency for the Evaluation of Medicinal Products (EMEA) for major bleeding (Table 66.3)[21] and the Thrombolysis In Myocardial Infarction (TIMI) criteria for major and minor bleeding of the TIMI studies (Table 66.4)[22] are widely used when considering the whole field of anticoagulant therapy. However, regarding VTE, the International Society for Thrombosis and Haemostasis (ISTH) criteria have been used in most recent works (Table 66.5).[23]

Table 66.1 Surrogate criteria for deep vein thrombosis or pulmonary embolism in asymptomatic patients

- Positive radiolabeled fibrinogen scan
- Venography filling defect
- Non-compressible venous segment on ultrasound scan
- High-probability ventilation–perfusion lung scan
- Filling defect on spiral computed tomography scan

Table 66.2 Objective confirmation of deep vein thrombosis or pulmonary embolism in symptomatic patients with findings on imaging studies consistent with clinical signs and symptoms

- Non-compressible venous segment on ultrasound scan
- Venography filling defect
- High-probability ventilation–perfusion lung scan
- Filling defect on spiral computed tomography scan or pulmonary angiogram

66.5 POST-THROMBOTIC SYNDROME

PTS is a frequent and serious outcome for patients with VTE. It is seldom taken into account in clinical trials, mainly because its evaluation requires long-term follow-up that exceeds the study time course of most trials regarding anticoagulant therapy in VTE. However, the prevalence of PTS at 10 years after a first episode of DVT is higher than 30%[24–26] and is increased in patients with obesity,[27–29] underlying thrombophilia,[30] ipsilateral recurrence of DVT,[29] inadequate anticoagulation,[29] and possibly when a vena cava filter is placed.[31,32] Until recently, it was thought to be decreased as a result of

Table 66.3 European Agency for the Evaluation of Medicinal products (EMEA) criteria for major bleeding

- Fatal bleeding
- Clinically overt bleeding with a fall in hemoglobin level of 20 g/L or more
- Clinically overt bleeding leading to transfusion of two or more units of packed cells or whole blood
- Retroperitoneal or intracranial bleeding
- Bleeding warranting treatment cessation

Source: The European Agency for the Evaluation of Medical Products. Clinical investigation of medicinal products for prophylaxis of intra- and post-operative thromboembolic risk. http://www.emea.europa.eu/pdfs/human/ewp/070798en.pdf (June 2000).

Table 66.4 Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria

Major bleeding	Minor bleeding	"Loss no site"
• Hemoglobin drop >5 g/dL (with or without an identified site) • Intracranial hemorrhage • Cardiac tamponade	• Hemoglobin drop >3 g/dL but ≤5 g/dL, with bleeding from a known site • Spontaneous gross hematuria, hemoptysis, or hematemesis	• Hemoglobin drop >4 g/dL but ≤5 g/dL without an identified bleeding site

Source: Adapted from Bovill EG et al. *Ann Intern Med* 1991; 115:256–65.

Table 66.5 International Society of Thrombosis and Haemostasis (ISTH) definitions of major bleeding in non-surgical patients

1. Fatal bleeding
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome
3. Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

Source: Adapted from Schulman S and Kearon C. *J Thromb Haemost* 2005;3:692–4.

compression therapy,[33,34] although the SOX trial challenged this belief.[35] Early clot removal was shown to be useful in surgical thrombectomy,[36] systemic[37] or catheter-directed[38] thrombolysis, or combined pharmacomechanical therapy.[39]

PTS is most often associated with deep vein reflux,[40] which appears early and is sometimes used as a diagnostic criterion for PTS.[41] In some studies, deep vein reflux was used as a surrogate endpoint for PTS, although clearly it does not always have a clinical manifestation.

Leg ulcers are the most disabling late complications of venous thrombosis; approximately 40% of all leg ulcers are related to a previous DVT.[42] However, earlier clinical manifestations of PTS also alter quality of life and they should also be taken into consideration.

66.6 INCIDENCE OF PTS

The incidence of PTS is a meaningful outcome issue in patients with VTE disease. Although their definition is conceptually straightforward, their operational determination requires the use of validated clinical tools. Outcome assessment for chronic venous disease is discussed in much detail in Chapter 67, but a few issues need to be mentioned here, since these tools should be part of the evaluation of patients with acute disease as well. For the purpose of evaluating the incidence of PTS after acute VTE, two specific diagnostic tools were developed: the Ginsberg measure (Table 66.6),[43] based on the persistence or the new onset of persistent leg pain and swelling at 6 months after a DVT; and the Villalta scale, composed of 11 four-point scales scoring symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and signs (pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness, and pain during calf compression). The scale is discussed in more detail in the next chapter presenting outcome assessment for chronic venous disease (Table 67.8, Chapter 67).[44,45] A Villalta score of higher than 5 represents mild PTS and a score of 15 or more means severe PTS. A third score had been proposed by Brandjes et al.,[33] but, being less practical, it was only used in one trial. A comparison study showed that the Villalta score is more sensitive than the Ginsberg measure,[41] and another study found that it correlates with ambulatory venous pressure.[46] The Villalta score was found to be the most suitable for the diagnosis of PTS in a systematic review.[47] Its use was recommended by the ISTH[48] and endorsed by the recent American Heart Association (AHA) guidelines.[49]

Table 66.6 Ginsberg measures for the diagnosis of post-thrombotic syndrome

- Presence of daily leg pain and swelling for 1 month
- Occurring 6 months or more after deep vein thrombosis
- Made worse by standing/walking
- Relieved by rest/leg elevation

Source: Adapted from Ginsberg JS et al. *Arch Intern Med* 2000; 160:669–72.

66.7 SEVERITY OF PTS

Although the Villalta score is able to diagnose and classify PTS and severe PTS, it is not a quantitative measure of the severity of PTS. A study showed that it did not correlate well with the Venous Clinical Severity Score (VCSS) in the severe forms of PTS.[50] The VCSS was introduced by the American Venous Forum (AVF)[51] with the aim of measuring the clinical severity of chronic venous disorder by the physician, as well as its changes over time in patients with any kind of chronic venous disorders. Since then, this scoring system has been used in more than 100 studies and has shown good construct validity and satisfactory intra- and inter-observer reproducibility,[52] which should even improve with the revised version (Table 67.1, Chapter 67),[53] clarifying some grading definitions. Although there have not been many studies with VCSS specifically restricted to PTS patients, the VCSS has been shown to correlate with ambulatory venous pressure in this condition.[46] In a thrombophilia population, Ricci et al.[54] showed a good correlation of the VCSS with the results of ultrasound scans.

The health burden related to PTS should also be measured by a patient-reported outcome instrument. This kind of tool is observer independent and can evaluate either symptoms or quality of life. PTS significantly alters the quality of life, even when measured with a non-specific instrument such as Short Form 36 (SF-36).[41] A modification of the Chronic Venous Insufficiency Questionnaire (CIVIQ) QoL questionnaire is the CIVIQ2, which is made up of 20 simple questions (Table 67.2, Chapter 67).[55] It was specifically developed for chronic venous disease and successfully validated in several groups of patients, including those with severe PTS. Its practicability and availability in several languages make it widely used for patients with chronic venous disorders.

The Venous Insufficiency Epidemiologic and Economic Study of Quality-of-Life (VEINES QoL)/Sym questionnaire is certainly the most accomplished tool (Table 66.7).[56] It includes 10 questions assessing symptom severity and 15 questions evaluating venous disease-related quality of life impairment. Its acceptability, reliability, and validity of content have been thoroughly validated in a large population of more than 1500

Table 66.7 VEINES QoL/Sym questionnaire

1. During the past 4 weeks, how often have you had any of the following leg problems?

(Check one box on each line)	**Every day**	**Several times a week**	**About once a week**	**Less than once a week**	**Never**
1. Heavy legs	1	2	3	4	5
2. Aching legs	1	2	3	4	5
3. Swelling	1	2	3	4	5
4. Night cramps	1	2	3	4	5
5. Heat or burning sensation	1	2	3	4	5
6. Restless legs	1	2	3	4	5
7. Throbbing	1	2	3	4	5
8. Itching	1	2	3	4	5
9. Tingling sensation (e.g., pins and needles)	1	2	3	4	5

2. At what time of day is your **leg problem** most intense? *(check one)*

1. On waking
2. At mid-day
3. At the end of the day
4. During the night
5. At any time of day
6. Never

3. Compared with 1 year ago, how would you rate your **leg problem** in general now? *(check one)*

1. Much better now than 1 year ago
2. Somewhat better now than 1 year ago
3. About the same now as 1 year ago
4. Somewhat worse now than 1 year ago
5. Much worse now than 1 year ago
6. I did not have any leg problem last year

4. The following items are about activities that you might do in a typical day. Does your **leg problem** now limit you in these activities? If so, how much?

(Check one box on each line)	**I do not work**	**Yes, limited a lot**	**Yes, limited a little**	**No, not limited at all**
a. Daily activities at work	0	1	2	3
b. Daily activities at home (e.g., housework, ironing, doing odd jobs/repairs around the house, gardening, etc.)		1	2	3
c. Social or leisure activities in which you are standing for long periods (e.g., parties, weddings, taking public transportation, shopping, etc.)		1	2	3
d. Social or leisure activities in which you are sitting for long periods (e.g., going to the cinema or the theater, travelling, etc.)		1	2	3

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your **leg problem**?

(check one box on each line)	**Yes**	**No**
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (e.g., it took extra effort)	1	2

(*Continued*)

Table 66.7 (*Continued*) VEINES QoL/Sym questionnaire

6. During the past 4 weeks, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbors or groups? *(check one)*

1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely

7. How much leg pain have you had during the past 4 weeks? *(check one)*

1. None
2. Very mild
3. Mild
4. Moderate
5. Severe
6. Very severe

8. These questions are about how you feel and how things have been with you during the past 4 weeks as a result of your **leg problem**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

(check one box on each line)	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a. Have you felt concerned about the appearance of your leg(s)?	1	2	3	4	5	6
b. Have you felt irritable?	1	2	3	4	5	6
c. Have you felt a burden to your family or friends?	1	2	3	4	5	6
d. Have you been worried about bumping into things?	1	2	3	4	5	6
e. Has the appearance of your leg(s) influenced your choice of clothing?	1	2	3	4	5	6

Source: Adapted from Lamping DL et al. *J Vasc Surg* 2003;37:410–9.

patients with chronic venous disease,[56] as well as in a series of elderly post-DVT patients,[57] and it was found to correlate well with the Villalta scale[41,58] and the SF-36.[56] It is the most often used quality of life tool in recent studies evaluating the prevention of PTS.[59–64]

The spectrum of outcome assessment in acute venous disease is broad. Early studies mainly focused on PE, bleeding complications, and the risk of death. A comprehensive approach to all aspects, including late venous events, was developed more recently, emphasizing the importance of venous function preservation.

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67

Outcomes assessment for chronic venous disease

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67.1 INTRODUCTION

What is truth? This is an ambitious question that is worth asking in a chapter on outcomes after the treatment of venous disorders. Is truth absolute or relative to the situational context? The previous lead author of this chapter, Dr. Robert Rutherford, pursued vascular truth through standardized outcome measures. Indeed, individual results may be rewarding personally, but exist in ignominy. Unified results collected in a common language with the intention of answering the important questions are efficacious, truthful, and valuable, even when the measure is imperfect. Chronic venous disease (CVD) is complex and progressive, and it presents new challenges to physicians daily. In this chapter, we review the most commonly used outcome measures available for the treatment of venous reflux and obstruction. Subjecting our practices to a "measuring stick" enables us to assess ourselves as practitioners. If not for our own benefit, then for those who follow us.

67.2 RATIONALE

Recent developments in the number and quality of treatment modalities have increased health care provider interest in outcomes assessment. Uniform outcomes data are desirable to establish medical necessity for third-party payers. A valuable assessment tool measures and stratifies venous symptoms and elucidates the results of therapy and disease progression. Physician-generated instruments including the Clinical Etiology Anatomy Pathophysiology (CEAP) score (Table 67.1) and the Venous Clinical Severity Score (VCSS) measure mostly objective data (Table 67.2). Patient-reported assessments have also increased in popularity. There are four measurement tools that are frequently referenced in the venous literature, in addition to one newer promising tool. These are the Venous Insufficiency Epidemiologic and Economic Study of Quality-of-Life (VEINES-QOL/Sym), the Chronic Venous Insufficiency Questionnaire (CIVIQ) (Tables 67.3 and 67.4), the Aberdeen Varicose Vein Questionnaire (AVVQ), the Charing Cross Venous Ulceration Questionnaire (CXVUQ), and the Varicose Vein Symptom Questionnaire (VVSymQ) (Table 67.5). The novel idea of combining physician-generated and patient-reported assessment instruments is being explored. The benefit of a combination approach may be a more accurate evaluation of symptoms and treatment results in the same patient. A model that joins the elements of symptoms, treatment results, and ultrasound findings may be the framework for medical necessity and reimbursement in the future.

Standardization of tools is critical to enabling accurate comparisons. For venous disease, these tools are needed in order to assess clinical outcomes and quality of life (QoL) issues. The number of available outcomes assessment tools has increased markedly in recent years. In addition, there are demands from an increasingly restrictive payer network. The result is an array of similar but different assessment tools that reflect the measured outcomes.

The first Joint Vascular Societies reporting standards in venous disease was published in 1988. In part, this led to the formation of a task force by the American Venous Forum (AVF), which, together with an international task force, developed the CEAP classification. Subsequently, the VCSS, Venous Segmental Disease Score (VSDS) (Table 67.6), and the Venous Disability Score (VDS) (Table 67.7)—a

Table 67.1 Classification based on Clinical presentation, Etiology, Anatomy, and Pathophysiology (CEAP)

Feature	Score	Description
Clinical		
	0	No visible or palpable disease
	1	Telangiectasias, reticular veins
	2	Varicose veins
	3	Edema
	4	Skin changes such as stasis dermatitis, lipodermatosclerosis
	5	Skin changes with healed ulcer
	6	Skin changes with active ulcer
Etiology		
	Congenital	Present since birth
	Primary	Undetermined etiology
	Secondary	Known cause post-thrombotic, post-traumatic
Anatomy		
	Superficial	
	Deep	
	Perforating	
Pathology		
	Reflux	
	Obstruction	
	Reflux and obstruction	

modification of the original CEAP disability score—were developed by AVF in order to better assess the interventions for CVD. CEAP was identified as a good classification system, but was shown to be unreliable for assessing the effects of interventions. Subsequently, there have been modifications of these tools. Most tools are applicable to both insufficiency and obstruction, but identifying the best tools can be problematic.

In this chapter, we review the currently available validated tools for the assessment of the symptoms and manifestations of CVD, focusing on instruments that evaluate the results of therapy. We discuss their benefits and limitations. In addition to a systematic review of outcomes assessment, we address the possible future value of these instruments in consideration of emerging therapies.

67.3 CURRENTLY AVAILABLE ASSESSMENT TOOLS

The field of venous disease has changed markedly during the past 6 years since the previous edition of this volume. There remain two categories, consisting of physician-assessed or patient-reported instruments, but the tools available have undergone further validation, giving an improved view of the benefits and drawbacks of many instruments.

With many instruments available, it is challenging to choose the best one to provide the desired information easily, and it is also difficult to compare studies using different evaluative tools. Many clinicians do not use generic QoL instruments, including the Short Form 36 (SF-36). Although the SF-36 has been validated, it yields population-based and collective treatment results.[1,2] Instruments that are specific for venous disease symptoms and therapy have recently combined physician-generated tools and patient-reported outcomes.

67.3.1 Physician-generated tools

The CEAP and VCSS provide measurement of clinical parameters in the progression of venous disease. CEAP is a classification tool and is not adequate for the periprocedural representation of CVD. Therefore, CEAP is not used to assess treatment results as a standalone tool. CEAP has limited responsiveness to changes in condition with therapy, especially at class 4 and class 5 levels. The Revised VCSS is a more dynamic representation of the course of venous disease through serial reporting (Table 67.2).[3] Both CEAP and VCSS have gained acceptance due to their common descriptive platforms and ease of use, and have strong recommendations for use in the Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum[2] and the European Society for Vascular Surgery (ESVS) Guidelines[4] regarding the treatment of CVD.

The Revised VCSS is currently the most widely used physician-derived venous severity score and treatment outcome measure. In a detailed review of Medline, Embase, and Web of Science databases from 2010 to 2015, there were 101 articles that used VCSS as an outcome measure and 82 articles that cited VCSS literature. The original VCSS was criticized because of its interobserver variability. The VCSS was revised in 2010 (Table 67.2) with improvement in specificity of language, nomenclature, and interobserver variability, especially with regards to symptoms and pigmentation change. The Revised VCSS is currently incorporated into European and American venous registries. It is readily available on the AVF website. There remains debate about whether the VCSS should include the subjective category of compression therapy, and this may be addressed in future revisions.[1,3] Nevertheless, for venous insufficiency, the Revised VCSS has become the most globally accepted physician outcome assessment with validation in the scientific literature.

The feature that sets the Revised VCSS apart from other instruments is its ability to reflect response to therapy and provide a visual language because of the character of the categories that are subdivided into elemental aspects of venous disease. The clinical descriptors include vein size and location, use of compression therapy, skin changes, and edema. Pain is identified as aching, heaviness, fatigue, soreness, and burning. The Revised VCSS improves the sensitivity of the original VCSS and better identifies the issues of patients with milder venous disease. Several studies with

Table 67.2 Revised Venous Clinical Severity Score (VCSS)

Pain or other discomfort (i.e., aching, heaviness, fatigue, soreness, burning) Presumes venous origin	**None:** 0	**Mild:** 1 Occasional pain or other discomfort (i.e., not restricting regular daily activity)	**Moderate:** 2 Daily pain or other discomfort (i.e., interfering with but not preventing regular daily activities)	**Severe:** 3 Daily pain or discomfort (i.e., limits most regular daily activities)
Varicose veins "Varicose" veins must be ≥3 mm in diameter to qualify	**None:** 0	**Mild: 1** Few: scattered (i.e., isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	**Moderate:** 2 Confined to calf or thigh	**Severe:** 3 Involves calf and thigh
Venous edema Presumes venous origin	**None:** 0	**Mild:** 1 Limited to foot and ankle area	**Moderate**: 2 Extends above ankle but below knee	**Severe**: 3 Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases (i.e., vasculitis purpura)	**None**: 0 None or focal	**Mild**: 1 Limited to perimalleolar area	**Moderate**: 2 Diffuse over lower third of calf	**Severe**: 3 Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (i.e., erythema, cellulitis, venous eczema, dermatitis)	**None**: 0	**Mild**: 1 Limited to perimalleolar area	**Moderate**: 2 Diffuse over lower third of calf	**Severe**: 3 Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis, hypodermitis) Includes white atrophy and lipodermatosclerosis	**None**: 0	**Mild**: 1 Limited to perimalleolar area	**Moderate**: 2 Diffuse over lower third of calf	**Severe**: 3 Wider distribution above lower third of calf
Active ulcer number	0	1	2	≥3
Active ulcer duration (longest active)	N/A	<3 months	>3 months but <1 year	Not healed for >1 year
Active ulcer size (largest active)	N/A	Diameter <2 cm	Diameter 2–6 cm	Diameter >6 cm
Use of compression therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

the Revised VCSS have confirmed its ease of use by the busy practitioner (Figure 67.1).

67.3.2 Patient-reported outcomes

Patient-reported, venous disease-specific outcome reporting tools have gained popularity recently as subjective measures of the benefits of therapy.[2] The five assessments that are reported most frequently are the VEINES-QOL/Sym, CIVIQ, AVVQ, CXVUQ,[1] and VVSymQ scores. They focus primarily on symptoms and are effective measures for evaluating patients' perceptions of the effects of treatment.

The CIVIQ has been validated and is used effectively as a global measure of venous disease (Tables 67.3 and 67.4).

Table 67.3 Dimensions and items used in the Chronic Venous Insufficiency Questionnaire 20 (CIVIQ-20)

Dimension	Item
Pain	Pain in the legs
	Impairment at work
	Sleeping poorly
	Standing for long periods
Physical	Climbing several floors
	Squatting or kneeling
	Walking at a regular pace
	Doing housework
Psychological	Feeling nervous
	Having the impression of being a burden
	Being embarrassed to show legs
	Becoming irritable easily
	Having the impression of being disabled
	Having no desire to go out
	Having to take precautions
	Getting tired easily
	Difficulty in getting going
Social	Going to parties
	Performing athletic activity
	Traveling by car or plane

Table 67.4 Dimensions and items used in the Chronic Venous Insufficiency Questionnaire 14 (CIVIQ-14)

Dimension	Item
Pain	Pain in the legs
	Impairment at work
	Sleeping poorly
Physical	Climbing several floors
	Squatting or kneeling
	Walking at a regular pace
	Going to parties
	Performing athletic activities
Psychological	Feeling nervous
	Having the impression of being a burden
	Being embarrassed to show legs
	Becoming irritable easily
	Having the impression of being disabled
	Having no desire to go out

Table 67.5 Dimensions and items used in the Varicose Vein Symptom Questionnaire (VVSymQ)

Dimension	Items
Symptoms	Heaviness
	Achiness
	Swelling
	Throbbing
	Itching

Table 67.6 Venous Segmental Disease Score (VSDS)

Reflux		Obstruction	
Vein	Score	Vein	Score
Small saphenous	0.5		
Great saphenous	1	Great saphenous (groin to below knee)	1
Perforator, thigh	0.5		
Perforator, calf	1		
Calf veins, multiple	2	Calf veins, multiple	1
Posterior tibial	1		
Popliteal	2	Popliteal	2
Femoral	1	Femoral	1
Profunda femoris	1	Profunda femoris	1
Common femoral or iliac	1	Common femoral	2
		Iliac	1
		Inferior vena cava	1

Table 67.7 Venous Disability Score (VDS)

Score	Symptom
0	Asymptomatic
1	Symptomatic; can perform normal activities without compression garments
2	Symptomatic; requires compression or elevation to perform normal daily activities
3	Unable to perform normal daily activities, even with compression and leg elevation

It does not address specific manifestations of venous disease, but is valuable in overall assessment.[1] It has been validated in 17 versions for different languages.[5] There are two versions of the CIVIQ: CIVIQ-14 and CIVIQ-20 (Tables 67.3 and 67.4). For the CIVIQ-20, patient-generated reports of the signs and symptoms of venous disease were used to generate the questionnaire; the 20-item questionnaire has a comprehensive collection of relevant parameters for pain, physical, psychological, and social outcomes. Patient recall of symptoms was set at 4 weeks of the survey.

The CIVIQ-20 (Table 67.3) was incomplete in assessing social factors in divergent populations. Therefore, the CIVIQ-14 was developed, which combined social and pain factors to yield three categories: pain, physical, and psychological (Table 67.4). This questionnaire was validated internationally.

The issues addressed in the CIVIQ assess patients across the spectrum of venous disease, but target classes 0–4 (Table 67.1). Patients who have ulcers are excluded because factors relevant to patients in the earlier stages of CVD may not be relevant to patients who have ulcers present, including questions relating to participation in sports or limitations on social activities. The CIVIQ-20 showed strong

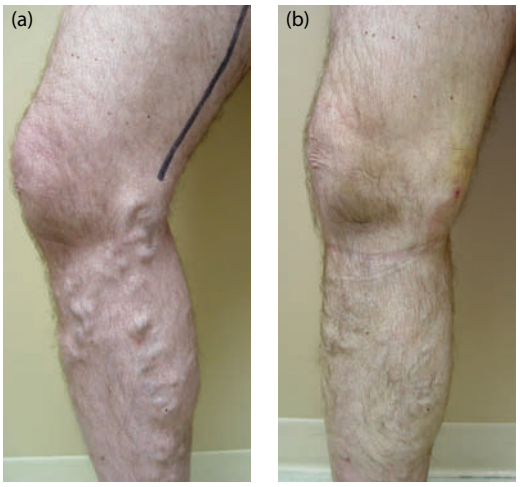

Figure 67.1 The visual language of the Revised Venous Clinical Severity Score (VCSS). The nomenclature enables clear, reproducible scoring of venous disease by multiple clinicians. **(a)** Pre-operative photograph of a leg with painful bulging varicose veins and edema. CEAP clinical class = 3. Total VCSS = 7 (pain = 1; varicose veins = 2; edema = 2; pigmentation = 0; inflammation = 0; induration = 0; active ulcers, size, duration = 0; compression therapy = 2). **(b)** Photograph of the same leg 1 week after saphenous vein ablation. CEAP clinical class = 2. Total VCSS = 3 (pain = 0; varicose veins = 1; edema = 0; pigmentation = 0; inflammation = 0; induration = 0; active ulcers, size, duration = 0; compression therapy = 2).

reliability for tracking changes after therapy. This has been validated in studies comparing treatment methods, including non-operative therapies.[5]

The VEINES-QOL/Sym is applicable to varied clinical conditions. It focuses on the underlying condition and changes in associated symptoms, not on therapy. It is useful in documenting symptomatic changes in studies using multiple treatments.[6] However, because it focuses on diagnostic elements, it is difficult to assess change in response to a specific therapy. In addition, there is limited focus on anatomic and physiologic elements, which might also clarify beneficial treatment options.[1]

The AVVQ considers all elements of venous disease, including cosmetic manifestations. The AVVQ is useful for many applications and venous disease findings, but it lacks sensitivity in elucidating change over time in individual patients, especially patients who have milder disease.[1]

The CXVUQ assesses QoL factors specifically in patients with venous ulcers, regardless of treatment options. For the CXVUQ to give a complete venous disease assessment in patients with ulcers, it should be combined with a traditional clinical outcome measure or generic instrument.[1]

The most recently described assessment tool is the VVSymQ score.[7] This is a symptom-focused, patient-reported outcome tool that was designed to evaluate the symptom burden of varicose veins before and after treatment of the great saphenous vein (GSV) in randomized controlled trials of polidocanol endovenous injectable microfoam. It is the only patient-reported outcome tool that meets the standards for reliability, sensitivity, and content validity described in the United States Food and Drug Administration guidance document titled *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.[8] The VVSymQ score is based on daily patient assessment of the varicose vein symptoms that are most important to patients as determined by research: heaviness, achiness, swelling, throbbing, and itching.

There is a correlation between instruments such as the VCSS, VEINES-QOL, and CIVIQ-20. In the polidocanol endovenous microfoam trials, the VVSymQ, VCSS, and VEINES-QOL were highly sensitive to changes following treatment.[6] A moderate correlation between the VVSymQ and VCSS indicated that both instruments may measure different aspects of the same disease. This is consistent with our understanding of the complementary characteristics of physician-generated and patient-reported tools.

Symptom ratings were recorded using a daily electronic diary and symptom scores were averaged over 7 days. This enabled proper completion of the questionnaire without health care provider influence. However, the VVSymQ is currently proprietary and not available for broad use. Discussions between the company, the American Venous Forum, and others may yield a modified single-encounter version of this instrument that may maintain good measurement properties.

The Villalta scale (Table 67.8) combines clinician assessment and patient ratings. The physician rates six criteria on a scale of 0–4 and patients answer five questions. The sum of the score is determined by the extent of disease; post-thrombotic syndrome (PTS) is defined by a score ≥5, mild PTS by a score of 5–9, and severe PTS by a score of >15 or venous ulceration. This is one of the most commonly used scales in current publications for the determination of the clinical outcomes of venous disease.

The VCSS may be less useful in studying PTS patients than the Villalta score.[9] The Revised VCSS was intended to assess patients at all stages of CVD, including patients with PTS, saphenous vein ablation, stenting for venous obstruction, and pharmacomechanical thrombolysis. In a recent review focusing on PTS, it was recommended that "the Villalta score combined with a venous disease-specific quality-of-life questionnaire be considered as the 'gold standard' for the diagnosis and classification of PTS."[9] Another study showed that a significant increase in the VCSS and VSDS paralleled CEAP clinical class in PTS patients.[10] In a comparison of the Villalta score and VCSS, both were considered important in the identification and follow-up of PTS. There is agreement between the two scores in detecting mild to moderate and severe disease.[11] The Villalta score was designed for PTS and the VCSS was not.

67.4 VENOUS OCCLUSIVE DISEASE

Chronic venous occlusion assessment should evaluate clinical outcomes, QoL issues, and risk for recurrent venous

Table 67.8 Villalta scale

Parameter	Symptom or sign	None (0)	Mild (1)	Moderate (2)	Severe (3)
Symptom (patient rated)	Pain	0	1	2	3
	Cramps	0	1	2	3
	Heaviness	0	1	2	3
	Paresthesia	0	1	2	3
	Pruritis	0	1	2	3
Sign (physician rated)	Pretibial edema	0	1	2	3
	Skin induration	0	1	2	3
	Hyperpigmentation	0	1	2	3
	Pain with calf compression	0	1	2	3
	Venous ectasia	0	1	2	3
	Erythema	0	1	2	3

Note: Score: <5 = no post-thrombotic syndrome; 5–14 = mild to moderate post-thrombotic syndrome; >15 = severe post-thrombotic syndrome.

thromboembolism (VTE). Although most tools can be applied to occlusive disease, validation has occurred predominantly in venous insufficiency.

67.5 VENOUS SEVERITY SCORING SYSTEMS

67.5.1 CEAP score

The CEAP score is commonly used and well known (Table 67.1). There are four components to it: clinical, etiology, anatomic location, and underlying pathophysiology. The clinical component assesses edema, skin changes, and ulcer development. The etiology component reports on whether reflux is congenital or secondary to prior obstructive disease. The pathophysiology component assesses whether ongoing obstruction is present. The anatomy component notes the involved venous segments. The Revised CEAP score contains descriptors in order to facilitate proper categorization. However, the CEAP score remains limited in its ability to assess outcomes of intervention after the patient has developed edema, which is common in post-phlebitic patients.

67.5.2 Revised VCSS

The VCSS commonly is used to assess patients undergoing interventions for venous insufficiency and can be applied to patients with obstructive disease (Table 67.2). The tool comprises nine categories, each graded on a scale of 0–3. Attributes including pain, venous edema, skin pigmentation, induration, inflammation, and ulcer formation may occur with outflow obstruction, reflux, or the combination of obstruction and reflux. The VCSS does not assess venous claudication or the effect of venous obstruction on QoL. It also does not address location of obstruction and its effect on outcomes, which is important for understanding the risk/benefit of interventions to treat venous thrombosis.

A previous study showed correlations between the VCSS, CEAP, the modified CIVIQ, and venous duplex findings.[3] The strongest correlations occurred with pain ($r = 0.55$; $P < 0.0001$) and swelling ($r = 0.3$; $P < 0.0001$). In this study, only 1.5% patients had residual obstructions in the femoral, popliteal, or saphenous segments.

67.5.3 Venous segmental disease score

Venous duplex is the tool most commonly used to assess for the propagation or resolution of a clot. However, standardization has been infrequent. The VSDS was created to complement the CEAP and VCSS and to standardize the reporting of disease location (Table 67.6) by condensing the 18 possible vein segments into eight groups; the small saphenous vein is not included in obstruction because it is unlikely to cause obstructive issues. The score can be completed with duplex or venography with complete occlusion at some portion, or >50% stenosis of half or more of the segment being scored. The maximum possible score is 10 for obstruction, with different veins attributing higher weights. The tool also assesses venous reflux, which is commonly present in the post-phlebitic limb. There have been no good studies that validate the VSDS in terms of assessing patients with chronic obstructive venous disease. In addition, the iliac vein does not receive a higher weight, even though it is of greater clinical importance and is more frequently treated with interventional therapy for deep vein thrombosis (DVT).

Concordance between the VCSS and CEAP using the VSDS was found in 13% of patients who had duplex abnormalities, and 14% were classified as scoring >1 despite no duplex evidence of abnormality.[12] The CEAP score had a good negative predictive value (NPV; 94%) and specificity (91.5%), but a poor positive predictive value (PPV; 36.7%) and sensitivity (32.1%). The VCSS had an excellent NPV (97.9%) and specificity (96.4%), but a low PPV (66.7%) and sensitivity (46.4%). Only one patient in this study had an obstructive component (GSV), and drawing conclusions regarding the utility for obstructive disease was not possible.[12]

67.5.4 Venous disability score

The VDS was originally developed as a modification of the CEAP (Table 67.7) and assesses activities of daily living before and after the development of venous disease. In the original version, it was assumed that normal activity included an 8-hour workday. This was modified to include specifying the ability to perform normal activities before disability developed secondary to venous disease, and support devices were modified to specify compression devices or limb elevation. Few studies incorporate the VDS for determining its validity for chronic venous occlusive disease.

67.5.5 Villalta scale

A sub-study in 367 patients of the REVERSE study of unprovoked proximal DVT assessed the Villalta score by comparing the ipsilateral (affected) to the contralateral leg in order to determine whether the score may reflect PTS symptoms accurately (Table 67.8).[13] The mean Villalta score was higher in the ipsilateral (3.7) than the contralateral leg (1.9; $P < 0.0001$), and there was a strong correlation between ipsilateral and contralateral Villalta scores ($r = 0.68$; $P < 0.0001$). The ipsilateral leg developed PTS in 31.6% of patients after initial VTE. The contralateral leg satisfied the criteria for PTS, despite never having had DVT, in 13.6% of patients. When PTS was present in the affected limb, 39.7% of patients had PTS according to the Villalta score in the unaffected leg. The study concluded that an elevated Villalta score and a diagnosis of PTS may be more related to prior underlying venous incompetence with or without obstruction, but not the isolated DVT.

A similar finding was observed in the ELATE trial, with 17% contralateral PTS according to Villalta score at 2 years, but assessment was complicated because of prior history of VTE. There was a 23% prevalence of abnormal Villalta scores in patients without a history of VTE.[14] Therefore, other causes of lower extremity edema may affect Villalta scores.

Another study observed a correlation between the CEAP, Villalta score, and success of thrombolysis for iliofemoral DVT in terms of preventing PTS.[15] Patients who had successful thrombolysis (≤50% residual thrombosis) had mean CEAP scores of 1 and mean Villalta scores of 2.21 versus unsuccessful intervention (>50% residual thrombosis), which had higher median CEAP scores (4; $P \leq 0.025$) and mean Villalta scores (7.13; $P \leq 0.011$).

The CaVenT study randomized patients to thrombolysis or conventional anticoagulation for iliofemoral DVT and assessed the outcomes of thrombolysis using the Villalta score at 24 months.[16] Frequency of PTS and patency were measured at 6 months. The study found a 14.4% absolute risk reduction in the development of PTS with thrombolysis.

67.6 QOL ASSESSMENTS

QoL is a major concern of patients with CVD because many are young and otherwise healthy. The ability to return to work or function normally is important to these patients. In addition, it is important to assess comparative effectiveness, taking into account the cost-effectiveness of various therapies for venous incompetence and obstructive diseases.

67.6.1 Generic QoL tools

Current generic QoL tools that have been used in the reporting of venous obstruction include the 36-item SF-36 and 12-item SF-12 health surveys.[17] The benefits of generalized QoL forms include the potential to compare QoL between venous and other diseases. The SF-36 includes two categories (physical and mental health) with eight domains that assess social functioning, role limitations due to impairment in physical or mental health, mental health, pain, vitality, physical functioning, and health perception. Higher scores indicate better health perception. The SF-12 is a subset of the SF-36 and can be completed in 2 minutes. However, these tools do not allow for a full assessment of specific venous issues.

67.6.2 Disease-specific QoL tools

Disease-specific tools for chronic occlusive venous disease include the CIVIQ, CXVUQ, VEINES-QOL/Sym, and Villalta scores.

A study using the CIVIQ showed improvements from venous stenting in patients who had chronic venous occlusion by assessing QoL before and after intervention.[18]

The CXVUQ is used to assess patients who have venous ulceration and it correlates well with the SF-36.[19]

A study assessing the outcomes of endovenectomy and iliocaval recanalization in patients with PTS using the VCSS, VEINES-QOL/Sym, CEAP, and duplex ultrasonography[20] found a decrease in the VCSS from 17 to 9.8 ($P = 0.02$) and improvement in QoL as determined with the VEINES-QOL/Sym score ($P = 0.01$). The CEAP showed minimal change.

In a study using a modified Villalta score to compare QoL outcomes using the VEINES-QOL/Sym tool for patients who developed VTE during pregnancy, a significant change in Villalta score was observed for patients who developed DVT (score >5; 42%) compared with controls (10%).[21] Patients who had PTS had markedly lower mean QoL scores on the VEINES-QOL/Sym tool (36.5 vs. 52.3).

67.7 UNRESOLVED ISSUES FOR CVD ASSESSMENT

The risk of recurrent VTE and the factors that affect the likelihood of recurrence are unknown. The factors associated with initial VTE risk are not necessarily the same as those responsible for recurrence. Hemodynamic assessment of venous disorders has been poorly studied and reported, and remains an issue because hemodynamic studies are not routinely included in assessment or reporting tools, nor are they used in many vascular laboratories that assess venous disease.

Other challenges in the reporting and assessment of venous disease include the frequent performance of multiple simultaneous interventions, potentially complicating the assessment of the effect of each intervention, such as simultaneous GSV ablation with treatment for incompetent perforators or iliofemoral obstruction. Although it may be reasonable to treat all possible issues in order to achieve improved outcomes for a given patient who has a non-healing ulcer, this practice limits the understanding of the effect of each intervention on outcomes. Studies that assess these procedures should distinguish between patients who have single or multiple procedures and be adequately powered.

67.7.1 Hemodynamic assessment tools

Noninvasive studies with standardized criteria and tools for the assessment of venous hemodynamics are important for the evaluation of the natural history and medical and interventional treatment of venous disease. Untreated obstructions may develop collaterals which may alleviate some obstructive symptoms. Therefore, to assess venous disease, it is important to understand the location of obstructions, the hemodynamic effect of each obstruction, and changes with time.

Objective hemodynamic tests include air plethysmography, venous pressure gradients, and venous occlusion plethysmography. Standardized air plethysmography has 13.4% variability in measurements.[21] During procedures, intravascular ultrasound can be used to assess anatomical area reduction of the vein quantitatively, but this does not assess the hemodynamic effect of this reduction or the associated improvement of hemodynamic function with treatment. Whether the degree of stenosis should be of major concern is unknown because few studies have assessed the concordance of hemodynamic assessment for venous obstructive disease with clinical outcomes or QoL measures.

In a retrospective review of patients who had symptomatic PTS, 29 patients with venous claudication,[22] and 63 healthy controls, CEAP, strain gauge plethysmography, and duplex scanning were used to assess obstruction. Fifteen underwent venography and 14 underwent computed tomography or magnetic resonance imaging. Computerized venous plethysmography used a capacitance mode to assess venous occlusion. Measurements included venous volume during occlusion, outflow volume, and outflow fraction (OF) during the initial 1 second (OF1) and 4 seconds (OF4) after deflation. Most patients (90%) had residual iliac thrombosis, including 14 complete occlusions and 12 residual stenoses. By CEAP classification, 11 were class 3, 10 were class 4, and three were class 5–6. Venous volume averaged 6.7 mL/100 mL for patients and controls. Outflow volumes and OFs were significantly decreased for patients, and OF was more sensitive than outflow volume. The most accurate variable was OF4, which was abnormal in 69% patients. This study concluded that OF4 was more accurate than OF1.

In a prospective study of the effect of compression therapy on hemodynamic performance (CEAP, VCSS, and VSDS) in 40 limbs with PTS, most issues were attributed to reflux (four out of five with the VSDS score). Air plethysmography was performed at baseline and after the application of stockings. Compressive stockings significantly improved the venous filling index regardless of stocking class (Venous Filling Index 19%–27%, Venous Filling Time 90 18%–36%, and venous volume [VV; mL/sec] 2%–17%).[23]

In a 10-year retrospective study of the long-term effects of iliofemoral DVT on venous hemodynamics, clinical outcomes, and QoL in 39 patients treated with anticoagulation alone, the incidence of venous claudication was 43.6% with treadmill testing.[17] Patients were assessed with VCSS, CEAP, venous duplex scanning, SF-36, and air plethysmography with a treadmill exercise challenge. Most limbs (81%) had reflux in both deep and superficial veins, and 19% only had superficial reflux. Although the assessed parameters included venous volume, venous filling index, ejection fraction, residual volume fraction, and OF, the only parameters that were not altered were ejection fraction and venous volume. The QoL was impaired in five of eight categories assessed, including physical function, physical role, general health, social function, and mental health.

67.7.2 Recurrence

Recurrence or progression are important for determining the duration of anticoagulation. A previous review suggested that there are differences between the risks of the initial and recurrent events.[24] Decreased mortality has not been proven for indefinite anticoagulation, and anticoagulation is associated with major risks.[25]

There are no widely used tools to guide the assessment of risk status and the appropriate timing of the discontinuation of anticoagulation. Several studies have assessed risk of recurrence. In an evaluation of idiopathic DVT, prior pulmonary embolism (PE) increased the risk of recurrent PE and DVT (60% recurrent PE). However, risk of any recurrence after isolated calf or upper extremity DVT was rare.[26] Recurrence was highest in patients who had multiple VTE, and 27.9% after a second DVT. Fewer data were available for multiple provoked VTE. Factors that increased risk included male gender, increased body weight, cancer, metastatic cancer, chemotherapy, continued oral contraceptives or hormone-replacement therapy, residual vein thrombosis, antithrombin deficiency, factor V Leiden, or G20210A. It is unknown whether these factors are additive. Several laboratory tests have been correlated with an increased risk of recurrence, including D-dimer level (>250 ng/mL after discontinuation of anticoagulation) and endogenous thrombin potential >100%. In the AUREC study, endogenous thrombin potential and D-dimer level were independent predictors of recurrence, and this was confirmed in other studies.[27,28]

DVT location impacts recurrence, with iliofemoral DVT having a 2.4-fold increased recurrence risk during the first 3 months of treatment.[29] Most studies have shown a 1.5- to 4.0-fold increased risk of recurrent thrombosis with residual thrombus.[30–33] In a study on iliofemoral thrombolysis

and clot burden, the recurrence rate at 3 years was 38% for patients who had >50% residual thrombus and 5% for patients who had <50% residual thrombus ($P \leq 0.0014$).[34]

A risk assessment tool was developed for use in patients who had unprovoked DVT or PE using the Vienna Prediction Model in a study of 929 patients enrolled upon discontinuation of anticoagulation.[26] There was an 18.9% incidence of symptomatic recurrence at a median of 43.3 months. Kaplan–Meier analysis showed the incidence rates of symptomatic recurrence to be 13.8% at 2 years, 24.6% at 5 years, and 31.8% at 10 years. A risk model categorized patients as having low risk, intermediate–low risk, intermediate–high risk, and high risk at 9.2%, 21.0%, 29.7%, and 33.1%, respectively, at 5 years for recurrence based on a D-dimer model (incorporating D-dimer level, gender, and initial VTE location). A limitation of this model was the exclusion of patients with hypercoaguable states and a lack of assessment of residual vein thrombosis.

Table 67.9 Risk of recurrent venous thromboembolism

Factor	Variable	Points
Deep vein thrombosis/ pulmonary embolus		
	Provoked	0
	Provoked >1	1
	Unprovoked, initial	2
	Unprovoked, multiple	3
Sex		
	Female	0
	Male	1
Cancer		
	None or previously	0
	Active	1
	Metastatic	2
Chemotherapy		
	No	0
	Yes	1
Hormone therapy		
	No	0
	Yes	1
Body mass index		
	Normal or mild overweight	0
	Obese or morbid obesity (>30 kg/m^2)	1
Residual venous thrombus >50%		
	Not present, or tibial or upper extremity vein only	0
	Femoral or popliteal vein	1
	Iliac or common femoral vein	2
Hypercoagulable state		
	None	0
	G20210A or factor V Leiden	1
D-dimer at discontinuation of anticoagulation		
	<250 ng/mL	0
	>250 ng/mL	2
Endogenous thrombin potential		
	<100%	0
	>100%	1

67.8 CONCLUSION

Further development and validation of comprehensive assessment tools are needed for the prediction of recurrent VTE. Such tools should include D-dimer, hypercoaguable states, anatomic levels of thrombus, residual thrombus, gender, body mass index, presence of malignancy, and use of hormonal therapy and chemotherapeutic agents (Table 67.9). These tools will help guide the appropriate duration of therapy.

There is a need to standardize hemodynamic assessment and increase assessment in vascular laboratories before and after interventions. Venous claudication symptoms should be included in revisions or new tools to assess clinical outcomes. QoL questionnaires should incorporate the full spectrum of issues associated with venous diseases, including cosmetic issues, reflux, and obstruction. Future studies should correlate clinical findings with QoL and economic outcomes.

No absolute measure of outcomes assessment in CVD exists, but we deferentially approach the truth. There are varied validated, reliable assessment instruments to measure symptoms and the results of treatment. New modalities of treatment are ever present, but comparison of outcomes is best performed when the same outcomes measures are used. Physician assessment and patient self-assessment serve complementary functions and should be combined to provide a more accurate clinical scenario.[1,9] We believe that in both primary and secondary CVD, the addition of patient-reported outcomes greatly complements and enhances physician scores for initial assessment and following treatment. Encouraging clinicians to use both score types is proper and important. We recommend that a combined scoring system that includes duplex findings would be a preferred way to establish medical necessity for those considering treatment and insurance reimbursement.

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Summary of guidelines of the American Venous Forum*

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
Part 1. Basic Considerations of Venous Disorders			
Guidelines 1.1.0 of the American Venous Forum on the development and anatomy of the venous system			
1.1.1	The main deep vein of the thigh between the popliteal and the common femoral vein is the femoral vein. The old term "superficial femoral vein" should be abandoned.	1	
1.1.2	The main superficial veins of the lower limb are the great saphenous vein and the small saphenous vein.	1	
1.1.3	The old terms "Cockett" and "Giacomini" veins should be replaced by the new terms "posterior tibial perforating vein" and "intersaphenous vein," respectively. The use of eponyms is discouraged.	1	
Guidelines 1.2.0 of the American Venous Forum on the physiology and hemodynamics of the normal venous circulation			
1.2.1	Venous return follows a continued dynamic pressure gradient. The majority of the energy imparted by the pumping action of the heart is dissipated in distribution to the arterial circulation.		A
1.2.2	The hydrostatic pressure in the venous system is directly related to the height of the column of blood in relation to the zero point of the right atrium.		A
1.2.3	Venous return against gravity is accomplished by the combined action of an active extremity muscle pump and one-way venous valves.		A
1.2.4	The plantar venous pump acts to prime the calf muscle pump.		C

(*Continued*)

* Disclaimer: Guidelines listed in the 4th Edition of the Handbook of Venous and Lymphatic Disorders are based on previously published peer reviewed, evidence based guidelines of the American Venous Forum, the Society for Vascular Surgery or other national or international societies dedicated to the care of venous disease. If published guidelines were not available, grading the strength of recommendations and evaluating the level of evidence were based on expert consensus of the authors of the appropriate chapter and of the Editorial Board.

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.2.5	The thigh muscle pump contributes little to venous return.		B
1.2.6	The anatomic structure of a vein allows for great variation in its diameter. This facilitates the capacitance function of the venous system for adjustment to volume and temperature changes.		A
1.2.7	External pressure on collapsible proximal veins increases distal venous pressure.		B
Guidelines 1.3.0 of the American Venous Forum on the classification and etiology of chronic venous disease			
1.3.1	We recommend using the CEAP (clinical class, etiology, anatomy, pathophysiology) classification to describe chronic venous disorders. The system has been validated.	1	B
1.3.2	We recommend using the basic CEAP classification to aid clinical practice and the full CEAP classification for clinical research.	1	B
1.3.3	We recommend distinguishing between primary and secondary venous insufficiency, because the two conditions distinctly differ in pathophysiology and management.	1	B
Guidelines 1.4.0 of the American Venous Forum on the pathophysiology and hemodynamics of chronic venous insufficiency			
1.4.1	Persistent ambulatory venous hypertension due to venous obstruction or valvular incompetence is the main cause of chronic venous insufficiency.		A
Guidelines 1.5.0 of the American Venous Forum on the pathogenesis of varicose veins and cellular pathophysiology of chronic venous insufficiency			
1.5.1	Genetics and deep venous thrombosis are predisposing factors for varicose veins.		A
1.5.2	Age, female gender, pregnancy, weight, height, race, diet, bowel habits, occupation, and posture are predisposing factors for varicose veins.		C
1.5.3	Vein wall remodeling and fibrosis, affected by hemodynamic factors, matrix metalloproteinases, and plasminogen activators, lead to varicose vein formation.		C
1.5.4	In chronic venous insufficiency, the transmission of high venous pressures to the dermal microcirculation causes extravasation of macromolecules and red blood cells that serves as the underlying stimulus for inflammatory injury.		A
1.5.5	Transforming growth factor-β1 and matrix metalloproteinases play key roles in the inflammatory injury that leads to lipodermatosclerosis and chronic skin changes.		B
Guidelines 1.6.0 of the American Venous Forum on venous ulcer formation and healing at cellular levels			
1.6.1	We recommend a basic practical knowledge of venous physiology and venous leg ulcer pathophysiology for all practitioners caring for venous leg ulcers.		Best practice
1.6.2	Age, genetic, and environmental factors predispose to venous ulcers.		B
1.6.3	Shear stress, glycocalyx injury, and expression of adhesion molecules with venous endothelial activation allow attachment of leukocytes and are key steps in the progression of chronic venous insufficiency.		B

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.6.4	Leukocyte activity and interaction with endothelial cells initiates a cascade of inflammatory events.		B
1.6.5	Macrophages have a major role in ulcer formation.		C
1.6.6	Dysfunctional leukocytes, senescent fibroblasts, and keratinocytes contribute to delayed ulcer healing.		B
1.6.7	Key regulatory cell cycle proteins (p21 and pRb) affect fibroblast proliferation and delay wound healing.		B
1.6.8	Venous ulcer fluid has elevated inhibitory cytokines and matrix metalloproteinases (MMPs). MMPs have an integral role in venous ulcer formation.		A
1.6.9	Factor XIII, plasminogen, and extracellular MMP inducer modulate MMP activity and contribute to venous ulcers.		C
Guidelines 1.7.0 of the American Venous Forum on acute and chronic venous thrombosis: pathogenesis and new insights			
1.7.1	Acute venous thrombosis causes an acute to chronic inflammatory response in both the vein wall and the thrombus. This leads to thrombus amplification, organization, and recanalization, as well as damage to the vein wall and the valves.		A
1.7.2	D-dimer, endothelium, platelet-derived microparticles, and soluble P-selectin are markers of thrombosis and they are increased in patients with acute venous thromboembolism.		A
1.7.3	Resolution of the thrombus is modulated by natural anticoagulants such as antithrombin III, protein C, protein S, and thrombin.		B
1.7.4	Polymorphonuclear cells promote both fibrinolysis and collagenolysis and they play key roles in thrombus resolution. Monocytes are essential in late thrombus resolution.		A
Guidelines 1.8.0 of the American Venous Forum on the epidemiology and risk factors of acute venous thrombosis			
1.8.1	The prevention and management of venous thromboembolism requires an understanding of the interaction of underlying risk factors. All episodes of venous thromboembolism should be characterized as primary (unprovoked and idiopathic) or secondary (provoked).	1	A
1.8.2	All hospitalized patients should have a thorough assessment of thromboembolic risk factors at the time of admission.	1	A
1.8.3	Recognized models, such as the Rogers or Caprini scores, should be used to assess thromboembolic risk in surgical patients.	1	B
1.8.4	Established evidence-based guidelines should be followed for deep vein thrombosis prophylaxis in high-risk patients.	1	A
1.8.5	Thrombophilia screening should be limited to patients included in established guidelines.	1	A
Guidelines 1.9.0 of the American Venous Forum on the epidemiology of chronic venous disorders			
1.9.1	The prevalence of varicose veins in the adult population is more than 20% (21.8%–29.4%).		A
1.9.2	About 5% (3.6%–9.6%) of the adult population has skin changes or ulcers due to chronic venous insufficiency.		A

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
1.9.3	Active venous ulcers are present in 0.1%–0.7% of the adult population, and 0.6%–1.4% have healed ulcers.		B
1.9.4	Advanced age is a risk factor for varicose veins and chronic venous insufficiency.		A
1.9.5	Positive family history, female gender, and multiparity are risk factors for varicose veins.		A
1.9.6	Age and obesity are risk factors for chronic venous insufficiency.		A
Part 2. Diagnostic Evaluations and Venous Imaging Studies			
Guidelines 2.1.0 of the American Venous Forum on the evaluation of hypercoagulable states and molecular markers of acute venous thrombosis			
2.1.1	Patients with the following conditions are considered for evaluation for thrombophilia: 1. Unexplained or "idiopathic" thromboembolism (first event) 2. Secondary, non-cancer-related first event and age <50 years (includes thrombosis on oral contraceptives and hormone-replacement therapy) 3. Recurrent "idiopathic" or secondary non-cancer-related events 4. Thrombosis at unusual sites (portal vein, sinus veins, etc.) 5. Extensive thrombosis 6. Strong family history of venous thromboembolism	1	C
2.1.2	Testing for thrombophilia is recommended to most patients 2–4 weeks after completing the typical course (usually 6 months) of anticoagulant therapy.	1	C
2.1.3	Long-term, primary pharmacologic thromboprophylaxis of asymptomatic thrombophilic patients is not recommended.	2	B
2.1.4	Patients with thrombophilia should be considered for thromboprophylaxis at times of high thrombotic risk such as surgery, trauma, prolonged immobility, pregnancy, or acute illness.	1	A
2.1.5	Patients with thrombophilia should be considered for prolonged anticoagulation following acute deep vein thrombosis.	1	B
Guidelines 2.2.0 of the American Venous Forum on duplex ultrasound scanning for acute venous disease			
2.2.1	Duplex ultrasound scanning is recommended to be the standard of care for diagnosing acute deep vein thrombosis (DVT) of the limbs.	1	A
2.2.2	We recommend that duplex examination for DVT includes three components in each vein segment studied: thrombus visualization, venous coaptability or compressibility, and detection of venous flow.	1	A
2.2.3	We suggest that duplex scanning has a sensitivity of ≥90% for the detection of symptomatic femoropopliteal thrombosis and a range of 50%–70% for calf vein thrombosis.	2	B
2.2.4	We suggest that duplex scanning for upper extremity DVT has a sensitivity of between 78% and 100% and a specificity of between 82% and 100%.	2	B

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
Guidelines 2.3.0 of the American Venous Forum on duplex ultrasound scanning for chronic venous obstruction and valvular incompetence			
2.3.1	Duplex scanning is recommended as the first diagnostic test for all patients with suspected chronic venous obstruction or valvular incompetence. The test is safe, noninvasive, cost-effective, and reliable.	1	A
2.3.2	We recommend that four components included in duplex scanning examinations for chronic venous disease are visualization, compressibility, venous flow, and augmentation.	1	A
2.3.3	Duplex scanning is recommended to distinguish acute from chronic venous occlusion.	2	B
2.3.4	We suggest that reflux is elicited in two ways: increased intra-abdominal pressure using a Valsalva maneuver or manual or cuff compression and release of the limb distal to the point of examination.	2	B
2.3.5	We recommend that reflux is elicited in the upright position in one of two ways: either with increased intra-abdominal pressure using a Valsalva maneuver to assess the common femoral vein and the saphenofemoral junction; or, for the more distal veins, use of manual or cuff compression and release of the limb distal to the point of examination.	1	A
2.3.6	A cut-off value of 1 second is recommended to define abnormally reversed flow (reflux) in the femoral and popliteal veins and of 500 ms for the great saphenous vein, the small saphenous vein, and the tibial, deep femoral, and perforating veins.	1	B
2.3.7	We recommend that in patients with chronic venous insufficiency, duplex scanning of the perforating veins is performed selectively. We recommend that the definition of "pathologic" perforating veins includes those with an outward flow of duration of ≥500 ms, with a diameter of ≥3.5 mm and a location beneath healed or open venous ulcers (CEAP class C5–C6).	1	B
Guidelines 2.4.0 of the American Venous Forum on the evaluation of venous function by indirect noninvasive testing (plethysmography)			
2.4.1	We suggest that venous plethysmography is used selectively for the noninvasive evaluation of the venous system in patients with simple varicose veins (CEAP class C2).	2	C
2.4.2	We suggest that venous plethysmography is used as a noninvasive evaluation of the venous system in patients with advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C3–C6).	2	B
Guidelines 2.5.0 of the American Venous Forum on direct contrast venography			
2.5.1	We recommend contrast venography before performing endovenous reconstructions for acute or chronic venous disease.	1	B

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
2.5.2	We suggest contrast venography for patients suspected of having acute deep vein thrombosis only if other imaging modalities are inconclusive.	2	B
Guidelines 2.6.0 of the American Venous Forum on computed tomography and magnetic resonance imaging in venous disease			
2.6.1	Computed tomography with intravenous contrast is recommended for evaluation of the obstruction of large veins in the chest, abdomen, and pelvis. Computed tomography accurately depicts the underlying pathology, confirms extrinsic compression, tumor invasion, traumatic disruption, anatomic variations, extent of thrombus, and position of a caval filter.	1	B
2.6.2	Computed tomography with intravenous contrast is recommended to diagnose pulmonary embolism. Sensitivity and specificity approach 100% for central emboli, whereas for small, subsegmental pulmonary emboli, sensitivity and specificity are 83% and 96%, respectively.	1	A
2.6.3	Magnetic resonance venography is recommended for the diagnosis of acute iliofemoral and caval deep vein thrombosis. A sensitivity of 100% and a specificity of 96% were reported. The study is also recommended for diagnosing portal, splenic, or mesenteric venous thrombosis.	1	A
2.6.4	Magnetic resonance imaging and magnetic resonance venography are highly accurate for imaging inferior vena cava thrombus associated with renal, adrenal, retroperitoneal, primary caval, or metastatic malignancies. Magnetic resonance venography reveals the presence or absence of bland thrombus or tumor thrombus in the renal veins and inferior vena cava.	1	A
Part 3. Management of Acute Thrombosis			
Guidelines 3.1.0 of the American Venous Forum on the clinical presentation of the natural history of acute venous thrombosis			
3.1.1	Based on differences in natural history, we recommend that lower extremity deep vein thrombosis (DVT) be precisely characterized as involving the iliofemoral veins, the femoropopliteal veins, or being isolated to the calf veins, rather than being simply designated as involving the proximal or distal veins.	1	A
3.1.2	We recommend formal determination of the pre-test probability of DVT using a validated scoring system in all patients presenting with signs and symptoms of acute DVT.	1	A
3.1.3	We recommend that the risk of recurrent venous thromboembolism be thoroughly assessed prior to discontinuing anticoagulation, particularly among those with idiopathic DVT.	1	A

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.1.4	We suggest a strategy of early thrombus removal in selected patients meeting the following criteria: (A) a first episode of acute iliofemoral DVT; (B) symptoms <14 days in duration; (C) a low risk of bleeding; and (D) ambulatory with good functional capacity and an acceptable life expectancy.	2	C
3.1.5	We recommend the use of 30–40 mmHg knee-high compression stockings to reduce the risk of post-thrombotic syndrome in compliant patients after an episode of acute DVT.	1	C
Guidelines 3.2.0 of the American Venous Forum on the diagnostic algorithms for acute deep venous thrombosis and pulmonary embolism			
3.2.1	In symptomatic outpatients with suspected acute deep vein thrombosis (DVT), we recommend to obtain first a clinical score and D-dimer level to select patients for further diagnostic studies.	1	B
3.2.2	D-dimer levels are inaccurate for diagnosing DVT in several clinical conditions, including recent surgery, pregnancy, malignancy, infection, elevated bilirubin, trauma, and heparin use. In these situations, alternative diagnostic modalities are recommended.	1	B
3.2.3	We recommend to repeat duplex scan or alternative imaging modality in the follow up of patients with negative duplex studies and high clinical suspicion of DVT.	1	B
3.2.4	We suggest that combination of clinical probability score and D-dimer level has similar utility in the diagnosis of DVT to a computed tomography scan.	2	B
3.2.5	We suggest judicious use of Gadolinium in patients with renal insufficiency because of the risk of nephrogenic systemic fibrosis.	2	C
Guidelines 3.3.0 Summary of key recommendations to the American Venous Forum on the medical therapy of acute deep vein thrombosis and pulmonary embolism			
3.3.1[a]	If home circumstances are adequate, we recommend that initial treatment of acute deep venous thrombosis (DVT) take place at home rather than in the hospital.	1	B
3.3.2[a]	We suggest low-molecular-weight heparin (LMWH) over unfractionated heparin for the treatment of acute DVT.	2	B
3.3.3[a]	We suggest once- over twice-daily administration of LMWH for the treatment of acute DVT.	2	C
3.3.4[b]	We suggest LMWH over NOACs or VKAs for patients with cancer and acute DVT.	2	C
3.3.5[b]	In patients with acute DVT and no cancer, as a long-term anticoagulant therapy we susggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K agonist (VKA) therapy.	2	B
3.3.6[b]	We suggest that patients with an unprovoked proximal DVT who are stopping anticoagulant therapy should take an aspirin to prevent recurrent VTE.	2	B

[a] Based on the recommendations of: Kearon C et al. *Chest* 2012;142:1698–704;

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.3.7[b]	We recommend 3 months of treatment for acute proximal DVT provoked by transient risk factors (surgical or non-surgical).	1	B
3.3.8[b]	We suggest monitoring over 2 weeks with serial imaging over anticoagulation for the treatment of acute isolated distal DVT without severe symptoms or risk factors.	2	C
3.3.9[b]	We suggest anticoagulation for acute isolated distal DVT with severe symptoms and risk factors.	2	C
3.3.10[b]	We suggest extended anticoagulation therapy in patients with an acute unprovoked proximal DVT who have low or moderate bleeding risk.	2	B
3.3.11[b]	We recommend 3 months of anticoagulant therapy rather than extended therapy in patients with an acute unprovoked proximal DVT who have high bleeding risk.	1	B
3.3.12[b]	We recommend extended anticoagulation beyond 3 months for acute DVT of the leg in the setting of active cancer if the risk of bleeding is not high.	1	B
3.3.13[b]	We suggest that anticoagulation be preferred over catheter directed thrombolysis for acute proximal DVT.	2	C
3.3.14[b]	We suggest systemic thrombolysis for pulmonary embolism associated with hypotension or when hypotension is likely without a high bleeding risk.	2	C
Guidelines 3.4.0 of the American Venous Forum on catheter-directed thrombolysis and venous thrombectomy for acute deep vein thrombosis			
3.4.1	In patients with symptomatic deep vein thrombosis and large thrombus burden, particularly in iliofemoral deep vein thrombosis, we recommend a treatment strategy that includes thrombus removal.	1	B
3.4.2	In patient with symptomatic iliofemoral deep vein thrombosis with symptoms of <14 days in duration, we recommend catheter-directed thrombolysis if appropriate expertise and resources are available to reduce acute symptoms and post-thrombotic morbidity.	1	B
3.4.3	We suggest pharmacomechanical thrombolysis, with thrombus fragmentation and aspiration, over catheter-directed thrombolysis alone in the treatment of iliofemoral deep vein thrombosis to shorten treatment time if appropriate expertise and resources are available.	2	B
3.4.4	In patients with acute DVT, systemic thrombolysis is not suggested.	2	B
3.4.5	For patients with symptomatic iliofemoral deep vein thrombosis who are not candidates for catheter-directed thrombolysis, we recommend surgical thrombectomy.	1	B
Guidelines 3.5.0 of the American Venous Forum on the endovascular and surgical management of acute pulmonary embolism[c]			
3.5.1	We recommend therapeutic anticoagulation with subcutaneous low-molecular-weight heparin, subcutaneous fondaparinux, or intravenous unfractionated heparin for initial anticoagulation for acute pulmonary embolism (PE).	1	A

[b] Kearon C et al. *Chest* 2016;149(2):315–352, and Meissner MH et al. *J Vasc Surg* 2012;55:1449–1462.
[c] Adapted from Jaff MR et al. *Circulation* 2011;123(16):1788–830.

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.5.2	Anticoagulation alone is recommended for low-risk PE or sub-massive PE with mild right ventricle dysfunction.	1	B
3.5.3	Thrombolysis is recommended for massive PE if bleeding risk is acceptable.	1	B
3.5.4	Thrombolysis is suggested for sub-massive acute PE felt to have poor prognosis if bleeding risk is acceptable.	2	C
3.5.5	Catheter thrombectomy, thrombus fragmentation, or surgical embolectomy is recommended for patients with massive PE and who are contraindicated for thrombolysis, depending on local expertise.	1	C
3.5.6	Catheter thrombectomy, thrombus fragmentation, or surgical embolectomy is recommended for patients with massive PE and who remain unstable after thrombolysis if local expertise is available.	1	C
3.5.7	Catheter thrombectomy or surgical embolectomy is suggested for patients with sub-massive PE who are judged to have a poor prognosis.	2	C
3.5.8	We suggest against catheter thrombectomy or surgical embolectomy for low-risk PE or sub-massive PE with minor right ventricle dysfunction.	2	C
Guidelines 3.6.0 of the American Venous Forum on the treatment algorithm for acute deep venous thrombosis			
3.6.1	Low-molecular-weight heparin (LMWH) is now preferred over standard unfractionated heparin (UFH) for the initial treatment of deep vein thrombosis (DVT).	1	A
3.6.2	The criteria for the discontinuation of oral anticoagulation include thrombosis risk, residual thrombus burden, and coagulation system activation (as suggested by D-dimer measurements).	1	A
3.6.3	Heparin-induced thrombocytopenia remains a problem with all heparin preparations, but is more frequent with UFH than LMWH. Alternative agents include hirudin, argatroban, and fondaparinux.	1	C
3.6.4	The use of strong compression and early ambulation after DVT treatment can significantly reduce the long-term morbidities of pain and swelling resulting from the DVT.	1	A
Guidelines 3.7.0 of the American Venous Forum on the current recommendations for the prevention of deep vein thrombosis			
3.7.1	When the risk of bleeding from pharmacologic agents is high, we suggest using non-pharmacologic methods of venous thromboembolism prophylaxis, including elastic compressive stockings, intermittent pneumatic compression devices, leg elevation, and early ambulation. Each of these reduces venous thrombotic events by approximately 20%.	2	C
3.7.2	For patients at very high risk of venous thromboembolism, we suggest non-pharmacologic methods of venous thromboembolism prophylaxis in combination with pharmacologic agents.	2	C

Note: LMWH: low-molecular-weight heparin; IV: intravenous; UFH: unfractionated heparin; PE: pulmonary embolism; RV: right ventricle.

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.7.3	For patients with acute venous thromboembolism within 1 month who undergo urgent/emergency surgery or if other circumstances prohibit anticoagulation, we recommend placement of an inferior vena cava filter.	1	B
3.7.4	We suggest against inferior vena cava filter therapy as primary prophylaxis for unselected trauma patients.	2	C
3.7.5	We suggest that the indications for temporary, retrievable, or optional inferior vena cava filters are the same as those for permanent inferior vena cava filters.	2	C
3.7.6	Aspirin may provide modest risk reduction following major joint surgery when added to other prophylaxis therapies.	1	B
3.7.7	For very-low-risk patients (Caprini score 0), the risk of venous thromboembolism is sufficiently low such that early ambulation alone is recommended.	1	B
3.7.8	For low-risk patients (Caprini score 1–2), intermittent pneumatic compression pumping is suggested.	2	C
3.7.9	For moderate-risk patients (Caprini score 3–4), we suggest low-dose unfractionated heparin, prophylactic-dose low-molecular-weight heparin (LMWH), or intermittent pneumatic compression pumping.	2	B
3.7.10	For high-risk general surgery patients (Caprini score ≥5), either low-dose heparin or prophylactic-dose LMWH are recommended.	1	B
3.7.11	For patients undergoing cancer-related surgery, we recommend pharmacologic prophylaxis extended for 4 weeks post-operatively.	1	B
3.7.12	For surgery patients at high risk of major bleeding, mechanical prophylaxis with intermittent pneumatic compression pumping is suggested over pharmacologic prophylaxis.	2	C
3.7.13	Following total joint replacement or hip fracture surgery, we recommend appropriate venous thromboembolism prophylaxis for 10 days.	1	A
3.7.14	For patients undergoing total hip arthroplasty, we recommend either LMWH, fondaparinux (2.5 mg/day), or vitamin K antagonism with warfarin (goal international normalized ratio: 2.0–3.0) for prophylactic regimens. Based on the RECORD and ADVANCE trials, both rivaroxaban and apixaban are similarly acceptable options for this indication. Neither dabigatran nor edoxaban are Food and Drug Administration (FDA) approved for venous thromboembolism prophylaxis following hip replacement surgery.	1	B
3.7.15	For patients undergoing total knee replacement surgery, either LMWH, fondaparinux (2.5 mg/day), or vitamin K antagonism with warfarin (goal international normalized ratio: 2.0–3.0) are recommended as prophylactic regimens for this indication. The RECORD and ADVANCE trials justify the use of either rivaroxaban or apixaban as reasonable alternative agents. Neither dabigatran nor edoxaban are FDA approved for venous thromboembolism prophylaxis following knee replacement surgery.	1	B

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.7.16	For patients undergoing hip fracture surgery, fondaparinux, LMWH, or vitamin K antagonism with warfarin are recommended for prophylactic regimens for this indication.	1	B
3.7.17	For patients undergoing hip fracture surgery, intermittent pneumatic compression pumping is recommended as an acceptable alternative for patients at high risk of major bleeding.	1	C
3.7.18	Low-dose unfractionated heparin, LMWH, or fondaparinux are recommended as safe and effective prophylaxis strategies for hospitalized patients with other general medical conditions.	1	B
3.7.19	For bleeding patients, we suggest intermittent pneumatic compression for thrombosis prophylaxis.	2	C
Guidelines 3.8.0 of the American Venous Forum on the management of axillosubclavian venous thrombosis in the setting of thoracic outlet syndrome			
3.8.1	For primary axillosubclavian venous thrombosis in patients with venous thoracic outlet syndrome, we recommend venous thrombolysis followed by thoracic outlet decompression. This combination is safe and effective.	1	B
3.8.2	We recommend against stenting of the subclavian vein for venous thoracic outlet as an alternative to operative decompression.	1	A
3.8.3	Stenting of the subclavian vein after surgical decompression for venous thoracic outlet syndrome is recommended for significant refractory lesions, but evidence as to the long-term safety of this approach is lacking.	1	C
3.8.4	For patients with residual stenosis following thrombolysis and first rib resection for subclavian vein thrombosis in the setting of venous thoracic outlet syndrome, we recommend observation alone, as most of these patients will do well clinically and many will recanalize/remodel.	1	C
3.8.5	For patients with costoclavicular junction stenosis in the setting of an ipsilateral arteriovenous fistula and swelling, pain, or dysfunction, we recommend thoracic outlet decompression and endolumenal intervention; this approach is safe and effective.	1	B
Guidelines 3.9.0 of the American Venous Forum on acute central vein thrombosis in the setting of central lines, pacemaker wires, and dialysis catheters			
3.9.1	To decrease the risk of central venous thrombosis, we recommend placement of the tip of the central venous catheter at the junction of right atrium and superior vena cava.	1	B
3.9.2	We recommend 3 to 6 months anticoagulation for treatment of symptomatic acute central venous thrombosis in the setting of central lines, pacemaker wires or dialysis catheter. Removal of central line or catheter is recommended only if they are no longer needed.	1	B

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
Guidelines 3.10.0 of the American Venous Forum on the indications, techniques, and results of inferior vena cava filters			
3.10.1	We recommend placement of inferior vena cava (IVC) filters: • In patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and a baseline contraindication to anticoagulation • In patients who suffer a complication from anticoagulation • In patients who develop recurrent DVT or PE despite adequate anticoagulation • In patients who previously have had a massive PE and cannot tolerate further cardiopulmonary insult that would be associated with an additional PE	1	A
3.10.2	We suggest placement of an IVC filter in patients with a free-floating thrombus greater than 5 cm in length within an iliac vein or the IVC.	2	B
3.10.3	We suggest prophylactic filters to patients if their associated medical conditions (malignancy or traumatic injuries) predispose to DVT or PE.	2	B
3.10.4	We suggest caution in special situations prior to filter placement for: • Patients with untreated or uncontrolled bacteremia • Pediatric patients and pregnant women due to the uncertain long-term effects and durability of the filters	2	C
3.10.5	We suggest bedside placement of IVC filters by using either transabdominal duplex or intravascular ultrasound guidance. Both have been shown to be safe and effective.	2	B
3.10.6	We suggest performing additional studies to document the safety and efficacy of the placement of retrievable filters in patients with time-limited contraindications to anticoagulation.	2	B
3.10.7	We suggest follow-up examination annually for patients with vena caval filters to evaluate the mechanical stability of the filter. In addition, the condition of the lower extremities is evaluated to monitor the ongoing risk for recurrent thrombosis.	2	B
Guidelines 3.11.0 of the American Venous Forum on superficial thrombophlebitis			
3.11.1	For saphenous vein thrombophlebitis within 3 cm of the saphenofemoral or saphenopopliteal junctions, we recommend therapeutic anticoagulation.	1	B
3.11.2	For moderate thrombophlebitis with at least 5-cm thrombus length and at least 3 cm distal to the saphenofemoral junction, we recommend fondaparinux 2.5 mg daily or low-molecular-weight heparin 40 mg daily for 45 days.	1	B
3.11.3	For thrombophlebitis localized in the distal segment or in tributaries of the great saphenous vein with thrombus length <5 cm, we suggest ambulation, warm soaks, and non-steroidal anti-inflammatory agents.	2	B

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
3.11.4	For moderate thrombophlebitis as described above or thrombophlebitis within 3 cm of the saphenofemoral junction, if anticoagulation is contraindicated, high ligation and division of the great saphenous vein is suggested.	2	B
3.11.5	In patients with saphenous thrombophlebitis, we suggest ablation, once the inflammation resolves, if there is evidence of venous insufficiency confirmed by duplex ultrasound scanning.	2	B
Guidelines 3.12.0 of the American Venous Forum on mesenteric vein thrombosis			
3.12.1	We recommend computed tomography angiography and magnetic resonance angiography for the diagnosis of mesenteric venous thrombosis (MVT).	1	B
3.12.2	We recommend immediate anticoagulation for the treatment of MVT to improve outcomes.	1	B
3.12.3	We recommend surgery to patients with MVT if they have evidence of peritonitis or perforation.	1	B
3.12.4	In patients with high-risk inherited thrombotic disorders or other permanent risks for thrombosis, we recommend long-term anticoagulation.	1	B
Part 4. Management of Chronic Venous Disorders			
Guidelines 4.1.0 of the American Venous Forum on the clinical presentation and assessment of patients with venous disease			
4.1.1	For clinical examination of the upper limb, we recommend inspection with comparison with the contralateral limb, palpation, auscultation, and examination of the axilla for adenopathy. In patients with adenopathy or swollen arms, we recommend examination of the breast to exclude malignancy.	1	B
4.1.2	For clinical examination of the lower limbs in patients with suspected acute deep vein thrombosis, we recommend inspection (edema, cyanosis, and varicosity), palpation (tenderness and pitting edema), auscultation (arterial bruit and heart and lung examination), and examination of the deep and superficial veins and calf muscles.	1	B
4.1.3	We suggest the use of the clinical scoring system of Wells to predict the pre-test probability of deep vein thrombosis.	2	B
4.1.4	For clinical examination of the lower limbs for varicosity and chronic venous insufficiency, we recommend inspection (varicosity, edema, skin discoloration, corona phlebectatica, ulcer, and lipodermatosclerosis) palpation (cord, varicosity, tenderness, induration, reflux, pulses, and thrill) auscultation (bruit), and examination of the groin and abdomen (masses, collateral veins, or lymphadenopathy) and ankle mobility.	1	B

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.1.5	Clinical presentation of patients with varicose veins may include symptoms such as aching, heaviness and tension, sensation of swelling, tiredness, restless legs, nocturnal cramps, and itching. We suggest that there is little or no relationship between these symptoms and the presence and severity of varicose veins or the pattern and severity of reflux.	2	B
Guidelines 4.2.0 of the American Venous Forum on the diagnostic algorithm for telangiectasia, varicose veins, and venous ulcers			
4.2.1	We recommend that in patients with telangiectasia, varicose veins, and chronic venous insufficiency, a complete history and detailed physical examination is complemented by duplex scanning of the deep, superficial, and, selectively, the perforating veins to evaluate valvular incompetence.	1	B
4.2.2	We recommend that in patients with telangiectasia, varicose veins, and chronic venous insufficiency, laboratory examination is needed selectively for those with a personal or family history of thrombophilia (screening for hypercoagulability), in patients with long-standing venous stasis ulcers (blood count and metabolic panel), and in a case of general anesthesia for the treatment of chronic venous disease.	1	B
4.2.3	We recommend in patients with telangiectasia, varicose veins, and chronic venous insufficiency selective use of plethysmography, computed tomography, magnetic resonance imaging, ascending and descending venography, and intravascular ultrasound.	1	B
4.2.4	We suggest laboratory evaluation for thrombophilia in patients with a history of recurrent venous thrombosis and chronic recurrent venous leg ulcers.	2	C
4.2.5	We recommend arterial pulse examination and measurement of Ankle–Brachial Index in all patients with venous leg ulcer.	1	B
Guidelines 4.3.0 of the American Venous Forum on compression therapy for venous ulceration			
4.3.1	We recommend compression therapy to heal venous ulcers.	1	A
4.3.2	We suggest compression therapy to decrease the risk of ulcer recurrence.	2	B
4.3.3	We suggest the use of multicomponent compression bandage over single-component bandages for the treatment of venous leg ulcers.	2	B
4.3.4	We suggest enforcing compliance since it is integral to the success of compression therapy.	2	B
4.3.5	We suggest use of intermittent pneumatic compression when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
Guidelines 4.4.0 of the American Venous Forum on the drug treatment of varicose veins, venous edema, and ulcers			
4.4.1	We suggest venoactive drugs (Diosmin, Hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, horse chestnut seed extract [aescin], ruscus, and dobesilate) in addition to compression for patients with pain and swelling due to chronic venous disease in countries where these drugs are available.	2	B
4.4.2	Long-standing or large venous ulcers may benefit from treatment with either pentoxifylline or micronized purified flavonoid fraction used in combination with compression.	1	B
4.4.3	We suggest Diosmin and Hesperidin in trophic disorders, as well as cramps and swelling. We suggest rutosides in patients with venous edema.	2	B
Guidelines 4.5.0 of the American Venous Forum on liquid sclerotherapy for telangiectasia and varicose veins			
4.5.1	We recommend liquid or foam sclerotherapy for telangiectasia, reticular veins, and varicose veins.	1	B
4.5.2	For the treatment of the incompetent saphenous vein, we recommend endovenous thermal ablation over chemical ablation with foam.	1	B
Guidelines 4.6.0 of the American Venous Forum on percutaneous laser therapy of telangiectasia and varicose veins			
4.6.1	For telangiectasias with vein diameters below 0.5 mm and for telangiectatic matting, we recommend flashlamp pumped dye lasers at 595-nm wavelengths.	1	C
4.6.2	For telangiectasias with diameters below 0.7 mm, we recommend the potassium titanyl phosphate laser at 532-nm wavelengths.	1	C
4.6.3	For large telangiectasias of up to 3 mm vein diameter, we suggest treatment with long-pulse neodymium-doped yttrium aluminum garnet lasers at 1064-nm wavelengths.	2	C
4.6.4	During laser treatment, we recommend cooling to avoid thermal skin damage using dynamic spray cooling, contact cooling, or cooled air.	1	C
4.6.5	We do not recommend cosmetic laser treatment of leg telangiectasia in tanned skin with increased melanin content after sun exposure.	1	A
Guidelines 4.7.0 of the American Venous Forum on foam sclerotherapy			
4.7.1	We recommend foam sclerotherapy in the treatment of truncal primary and recurrent varicose veins. This is applicable to patients with CEAP clinical grade C2–C6.	1	A
4.7.2	We recommend using ultrasound-guided foam sclerotherapy over liquid sclerotherapy for the treatment of truncal varicose veins.	1	B
Guidelines 4.8.0 of the American Venous Forum on the surgical treatment of the incompetent saphenous vein			
4.8.1	For the treatment of the incompetent saphenous vein in association with symptomatic varicose veins, we recommend saphenous vein ablation over compression therapy for appropriate candidates.	1	B

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.8.2	For the treatment of the incompetent great saphenous vein in association with symptomatic varicose veins, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee.	2	B
4.8.3	For the treatment of the incompetent small saphenous vein associated with symptomatic various veins, we suggest high ligation at the knee crease 3–5 cm distal to the saphenopopliteal junction and selective stripping of the vein.	2	B
4.8.4	To decrease the risk of infection during open saphenous surgery, we recommend prophylactic systemic antibiotics.	1	B
4.8.5	To reduce swelling, hematoma formation, and pain, we recommend post-operative compression for a period of 1 week.	1	B
Guidelines 4.9.0 of the American Venous Forum on radiofrequency ablation of the incompetent saphenous vein			
4.9.1	Endovenous thermal ablations (laser and radiofrequency ablations) are safe and effective, and we recommend them for the treatment of saphenous incompetence.	1	B
4.9.2	Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery.	1	B
Guidelines 4.10.0 of the American Venous Forum on the laser treatment of the incompetent saphenous vein			
4.10.1	Endovenous laser therapy of the great saphenous vein is safe and effective and we recommend it for the treatment of saphenous incompetence.	1	A
4.10.2	Clinical outcome after endovenous laser therapy at up to 3 years is comparable to traditional stripping and ligation and we recommend it for the treatment of the incompetent great saphenous vein.	1	C
Guidelines 4.11.0 of the American Venous Forum on emerging endovenous technology for chronic venous disease: mechanical occlusion chemically assisted ablation, cyanoacrylate embolization, and V block-assisted sclerotherapy			
4.11.1	We suggest mechanical occlusion chemically assisted (MOCA) ablation for: • Small saphenous vein (SSV) incompetence with diameter <10 mm • Mildly tortuous great saphenous vein (GSV)/SSV due to steerable wire • Below-knee (BK) GSV incompetence to the ankle for C2–C6 disease	2	B
4.11.2	We also suggest MOCA ablation for epifascial axial vein incompetence.	2	C
4.11.3	We suggest cyanoacrylate embolization (CAE) for: • BK GSV incompetence in C2–C6 disease • SSV incompetence	2	C
4.11.4	We suggest against CAE treatment of epifascial axial veins.	2	C
4.11.5	We suggest V block-assisted sclerotherapy (VBAS) for above-knee (AK) GSV incompetence with diameter <12 mm.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.11.6	We suggest polidocanol endovenous microfoam (PEM) for tortuous axial veins (GSV).	2	B
4.11.7	We suggest PEM for branch varicosities <6 mm.	2	C
4.11.8	As overall non-thermal non-tumescent (NTNT) technique guidelines, we recommend MOCA ablation, CAE, and PEM for AK GSV treatment for diameters <12 mm.	1	B
4.11.9	We recommend thermal tumescent techniques for vein diameters >12 mm.	1	C
4.11.10	We suggest NTNT not be used for vein diameters >12 mm.	2	B
4.11.11	We suggest NTNT not be used for post-thrombotic recanalized veins.	2	C
Guidelines 4.12.0 of the American Venous Forum on phlebectomy			
4.12.1	We recommend ambulatory phlebectomy—an outpatient procedure performed under local anesthesia—as an effective and definitive treatment for varicose veins. The procedure is performed after saphenous ablation, either during the same procedure or at a later stage.	1	B
4.12.2	Transilluminated powered phlebectomy has been shown to be effective in multiple studies for the treatment of varicose veins. We suggest it as an option.	2	C
4.12.3	We suggest phlebectomy over sclerotherapy for the treatment of varicose veins.	2	B
Guidelines 4.13.0 of the American Venous Forum on the management of recurrent varicose veins			
4.13.1	For clinical description of varicose vein recurrence, we recommend using the recurrent varices after surgery classification.	1	B
4.13.2	For evaluation of varicose vein recurrence, we recommend duplex ultrasound scanning of the location of the varicosities, as well as the source of the recurrence.	1	B
4.13.3	For the treatment of varicose vein recurrence, we suggest endovenous techniques, ultrasound-guided foam sclerotherapy, or phlebectomies, depending on the etiology and extent of varices.	2	C
Guidelines 4.14.0 of the American Venous Forum on the treatment of varicose veins			
4.14.1	We suggest venoactive drugs (Diosmin, Hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chestnut seed extract [aescin]) in addition to compression for patients with pain and swelling due to chronic venous disease in countries where these drugs are available.	2	B
4.14.2	We recommend ablation or stripping as the primary treatments for varicose veins. We recommend compression therapy using moderate pressure (20–30 mmHg) for those who are not candidates for a procedure.	1	B
4.14.3	We recommend endovenous thermal ablation in preference to high ligation and stripping or foam sclerotherapy for the management of saphenous vein incompetence.	1	B

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.14.4	In highly selected patients, we suggest using non-thermal venous ablation procedures in preference to high ligation and stripping or endothermal venous ablation for the management of saphenous vein incompetence.	2	C
4.14.5	We suggest mini-phlebectomy, foam sclerotherapy, or endovenous thermal ablation for recurrent varicose veins.	2	B
4.14.6	We suggest mini-phlebectomy over sclerotherapy for the treatment of tributary varicosities once axial reflux has been addressed.	2	B
4.14.7	In the clinical practice, we recommend that the basic CEAP clinical classification in combination with the revised Venous Clinical Severity Score should be used to follow outcomes.	1	B
Guidelines 4.15 of the American Venous Forum on the surgical repair of deep vein valve incompetence for primary reflux			
4.15.1	For deep venous reflux with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest individual valve repair for those who have axial reflux with structurally preserved deep venous valves in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. Valve reconstruction should be considered in primary valvular incompetence after less invasive therapies have failed.	2	C
Guidelines 4.16.0 of the American Venous Forum on the surgical treatment of post-thrombotic valvular incompetence			
4.16.1	Surgical treatment of postthrombotic valvular incompetence is suggested in patients with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), or healed/active venous leg ulcer (C5–C6). These procedures should be done in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.16.2	In a patient with advanced postthrombotic syndrome (C4b, C5–C6), we suggest against ligation of the femoral or popliteal veins as a routine treatment.	2	C
4.16.3	In a patient with advanced postthrombotic syndrome (C4b, C5–C6), we suggest individual valve repair in addition to standard compression therapy for those who have axial reflux with structurally preserved deep venous valves, to aid in venous ulcer healing and to prevent recurrence.	2	C
4.16.4	In a patient with advanced postthrombotic syndrome (C4b, C5–C6), we suggest valve transposition or transplantation for those with absence of structurally preserved axial deep venous valves and competent outflow venous pathways that are anatomically appropriate for venous outflow. This procedure should be done in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.16.5	In a patient with advanced postthrombotic syndrome (C4b, C5–C6), we suggest consideration of autogenous valve substitutes such as a neovalve by surgeons experienced in these techniques in those with no other option available. This procedure should be done in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
Guidelines 4.17.0 of the American Venous Forum on endovascular reconstruction for primary iliac vein obstruction			
4.17.1	We recommend endovenous stenting as the current "method of choice" for the treatment of primary iliac vein obstruction.	1	B
4.17.2	To alleviate pain and swelling and promote sustained ulcer healing, we recommend venous stenting for the treatment of primary iliac vein obstruction. Venous stenting improves the quality of life of the patients.	1	B
Guidelines 4.18.0 of the American Venous Forum on the endovascular treatment of lower extremity post-thrombotic iliofemoral venous obstruction			
4.18.1	In a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis with or without lower extremity deep venous reflux disease that is associated with severe limb swelling (C3), with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend venous angioplasty and stent recanalization, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	1	B
Guidelines 4.19.0 of the American Venous Forum on the endovascular reconstruction of complex iliocaval venous occlusions			
4.19.1	We suggest endovascular stents for the reconstruction of complex iliocaval venous occlusions.	2	B
Guidelines 4.20.0 of the American Venous Forum on open surgical reconstructions for non-malignant occlusion of the inferior vena cava and iliofemoral veins			
4.20.1	For symptomatic patients with unilateral iliofemoral venous occlusions who fail attempts at endovascular reconstruction or in whom endovascular intervention is not feasible, we recommend open surgical bypass using the saphenous vein as a cross-pubic bypass (Palma procedure).	1	B
4.20.2	For symptomatic patients with iliac vein or inferior vena cava obstruction, we suggest open surgical bypass using externally supported polytetrafluoroethylene prosthesis if endovascular options fail or they are not possible.	2	B
Guidelines 4.21.0 of the American Venous Forum on the management of incompetent perforating veins with open and endoscopic surgery			
4.21.1	For open surgical treatment of incompetent pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath a healed or active ulcer, we suggest against the modified open Linton procedure owing to associated morbidities.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.21.2	For those patients who would benefit from pathologic perforator vein ablation, we suggest treatment by percutaneous techniques over subfascial endoscopic perforator surgery.	2	C
Guidelines 4.22.0 of the American Venous Forum on the radiofrequency and laser treatment of incompetent perforating veins			
4.22.1	In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins, in addition to standard compressive therapy to aid in ulcer healing and to prevent recurrence.	2	C
4.22.2	In a patient with skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. Treatment of the incompetent perforating veins can be performed simultaneously or staged.	2	C
4.22.3	In a patient with isolated pathologic perforator veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed, regardless of the status of the deep veins, we suggest ablation of the "pathologic" perforating veins, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.22.4	For those patients who would benefit from pathologic perforator vein ablation, we suggest treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin.	2	C
Guidelines 4.23.0 of the American Venous Forum on the local treatment of venous ulcers[d]			
4.23.1	For wound cleansing, we suggest that venous leg ulcers be cleansed initially and at each dressing change with a neutral, non-irritating, non-toxic solution, performed with a minimum of chemical or mechanical trauma.	2	C
4.23.2	We recommend that venous leg ulcers receive thorough debridement at their initial evaluation to remove obvious necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells.	1	B

[d] Adapted from O'Donnell TF Jr., Passman MA, Marston WA et al. *J Vasc Surg* 2014;60:3S–59S.

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.23.3	We suggest maintenance debridement to maintain the appearance and readiness of the wound bed for healing and suggest choosing one or more from several debridement methods, including sharp, enzymatic, mechanical, biologic, and autolytic.	2	B
4.23.4	We recommend local anesthesia (topical or local injection) to minimize the discomfort associated with surgical ulcer debridement. In selected cases, regional block or general anesthesia may be required.	1	B
4.23.5	We recommend surgical debridement for venous leg ulcers with slough, non-viable tissue, or eschar. Serial wound assessment will determine the need for repeated debridement.	1	B
4.23.6	We suggest hydrosurgical debridement as an alternative to standard surgical debridement.	2	B
4.23.7	We suggest against ultrasonic debridement over surgical debridement.	2	C
4.23.8	We suggest against enzymatic debridement over surgical debridement, with the exception of when no clinician trained in surgical debridement is available.	2	C
4.23.9	We suggest larval therapy for ulcers as an alternative to surgical debridement.	2	B
4.23.10	We recommend systemic Gram-positive antibiotic treatment for cellulitis surrounding the ulcer.	1	B
4.23.11	We suggest against systemic antimicrobial treatment of venous leg ulcer colonization or biofilms without clinical evidence of infection.	2	C
4.23.12	We suggest antimicrobial therapy for ulcers with clinical evidence of infection and $>1 \times 10^6$ Colony-forming unit (CFU)/g of tissue, or at lower levels of colony-forming units per gram of tissue in the presence of virulent or difficult-to-eradicate bacteria (such as β-hemolytic streptococci, *Pseudomonas*, and resistant staphylococcal species). We suggest a combination of mechanical disruption and antibiotic therapy as being most successful in eradicating venous leg ulcer infection.	2	C
4.23.13	We recommend oral systemic antibiotics, guided by sensitivities performed on wound culture, for ulcers with clinical evidence of infection. The duration of antibiotic therapy should be limited to 2 weeks unless wound infection persists.	1	C
4.23.14	We suggest against the use of topical antimicrobial agents for the treatment of infected ulcers.	2	C
4.23.15	We suggest a topical dressing that will manage ulcer exudate and maintain a moist, warm wound bed.	2	C
4.23.16	We suggest selection of a primary wound dressing for absorbing the wound exudate produced by the ulcer (alginates and foams) and for protecting the skin around the ulcer.	2	B

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.23.17	We suggest against the routine use of topical antimicrobial-containing dressings in the absence of infection.	2	A
4.23.18	We suggest lubricants underneath compression to reduce the dermatitis that commonly affects periulcer skin. If severe dermatitis is associated, we suggest topical steroids.	2	C
4.23.19	We suggest against the use of anti-inflammatory therapies for the treatment of venous leg ulcers.	2	C
4.23.20	We recommend adjuvant wound therapy options for non-healing ulcers after standard therapy for 4–6 weeks.	1	B
4.23.21	We suggest against split-thickness skin grafting as a primary therapy of venous ulcers, but suggest it for large ulcers without signs of healing for 4–6 weeks.	2	B
4.23.22	We suggest the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) in non-healing ulcers after standard therapy for 4–6 weeks.	2	A
4.23.23	We suggest a trial of compression and wound moisture control before cellular therapy.	2	C
4.23.24	Before using a bi-layered cellular graft, we recommend wound bed preparation including complete removal of slough, debris, and any necrotic tissue. We also recommend additional evaluation and management of increased bioburden levels.	1	C
4.23.25	We suggest reapplication of cellular therapy as long as the ulcer continues to respond.	2	C
4.23.26	We suggest porcine small intestinal submucosal tissue construct for the treatment of non-healing ulcers after standard therapy for 4–6 weeks.	2	B
4.23.27	We suggest against routine primary use of negative pressure wound therapy for venous leg ulcers.	2	C
4.23.28	We suggest against electrical stimulation therapy for venous leg ulcers.	2	C
4.23.29	We suggest against routine ultrasound therapy for venous leg ulcers.	2	B

Guidelines 4.24.0 of the American Venous Forum on the treatment of chronic venous disease in patients with venous ulcers[e]

4.24.1 Definition of Venous Ulcer, Venous Anatomy, and Pathophysiology

4.24.1.1 We suggest the use of a standard definition of venous ulcer as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension. (BEST PRACTICE)

4.24.1.2 We recommend the use of the International Consensus Committee on Venous Anatomical Terminology for standardized venous anatomy nomenclature. (BEST PRACTICE)

4.24.1.3 We recommend a basic practical knowledge of venous physiology and venous leg ulcer pathophysiology for all practitioners caring for venous leg ulcers. (BEST PRACTICE)

[e] Local treatment of venous ulcer corresponds to Chapter 51 and guidelines 4.23.0.

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No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.24.2	**Clinical Evaluation**		
4.24.2.1	We recommend that for all patients with suspected leg ulcers fitting the definition of venous leg ulcer, clinical evaluation for evidence of chronic venous disease be performed. (BEST PRACTICE)		
4.24.2.2	We recommend the identification of medical conditions that affect ulcer healing and other non-venous causes of ulcers. (BEST PRACTICE)		
4.24.2.3	We recommend serial venous leg ulcer wound measurement and documentation. (BEST PRACTICE)		
4.24.2.4	We suggest against routine culture of venous leg ulcers and to only obtain wound cultures when clinical evidence of infection is present.	2	C
4.24.2.5	We recommend wound biopsy for venous leg ulcers that do not improve with standard wound and compression therapy after 4–6 weeks of treatment and for all ulcers with atypical features.	1	C
4.24.2.6	We suggest laboratory evaluation for thrombophilia for patients with a history of recurrent venous thrombosis and chronic recurrent venous leg ulcers.	2	C
4.24.2.7	We recommend arterial pulse examination and measurement of Ankle–Brachial Index (ABI) for all patients with venous leg ulcer.	1	B
4.24.2.8	We suggest against routine microcirculation assessment of venous leg ulcers, but suggest selective consideration as an adjunctive assessment for the monitoring of advanced wound therapy.	2	C
4.24.2.9	We recommend comprehensive venous duplex ultrasound examination of the lower extremity in all patients with suspected venous leg ulcer.	1	B
4.24.2.10	We suggest selective use of venous plethysmography in the evaluation of patients with suspected venous leg ulcer if venous duplex ultrasound does not provided definitive diagnostic information.	2	B
4.24.2.11	We suggest selective computed tomography venography, magnetic resonance venography, contrast venography, and/or intravascular ultrasound in patients with suspected venous leg ulceration if additional advanced venous diagnosis is required for thrombotic or non-thrombotic iliac vein obstruction, or for operative planning prior to open or endovenous interventions.	2	C
4.24.2.12	We recommend that all patients with venous leg ulcer should be classified based on venous disease classification assessment including clinical CEAP, revised Venous Clinical Severity Scoring, and venous disease-specific quality of life assessment. (BEST PRACTICE)		

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.24.2.13	We recommend venous procedural outcome assessment including reporting of anatomic success, venous hemodynamic success, procedure-related minor and major complications, and impact on venous leg ulcer healing. (BEST PRACTICE)		
4.24.3	**Compression**		
4.24.3.1	In a patient with a venous leg ulcer, we recommend compression therapy over no compression therapy to increase the venous leg ulcer healing rate.	1	A
4.24.3.2	In a patient with a healed venous leg ulcer, we suggest compression therapy to decrease the risk of ulcer recurrence.	2	B
4.24.3.3	We suggest the use of multicomponent compression bandages over single-component bandages for the treatment of venous leg ulcers.	2	B
4.24.3.4	In a patient with a venous leg ulcer and underlying arterial disease, we do not suggest compression bandages or stockings if the ABI is 0.5 or less or if the absolute ankle pressure is less than 60 mmHg.	2	C
4.24.3.5	We suggest using intermittent pneumatic compression when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy.	2	C
4.24.4	**Operative and Endovascular Treatment**		
4.24.4.1	In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we suggest ablation of the incompetent veins, in addition to standard compressive therapy to improve ulcer healing.	2	C
4.24.4.2	In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we recommend ablation of the incompetent veins, in addition to standard compressive therapy to prevent recurrence.	1	B
4.24.4.3	In a patient with a healed venous leg ulcer (C5) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we recommend ablation of the incompetent veins, in addition to standard compressive therapy to prevent recurrence.	1	C
4.24.4.4	In a patient with skin changes at risk for venous leg ulcer (C4b) and incompetent superficial veins that have axial reflux directed to the bed of the affected skin, we suggest ablation of the incompetent superficial veins, in addition to standard compressive therapy to prevent ulceration.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.24.4.5	In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins, in addition to standard compressive therapy to aid in ulcer healing and to prevent recurrence.	2	C
4.24.4.6	In a patient with skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. Treatment of the incompetent perforating veins can be performed simultaneously with correction of axial reflux or can be staged with re-evaluation of perforator veins for persistent incompetence after correction of axial reflux.	2	C
4.24.4.7	In a patient with isolated pathologic perforator veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed, regardless of the status of the deep veins, we suggest ablation of the "pathologic" perforating veins, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.24.4.8	For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin.	1	C
4.24.4.9	In a patient with infrainguinal deep venous obstruction and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest autogenous venous bypass or endophlebectomy, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.24.4.10	In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest against deep vein ligation of the femoral or popliteal veins as a routine treatment.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.24.4.11	In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest individual valve repair for those who have axial reflux with structurally preserved deep venous valves, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	2	C
4.24.4.12	In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest valve transposition or transplantation for those with an absence of structurally preserved axial deep venous valve(s) when competent outflow venous pathways are anatomically appropriate for surgical anastomosis, in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence.	2	C
4.24.4.13	In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest consideration of autogenous valve substitutes by surgeons experienced in these techniques to facilitate ulcer healing and to prevent recurrence in those with no other option available, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence	2	C
4.24.4.14	In a patient with inferior vena cava and/or iliac vein chronic total occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, which is associated with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend venous angioplasty and stent recanalization, in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.	1	C
4.24.4.15	In a patient with inferior vena cava and/or iliac vein chronic occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, which is associated with a recalcitrant venous leg ulcer, and who have failed endovascular treatment, we suggest open surgical bypass using an externally supported expanded polytetrafluroethylene (ePTFE) graft, in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence.	2	C
4.24.4.16	In a patient with unilateral iliofemoral venous occlusion/ severe stenosis with recalcitrant venous leg ulcer who failed attempts at endovascular reconstruction, we suggest open surgical bypass using the saphenous vein as a cross-pubic bypass (Palma procedure) to aid in venous ulcer healing and to prevent recurrence. A synthetic graft is an alternative in the absence of autogenous tissue.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
4.24.4.17	For those patients who would benefit from an open venous bypass, we suggest the addition of an adjunctive arteriovenous fistula (4–6 mm in size) as an adjunct to improve inflow into autologous or prosthetic crossover bypasses when the inflow is judged to be poor to aid in venous leg ulcer healing and to prevent recurrence.	2	C
4.24.5	**Ancillary Therapy**		
4.24.5.1	We recommend that nutrition assessment be performed in any patient with a venous leg ulcer who has evidence of malnutrition and that nutritional supplementation be provided if malnutrition is identified. (BEST PRACTICE)		
4.24.5.2	For long-standing or large venous leg ulcers, we recommend treatment with either pentoxifylline or micronized purified flavonoid fraction used in combination with compression therapy.	1	B
4.24.5.3	We suggest supervised active exercise to improve muscle pump function and reduce pain and edema in patients with venous leg ulcers.	2	B
4.24.5.4	We suggest against adjunctive lymphatic drainage for the healing of the chronic venous leg ulcers.	2	C
4.24.5.5	We suggest balneotherapy to improve skin trophic changes and quality of life in patients with advanced venous disease.	2	B
4.24.5.6	We suggest against using ultraviolet light for the treatment of venous leg ulcers.	2	C
4.24.6	**Primary Prevention**		
4.24.6.1	In patients with clinical CEAP C3–C4 disease due to primary valvular reflux, we recommend 20–30 mmHg compression, knee or thigh high.	2	C
4.24.6.2	In patients with clinical CEAP C1–C4 disease related to prior deep vein thrombosis (DVT), we recommend compression, 30–40 mmHg, knee or thigh high.	1	B
4.24.6.3	As post-thrombotic syndrome (PTS) is a common preceding event for venous leg ulcers, we recommend current evidence-based therapies for acute DVT treatment.	1	B
4.24.6.4	For acute DVT treatment, we suggest the use of low-molecular-weight heparin over vitamin K antagonist therapy of 3 months' duration to decrease PTS. We also suggest catheter-directed thrombolysis in low-bleeding-risk patients with iliofemoral DVT of <14 days' duration.	2	B
4.24.6.5	In patients with C1–C4 disease, we suggest patient and family education, regular exercise, leg elevation when at rest, careful skin care, weight control, and appropriately fitting foot wear. (BEST PRACTICE)		
4.24.6.6	In patients with asymptomatic C1–C2 disease from either primary or secondary causes, we suggest against prophylactic interventional therapies to prevent venous leg ulcer.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
Part 5. Special Venous Problems			
Guidelines 5.1.0 of the American Venous Forum on the surgical and endovenous treatment of superior vena cava syndrome			
5.1.1	In patients with malignant superior vena cava obstruction, we recommend stenting as the primary therapy, unless the malignancy can be excised.	1	A
5.1.2	In patients with superior vena cava syndrome due to non-malignant etiology, we recommend endovascular treatment as the initial therapy.	1	B
5.1.3	We recommend open surgical reconstruction of the superior vena cava with spiral vein graft, autologous femoral vein, or expanded polytetrafluoroethylene graft if the patient is not suitable for or failed endovascular therapy.	1	B
Guidelines 5.2.0 of the American Venous Forum on the management of traumatic injuries of large veins			
5.2.1	For management of a grade I puncture injury, we recommend pressure or suture repair.	1	B
5.2.2	For management of a grade II injury—a laceration in a hemodynamically stable patient—we recommend lateral venorraphy or consideration of endovascular treatment.	1	B
5.2.3	For management of a grade III injury—a transection of a large vein in a hemodynamically stable patient—we recommend end-to-end anastomosis or interposition graft.	1	B
5.2.4	For management of a grade IV large vein injury in a hemodynamically unstable patient, we recommend bypass over ligation.	1	B
Guidelines 5.3.0 of the American Venous Forum on primary and secondary tumors of the inferior vena cava and iliac veins			
5.3.1	For patients with invasion of the wall of the inferior vena cava by primary or secondary tumor, we recommend caval replacement if the vein was patent before surgery and if the collateral circulation appears inadequate following caval resection. Repair with externally supported polytetrafluoroethylene graft is safe, effective, and durable.	1	B
5.3.2	For inferior vena cava tumor thrombus—usually a renal cell carcinoma—that extends into the right heart, we recommend removal with cardiopulmonary bypass, with or without hypothermic circulatory arrest.	1	B
Guidelines 5.4.0 of the American Venous Forum on arteriovenous malformations: evaluation and treatment			
5.4.1	For symptomatic arteriovenous malformations, we recommend endovascular treatment with embolization or sclerotherapy. We recommend it for both definitive treatment of surgically "inaccessible" lesions and for initial therapy of surgically "accessible" lesions.	1	B
Guidelines 5.5.0 of the American Venous Forum on the management of venous malformations			
5.5.1	For symptomatic venous malformations not responding to compression treatment, we suggest foam sclerotherapy over sclerotherapy with alcohol.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
5.5.2	For surgically accessible and localized symptomatic venous malformations, we suggest surgical excision as an alternative to sclerotherapy.	2	C
Guidelines 5.6.0 of the American Venous Forum on the management of venous aneurysms			
5.6.1	We recommend surgical repair of even asymptomatic lower extremity venous aneurysms because of the risk of thromboembolic complications.	1	B
5.6.2	For aneurysms of superficial veins of the arm or leg or of deep veins of the arm, we suggest observation unless cosmetic reasons or complications warrant repair.	2	B
5.6.3	For jugular vein aneurysms, we suggest observation unless cosmetic reasons or psychological reasons warrant surgical repair.	2	C
5.6.4	For abdominal venous aneurysms, we suggest repair because of the risk of rupture and thromboembolism.	2	C
5.6.5	Thoracic venous aneurysms are infrequently associated with rupture or thromboembolic complications and can be observed in most cases.	2	C
Guidelines 5.7.0 of the American Venous Forum on the management of pelvic venous congestion and perineal varicosities			
5.7.1	We recommend pelvic ultrasonography for the initial evaluation of patients with suspected pelvic varicose veins. Ultrasound will confirm pelvic varicose veins and may determine their etiology. We recommend computed tomographic venography or magnetic resonance venography for further evaluation.	1	B
5.7.2	We recommend selective contrast pelvic venography in the reversed Trendelenburg position to confirm the diagnosis and etiology of pelvic and perineal varicose veins, to delineate the anatomy, and to plan endovenous treatment.	1	B
5.7.3	We recommend endovenous ablation of the refluxing ovarian vein with coil embolization, with or without liquid or foam sclerotherapy.	1	B
5.7.4	We recommend an open surgical approach to ligate the refluxing symptomatic ovarian vein if endovascular treatment fails or is not possible.	1	B
5.7.5	We suggest liquid or foam sclerotherapy for the treatment of perineal and vulvar varicosities.	2	B
Guidelines 5.8.0 of the American Venous Forum on the management of nutcracker syndrome			
5.8.1	We suggest open surgical interventions, such as left renal vein transposition, as the primary treatment of nutcracker syndrome.	2	B
5.8.2	We suggest left renal vein stenting for the treatment of nutcracker syndrome in those patients who are not candidates for open surgery or who failed open surgical treatment.	2	C

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
Part 6. Lymphedema			
Guidelines 6.1.0 of the American Venous Forum on lymphedema: pathophysiology, classification, and clinical evaluation			
6.1.1	Lymphedema is divided into two major categories: primary and secondary. Primary lymphedema may be further subdivided into three categories: • Congenital lymphedema (10%) develops within 2 years of birth. Some of the congenital forms are hereditary. • Lymphedema praecox (80%) occurs between the ages of 2 and 25 years. Although sporadic cases are most common, a few forms are hereditary. • Lymphedema tarda (10%) has its onset in those over 35 years of age. Secondary lymphedema is caused by inflammation or obstruction of the lymph vessels. Some of the most common causes include filariasis, cancer, trauma (mostly iatrogenic), and infection/inflammation.		B
6.1.2	Lymphatic abnormalities can be divided into four anatomical categories: aplasia, hypoplasia, numerical hyperplasia, and hyperplasia.		B
6.1.3	There are three major categories of lymphatic pathophysiological abnormalities: obstruction, reflux, and overproduction of lymph fluid.		B
Guidelines 6.2.0 of the American Venous Forum on lymphoscintigraphy and lymphangiography			
6.2.1	We recommend lymphoscintigraphy and not contrast lymphangiography for the initial evaluation of patients with lymphedema.	1	B
6.2.2	We suggest lymphoscintigraphy, using visual interpretation of the images with a semi-quantitative scoring index, for documenting responses to the treatment of lymphedema.	2	B
Guidelines 6.3.0 of the American Venous Forum on lymphedema: physical and medical therapy			
6.3.1	To reduce lymphedema, we recommend multimodal complex decongestive therapy that includes manual lymphatic drainage, multilayer short-stretch bandaging, remedial exercise, skin care, and instruction in long-term management.	1	B
6.3.2	To reduce lymphedema, we recommend short-stretch bandages that remain in place for >22 hours per day.	1	B
6.3.3	To reduce lymphedema, we recommend daily treatment for a minimum of 5 days per week and continuing until normal anatomy or a volumetric plateau is established.	1	B
6.3.4	To reduce lymphedema, we suggest compression pumps in some patients.	2	B
6.3.5	For maintenance of lymphedema, we recommend an appropriately fitting compression garment.	1	A
6.3.6	For the maintenance of lymphedema in patients with advanced (stage II and III) disease, we recommend using short-stretch bandages during the night. Alternative compression devices may substitute for short-stretch bandages.	1	B

(*Continued*)

No.	Guideline	Grade of recommendation (1: strong; 2: weak)	Grade of evidence (A: high quality; B: moderate quality; C: low or very low quality)
6.3.7	For remedial exercises, we recommend wearing compression garment or bandages.	1	C
6.3.8	For cellulitis or lymphangitis, we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci. Examples include cephalexin, penicillin, clindamycin, and erythromycin.	1	A
6.3.9	For prophylaxis of cellulitis in patients with more than three episodes of infection, we recommend antibiotics with superior coverage of Gram-positive cocci, particularly streptococci, at full strength for 1 week per month. Examples include cephalexin, penicillin, clindamycin, and erythromycin.	1	A
6.3.10	For patients with lymphedema we recommend risk factor modifications by decreasing obesity, treating chronic venous insufficiency, and promoting skin care and exercise.	1	C
Guidelines 6.4.0 of the American Venous Forum on the principles of the surgical treatment of chronic lymphedema			
6.4.1	All interventions for chronic lymphedema should be preceded by at least 6 months of non-operative compression treatment.	1	C
6.4.2	We suggest excisional operations or liposuction only to patients with late-stage non-pitting lymphedema who fail conservative measures.	2	C
6.4.3	We suggest microsurgical lymphatic reconstructions in centers of excellence for selected patients with secondary lymphedema if performed early in the course of the disease.	2	C
Guidelines 6.5.0 of the American Venous Forum on the medical, open surgical, and endovascular treatment of chylous disorders			
6.5.1	For the primary treatment of chylous effusions and fistulas due to reflux, we recommend first a low-fat or medium-chain triglyceride diet, followed by drug therapy that may include somatostatin and its analogs, diuretics, and sympathomimetic drugs to enhance thoracic duct contractions. This is followed by percutaneous aspirations of chylous fluid by thoracentesis or paracentesis.	1	B
6.5.2	In patients with chylous effusions, we suggest percutaneous embolization using coils or glue as the first line of treatment once conservative management fails.	2	B
6.5.3	If endovascular treatment is not possible or fails, we suggest open surgery for the treatment of chylous effusions and symptomatic lymphangiectasia. These procedures include ligation of lymphatic fistulas, excision of dilated lymphatics, sclerotherapy, video-assisted thoracoscopy with pleurodesis, and ligation of the thoracic duct, lymphatic reconstruction, or, as a last resort, placement of a peritoneovenous shunt.	2	C

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