Current Management of Venous Diseases

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As I finish proofing this book, I cannot but pause and think about my life. Think about beloved ones who influenced my personality, shaped my path and made me who I am.

To Samia, my mother who taught me the value of resilience, perseverance, and hard work.

To Wafic, my uncle who raised me as his son and gave me more than I deserve.

To Sanya, my aunt, my second mother, and my guarding angel.

To Randa, my beloved wife and my ROCK.

To Leila, Sami, and Jena, the little shining lights of my life.

….. I dedicate this book.

Cassius Iyad Ochoa Chaar

Preface

Venous diseases are very common in the general population. The understanding and management of venous disorders are rapidly evolving. Patients with venous conditions get evaluated by a variety of specialists with different training backgrounds. The advances in endovascular therapy have increased the interest of physicians in treating venous diseases and resulted in an exponential increase in the use of certain procedures. This textbook provides an overview of venous diseases and focuses on clinical evaluation and management. It is intended to guide the treating physician by summarizing the evidence, giving technical tips, and outlining algorithms for common conditions. A unique feature of this book is clinical pearls given by experts in the field that will be highlighted in each chapter.

The first section of the book is titled clinical fundamentals and describes the essential anatomy and physiology/pathophysiology. Venous disease processes can be divided into venous reflux affecting predominantly the superficial veins and venous obstruction which is better known as venous thromboembolism in the acute phase and can have significant long-term sequelae in the form of chronic venous obstruction. As such, the organization of the book follows the basic pathophysiology of venous disorders with chapters addressing special conditions of common interest such as pelvic congestion syndrome, thoracic outlet syndrome, and May-Thurner syndrome. There is emphasis on novel treatment modalities and emerging technologies through dedicated chapters to anticoagulant agents, emerging modalities to treat superficial venous reflux and venous stent technology. Finally, this book is a melting pot for physicians who have shown dedication and passion to the care of patients with venous disease regardless of specialty or location.

I would like to thank all the authors who have contributed to this book. A special thank you to the senior authors who are all experts in the field and have shared their knowledge and professional experience to educate their peers and future generations. Several authors are former presidents, current officers and active members of the American Venous Forum, a fine society that inspired me as a fellow and sparked my interests in the field. This work would not have been possible without the help of the outstanding editorial team at Springer. I would like to thank my partners in vascular surgery at Yale for covering my patients and providing them with outstanding care in my absence. I acknowledge my chief Timur Sarac for supporting my academic

endeavors and setting the bar high for the care of patients with vascular diseases. Finally, I would like to express my gratitude to my mentor, partner, and friend Alan Dardik. Because of his support and encouragement, I became a vascular surgeon.

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Part I

Clinical Fundamentals

Venous Anatomy, Development, and Variations

1

Joann M. Lohr and Nicolas J. Mouawad

Abbreviations

CT	Computed tomography
DVT	Deep venous thrombosis
GSV	Great saphenous vein
IVC	Inferior vena cava
LE	Lower extremity
PLSVC	Persistent left superior vena cava
PV	Perforating veins
SMV	Superior mesenteric vein
SSV	Small saphenous vein
SVC	Superior vena cava
VEGF	Vascular endothelial growth factor

Clinical Pearls

1. Anatomic variations in venous anatomy are common.
2. A persistent left superior vena cava can affect central line placement.
3. Inferior vena cava atresia, duplication, and left-sided configuration can affect IVC filter placement.

Introduction

The vertebrate cardiovascular system, consisting of the heart, blood vessels, and blood, is the first organ to function during embryogenesis. All vertebrates require a mechanism to distribute oxygen and nutrients for metabolic needs in addition to a method to remove carbon dioxide and move metabolic waste products to the excretory organs. Blood (the carrier of oxygen, carbon dioxide, and metabolic products) is pumped by the heart through the arteries and then arterioles until it ultimately arrives at the capillary bed where exchange occurs. Following this, it returns to the heart through the venules and then veins. As John J Cranley stated, "Veins have tributaries but do not have branches." They get larger as they course centrally.

The circulatory system functions as a closed loop continuously recirculating blood with

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exchange of nutrients and waste, which is dependent on the essential division of the circuit into arterial and venous components. In fact, further developmental organogenesis is completely dependent on a functioning circulatory system, and any major lapse in this function leads to early embryonic lethality.

Early Vascular Development and Arterial-Venous Identity

Establishment of the cardiogenic field is based on the appearance of the vascular system during the third week of development, when the embryo is no longer able to fulfill its nutritional requirements by diffusion alone due to the limited diffusion distance of molecules such as oxygen [1]. As such, other mechanisms are required for nourishment and elimination of waste for the rapidly developing embryo.

Endothelial cell differentiation is initially observed during gastrulation, where cells invaginate through the primitive streak to form the mesoderm [2]. These newly formed mesodermal cells progress to form the axial mesoderm (notochord), paraxial mesoderm (somites), and the intermediate mesoderm (kidney and gonads). The dorsal sheet will form the body wall as it is in contact with the ectoderm, whereas the ventral sheet is in contact with the endoderm and forms the viscera.

The hemangioblast, a proposed progenitor cell derived from the mesoderm, is generally considered to be the precursor of both blood cell lineages and hematopoiesis as well as angioblasts, which give rise to the first vascular endothelial cells [3]. It was long thought that hemodynamic forces such as blood flow rate, direction, and pressure as well as contractility were the driving forces in differentiation of arterial and venous lineages. However, further and recent experimental studies have demonstrated that particular molecular markers are involved in arterial-venous identity; in fact, these molecular determinants have been demonstrated prior to the initiation of circulatory flow [4].

Signaling molecules such as vascular endothelial growth factor (VEGF) and its receptor VEGFR2 are the most critical drivers for embryonic vessel formation [5]. Furthermore, the first genes discovered to be differentially expressed in arterial and venous endothelium were ephrinB2 and EphB4, members of the Eph-ephrin subclass of receptor tyrosine kinases. Ephs and ephrins are both transmembrane proteins and Eph-ephrin signaling requires cell-to-cell contact. The landmark study by Wang and colleagues evaluating the molecular basis of arterial-venous cell fate used ephrinB2 and EphB4 tau-lacZ "knockins" to show that the two genes were differentially expressed in the arterial and venous endothelium of the mouse embryo prior to the commencement of circulation [6]. This in fact provided the first evidence noting that molecular differences between arteries and veins are not dependent on circulatory flow. It is now known that multiple other factors are involved in arterial-venous identity differentiation, including notch and the hedgehog family. Angioblasts are fated to become arterial or venous based on the attachment of VEGF either to the VEGFR2-NP-1 complex or just to VEGFR2. The former portends an arterial fate, whereas the latter stimulates a cascade that leads to venous differentiation.

Development of the Venous System

Three pairs of major veins can be distinguished in the fifth week of development:

1. The vitelline veins (or omphalomesenteric veins), carrying blood from the yolk sac to the sinus venosus—it eventually becomes the venous drainage of the intestines and includes the superior mesenteric vein (SMV), the portal vein, and the hepatic veins.
2. The umbilical veins carrying oxygenated blood to the embryo and originating in the chorionic villi.
3. The cardinal veins, which drain the embryo.

Much greater anatomic variation is present within the venous system as there are multiple different channels for venous networks to form and flow. Such anomalies will be discussed later.

Vitelline Veins

The vitelline veins form a plexus around the duodenum and pass through the septum transversum prior to entering the sinus venosus. A complex rearrangement ultimately creates the adult drainage of the liver and intestines as well as the creation of the hepatocardiac portion of the inferior vena cava (IVC). The right vitelline vein enlarges as blood from the left side of the liver is rechanneled toward the right, amplifying the hepatocardiac channel. This ultimately creates the hepatocardiac portion of the IVC. The proximal and distal part of the vitelline vein disappears, and the SMV derives from the right vitelline vein draining the primary intestinal loop. The venous channels around the duodenum coalesce to form the portal vein.

Umbilical Veins

The proximal part of both umbilical veins and the remainder of the right umbilical vein obliterate—only the left umbilical vein remains and carries blood from the placenta to the liver. The ductus venosus forms as the communication between the left umbilical vein and the right hepatocardiac channel; recall that the ductus venosus bypasses the liver. In adults, the left umbilical vein is manifest as the ligamentum teres of the liver, and the ductus venosus becomes the ligamentum venosum. This umbilical vein in the newborn is the site for umbilical vein catheter insertion if needed.

Cardinal Veins and the Venae Cavae

The paired cardinal veins become the main venous drainage of the embryo that persist into adulthood. The system consists of anterior (superior) cardinal veins, which are located cephalad to the heart, and the posterior (inferior) cardinal veins, which are located caudally. The anterior and posterior veins join to form the short common cardinal veins prior to entering the sinus horn. Further additional veins are formed including the subcardinal veins, which drain the kidneys; the sacrocardinal veins, which drain the lower extremities; and the supracardinal veins, which drain the body wall.

The cranial portions of the paired anterior cardinal veins become the internal jugular veins and connect with the external jugular veins, which have developed from venous plexuses of the face. The superior vena cava (SVC) is formed by an enlargement of the right common cardinal vein and the proximal portion of the right anterior cardinal vein. The left common cardinal vein becomes the coronary sinus. The left brachiocephalic vein is formed by an anastomosis of the anterior cardinal veins.

The supracardinal veins split into suprarenal and infrarenal components and undergo anastomosis with the subcardinal veins. The 4th to 11th right intercostal veins empty into the right supracardinal vein, which forms the azygos vein by a connection with a segment of the posterior cardinal vein. On the left side, the 4th to the 7th intercostal veins enter the left supracardinal vein, which is also now known as the hemiazygos vein.

The left renal vein is formed by the anastomosis between the subcardinal veins. Following this communication, the left subcardinal vein disappears and only its distal portion remains, the left gonadal vein, which drains into the left renal vein. The right subcardinal vein becomes the main drainage segment and becomes the pararenal IVC.

Inferiorly, the anastomosis between the sacrocardinal veins becomes the left common iliac vein. The sacrocardinal segment of the IVC is formed by the right sacrocardinal vein. At this point, when the pararenal segment of the IVC connects with the hepatic segment (which is derived from the right vitelline vein), the IVC is complete and consists of the hepatic, renal, and sacrocardinal segments.

Venous Anomalies of Development and Clinical Correlates

Variations are common during venous embryology due to the complicated process of caval development.

Superior Vena Cava (SVC)

Two major anomalies are noted during the development of the SVC, neither of which is clinically important—a double SVC or a left-sided SVC.

A double SVC is characterized by the persistence of the left anterior cardinal vein and the failure of its caudal section to regress, as well as a failure of the left brachiocephalic vein to form [7].

A left-sided SVC is caused by the persistence of the caudal section of the left anterior cardinal vein, where the caudal section of the right anterior cardinal vein regresses (ie, opposite of normal). The left anterior cardinal vein—the left SVC—now drains into the right atrium through the coronary sinus. This occurs in 0.3–0.5% of individuals in the general population and up to 12% of individuals with documented congenital heart abnormalities [8]. Persistent left SVC is the most common congenital anomaly of the thoracic systemic venous return (Fig. 1.1); it is rarely of clinical concern except during central line insertion (Fig. 1.2) [9, 10].

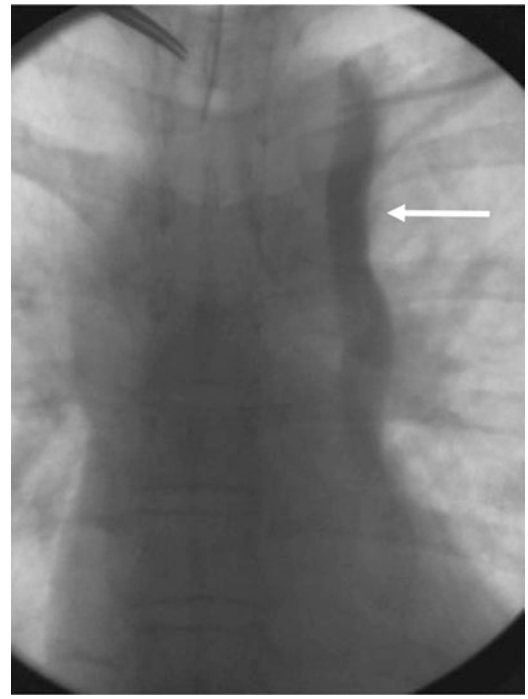

Fig. 1.1 Venogram of persistent left SVC (*arrow*). Used with permission from [9]. (c)2011 Povoski and Khabiri; licensee BioMed Central Ltd. This image is from an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited [9]

Inferior Vena Cava (IVC)

As with the SVC, duplication and/or a left-sided IVC is possible depending on persistence of the left supracardinal vein. If the left supracardinal vein fails to regress, a duplicated IVC is demonstrated (Fig. 1.3). If both supracardinal veins persist and join at the level of the renal veins, a double IVC is noted (Fig. 1.4).

If the left supracardinal vein persists while the right supracardinal vein regresses, then a left-sided IVC is observed and is a mirror image of the normal anatomy—the right adrenal vein and right gonadal vein will drain into the right renal vein, whereas the left adrenal vein and left gonadal vein will drain directly into the left-sided IVC (Fig. 1.5). This anatomy would make IVC filter retrieval more challenging because of the angulation of the cava (Fig. 1.6) [11, 12].

Absence of the IVC arises when the right subcardinal vein fails to connect with the liver and blood is shunted directly into the right supracardinal vein. In this manner, blood from the caudal part of the body reaches the heart through the azygos vein and the SVC (Figs. 1.7 and 1.8). Occasionally systemic to portal shunting may occur causing portal hypertension. Flow is reversed from the systemic system into the portal system unlike traditional portal systemic shunts (Fig. 1.9).

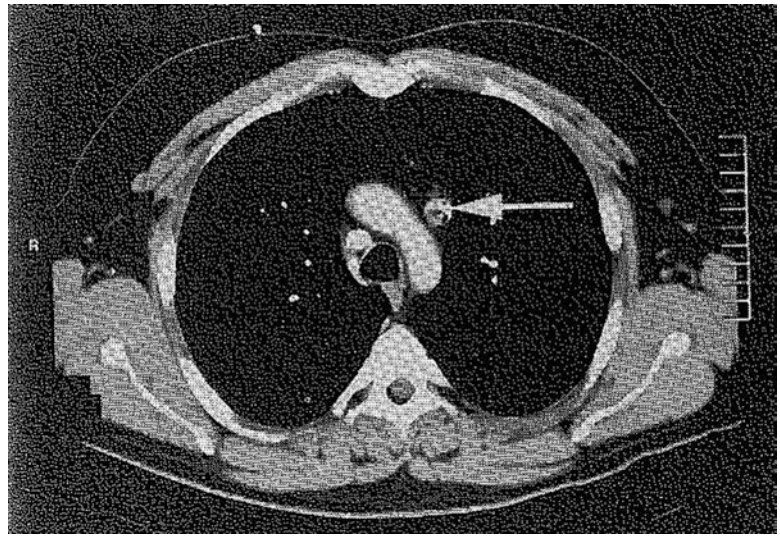

Fig. 1.2 CT scan of left-sided SVC (*arrow*). From: Lawler LP, Fishman EK. Thoracic venous anatomy: multidetector row CT evaluation. Radiol Clin N Am. (2003); 41(3): 545–60 [10]. Used with permission

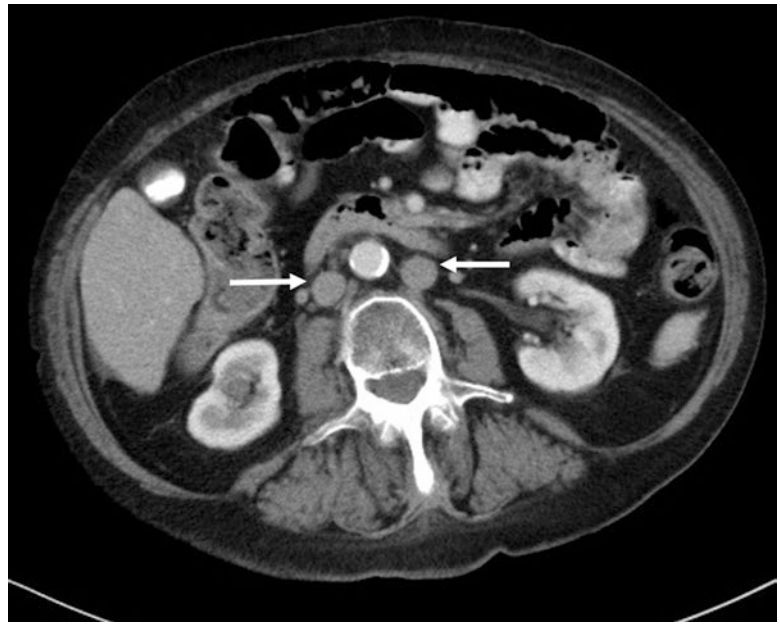

Fig. 1.3 CT scan with axial views of duplicated IVC (*arrows*)

Renal Veins

Knowledge of the variants of the renal veins is important during open dissection of the pararenal aorta. Most efforts are focused on the left renal vein due to its course. A retroaortic left renal vein is observed when the posterior left renal vein persists and the anterior left renal vein regresses (ie, opposite to normal development). In some instances, when both the anterior and the posterior left renal veins persist, a circumaortic left renal vein is observed [13, 14] (Figs. 1.10 and 1.11). The incidence of major IVC and renal vein anomalies is summarized in Table 1.1 [15].

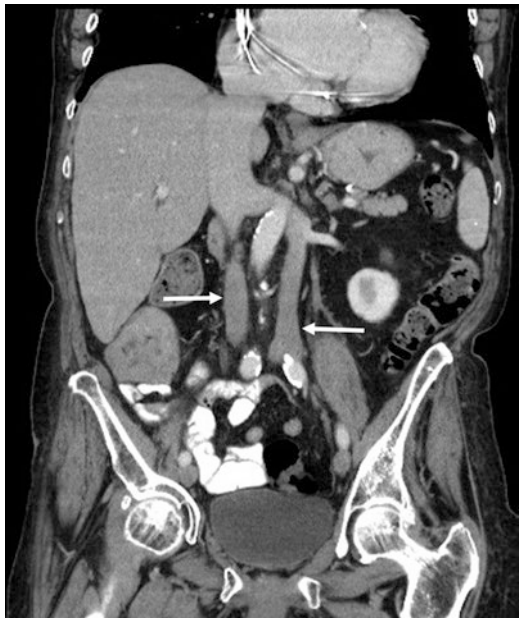

Fig. 1.4 CT scan with coronal views of duplicated IVC (*arrows*)

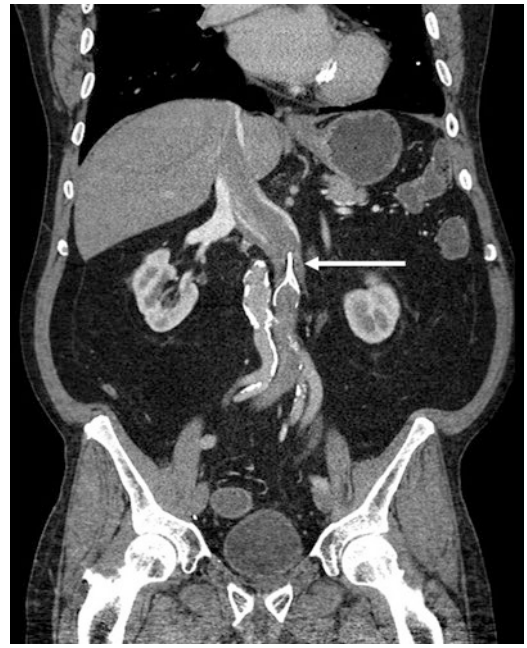

Fig. 1.6 IVC filter in left-sided cava (*arrow*)

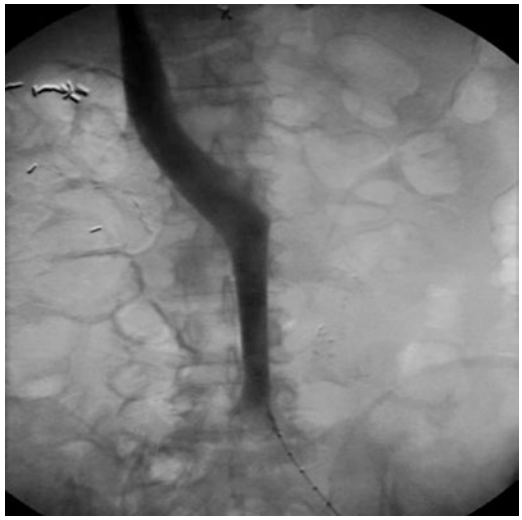

Fig. 1.5 Venogram of a left-sided IVC

Fetal Circulation

Before birth, oxygenated blood from the placenta courses through to the fetus via the umbilical vein. Most of this blood flows through the ductus venosus into the IVC, essentially bypassing the liver proper. Within the IVC, it is admixed with returning deoxygenated blood from the lower extremities prior to entering the right atrium. It is then guided through the foramen ovale to the left atrium by the terminal valve of the IVC. At this point, it mixes with desaturated blood from the head and upper extremities through the SVC.

Blood flows from the left atrium into the left ventricle. With the high pulmonary resistance in the fetus, most of the blood is now shunted through the ductus arteriosum in the proximal descending thoracic aorta, where ultimately the viscera are supplied and the blood then flows to the placenta through the two-paired umbilical arteries.

Venous Histology and Function

The vein wall is relatively thin compared to its arterial counterpart, but nevertheless it is composed of three layers—the intima, media, and adventitia.

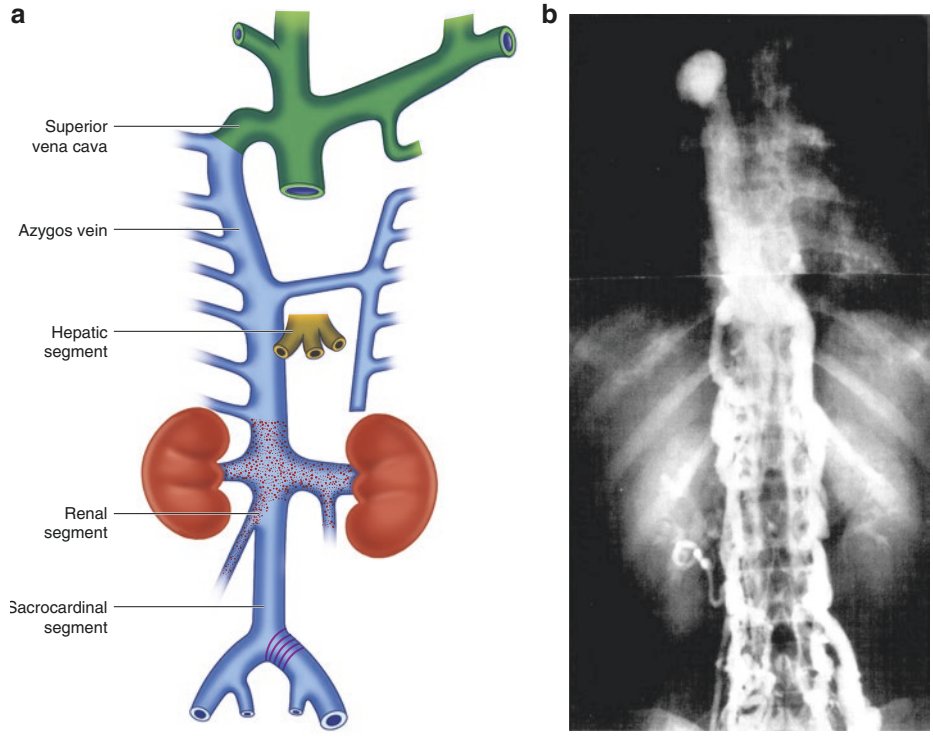

Fig. 1.7 (**A**) Diagram of an absent IVC.The lower half of the body is drained by the azygos vein which enters the SVC. The hepatic vein enters the heart at the site of the IVC. (**B**) A venogram showing absence of the IVC. The venous return is through both ascending lumbar veins and the azygos and hemiazygos veins. This was thought to be congenital in origin because it was noted early in life and there was no history to suggest venous thrombosis

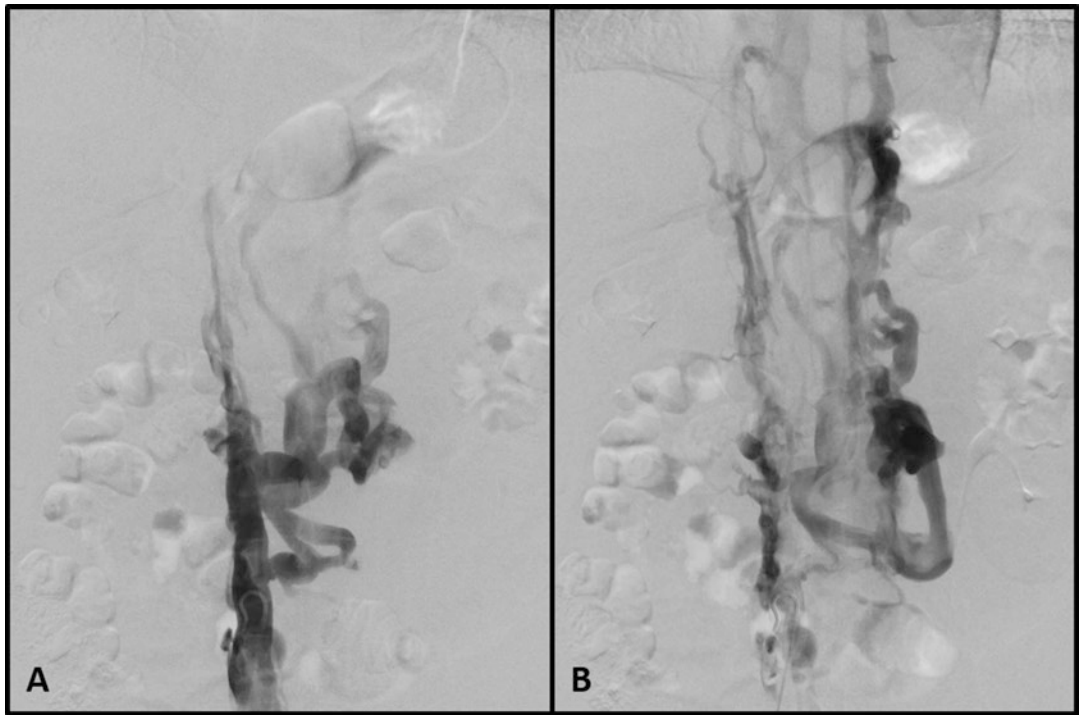

Fig. 1.8 (**A**) Venogram of congenital IVC atresia, (**B**) congenitally absent IVC filling azygos and hemiazygos systems. Note lumbar venous collaterals

The intima is actively antithrombogenic with in situ production of multiple glycosaminoglycan cofactors such as thrombomodulin, antithrombin, and tissue-type plasminogen activator [16, 17]. The single layer of endothelial cells allows a low-friction smooth surface for flow. Damage to the tunica intima from traumatic cannulation, hyperosmolar solutions or even inflammation will

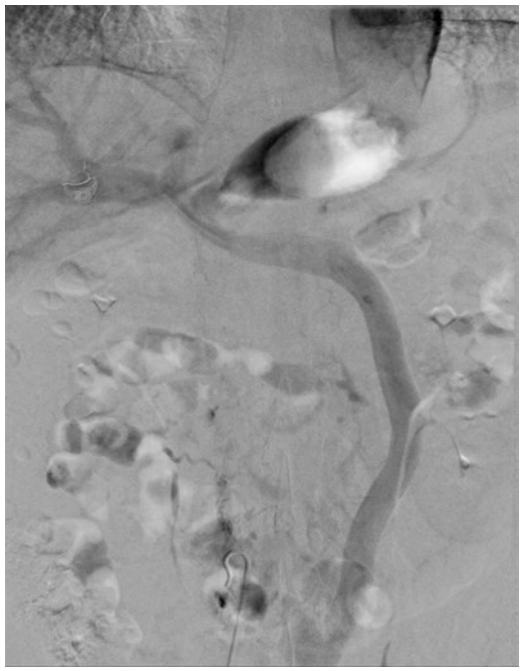

Fig. 1.9 SMV filling portal vein venogram congenital absence of IVC. Large systemic to portal shunt

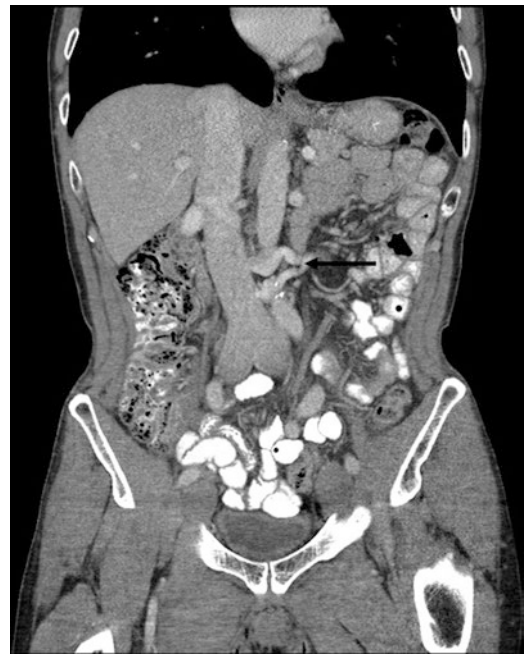

Fig. 1.11 Duplicate retroaortic left renal veins (*arrow*)

Table 1.1 Incidence of major inferior vena cava and renal vein anomalies

Venous anomaly	Incidence
Circumaortic renal vein	1.5–8.7%
Duplicated inferior vena cava	2.2–3.0%
Posterior left renal vein	1.8–2.4%
Left-sided inferior vena cava	0.2–0.5%

From: Nicholson CP, Gloviczki P. Embryology and development of the vascular system. In: White RA, Hollier LH, editors. Vascular surgery: basic science and clinical correlations. 2nd ed. Malden, MA: Blackwell Publishing; (2005). pp. 3–18 [15]. Used with permission

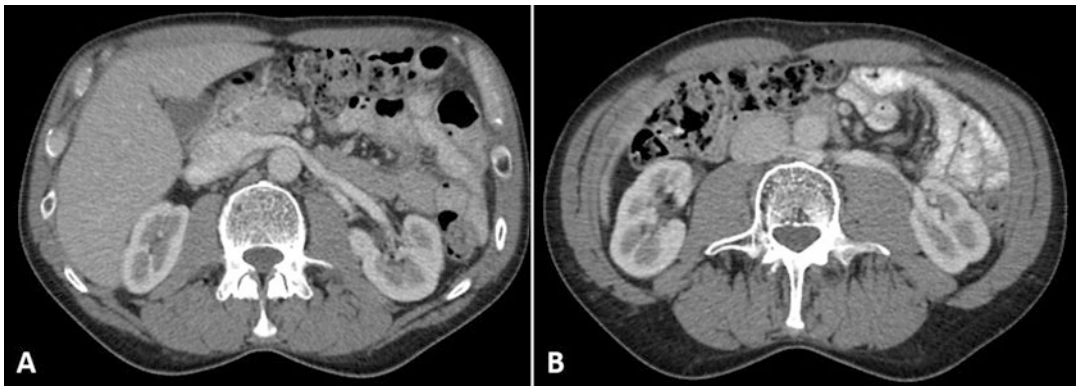

Fig. 1.10 (**A**) Anterior left renal vein, (**B**) circumaortic left renal vein

expose the subendothelial layer and activate the platelet cascade.

The tunica media consists of a band of smooth muscle cells combined with collagen and elastin, and is adrenergically innervated. This layer can withstand both longitudinal and circumferential stress; this allows elastic recoil to accommodate changes in flow and pressure. Histologically, the internal and external elastic laminae are very thin, if not absent. Traditionally, the presence or absence of the internal elastic lamina was a major criterion in distinguishing an artery from a vein on specimen analysis. Recent studies, however, suggest that smooth muscle pattern is more reliable (and carries a higher interobserver concordance) than an evaluation of the internal elastic lamina for vessel discrimination [18].

The tunica adventitia is well developed and in some instances contains longitudinally oriented bundles of smooth muscle. The veins of the lower extremities tend to be thicker than those more cephalad.

Veins function as storage organs and tend to hold upward of 70% of the blood volume being returned to the heart. Veins have thinner walls but larger diameters and a larger capacitance as compared to arteries, while maintaining a lower resistance. In addition, they tend to have a larger percentage of vasa vasorum, most likely due to the lower oxygen tension present within venous blood.

Venous flow is influenced by a variety of factors dependent on anatomic and physiological mechanisms. These included gravity, hydrostatic pressure, competence of unidirectional valves, respiration, and compressive forces generated by lower extremity (LE) muscle groups. In fact, approximately 90% of the deep venous return from the lower extremities is managed by the compartmental muscle groups of the thigh, calf, and foot [19].

Bicuspid (ie, having an anterior and a posterior cusp) unidirectional valves are identified within veins and are noted in increasing frequency caudally—they decrease in number centrally and are not present in the head and neck as the function of gravity promotes central flow [17, 20]. Valves function to decrease the hydrostatic pressure generated by the column of blood into lower pressure segments in addition to facilitating central flow of blood.

One in four external iliac veins (24%) contains a valve. More than 2/3 of these are competent. Valves in the common iliac vein are not as rare as formerly believed, but few, if any, are competent. Valves are not seen in the adult IVC. The femoral vein contains an average of three valves. Rarely, there may be none and uncommonly as many as six. Almost all of these are competent on macroscopic evaluation. The most common site for a valve in the femoral vein is just distal to the mouth of the profunda tributary (about 90% incidence). The second most common site is at or just distal to the inguinal ligament where over 2/3 of all femoral veins have a valve [21]. A variety of venous pathologies are present due to valvular incompetence and reflux, particularly in the lower extremities (Table 1.2). Several clinical syndromes are associated with congenital vascular malformations (Table 1.3).

Adult Venous Anatomy

Head and Neck

The dural venous sinuses are endothelium-lined spaces between the periosteal and meningeal layers of the dura within the cranium. Large veins from the surface of the brain drain into these sinuses including the superior sagittal sinus, inferior sagittal sinus as well as the straight sinus, transverse sinus, petrosal sinus, and others—ultimately, they drain into the internal jugular veins. The internal jugular veins run anterior and lateral to the carotid arteries within the carotid sheath and are joined by multiple tributaries from the anterior face, cervical viscera, and upper neck. They commence at the jugular foramen in the posterior cranial fossa as the direct continuation of the sigmoid sinus. The internal jugular veins unite with the subclavian veins draining the upper extremities posterior to

Table 1.2 Definition of clinical terms for venous dysfunction

International term	Definition
Chronic venous disorder	The entire spectrum of morphological and functional abnormalities involving the vascular system
Chronic venous disease	Any longer-lasting morphological or functional abnormality of the venous system, which is characterized by symptoms and/or abnormalities in diagnosis and/or requires therapy
Chronic venous insufficiency (C3–C6)	Advanced chronic vascular disorder with functional disturbances of the venous system resulting in edema, skin changes, or venous ulcerations
Venous symptoms	Symptoms caused by vascular disease such as a tingling sensation, pain, burning, muscle cramps, swelling, throbbing, heavy feeling, itching, restlessness, fatigue. Additional clinical signs and/or diagnoses suggest a relationship between symptoms and vascular disease
Venous signs	Visible manifestations of vascular disturbance including vessel dilation (eg, telangiectasias, reticulated veins, varicose veins), edema of the legs, skin changes, and ulcerations as listed in the CEAP classification [22]
Recurrent varices	Recurrent varices in a successfully treated region
Residual varices	Varicose veins that persist after treatment and cannot be eliminated
PREVAIT = presence of varices (residual or recurrent) after intervention	Varices present after intervention—residual or recurrent vessels
Post-thrombotic syndrome	Chronic venous symptoms and/or signs that are seen as a result of deep leg thrombosis or its complications
Pelvic congestion syndrome	Chronic symptoms such as pelvic pain, perineal discomfort, or postcoital pain or incontinence due to reflux or obstruction of pelvic or ovarian veins. Usually associated with vulvar, perineal, and/or leg varices
Varicocele	Scrotal varices

From: Reich-Schupke S, Stücker M. Nomenclature of the veins of the lower limbs – current standards. J Dtsch Dermatol Ges. 2011;9(3):189–94 [23]. Used with permission

the sternal head of the clavicle where they form the brachiocephalic vein. Of note, the smaller more superficial external jugular veins, which accept some tributaries from the shoulder, drain into the internal jugular veins.

The internal jugular veins are the most common sites for the placement of a central venous catheter, especially for dialysis. They are easily accessible and easily compressible. The right internal jugular vein is preferred as it has a more direct route to the right atrium resulting in less central venous stenosis.

Thorax

The thoracic cavity involves the brachiocephalic veins, the SVC, the intercostal veins, as well as the azygos and hemiazygos veins.

Brachiocephalic Veins

The brachiocephalic veins are formed by the unity of the respective internal jugular veins and their ipsilateral subclavian veins; they are devoid of venous valves [24].

The right brachiocephalic vein begins behind the sternal edge of the clavicle and descends almost vertically caudally where it joins the left brachiocephalic vein to form the SVC just below the cartilage of the first rib in proximity to the right border of the sternum; it usually measures around 2–3 cm in length. It lies anterior to the brachiocephalic (innominate) artery and receives tributaries from the right vertebral vein, right internal mammary, right inferior thyroid veins, and at times, the first intercostal vein. The right brachiocephalic vein has the most direct course to the right atrium, and at times is considered a cephalic extension of the SVC.

Table 1.3 Clinical syndromes associated with congenital vascular malformations

Syndrome	Inheritance	Type of vascular malformation	Location	Characteristic features	Treatment	Prognosis
Parkes Weber	No	Arteriovenous malformation (AVM; intraosseal or close to epiphyseal plate), port-wine stain	Extremity, pelvis	Soft tissue and bony hypertrophy, varicosity (atypical), hemangioma	Observation, elastic support, embolization ± excision	Deep diffuse lesions have poor prognosis
Klippel-Trenaunay	No	No or low-shunt AVM, venous or lymphatic VM, port-wine stain	Extremities, pelvis, trunk	Soft tissue and bony hypertrophy, varicosities (lateral lumbar to foot pattern), hemangioma, lymphangioma	Elastic support; seldom: epiphyseal stapling	Usually good
Rendu-Osler-Weber (hereditary hemorrhagic telangiectasia)	Autosomal dominant	Punctate angioma, telangiectasia	Skin, mucous membrane, gastrointestinal (GI) tract, liver, lungs, kidney, brain, spinal cord	Epistaxis, hematemesis, melena, hematuria, hepatomegaly, neurologic symptoms	Transfusions, embolization vs. laser treatment ± excision	Good if bleeding can be controlled and no central nervous system (CNS) manifestations
Sturge-Weber (encephalotrigeminal angiomatosis)	No	Port-wine stains	Trigeminal area, leptomeninges, choroid, oral mucosa	Convulsions, hemiplegia, ocular deformities, mental retardation, glaucoma, intracerebral calcification	Anticonvulsants, neurosurgical procedure	Guarded; depends on intracranial lesion
Von Hippel-Lindau (oculocerebellar hemangioblastomatosis)	Autosomal dominant	Hemangioma	Retina, cerebellum	Cysts in cerebellum, pancreas, liver, adrenals, kidneys	Excision of cysts	Depends on intracranial lesion
Blue rubber bleb nevus	Autosomal dominant	Cavernous venous hemangioma	Skin, GI tract, spleen, liver, CNS	Bluish, compressible, rubbery lesions, GI bleeding, anemia	Transfusions, electrocoagulation, excision	Depends on CNS and GI involvement
Kasabach-Merritt	Autosomal dominant	Large cavernous hemangioma	Trunk, extremity	Thrombocytopenia, hemorrhage, anemia, ecchymosis, purpura	Compression, transfusion of blood, platelets	Death from hemorrhage or infection
Maffucci (dyschondroplasia with vascular hamartoma)	Probably autosomal dominant	AVM, cavernous hemangioma, lymphangioma	Fingers, toes, extremity, viscera	Enchondromas, spontaneous fractures, deformed, shorter extremity, vitiligo	Orthopedic management	20% chance of malignancy

From: Nicholson CP, Gloviczki P. Embryology and development of the vascular system. In: White RA, Hollier LH, editors. Vascular surgery: basic science and clinical correlations. 2nd ed. Malden, MA: Blackwell Publishing; (2005). pp. 3–18 [15]. Used with permission

The left brachiocephalic vein is longer and more transverse in its course; it usually measures approximately 7 cm in length. It begins posterior to the sternal end of the left clavicle and descends obliquely to the right and downward toward the right costal cartilage. Here, it joins its right-sided counterpart to form the SVC. The left brachiocephalic vein lies anterior to the great vessels arising from the aortic arch as well as the vagus and phrenic nerves. It also accepts the left vertebral vein, the left internal mammary, the left inferior thyroid, and the left highest intercostal vein; occasionally, it drains thymic and pericardial veins.

When placing central venous catheters, it is important to note the anatomic differences between the right and left brachiocephalic veins, particularly the acuteness of their trajectory, in order to mitigate concerns for central vein perforation [25].

Superior Vena Cava (SVC)

The SVC is formed by the junction of the two brachiocephalic veins behind the lower border of the first costal cartilage adjacent to the sternum. It descends in a vertical fashion with a slight posterior convexity behind the first and second intercostal spaces to end in the upper portion of the right atrium. The SVC lies anterolateral to the trachea and posterolateral to the ascending aorta. Just before it enters the pericardium, it receives the azygos vein and other small pericardial veins.

A high index of suspicion is necessary as anatomic variants are noted with the SVC, in particular a left-sided SVC. A persistent left superior vena cava (PLSVC) represents the most common venous anomaly of the thoracic cavity and is found in 0.3–0.5% of individuals in the general population; in patients with congenital cardiac anomalies, it is reported to be as high as 12% [26–28].

Azygos and Intercostal Veins

The azygos and hemiazygos veins drain the thoracic and abdominal walls as well as the back. The intercostal veins accompany the intercostal arteries and nerves and lie most superior within the intercostal grooves. Eleven posterior intercostal veins and one subcostal vein are on each side. Most posterior intercostal veins end in the azygos venous system that ultimately drains blood into the SVC.

The azygos vein usually arises from the posterior aspect of the IVC at the level of the first or second lumbar vertebra and ascends into the thorax through the aortic hiatus of the diaphragm. It connects the IVC to the SVC. In fact, it offers an alternative method of drainage of the lower body back toward the SVC and the heart if an obstruction to the IVC is encountered. It ascends in the posterior mediastinum close to the vertebral bodies of the inferior eight thoracic vertebrae and arches over the root of the lung to pierce the pericardium. The hemiazygos provides venous drainage for the left chest and upper abdomen and connects with the azygos system.

Abdomen and Pelvis

The abdominal cavity venous system is primarily divided into a portal section and a systemic section.

Portal Vein

The portal vein is the main channel of the portal venous system, where poorly oxygenated yet nutrient-rich blood from the gastrointestinal tract is carried to the liver. It is created by the unity of the SMV and the splenic vein behind the neck of the pancreas. The portal vein supplies 70% of the blood to the liver, where the hepatic artery fulfills the remaining 30%. The portal vein branches into an expanded network of capillaries within the liver proper, called the venous sinusoids of the liver. Almost all the blood from the digestive tract is collected by the portal system and passes through these hepatic veins to the retrohepatic IVC.

Inferior Vena Cava (IVC)

The IVC is the largest vein in the body, with no valves except for a variable nonfunctional valve noted at its orifice in the right atrium. It returns poorly oxygenated blood from the lower extremities, abdominopelvic viscera, the back, and abdominal walls.

It commences anterior to the L5 vertebra by the union of the common iliac veins. This confluence occurs approximately 2.5 cm to the right of the midline, inferior to the bifurcation of the aorta, and posterior to the proximal part of the right common iliac artery. It ascends on the right psoas major to the right of the aorta and enters the thorax through the caval foramen of the diaphragm.

Recognition of anatomic anomalies such as a double IVC, left-sided IVC, or absent IVC is important for the clinician, particularly when involved in endovenous recanalization or placing an IVC filter (Fig. 1.12).

Tributaries of the IVC consist of the common iliac veins, formed by the union of the external and internal iliac veins; the 3rd and 4th lumbar veins; the right gonadal vein (testicular or ovarian); the renal veins; the ascending lumbar (ie, azygos/hemiazygos) veins; the right suprarenal vein; the inferior phrenic veins; and the three hepatic veins.

Iliac and Pelvic Veins

The external and internal iliac veins drain the LE and pelvis, respectively. They join to form the common iliac veins on each side, which ultimately become the IVC.

The external iliac vein is the ascending continuation of the common femoral vein when it passes the inguinal ligament. It traverses superomedially and is joined by the internal iliac vein to form the common iliac vein. It frequently contains 1–2 valves. The external iliac vein also receives the inferior epigastric vein, deep circumflex iliac vein, and other smaller pelvic veins.

The common iliac veins join on the right side of the midline at the level of the fifth lumbar vertebra. The right common iliac vein ascends rather vertically toward the IVC, whereas the left common iliac vein has a longer course and travels posterior to the right common iliac artery. This, in turn, may predispose to a clinical condition described as May-Thurner syndrome, where the right common iliac artery compresses the left common iliac vein resulting in outflow obstruction of venous blood of the left LE and is manifest by heaviness, achiness, left LE edema, and even chronic venous insufficiency (Fig. 1.13). This may result in deep venous thrombosis

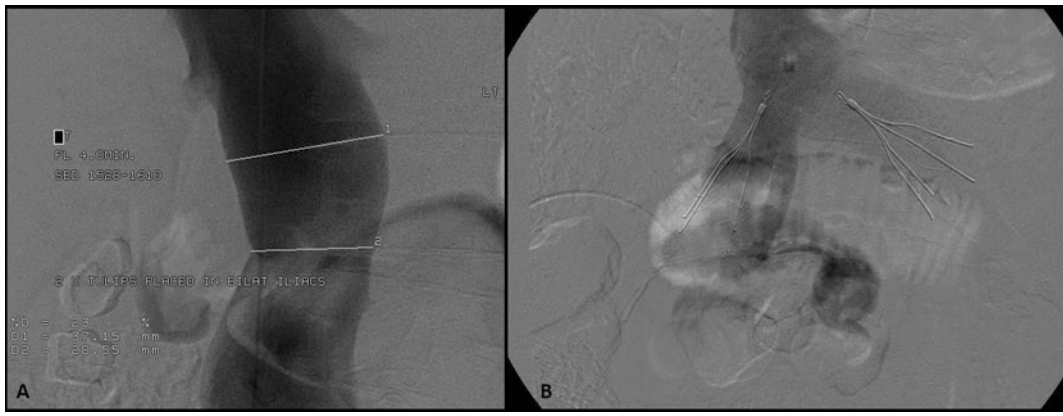

Fig. 1.12 (**A**) Megacava 37 mm, (**B**) Protective filters in common iliac. Important to size cava before selecting IVC filter as may embolize if too small a filter is selected. Filters placed in bilateral common iliacs to protect patient

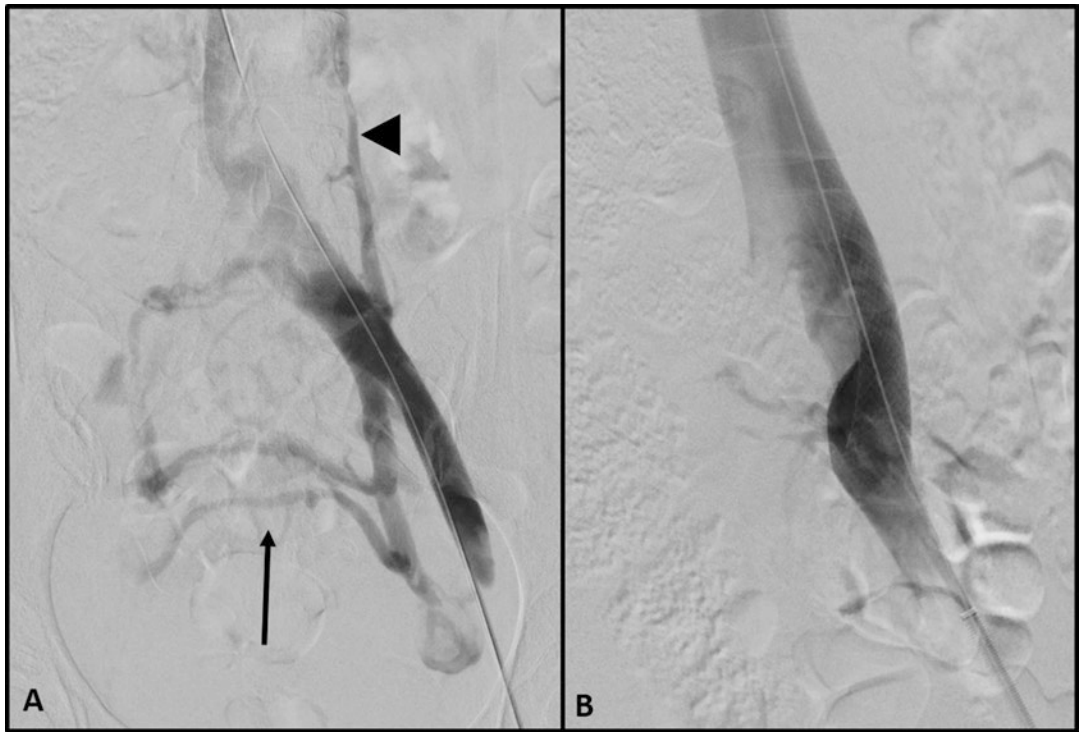

Fig. 1.13 (**A**) Venogram of the pelvis showing May-Thurner syndrome with filling of pelvic collaterals (*arrow*) and paravertebral collaterals (*arrowhead*), (**B**) Left common iliac vein stenting with resolution of filling of collaterals

(DVT) as well. The left LE is involved in venous problems of pregnancy nine times more commonly than the right LE.

The pelvic venous system is a complex and rich plexus interconnecting the LE deep and superficial veins, the parietal and visceral plexuses of the pelvis, and the iliocaval venous systems [20]. The internal iliac veins drain the visceral (ie, hemorrhoidal, vesicoprostatic, uterine, gonadal, and vesicovaginal) and parietal (ie, superior and inferior gluteal, sacral, sciatic, lumbar, obturator, and internal pudendal) plexuses through a very extensive and valveless network [20, 29, 30].

Recall that the left gonadal vein drains into the left renal vein, as does the left suprarenal vein. Valves in the gonadal veins prevent reflux. Significant reflux of the ovarian vein can cause vulvar varicosities, dyspareunia, and heaviness in females consistent with pelvic congestion syndrome [31] (Fig. 1.14).

Upper Extremity

Both superficial and deep veins exist in the upper extremity. They do not function against gravity in the same manner as the LE veins and, as such, do not have as many valves.

Subclavian Vein

The subclavian vein, the major venous channel draining the upper extremity, passes through the inferior part of the posterior triangle of the neck. It passes anterior to the anterior scalene muscle and phrenic nerve and unites at the medial border of this muscle with the internal jugular vein to form the brachiocephalic vein, posterior to the medial head of the clavicle. The subclavian vein is another commonly used vessel for central venous access. The left subclavian vein has a

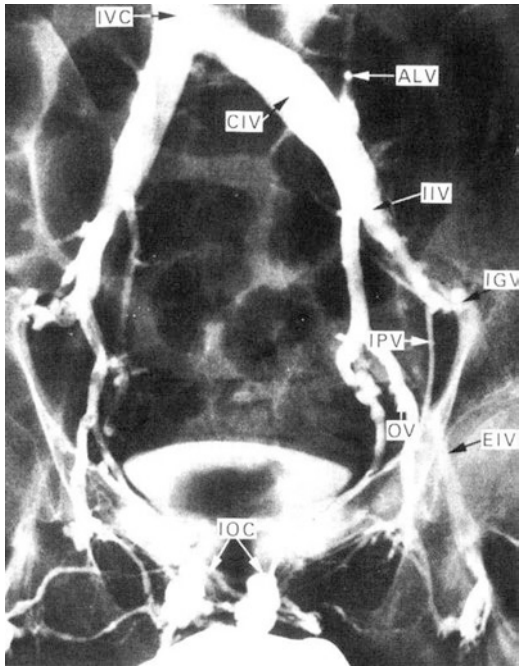

Fig. 1.14 Internal iliac venous collateral pelvic network. Internal iliac veins shown by bilateral intraosseous injections into the pubic bones in the supine position. This technique allows complete visualization of all the tributaries but is rarely required. *ALV* ascending lumbar vein, *CIV* common iliac vein, *EIV* external iliac vein, *IGV* inferior gluteal vein, *IIV* internal iliac vein, *IOC* intraosseous cannulae, *IPV* internal pudendal vein, *IVC* inferior vena cava, *OV* obturator vein. Used with permission from [31]

longer, more transverse course, and is easier to cannulate than the right subclavian vein.

Axillary Vein

The axillary vein is formed by the confluence of the paired brachial veins with the basilic vein at the inferior border of the teres major. It ends at the lateral border of the first rib where it becomes the subclavian vein. The veins of the axilla are highly variable and much more abundant than the arteries.

Deep Veins of the Arm and Forearm

The superficial and deep palmar venous arches accompany their corresponding palmar arterial arches. The dorsal digital veins drain into three dorsal metacarpal veins which unite to form the dorsal venous network and arcade. These then give rise to paired radial and ulnar veins that also accompany their corresponding arteries while receiving tributaries from the veins leaving the muscles with which they are related. They ultimately ascend to the brachial vein and profunda brachii vein.

Superficial Veins of the Arm and Forearm

The main superficial veins of the arm and forearm are the cephalic, basilic, medial cubital, and antebrachial veins and their tributaries. The cephalic vein arises on the lateral (ie, radial) side of the dorsal venous arch and ascends along the lateral border of the forearm where it communicates with the basilic vein through the medial cubital vein. The cephalic vein then remains in this lateral position until it drains into the axillary vein. The basilic vein ascends posteromedially along the medial (ie, ulnar) side of the forearm after arising from the medial aspect of the dorsal venous arch of the hand. It reaches its anterior surface just distal to the elbow, where it is joined by the median cubital vein. The median antecubital vein drains the subcutaneous tissue in the anterior aspect of the wrist and forearm, and usually ends in the basilic vein.

Lower Extremity (LE)

The LE veins are divided into superficial, deep, and perforating veins.

Superficial Veins

The superficial veins of the LE are located above the muscular fascia and, in fact, are contained within a subcomponent known as the saphenous fascia. This superficial system is composed of a complex interconnecting web of collecting veins and venules, as well as larger, thicker-walled truncal veins. Also included are the reticular veins and subcapillary venous plexus.

The great saphenous vein (GSV) is the largest, most continuous, superficial vein of the LE. It is generally between 3–4 mm in diameter and contains between 10–20 valves, most of which are concentrated caudally. The GSV originates from the medial marginal vein of the foot and ascends anterior to the medial malleolus in close approximation to the sensory saphenous nerve. It terminates into the common femoral vein after it pierces the cribriform fascia at the saphenofemoral junction, and generally receives blood from the superficial external pudendal, superficial epigastric, and superficial circumflex iliac veins [30].

The small saphenous vein (SSV) originates from the lateral marginal vein of the foot and travels posterior to the lateral malleolus as it ascends from lateral toward the midline posteriorly, where it perforates the deep fascia to join the popliteal vein between the heads of the gastrocnemius muscles. It typically measures less than 3 mm in diameter and contains about 9–12 valves. Termination of the SSV is highly variable with several common configurations: (A) direct termination into the popliteal vein; (B) termination into the popliteal vein with another branch continuing cranially as the intersaphenous vein; and (C) no direct communication with the popliteal vein and only a cranial extension.

Actual anatomical duplication is uncommon, occurring in less than 1% for the GSV and less than 5% in the SSV [30].

Deep Veins

The deep veins of the LE course from the foot to the upper thigh into the common femoral vein.

The deep veins of the foot include the medial and lateral plantar veins, which converge into a plexus near the calcaneus, where they ascend into paired posterior tibial veins. Interestingly, the valves of pedal perforators are oriented such that blood travels from deep to superficial, unlike the perforating veins of the calf and thigh, which direct blood from superficial to deep [32].

The deep calf veins include the tibial, peroneal, soleal, and gastrocnemius veins. Venous sinusoids and reservoirs within the posterior calf muscles serve as a collecting system of the calf muscle pump. Soleal venous sinuses generally communicate with the posterior tibial veins, whereas the gastrocnemius sinuses anastomose into gastrocnemius veins, which drain into the popliteal system directly. The anterior tibial, posterior tibial, and peroneal veins are usually paired with their corresponding artery, and the former two join the latter to become the popliteal vein proper.

The deep thigh veins include the popliteal, femoral, and common femoral veins. The popliteal vein originates at the inferior border of the popliteus muscle and continues through the popliteal fossa until it passes under the adductor hiatus to become the femoral vein. The popliteal vein generally receives the SSV.

The femoral vein accompanies the superficial femoral artery along the length of the thigh, changing course from lateral to medial as it ascends. The femoral vein is joined by the profunda vein and the GSV prior to becoming the common femoral vein. The femoral vein generally has three valves. The profunda vein receives blood from the corresponding perforating venous branches of the profunda femoris artery. It drains the deep muscles of the lateral thigh and may communicate with the popliteal vein.

The common femoral vein transitions to the external iliac vein at the inguinal ligament.

Perforating Veins (PV)

According to their morphologic characteristics and functional behavior, the perforating veins (PV) of the lower limb are divided into four principal groups: direct communicating veins (vena communicantes directae), indirect communicating veins (vena communicantes indirectae), mixed communicating veins (vena communicantes mixtae), and atypical communicating veins (vena communicantes atypicae). They share certain characteristics in common and others, which are typical for each group mentioned [33].

Perforating veins consist of four clinically significant groups. They used to be known

eponymously until the nomenclature was revised. The groups include the foot, the medial calf, the lateral calf, and the thigh. These veins vary widely in location and size. They connect the superficial system to the deep system with unidirectional valves, promoting flow from superficial to deep. Again, and uniquely, pedal perforators direct flow from deep to superficial. Reflux in PVcan result in clinically significant venous disease (Tables 1.4 and 1.5).

Current Nomenclature

Accurate anatomic classification and terminology are the basis of appropriate exchange of medical information. In 2001, an International Interdisciplinary Committee was convened by the presidents of the International Union of Phlebology (UIP) and the International Federation of Associations of Anatomists (IFAA) to update the official *Terminologia Anatomica*

Table 1.4 Nomenclature of the perforating veins

Foot perforators	Dorsal foot PV or intercapitular veins Medial foot PV Lateral foot PV Plantar foot PV
Ankle perforators	Medial ankle PV Anterior ankle PV Lateral ankle PV
Leg perforators	Medial leg PV • Paratibial PV • Posterior tibial PV (Cockett PV) Anterior leg PV Lateral leg PV Posterior leg PV • Medial gastrocnemius PV • Lateral gastrocnemius PV • Intergemellar PV • Para-achillean PV
Knee perforators	Medial knee PV Suprapatellar PV Lateral knee PV Infrapatellar PV Popliteal fossa PV
Thigh perforators	Medial thigh PV • PV of the femoral canal • Inguinal PV Anterior thigh PV Lateral thigh PV Posterior thigh PV • Posteromedial • Sciatic PV • Posterolateral Pudendal PV
Gluteal perforators	Superior gluteal PV Mid-gluteal PV Lower gluteal PV

PV perforating veins

Adapted from: Caggiati A, Bergan JJ, Gloviczki P, Eklöf B, Allegra C, Partsch H. Nomenclature of the veins of the lower limb: extensions, refinements, and clinical application. J Vasc Surg. 2005;41(4):719–24 [34]. Used with permission

Table 1.5 Studies on the location of direct medial perforating veins in the leg

–	Number of legs		Location of medial perforating veins[a]		
First author (year)	Anatomic dissections	Surgical findings	Middle posterior Tibial perforator	Upper posterior Tibial perforator	Proximal paratibial perforating veins
Linton (1938) [35]	10	50	Distal third of the leg	Middle third of the leg	Proximal third of the leg
Sherman (1949) [36]	92	901	13.5 cm	18.5 cm	24 cm, 30 cm, 35 cm, 40 cm
Cockett (1953) [37]	21	201	13–14 cm	16–17 cm	At the knee
O'Donnell (1977) [38]	–	39	Half of the incompetent perforating veins are between 10 to15 cm[b] (15–20 cm[a])		Few incompetent perforating veins
Fischer (1992) [39]	–	194	Random distribution of incompetent perforating veins		
Mózes (1996) [40]	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])

Adapted from: Gloviczki P, Mózes G. Development and anatomy of the venous system. In: Gloviczki P, editor. Handbook of venous disorders. 3rd ed. London: Hodder Arnold; (2009). p. 19 [41]. Used with permission

[a]Distances measured from the sole

[b]Distances measured from the lower tip of the medial malleolus

Table 1.6 The most common "old" anatomic terms describing lower extremity (LE) veins and their "new" counterparts

"Old" term	"New" term
Greater or long saphenous vein	Great saphenous vein (GSV)
Smaller or short saphenous vein	Small saphenous vein (SSV)
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
Superficial femoral vein	Femoral vein
Cockett perforators (I, II, III)	Posterior tibial perforators (lower, middle, 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

Adapted from: Mózes G, Gloviczki P. New discoveries in anatomy and new terminology of leg veins: clinical implications. Vasc Endovascular Surg. 2004;38(4):367–74 [42]. Used with permission

regarding the LE veins. With the increased knowledge of the physiology and pathophysiology of venous disease, this update was vital as incorrect interpretation of these veins had commonly led to inappropriate treatment of diseases. For instance, the main vein of the thigh—the superficial femoral vein—is in fact a deep vein and, due to its name, was not being treated in episodes of deep vein thrombosis. Furthermore, eponymous names of the LE perforators are now discussed by their anatomic location. The current terminology is presented in Table 1.6.

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Venous Physiology and Pathophysiology

2

James Laredo and Byong Boong Lee

Clinical Pearls

1. Chronic venous disease is caused by venous reflux, obstruction, or a combination of both.
2. Primary varicose veins result from superficial venous dilatation or valvular incompetence without previous DVT.
3. DVT is the most common cause of deep valvular insufficiency and/or obstruction and causes secondary varicose veins.

Venous System

The function of the venous system is to deliver deoxygenated blood from the organ systems and tissues to the right heart. The blood in the right ventricle then enters the pulmonary circulation and lungs where it is oxygenated. From the lungs, the oxygenated blood is then delivered to the left heart where the left ventricle pumps the blood into the arterial system delivering oxygenated blood to the rest of the body.

Lower extremity veins are essentially tubes with valves that function as passive conduits for blood flow. These structures also have a reservoir function with variable capacity accommodating up to 60–70% of the body's total blood volume [1]. Blood flow through the venous system is under neuromuscular control and is affected by gravity and muscular contractions. Venous flow is intermittent and ranges from high velocity to no flow, and its flow patterns are more complex than those observed in arteries [1].

The hydrostatic pressure at any point in the venous system results from the weight of the column of blood from the level of the heart to that point. This pressure is dependent on body position and varies with the height of the column of blood where the pressure at the ankle changes from a negative value with the legs elevated in a person supine, to around 10 mmHg with the legs lying flat. In an upright, standing person, the hydrostatic pressure at the ankle is around 90 mmHg. Muscular activity such as moving, walking, or running reduces the hydrostatic pressure from 90 to 30 mmHg in a person with normal venous function due to competent venous valves that fractionate the pressure column during lower extremity muscular contraction (systole) and relaxation (diastole) [1, 2].

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In patients with venous disease, venous insufficiency predominantly occurs below the knee as excessive hydrostatic pressure cannot be reduced in the upright position because of valvular incompetence or outflow obstruction. The normal function of venous valves is called dynamic fractioning of the hydrostatic pressure [1, 2].

The behavior of a vein depends on the structure of the three layers that comprise the vein wall. In diseased veins such as varicose veins, the venous wall structure is altered, while an abnormal intraluminal thrombus adherent to the intima can add an additional internal layer. Both of these situations produce complex mechanical responses.

Volume and pressure in veins can change under different conditions. The venous volume depends on the transmural pressure, active tone of the muscular media layer, and passive compliance of the adventitial layer [1]. Large-diameter veins have a high passive compliance and variable venous tone and can store blood with a low variation of transmural pressure. These high capacitance vessels can store 60–70% of the blood volume [1]. This phenomenon is known as the "reservoir effect" of the venous system. By increasing the tone of the venous wall, this blood can be mobilized when needed.

Venous Valves and Valvular Function

Venous valves are present in nearly all of the veins of the lower extremities. Valves are found in the deep and superficial veins and inside most perforating veins. In the venous system, the further away from the central circulation, the more frequent a venous valve is present [1]. Venous valves are often absent in the iliac veins and inferior vena cava. The valves are usually bicuspid where the orientation of the leaflets results in centrally directed venous blood flow [3].

In the majority of perforating veins, the valve leaflets are oriented toward the deep system, while in some veins, the valves are absent [4]. The valves in each perforating vein are usually located below the fascia, and their number may vary from one to three.

Normal valve function consists of a water-tight closure against a retrograde pressure gradient opposite to the direction of the leaflets. The valve leaflets remain passively open when the pressure gradient is antegrade in the same direction as the leaflets [5]. This function ensures unidirectional flow and emptying of venous compartments and physiologic drainage and flow of blood from superficial to deep, regardless of posture or changes in intra-abdominal or intrathoracic pressures [6]. Normal valve closure also produces dynamic fracturing of the gravitational hydrostatic pressure and is essential for proper function of the peripheral muscle pumps [1, 2].

Venous Muscle Pump Systems

During normal walking, the three vein-pumping systems (the foot, calf, and thigh) compress in sequence to promote venous return. Even moderate muscular movements of the feet and legs in the seated position are able to activate the pumping mechanism and reduce the distal vein pressure [1, 7].

The calf muscle pump is activated at the beginning of a step and starts with dorsiflexion of the foot as the foot is lifted [1]. The anterior compartment muscles contract and empty their veins. Dorsiflexion then passively stretches the Achilles tendon and thus empties blood from the lower portions of the peroneal and posterior tibial veins. As the foot strikes the ground, weight bearing and contraction of the foot muscles activate the foot pump, a second phase where the plantar venous plexus is able to overcome the hydrostatic pressure within the deep venous system of the calf [1, 8, 9]. The weight of the body and contraction of the plantar muscles result in compression of the lateral plantar veins where the middle portion is dilated and acts like a reservoir [1, 10]. Each step squeezes a small volume of blood, approximately 20–30 mL [11]. Plantar flexion initiates a third phase as the foot comes up on its toes. During this phase, the muscles of the posterior compartments, mainly the gastrocnemius and soleus muscles, contract to empty the calf venous sinuses.

The Calf Pump

The calf muscle pump is the most active pump in the lower extremity where the soleus and gastrocnemius muscles are rich in venous sinuses. During walking, contraction of the soleus and gastrocnemius muscles compresses the venous sinuses propelling blood out of the calf. During each step, calf muscle pressures exceed 200 mmHg, and calf blood volume decreases by 80% [12].

Calf muscle contraction (systole) produces a significant pressure gradient between the deep veins in the calf and the popliteal vein resulting in rapid efflux of blood from the calf into the thigh. The venous pressure exceeds the intramuscular pressures in the calf compartments, and competent venous valves prevent retrograde blood flow [10]. During calf muscle relaxation (diastole), venous pressure falls below the pressure at rest. In the deep veins, the fall in pressure is greater than that observed in the superficial veins. Perforating veins allow blood to flow from the superficial veins into the deep veins. There is no significant change in the popliteal vein pressure during calf muscle relaxation. Competent venous valves prevent backflow from the popliteal vein into the calf veins [10].

Effect of Exercise on Venous Function

When a person moves from the horizontal to the standing position, the hydrostatic pressure increases equally in both the arteries and veins of the foot by 80–90 mmHg and is dependent on the distance of the foot from the right atrium. Because the arteriovenous pressure gradient remains unaffected, arterial blood flow in a normal limb is unchanged. However, blood flow in the veins is temporarily reduced until they become fully distended with increased venous volume. When the pressure in the veins is increased by 40 mmHg or more, a venoarteriolar reflex is elicited producing arteriolar vasoconstriction which together with the decreased blood flow results in a protective mechanism to minimize edema formation [13–15].

Exercise (walking, running, or tiptoeing) is very effective in emptying veins resulting in a significant reduction in hydrostatic pressure. Intramuscular pressures in the gastrocnemius and soleus muscles increase from 9–15 mmHg when they are relaxed to 215–250 mmHg during muscle contraction [1, 8]. In normal individuals, tiptoeing causes the pressure in the foot to reduce from 80–90 mmHg to 25 mmHg. As a result, the pressure gradient from arterioles to venules is increased allowing the high blood flow required by the leg muscles and increased blood supply to the right atrium required to maintain an increased cardiac output [1, 8].

Early experiments demonstrated that during walking the mean venous pressure is decreased in a normal limb by approximately 60 mmHg after 3–12 steps reaching a steady state which is approximately 22 mmHg at 1.7 miles per hour (40 steps per minute) [16]. There is very little further decrease in pressure at higher speeds. However, below this speed the decrease in pressure (steady state) is proportional to the walking speed [17, 18]. At the end of exercise, the pressure returns to the resting level within 30 s. Figure 2.1 shows a typical recording of venous pressure measured in a dorsal vein of the foot during standard tiptoe movements in a patient with varicose veins, saphenofemoral incompetence, and competent valves in the deep venous system [19]. The exercise was repeated after inflating a 10-cm-wide pneumatic cuff just below the knee to occlude the superficial veins [1, 28]. By eliminating the venous reflux with the pneumatic cuff, the pressure recording became completely normal [19].

Deep Vein Thrombosis

The hemodynamic changes that occur in patients with acute deep vein thrombosis (DVT) are dependent on the level of thrombosis, its extent, and whether thrombus progression is slow or rapid. The severity of the hemodynamic disturbance caused by the venous obstruction will determine the development and magnitude of the presenting symptoms and signs experienced by the individual.

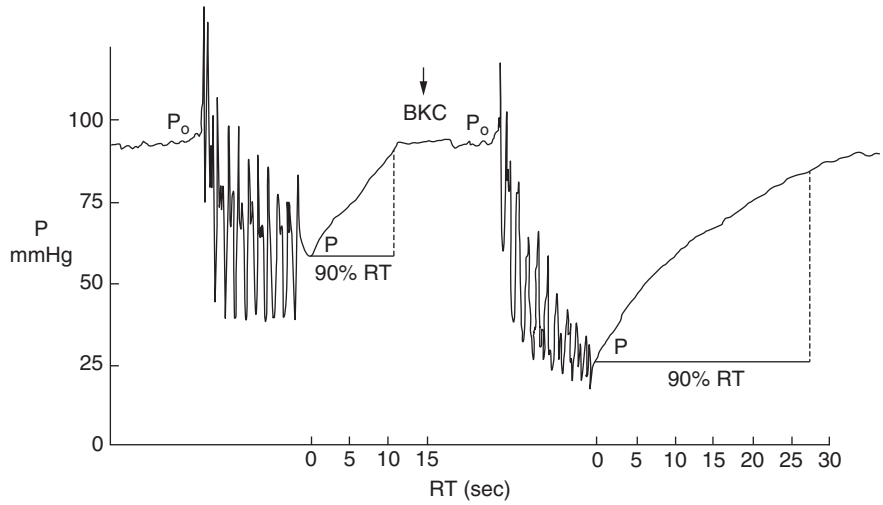

Fig. 2.1 Recording of ambulatory venous pressure at rest and during ten tiptoe movements in a patient with varicose veins and saphenofemoral incompetence. The first recording was without a below-knee cuff and the second recording was with a below-knee cuff (*BKC*) which occluded the great and small saphenous veins normalizing the ambulatory venous pressure (*P*) and the refilling time (90% *RT*) (modified from Ref [19])

Localized DVT in one or two veins in the calf as shown by venography is often asymptomatic producing mild ankle edema and calf tenderness in only 50% of patients [20]. In contrast, extensive calf DVT involving the popliteal vein is often symptomatic. Significant lower extremity edema will not occur as long as the thrombus is confined to the femoral vein distal to the junction with the deep femoral or the great saphenous veins which act as collateral drainage channels. When thrombosis involves these junctions or occurs proximal to them, massive limb edema is likely to occur [21]. Furthermore, rapid progression of thrombus proximally may not allow development of a collateral circulation and may result in venous gangrene.

Plethysmographic studies of patients with lower extremity DVT have demonstrated reduced venous volume and increased outflow resistance [22–24]. The reduced venous volume is thought to be due to the reduced capacity of the lower extremity veins when they are filled with thrombus in patients with proximal obstruction. In addition, increased extravascular tissue pressure due to edema decreases the distensibility of the veins further decreasing venous volume [22–27].

Lower extremity venous pressure is increased in patients with acute DVT [28]. In patients with DVT, venous pressure was measured in the foot in patients in the horizontal position. Venous pressure was 8.5–18.4 mmHg when thrombosis was confined to the calf and/or popliteal vein, 20–51 mmHg when thrombosis involved the femoral vein, and 32–83 mmHg in patients with iliofemoral DVT [21]. Limb edema was rarely present in patients with venous pressures less than 20 mmHg and always present in patients with venous pressures greater than 50 mmHg.

Venous flow and velocity are phasic with respiration in normal limbs in the horizontal position. During inspiration, intra-abdominal pressure increases with contraction of the diaphragm. The increase in intra-abdominal pressure is transmitted to the inferior vena cava and iliac veins resulting in a decrease in the pressure gradient between the lower extremity vein and the inferior vena cava. The end result is a decrease in blood flow from the lower extremities.

During expiration, the reverse occurs as the diaphragm relaxes and intra-abdominal pressure decreases. The decrease in intra-abdominal pressure results in an increase in the venous pres-

sure gradient between the inferior vena cava and lower extremity veins. This results in an increase in venous flow and velocity from the lower extremity veins.

In patients with acute iliofemoral DVT, the outflow resistance increases much more than the respiratory fluctuations so that this becomes the limiting factor, and flow in the deep veins distal to the obstruction loses phasicity and velocity decreases [1]. In contrast, flow and velocity in the collateral circulation increase, and higher velocities are observed. These findings explain why an ultrasonographer should look for a more proximal obstruction when performing a DVT scan in a patient with the dual finding of the absence of respiratory phasicity in the deep veins and increased velocity in the collateral veins of the lower extremity [1].

Chronic Venous Disease

Chronic venous disease (CVD) is a term that includes all long-term morphological and functional abnormalities of the venous system, manifested either by symptoms or signs indicating a need for investigation and treatment. In patients with CVD, hemodynamic disturbances occur which result in the inability of valves, pumps, and conduits in the venous system to maintain a normal venous pressure and normal flow toward the heart. Hemodynamic disturbances are primarily caused by venous reflux, obstruction, or a combination of both [1].

Varicose Veins

Varicose veins are a common manifestation of CVD and are believed to result from the abnormal distension of connective tissue in the vein wall. Veins from patients with varicosities have different elastic properties than those from individuals without varicose veins [29, 30]. There is hypertrophy of the vein wall with increased collagen content [31], fragmentation of elastin fibers [32] with degradation, and accumulation of extracellular matrix [33].

Primary varicose veins result from venous dilatation and/or valve damage without previous DVT. Secondary varicose veins develop as a result of a prior DVT, congenital venous malformation, or arteriovenous malformation [34].

Varicose veins may also be associated with pelvic vein reflux in the absence of incompetence at the saphenofemoral junction (SFJ), thigh, or calf perforating veins. Retrograde reflux in ovarian, pelvic, vulvar, pudendal, or gluteal veins may be also associated with clinical symptoms and signs of pelvic congestion [35–38].

Elevated venous pressure is considered to be the main precipitating factor in the development of varicose veins. Varicose veins would not occur without hydrostatic pressure from a gravitational force [1]. The effect of dilatation is easily understood from the unrelenting radial forces against the wall of the varicose vein. What is not understood is why the dilatation of varicose veins predominantly occurs in the thigh portion of the great saphenous vein (GSV) in many patients and not in the ankle portion where the hydrostatic pressure is highest (descending theory) [1]. In addition, it is also unknown as to why superficial veins dilate and become tortuous forming varicose veins; in contrast, the GSV usually dilates and rarely becomes tortuous within the saphenous fascia.

Varicose veins have increased wall thickness and increased diameter and length [39]. This is likely due to the different elastic properties observed in varicose veins compared to normal veins [29, 30]. The ratio between collagen I and collagen III is altered as are dermal fibroblasts from the same patients suggesting a systemic disorder with a genetic basis [40]. Leukocyte activation, adhesion, and migration through the endothelium as a result of altered shear stress [41–43] contribute to the inflammation and subsequent remodeling of the venous wall and valves [44–47].

Cell culture studies have shown that smooth muscle cells have undergone phenotypic modulation from a contractile state to a proliferative and secretory state [48]. Reduction in shear stress stimulates production of transforming growth factor-β1 (TGF-β1) by activated endo-

thelial cells and smooth muscle cells (SMCs) inducing SMC migration into the intima and subsequent proliferation as well as phenotype change. Fibroblasts proliferate and synthesize matrix metalloproteinases (MMPs) overcoming the effect of tissue inhibitors of metalloproteinases (TIMPs). The MMP/TIMP imbalance results in degradation of elastin and collagen [42, 49, 50]. These effects may contribute to the development of hypertrophic and atrophic venous segments and valve destruction that is observed in varicose veins. Remodeling of the venous wall and abnormal venous distension prevents valve leaflets from closing properly resulting in valve failure and reflux.

Genetic factors may also play a role in the development and subsequent progression of primary varicose veins to advanced CVD. A relationship between the C282Y polymorphism in hemochromatosis (HFE gene) and venous ulceration has been described [51].

Deep Venous Insufficiency

Imaging studies in patients with deep venous insufficiency have shown that approximately 30% of these patients have primary valvular incompetence rather than findings consistent with post-thrombotic injury [52, 53]. Valve agenesis or aplasia is a less likely cause of deep venous reflux [54].

Following the development of a DVT, spontaneous lysis often occurs over days or weeks, and recanalization that occurs over months or years can be found in 50–80% of patients [55–57]. Rapid thrombus resolution after DVT is associated with a higher incidence of valve competency [55, 58]. The duration of DVT recanalization and resolution depends on thrombus extent, location, local inflammation, potency of local fibrinolytic agents and proinflammatory mediators [59, 60]. Recanalization may give rise to relative obstruction and reflux in deep, superficial, and perforating veins [57]. Incomplete recanalization following DVT can lead to outflow obstruction. Less frequently, obstruction results from extramural venous compression (most commonly left common iliac vein compression by the right common iliac artery) [61, 62], from intraluminal changes [63–65], or rarely from congenital agenesis or hypoplasia [66].

Most post-thrombotic symptoms result from venous hypertension due to valvular incompetence, outflow obstruction, or a combination of both. Venous hypertension increases transmural pressure in postcapillary vessels leading to skin capillary damage with increased microvascular permeability, [67] followed by lipodermatosclerosis and, ultimately, ulceration [68]. Edema will develop when the increased lymphatic transport fails to adequately compensate for increased fluid filtration into the tissue, and thus long-standing venous hypertension is invariably associated with damaged lymphatic drainage in the skin and subfascial space in cases of post-thrombotic syndrome [69, 70]. The reported prevalence of post-thrombotic syndrome following DVT has been variable (35–69% at 3 years and 49–100% at 5–10 years) and depends on the extent and location of thrombosis and treatment [71–81].

Patients with both chronic obstruction and reflux have the highest incidence of clinical C of CEAP 4–6 disease [71]. The risk of ipsilateral post-thrombotic syndrome is highest in patients with recurrent thrombosis and is often associated with congenital or acquired thrombophilia [82–85]. More recent studies suggest that skin changes and/or ulceration are less frequent (4–8% in 5 years) in patients with thrombosis proximal to the knee if they have been treated with adequate anticoagulation, early mobilization, and long-term compression therapy [86, 87]. Mechanical dysfunction of the calf muscle pump may enhance development of leg ulceration suggesting the importance of the range of ankle motion [88] and patient activity [89] in relation to progression of disease. Obesity is another risk factor for severe venous disease and may be related to its association with decreased fibrinolytic activity in blood and tissues [90].

Perforating Veins

Incompetent perforating veins (IPVs) can be defined as those that penetrate the deep fascia and allow blood flow from the deep to the superficial system. The flow in IPVs in the calf is usually bidirectional, outward during muscular contraction and inward during relaxation. In normal legs and in the majority of patients with primary uncomplicated varicose veins, the net flow is inward from superficial to deep (reentry perforating veins) [91, 92]. The net flow is also inward in patients with femoral vein reflux, provided the popliteal valves are competent. However, flow is predominantly outward in the presence of popliteal valve incompetence (axial reflux) and especially when there is associated deep venous obstruction [92, 93]. The IPVs are associated with superficial and/or deep venous reflux but are rarely found in the absence of reflux [94–96]. In the majority of IPVs, their diameter, volume flow, and velocity increase with clinical severity of CVD whether or not there is coexisting deep venous incompetence [92, 97–102]. Up to 10% of patients, often women, presenting with clinical C of CEAP 1–3 disease, have non-saphenous superficial reflux in association with unusually located IPVs [103].

Superficial Venous Insufficiency

The valves and walls of superficial veins are more prone to structural failure than deep veins because they are surrounded by connective tissue and subcutaneous fat. In contrast, deep veins are surrounded by rigid structures such as muscle and fascia. Therefore, the walls and valves of the superficial veins are more vulnerable to the changes in shear stress and hydrostatic pressure [104–106].

The concept of retrograde flow in the GSV and the presence of a "private recirculation" were first demonstrated by Trendelenburg in 1891 [91] by placing a tourniquet at mid-thigh and asking the patient to tiptoe repeatedly when it was observed that veins emptied with refilling from above when the tourniquet was released. We now know that the circuit consists usually of a reflux source feeding a saphenous trunk, conduction of reflux, down toward the foot, and reentry points back into deep veins via perforating veins. The presence of this phenomenon has been demonstrated using two simultaneous duplex probes, above and below the knee [107]. In this study, reflux was demonstrated to start and stop simultaneously, even when the probes were swapped around. In another study, volume displacements in patients were quantified within saphenous trunks using duplex ultrasound in response to calf compression [108]. The findings of bidirectional flow in the GSV and perforating veins by Bjordal [109, 110] were confirmed in the same year by Folse [111] who used the CW Doppler which had just become available and by duplex ultrasound scanning in later years. The conclusion was that in the presence of competent deep veins, despite inward and outward flow in perforating veins during walking, the net effect is inward. However, when deep venous valves were incompetent and valves in the GSV were competent, Bjordal found that calf contraction caused upward flow in the saphenous vein and that in limbs with both deep and superficial venous reflux, walking produced bidirectional flow in IPVs with the net effect being outwards [109, 110]. It is now recognized that in the majority of patients, the origin of the downward flow in the superficial system of veins is through the SFJ, thigh IPVs, the SPJ, or a combination of two or even all three and that calf IPVs are reentry points. This is the basic rationale for the CHIVA technique [1]. However, two RCTs have shown that following ablation of superficial incompetence, only 35–40% of IPVs function normally and that new IPVs appear over time [112, 113]. Furthermore, some 6–8% of ulcer patients show only isolated IPVs as a possible cause for their ulcers [114].

Manifestations of Venous Hypertension

Changes in the hemodynamics of veins that result in venous hypertension are transmitted into the microcirculation resulting in an increase in the

hydrostatic pressure in capillaries. This results in transcapillary filtration that exceeds lymphatic drainage and contributes to interstitial edema formation. Venous hypertension slows blood flow in the capillaries allowing leukocyte adhesion to capillary endothelium and initiating an inflammatory reaction [115]. One theory contends that inflammation opens gaps between endothelial cells through a mechanism involving vascular endothelial growth factor (VEGF), nitric oxide synthase (NOS), and contraction of actin and myosin filaments present in endothelial cells [116]. If the gaps continue to enlarge, this results in increased capillary permeability to fluid and macromolecules, allowing extravasation of red and white blood cells into the interstitial space with edema formation. Swollen endothelial cells with enlarged intercellular spaces make the capillary lumen irregular. The subsequent increase in macromolecular permeability causing plasma, fibrinogen, and red blood cell leakage impairs nutrient exchange [117, 118].

The skin is the final target of chronic venous hypertension and the hemodynamic changes in veins. Clinical manifestations caused by alteration in skin capillaries are hyperpigmentation, venous eczema, lipodermatosclerosis, atrophie blanche, and eventually venous ulceration (Fig. 2.2). Several mechanisms for the development of venous ulcers have been postulated of which the theory of "leukocyte trapping" is the most likely [119]. It is hypothesized that the primary injury to the skin is extravasation of macromolecules such as fibrinogen and alpha-2-macroglobulin as well as red blood cells causing pigmentation into the dermal interstitium [120, 121]. Red blood cell degradation products and extravasation of interstitial proteins are potent chemoattractants and presumably generate an initial inflammatory signal that results in leukocyte recruitment and migration into the dermis [115]. Pathologic events occur during leukocyte migration into the dermis, and the end product is dermal fibrosis. An increase in transforming growth factor beta-1 (TGF-β1), released by macrophages and mast cells or auto-induced by dermal fibroblasts, causes an imbalance in tissue remodeling which results in increased collagen synthesis and affects matrix metalloproteases (MMPs) as well as their tissue inhibitors (TIMPs). It is hypothesized that an imbalance in MMPs and their regulation may cause or contribute to venous ulcer formation. A cascade of inflammatory events results in cutaneous changes which include skin hyperpigmentation caused by hemosiderin deposition and eczematous dermatitis. Fibrosis may develop in the dermis and subcutaneous tissue lipodermatosclerosis. There is an increased risk of cellulitis and leg ulceration [118, 120, 121].

Lymphedema

The function of the lymphatic vessels is very important. They are involved in the recirculation of lymphocytes and proteins, transport of microorganisms by lymph, and drainage of interstitial fluid to blood. The average human body weighing 65 kg contains 3 L of blood plasma and 12 L of interstitial fluid. Up to 8–12 L of afferent lymph are produced each day of which 4–8 L of ultrafiltrate are reabsorbed into the bloodstream. The concentration of proteins in plasma, interstitial fluid, afferent lymph, and efferent lymph is 70 g/L, 20–30 g/L, 20–30 g/L, and 60 g/L, respectively. The fluid turnover reaches up to two thirds of the total volume of interstitial fluid daily [122]. The skin on the lower extremities contains a denser and more extensive network of lymphatic capillaries than the skin of the upper extremities [123]. Due to orthostatism, lower extremities have higher filtration pressure and influx of fluids, and it is thought that the capacity for lymph transport in the lower extremities is greater in order to compensate for the higher influx of interstitial fluid caused by the effects of orthostatism and gravity. Spontaneous contractility of lymphatic vessels contributes to lymph transport. Regular contractions of lymph vessels at a frequency of 2–4 per minute were observed in vitro, and spontaneous contractions of prenodal lymphatic vessels that drive lymph have been observed in human legs [124]. Internal extensions of lymphatic endothelial cells act as valves and guarantee a one-way lymph flow

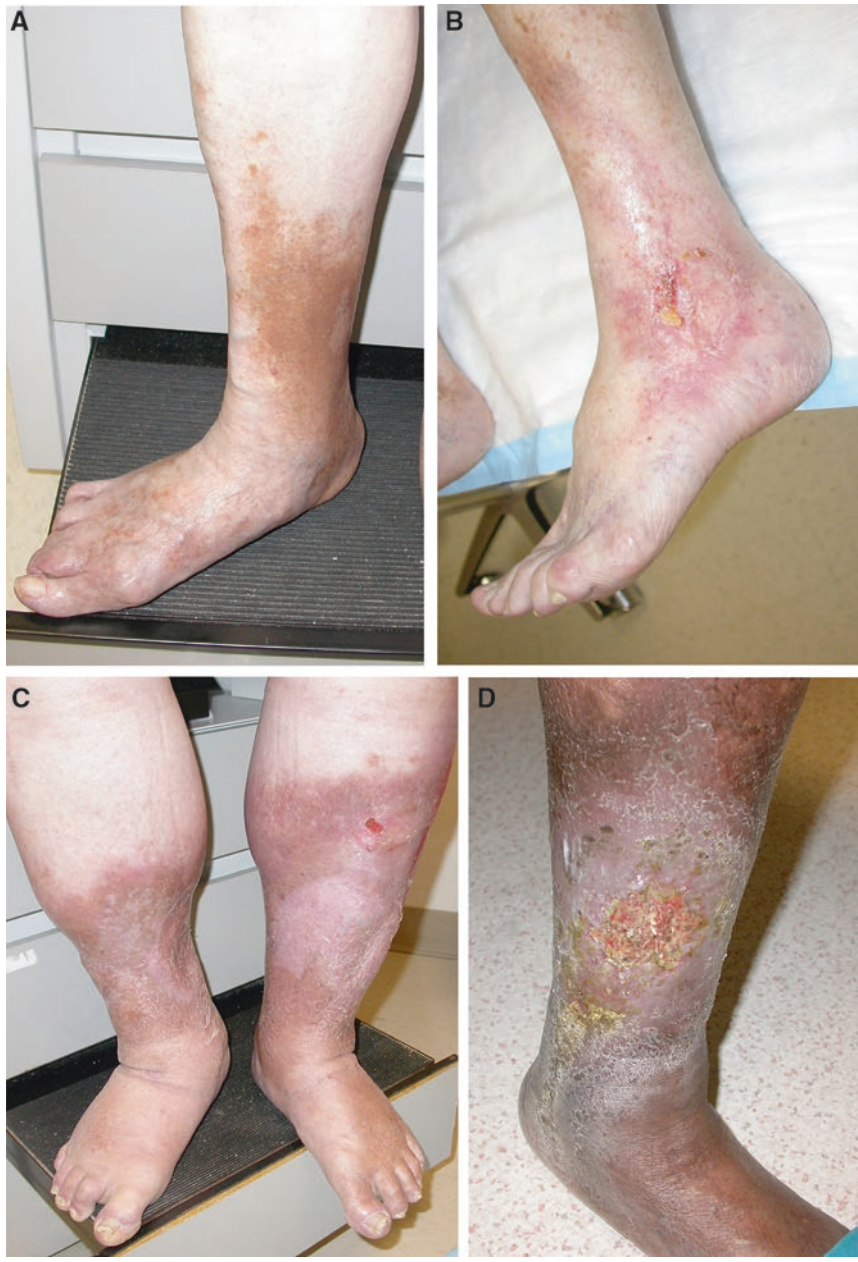

Fig. 2.2 Skin changes associated with chronic venous insufficiency. (**a**) Hemosiderin pigmentation. (**b**) Stasis dermatitis. (**c**) Lipodermatosclerosis. (**d**) Ulceration

[122]. In a steady state, extravasation of fluids and proteins from blood vessels is balanced by lymphatic drainage and return into the bloodstream. If microvascular filtration in blood capillaries and venules as occurs in advanced CVD exceeds the capacity for lymphatic drainage for sufficiently long periods, edema develops in afflicted areas by accumulation of tissue fluid in the interstitium. In addition, lymphatic dysfunction and structural damages to the lymphatic network are associated with varicose veins, and subsequent lymph stasis and reduced lymph

transportation lead to inflammation [125]. This is associated with lipid accumulation in the media of the diseased veins. Such accumulation of inflammatory lipids in the vein wall might further damage adventitial lymphatic vessels.

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Diagnostic Imaging for Veins

3

Fedor Lurie, Jihad T. Abbass, and John H. Fish III

Clinical Pearls

1. Ultrasound is the diagnostic modality of choice for the peripheral veins.
2. Deep vein thrombosis is diagnosed by the vein being enlarged and noncompressible and the absence of flow on color Doppler.
3. Pathological reflux is defined by flow away from the heart across a valve for more than 0.5 s.

Venous disorders include a wide range of acute and chronic conditions caused and influenced by a complex interaction of inherited, acquired, and environmental factors. The diagnostic workup for a venous patient should be individualized based on the specific pathology and state of the disease and aim to identify correctible pathology. Of all imaging modalities that are currently used for venous patients, diagnostic ultrasound became the most practical initial test. For many clinical situations, ultrasound can provide a definitive management answer, but for some additional modalities are needed. This chapter is intended to provide a basic review of these modalities and their most common applications.

Ultrasound Diagnosis of Acute DVT

Noninvasive nature and relatively low cost made ultrasound a dominant modality in the diagnosis of deep venous thrombosis (DVT). However, the ability of clinical decision rules, such as the Wells score, to identify patients with low probability of DVT and the addition of d-dimer assays increasing the accuracy of such identification approaching 100% made any imaging test less relevant for this category of patients. The false-positive rate of ultrasound scans is above 4% and the false-negative rate exceeds 10% [1]. The accuracy of ultrasound testing is especially low when the thrombus is fresh, affects a small segment of the vein, and is located above the inguinal ligament. Such diagnostic properties result in unnecessary treatment of some patients without a benefit of more reliable identification of patients with DVT when ultrasound is used as initial diagnostic step. Current evidence-based guidelines emphasize that the

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diagnostic process for patients with suspected DVT must begin with risk stratification [2]. If the probability of DVT is low, a negative d-dimer test sufficiently rules out DVT. In high-risk patients, the treatment should be initiated based on their risk, and imaging (including ultrasound testing) plays confirmatory role and thus can be safely delayed.

The outlined strategy is supported predominantly by the evidence obtained in a population of symptomatic outpatients, and the data on other patient populations, such as inpatients, pregnant women, children, surgical patients, and cancer patients is insufficient for making similar recommendations. Additionally, such strategy is only applicable for the initial diagnostic step. In high-risk patients and in patients who remain symptomatic, duplex ultrasound scan can provide valuable information that can change patient management. This includes identification of iliofemoral DVT that may require more aggressive treatment compared to femoropopliteal and to calf vein thromboses. It also may help to identify other causes of patient symptoms, such as intramuscular hematoma and Baker's cyst. Many other conditions that cause similar symptoms and signs in the leg cannot be diagnosed with ultrasound; thus the diagnostic value of the whole leg ultrasound for suspected DVT remains to be defined.

Significantly higher incidence of pulmonary embolism (PE) and postthrombotic syndrome PTS [3] justifies more aggressive management of patients with iliofemoral DVT compared to those with distal DVT. Performing surgical thrombectomy and catheter-directed thrombolysis is not currently universally practiced. For institutions performing these procedures, using urgent ultrasound examination to identify eligible high-risk patients may be a reasonable policy. If such treatment is not considered or not possible, urgent ultrasound scans cannot be sufficiently justified, and a delayed scan is a reasonable approach for determining whether anticoagulation should be stopped or continued.

Diagnostic Criteria of Acute DVT

Whole-leg duplex ultrasound allows to use the five basic criteria for diagnosis of acute DVT. They are non-compressibility of the vein, the absence of spontaneous blood flow, inability to augment the flow in the vein by compressing more distal limb, the presence of echogenic material in the lumen of the vein, and the increased diameter of the vein. Non-compressibility is the most reliable of these criteria and can be used as the sole diagnostic criterion in two- or three-point compression ultrasound [4]. In significantly swollen limbs and in obese patients, compressing the vein by applying pressure to the ultrasound transducer is often difficult or impossible, making the whole-leg duplex scan a more appropriate technique [5, 6].

The whole-leg duplex ultrasound, however, is not the most ideal diagnostic tool, as its false-positive and false-negative rates are quite high in some patient populations [1].

Ultrasound Diagnosis of Recurrent Thrombosis and Postthrombotic Disease

Following the acute phase, venous thrombus undergoes a complex transformation that results in different degrees of lysis and organization. In addition, inflammation takes place in the thrombus and vein wall, leading to the wall remodeling. Within 7–10 days, thrombus becomes adherent to the vein wall, making treatment modalities such as systemic thrombolysis and thrombectomy less effective or impossible in the third of the patients [7–9].

It is desirable, therefore, to be able to diagnose an acute DVT and to determine the age of the thrombus. The onset of the clinical manifestations of DVT is an unreliable indicator of the start of thrombosis, and conventional imaging techniques are rarely helpful in determining the age of the thrombus [10]. Initial results with ultrasound elastography to gauge thrombus age were promising [11, 12] but were later shown to be inconsistent [13]. Most of the studies of ultrasound elastography were done in animal models or ex vivo [14], and clinical validation of this technique has yet to be performed. The use of radiolabeled markers, such as recombinant tissue plasminogen activator, showed the ability to determine if the thrombus is more than 30 days of

age [15], and MRI may show that the time from onset of thrombosis exceeds 6 months [16].

In addition to the ability to estimate the age of the thrombus, these tests are suitable for the diagnosis of rethrombosis. If thrombus neither lyses spontaneously nor is removed by treatment, pathologic processes continue predisposing patients to recurrent thrombosis [17]. Data from placebo groups of randomized controlled trials showed that recurrent DVT occurs in 11–18% of patients during the first year after DVT [18–20].

The major challenge in the diagnosis of recurrent ipsilateral DVT is that clinical presentation of rethrombosis is frequently identical to manifestations of postthrombotic disease. This makes risk assessment tools, such as the Wells score ineffective. D-dimer level remains elevated for at least 3 months after thrombus resolution in 46% of the patients [21]. Even when d-dimer is used in combination with risk assessment tools, its negative predictive value is unacceptably low in patients with recurrent DVT [22, 23].

Imaging diagnostic modalities are unable to reliably detect acute thrombus when postthrombotic changes are present in the venous wall and vessel lumen. Ultrasound in such cases shows partial or complete incompressibility of deep veins in up to 70% of patients at 3 months and 40% of patients at 12 months [24]. Such findings increase the frequency of false-positive results when this criterion is used for recurrent DVT. The false-negative results of compression ultrasound have been reported in 5% of patients with suspected recurrent DVT [24, 25].

Availability of ultrasound images obtained before an episode of suspected recurrence may be helpful; however, the interpretation of such images has been shown to have poor to moderate intraobserver agreement [26]. MRI may be able to differentiate thrombi from fibrotic changes in the vein at 6 months after acute DVT [16], but neither MRI nor CTV has been tested in patients with suspected recurrence. In the absence of a reliable test, the diagnosis of recurrent DVT relies mainly on the clinical judgment.

Ultrasound Diagnosis of Upper Extremity DVT

Swelling of the upper extremity or the neck is the most common reason to rule out thrombosis with duplex ultrasound. Other indications for upper extremity venous ultrasound include tenderness or pain in the arm or neck, evaluation for thrombosis of a venous access line, vein mapping for the creation of dialysis access, and surveillance of either a previously documented upper extremity DVT or a dialysis fistula or graft.

Duplex ultrasound continues to be the methodology of choice for establishing the initial diagnosis of upper extremity deep vein thrombosis. Imaging of the upper extremities should routinely include compression and color flow analysis with and without augmentation in the internal jugular, radial, ulnar, brachial, and axillary veins. The brachial veins are often paired, although there can be variations in anatomy. Both subclavian veins should always be assessed (even in unilateral studies) with color flow and grayscale images, but compression images are not usually possible because of the depth and interference from the clavicle. The cephalic and basilic veins are also commonly imaged along their entire span in the arms. As in the evaluation for lower extremity thrombosis, evidence for intraluminal obstructive mass needs to be characterized based on echogenicity and evidence for associated dilation of the vessel. Noncompressibility, echolucency, and vessel dilation are all strongly suggestive for an acute thrombosis. On the other hand, partial compressibility with bright echos favors a chronic postthrombotic fibrous intimal scar. Spontaneous Doppler flow should show variation with breathing (respirophasicity), but the augmented cardiopetal phase is reversed when compared to the lower extremities; venous inflow is augmented with deep inspiration in the upper extremities because of decreased intrathoracic pressure. This is in contrast to the lower extremities where inspiration leads to a concurrent increase in intra-abdominal pressure and flow into the vena cava is dampened. In addition to respirophasicity, flow is often pulsatile in the innominate,

jugular, and proximal subclavian veins due to the proximity to the right atrium with dual reflection of the *a* and *v* components of the atrial pressure wave.

Scanning protocols for upper extremity veins often begin with imaging of the internal jugular veins in transverse and longitudinal planes from the angle of the jaw down to their junction with the subclavian vein. Compression maneuvers should be performed in the neck down to the level of the clavicle along with standard Doppler and color flow analysis. The innominate and subclavian veins are imaged next, but compression maneuvers are not likely to be successful given the proximity of the clavicle unless the transducer head has a small footprint. Distal augmentation maneuvers should also be performed in all upper extremity veins. The axillary vein is imaged next but may require abduction of the arm to be adequately imaged. The often paired brachial veins are also best imaged with 90 degrees of abduction, adjacent to the brachial artery. Medial to the brachial veins, the basilic vein can next be identified in the upper arm and followed distally toward the wrist. With the arm in a neutral position, the cephalic vein can be identified in the transverse plane in the antecubital fossa and followed up the lateral aspect of the upper arm up to its confluence with the subclavian vein. In unilateral studies, the final images are Doppler spectral waveforms of the contralateral subclavian vein for comparison.

Thrombosis in upper extremity veins will have similar ultrasound characteristics to those found in the lower extremities. Noncompressible, dilated, and sometimes echolucent veins seen in the transverse plane suggest acute thrombosis versus characteristics such as partial compressibility and bright echogenicity which would favor a more chronic process (Fig. 3.1). Respirophasic flow will also be compromised or lost with proximal thrombosis or obstruction. Furthermore, in the jugular, innominate, subclavian, and axillary veins, a loss of pulsatility or an absence of flow from the atrial pressure wave will occur with innominate or SVC occlusion (Fig. 3.2).

Ultrasound Diagnosis of Chronic Venous Disease

Venous Reflux

Current diagnosis and management of chronic venous disease (CVD) is predominantly based on identification and correction of two hemodynamic abnormalities: obstruction of the venous flow and venous reflux. In primary CVD, reflux is the only identifiable hemodynamic abnormality, while in the secondary CVD (postthrombotic disease), reflux can be present as the sole finding or in combination with obstruction or it can be absent.

Venous reflux is a hemodynamic phenomenon of reversal of the venous flow. Unidirectionality of the blood flow in veins is secured by function of competent venous valves. This frequently leads to misconception that the presence of reflux indicates valvular incompetence. Some venous segments may have reversed flow without valvular incompetence, for example, a venous segment between two competent valves with two or more tributaries joining it and a competent perforator vein. The flow in this segment sometimes is directed from the tributaries through the segment into the perforator vein. Thus, measuring the flow in this segment results in the detection of reversed flow, which is a reflux, but does not indicate that any of the valves are incompetent. The absence of reflux also does not mean that the valves are competent. Proximal venous obstruction or overload of more distal venous segments results in the absence of reversed flow regardless of the venous valve competency. Current clinical diagnostic testing, however, is unable to directly examine the function of venous valve, and the detection of reflux remains the only indirect indication of abnormal function of venous valves.

Technique

Reflux can be detected during ultrasound examination without performing any special maneuvers. However, this happens rarely and cannot be quantified or judged if this is a pathological sign.

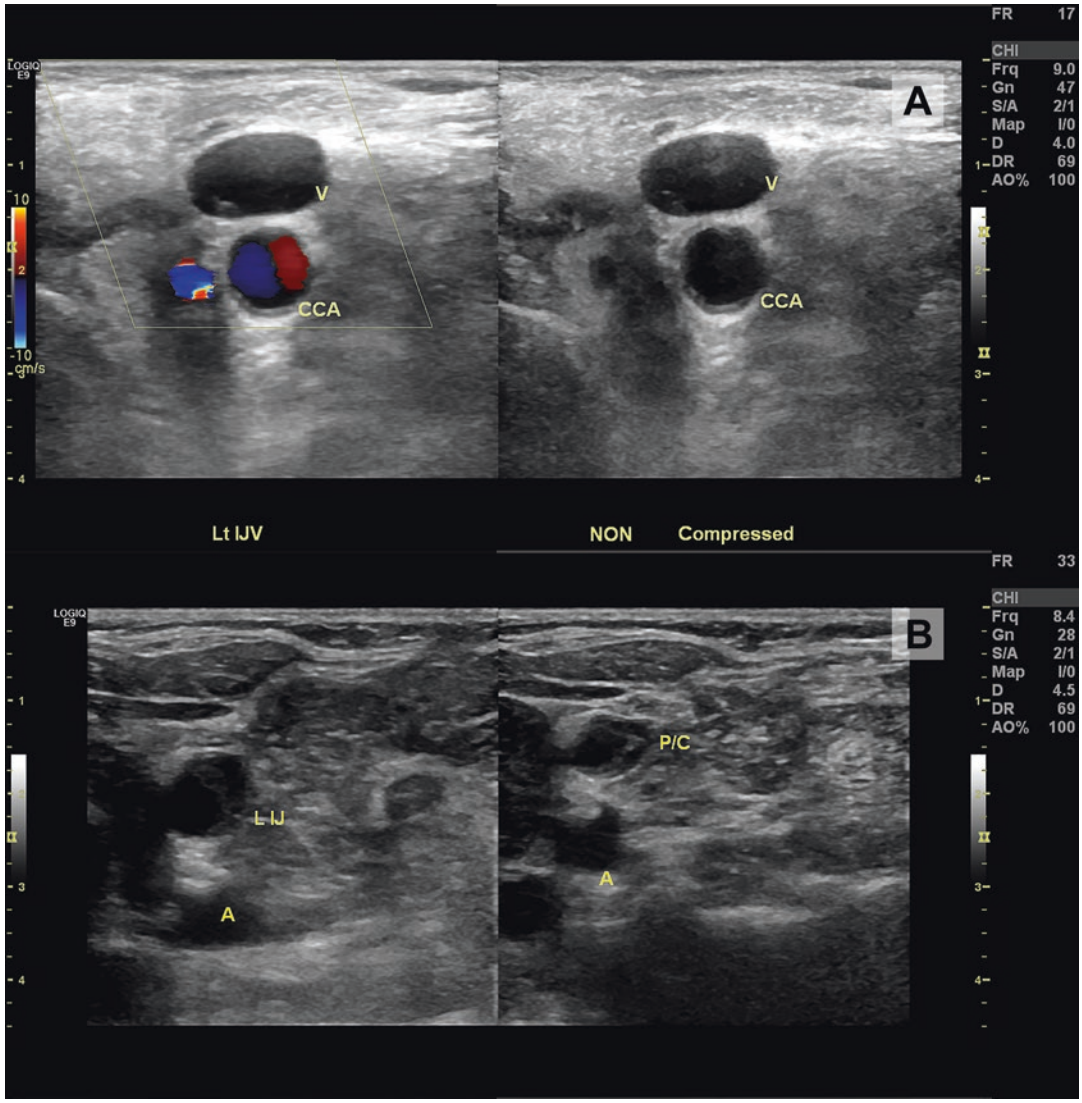

Fig. 3.1 Noncompressible, dilated echolucent internal jugular vein seen in the transverse plane suggests acute thrombosis of the upper extremity (**A**) versus characteristics such as partial compressibility and bright echogenicity which would favor a more chronic process (**B**)

The standard methodology for reflux detection involves reflux-provoking maneuvers such as Valsalva and distal compression-decompression. Valsalva maneuver increases abdominal pressure creating reverse pressure gradient in the veins. This, however, is mostly limited to venous segments in the proximal lower extremity where the valves are absent common femoral vein (CFV) or incompetent. Since there is no emptying of the more distal venous segments prior to performing Valsalva maneuver, their filling with blood may obstruct the ability to detect reflux. Emptying of the venous segments by compression of the segment of the leg distal to the visualized venous segment, followed by a rapid release of the pressure, is the most reliable way to induce venous reflux. This can be done by using operator's hand—or in a more standard fashion, using a pneumatic cuff with a rapid compression-relief device.

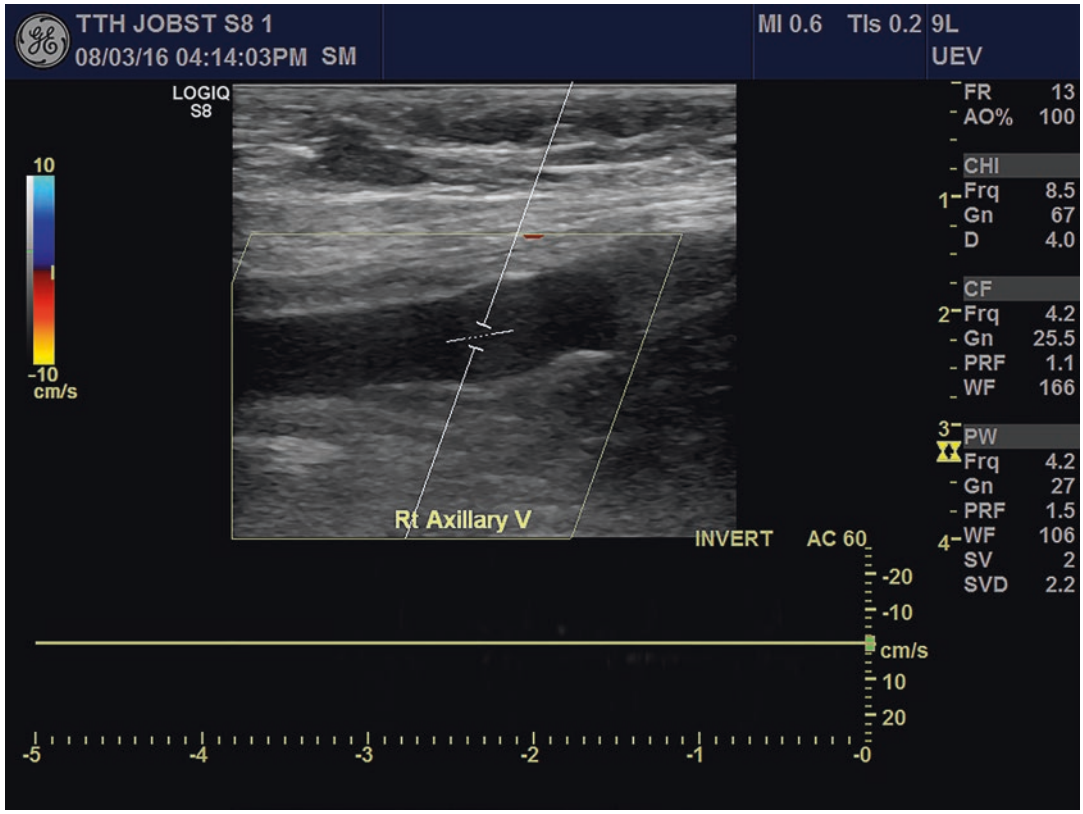

Fig. 3.2 Absence of flow from the atrial pressure wave will occur with innominate or SVC occlusion in the jugular, innominate, subclavian, and axillary veins

Most institutions prefer examining patient in a standing position with the weight of the patient on the contralateral leg. The extremity that is examined is slightly bended in the knee and rotated externally, allowing examination of the entire venous system from the CFV to the veins of the ankle. It has been shown that such position results in more repeatable results [27]. In practice, examining a standing patient is not always possible or desirable. Many patients are unable to stand for the time of the test, and performing the test in this way requires additional equipment or introduces substantial challenges to the ultrasonographer. Performing the study in the reversed Trendelenburg position generates almost identical results and is much more practical [28].

Examining perforating veins (PVs) requires slightly different technique. Thigh PVs can be examined in either standing or reversed Trendelenburg positions, but calf PVs are better seen in patient sitting with legs hanging off the examining table. Ultrasound transducer should be in transverse or oblique plane which is parallel to IP axis. Most of the clinically relevant PVs are located close to the GSV and SSV, so scanning along these vessels and their tributaries is the most efficient way to identify incompetent perforators.

Proper identification of reflux requires real-time duplex or triplex examination. This means that the spectrum Doppler recordings should be performed simultaneously with imaging (B-mode with or without color Doppler). Any other technique introduces uncertainty of which vessel was insonated during reflux-provoking maneuver. These maneuvers result in movements of all anatomical structures, veins including, making possible movement of artifacts and insonation of a tributary, adjoin vessel, or nonvascular structure, increasing false-negative and false-positive findings.

Definition of pathological reflux is consensus-based but is universally accepted around the world. It is based on the time of the reversed flow, and commonly used cut-off points are 1 s and 0.5 s for truncal veins. A multicenter study that most rigorously examined factors influencing reliability of reflux measurements demonstrated that using 0.5 s value has advantage for both superficial and deep veins [27]; however, some laboratories are using different criteria for deep and superficial veins based on their clinical experience and beliefs. The same study demonstrated that the time of the ultrasound examination introduces the highest variability of the measurements. The likelihood of getting different results of the repeated test in the same patient (presence vs. absence of reflux) is much higher when patient is examined at different time of the day than if he was examined in different positions and using different provoking maneuvers.

PVs have a different definition of pathological reflux, which is based on the reflux time (>0.5 s), diameter (≥3.5 mm), and a location beneath open or healed ulcer [29].

Venous Compression Syndrome

Upper extremity venous compression syndromes such as venous thoracic outlet syndrome (VTOS) often require additional imaging for conformation. Venous thoracic outlet disease is sometimes also referred to as thoracic inlet syndrome. Thrombosis of the upper extremity veins can be ruled out with a standard scanning protocol (as outlined above), but in the absence of "effort" thrombosis (Paget-von Schroetter syndrome) which can be a presenting feature of VTOS, other maneuvers may be indicated to confirm a suspected diagnosis. In addition to color Doppler and spectral waveform analysis in the neutral position, the patient is subjected to a variety of maneuvers including arm abduction at 45°, 90°, and 120°, the so-called military position (chest thrust forward with shoulders rolled back), and the Adson maneuver which tests the role of compression from the scalene muscles on the structures of the thoracic outlet (subclavian vein, subclavian artery, and the upper and lower brachial plexuses) by rotating the head toward the affected side and taking a deep inspiration (Fig. 3.3). The radial pulse can simultaneously be assessed for dropout while performing the Adson maneuver to assess concurrently for arterial compression. A positive study with TOS maneuvers will demonstrate loss of pulsatile or respirophasic flow with monophasic characteristics or complete obliteration of flow. Simultaneous duplex assessment of the subclavian artery during the maneuvers may be requested as well since arterial and venous compression may coexist. CT, MR, and conventional venography are rarely necessary for the diagnosis of VTOS but may assist with evaluating for the anatomic cause of thoracic outlet compression when surgical corrective measures are considered.

Venous compression involving the lower extremities usually manifests in the pelvic region in the form of May-Thurner syndrome or rarely at the knee as a type 5 popliteal entrapment syndrome. May-Thurner compression, classically defined as compression from the right common iliac artery onto the left common iliac vein as the vein passes anterior to the lumbar spine, has increasingly been appreciated to be present in cases of left iliofemoral DVT. Atypical May-Thurner iliac vein compression has also been described, which can involve the right common iliac vein as well. Diagnostic imaging for all types of suspected iliac vein obstruction usually begins with lower extremity venous duplex images, which should be carried as proximal into the iliac region as the habitus of the patient will allow. Blunted signals with respiration and augmentation in Doppler flow analysis will serve as clues for proximal obstruction. Thrombosis is not uncommonly encountered extending to or beyond the proximal lower extremity veins. CT venography is most commonly employed to assess the compression and degree of any associated thrombosis since venous ultrasound is not always reliable in the pelvic region. Involvement of the IVC can also be ascertained with either CT or MR venography.

Popliteal artery entrapment is a rare entity, which uncommonly can involve significant

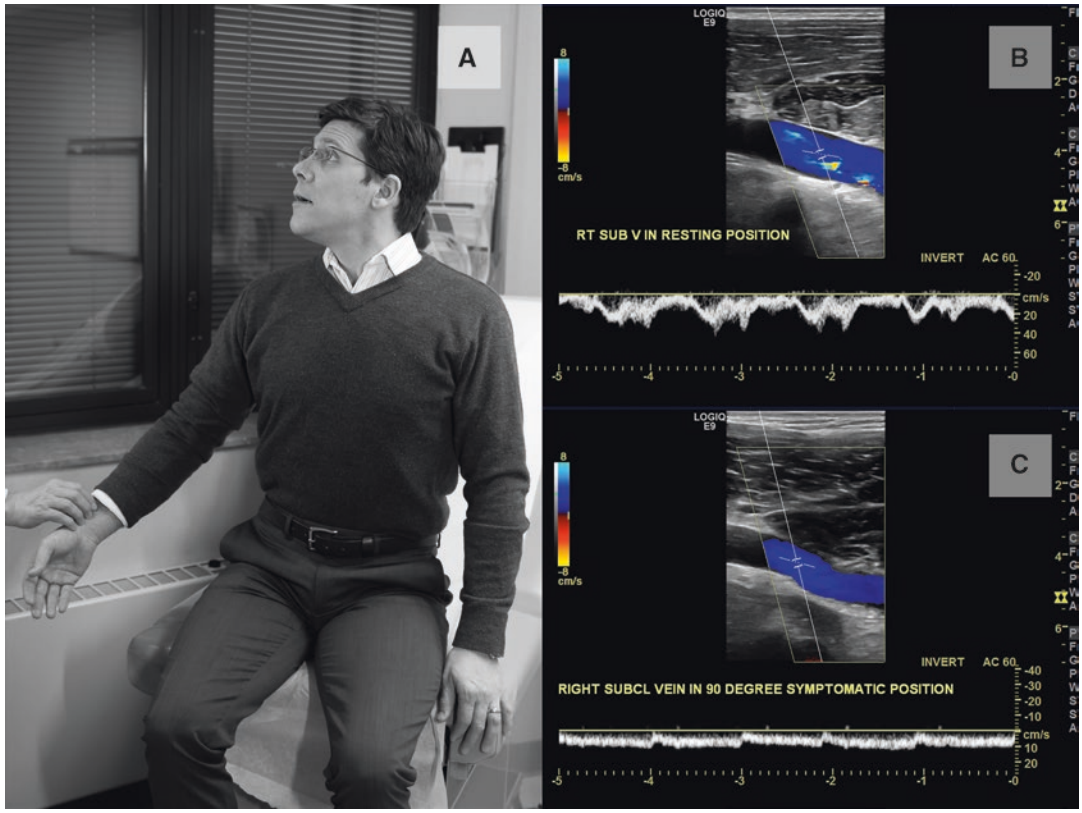

Fig. 3.3 The Adson maneuver depicted in panel (**A**) tests the role of compression from the scalene muscles on the structures of the thoracic outlet by rotating the head toward the affected side, extending the neck, and taking a deep inspiration. Panel (**B**) demonstrates normal respiratory phasic venous flow in the right subclavian vein in a neutral position, and panel (**C**) shows blunted cephalad flow in the same area with a provocative maneuver such as 90° of arm abduction from compression at the thoracic outlet

venous compression as well. This is referred to as a type 5 compression, which will often involve both the vein and artery. Ultrasound can be used as an initial diagnostic tool in the popliteal fossa with both passive and active dorsiflexion of the ankle. Blunted phasic Doppler waveforms or loss of augmentation proximal to the popliteal vein with maneuvers can serve as a clue to the presence of compression. MR angiography is the imaging modality of choice to supplement physiologic testing when assessing for any type of popliteal entrapment in order to ascertain the exact anatomic subset of vascular compression.

Visceral venous compression is rare but has been described in the left renal vein when it is compressed by the superior mesenteric artery and the aorta. This is referred to as the Nutcracker syndrome and can cause renal venous hypertension leading to hematuria and flank pain or gonadal pain. The gold standard for imaging has classically been left renal venography, but CT venography is now used routinely as an initial assessment given the additional anatomic information it provides and the often wide differential that is entertained when patients present with flank or gonadal pain associated with hematuria.

Imaging for vascular malformations needs to be tailored to the region and the type of malformation that is suspected. Arteriovenous fistulas) are most frequently acquired, usually as a minor complication following a percutaneous procedure. Given the relative superficial location with high flow, ultrasound is usually best suited for evaluation, especially in the inguinal areas. The typical

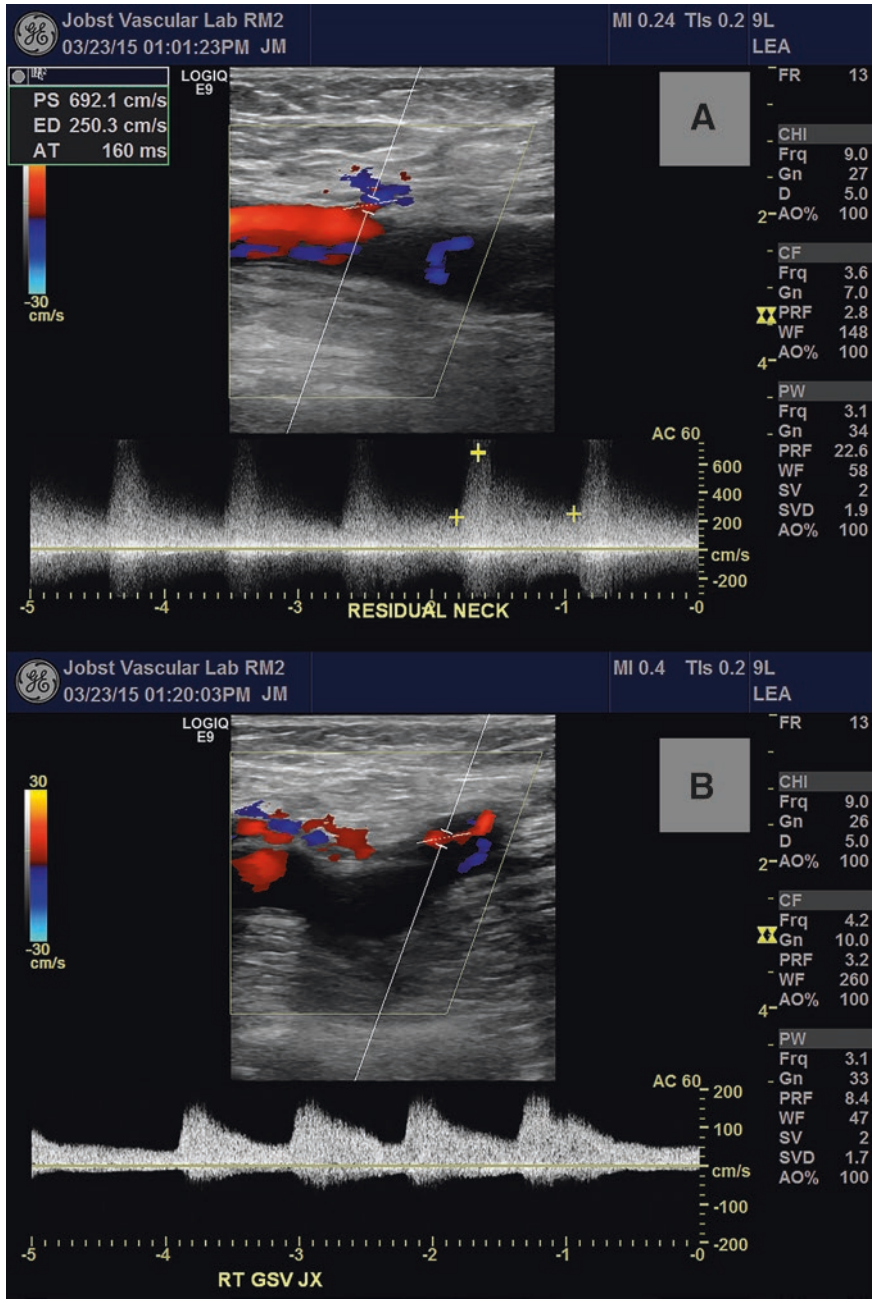

Fig. 3.4 Ultrasound demonstrating an arteriovenous fistula with findings of a high flow "jet" connecting an artery to a branch of the great saphenous vein (**A**) with arterialized flow in the great saphenous vein near the saphenofemoral junction proximal to the fistula (**B**)

ultrasound finding is a high flow "jet" connecting an artery to a vein with arterialized flow in the vein immediately proximal to the fistula (Fig. 3.4). This is in distinction to the "to-fro" flow leading from an artery to a blind-ended cavity with pseudoaneurysms (Fig. 3.5). Other types of vascular malformation sometimes present diagnostic challenges, especially when they are small with low

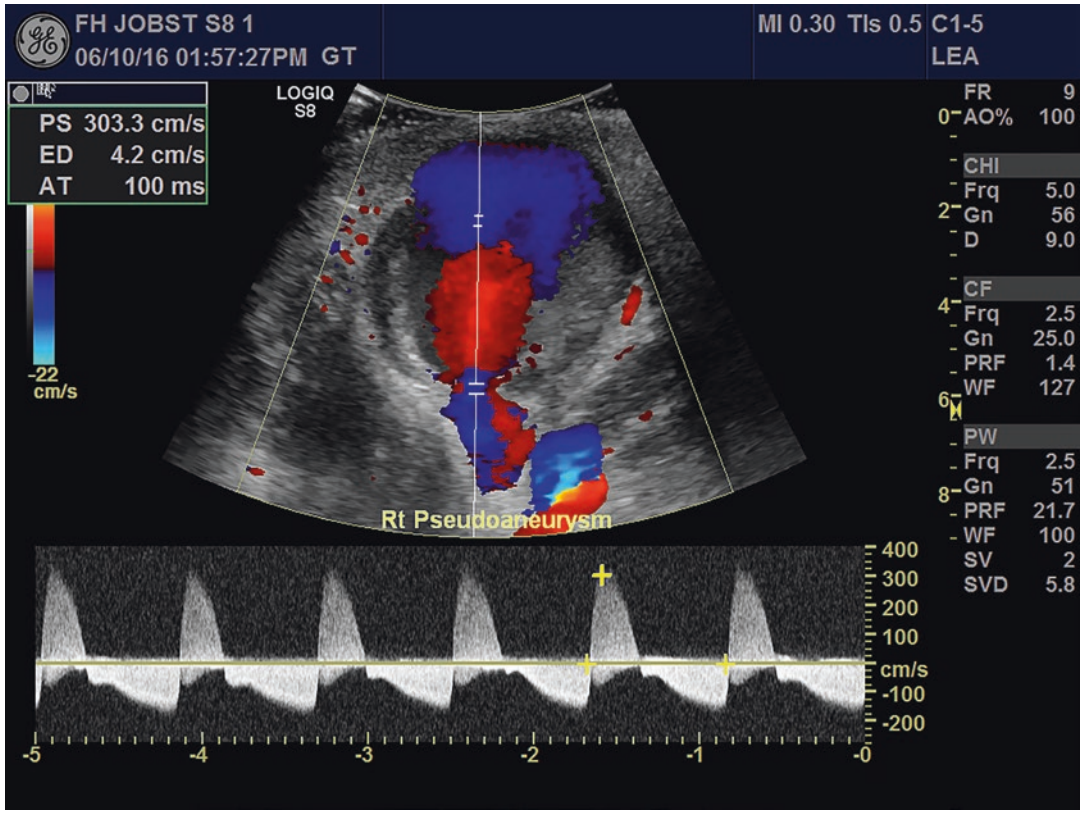

Fig. 3.5 Ultrasound findings demonstrating "to-fro" flow leading from an artery to a blind-ended cavity typical for pseudoaneurysms

flow. Venous malformations can appear as low flow areas of phlebectasia, disorganized aneurysm, or spongiform hypoechoic mass. Lymphatic malformations, on the other hand, often appear cystic on ultrasound. MR venography is often useful when there are multiple suspected venous malformations such as in Klippel-Trenaunay syndrome. Findings on MRI include uniform enhancement around venous structures versus rim or septal enhancement of cyst walls and high T2 signal intensity that is typical for lymphatic malformations. The presence of signal voids provides a clue to the presence of phleboliths characteristic of venous malformations. Finally, conventional venography is often the gold standard for both imaging the associated deep and superficial components of a venous malformation. This often precedes endovascular treatment with sclerosing) or occluding agents or devices for definitive treatment of problematic venous malformations.

Other Imaging Modalities

Venography

Contrast venography is almost completely replaced by duplex ultrasound as an initial test for diagnosing DVT; however, it continues to be the main tool for invasive treatment of deep veins. It is expensive and inconvenient compared with other diagnostic modalities and potentially causes patient discomfort and complications [30, 31]. Direct comparison of diagnostic accuracy of Duplex ultrasound and contrast venography demonstrated a sensitivity and specificity of 96% and 91%, respectively, for contrast venography and 78% and 97% for duplex ultrasonography [32, 33], suggesting that venography still has a place as a backup test for patients with suspected DVT and negative ultrasound [34]. In practice, however, immediate anticoagulation is a better strategy for such patients, and justification

for performing an invasive test is questionable in majority of the cases.

Computed Tomographic Venography

Computed tomographic venography (CTV) has major diagnostic advantages in diagnosis of proximal DVT compared with duplex ultrasound; it has a sensitivity of 98% and specificity of 100% in the thigh and sensitivity and specificity of 94% and 100%, respectively, in the pelvis. In a meta-analysis of 13 studies evaluating CTV for the diagnosis of DVT in patients with suspected DVT and PE, the sensitivity ranged from 71 to 100% and the specificity from 93 to 100% [35]. The pooled estimate of sensitivity was 95.5%, whereas the pooled estimate of specificity was 95.2%. They concluded that CTV has a sensitivity and specificity similar to those of ultrasonography for the diagnosis of acute DVT but must be viewed with caution, as duplex ultrasound does not have perfect sensitivity or specificity, which may lead to overestimation of the accuracy of CTV. In addition, when CTV is used in conjunction for evaluation of PE, it adds only 3–5 min to the examination, making it an attractive option as the sole diagnostic modality for acute lower-extremity DVT [36]. The specificity is the most questionable aspect of CTV. Peterson et al. [37] demonstrated that the ability of CTV to accurately diagnose DVT has a specificity of 71%, giving a positive predictive value of only 53%. Others have shown a 50% false-positive rate for CTV for pelvic DVT; at the same time, magnetic resonance venography had a 100% rate of false positivity [38].

Magnetic Resonance Venography

Magnetic resonance venography (MRV) can be used with or without contrast enhancement. Non-contrast-enhanced techniques include time-of-flight imaging and the phase-contrast technique relying on flow-related enhancement [39]. Contrast-enhanced MRV can provide the user with three-dimensional imaging, provided contrast material is injected in a timed sequence. Post-processing can then remove the arterial anatomy leaving only the venous segments in the display image [40].

MRV is used mainly to diagnose acute DVT in larger venous segments, as its sensitivity diminishes when smaller diameter veins are evaluated. Diagnostic properties of MRV are reported as almost identical to contrast venography [40, 41]. In addition, vessel wall enhancement can be visualized with acute thrombus, allowing the examiner a crude detection of thrombus age [42].

Comparisons between the two modalities of MRV have also been examined. Positive and negative predictive values were 90% and 94%, respectively [40]. When more proximal iliocaval DVT is examined, time-of-flight MRV had 100% sensitivity and specificity compared with contrast venography versus 87% and 85%, respectively, for duplex ultrasonography [41]. Perhaps the most impressive and useful aspect of time-of-flight MRV was its 95% sensitivity and 99% specificity in detection of the proximal extent of thrombus in the iliocaval segment compared with 46% and 100%, respectively, for duplex ultrasonography [40]. Contrast-enhanced MRV demonstrated 100% sensitivity and specificity for iliac thrombus and 100% sensitivity with a 97% specificity for the detection of femoral thrombus [43], in addition to being more reliable in distinguishing the proximal extent of these thrombus burdens [42].

Despite such a high diagnostic accuracy, MRV has serious practical disadvantages. It demands a nonmoving patient and long imaging times that, when paired, can be a significant hurdle. The below-knee segments of venous anatomy are often paired, accounting for significant artifact during post-processing of the images [39, 44]. In addition, gadolinium can be toxic in patients with renal dysfunction, and the need for frequent examinations can produce problematic utilization issues in larger institutions. However, MRV certainly has a role in the diagnosis of DVT, especially in the detection of thrombus in centrally located venous structures not always accessible to duplex ultrasonography. Not only is MRV useful for detection of hypogastric venous thrombosis [40], a remarkable 27% of patients who sustained a PE with no detectable

source of thrombus by duplex ultrasound had thrombus identified with MRV [45].

In conclusion of this brief review of the imaging modalities that are currently used for diagnosis and management of venous diseases, it is reasonable to emphasize that not a single one of them was developed specifically for this purpose. The situation when new technologies find venous disease as their additional application makes any of the existing imaging modalities less than ideal for practical use. Development of more effective, safer, and more practical treatment options resulted in the situation when the majority of patients with suspected DVT do not need any of the existing imaging tests. In chronic venous diseases, existing imaging tests are incapable to answer the most basic clinical questions, such as assessing the severity of venous obstruction and reflux. Since there are few alternatives, imaging remains one of the main modalities for management patients with venous diseases, but the results of these tests should always be considered as confirmatory to the clinical diagnosis.

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Evaluation of Edema of the Extremity

4

John H. Fish III and Fedor Lurie

Clinical Pearls

1. The evaluation of symmetry in patients with lower extremity edema can help guide the differential diagnosis and evaluation.
2. Lymphedema is associated with chronic skin changes and a positive Stemmer sign (inability to pinch the skin at the base of the second toe).
3. Lipedema is common in obese patients and typically spares the feet.

Introduction

Extremity edema involves the accumulation of extravascular, interstitial fluid and is influenced by a variety of factors. These include many systemic influences such as alterations in blood volume and capillary blood pressure, changes in colloid oncotic pressure, sodium and water retention, increased capillary permeability, and increase in tissue compartment pressure. A disruption in the Starling forces in the extracellular space will lead to fluid shifts which may lead to an expansion of the extracellular water volume. These forces include increased hydrostatic pressure, decreased oncotic pressure, and increased vascular permeability. Excess interstitial water will lead to findings of pitting edema, defined as the presence of an indentation in the skin after 5 s of pressure application. In addition to these major physiologic principles, adequate lymphatic outflow is an additional contributing factor for normal fluid homeostasis in the extracellular space of bodily tissues.

Alterations in capillary blood pressure within venules can occur in situations such as a deep venous occlusion. This can decrease the degree of venular fluid reabsorption, resulting in interstitial edema. Oncotic pressures are created by the concentration of electrolytes, glucose, urea, and proteins in the extracellular fluid. Oncotic fluid shifts are primarily driven by the pressure exerted by large proteins which are impermeable to the capillary wall. In the normal state, plasma contains a much higher concentration of osmotically active proteins compared to interstitial fluid. An imbalance caused by a decrease in plasma protein concentration or an increase in the protein concentration of the interstitial fluid would impair water reabsorption in the venule. Increases in capillary permeability will also affect the passage of both fluid and protein into the interstitium, leading to edema formation.

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Table 4.1 Subdivisions of primary lower extremity edema etiologies

Primary etiology for edema	Unilateral	Bilateral
Vascular	DVT[a] ↔ CVI[a] ↔ Lymphedema[a] ↔ Post-revascularization Popliteal aneurysm Vascular compression Compartment syndrome Vascular anomalies: • KTS, Parkes-Weber syndrome	*High-risk patients* (i.e., *cancer*) *often asymmetric when bilateral secondary causes* (i.e., *malignancy*) **Vascular CVH**: • **Vena cava obstruction**, vena cava anomalies Capillary leak syndromes: • Shock, thermal injury
Nonvascular	**Infectious/inflammatory**: • **cellulitis**, **OM**, **abscess** **Trauma** **Calf muscle disuse/atrophy** Popliteal cyst Tumor/lymphoma Neurogenic causes: • CRPS, neuropathy, Charcot foot Hemihypertrophy Retroperitoneal fibrosis[a] ↔ Factitial limb swelling[a] ↔	**CHF/RV dysfunction** **Nonvascular CVH**: • **OSA**, **PH**, **COPD** **Pseudoedema**: • **Lipedema**, **Obesity** **Drug induced** Pregnancy CKD/nephrotic syndrome Cirrhosis Protein deficiency Hormonal imbalances: • Cushing's syndrome, exogenous steroid, hypo- and hyperthyroidism (pretibial myxedema) Idiopathic (cyclic) edema

More common etiologies are listed first in each category with the most common causes in bold
DVT deep vein thrombosis, *CVI* chronic venous insufficiency, *KTS* Klippel-Trenaunay syndrome, *OM* osteomyelitis, *CRPS* chronic regional pain syndrome, *CVH* central venous hypertension, *CHF* congestive heart failure, *RV* right ventricle, *OSA* obstructive sleep apnea, *PH* pulmonary hypertension, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease
[a]Indicates primarily a unilateral disorder but could present with bilateral lower extremity involvement

Causes for edema can also be simplified by grouping them into vascular and nonvascular etiologies as well as unilateral versus bilateral involvement. Within these categories, there are typical physical patterns which include not only symmetry but also appearance, skin texture, onset, progression, and other skin manifestations. The presence of wounds, pain, inflammation and responses to compression, elevation, and diuresis all provide further clues. Table 4.1 reviews the causes for edema grouped by unilateral versus bilateral involvement for both vascular and nonvascular etiologies.

Vascular Edema

Venous Edema

Edema of the lower extremities related to localized venous hypertension often consists of low-viscosity, protein-poor interstitial fluid. This accumulation of fluid is directly related to increased capillary filtration and/or decreased venular reabsorption. If local venous pressure increases, as with either deep venous obstruction or deep valvular incompetence, localized venous pressure in that extremity increases with downstream (retrograde) transmission of pressure. The most dependent areas of the ankles (gaiter region) are affected to the highest degree, and pathways of venous incompetence can influence the accumulation of edema and related stasis skin manifestations such as hemosiderin deposition, inflammation, and skin ulceration.

Chronic venous valvular incompetence usually develops over long periods of time such that edema and hyperpigmentation follows an indolent course. Valvular dysfunction of the lower extremity deep veins is often a consequence of prior intraluminal damage from inflammation and fibrosis, due to the incomplete resolution of a prior thrombosis (the post-thrombotic syndrome). Valvular dysfunction

of superficial lower extremity veins such as the axial saphenous systems may be related to a variety of causative factors. Whether the dysfunction is related to deep, superficial, or perforator veins in the lower extremities, edema is usually first noted in the ankles with indentations created by conventional stockings. At this stage, elevation is quite effective at controlling swelling that is directly related to the degree of dependency and inversely related to the degree of calf muscle activity. Histologic evaluation at this stage reveals dilated venules and lymphatic spaces with extracellular edema and separation of collagen bundles. In time, however, dermal and subdermal inflammation develops, which can lead to extravascular fibrin deposition and sclerosis. This can lead to the obliteration of lymphatics and microvasculature, and perivascular fibrosis can result in diminished nutrition of the epidermis. Capillaries become quite dilated with tuft formation and venules will become tortuous at this stage. In all stages there is extravasation of erythrocytes with hemosiderin uptake by macrophages, leading ultimately to the typical orange to brown or even violaceous staining of the skin.

Lipodermatosclerosis is the term to describe the inflammation and induration in the lower third of the leg which is often described as resembling an "inverted champagne bottle" or a "piano leg" (Fig. 4.1), with edema both above and below the sclerotic tissue. When local lymphatic outflow is adversely affected to the degree that the limb begins to develop secondary evidence for lymphatic congestion (see patterns listed in the lymphedema section), the term *phlebolymphedema* is often used to describe this pattern of edema (Fig. 4.2). With this terminology, the presumed primary cause is usually listed first (phlebo) followed by the secondary vascular insult (lymphedema). Phlebolymphedema should be regarded as an end-stage manifestation of severe chronic venous insufficiency, with the aforementioned destruction of distal lymphatic vessels and the conversion of chronic edema from a more typical foot-sparing pattern in lesser stages of venous insufficiency to the involvement of the foot and toes more typical for lymphedema as depicted in Fig. 4.2.

Obstruction of the deep veins of the lower extremities as a consequence of DVT often leads

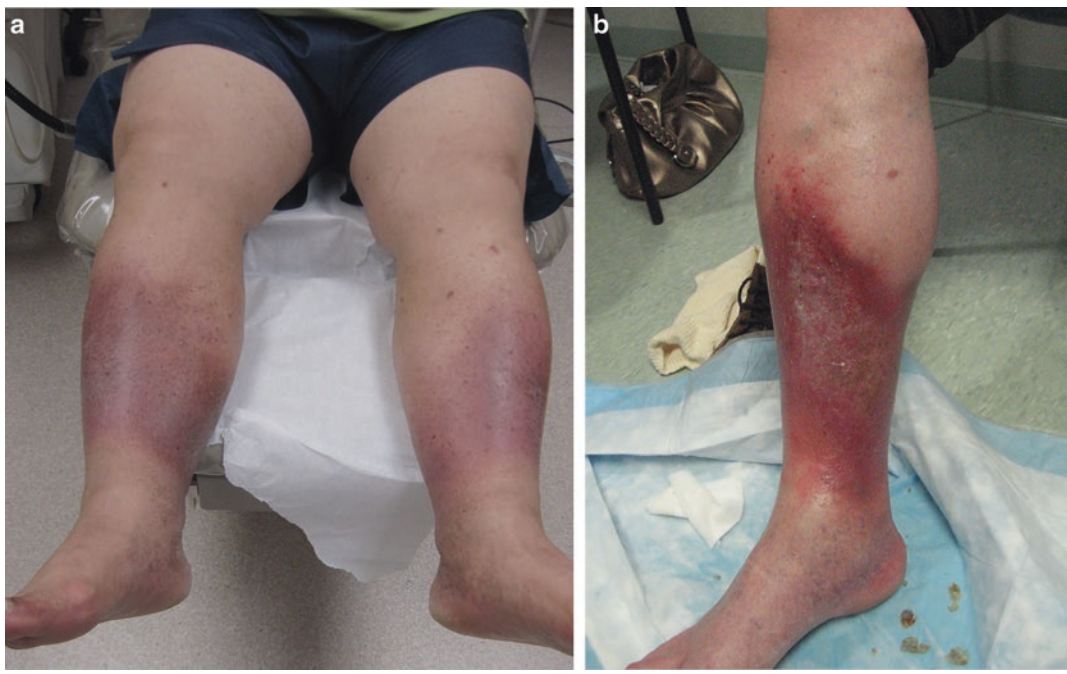

Fig. 4.1 Lipodermatosclerosis in chronic venous insufficiency. Panel (**a**) displays typical violaceous-brown discoloration with nearly circumferential dermal thickening. In panel (**b**) there is a shiny appearance with various degrees of dermatitis at the borders. This image also displays a central papular texture with islands of atrophie blanche (class C4b)

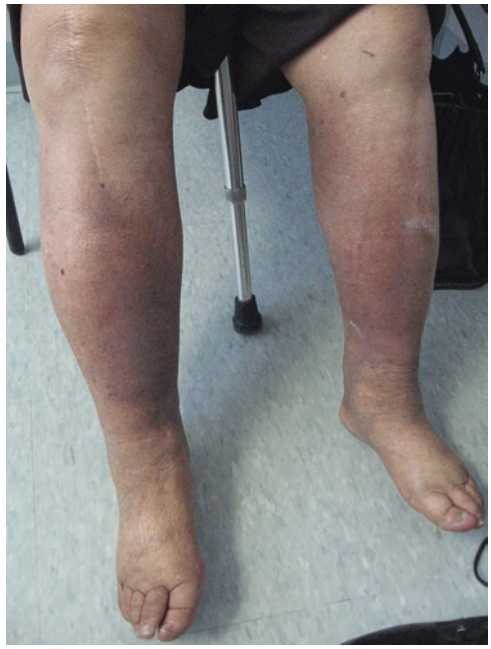

Fig. 4.2 Phlebolymphedema. Significant stasis hyperpigmentation is present in the gaiter regions of this patient with an edema pattern on the right consistent with lymphatic congestion. Notice the involvement of the dorsum of the foot with deepening of skin fissures at the base of the toes

to painful venous congestion in the effected limb in the acute setting. In extreme cases, the edema can be tense with cyanosis of the extremity and the development of ischemia. *Phlegmasia alba dolens* reflects early diminished arterial inflow and is classically known as a "milk leg" given the white appearance and its association with the third trimester of pregnancy or postpartum DVT development. The more advanced venous congestion of *phlegmasia cerulea dolens* refers to pre-gangrenous changes often with bullae formation, intractable pain, and features which can also mimic acute limb ischemia (pulselessness, paresthesia, and paralysis) when this entity begins to develop into venous gangrene. This can be a limb-threatening condition if the severity is not recognized in a timely manner since anticoagulation and elevation alone may not suffice.

It is important to recognize that not all swelling is edema in patients with vascular anomalies. Hemihypertrophy and venous congestion of a limb due to congenital arteriovenous fistulas can be seen in Parkes-Weber syndrome. Muscular hypertrophy is also a part of the triad in Klippel-Trenaunay syndrome which also includes the presence of varicose veins and a port-wine stain. Aside from congenital malformations, spontaneous or iatrogenic arteriovenous fistulas, when large enough to increase venous pressure, can lead to chronic venous congestion and limb swelling.

Venous congestion of the upper extremities is usually associated with acute thrombosis of the deep or superficial veins but usually resolves within days to weeks after appropriate treatment with anticoagulation, elevation, and compression. One exception to this is in the case of venous thoracic outlet syndrome ("effort thrombosis"), where there is persistent extrinsic vascular compression. This will often lead to a chronically swollen limb with limited improvement with the aforementioned treatment unless the mechanical compression can be addressed through an appropriate surgical decompression based on the anatomic structures that are involved (often requiring a first rib resection).

Aside from venous obstruction and valvular dysfunction, leg muscle inactivity and weakness can be a major contributing factor of increased local venous hypertension. Such muscular inactivity of the gastrocnemius and soleal muscle groups is often referred to as "calf muscle pump dysfunction." Compared to the foot and thigh musculature, the calf muscle pump is considered the most efficient, given the ability to generate pressures that can exceed 200 mmHg during contraction [1]. Dysfunction of the calf muscle pump can be quantified with the calf ejection fraction measured with air plethysmography (APG), and it is often defined as a fraction of 40% or less of the volume of blood in the calf ejected after a standard set of repetitive plantar flexion exercises.

Lymphedema

Lymph in the extremities consists of protein-rich interstitial fluid which is normally transported from terminal lymphatic capillaries to major collecting channels located subcutaneously and in deep limb compartments. The deep lymphatic system follows the tibial, popliteal, and femoral vessels, but the more extensive subcutaneous lymphatic system carries 80% of lymphatic fluid [2, 3]. A large percentage of subcutaneous lymphatic return in the lower extremities is along major channels adjacent to the great saphenous vein.

Like veins, unidirectional flow is partially dependent on competent bicuspid valves along major channels. However, valves are not present in the dermal capillaries. Either congenital or acquired obstruction of lymphatic flow will therefore promote the accumulation of the protein-rich fluid in the subcutaneous space, especially when local collateral lymphatic circulation is overwhelmed. Trauma, radiation, and surgery (particularly lymphadenectomy), as well as malignancy, chronic inflammation, and filariasis (the most common cause of lymphedema in non-industrialized countries), are all causes for the development of secondary lymphedema which can develop months or even years after the initial insult causing interruption of normal lymphatic flow. This latent development can also be explained by gradual lymphatic stasis from progressive dilation of lymph vessels causing valvular incompetence, increased incompetency of endothelial junctions within lymph capillaries, fibrosis of lymphatics with the loss of permeability, and the eventual exhaustion of extra lymphatic interstitial protein transport from macrophages. As a result of these processes, local immune defenses are impaired and chronic or acute bacterial or fungal infection can result in fueling the inflammatory degeneration of lymphatic structures and surrounding tissue.

Primary lymphedema can be in the form of a congenital familial disease (*Milroy Disease*), which is present at birth or becomes evident at a very early age. This disease is considered to be related to mutations in the vascular endothelial growth factor (VEGF)-3 receptor in the endothelium causing impaired lymphangiogenesis. Mutations in the FOXC2 gene have been described in the autosomal dominant form of primary lymphedema known as *Meige disease* which has a more latent presentation. Primary lymphedema can also be associated with Turner syndrome, Noonan syndrome, Down syndrome, yellow nail syndrome, and venous malformation syndromes such as Klippel-Trenaunay syndrome.

When lymphedema presents during late development around puberty into the early twenties, this form of primary, non-hereditory lymphedema is known as *lymphedema praecox*. Women are disproportionately affected with this form of lymphedema; classic series of lymphedema patients suggest a female to male ratio of 10:1 [2]. Although lymphedema in later adult life is usually secondary to an identifiable cause, primary lymphedema can still present in older individuals and is referred to as *lymphedema tarda* when diagnosed after the ages of 30–40 years old.

The clinical presentation generally begins as painless fullness in the dorsum of the foot or in the hand. At this early stage, the edema is subject to fluctuation with dependency or elevation of the limb and will often pit with a soft texture. The progression is usually from distal to proximal, although pelvic malignancies can sometimes produce a pattern of early isolated thigh edema which progresses distally. Over time, edema becomes fixed, accompanied by an array of characteristic dermal changes (see next paragraph). The forefoot will often have a dorsal "buffalo" hump with thickening of the dermis. The classic inability to pinch the skin at the base of the second toe is consistently demonstrated as a positive *Stemmer sign* in nearly all patients with lymphedema at this stage.

As the dermis thickens and becomes more fibrotic, edema becomes firmer and will no longer pit to digital compression. A velvety texture will often form on the toes, which begin to assume a squared-off appearance with deepening of the skin fissures at the base of the toes and between

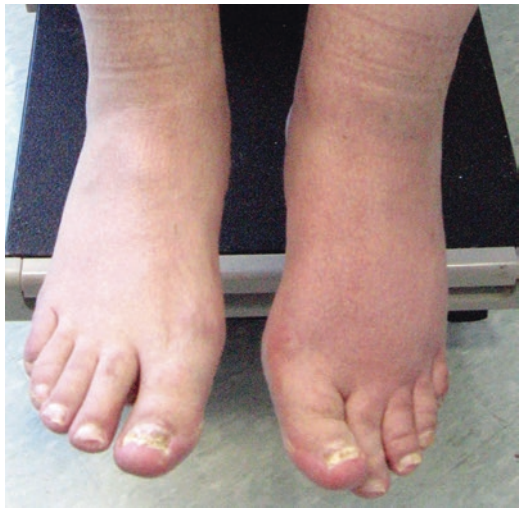

Fig. 4.3 Early lymphedema findings. The left foot displays a "dorsal hump" with squaring of the toes and deepening of skin fissures and creases. There is a lack of such findings in the right leg of this unilateral presentation of early lymphedema tarda

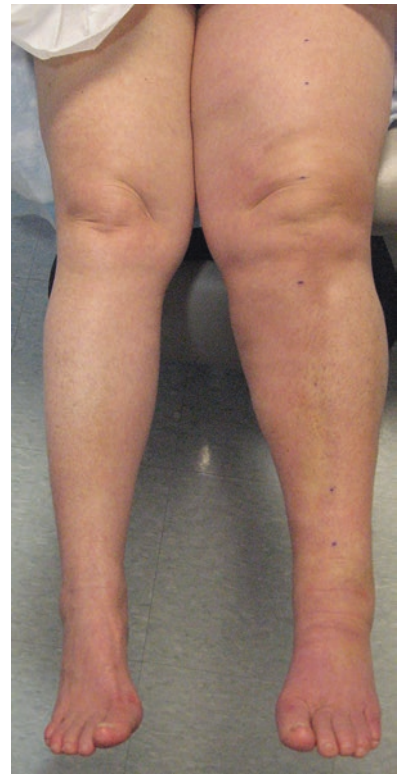

Fig. 4.4 Stage II lymphedema. Fixed edema is present in the left lower extremity with firm, non-pitting characteristics in the ankle and foot. Notice the asymmetry which extends from the proximal thigh down to the toes in this patient

the phalanges (Fig. 4.3). Toenails will also thicken, becoming brittle and yellow in color. The velvety texture of the skin on the dorsal surface of the distal foot can progress to a cobblestone appearance with warty outgrowths with papillomas from local dermal lymphostasis. Woody fibrosis can progress proximally up into the gaiter area, and the skin may begin to resemble the peel of an orange (*peau d'orange* appearance). Hallmarks of chronic venous insufficiency such as hyperpigmentation and varices are usually absent in lymphedema unless it occurs as a secondary process of progressive degeneration of lymphatics in advanced chronic venous insufficiency. The International Society of Lymphology categorizes lymphedema into three stages based on clinical characteristics. The first stage is characterized by soft, non-fibrotic edema which can be reduced with leg elevation. The second stage is differentiated by the progression to dermal fibrotic changes which resist pitting pressure and do not reduce with elevation (Fig. 4.4). Finally, stage 3 lymphedema represents lymphostatic elephantiasis with trophic skin changes, advanced dermal fibrosis, acanthosis, and warty, nodular overgrowths (Fig. 4.5). Elephantiasis of a limb with a particularly severe nodular presentation has been termed *elephantiasis nostras verrucosa*. In some cases, limb heaviness can be reported by patients prior to the clinical development of edema, as can often occur in the upper extremities of breast cancer patients. Because of this type of subclinical presentation, some have suggested labeling this as stage 0 lymphedema. A 2013 consensus document published by the International Society of Lymphology further suggests that within each stage, functional severity can be estimated as minimal (<20% increase in limb volume), moderate (20–40% increase), or severe (>40% increase) [4].

The diagnosis of lymphedema is largely supported by the history and physical exam alone. The history should focus on the temporal development of findings and symptoms. One should

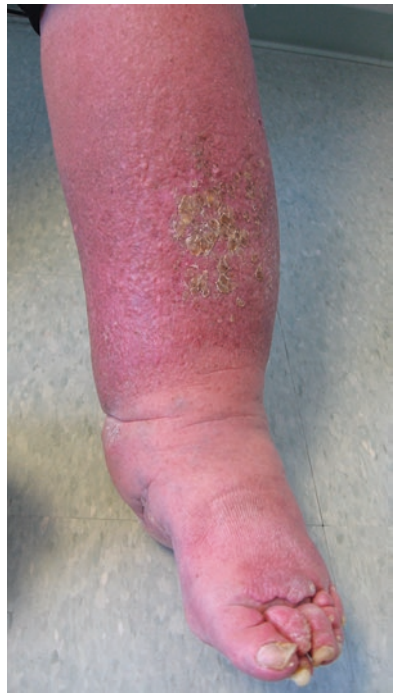

Fig. 4.5 Stage III lymphedema. At this stage, advanced fibrotic changes are present with wart-like nodularity and hyperplastic overgrowths seen at the base of the toes

consider a potential correlation with limb injury, limb or abdominal/pelvic surgery, radiation therapy, or a history of lymph node dissection. Confounding conditions such as morbid obesity, endocrine dysfunction, and venous insufficiency may complicate the clinical picture. Obstructive causes such as a unilateral pelvic mass or visceral tumor may need to be considered. In females who have an elevated risk for pelvic malignancy, for example, a CT scan may be indicated when lymphedema develops after the age of 40. Comorbid conditions which lead to edema should also be considered, especially when the presence of such conditions (i.e., congestive heart failure) may preclude the ability to adequately elevate, compress, or manually decompress the limb. The role for imaging in lymphedema, especially as it pertains to confirming the diagnosis, determining the extent, and identifying a potential level of obstruction is discussed in the Diagnostic Workup of Edema section.

Current treatment of lymphedema is primarily focused on nonoperative therapies. Complete decongestive therapy (CDT) is supported by years of experience and is usually divided into two distinct phases. The first phase consists of intensive skin and wound care, manual lymph drainage (MLD), range of motion exercises, and multilayered bandaging. The second phase involves converting to a short-stretch bandage or graduated compression stocking, repetitive light massage, and pneumatic lymphatic pumping (usually arranged to be performed at home by the patient).

Drug therapy for lymphedema is currently limited. Diuretics should be reserved for patients with comorbid conditions that require their administration. Diuretic use solely for controlling lymphedema is discouraged because of its marginal benefit due to the concentrating effect on protein in the interstitial space which can lead to significant rebound edema. Other oral agents such as benzopyrones (including rutosides, bioflavonoids, and coumarin) have theoretical benefits by hydrolyzing tissue proteins and facilitating absorption.

Surgery is infrequently employed for very select patients who are refractory to conservative measures, especially when there are severe physical limitations because of grotesquely bulky lymphedema. Debulking, ablative, or excisional surgery can be offered to reduce the subcutaneous fat and fibrous overgrowth. Liposuction can also be employed to remove excessive adipose tissue from the epifascial compartment. Indications for surgery beyond failure to respond to standard therapy can be expanded to the development of chylous reflux or serious refractory infections which can compromise the function of the affected limb. Reconstructive surgery with microsurgical techniques such as lymphovenous anastomoses may be available in very select centers.

A particularly morbid, late complication is the rare secondary development of lymphangiosarcoma. This can present in patients with chronic lymphedema as a bruise-like lesion of the affected extremity which develops painlessly. The lesion will expand rapidly, often with central ulceration

and early metastasis. The prognosis is often poor unless early wide excision or amputation is undertaken.

Nonvascular Edema

A variety of systemic disease states must be considered in patients with peripheral edema, especially if it presents as a bilateral manifestation. Drugs or disorders that lead to right ventricular dysfunction, cirrhosis, renal failure, or the nephrotic syndrome should be ruled out. Aside from imaging and lab testing, the history and physical exam can often be very suggestive of the cause and there are patterns of edema that may otherwise go unrecognized if the clinician is not observant. Ascites may sometimes be underappreciated in morbidly obese individuals with underlying cirrhosis causing lower extremity edema. Patients with global cardiomyopathy will often have pulmonary congestion along with peripheral edema. Right ventricular dysfunction will sometimes lead to wide or fixed splitting of the S2 heart sound or less commonly a gallop (S3 and S4 heart tones are more commonly ascribed to left ventricular etiologies). Some drugs cause edema, which will often profoundly affect the ankles and feet such as pregabalin or calcium channel blockers. Central venous pressure can also be estimated with the physical exam by knowing how to read the level of jugular venous pressure.

Unilateral causes for peripheral edema may involve compression of venous outflow such as with the May-Thurner syndrome or as a complication from a space-occupying mass such as pelvic or limb tumors, hematomas, or even a very large popliteal cyst.

Infection must be considered in the differential if there are exam findings of wounds, acute or chronic skin inflammation, or cellulitis. Even in the absence of dermal findings, a large abscess can cause vascular compression. Chronic deep tissue inflammation such as with osteomyelitis or a Charcot foot in diabetics can lead to destruction of the bony architecture of the foot, often with severe pedal edema.

Neuropathy can also lead to pedal edema likely due to secondary chronic dependency and abnormal foot and ankle mechanics which lead to inefficient priming of the venous sinusoids of the calf muscle pump. Another neuropathic cause for intermittent swelling of a limb is chronic regional pain syndrome (CRPS). The swelling associated with CRPS is episodic and exquisitely painful and tender, often with rubor and elevated skin temperature. This form of edema is often misdiagnosed as having an inflammatory cause and occurs following trauma or surgery in the effected extremity.

Bilateral edema, especially when it is symmetric in the lower extremities, often has nonvascular causation. As mentioned previously, although lower extremity lymphedema may present bilaterally, when lymphedema is symmetric, tumors, lymphoma, pelvic malignancy, or a history of pelvic irradiation should be considered as a cause.

Central venous hypertension (CVH) will often lead to bilateral symmetric edema with findings of elevated jugular pressure. Volume expansion needs to be considered in this scenario such as with biventricular failure or primary renal sodium retention. A urinalysis, blood urea nitrogen, plasma creatinine, and B-type natriuretic protein (BNP) can aide in distinguishing between underlying renal disease and heart failure. Some secondary causes for CVH are becoming more common such as right ventricular dysfunction from obesity/hypopnea syndrome or obstructive sleep apnea with the current obesity pandemic. Other less common causes for secondary pulmonary hypertension can lead to symmetric lower extremity edema such as cor pulmonale from end-stage COPD. If CVH needs to be confirmed, pressures can be estimated with echocardiography or measured with a Swan-Ganz catheter, especially if plasma volume status is in question.

Along with peripheral edema, patients with nephrotic syndrome may present with ascites or periorbital edema. Fluid retention can be ascribed to both the reduced oncotic pressure caused by hypoproteinemia and also sodium retention from often associated renal tubular disease. The

diagnosis is confirmed by documenting proteinuria which exceeds 3.5 g daily.

Patients with cirrhosis not only develop ascites but because of the dilated venous tributaries and small arteriovenous fistulae, cirrhotic patients often have an elevated total blood volume with a decreased effective blood volume. CVP is usually normal or even reduced. Low serum albumin and altered sodium and water reabsorption is often present in cirrhotic patients with peripheral edema. Hypoalbuminemia can also be caused by severe malnutrition, protein-wasting syndromes, or decreased protein synthesis leading to symmetric dependent edema.

Hormonal causes for edema are often complex and difficult to diagnose. Exogenous steroids are a more obvious cause with generalized edema that can involve all four extremities and the face. This has been attributed to the increased tubular sodium reabsorption which occurs with high concentrations of steroids with mineralocorticoid activity and is also seen in Cushing's Syndrome. Pretibial myxedema from hypothyroidism or even autoimmune hyperthyroidism (Grave's disease) causes chronic symmetric edema in the pretibial regions and dorsi of the feet which is usually non-pitting with raised, thickened dermis which may be subtly hyperpigmented. This can be attributed to the accumulation of mucopolysaccarides in the dermis. Hypothyroidism also leads to accumulation of interstitial proteins likely due to an elevation in capillary protein permeability. Excess interstitial protein and the resulting fluid in turn cannot be adequately cleared because of altered lymphatic flow in myxedema [5]. Adult-onset growth hormone deficiency (either primary or secondary to hypopituitarism) presenting with extremity edema resembles lipedema but often involves the arms as well as the legs. This is not a true edema but a condition where muscle mass is replaced with fat.

Idiopathic (cyclic) edema is a condition affecting premenopausal women which remains poorly understood. Fluid retention can occur not only in all of the limbs but also in the face and trunk. The condition is usually associated with an upright position with documented weight gain throughout the day. This weight gain will often exceed a normal 0.5–1.5 kg gain attributed to a fall in urine sodium excretion because of volume depletion from venous pooling in the legs. It should not be confused with edema associated with the menstrual cycle. Several mechanisms have been proposed such as capillary leak, secondary hypoaldosteronism, excessive secretion of antidiuretic hormone, chronic diuretic use, refeeding edema, defects in venular vasomotor tone, and others. The diagnosis is one of exclusion and therefore requires a workup to rule out renal, cardiovascular, or hepatic disorders. Therapy for this condition needs to be tailored to the individual but should include salt and free water restriction, a holiday from diuretic therapy and elevation. Many other treatments have been recommended such as treating a potential dopamine deficiency or increasing sympathetic activity [6] since the mechanisms underlying the development of edema in this cohort are likely to be heterogeneous and multiple.

Drugs which cause edema of the lower extremities may act through a variety of mechanisms. Arteriolar vasodilation is the most common mechanism leading to soft, pitting edema which resolves after the drug is withdrawn. These drugs are numerous and include hydralazine, minoxidil, dihydropyridine calcium channel blockers, and alpha blockers. Renal sodium retention can also lead to peripheral edema from a variety of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones, insulins, estrogens, progestins, androgens, aromatase inhibitors, and tamoxifen. Some drugs are administered with either high volumes of fluids or have high sodium concentrations (carbenicillin). Increased capillary permeability may be induced through interleukin-2 therapy. Other drugs such as anticonvulsants (gabapentin and pregabalin), chemotherapy agents (cisplatin), antidepressants, and dopamine agonists (pramipexole, ropinirole) cause peripheral edema through unclear mechanisms.

Increased capillary permeability can be the result of drugs, shock, or injury to the capillary membrane. Thermal injury, with either significant heat or cold exposure, can result in damage

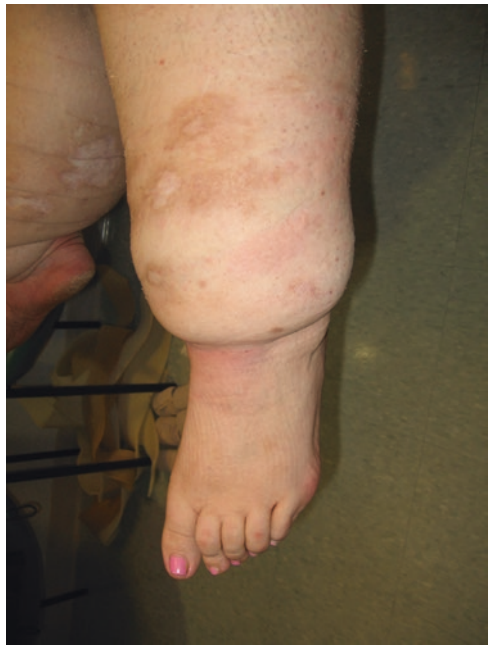

Fig. 4.6 Lipedema. This leg displays typical features of lipedema with bilateral, symmetric globular fat distribution involving the lower legs with sparing of the feet (so called "ankle cuff sign"). Notice the scarring in the medial and posterior calf from a history of skin ulceration from friction complicated by cellulitis

to capillary membranes and produce a swollen limb from the flow of plasma proteins into the interstitial space. With severe cold exposure, edema will occur during rewarming.

Another example of a condition of an enlarged limb which is not a true edema is the underappreciated condition of lipedema. This condition is the result of a familial pattern of fat maldistribution which is amplified by obesity. Lipedema is seen predominantly in women, which has led to the proposal of a relationship with female hormones, although the nature of this relationship is not understood. Further support for this hormonal hypothesis is its development during female puberty and the fact that men with this condition often have cirrhosis or are receiving hormone therapy. The typical pattern is symmetric with involvement of the hips (sometime buttocks), thighs, and lower legs but classically spares the feet (Fig. 4.6). This was first described by Allen and Hines in 1940 but has received very little appreciation or mention in the literature over the past 75 years [7]. It occurs may be associated with heaviness of the legs and tenderness, especially if tight elastic compression is used.

Factitial limb swelling is edema caused by constrictive bands, tourniquets, or straps that are either purposely or inadvertently placed on the limb. The history may be difficult to ascertain due to a fluctuating pattern that is reported and may elude recognition for months. A major clue to factitial edema is a sharp demarcation at the edge of edema with evidence for skin marks from the device that is used as a tourniquet. Treatment for this condition will often require behavioral modification through counseling and the involvement of psychiatry.

Diagnostic Workup of Edema

In the majority of cases, the diagnosis of edema can be made by clinical examination alone. Table 4.2 helps identify edema patterns based on history and examination. Commonly, adjunctive lab testing will be helpful to evaluate edema when a nonvascular cause is considered. Figure 4.7 outlines an algorithm to aide in the clinical workup of lower extremity edema. This often includes a metabolic profile, urinalysis, and thyroid function. System-specific testing such as looking for heart failure (BNP) or liver dysfunction (hepatic panel) may be indicated. In order to differentiate between the many etiologies of edema, however, the clinical examination is not always sufficient, and imaging can be helpful. Imaging may also be necessary to define management options in cases of venous edema and edema with mixed etiology.

Duplex ultrasound still remains the first-line test in the diagnostic workup of patients with limb edema. Duplex ultrasound identifies acute and chronic venous obstruction, the presence and extent of venous reflux, and the presence of vascular malformations. It can help to identify some abnormalities that either cause swelling (Baker cyst) or mimic edema (intramuscular hematoma). Identification of arterial disease may also be necessary in selected cases.

Table 4.2 Typical edema patterns

	CVI	DVT	Primary lymphedema (praecox, tarda)	Secondary lymphedema (obstruction)	Lipedema	CHF
Onset	Gradual	Rapid	Slow, insidious	Variable	Gradual	Variable
Location	Below knee or below level of obstruction	Distal to level of thrombosis	Initially foot and toes	Initially pelvis and thighs	Spares feet	Dorsal foot hump
Progression	Slow	Rapid without treatment	Slow; distal to proximal	Slow; proximal to distal	Associated with weight gain	Variable; distal to proximal
Skin findings	Hyperpigmentation, brawny, taut skin. Lipodermatosclerosis, atrophie blanche	Tense edema	Hyperkeratosis, velvety papillomatosis, warty nodules, squaring of toes, Stemmer sign	Skin distention, stemmer sign	Loose, flabby skin folds	Doughy edema
Pitting	Minimal	Variable	Minimal	None	None	Marked
Discomfort	Ache; variable	Pain; variable. Tenderness and cramping	Heaviness	Tenderness; variable	Mild sensitivity	Heaviness. Pain with skin distention
Response to elevation	Reduction	Marked reduction	Minimal change	Minimal change	None	Reduction

CVI chronic venous insufficiency, *DVT* deep vein thrombosis, *CHF* congestive heart failure

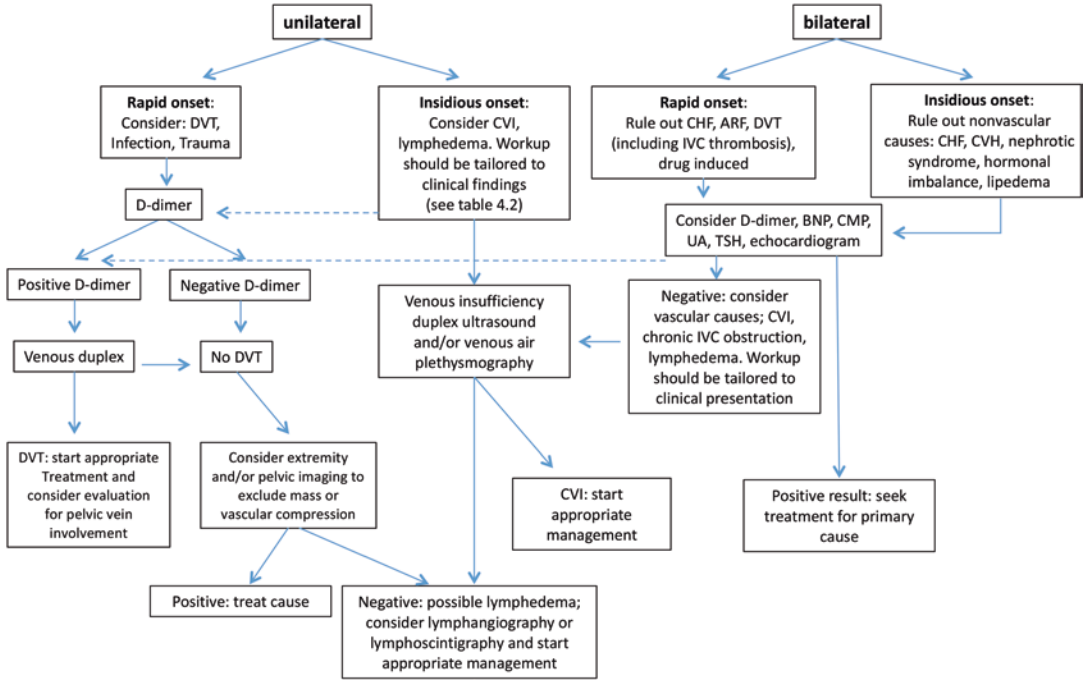

Fig. 4.7 Basic Algorithm for the work up of lower extremity edema. *DVT* deep vein thrombosis, *CVI* chronic venous insufficiency, *CHF* congestive heart failure, *ARF* acute renal failure, *IVC* inferior vena cava, *BNP* brain natriuretic protein, *CMP* complete metabolic panel, *UA* urinalysis, *TSH* thyroid-stimulating hormone

Duplex ultrasound can be used to evaluate the severity of edema and for objective assessment of treatment success. Changes in skin thickness, subcutaneous tissue thickness, and echogenicity have been shown to be diagnostic for clinical stages of lymphedema [8]. The distribution of echo-free spaces can help to differentiate between dependent edema, early stages of lymphedema, and venous edema [9]. In the early stages of lymphedema, the echogenicity of subcutaneous tissue increases in the thigh and calf, with echo-free spaces distributed throughout the entire calf. In cases of dependent edema, the increase of echogenicity is limited to the calf, and the echo-free spaces are predominantly located in the lower lateral leg. In contrast to lymphedema, ultrasound findings in limbs affected by lipedema consist of normal skin thickness and echogenicity of subcutaneous tissues [10].

Similar to ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) provide morphological information related to skin and subcutaneous tissue. These advanced imaging modalities may provide better resolution and more quantifiable information on relative volumes of limb segments, along with the distribution of edema. They may also provide more information regarding other soft tissue structures such as lymph nodes and tumors. CT may be helpful in differentiating between lymphedema, cellulitis, and edema of other etiologies [11]. MRI is capable of visualizing lymphatic vessels, and enhancement with contrast can assess lymphatic function with accuracy similar to lymphoscintigraphy [12, 13].

Lymphoscintigraphy is performed to gain specific information on regional lymphatic function and requires radionuclide injection in the web spaces of the feet or hands. Advantages of lymphoscintigraphy are that it provides a quantitative assessment of the time of absorption and transport of the injected radiolabeled substance by the lymphatic system and a qualitative assessment of the lymphatic network pattern along with potentially identifying the level of obstruction to the lymphatic flow. Although lymphoscintigra-

phy is recommended by several guidelines as a first-line diagnostic test for lymphedema, this technique lacks strict standardization (various radiotracers, doses, injection volumes, and static versus dynamic imaging techniques) and is subject to institutional standards, complicating the relevance of the interpretation [4].

The use of fluorescence agents has opened an opportunity to visualize lymphatic vessels and assess lymphatic function in typical clinical settings. A technique using photolymphoscintigraphy with indocyanine green and near-infrared light is particularly promising. The penetration depth of up to 4 cm allows visualization and functional assessment of lymphatic vessels not only in the skin but also in subcutaneous tissue and muscle [14–16].

Conclusion

Segregating the etiologies for vascular or non-vascular edema into bilateral versus unilateral causes aides in simplifying the workup for patients who present for consultation with peripheral edema to a vascular clinic. Many patients present, however, with multiple comorbidities with the potential for overlapping multifactorial causation for their edema. The swollen limb of a patient is not only a common problem but one which often presents a true diagnostic challenge. Diagnostic testing may be useful but is often superfluous. The clinician must therefore have proper exam and history-taking skills and an appreciation for the wide array of causes for a swollen limb. It is with this solid foundation that one can arrive at the correct diagnosis and institute appropriate, cost-effective, and timely therapy.

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Compression Therapy in Venous Disease

5

Robert R. Attaran and Cassius Iyad Ochoa Chaar

Clinical Pearls

1. Compression therapy is essential for the treatment of venous disease affecting the lower extremities.
2. Compression therapy promotes healing and decreases recurrence of venous ulcers.
3. Compression therapy decreases the risk of DVT, decreases discomfort after developing a DVT, but does not necessarily decrease the risk of post-thrombotic syndrome.

Introduction

Chronic venous disease (CVD) is a very common condition affecting up to a third of the adult population [1, 2]. It can lead to varicosity, edema, and even intractable leg ulcers requiring prolonged wound care. Regardless of the pathophysiology, reflux, or obstruction, the mainstay of therapy remains compression [3]. Compression stockings are utilized as they are thought to compensate for increased ambulatory venous pressure, for prevention of deep and superficial vein thrombosis, and for reduction in inflammation, swelling, and pain. In addition to various forms of stocking, compression can be provided with bandages as well as pneumatic devices.

Hippocrates (460-370BC) and Aurelius Celsus (25BC-AD14) both utilized compression in their treatment of venous disease [4, 5]. Conrad Jobst made the observation that hydrostatic pressures in a pool relieved venous insufficiency symptoms. The applied pressure was greater with depth. In the 1950s he developed compression stockings to emulate those pressures [6]. This chapter will review some of the evidence behind compression therapy.

Mechanisms of Benefit

The ankle venous pressure represents the weight of the column of blood leading to the right atrium. Low in the supine position, ankle venous pressures rise closer to 80–100 mmHg upon standing. When venous valves are healthy, the use of the calf pump dramatically reduces this pressure. In venous insufficiency, compression stockings can help

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improve venous return and reduce ambulatory venous pressure [7, 8] in part by using a Starling gradient that favors edema resolution [9]. The fluid shift from the interstitium into the lymphatics may also improve conditions for oxygen and nutrient transport.

Compression of a vein can reduce its radius and increase flow velocity [10, 11]. Increased velocity in the microcirculation may lead to endothelial neutrophil detachment [12]. Compression therapy has been shown to reduce elevated levels of the inflammatory cytokines vascular endothelial growth factor and tumor necrosis factor-α in patients with venous ulcers [13]. Ulcer healing seems to correlate with falling cytokine levels.

Two physical laws apply to compression therapy: (1) Pascal's law, external static pressure exerted on a confined fluid is distributed evenly, and (2) Laplace's law, pressure applied by compression is proportional to the tension at the interface with skin and inversely proportional with limb radius (P α tension/radius).

These physical laws have several implications:

1. Each additional bandage layer adds to pressure.
2. Increased applied pressure reduces vessel radius.
3. The same tension applied at the ankle will generate more pressure than if applied at the calf, due to the smaller radius at the ankle (Fig. 5.1).

These laws, however, do not entirely explain how pressure distributes with compression [14]. Chassagne et al. [15] utilized pneumatic pressure sensors in healthy subjects at three locations: the ankle, interface of the Achilles tendon, and the gastrocnemius muscle (where calf circumference is greatest). Interface pressure increased, as expected, with greater bandage overlap. Men demonstrated slightly greater rise in interface pressure with standing than women. As expected, the interface pressure decreased higher up, as leg circumference increased. The relationship between applied pressure and elastic modulus was nonlinear.

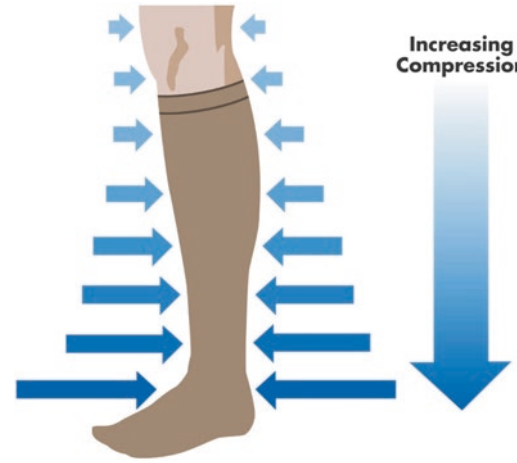

Fig. 5.1 Compression therapy relies on placement of circumferential garments that provide pressure on the leg with maximal intensity at the level of the ankle

Elastic compression hosiery by its very nature demonstrates a degree of hysteresis, i.e., the ability to return to its original length after being stretched. More layers of elastic compression bandaging not only increase compression, but they will also result in a less elastic bandage. This is in part due to friction between the layers. Less elastic bandages exert greater compressive pressure when the wearer stands from a supine position, likely due to muscle expansion [15].

Compression Pressure

Compression stockings are available in different grades of pressure (Table 5.1). The classification of pressure varies between countries. One international consensus group, for example, categorized "mild" compression as <20 mmHg, "moderate" as =20–40 mmHg, "strong" as =40–60 mmHg, and "very strong" as ≥60 mmHg, at the ankle [16].

Partsch [8] used ultrasound to evaluate the mid-calf small saphenous vein (SSV) and posterior tibial vein in 14 patients (5 with varicose veins). Narrowing was observed at 30–40 mmHg, occlusion at 70 mmHg, when standing. Lord [17] evaluated 30 patients (13 with varicose veins) who wore waist-high 20–30 mmHg compression

Table 5.1 Grades of compression

United States	German standard	British standard	Pressure (mmHg)[a]	Suggested indication
Light	KK1	3A	<20	Mild C1-3 disease and unable to apply or tolerate class I
Class I (moderate)	KK2	3B	21–30	Mild C1-3 disease
Class II (high)	KK3	3C	31–40	More severe C2-3 disease, C4 disease and higher, PTS
Class III (very high)	KK4	3D	>40	C5-6 disease (if did not respond to class II and if tolerated)

PTS post-thrombotic syndrome
British standards for bandages, German standards for compression stockings [64, 65]. *KK* class of compression
[a]The pressure range for the German standard is different (KK1 = 18–21, KK2 = 23–32, KK3 = 34–46, KK4 ≥ 49 mmHg)

stockings. The great saphenous vein (GSV) was not compressed when standing. Among the varicose vein patients, the GSV was not compressed even when supine. Additional imaging studies utilizing ultrasound and MRI suggest that in order to compress the GSV while standing, 40–50 mmHg compression pressure is required [18–20].

Accomplishment of vein occlusion or compression, however, may not be the ideal outcome to study. Sarin et al. [21] study using duplex found that cuff pressures required to achieve valve function restoration were lower than pressures to achieve occlusion. Some practitioners choose grades of compression based on severity of disease. The CEAP (clinical-etiology-anatomy-pathophysiology) classification system has been widely adopted to standardize research and dialogue in venous disease [22, 23].

In one study, treatment of patients with predominantly C2–C3 venous disease (varicose veins and edema) with 30–40 mmHg compression led to improved pain, pigmentation, and swelling [24]. High pressure compression (>40 mmHg) is better than low pressure compression for venous ulcer healing [25]. For venous ulcer disease, a systematic review [26] showed that 30–40 mmHg compression hosiery is more effective than lower pressures for healing and lowering recurrence. The Society for Vascular Surgery and the American Venous Forum Guidelines suggest 20–30 mmHg stockings for simple varicose veins (C2 disease) [27].

The Role of Compression as Stand Alone Therapy

In a systematic review of stand-alone compression therapy, that is, not after an ablative procedure, in varicose vein patients, symptoms (e.g., pain, discomfort, edema) were improved. However, there was lack of evidence for post-treatment efficacy in reduction of progression or recurrence of varicose veins [28]. A Cochrane review in patients with venous insufficiency (C2–C4 disease) found insufficient high-quality evidence to determine effectiveness of compression [29]. For C5/C6 disease (healed or active venous ulcer), two Cochrane reviews reported lower ulcer recurrence with compression therapy. Furthermore, compression noncompliance is associated with lower ulcer healing and greater recurrence [3, 30]. Various compression lengths are available to adapt to patient needs (Fig. 5.2).

Compression after Sclerotherapy or Ablation

In the 1960s, Fegan described the empty vein technique, where veins would be compressed after sclerotherapy [31]. While the concept sounds logical, evidence for the optimal duration of compression after sclerotherapy or whether it is necessary is scant. Furthermore, there exists a wide variation across the globe on utilization of compression after ablative procedures.

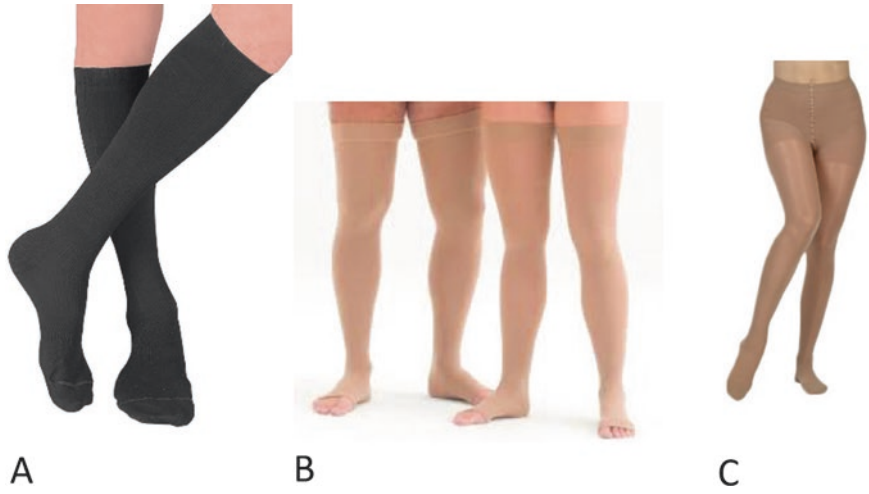

Fig. 5.2 Different length of compression garments available on the market: (**a**) knee high, (**b**) thigh high, (**c**) Pantyhose

Kern randomized 100 patients undergoing sclerotherapy for lateral thigh reticular and spider veins to no versus 3 weeks of post-procedure compression (23–32 mmHg). Improved clearance was reported in the compression group at 7 weeks [32]. El-Sheika's [33] systematic review of randomized control trials found seven suitable for analysis. Three studies were surgical; two used sclerotherapy and two endovenous laser ablation (EVLA). Heterogeneity in study quality and duration of compression was found which made meta-analysis difficult. No specific conclusions could be drawn about efficacy or optimal duration of compression therapy.

Two of the evaluated studies suggested that longer compression resulted in less pain. Bakker et al. [34] prospectively randomized patients undergoing EVLA of the GSV to 2 versus 7 days of compression stockings (35 mmHg). Sixty-nine patients were analyzed. At 1-week follow-up, the 7-day compression group reported less pain and better physical function. At 6 weeks no significant difference was found. Another similarly designed prospective study noted a small but significant reduction in pain scores when compression was worn after EVLA [35]. These studies did not demonstrate any difference in procedural success or efficacy.

Compression for Venous Ulcer Disease

Venous ulcers represent the most severe form of venous disease. A 2012 Cochrane systematic review evaluated 48 randomized clinical trials (n = 4321), concluding that compression led to greater ulcer healing compared to no compression. Both ulcer healing and reduction in recurrence are enhanced with compression [3, 26]. Multicomponent systems (as opposed to single layer) or those with elastic components appeared to work better. Higher compression pressures appear to heal ulcers better [3]. In another systematic review, Cullum et al. [36] found that multilayered high compression was more effective than moderate compression, in the prevention of ulcer recurrence. Another Cochrane review [30] determined that high pressure compression may work better than medium compression to prevent recurrence. Overall, there was insufficient evidence when comparing types or lengths of compression.

Prevention of Deep Vein Thrombosis

Compression hosiery prevents venous thromboembolism in the perioperative setting. Its mechanism of benefit might be through decreasing

venous stasis and stimulating tissue factor pathway inhibitor [37].

A Cochrane database review found 19 randomized controlled trials, 18 evaluating surgical patients, and 1 medical patients [38]. The graduated compression-stocking group developed DVT in 9% compared to 21% among controls ($P < 0.00001$). The incidence of pulmonary embolism based on 5 included studies was 2% in the treatment group versus 5% in controls ($P = 0.04$).

Post-thrombotic Syndrome

Post-thrombotic syndrome (PTS) is a chronic, potentially disabling, disorder that can occur after acute DVT, affecting at least 30% of patients [39]. In the affected leg, skin changes, edema, and ulceration can occur along with pain. It has been postulated that compression may alleviate venous reflux, hypertension, and sequelae, if applied early following a DVT. Subfascial lymphatic function can be reduced with deep vein thrombosis and deep venous incompetence due to a post-thrombotic syndrome but may be treated with compression [40, 41].

Three randomized trials have evaluated compression stockings in the prevention of PTS. Two small randomized trials appear to suggest an approximately 50% reduction in PTS with compression stockings [42, 43]. The SOX trial [44] randomized 410 patients with proximal DVT to 30–40 mmHg below-knee graduated compression stockings versus <5 mmHg placebo stockings. The stockings were mailed to participants within 2 weeks of DVT diagnosis. They were asked to be worn on the affected leg for 2 years, during waking hours. Participants were asked to report frequency of stocking use. At 24 months there was no significant difference in the proportion of patients with PTS. Adherence was recorded as being equivalent.

A number of criticisms have been directed against the study. Compression stockings were not applied immediately upon diagnosis of DVT but rather up to 2 weeks later. In addition, 83% of participants provided a wrong guess or "uncertain" reply as to whether they had been receiving real compression or placebo stockings. This may suggest that a sizeable number had not worn the compression stockings at all. The benefit of compression hosiery post-DVT to prevent PTS is controversial, but in our view, compression hosiery should be applied immediately following DVT, as in the least, it appears to decrease swelling and provide comfort.

Compression Modalities Compared

A diverse selection of compression modalities exists, from those compressing around the ankle region to those compressing up to the waist. Bandages, stockings, and pneumatic compression devices have been utilized. Single to multilayer bandages have been used. Bandages and stockings can vary in power and elasticity (Fig. 5.3).

Inelastic compression bandages tend to generate lower resting pressures but the pressure increases with walking due to calf muscle expansion [45]. They are therefore not ideal for immobile patients. Inelastic bandages should be reapplied once edema has improved. Increased layers not only augment the pressure applied but also tend to render the compression less elastic.

A small randomized study compared venous ulcer healing rates using five compression modalities: pneumatic compression, multilayer bandages (45–50 mmHg), compression stockings (30–40 mmHg), two-layer bandages (20–30 mmHg), and Unna boots. More patients had superficial than deep reflux. No ablative intervention was performed. At 2 months, ulcer healing rates were best (57–59%) in the groups that received pneumatic compression, 30–40 mmHg compression and multilayer bandages (45–50 mmHg). Ulcer healing rates were lowest in those assigned to Unna boots (20%) and two-layer bandages (17%) [46].

In a randomized trial of 200 patients undergoing EVLA to the GSV, one group wore 23–32 mmHg thigh-high compression stockings. The second group wore the same compression stockings with an added eccentric medial compression band,

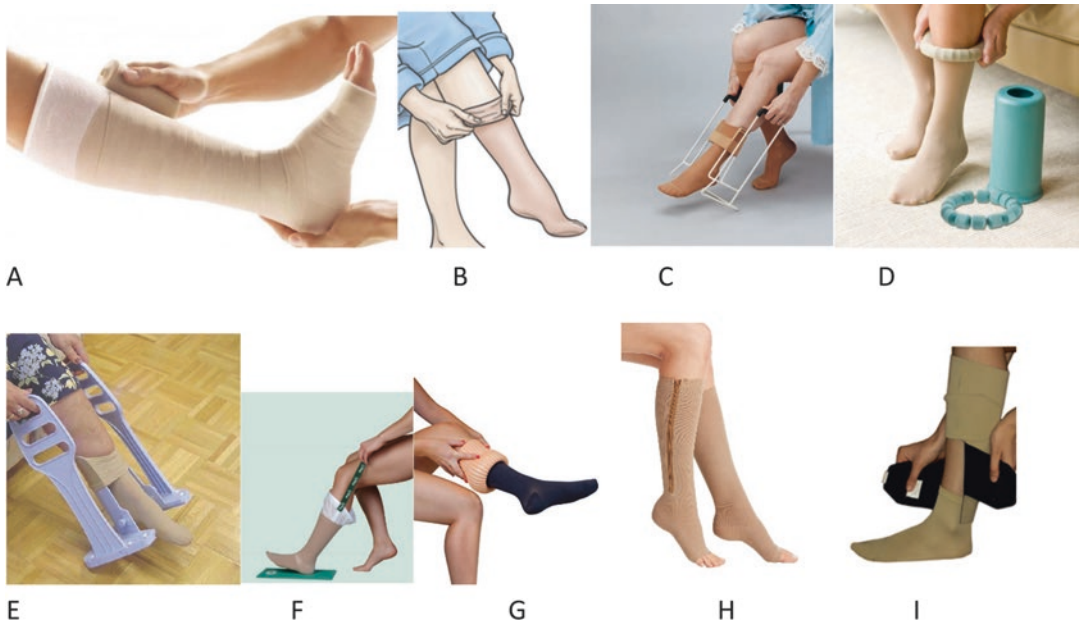

Fig. 5.3 Typical compression modalities and applications. Compression can be provided using an elastic wrap (**a**). More commonly graduated compression stockings can be prescribed that are commonly applied by manual rolling (**b**). For patients who have difficulty using the stockings, several commercial frames and inserts (**c**–**g**) are available to assist in stockings placement. Some stockings have a zipper to enable tightening after the application on the leg (**h**). Finally, Velcro stockings are available also as an alternative compression modality (**i**)

approximating the GSV location. The group with added medial compression reported significantly less post-EVLA pain. GSV closure rates were not evaluated [47]. A 2009 meta-analysis of eight RCTs found faster ulcer healing with purpose-made compression stockings than "diverse" bandages in venous ulcer disease [48]. There was a greater proportion of healed ulcers (62.7% with stockings vs 46.6% with bandages; $P < 0.0001$) and stocking use resulted in 3 weeks shorter mean ulcer healing time ($n = 535$, $P = 0.0002$) and lower pain scores ($P < 0.001$) than with bandages [48].

Inelastic compression stockings typically require application by a trained individual. Adjustable devices may present a better future alternative while also being easier to apply. Mosti et al. [49] demonstrated efficacy in edema reduction among C3 patients when comparing an adjustable Velcro compression device to inelastic bandages. They randomly assigned 20 limbs to multi-component multilayer inelastic bandages versus 20 to the Velcro device for 7 days. The Velcro group was instructed to tighten the device if it felt loose, whereas the inelastic bandage group was asked not to adjust theirs. At baseline the inelastic bandage exerted a supine mean pressure of 63 mmHg versus 43 mmHg with the Velcro device. However, the inelastic bandage pressures fell >50% over 7 days whereas remained stable in the Velcro group. Furthermore, there was greater limb volume reduction in the Velcro group (26 versus 19% at 7 days; $P < 0.001$), without a significant difference in patient discomfort.

Concurrent Peripheral Arterial Disease

In patients with concurrent arterial and venous disease, some authors have advised caution with compression therapy, as it may further decrease skin perfusion [50]. Some investigators have recommended avoidance of compression for ankle brachial pressure indices (ABIs) <0.5 [51].

In a small study on mixed arteriovenous ulcer disease with ABI >0.5 and ankle pressure

>60 mmHg, inelastic compression stockings (more specifically pressure range 20–40 mmHg) did not appear to impede arterial flow while improving venous pump function [52]. However, no longer-term clinical follow-up was made. Ladwig et al. [53] studied a relatively inelastic 2-layer bandage system in 15 subjects with ABIs 0.5–0.8. Average standing sub-bandage pressures measured at the junction of the calf muscle with the Achilles tendon were 30 mmHg. Over 14 days of follow-up, the compression appeared well tolerated and safe.

It may be the case that carefully fitted inelastic compression hosiery are more appropriate in peripheral arterial disease (PAD) as they produce higher working pressures. Regardless, we recommend prompt follow-up and examination of patients fitted with compression hosiery. Some PAD patients have calcified pedal vessels and falsely elevated ABIs. Relying on the ABI alone, therefore, is not advisable. Toe or skin perfusion pressures can therefore be evaluated [54, 55].

Compliance Issues

Ideal compression should compensate for elevated pressures when standing [8, 11] while allowing for the patient to remain ambulatory and comfortable. Patients with obesity, frailty, or arthritis will struggle to apply elastic compression stockings. Even light compression (<20 mmHg) hosiery can be uncomfortable after application. In one report at least 15% of elderly patients could not apply stockings [56]. In a study of post-sclerotherapy compression, only 40% were compliant with daily posttreatment compression, mainly due to discomfort [57]. Noncompliance is noted even among those with ulcer disease [58]. In Coughlin's study of pregnant women with varicose veins, 33% refused to participate once randomized to compression [59]. After 6 weeks follow-up compliance was only 32%.

Non-adherence with compression is associated with reduced and slower ulcer healing, as well as greater recurrence [60]. So-called donning devices that assist in the wearing of compression hosiery are available, although their efficacy in improving adherence is unclear. Individuals unable or unwilling to wear compression hosiery may find pneumatic compression devices easier to tolerate, though the data is limited. In a small controlled study ($n = 28$), females with painful varicose veins received sequential pneumatic compression therapy for 30 min, 5 days a week, totaling 6 weeks. The treatment group reported improved symptoms and quality of life [61].

Conclusion

Despite the paucity of data, compression remains the mainstay of treatment for chronic venous insufficiency, in particular for venous leg ulcers. Higher pressures are required to maintain compression when standing. Before prescribing compression hosiery, a careful evaluation of the target limbs must be performed. Delicate and friable skin, bony prominences and the presence of neuropathy can increase risk of damage. Compression grades, as a guide, can be based on severity of disease and the patient's ability to comply.

Discomfort and poor compliance remain a major barrier. Currently in the United States, compression stockings are not typically reimbursed by health insurance and can be costly. We recommend below-knee compression hosiery rather than thigh high, in general, as the latter can be even more uncomfortable [62]. With thigh-high hosiery, there can be popliteal discomfort particularly during sitting, and slippage can occur [63].

At least a week of compression therapy after ablation procedures may minimize patient discomfort though there is scant evidence that compression improves ablation outcomes such as vein closure. For venous ulcer disease, long-term and higher pressure compression stockings (30–40 mmHg) are advised [3, 30].

Compression reduces the risk of perioperative DVT, but its role in prevention of PTS is controversial. The authors recommend against compression stockings in ABI <0.5 or ankle pressure <60 mmHg and suggest prompt follow-up and examination of PAD patients fitted with compression hosiery.

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Part II

Venous Insufficiency

Clinical Presentation of Venous Insufficiency

6

Lisa E. Amatangelo
and M. Emily Wilcox Cummings

Clinical Pearls

1. Lower extremity edema from venous insufficiency is typically worse after prolonged standing and relieved with leg elevation.
2. A trial of compression therapy can help differentiate pain from venous etiology from pain from musculoskeletal pain such as arthritis/plantar fasciitis.
3. CEAP classification is most commonly used for description of physical findings in patients with venous insufficiency.

Introduction

Chronic venous disease, whether caused by superficial and/or deep venous insufficiency, is an incredibly common condition that affects a significant portion of the population in the United States and the Western world. Being one of the most common chronic medical conditions, it is a cause of significant morbidity as well as an important socioeconomic and public health issue [1, 2]. It is estimated that more than 50% of patients over the age of 40 have spider and larger varicose veins [3]. The prevalence of varicose veins is estimated to affect approximately 30% of the population, but variable figures exist in the literature, with 2–56% of men and <1–60% of women being affected [2, 4]. Additionally, the Bonn Vein study suggests that chronic venous disease is a progressive disease, and if left untreated, a significant proportion of patients will progress from varicose veins to edema, to skin changes, and to ulceration [5]. Prevention of disease progression then is very important.

Clinical Evaluation of the Patient

Chronic venous disease is ubiquitous. Considering the entire spectrum of disease including telangiectasia, prevalence rates have been reported as high as 80% for men and 85% for women [6]. As such, the likelihood of encountering some degree of venous insufficiency in clinical practice is high. Presentation of venous insufficiency includes patient-reported symptoms in addition to physical exam findings or signs. While signs and symptoms have been shown to correlate with disease severity in some studies, others show discordance [7–9]. Venous disease is common, but it is important to recognize the idiosyncrasies of the presentation of venous insufficiency and not assume all signs and

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symptoms are venous in origin, thereby missing a diagnosis or, worse, treating the wrong condition. (First, do no harm.) This chapter addresses the signs and symptoms of venous disease: symptoms being the complaints reported by the patient during the history and signs being the physical findings noted by the provider during the examination.

Risk Factors

There are certain populations where venous disease is more likely to exist. Epidemiologic studies list older age, family history of venous disease, standing occupation, obesity, and a history of phlebitis as risk factors for venous insufficiency [1]. Some studies suggest that behaviors, including occupations or activities that require prolonged immobility or standing, contribute to the risk of developing venous insufficiency. [10–12].

Clinical Presentation

What the practitioner appreciates or measures on exam is a sign. What the patient complains of is a symptom. Often patients use diagnostic terminology rather than describing symptoms. For example, "I have bad circulation," is a complaint often heard in our vein practice, which may be true, but is less helpful in understanding and making a diagnosis than a description of the pain, ache, or restlessness that the patient is experiencing.

Symptoms

Symptoms that are suggestive of venous etiology include leg aching or pain, heaviness or fatigue, itching, swelling, cramping, and restlessness [13]. Swelling is sometimes included as a symptom although it is better categorized as a sign because it can be appreciated on physical exam. However, patients certainly notice indentations on their lower legs when they remove their stockings or the absence of ankle landmarks at the end of the day and will complain of swelling or a sensation of swelling. Certainly none of these signs are exclusive to venous disease, and other causes must be considered. The patient history is useful in differentiating venous from other potential etiologies. Generally, most venous symptoms are more pronounced in the lower leg and sometimes in the location of the varicosities. Symptoms that are venous are typically worse at the end of the day or, if a patient works nights, at the end of a day's work. Often prolonged immobility (standing or sitting) can exacerbate the symptoms. Walking or other activities that activate the calf muscle pump can provide some relief; however, prolonged activity may actually increase symptoms. Patients frequently report that their legs feel better with rest, but this is different than the rest that relieves arterial insufficiency. Rest required to relieve venous symptoms is not just a pause in activity or sitting down but rather a night in a supine position with legs elevated to the level of the heart or higher. Therefore, patients that sleep in recliners may report no relief with rest. Another consideration for female patients is hormones. Some women report worsening symptoms with cyclical hormone fluctuations or pregnancy or when taking hormone medication. Relief with measures such as compression stockings and leg elevation is also suggestive of a venous etiology.

When assessing patient symptoms, it may be helpful to consider the differential for each complaint. Aching or pain may be from venous, arterial, musculoskeletal, infectious, or neurologic pathology. Often patients will describe the ache as dull or "like a toothache in the leg." There are several common masqueraders of venous symptoms. Patients frequently present with knee arthritis or plantar fasciitis believing their symptoms are related to their varicose veins. Another mimicker is lumbar spine pathology or meralgia paresthetica with radiculopathy causing the leg pain. Usually there are varicosities in the area of pain which leads the patient to believe that the symptoms are venous in origin. In the case of arthritis and plantar fasciitis, activities that exacerbate the pain can help to distinguish between musculoskeletal and venous sources. For example, knee pain

when climbing stairs or foot pain with the first step are not typical venous symptoms. Physical exam eliciting tenderness at the knee joint space, crepitation with knee flexion and extension, or tenderness with palpation of the medial calcaneal tuberosity can provide clues to the actual source of the pain. A history of claudication or rest pain is more suggestive of arterial issues. Known lumbar pathology, weight gain, or clothing that compresses the lateral femoral cutaneous nerve can assist in identifying radicular causes. Other culprits of lower extremity pain are infection, be it osteomyelitis or cellulitis, and fibromyalgia.

Leg heaviness and fatigue are frequent venous symptoms. Patients with lymphedema, lipedema, or obesity may also have symptoms of leg heaviness. History is minimally useful for distinguishing the cause of this symptom since heaviness tends to be worse at the end of the day for all of these conditions. Physical examination can be helpful in differentiating the cause of leg heaviness as the non-venous entities present with non-pitting edema. Although lipedema and lymphedema present with non-pitting edema, lymphedema may have pitting edema in its early stages. Lymphedema also presents with a dorsal hump on the foot, while lipedema typically spares the foot.

Leg cramping, while potentially venous, can be secondary to electrolyte abnormalities, hypoparathyroidism, or low iron levels. If the remainder of the history does not point to venous disease, laboratory evaluation may be useful in ruling out these causes.

Another complaint of patients with venous disease is itching. The itching may be secondary to swelling or located at the site of varicosities. Other considerations would include dermatitis which is difficult to distinguish particularly in large patients.

Restlessness can be a manifestation of venous disease. There are also neurogenic causes, and venous treatment will do little to alleviate this symptom if not related to venous insufficiency. Fortunately, low-risk treatments such as compression stockings are generally well tolerated and can relieve lower extremity restlessness. A trial of compression therapy can aid in diagnosis and is relatively safe.

The most dramatic symptom for patients with varicose veins is bleeding. Variceal hemorrhage is unique and typically memorable for the patient. The history usually includes water, either swimming or showering, with the patient standing in a warm environment. This provides macerated skin, increased hydrostatic pressure, and vasodilation. Upon drying off, the skin breaks and the varix will bleed. Patients like to show video or pictures on their phones of the impressive mess a variceal hemorrhage makes in their bedroom or bathroom.

Physical Exam

The initial clinical presentation of the patient with venous insufficiency varies widely. Physical findings can include telangiectasia, reticular veins, varicose veins, edema, inflammation, dermatitis, and/or ulceration. A patient may have none, some, or all of these findings.

To facilitate meaningful communication about chronic venous disorders, the CEAP classification, a descriptive classification, was developed in 1994 by an international ad hoc committee of the American Venous Forum, endorsed by the Society for Vascular Surgery, and incorporated into "Reporting Standards in Venous Disease" in 1995. In 2004, the classification system was revised and refined, and a basic CEAP version was introduced to be used as an alternative to the full (advanced) CEAP classification. Today, the classification is widely accepted, and most published clinical papers on chronic venous disease use all or portions of CEAP [14].

CEAP Classification

C: Clinical Classification

C_0: no visible or palpable signs of venous disease

It is estimated that 20% of patients with symptoms consistent with chronic venous disease have no visible or palpable signs of venous disease. However, venous reflux is identified

by duplex ultrasound in approximately 20% of these patients [7].

C_1: telangiectasias or reticular veins (Fig. 6.1)

Telangiectasias are a confluence of dilated intradermal venules less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins. Reticular veins are dilated bluish subdermal veins, usually 1 mm to less than 3 mm in diameter. They are usually tortuous. Normal visible veins in persons with thin, transparent skin are not considered reticular veins. Synonyms include blue veins, subdermal varices, and venulectasies [15].

C_2: varicose veins (Fig. 6.2)

Varicose veins are distinguished from reticular veins by a diameter of 3 mm or more, measured in the upright position. They are subcutaneous, dilated, and usually tortuous and may involve saphenous veins, saphenous tributaries, or nonsaphenous superficial leg veins. Synonyms include varix, varices, and varicosities [15].

C_3: edema (Fig. 6.3)

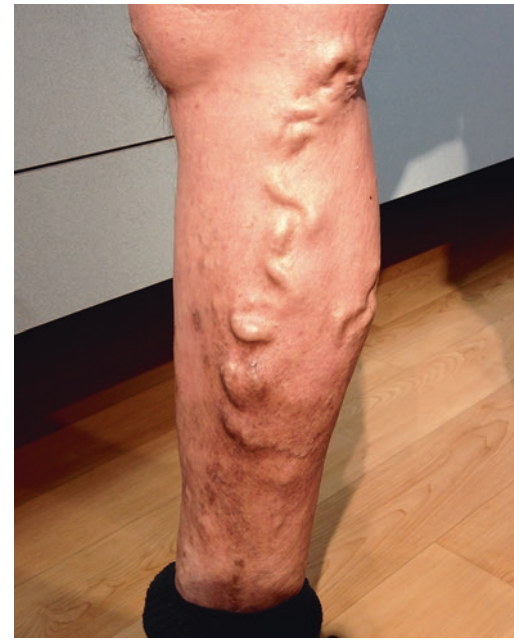

Fig. 6.2 Large varicose veins over medical aspect of the calf

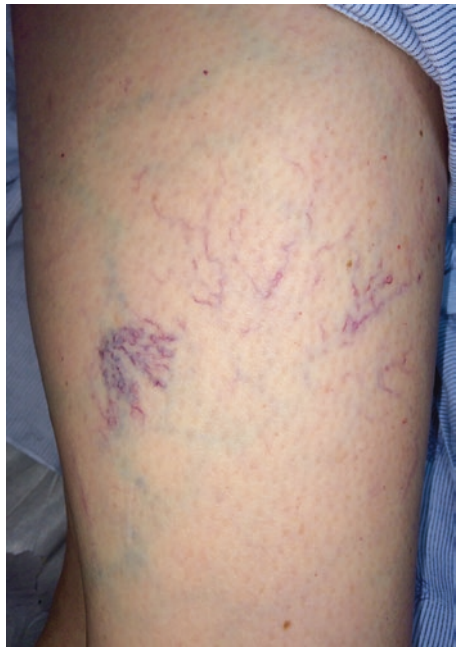

Fig. 6.1 Telangiectasias/spider veins affecting the posterior calf

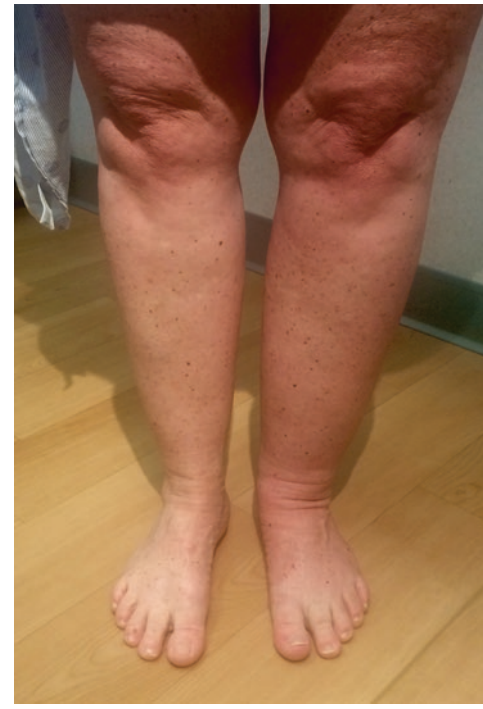

Fig. 6.3 Swelling at the ankle *left* worse than *right*

Edema is a perceptible increase in volume of fluid in the skin and subcutaneous tissue, characteristically indented with pressure. Venous edema usually affects the ankle region but may also extend into the leg and foot [15].

However, there are many causes of lower extremity edema. Edema caused by venous insufficiency is typically limited to the lower extremities and often affects only one leg, and other signs of venous disease (i.e., varicose veins, hyperpigmentation) are typically present. In contrast, generalized edema is usually bilateral and not limited to the lower extremities. Venous edema typically improves with recumbency, in comparison to edema due to lymphatic disease, which does not subside with recumbency. Central venous pressure is normal with venous edema, unless there is concomitant heart failure. Venous edema also responds poorly to the use of diuretics.

C_4: changes in skin and subcutaneous tissue secondary to chronic venous disease

C_{4a}: pigmentation or eczema

Pigmentation is defined and brownish darkening of the skin, resulting from extravasation of blood. It usually occurs in the ankle region but may extend to the leg and foot. It is due to hemosiderin deposition due to the extravasation of red blood cells through damaged capillaries into the dermis [15].

Eczema is described as an erythematous dermatitis, which may progress to blistering, weeping, or scaling eruption of the skin of the leg. It is most often located near varicose veins but may be located anywhere along the leg. It is usually seen in uncontrolled chronic venous disease but may also reflect sensitization to local therapy. The pruritus associated with venous eczema is often difficult to relieve. Patients can present with excoriations, making them vulnerable to skin infections [15].

C_{4b}: lipodermatosclerosis or atrophie blanche (Fig. 6.4)

Lipodermatosclerosis (LDS) is 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. It is characterized by areas of firm induration that can begin at the medial ankle but can progress to involve the entire leg circumferentially. There is usually heavy pigmentation and fibrosis that constricts the leg, impeding venous and lymphatic flow. LDS is sometimes preceded by diffuse inflammatory edema of the skin, which may be painful and which is often referred to as hypodermitis. LDS should be differentiated from lymphangitis, erysipelas, or cellulitis. However, patients with LDS are prone to cellulitis caused by staphylococcal and streptococcal organisms. LDS is a sign of severe chronic venous disease, and in its most advanced form, the limb can begin to resemble an inverted champagne bottle. The fibrosed ankle area represents the neck of the bottle and, the edematous leg, the rest of the bottle [15].

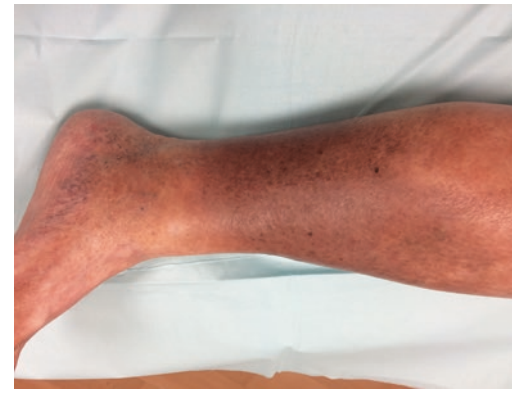

Fig. 6.4 Lipodermatosclerosis affecting the *left leg*

Atrophie blanche (white atrophy) is localized, often circular whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. Healed ulcer scars may have a very similar appearance but are distinguishable from atrophie blanche by a history of ulceration [15].

C_5: healed venous ulcer (Fig. 6.5)

C_6: active venous ulcer (Fig. 6.6)

Venous ulcers are full-thickness defects of the skin, most frequently found in the ankle region. They fail to heal spontaneously and are caused by chronic venous hypertension, the most common cause of lower extremity

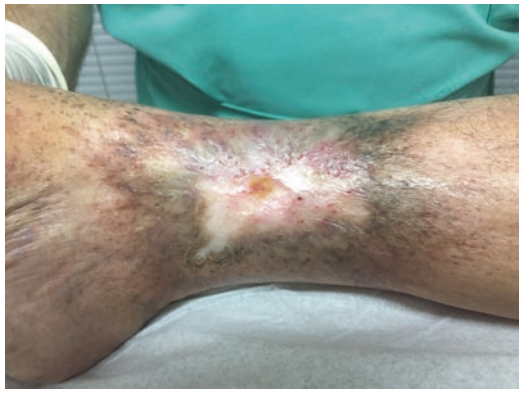

Fig. 6.5 Healed large area of venous ulceration over medial malleolus

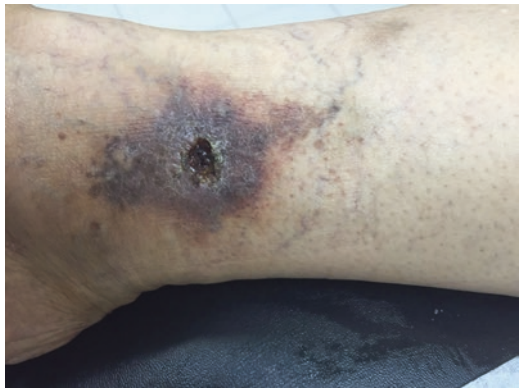

Fig. 6.6 Venous ulcer over medial malleolar area

ulcers [15]. It is estimated that venous insufficiency accounts for about 45–80% of chronic leg ulcers. Venous ulcers are often located over a perforator vein or along the course of the great or small saphenous vein. They do not affect the forefoot nor do they present above the knee. They can be single or multiple, tender, shallow, and exudative. They have irregular, but not undermined borders and a granulated base. If advanced, they can affect the leg circumferentially [7].

It is important to distinguish venous ulcers from other lower extremity ulcers or other lower extremity skin abnormalities. Arterial insufficiency is the cause of approximately 5–20% of chronic leg ulcers. Arterial ulcers are usually found over pressure points and over the toes. They are painful, full-thickness wounds and have a punched-out appearance. Often, other signs of arterial insufficiency are present, including shiny, atrophic, hairless skin; poor or absent peripheral pulses; diminished capillary refill; and hypertrophic deformed toenails. Symptoms of arterial insufficiency, including claudication and rest pain, are also usually present.

Diabetic or other neuropathic foot ulcers account for about 15–25% of all chronic leg ulcers. They occur over bony prominences or areas of increased pressure. They are often hyperkeratotic with undermined borders. There is usually accompanying diminished sensation of the ulcer as well as the extremity.

There are other causes of lower extremity ulcers, including rheumatoid arthritis, systemic sclerosis, vasculitis, sickle cell disease, pyoderma gangrenosum, and skin cancer, including squamous and basal cell carcinoma. Biopsy may be necessary to determine the etiology of a lower extremity ulcer.

S: symptomatic

Symptoms may include aching, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction.

A: asymptomatic

No symptoms or complaints attributable to venous dysfunction are present.

E: Etiologic Classification

E_c: congenital

Congenital etiologies may include arteriovenous malformations and avalvulia, the hereditary absence of venous valves [15].

E_p: primary

Primary valvular reflux is present. There is no other known cause of the chronic venous disease.

E_s: secondary (postthrombotic)

Secondary etiologies are any known cause of the chronic venous disease. Typically the cause is thrombosis, but trauma and surgical alteration are also considered secondary etiologies.

E_n: no venous cause identified

If there is not an evident etiology of chronic venous disease, the n subscript is used.

A: Anatomic Classification

Basic CEAP assigns a limb to one or more of three commonly recognized anatomic venous systems—superficial, perforator, and/or deep.

A_s: superficial veins

The superficial system includes the great and small saphenous systems and any branch varicosities.

A_p: perforator veins

The perforator system includes veins that communicate between the superficial and deep systems.

A_d: deep veins

The deep system includes the calf veins and sinuses; popliteal, femoral, and iliac veins; and the vena cava.

P: Pathophysiologic Classification

Basic CEAP describes the presence of reflux and/or obstruction. They may occur alone or in combination.

P_r: reflux

Reflux is defined as the reversal of venous blood flow with a duration >0.5 s by duplex analysis [10].

P_o: obstruction

Obstruction is confirmed by visualization of an occluded vein segment by imaging or by demonstrating prolonged outflow via a noninvasive study such as plethysmography [10].

P_n: no venous pathophysiology identifiable

If no venous pathophysiology can be identified, the subscript "n" is used (Table 6.1).

Advanced CEAP is used for precise reporting because the anatomic location of the venous abnormality (P) is specifically described [15, 17]. *See* Table 6.2.

Date of CEAP Classification

Because the CEAP classification can be reclassified at any time, the date of any assessment should be included in the CEAP classification. Limbs should be reclassified after any form of medical or surgical treatment [15].

Table 6.1 CEAP classification for chronic venous disorders

Clinical classification	
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias or reticular veins
C_2	Varicose veins
C_3	Edema
C_4	Skin changes related to venous disease
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
Etiologic classification	
E_c	Congenital
E_p	Primary
E_s	Secondary (postthrombotic)
E_n	No venous cause is identified
Anatomic classification	
A_s	Superficial veins
A_p	Perforator veins
A_d	Deep veins
A_n	No venous location identified
Pathophysiologic classification	
P_r	Reflux
P_o	Obstruction
$P_{r,o}$	Reflux and obstruction
P_n	No venous pathophysiology identifiable

Level of Investigation

The diagnostic evaluation of chronic venous disease can also be assigned a level based on the type(s) of testing performed [15].

Level I: This would include an office visit with history and clinical examination and may also include the use of a handheld Doppler.

Level II: This would include noninvasive vascular laboratory testing, including duplex color scanning and possibly plethysmographic testing as well.

Level III: This would include invasive or more complex imaging, including ascending and

Table 6.2 Advanced CEAP: anatomic localization of pathology

Superficial veins
1. Telangiectasias/reticular veins
2. Great saphenous vein (above the knee)
3. Great saphenous vein (below the knee)
4. Small saphenous vein
5. Nonsaphenous veins
Deep veins
6. Inferior vena cava
7. Common iliac vein
8. Internal iliac vein
9. External iliac vein
10. Pelvic: gonadal, broad ligament and other veins
11. Common femoral vein
12. Deep femoral vein
13. Femoral vein
14. Popliteal vein
15. Crural: anterior tibial, posterior tibial, and peroneal veins (all paired)
16. Muscular: gastrocnemial and soleal veins, others
Perforator veins
17. Thigh
18. Calf

descending venography, venous pressure measurements, CT, MRI, and others.

CEAP Classification Examples

A patient evaluated on February 11, 2012 has aching legs, varicose veins, and ankle swelling. An ultrasound demonstrated reflux affecting the popliteal and small saphenous veins, as well as an incompetent calf perforator. There was no evidence of deep or superficial venous thrombosis.

Basic CEAP: $C_{3,s,}E_{p,}A_{s,p,d}P_r$

Advanced CEAP: $C_{2,3,s,}E_{p,}A_{s,p,d,}P_{r,4,14,18}$ (2012-02-11, L II)

Prevalence of CEAP Clinical Classifications

Recently, the more current epidemiologic studies of venous diseases in which the CEAP classification was used were reviewed. Based on this review, the prevalence of CEAP clinical classes C_0 and C_1 was estimated to be 60–70%, C_2 and C_3 was approximately 25%, and C_4 to C_6 was up to 5%. The incidence of varicose veins was approximately 2% per year [16].

Clinical Assessment of Disease Severity and Quality of Life

The purpose of collecting complaints and symptoms from patients is to secure an accurate diagnosis and to assess the impact of disease on their quality of life. Tools for assessing quality of life can be useful in evaluating disease severity and measuring treatment success. Several scores exist; some are physician reported, and some obtain responses from patients. Venous disease-specific instruments include the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ) in the 20 and 14 question versions; the Venous Insufficiency Epidemiological and Economic Study (VEINES-QOL/Sym); the Aberdeen Varicose Vein Questionnaire (AVVQ); the Charing Cross Venous Ulceration Questionnaire (CXVUQ); the Villalta scale; and the Venous Clinical Severity Score (VCSS) [17]. All have strengths and weaknesses, and from their names, it can be determined that the instruments are specific to particular disease situations such as varicose veins, ulceration or thrombosis. The CIVIQ-20, CIVIQ-14 and AVVQ are patient reported and assess superficial and chronic venous insufficiency. CXVUQ is also patient reported but specific for venous ulcers. The Villalta scale is physician reported and assesses the severity of post thrombotic syndrome. The physician reported VCSS covers superficial and chronic venous insufficiency. The VEINES-QOL/Sym is patient reported and is applicable to the full range of venous disease including varicose veins, thrombosis and ulceration. In a recent comparison of these instruments the VEINES-QOL/Sym was considered the most valid with the broadest application to venous disease [18]. Not included in this comparison is the VVSymQ™, a patient-reported outcome tool intended to measure quality of life outcomes

after great saphenous vein treatment. The VVSymQ™ was used to measure symptoms reported by 40 patients who received outpatient treatment for varicose veins. The patient-reported symptoms were compared to clinician-reported outcomes and there was no clear correlation between the patient-reported symptoms and the clinician-reported outcomes [19]. This suggests that acquiring symptom information directly from the patient may be more accurate and perhaps useful than what the clinician interprets and records.

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Open Surgical Treatment of Superficial Reflux

7

Andreas M. Lazaris and George Geroulakos

Abbreviations

ASVAL	Ambulatory selective varices ablation under local anesthesia
CFV	Common femoral vein
CHIVA	Cure conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire
GSV	Great saphenous vein
HL	High ligation
SFJ	Saphenofemoral junction
SPJ	Saphenopopliteal junction
SSV	Short saphenous vein
VVs	Varicose veins

Clinical Pearls

1. Consider open ligation and stripping of large saphenous veins with size ≥25 mm at the junction.
2. To prevent recurrence after open surgery, all branches close to the saphenofemoral junction and draining into the femoral vein should be ligated.
3. To prevent cutaneous nerve injuries, avoid stripping the distal portions of the veins in the calf region.

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History

The history of treatment of lower limb varicosities goes back thousands of years. The papyrus of Ebers at about 1550 BC mentioned varicose veins, but the authors described against operation [1]. The first illustration of a varicose vein was discovered in the Acropolis of ancient Athens back to the fourth century BC. It was supposed to be a gift from Lysimachides to the hero-physician Amynos. However, Hippocrates did not recommend excision of the varicose veins; instead, he suggested compression after multiple punctures. Later (25 BC to 15 AD), Roman physician Celsus wrote a medical document describing ligation surgery and the surgical excision of varicosities, as well as their possible complications. A few years later, the Greek physician Galen described a technique similar to the saphenous stripping. In his technique varicosities were directly irritated by a hooked tool wire, aiming to extract as much of the vein as possible.

The era of surgical treatment of varicose vein disease begins at the end of nineteenth century when Friedrich Trendelenburg [2] performed the first ligation of the great saphenous vein (GSV)

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with a transverse incision in the middle of the thigh. The Mayo brothers [3] thought about the additional benefit of the excision of GSV additionally to its ligation and accomplished it with a long incision from the groin to the knee. This concept was improved, in terms of lesser wound injury, by the introduction of the endovenous stripping by Babcock [4], which allowed a complete excision of the GSV from the ankle to the groin. Later on, Homans [5] described the ligation of GSV on a higher level close to the saphenofemoral junction (SFJ). Additionally, to GSV excision, phlebectomies with large incisions in the area of varicosities became the gold standard. Later on, a few refinements of the procedure were presented. The invagination stripping claimed to reduce the perivenous bleeding during GSV excision. In 1966 Muller [6] described the stab or hook or mini-phlebectomies through tiny skin incisions using specially designed hooks and forceps that offered better cosmetic results. This allowed the ambulatory phlebectomies done under local anesthesia in an office-based setting. In the twenty-first century, new less invasive techniques have been introduced leading to thermal or nonthermal ablation of the GSV, aiming to minimize the operative trauma and permit an almost instant mobilization of the patient with minimal cosmetic defects. Although the current guidelines propose the ablation techniques as the first treatment option of the superficial vein incompetence, open techniques remain an excellent solution, their proper use offering great and long-standing results.

Pathophysiology

The development of varicose veins is historically based on the descending theory. According to the descending theory, reflux begins at the saphenous junctions and progresses downward through the saphenous axes leading to venous hypertension and subsequently wall dilation and dilation of tributaries which become varicose veins [7]. Various studies have shown various anatomical defects in patients with varicose veins such as lower number of valves or alterations in structure of valves [8]. Nevertheless, various publications challenge the descending theory, mainly based on duplex and clinical data suggesting the concept of ascending or multifocal evolution of varicose veins. According to this concept, progression of the disease begins in subcuticular veins, outside the saphenous compartment, creating a dilated and refluxing venous network. When this network becomes large enough, it creates a filling effect in the saphenous vein, leading to decompensation of the saphenous vein wall, moving on to reflux of the saphenofemoral or saphenopopliteal junction [7].

Based on the different pathophysiologic approaches, two different treatment philosophies exist. Based on the descending theory, the high ligation (HL) usually with main vein stripping, followed by phlebectomies, is suggested. Based on the ascending pathophysiologic concept, saphenous sparing techniques such as the ambulatory selective varices ablation under local anesthesia (ASVAL) method and the Cure conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire (CHIVA) method have been proposed.

Indications

Varicose vein surgery using either endovenous or open techniques is indicated in the following situations:

1. Symptomatic venous insufficiency (leg pain associated with varicosities, leg pain and heaviness after prolonged standing, leg edema)
2. Complications related to varicose vein disease (lipodermatosclerosis, leg ulceration of venous etiology, superficial thrombophlebitis, history of bleeding from the varicosities)
3. Cosmetic reasons

However, there are conditions that the endovenous techniques are contraindicated. In these cases open surgery has a primary role. These situations include:

1. The distance of the target vein (GSV, SSV) from the skin is less than 1 cm, or adheres closely to it, or it is not possible to create a 1 cm zone between the vein and the skin with

the tumescent anesthesia. In these cases, the risk of skin thermal injury during thermal ablation is increased.
2. Dilated or aneurysmal saphenous vein greater than 2.5 cm, as they may not ablate effectively increasing the risk of local thrombotic complications with the endovenous techniques.
3. Tortuosity of the GSV or partial occlusion of the GSV not allowing the advance of endovenous ablation catheter. In these cases, the rigid stripper can more easily pass through the occlusion, and in cases this is not possible, the ligation of the saphenofemoral junction and phlebectomies may be appropriate.
4. The presence of a large visible saphenous varix adjacent to the SFJ greater than 2 cm in diameter. Such a saphenous vein cannot be treated by endovenous ablation as the technique spares the proximal 2 cm of GSV distal to the SFJ.
5. Acute thrombosis of the target vein, which increases the risk of thromboembolic events during the retrograde passage of the endovenous catheter. Additionally, thrombus reduces the effect of the endovenous ablation procedure.
6. Economic reasons related to the use of the disposable endovenous ablation systems.

Pitfalls and Danger Points

1. *Recurrence*. The most common reason for recurrence is an incomplete ligation of the GSV. To avoid this a complete dissection of the common femoral vein adjacent to the saphenofemoral junction is necessary. Apart from the branches directly from the GSV, all branches found from the CFV close to the GSV junction should be ligated. It is worth noting that there are reports in the literature supporting that overdissection of the groin region may result in neovascularization and thus recurrence [9]. Finally, inadequate preoperative duplex evaluation may not identify segments that contribute to venous reflux or the presence of a duplicate GSV that could be responsible for residual or recurrent varicosities.
2. *Nerve injuries*. Surgery of the superficial venous system may be complicated and this must always be kept in mind. The saphenous nerve accompanies the GSV along its way on the calf, and there is always risk of injury during stripping, especially when it involves the total length of GSV from the ankle to the groin [10]. Injury of the saphenous vein leads to sensory deficit to the medial lower leg and foot. Saphenous nerve injury may be prevented avoiding stripping the portion of the GSV at the calf region. Additionally, invagination stripping, as well stripping at a caudal direction from the groin to the calf, may decrease risk [10]. The sural nerve, respectively, is in low anatomic relation to the short saphenous vein. Careful dissection in the popliteal fossa and avoidance of stripping SSV to the ankle level may reduce the possibility of injuring. During the saphenopopliteal junction dissection in the popliteal fossa, several motor nerves may arise or course through, thus been susceptible to injury. These include the tibial nerve, the common peroneal nerve, and occasionally a low-lying sciatic nerve. Surgical magnification during short saphenous vein surgery may assist the surgeon on the recognition of the various anatomic elements. Finally, there is risk of injury of the common peroneal nerve during stab vein avulsions, especially on the lateral area of the calf close to the head of the fibula. Surgeon should be very cautious when performing hook phlebectomies in this area as an injury of the nerve may cause the dreadful complication of foot drop.
3. *Arterial injury*. Ligation and stripping of the posterior tibial artery has been reported when it is mistaken for the great saphenous vein at the ankle.
4. *Venous injury*. Ligation of the common femoral vein may occur if it is mistaken for the great saphenous vein. To avoid this the surgeon should always recognize apart the great saphenous vein and the common femoral vein superiorly and inferiorly to the saphenofemoral junction. An increased risk of venous injury and hemorrhage exists during reoperation in the groin area for local recurrence. This can be avoided by using the lateral approach to the femoral vein and saphenofemoral junction. Meticulous technique and surgical magnification are necessary prerequisites for a safe procedure.

5. *Great saphenous vein stump*. Ligation and division of the great saphenous vein leaving a substantial blind stump may lead to thrombus formation with risk of deep vein thrombosis and pulmonary embolism. A stump less than 0.5 cm long is considered safe.
6. *Hematoma*, *extensive ecchymosis*, *and pain*. A diffuse ecchymosis and moderate hematomas are relatively common, especially on the route of the GSV and on the areas of phlebectomies. A piece of lidocaine- and epinephrine-soaked gauze attached to the vein stripper can be left in place temporarily to provide compression of avulsed tributary veins, absorb blood, and deliver epinephrine and anesthesia to the traumatized area. The gauze is then removed before wound closure. Invaginating, stripping, and compression bandaging may decrease their incidence. Special care must be given to the groin hematoma. A groin hematoma may be due to common femoral vein injury or slipping of ligatures but also to blood accumulating in the area from the saphenous canal after stripping. The latter may be avoided by closing the entrance to the canal in the groin with an absorbable suture just before the groin wound closure. In any case a low threshold for re-exploration must exist for quickly expanding groin hematomas.
7. *Calf compartment syndrome*. This rare complication may exist after a very tight rapping of the calf at the end of the procedure. Thus, patient's toe capillary refilling time and toe sensation and motion must be always assessed after the procedure.

Preoperative Duplex Ultrasound Scan

An ultrasound scan performed preoperatively either by the surgeon or by a technician in close communication to the surgeon is useful. The ultrasound scan is accomplished with proper marking of certain points of interest, which could be useful during the procedure. The benefits of the ultrasound scan are the following:

1. *Identification of the saphenofemoral or the saphenopopliteal junction*. This minimizes skin incisions and decreases the dissections during the procedure, improving the cosmetic result of the procedure.
2. *Recognition of various anatomic variations*. There are lots of variations in the lower limb's superficial vein anatomy. GSV normally lies between the superficial and the deep fascia (saphenous sheath) all the way down to the upper third of the knee where it is divided in two major branches, the great saphenous vein going straight down to the medial malleolus and the posterior arcuate branch (vein of Leonardo), which lies more posteriorly on the medial aspect of the cuff. Occasionally, the GSV can come to a superficial level close to the skin just after a short distance into the saphenous sheath. The GSV may also be duplicated [11].
3. *Identification of incompetent perforating veins*. This can facilitate their complete removal during the procedure, with a minimal skin incision.
4. *Identification of the source of reflux in cases of varicose veins recurrence*. This is especially useful when the source is from the common femoral vein. Whether the reflux is from the CFV or not is crucial as it regards the proper treatment needed. Reflux from the CFV needs surgical treatment with ligation usually through a lateral approach while recurrent VVs without CFV involvement may be treated with simple phlebectomies or other less invasive techniques such as foam sclerotherapy.

Nowadays, it is quite common to use a portable duplex ultrasound scan in the operating theater. It is a prerequisite in all types of thermal and nonthermal ablations, but it can be also used in open procedures. It can be used after phlebectomies for the identification of remnants of varicosities after the avulsions, achieving a better cosmetic result as well as reducing recurrent varicose veins.

Operative Procedure

Preoperative Vein Marking

Before the procedure it is necessary to skin mark the areas of varicosities as well as the points of the skin incisions. This is done with the patient on an upright position, using a permanent skin marker. There are various types of skin marking. We prefer marking the outline of the varicose veins, as well as the point of most emerging varicosities as the points of skin incisions (Fig. 7.1). To avoid any tattooing after skin incision, it is better not to make the skin incision exactly on the marked skin. To minimize the size of the groin incision, it is useful to also mark the point of saphenofemoral junction using the duplex scan, although SFJ is in a relatively stable anatomic location as opposed to the frequently varying location of the SPJ.

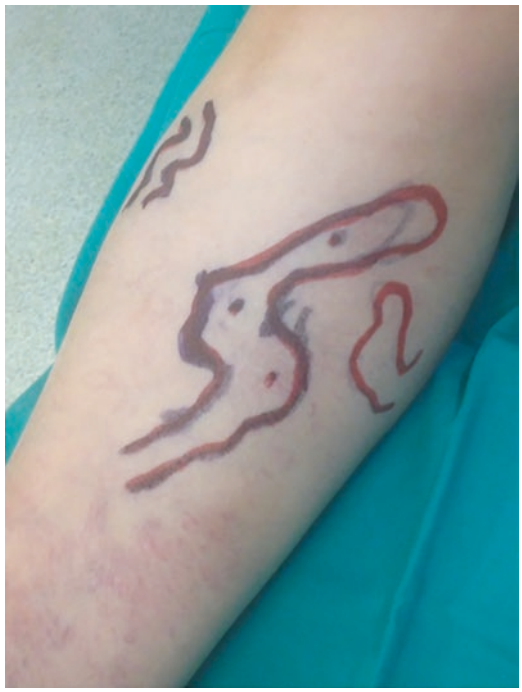


Fig. 7.1 Varicose vein preoperative skin marking: the outline of the varicose vein and the most emerging points are marked with a permanent skin marker

Great Saphenous Vein High Ligation

An oblique incision 3–4 cm long on the saphenofemoral crease is made, just above the saphenofemoral junction, as this has been defined with the preoperative ultrasound scan. If an ultrasound scan and a great saphenous vein marking have not been done before the procedure, the skin incision starts at the point of the femoral pulse and extends medially at a length of about 6–8 cm length. Using electrocautery, the subcutaneous tissue is divided. The superficial femoral fascia (saphenous fascia) is divided with the electrocautery as well. At this level a self-retainer retractor can be inserted across the skin incision under the fascial layers, and this usually reveals the great saphenous vein underneath, lying over the deep femoral fascia. Alternatively, a swab may be used to wipe away the adipose tissue from the great saphenous vein. Once the saphenous vein is identified, it is dissected free using forceps and scissors. A blunt grasp of the saphenous vein with the forceps facilitates its handling and dissection, minimizing the possibility of vein tear. Alternatively, two pairs of forceps can be used, one holding the vein and the other one grasping the surrounding tissues and pulling them away.

All the branches of the great saphenofemoral junction should be double ligated and divided, until the identification of the saphenous opening of the deep femoral fascia (fascia lata). Normally, there are six tributaries of the GSV close to its junction to the common femoral vein. However, this number may vary, and therefore it is necessary to dissect not only the GSV but the common femoral vein above and below the saphenous confluence. All the additional tributaries found directly from the common femoral vein should also be ligated. The common femoral vein can be clearly seen through the saphenous opening, and its course upward and downward underneath the fascia lata can be identified (Fig. 7.2). The recognition of the common femoral vein at the level of saphenofemoral junction "going up and going down" underneath the fascia lata should always precede the division of great saphenous

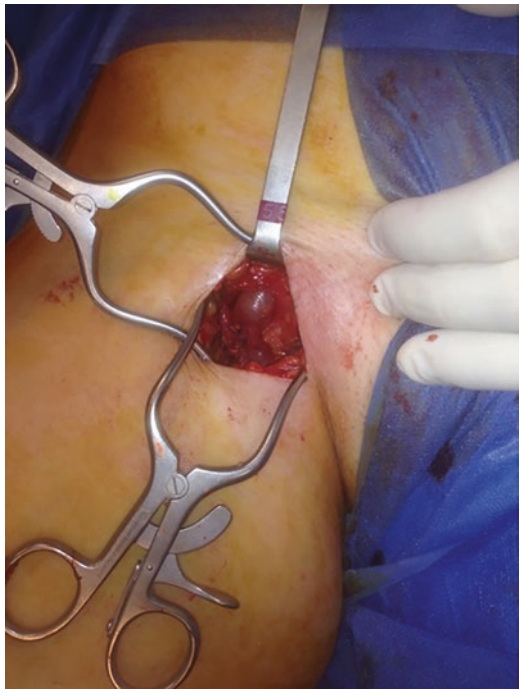


Fig. 7.2 SFJ dissection: note the common femoral vein is totally dissected and the GSV confluence is clearly seen

vein. This is a critical step during the procedure. It is possible, especially in thin patients where the subcutaneous tissue is minimal and when the saphenous junction lies on a lower level than the inguinal crease, to dissect straight the common femoral vein instead of the great saphenous vein. In this rare case, if the surgeon does not recognize correctly the anatomy, it can result in the catastrophic complication of dividing and stripping the femoral vein instead of the great saphenous vein. On the contrary, this will never happen if the three main venous components are identified: the common femoral vein "going up," the common femoral vein "going down," and the great saphenous vein "going anteriorly" above the fascia lata.

After the proper recognition of the great saphenous vein emerging from the common femoral vein, the surgeon may double clamp and divide the GSV. This can be done by inserting two vascular clamps, the first one at about 0.5 cm from the SFJ and the second one about 4 to 5 cm distally. The vein is divided with scissors, and the proximal stump of the GSV is ligated with a 2.0 silk suture. We use to double-ligate the saphenous vein stump with a suture ligature 3.0 silk. This is achieved with a simple maneuver: when the surgeon ties the first knot of the GSV stump, the assistant releases temporarily the vascular clip, moves it 2–3 mm proximally, and reattaches this on the vein. Then, the surgeon may set the transfixion stitch under the vascular clip but at the same time above the first knot of the 2.0 silk suture.

Before going on to the next step, the surgeon must give a final look at the saphenous stump and around the CFV nearby. First, he/she must check whether the stitches are securely set on the GSV stump. Second, an inspection on both sides of the common femoral vein must be done laterally and medially. As explained previously, if any small branch directly from the common femoral vein is identified, it should be double-tied and divided. This is necessary when the branch is found on the medial side of the CFV as this can be a remaining branch of the SFJ, and this could be a reason for an early recurrence.

If only ligation of the SFJ and not stripping of the GSV is planned, the dissection should be extended caudally for about 10 cm to ensure division of any hidden tributaries, as lateral and medial accessory saphenous veins may enter the main saphenous trunk at a varying distance from the confluence.

GSV Stripping

The distal end of the divided GSV is grasped with two mosquito clips (Fig. 7.3) and the stripper is inserted. We prefer using a metallic Oesch® pin stripper although a plastic stripper can be used as well. Occasionally there is some difficulty in advancing the stripper due to the existing venous valves of the GSV, but with slight massaging on the skin over the stripper, the surgeon can assist the stripper go through the valves all the way down the GSV to the upper third of the calf. We usually avoid to get the stripper lower close to the ankle level for various reasons. First, the part of the GSV on the calf is usually competent; thus,

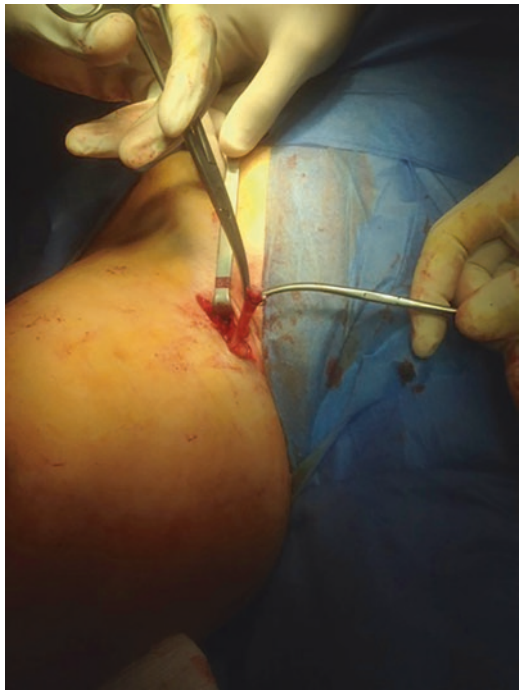


Fig. 7.3 After GSV division, its distal part is grasped with two pairs of hemostatic clips, ready to accommodate the stripper

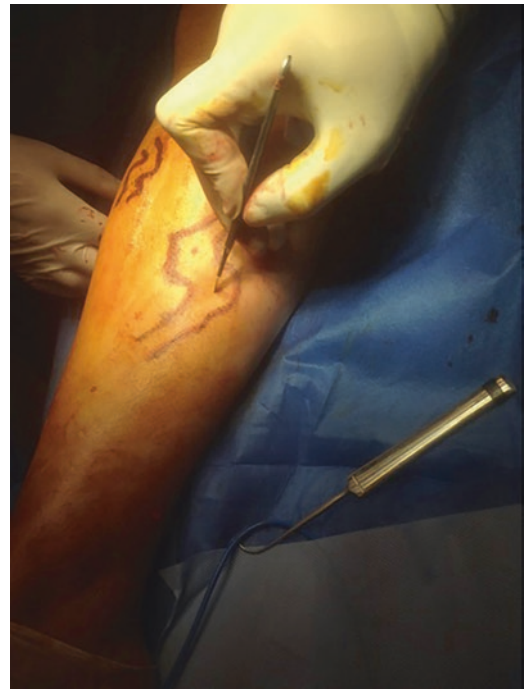


Fig. 7.4 Using a 11-blade a stab is made on the most emerging point of varicosities as it has been identified preoperatively. Note the longitudinal direction of the skin incision. On the right one can see an Oesch® phlebectomy hook instrument

there is no need to remove it. In cases where the GSV is incompetent all way down to the ankle level, this part of the GSV can be stripped-out as well. Second, the saphenous nerve is in close relation to this part of the GSV, thus a stripping of this part of the vein could result in saphenous nerve injury, causing permanent sensory disturbances on the patient's medial part of the foot. Last but not least, the various perforating veins in the calf do not emerge from the GSV but instead from the vein of Leonardo; thus, a removal of this part of GSV would not offer the benefit of perforating veins removal (Fig. 7.4).

At the upper part of the calf, the stripper is taken out after a stab of the skin just above the end of the stripper. In case where a metallic stripper like the Oesch® pin stripper is used [12], the exit point of the stripper is clearly identified with a slight push of the stripper. In case where a plastic stripper is used, its end is palpated with the fingers and a stab is done just above it. Using a mosquito clip, the end of the stripper is grasped usually together with the vein and pulled out of the skin. After the tip of the stripper is outside the skin, it is grabbed with heavy hemostatic forceps. Its proximal part in the groin is secured on the GSV with a heavy tie which is left as long as the length from the groin to the exit site of the stripper on the upper calf. Then, the stripper is pulled out distally. We prefer performing an eversion stripping as this can minimize the damage of the surrounding tissues of the vein, thus reducing the postoperative bleeding inside the saphenous canal. In case where the GSV is torn during stripping and there is a doubt whether it has been totally removed or not, a second stripper is tied on the long remnant of the heavy suture and passed again through the saphenous canal to the same exit point. In this case, we prefer performing a classic stripping using the suitable stripper head, avoiding another eversion stripping. After the GSV has been removed, the assistant pressures

the area of GSV canal using big surgical pads for about 5 min, to reduce any post-stripping intracanal hemorrhage.

Phlebectomies

Stab phlebectomies follow stripping. Using an 11-blade or even a 14G needle, small incisions are done at the more emerging points of varicosities. For better cosmetic results, the directions of the skin incisions must follow the Langer's lines (Fig. 7.4). Generally, the incisions should be longitudinal everywhere except the areas around joints, such as the knee or ankle, where they would better be transverse. Through the incision, a suitable vein hook is inserted and the vein is hooked (Fig. 7.5). To hook the vein, the surgeon performs a slight semicircular or circular motion; this varies depending on the specific instrument used. Special care should be taken to avoid hooking other elements than veins, such as muscle fibers, adipose tissues or more serious elements like nerves and arteries. After the vein is hooked,

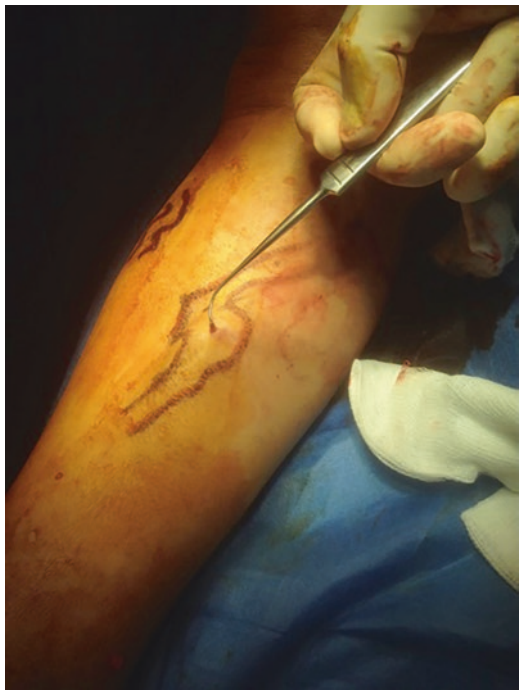


Fig. 7.5 Using a specially designed vein hook, the vein is pulled through the tiny skin incision

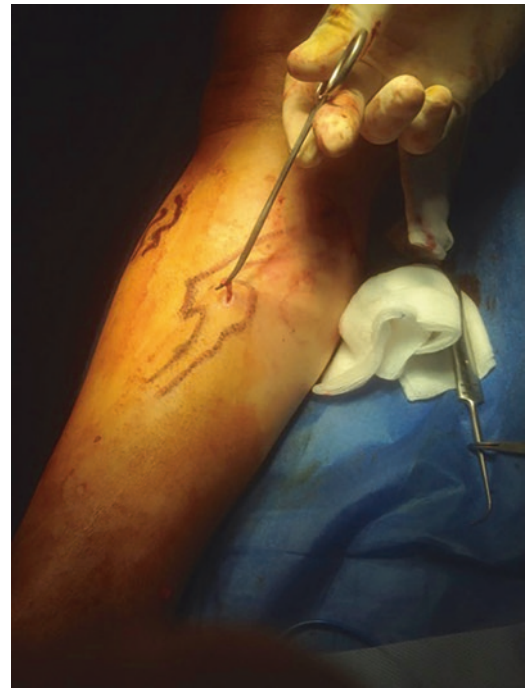


Fig. 7.6 Using hemostatic clips the varicose vein is avulsed away from the skin

it is pulled out of the skin with slight small pendulum motions. When a part of the vein has been pulled out of the skin, it is grasped with a pair of forceps, and using subsequent forceps, the vein is pulled out of the skin as much as possible (Fig. 7.6). Finally, the vein either is totally removed or more often is torn with a part of it remaining in the leg. Obviously, it is the best to remove as many veins as possible and avoid leaving even small remnants. However, if the main tract has been removed, then usually, the remaining part is thrombosed and generally becomes invisible after the procedure. If there is continuous bleeding from the stab avulsion site after vein removal, then a slight local pressure for a couple of minutes will eliminate it. In case of persistent hemorrhage, a further exploration of the wound for remaining large venous branches using a hook is necessary. Perforating veins are removed using the same techniques. However, due to their connection with the deep vein system, persistent bleeding after vein removal may be noted. This is treated with local digital pressure for some minutes. Special attention must be paid on the

areas of possible damage of underlying anatomic elements. Mainly these are the area around the head of the fibula, on the upper lateral calf, where there is danger of damaging the deep peroneal nerve, a complication that can be devastating as it can lead patient to a drop foot. Similarly, care should be given on avulsions around the ankle area, where there is danger of damaging the posterior tibial artery (medially), the dorsalis pedis artery (dorsal area of the foot), or the sural nerve (laterally).

Closure

After saphenectomy and phlebectomies, the skin is closed. There are two types of wounds: the small phlebectomy wounds and the larger groin crossectomy wound. Generally, the skin incisions for the phlebectomies do not require formal suture closure. Just using adhesive tapes like Steri-Strips of ¼″ or ½″ wide is sufficient (Fig. 7.7). The larger groin wound needs formal closure in two layers, first layer consisting of the superficial fascia with isolated 2.0 Vicryl sutures and the second layer consisting of the skin, either isolated skin stitches or usually with an absorbable continuous subcutaneous suture Vicryl 3.0. Before closing the superficial fascia, we prefer closing the opening of the saphenous canal, from within the wound using an absorbable 2.0 suture. This way we minimize the possibility of groin hematoma from any blood and clots coming to the groin from the saphenous canal, after the saphenectomy. After the skin is closed, the whole leg is cleaned and covered with either an elastic stocking up to the groin or wrapped by elastic bandaging to the same level starting from the foot. The elastic support of the leg is continuous for 2–3 weeks, the first week on a 24-h basis, and then only during the standing hours.

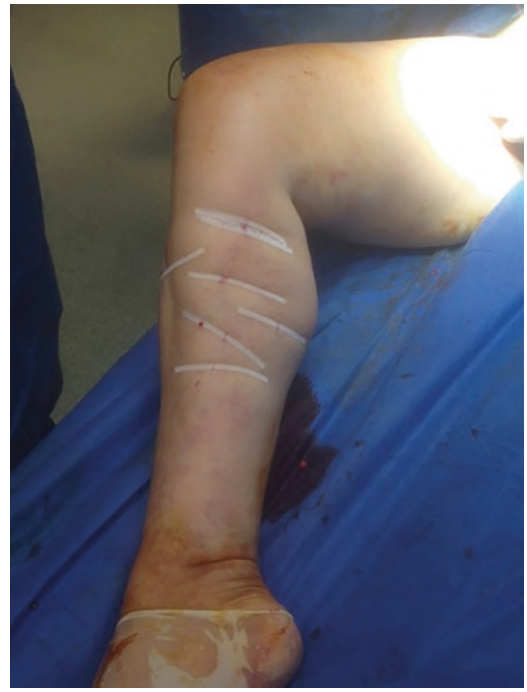


Fig. 7.7 No skin sutures are necessary. Skin adhesive tapes of ¼″ or ½″ wide can achieve a cosmetically satisfying skin closure

Post-procedure Care

After the procedure and for the first 3–6 h after the procedure, the patient is checked for three possible complications: bleeding from either the groin or the phlebectomy sites, impaired perfusion of the foot, and altered sensation of the foot. When the bleeding exists on the areas of the skin avulsion, the limb can be wrapped with an elastic bandage, and the patient remains with the limbs elevated on 30–45° for 2–3 h. In case of bleeding from the groin, this can be treated with local pressure. However, due to a potential risk of any damage on the femoral vein, a low threshold for groin re-exploration may exist, especially in case of persisting hemorrhage or an expanding hematoma despite local pressure. Impaired perfusion or altered sensation of the foot may exist from severe wrapping of the leg with elastic bandaging. This can be treated with loosing of bandaging.

Generally, the patient is asked to mobilize as soon as possible and definitely within the day of the procedure. Most of the times, the procedure is performed as outpatient, and the patient can be discharged home a few hours after the procedure. After the procedure, our practice is to prescribe a low-dose aspirin for 5 days, until the patient is

considered as fully mobilized. Any removable stitches are removed 1 week after the procedure. The patients are instructed that bruises will remain for around 3 weeks after the operation and advised to be as mobile as possible.

Lateral Approach of the Saphenofemoral Junction

Occasionally, when there is recurrence of varicose veins due to reflux from the common femoral vein or from an existing saphenofemoral junction, a re-exploration of the groin incision may be necessary. In these cases, an approach through the previous incision may be annoying and even troublesome, as the recurrent varicosities may be fragile, and severe bleeding from the common femoral vein may exist. In the cases where a new exploration of the saphenofemoral junction is necessary, a lateral approach to the common femoral vein can be used [13–15].

A duplex scan must be performed before the procedure to ensure the existence of a reflux from common femoral vein into a large vein branch or the saphenofemoral junction itself.

The incision is oblique, about 1–2 cm higher and parallel to the previous incision. This way, the scar tissue of the previous operation over the saphenofemoral junction can be avoided, thus minimizing the danger of a common femoral vein injury. The incision is carried out down to the external oblique muscle aponeurosis, the lower border of which forms the inguinal ligament. Just below the inguinal ligament, the common femoral artery can be palpated. The common femoral vein is dissected on its lateral border, and the common femoral vein is recognized and dissected free. By using a Farabeuf retractor and with careful sharp dissection, the common femoral vein is dissected downward until the saphenofemoral junction or the refluxing branch is visualized (Fig. 7.8). Careful dissection is followed around the branch which is double tied and divided. This maneuver must be done carefully and as precisely as possible to avoid injury on the femoral vein. If the femoral vein inadvertently gets injured, this can be

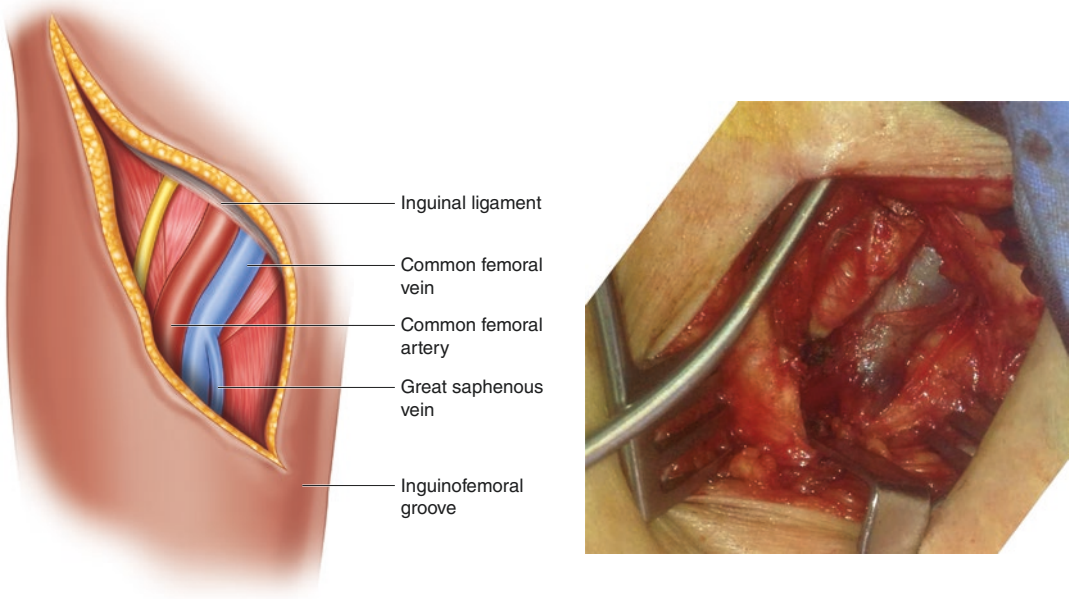


Fig. 7.8 Lateral approach to the common femoral vein. Through an oblique incision about 1 fingerbreadth above the inguinofemoral groove, the CFV and the GSV are found, medial to the common femoral artery, just below the inguinal ligament

repaired primarily with a 5.0 prolene suture. Following the ligation of the large femoral branch, phlebectomies of any varicose veins are performed with the described technique of stab avulsions. The femoral wound is closed in two layers (subcutaneous and the skin). Occasionally a relatively extensive dissection is necessary during this procedure, which can result in injury of lymphatic vessels. As a consequence, a varying degree of lymphedema can be observed after the procedure in about 30% of the patients, a complication that must have been explained to the patient in advance. A class II knee stocking (22–25 mm Hg) for at least 3 months may be used to reduce the edema. Alternatively, to the oblique incision, a longitudinal incision along the course of the femoral artery can be done, but the cosmetic result lacks this of the oblique incision. Following the skin incision, the femoral vein is dissected free, and the saphenofemoral junction or any other refluxing branch is identified and ligated.

Small Saphenous Vein Incompetence

When incompetence of the small saphenous vein is responsible for the varicose vein, a saphenopopliteal disconnection is necessary. A duplex scan is always necessary before the procedure as there is significant variation at the level of the junction in the popliteal fossa. Duplex scan can identify precisely the location of the SPJ, which must be marked on the skin with permanent dye. The course of the small saphenous vein is close in relation with the sural nerve which must be always identified and preserved. Also, deep vein branches from the soleus muscle may emerge from the short saphenous vein at a higher level than the femoropopliteal junction, as well as an existing saphenofemoral vein (Giacomini vein). These branches must be recognized and securely divided before the ligation of the saphenopopliteal junction.

Position

We prefer performing the procedure with the patient in a prone (face-down) position although a supine position can also be used.

Incision

A transverse incision is done at about 2 fingerbreadths below the saphenopopliteal junction as this has been defined using the preoperative duplex scan. The superficial fascia is incised, and the short saphenous vein is identified. The vein is carefully dissected from the surrounding tissues ensuring that the sural nerve which adheres to the vein is not injured. The vein is divided between two hemostatic clips. The proximal stump of the small saphenous vein is carefully dissected using Metzenbaum scissors and a pair of forceps down to the saphenopopliteal junction. All the vein branches are divided after proximal and distal ligation. The gastrocnemial veins and the Giacomini vein, if present, are similarly divided. The popliteal vein should be recognized inside the popliteal fossa, and the small saphenous vein should be doubly ligated at a distance of about 0.5 cm from the junction.

It is not necessary to strip the small saphenous vein at its total length. A full stripping puts in danger the sural nerve especially at the area of the lateral ankle. Alternatively, we prefer to excise a long segment of the small saphenous vein around 10 cm in length after it has been visually dissected away from the sural nerve. After the mobilization of the abovementioned length of the SSV, a deep stab incision is made at the level of distal mobilization and a closed hemostatic clip inserted from the point of stab incision toward the popliteal wound taking care to avoid the sural nerve. The proximal end of the divided end of the SSV is grasped and taken out from the stab wound. There the SSV is ligated and divided. This way, a long enough segment of the SSV is excised eliminating the risk of recanalization, and injury of

the sural nerve from blind stripping is avoided. The procedure is completed with phlebectomies of all varicosities using the stab avulsion technique described above.

Closure

Special care is taken to securely close the fascia, using an absorbable 2.0 suture. If the popliteal fascia is not sutured properly, a hernia in the popliteal fossa may develop later, leading to an annoying bulging on the area. Stab avulsions are usually closed using Steri-Strip adhesive tapes, while the popliteal wound skin is closed with a subcuticular suture. After the procedure, the patient is rotated in the supine position on a different operating table and the limb is wrapped with elastic bandages from the toes to knee. The patient is mobilized after recovery from anesthesia and can be discharged typically the same day.

Other Surgical Approaches

Ambulatory Selective Varices Ablation Under Local Anesthesia (ASVAL) Technique

The ASVAL method consists of phlebectomies with the preservation of the saphenous trunk. This method is based on the concept of ascending or multifocal evolution of varicose veins. An abolition of GSV reflux using this treatment concept has been described in 50% of patients that received ASVAL in a prospective study, with a significant reduction of GSV diameter and an improvement in quality of life [16].

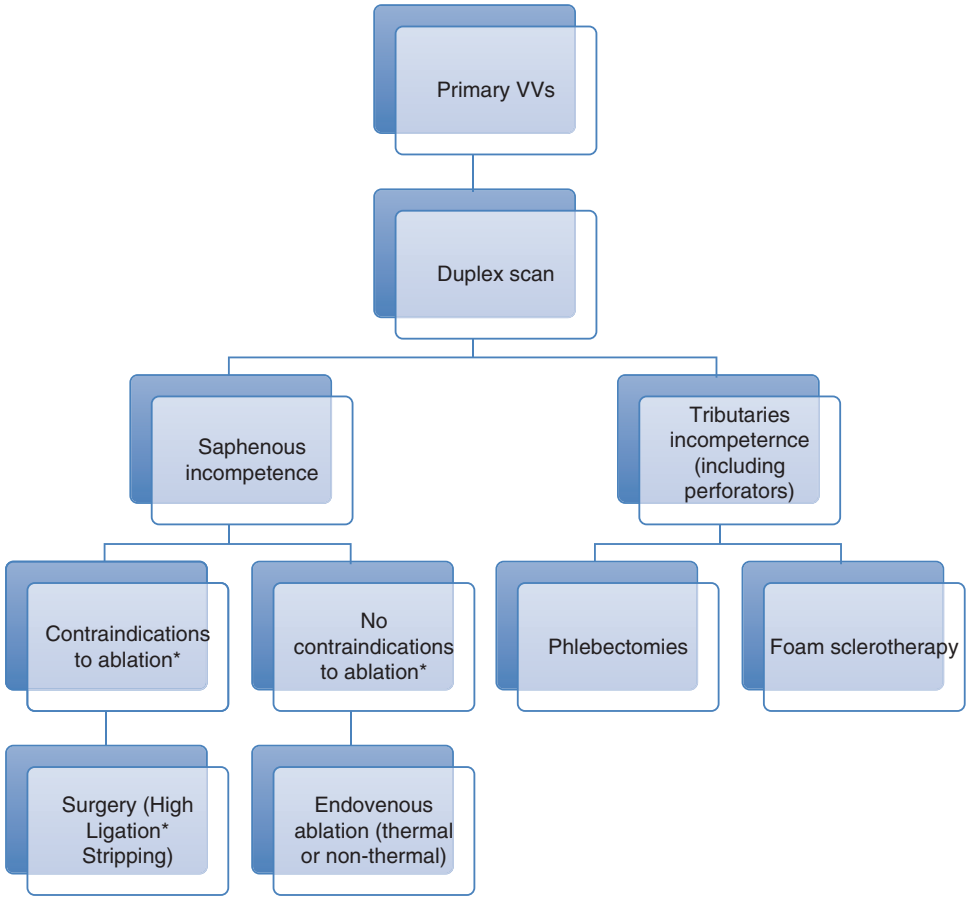
Cure Conservatrice et Hemodynamique de l'Insuffisance Veineuse en Ambulatoire (CHIVA)

CHIVA is a surgical technique that aims to improve hemodynamics of the superficial venous network by interrupting the column of hydrostatic venous pressure at strategic levels. The points of interruption are located on a precise preoperative vein duplex evaluation and involve either the main venous trunk or its tributaries. The procedure is supposed to achieve finally a well-drained superficial venous system with high flow and low pressure [17].

Role of Open Procedures in the Endovenous Era: Treatment Algorithm

The incorporation of the various endovenous techniques in the treatment of the superficial vein incompetence has limited the space for the open techniques. According to the Clinical Practice Guidelines of the European Society of Vascular Surgery, the thermal ablation techniques primarily (laser, radiofrequency) and the nonthermal ablation techniques secondarily (foam sclerotherapy; mechanochemical ablation, MOCA; and cyanoacrylate glue ablation) have been proposed as the main treatment options [7]. Nevertheless, open surgical procedures (high ligation with or without stripping and phlebectomies) still remain an equal alternative. It is worthy of note that a recent review from the Cochrane Database [18] which includes 13 trials and 3081 randomized patients emphasized that foam sclerotherapy, radiofrequency ablation, and endovenous laser ablation are at least as effective as surgery in treatment of great saphenous vein incompetence. Based on published data, the surgical option seems a consistent and logical approach, and this should be obvious as part of treatment guidelines [19]. Additionally, as described previously, there are specific situations where the ablation techniques cannot be used. In these cases, the standard surgical treatments remain a prudent alternative. Based on current guidelines, suggested treatment algorithms of the primary and recurrent superficial vein incompetence are presented in Figs. 7.9 and 7.10.

For the primary varicose vein disease (Fig. 7.9), the duplex scan will reveal whether



VVs: Varicose Veins

**** Contraindications to ablation:** A. Excessive tortuosity of the target vein (GSV or SSV) not allowing the passage of the catheter. B. Inability to create a layer of at least 1 cm between the target vein and the skin. C. Vein diameter > 2.5 cm. D. Acute target vein thrombosis. E. Economical reasons*

Fig. 7.9 Treatment algorithm of primary varicose vein disease

there is an axial (GSV or SSV) reflux together with reflux of the corresponding proximal junction or not. If axial reflux is confirmed, a closure or stripping of the main target vein (GSV or SSV) is mandatory, with the open techniques left for the cases when the ablation techniques are contraindicated. For the local varicosities, stab miniphlebectomies or sclerotherapy can be used alternatively.

The scope of traditional open surgery for the management of recurrent varicose veins has been significantly limited by the development of the endovenous techniques. However, in the unusual circumstances where the endovenous techniques are either unavailable or contraindicated, a reexploration of the groin with a modified technique through the lateral approach may be considered [20]. Such circumstances can be due to the occurrence of a large single lumen recurrent varicosity directly from the common femoral vein, or the presence of a large varix at the level of SFJ, and generally the situations where endovenous techniques cannot be used due to the significant risk of complications. As it regards the

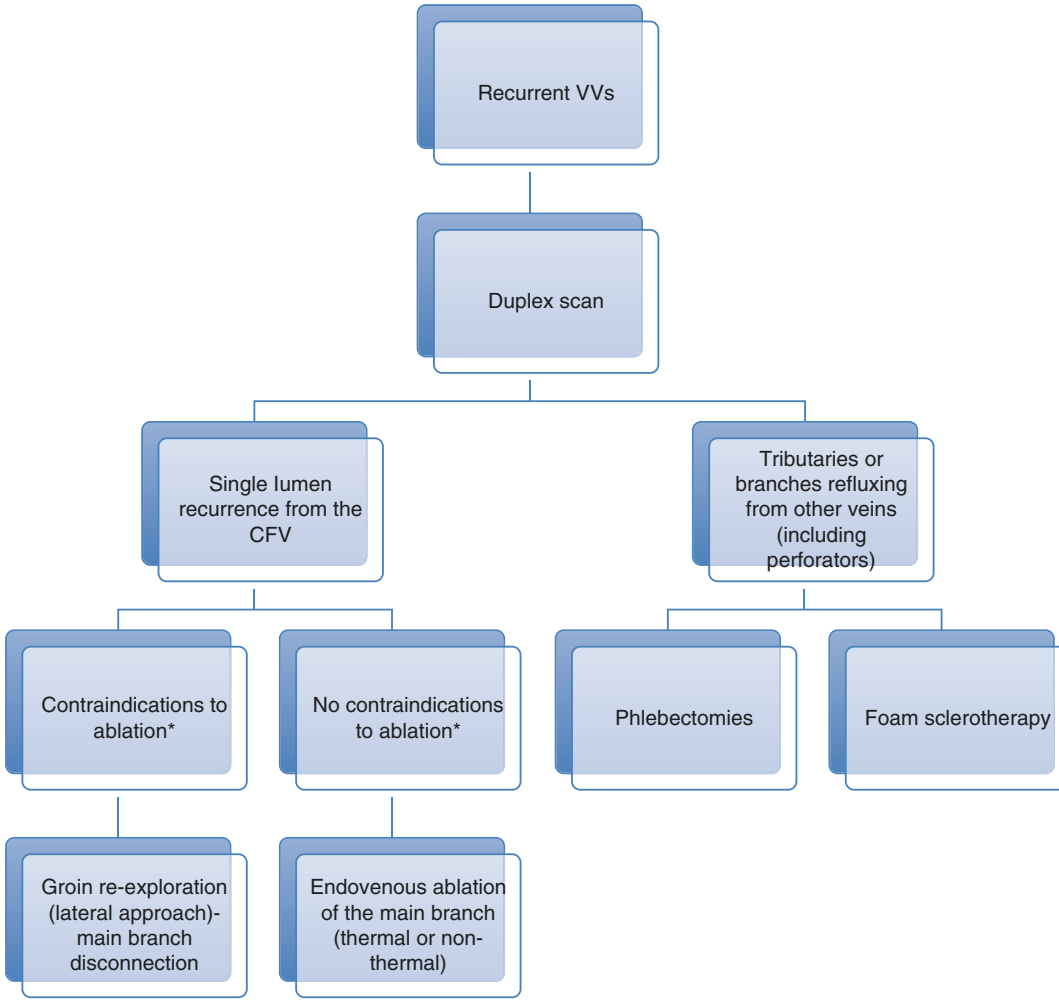


Fig. 7.10 Treatment algorithm of recurrent varicose vein disease

recurrent tributaries, recurrence from the popliteal vein or from perforator veins should be treated either with foam sclerotherapy or phlebectomies (Fig. 7.10).

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Laser Ablation for Venous Reflux

8

Mikel Sadek and Lowell S. Kabnick

Clinical Pearls

1. Water-specific laser wavelengths (1320, 1470, and 1510 nm) are better absorbed by the vein wall compared to hemoglobin-specific laser wavelengths (810, 940, 980, and 1064 nm) and allow treatment of the vein with lower energy.
2. The best outcomes are obtained with the 1470 nm laser with the use of a jacket-tip fiber.
3. The pullback rate for laser ablation should be 1 cm every 3–5 s which would equate to a range of 12–20 cm/min

Introduction

Endovenous laser ablation (EVLA) revolutionized the treatment of peripheral venous reflux. Prior to the use of EVLA, surgical treatment of the saphenous vein with the use of high ligation and stripping was considered the standard treatment for managing superficial truncal reflux [1]. This consisted of performing at least two incisions, the potential ligation and manipulation of junctional tributaries, the passage of a dilator, and the mechanical removal of the offending truncal vein. This often required general anesthesia and resulted in significant bleeding, bruising, and an extended post-procedural recovery. Although requiring minimal equipment, being widely available nationally and internationally, and exhibiting a long track record of safety and efficacy, open high ligation and saphenectomy have given ways to the endovenous treatments [2, 3]. Endothermal ablation has evolved into the standard of care when it comes to the treatment of symptomatic truncal reflux [4].

With regard to EVLA, the treatment was first approved by the US Food and Drug Administration in 2001. Thereafter, it has undergone a rapid rise in popularity bolstered by a track record of safety, efficacy, and durability. The transition to the ambulatory setting, with all of its attendant implications and consequences, has further bolstered the use of EVLA for the treatment of truncal reflux. Moreover, EVLA is a technology characterized by significant malleability, whereby successive device and procedural iterations have resulted in incremental improvements in treatment efficacy and patient outcomes [5, 6]. Some of the parameters that can be and have been modified include the power, linear endovenous energy density (LEED), wavelength, and fiber type.

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The following chapter will provide an overview of the EVLA procedure, the various parameters, their modifications, the theoretical and practical implications, and the data as they relate to clinical outcomes.

Mechanism of Action

Discussion of the mechanism of action is intimately related to the various evolutions in technique and technology, and therefore they will be introduced in this section and further elaborated in the subsequent sections. Initially, it was thought that as a thermal ablation technology, EVLA treatment success was predicated on direct contact between the laser fiber and the vein wall. This was found to be false, and in fact the wavelengths target specific chromophores. The shorter wavelengths target hemoglobin as the chromophore (hemoglobin-specific laser wavelengths), and the longer wavelengths target water as the chromophore (water-specific laser wavelengths); this has significant implications on the efficiency of treatment and the resulting symptomatology. Ultimately, the transmitted thermal energy results in endothelial injury and a subsequent thrombotic/fibrotic occlusion. Experimentally, this has been further corroborated by certain in vitro studies where thermal energy was not transmitted in saline or plasma as compared to being transmitted in hemolyzed blood [7]. When water is targeted as the chromophore, it results in a more efficient absorption of transmitted energy. Therefore, when water within the vein wall is targeted directly, theoretically, lower energy settings are required to effect the same degree of endothelial injury and venous ablation, and this may occur by a factor of 40 [6, 8].

Pre-procedural Planning

As with all procedures, the EVLA procedure begins with careful pre-procedural planning and preparation. With regard to planning, EVLA is versatile enough that it may be used to treat all variants of refluxing truncal veins (Table 8.1). Although this is reviewed elsewhere, the standard indication for treatment would be truncal reflux of greater than 0.5 s along with symptomatic chronic venous insufficiency. With regard to perforator ablation, this would have to be further accompanied by a refluxing perforator of greater than 3.5 mm in diameter, with greater than 0.5 s of reflux and with the pathologic vein being in the distribution of an active or healed ulceration [4].

Table 8.1 Pre-procedural planning

Veins amenable to EVLA
Great saphenous vein
Small saphenous vein
Anterior accessory saphenous vein
Anterior thigh circumflex
Posterior thigh circumflex
Intersaphenous vein
Perforators
Indications favoring EVLA
Large diameter veins (>10 mm)
Increased vein tortuosity
Recanalized veins following prior treatment
Recanalized veins following superficial vein thrombosis

EVLA Endovenous laser ablation

With regard to the theoretical advantages to the utilization of the EVLA modality specifically, it may be particularly useful for the treatment of larger refluxing veins, as well as tortuous refluxing veins, such as the anterior thigh circumflex, or veins that have recanalized, whereby the intraluminal lesions may increase the complexity of traversing the entire vein. Much of the versatility of EVLA may be attributed to the fact that EVLA utilizes a low-profile device in an over-the-wire procedure that may also be guided by ultrasound. Consequently, the ability to routinely traverse the vein first with the wire prior to advancing with the sheath/catheter system offers a distinct advantage as compared to radiofrequency ablation, for example. However, both modalities are indicated for all vein types, and the practice patterns and indications for these procedures are ultimately left to the discretion of the operator.

EVLA Procedure

As stated previously, success of the procedure is predicated on adequate patient preparation. To maintain maximum distension of the refluxing truncal vein, the patient should be well hydrated, warm, and relaxed. Certain environmental manipulations like keeping a warm procedure room, using warmed ultrasound gel, and administering a single dose of a relaxing agent such as a benzodiazepine (e.g., alprazolam) may help to mitigate against venospasm. The area of treatment may also be mapped with a surgical marking pen. The latter helps especially during the early phase of the learning curve when performing ultrasound-based procedures.

The nuances of treatment vary slightly depending on the target vein; however, the principles remain the same. The procedure begins with obtaining access. Local anesthetic may be administered, and using a micropuncture set with a 21-gauge needle, the great saphenous vein (GSV) or small saphenous vein (SSV), for example, may be accessed. With regard to the GSV, this is performed at or slightly below the knee area and typically central to where the vein becomes epifascial [6]. This prevents thermal skin injury and by not venturing too peripherally down the calf, this reduces the risk of nerve injury resulting in paresthesias in the saphenous nerve distribution. Similar precautions should be taken with treatment of the SSV and the potential injury that may occur to the sural nerve [9, 10]. Following intraluminal confirmation, the inner dilator and microwire are withdrawn, and a 0.035 inch wire is advanced to the saphenofemoral (SFJ) or saphenopopliteal junction (SPJ). The sheath is advanced over the wire to a point of 2 cm to greater than 2.5 cm from the respective deep venous junction [11]. After confirming and recording appropriate positioning using ultrasound, the dilator and wire are withdrawn, and the laser fiber is advanced to the same point. At this point, the laser fiber is connected to the generator, and the aiming beam is used to help localize the fiber's location subcutaneously. The sheath is withdrawn over the laser fiber and confirmed to remain at 2 cm or greater than 2.5 cm peripheral to the respective deep venous junction. The sheath and the laser fiber are connected using a Luer-lock mechanism. Given that EVLA is a form of endothermal ablation, tumescent anesthesia is administered perivenously with the goal of creating a diameter of fluid around the vein of approximately 10 mm [12, 13]. This helps to reduce the risks of thermal injury to the adjacent tissues resulting in skin burns, pigmentation, paresthesias, etc. Additional procedural modifications exist that may slightly alter the technical aspects of the procedure. Examples of procedural modifications include the utilization of a 0.018 inch system in order to eliminate the use of the original micropuncture catheter or the use of a short sheath while advancing the laser fiber to position in a "bare-back" fashion.

Once in position, the EVLA procedure may be performed. Following confirmation of laser positioning, the laser is switched to the ready mode, and the foot pedal is engaged. The laser fiber and sheath are withdrawn simultaneously, and the vein is treated up to 1–3 cm from the access site in order to minimize the risk for thermal injury to the skin. The supporting data is presented later in the chapter, but the average LEED that is utilized should range between 60–100 J/cm and 30–50 J/cm depending on the technology being used in order to maximize treatment efficacy while minimizing the procedural complications as they relate to thermal injury, such as pain bruising [6, 14]. Compression is not applied during the treatment in order to minimize post-procedural pain and bruising. Ultrasound is used to confirm successful ablation of the treated vein and the absence of an associated deep vein thrombosis.

Procedural Variables

There are many variables that can be adjusted in order to effect the desired outcome. Some procedural technique variables that can be manipulated include the pullback time, the power setting, and the linear endovenous energy density (LEED). Moreover, the laser catheter itself comes in varied iterations of fiber type and wavelength.

Laser Wavelength

The use of different laser wavelengths has evolved over time. The progression of technology has moved steadily along the wavelength spectrum. The initial lasers comprised the lower end of the wavelength spectrum (810, 940, 980, and 1064 nm), represented by the hemoglobin-specific laser wavelengths (HSLWs) [15] (Fig. 8.1). The name is derived from the target chromophore, which is hemoglobin. In vitro studies have demonstrated that as the hemoglobin within the red blood cell absorbs the energy from the laser, this results in a combination of heat and steam bubble formation [7]. Endothelial destruction ensues resulting in a thrombotic occlusion.

Of note, the mechanism of action does not require direct contact between laser fiber and the vein wall. With regard to the treatment itself, this has implications. Initially, the thought was that vein wall contact was necessary in order to effect a technically successful ablation. Therefore, direct pressure was applied during the procedure traditionally, and this resulted in increased pain and bruising. In vitro studies identified a direct correlation between fiber/vein wall contact, vein wall perforation, and pain and bruising [7]. As a result compression is no longer a part of the standard procedure. Moreover, pulsed energy lasers have fallen out of favor for similar reasons, given that the bursts of increased thermal injury may have resulted in increased vein wall perforations, manifested by increased pain and bruising. Therefore, continuous energy lasers are now used predominantly [12, 16, 17].

Progressing further with laser technology, longer wavelength lasers were found to have a greater affinity for water as the chromophore (1320, 1470, and 1510 nm) (Fig. 8.1). These are known as the water-specific laser wavelengths (WSLWs). Water, as compared to hemoglobin, functions more efficiently as a chromophore resulting in a 40-fold improvement in energy absorption when the comparison is made. The mechanism of action is thought to be more selective as compared to the HSLW, because water within the vein wall is targeted directly, resulting in direct damage to the intima [8]. Consequently, lower power settings are required in order to achieve the same effective LEED [6, 18, 19].

The data supporting the varying laser wavelengths have evolved over time, and the general progression has been from the lower wavelengths (HSLWs) to the higher wavelengths (WSLWs). As an example, one of the original randomized studies compared the 810 and 980 nm lasers, both

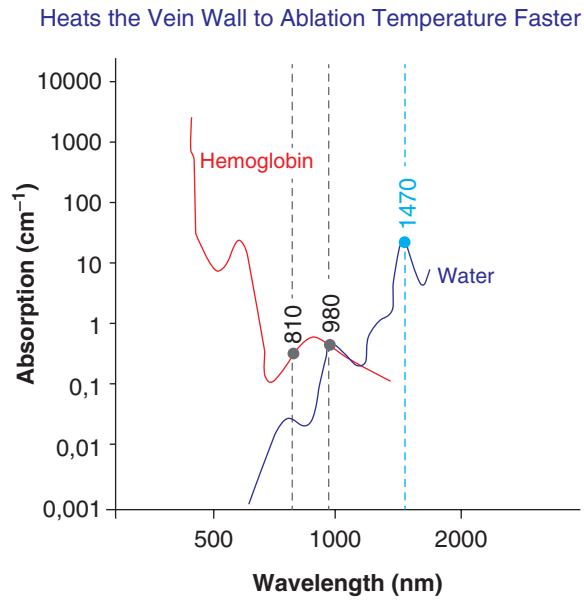

Fig. 8.1 Graph delineating laser wavelength (nm) versus absorption (Modified from http://venacure-evlt.com/endovenous-laser-vein-treatment/angiodynamics/products/laser/venacure-1470nm-laser/)

HSLWs, using the same LEED. Fifty-one patients underwent treatment, and technical success for the treatment did not differ between the two groups (one treatment failure per group); however, pain and bruising were less in the 980 nm group [6]. Continuing with the progression, longer wavelength lasers underwent pairwise comparisons. Proebstle et al. compared the 940 nm HSLW laser to the 1320 nm WSLW laser. Care was taken to maintain the same LEED across the comparison groups, approximately 60 J/cm for the 940 nm group (power = 30 W) and 60 J/cm for the 1320 nm group (power 8 W) [20]. Corroborating the increased specificity for the vein wall when using the WSLW laser, the amount of pain and bruising was less in the 1320 nm group while maintaining the same level of treatment efficacy. This relationship held true even when the same patient underwent treatment in one leg with the 810 nm HSLW laser while undergoing treatment in the other leg with the 1320 nm WSLW laser [15]. Use of the 1470 nm WSLW laser has also contributed to the trend of maintaining treatment efficacy while further decreasing post-procedural symptomatology. Shutze et al. evaluated the treatment of 1439 veins, where the 1470 nm laser was used in 295 procedures and the 810 nm laser was used in 1144 procedures [21]. Pain and bruising as well as quality of life scores were improved in the 1470 nm cohort. Moreover, the incidence of endothermal heat-induced thrombosis (EHIT) was diminished in the 1470 nm group as compared to the 810 nm group (2.4 vs 6.0%, $P = 0.0122$). In a three-way comparison of the 810, 980, and 1470 nm fibers, the pain and bruising scores improved progressively with each successive increase in wavelength while maintaining equal efficacy [22]. An in vitro adjunct was performed as part of the same study, and thermal injury depths were found to be less in the 1470 nm laser as compared to the 810 nm laser, which is consistent to the results that are identified clinically.

Fiber Tip

In addition to research being applied to laser wavelength in order to improve the specificity of treatment to the vein wall, mechanical factors have also been manipulated in order to enhance the specificity of treatment to the vein wall. This has been best exemplified by the modifications to the fiber tip. The original laser fibers were bare-tip fibers. Along with the original procedural methodology to apply manual compression to the site of treatment, the factors worked in concert to promote contact between the fiber tip and the vein wall. This resulted in an increased incidence of vein wall perforation and increased post-procedural pain and bruising [7]. Consequently, jacket-tip fibers were developed, and they come in various iterations, including ceramic and metallic types. The jacket-tip functions to act as a mechanical barrier preventing direct contact between the laser fiber and the vein wall, and some jacket-tip fibers are configured to reduce the energy density supplied by diverting and dispersing the laser energy. As a physical barrier, the metallic jacket tip results in a 0.010 inch physical barrier between the laser fiber and the vein wall. Moreover, the configuration of the jacket tip results in a 15° divergence of the emitted laser light, increasing the effective diameter of emitted energy from 600 to 905 μm [23] (Fig. 8.2). With regard to dispersing the laser-emitted energy and taking this concept to its fullest extent, a radial-emitting fiber was created that results in 360° dispersion by deflecting the laser energy orthogonally out of the side of the catheter [24].

The theoretical advantages behind the evolution in fiber-tip design have translated to improvements in clinical outcomes. One of the initial studies to evaluate fiber-tip design in a randomized fashion compared patients treated using a 980 nm laser using either a bare-tip or a jacket-tip fiber [23]. The LEED was normalized to 100 J/cm in both groups, and technical success was achieved in all treated patients. The pain scores improved significantly in the jacket-tip group as compared to the bare-tip group. The relationship was further evaluated using the 1470 nm WSLW laser. Three different kinds of fiber tips were compared, including a bare tip, jacket tip, and radial-emitting tip [24]. Once again, treatment efficacy was found to be equivalent between all groups. Pain scores improved successively when

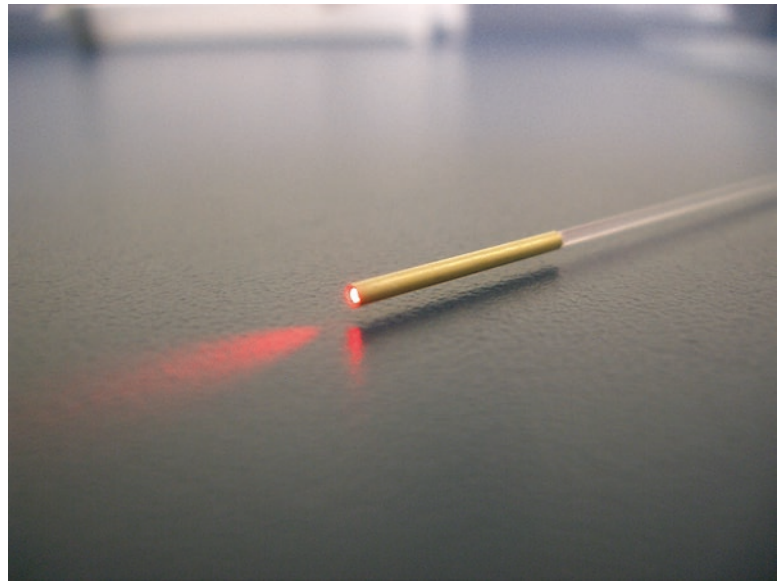

Fig. 8.2 Jacket-tip fiber as illustrated by the NeverTouch gold-tip laser fiber which results in an increased effective diameter of 905 μm as compared to the 600 μm of the standard bare-tip laser fiber (Reference: http://venacure-evlt.com/endovenous-laser-vein-treatment/angiodynamics/products/kits/nevertouch-procedure-kit/)

transitioning from the bare tip to the jacket tip and then to the radial-emitting tip.

More recently, investigators have attempted to tease out the variety of wavelength/fiber-tip combinations and their relative importance in affecting procedural outcomes [22]. The study was a combination of an in vitro as well as a clinical analysis comparing the 810, 980, and 1470 nm fibers using bare-tip or jacket-tip fibers. As alluded to previously, the pain and bruising scores improved in direct correlation with increasing wavelength, and this was corroborated by the in vitro data. When evaluating bare-tip versus jacket-tip fibers, the depth of thermal injury was worse in the bare-tip group as compared to the jacket-tip group in the 810 nm group (1.05 mm ± 0.34 mm vs 0.36 mm ± 0.26 mm; $P < 0.0005$) and in the 1470 nm group (0.71 mm ± 0.31 mm vs 0.20 mm ± 0.16 mm; $P < 0.0005$). Moreover, a multivariate analysis was performed to compare all variables. Both the in vitro data and the clinical data demonstrated that the fiber type was a more dominant variable, as compared to the laser wavelength, in improving outcomes. The results were additive, with the best outcomes obtained in the 1470 nm laser with the use of a jacket-tip fiber [22].

Technique Variables

Once the procedural equipment is in place, there are myriad procedural variables that can be manipulated to alter safety and efficacy outcomes. Moreover, the variables are often dependent on the type of laser being used, and this will be delineated further below. Briefly, the procedural variations are related to the pullback time and to the power settings, both of which interact to produce the linear endovenous energy density (LEED).

Initial modes of treatment were performed using a pulse mode, and over time this has evolved to a continuous mode due to decreased pain and bruising [12]. With further collective experience, the pullback rate increased from 3 mm/s to 1 cm every 3–5 s. The pullback rates in general would equate to a range of 12–20 cm/min. Furthermore, the accuracy and reproducibility of the pullback rate have improved over time; the original sheaths did not exhibit markers as compared to the newer sheaths that are available today, which exhibit distance markers. With regard to the technique, this has implications because the user performs a continuous pullback gauging the 1 cm markers on the cath-

eter relative to the amount of energy used, and this has been more accurate than gauging the timing of the pullback. This technique is also less dependent on the power setting, which can vary significantly based on the laser wavelength being used.

With regard to power settings, this has also been a variable with significant evolution in use over time. The general available range for treatment with regard to power is 1–15 W. Initially, the higher the power setting the better, and users advocated power settings in the 14–15 W range [12]. This has evolved to relative power settings depending on the diameter of the vein, low power settings, and all combinations thereof [6, 25]. In order to better standardize treatment and to maintain efficacy, normalization of the energy used per distance or the linear endovenous energy density (LEED) has supplanted to the use of an absolute power number [26]. The LEED is the standard measurement that is now used for reference given that it may be normalized across the broad range of available laser technologies and the respective techniques employed.

In order to establish the appropriate range for power and LEED settings, studies were performed initially to determine the appropriate range of parameters that would be efficacious. Proebstle et al. compared different power settings (15 vs 30 W) using a 980 nm laser. Based on the treatment algorithm, the average LEEDs were 18.4 and 68.5 J/cm, respectively. In the 15 W group with the correspondingly lower LEED, there were 11 treatment failures out of 114 GSVs treated, and there were no treatment failures out of 149 GSVs treated in the comparison group [27]. Pain and bruising did not differ between the groups. In order to corroborate the findings identified using HSLW lasers (e.g., 980 nm), similar studies have been performed using the WSLWs (e.g., 1470 nm). In one such early study, the power settings were quite high with both cohorts being 15 and 25 W, respectively [24]. This corresponded to an average LEED of 110 and 133 J/cm, respectively. As proof of principle, pain and bruising were high in both groups but were still lower in the 15 W cohort. There were no treatment failures in both groups.

In order to further coalesce the data to come up with more practical recommendations, there were observations made that suggested certain power/LEED settings were optimal for effecting proper treatment durability while also minimizing post-procedural pain and bruising. Additional data from Timperman et al. demonstrated that when using the 810 nm laser, treatments performed with a LEED > 80 J/cm proved to be more durable as compared to treatments performed with a LEED < 80 J/cm [26, 28]. Theivacumar et al. demonstrated that effective treatment was still possible with a LEED > 60 J/cm [13]. Once again, evaluation of the 1470 nm laser demonstrated treatment efficacy at a LEED > 100 J/cm; however, this came at the cost of increased pain, bruising, and paresthesias. Paresthesias did decrease significantly in patients treated with the 1470 nm laser using LEED < 100 J/cm [29]. The recommendation based on the data at the time was to perform treatments between the LEED parameters of 60 and 100 J/cm; therefore, this would mean varying the power setting based on the laser wavelength utilized and the corresponding efficiency in delivering energy to the vein wall. In general, this meant using lower power settings for longer wavelength lasers. This has since evolved further with the longer wavelength lasers such that lower power levels with decreased LEEDs have been found to be equally effective. For example, current data for the WSLW lasers is to treat with a target power of 5–7 W and a corresponding LEED of 30–50 J/cm [22, 30].

EVLA Complications

In evaluating the variety of procedural variables, some of the complications were alluded to. In general, the complications as they relate to EVLA are local in nature, and most complications exhibit some relationship to the thermal component of the procedure. The complication rates are very low in general, and systemic complications are exceedingly rare given the nature of the procedure. Some of the potential complications include bruising and hematoma formation, presumably secondary to vessel wall perforation.

Thrombotic complications such as endothermal heat-induced thrombosis (EHIT) or deep vein thrombosis (DVT) may also occur. More rare still is the development of a pulmonary embolus. Additional local complications include phlebitis, infection, pigmentation, and skin burns. Thermal injury to adjacent nerves may result in paresthesias and/or pain. Thermal injury may also induce injury to adjacent arteries resulting in arteriovenous fistula formation [31]. The tumescent solution itself may result in adverse reactions.

The initial experience by Min et al. demonstrated a relatively high rate of bruising, in patients treated using the 810 nm laser [12]; in 499 limbs treated, 24% of patients exhibited significant bruising. Interestingly, no other complications were noted. Kim and Paxton performed an evaluation of patients treated with the 980 nm laser, and the rate of ecchymosis was 27% [32]. Again, there were no reported cases of DVT or nerve injury. In general, the reports in the literature of other complications vary widely: superficial thrombophlebitis (0–25%), nerve injury (0–22%), EHIT or DVT (0–5.7%), and skin burns (<1%) [9, 10]. As alluded to previously, there is also the case reportable risk of arteriovenous fistula formation [31] (Fig. 8.3). This is a rare entity that may occur at the site where the external pudendal artery crosses deep to the GSV. Those that have been reported generally remain asymptomatic, and the natural history is still being elucidated.

Pain and ecchymosis remain the dominant "complications" associated with EVLA, and the exact mechanism remains unclear; however, it is thought to correlate with microperforations that occur along vein wall perforation secondary to transmural thermal injury [10, 20]. The previous sections described the evolution in laser wavelength and jacket-tip fibers. In summary, the WSLWs target water within the vein wall more specifically, allowing for lower power setting, and the diminished risk for excess transmission of thermal energy, theoretically resulting in transmural injury to the vein wall. Similarly, jacket-tip or radial-emitting fibers disperse the energy emanating from the laser tip and minimize direct contact between the laser fiber and the vein wall, thereby presumably reducing transmural injury to vein wall, which would

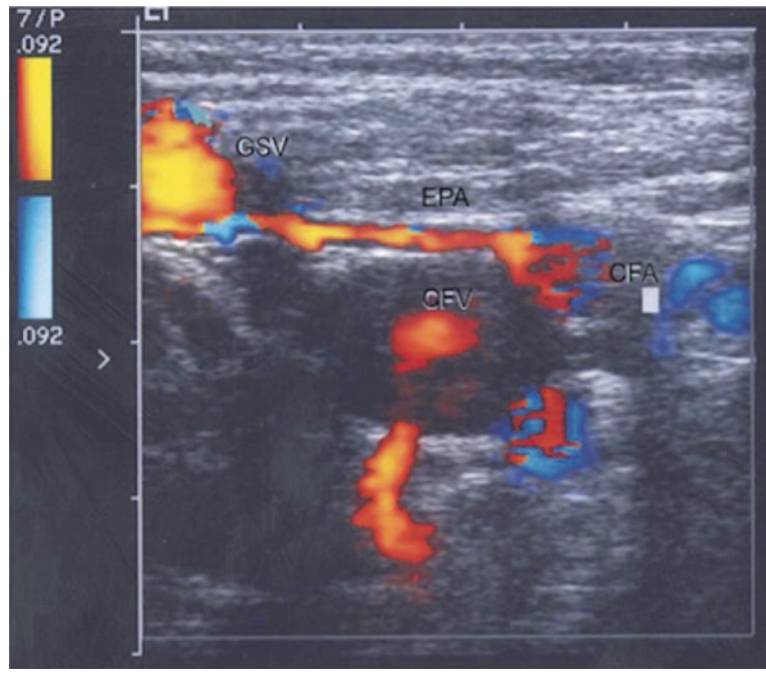

Fig. 8.3 Duplex ultrasound of arteriovenous fistula between the great saphenous vein (*GSV*) and the external pudendal artery (*EPA*). *CFA* Common femoral artery, *CFV* common femoral vein (Reference: Rudarakanchana N, Berland TL, Chasin C, Sadek M, Kabnick LS. Arteriovenous fistula after endovenous ablation for varicose veins. J Vasc Surg. 2012;55(5):1492–1494)

result clinically in increased pain and bruising. The data continue to be gathered, but one study that attempted to tease out the relative impact of these laser wavelengths versus fiber-type variables demonstrated fiber type played a more dominant role clinically in reducing pain and bruising as compared to laser wavelength. These results were corroborated in vitro, whereby tissue thermal injury depth was reduced as wavelength increased, and with the use of jacket-tip fibers, with more dominating factor being the presence of a jacket-tip fiber [30].

Endothermal Heat-Induced Thrombosis (EHIT)

Endothermal heat-induced thrombosis (EHIT) is a unique complication that bears special attention when it comes to any discussion of endothermal ablation including EVLA. Essentially, it refers to the central propagation of thrombus into the respective deep venous junction—the common femoral vein in the setting of the GSV and the popliteal vein in the setting of the SSV. The pathophysiology is thought to relate to the underlying endothelial injury with the associated stagnation of the flow at the level of the saphenofemoral or saphenopopliteal junction. The degree of central propagation may have implications with regard to prognosis and treatment, and therefore, a classification scheme was developed (Table 8.2) [33].

In the early literature of endothermal ablation, the incidence of any associated DVT was as high as 16% [34]. This did not pertain specifically to EVLA, and once the entity was defined more clearly and certain procedural methodologies were clarified (i.e., ablation distance to be started at least 2 cm from the saphenofemoral junction), then the incidence of EHIT remained improved over the collective subsequent literature. For example, a combined review of EVLA and radiofrequency ablation (RFA) demonstrated an EHIT rate of 4.0% [35]. In an additional combined evaluation of RFA and EVLA, it was also determined that increasing the ablation distance from 2 to 2.5 cm or more from the respective deep vein junction further diminished the rate of EHIT from 2.3% to 1.3% [11].

The risk factors that may predispose to EHIT formation include large vein diameter, obesity, male gender, and the severity of the underlying chronic venous insufficiency [36, 37]. Given that large vein diameters and more challenging anatomy may be more amenable to EVLA, nonrandomized data has at times demonstrated a possible increased incidence of EHIT in EVLA as compared to RFA; however, selection bias may have been at play. For example, one series on univariate analysis showed an increased incidence of EHIT in patients treated with EVLA; however, these patients were found to have a higher Caprini score, indicative of increased disease severity, and on multivariate analysis, EVLA did not appear to contribute significantly to the development of an EHIT [36].

Ultimately, the presence of an EHIT 2 or greater may warrant careful observation and/or treatment. Given the low incidence of the entity, there has been no prospective evaluation regarding the treatment of EHIT with anticoagulation. The majority of treatment recommendations are based on expert opinion, on practitioner preference, and on the apparent natural history that the majority of EHITs will resolve fully in 1–2 week's time, when followed by surveillance duplex [37]. There is also a loose association to the treatment of DVT in general. One treatment recommendation set forth has been to treat EHIT1 as a benign entity that does not warrant further treatment, to treat EHIT 4 as an occlusive DVT that warrants the standard treatment for

Table 8.2 Endothermal heat-induced thrombosis (EHIT) classification

EHIT classification	Description
I	Up to and including the deep vein junction
II	Propagation into the deep vein but <50% of the lumen
III	Propagation into the deep vein but >50% of the lumen
IV	Occlusion of the adjacent deep vein

EHIT Endothermal heat-induced thrombosis

DVT, and to find a middle road for patients who develop EHIT 2–3 [11]. The "middle-of-the-road" recommendation is to treat the entity of EHIT 2 or 3 with full anticoagulation while obtaining weekly duplexes, with treatment cessation upon resolution of the EHIT 2 or 3. This remains a matter of controversy given the overall benign nature of this condition and the cost-effectiveness of obtaining early duplexes just to be able to identify and EHIT.

EVLA Outcomes

The data supporting the safety and efficacy of EVLA have been outstanding, and this has been further supplemented by outstanding data on durability. The original trial by Min et al. demonstrated a 93.4% continued success rate at 2 years follow-up (59). This has been corroborated by additional trials, such as another evaluation of the 980 nm laser that demonstrated a 97.1% continued success rate at 4 years follow-up (65). The International Endovenous Laser Working Group evaluated the long-term outcomes of the treatment of great and small saphenous vein reflux [38]. Using the 980 nm bare-tip fiber, 1020 limbs were evaluated. Using Kaplan-Meier analysis, the failure rates by duplex were 7.7% at 1 year and 5.4% at 2 years and no further failure rates at 3 years, again illustrating the very high success rate even across multi-institutional evaluations.

In addition, data comparing EVLA, RFA foam sclerotherapy, and surgery have corroborated the excellent data supporting the use of EVLA. One meta-analysis of 12,320 patients across 64 studies demonstrated reasonable success rates across all modalities; however, RFA and EVLA were considerably more durable as compared to sclerotherapy at 36 months follow-up [9]. Consequently, RFA and EVLA were also found to be more cost-effective as compared to sclerotherapy, due to the decreased need for re-intervention. Rasmussen et al. performed the same evaluation; however, in a randomized controlled trial, 580 limbs were evaluated. EVLA was performed with both 980 and 1470 nm bare-tip lasers. Ultimately, procedural failure at 1 year was (RFA 4.8%, EVLA 5.8%, sclerotherapy 16.3%, and surgery 4.3%) [39]. Interestingly, all patients had improvements in the venous clinical severity score (VCSS) at the 1-year interval.

Conclusion

Long-term data for EVLA are still being accrued, and additional prospective evaluations will shed some light on how patients will fair 10, 15, and even 20 years post-procedure. This is especially critical given the broad age range of the patients being treated. As a result of the data laid out in this chapter and the adjudication thereof, EVLA and RFA are considered the preferred methods of treatment based on the evidence, and this is reflected in the American Venous Forum (AVF) societal guidelines for the treatment of chronic venous insufficiency [4].

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Radiofrequency Ablation for Lower Extremity Venous Reflux

9

John Blebea and Zhamak Khorgami

Abbreviations

CVI	Chronic venous insufficiency
DVT	Deep venous thrombosis
EHIT	Endovenous heat-induced thrombosis
EVLA	Endovenous laser ablation
GSV	Great saphenous vein
PAD	Peripheral arterial disease
PE	Pulmonary embolus
RFA	Radiofrequency ablation

Clinical Pearls

1. Keep the vein at least 1 cm away from the skin surface using tumescent infiltration.
2. In large veins, consider treating all segments with two cycles of RFA.
3. In tortuous veins, use a 0.025 in. guidewire to facilitate the catheter advancing through turns.
4. If catheter is not advancing beyond an area, place an additional access cephalad and treat the two parts of the vein separately.

Introduction

Lower extremity chronic venous insufficiency (CVI) remains a significant public health problem, estimated to affect more than 25 million adults in the United States [1, 2]. Indeed, up to 17% of adult men and 40% of women suffer from some degree of venous insufficiency. The estimated direct cost for treatment of CVI in the United States each year has been estimated to be up to $2.5 billion [3]. Surgical high ligation and stripping of the great saphenous vein (GSV) was the historical standard treatment for superficial reflux and insufficiency for patients who did not have alleviation of symptoms after medical management with compression therapy. This procedure entailed the ligation of the GSV and its multiple draining branches at its junction with the common femoral vein, along with its entire removal, most commonly from the groin all the way to the ankle. This surgical procedure usually required general anesthesia and was associated with 2–4 weeks recovery time during which patients typically could not go to work. During the past two decades, in association with advancements in ultrasound venous imaging, far

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less invasive treatments have been developed for the treatment of CVI which would attain the same physiologic effect as ligation and stripping without its significant morbidity. Until very recently, these have focused on procedures utilizing endoluminal thermal ablation to close the saphenous vein and thereby eliminate any possible reflux. The heat source was provided by either a laser or radiofrequency generator, but there were some differences in catheter or fiber energy delivery, sizes, and treatment techniques. Both modalities, although different in usage methodology, have demonstrated similar clinical efficacy and have largely replaced surgical ligation and stripping. In this chapter, we will review the RFA technique and its results and efficacy in comparison to other options.

Radiofrequency Ablation Therapy

Radiofrequency was first introduced in the early 1990s primarily for percutaneous tumor ablation, but its application has been expanded to other disciplines including ablation for cardiac dysrhythmia, denervation in low back pain, Barrett esophagus, and lower extremity chronic venous disease. It utilizes alternating electrical current which, when passing through body tissues, induces heating of the tissue due to its electrical resistance. The RFA device creates this current by making a closed-loop circuit beginning with the electrical generator, an electrode inserted into the vein (Fig. 9.1), a resistor (body tissues in the patient), and the grounding pads. Initiating the electrical current induces dipolar molecules (mostly water) next to the electrode to rapidly vibrate because of the changes in their alignment in the interchanging direction of the alternating current. The associated local energy deposition results in an increase in temperature of the surrounding blood or tissue. This heat is transmitted either indirectly to the luminal surface of the vein through the blood or by direct electrode contact [4]. The effects on the venous wall and nearby tissue depend cumulatively on the applied energy (electrical current), the induced elevation in temperature, and the duration of application (time). In general, irreversible cellular damage begins at a temperature of 45°C and proceeds to coagulation, tissue necrosis, vaporization, and carbonization at higher temperatures [4, 5]. In order to increase heating efficacy and decrease tissue charring, newer RFA devices have been developed with higher power generators and the ability to monitor the impedance (electrical resistance) and local sensor temperature during ablation. These devices can automatically adjust the power output to assure a consistent flow of current to the tissue and maintain a selected target temperature [5]. The present RFA generator produces a temperature of 120°C.

There is a single approved device for RFA of veins in the United States, the ClosureFast™ device (Medtronic; Minneapolis, MN). It utilizes a segmental ablation technique wherein the catheter has a 7 cm distal electrode (and shorter 3 cm electrode for shorter segments or tributaries) which is meant to touch the vein wall circumferentially. Because refluxing veins are much larger than the diameter of the catheter, such direct contact is induced through vasoconstriction of the vein by the surrounding tumescent anesthesia (which commonly includes epinephrine) as well as external pressure applied by the ultrasound probe at the site of the electrode. In this manner the catheter delivers direct controlled heat to the vein wall leading to destruction of the endothelium, collagen contraction and denaturation in the media, and ultimate fibrosis with near permanent vessel closure without coagulating nearby blood. ClosureFast™ was introduced for ablation of the saphenous veins (great, small, or accessory) as an alternative to surgical ligation and stripping. There is also a ClosureRFS™ stylet which is specifically intended for the treatment of incompetent perforator and tributary veins which works along the same principles.

Indications and Limitations

Radiofrequency ablation, like other interventional modalities for the treatment of chronic venous insufficiency of the lower extremities, is indicated in patients with symptomatic CVI. The

Fig. 9.1 The ClosureFast radiofrequency generator and attached 7 cm segmental ablation catheter. The data display shows the catheter temperature (120°C), treatment time (17 s), and power applied to maintain the temperature at 120°C (31 W)

Society for Vascular Surgery and the American Venous Forum have established clinical guidelines for treatment of patients with venous disease. In those with more severe diseases (C4b, lipodermatosclerosis of the skin; C5, healed ulcers; C6, open active ulceration), they have made several recommendations [6]. In such circumstances, ablation of incompetent superficial veins that have axial reflux directed to the bed of the ulcer or affected skin is recommended, in addition to standard compressive therapy, both to improve ulcer healing and prevent ulcer recurrence or occurrence (Guidelines 6.1–6.4). However, reflecting the relative paucity of prospective randomized trials, all of these recommendations are grade 2 (weak) with a level of evidence of C (weak) except in the case of C6 disease which carries a grade 1 (strong) recommendation based on a moderate (B) level of evidence. In patients with less severe disease, manifested primarily by symptomatic varicose veins (C2) or venous swelling (C3), other clinical guidelines by the Society for Vascular Surgery and the American Venous Forums have been published [4]. These conclude that endovenous thermal ablations (laser and radiofrequency) are safe and effective and recommend them for treatment of saphenous incompetence (Guideline 11.1). In addition, because of the reduced convalescence and less pain and morbidity, they recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery (Guideline 11.2). Both guidelines were strong recommendations (grade 1) with moderate level of evidence (B).

In clinical practice, persistent signs and symptoms of venous disease, after failure of compression medical management, is the usual indication for vein ablation. RFA is most commonly used for ablation of the great or small saphenous veins and, less frequently, anterior or posterior accessory saphenous veins. The use of RFA for perforator veins is approved but less common. Before intervention, a complete venous duplex ultrasound must be performed to document the presence and location of reflux in the respective vein. Abnormal reflux is considered to be retrograde flow of longer than 0.5 s, but most clinicians require the time to be greater than 1 s to be clinically significant [2]. Many symptomatic

patients have reflux times greater than 10 s. The refluxing vein needs to be large enough (usually diameter > 4 mm) to be easily cannulated with the RFA catheter. Extremely dilated veins (>20–25 mm) may be considered as a relative contraindication to RFA due to a higher risk of non-closure although successful RFA has been reported in veins as large as 2.5 cm with utilization of sufficient perivenous tumescent infiltration and focal compression [7, 8].

Pregnancy, superficial phlebitis, deep vein thrombosis, and peripheral arterial disease are relative contraindications to RFA. Treatment should probably be deferred to after pregnancy to prevent any potential complications of the procedure that may affect the outcome of the pregnancy and to ensure greater probability of vein closure when the venous hypertension and vein size is decreased. Prior superficial thrombophlebitis with a resulting partially obstructed saphenous vein may make catheter advancement difficult, while RFA in an acutely thrombosed vein can potentially extend the thrombosis. However, ablation of a proximal thrombus-free segment has been reported in patients with distal superficial vein thrombosis by avoiding passing the catheter through the thrombosed segment [9]. Patients with extensive deep venous occlusion should only selectively undergo superficial ablation because the superficial veins in these patients may be important for venous outflow [4]. No data exists regarding the use of RFA in patients with peripheral arterial disease (PAD). In patients with severe PAD, healing of wounds can be more problematic, and therefore management of the arterial disease should first be considered. Immobility, congenital venous abnormalities (e.g., Klippel-Trenaunay syndrome), and advanced systematic diseases that prevent significant improvement in quality of life are other considerations that should be taken into account before proceeding with RFA. Finally, the concomitant use of anticoagulants has not been found to lead either to greater major bleeding complications or lower rates of procedural success [10].

An additional important component before the procedure is appropriate patient counseling in order to explicitly address all of the patient's expectations. The patient should know about the expected results and possible technical failures such as non-closure and late secondary failure due to recanalization. The options for simultaneous or staged phlebectomy of varicose vein segments should be discussed and patients need to know that untreated varicosities may not completely disappear, other varicosities may later develop, and additional procedures such as phlebectomy or sclerotherapy may be needed in the future [11]. For patients with ulcers, it should be mentioned that ulcer healing will not be immediate and that ulcers may recur as they are not dependent solely on segmental reflux ablation. Potential complications of the procedure, particularly pain, ecchymosis, deep venous thrombosis, skin ulceration, and nerve injury, should be reviewed. Alternative treatments to RFA, including surgical removal, laser ablation, and sclerotherapy, should be discussed. Finally, the use of a detailed informed consent, such as that available from the American Venous Forum, is recommended [12].

Technique

A complete history and thorough physical examination is important, particularly if intravenous sedation is to be utilized and the procedure is performed in an office-based center where less assistance is available. Antiplatelet agents and nonsteroidal anti-inflammatory medications can be continued, but the patient should be informed that these may increase postoperative bruising and ecchymosis. In a similar manner, warfarin anticoagulation is not a contraindication for the procedure, and safe ablations have been reported with successful outcomes in anticoagulated patients without an increase in major bleeding events [9]. No specific guidelines have been established nor published with the use of the new oral direct thrombin or factor Xa inhibitors. However, both with warfarin and other anticoagulants, clinical judgment is employed in anticoagulant management. If the patient is considered to be at low risk of a thromboembolic event, we

generally hold warfarin for 2 days and low-molecular-weight heparin and the new oral anticoagulants for 24 h before the procedure. Deep vein thrombosis prophylaxis is generally not used for these usually quick procedures but employed selectively in high-risk patients who are not already on anticoagulation. Determination of high risk can be established with the use of the Caprini scoring system [13], but patients with a history of thrombophlebitis, DVT, and known thrombophilia are generally administered thromboprophylaxis with a single dose of low-molecular-weight heparin before the beginning of the procedure [14]. The usefulness of prophylactic antibiotics has not been studied except in the case of RFA combined with open ligation at the saphenofemoral junction [15]. Nonetheless, the institutionalization of the SCIP (Surgical Care Improvement Project) [16] checklist for prophylactic antibiotics for vascular procedures has resulted in most such patients routinely receiving a single dose of cefazolin antibiotic before vein ablation. Procedural management in both the preparation and treatment of the patient along with optimal documentation has been well outlined by the Intersocietal Accreditation Commission for Vein Centers [17].

Venous duplex ultrasonography is a critical part of not just the preoperative evaluation but the procedure itself. During the diagnostic evaluation of the patient, high-quality venous imaging by an experienced certified vascular sonographer, preferably in an accredited vascular laboratory, will have already examined the saphenous vein for anatomic anomalies such as duplication, areas of obstruction or stenosis from prior episodes of phlebitis, and irregular entry points into the deep venous system. Specific locations of reflux, and refluxing perforating veins that may account for segmental saphenous reflux, will have also been identified [8]. In our practice, on the day of intervention, the ultrasound examination is repeated to confirm reflux in the vein. In circumstances when associated stab phlebectomies are to be performed in association with the RFA, the ultrasound examination must be done before the procedure with the patient in the standing position. The primary purpose is to mark the varicosities that will be treated as these will no longer be as evident with the patient in a recumbent supine position (Fig. 9.2). In these patients, the great or small saphenous vein is also marked along its path as well as the optimal entry point of cannulation for the RFA catheter. Either preoperatively or intraoperatively, this ultrasound examination (preferably by the surgeon) confirms the previous diagnosis and provides visualization of the vein to be treated along with measurement of its size and depth below the surface of the skin.

After preparing the leg with antiseptic solution and circumferential sterile draping, the patient is placed in a reverse Trendelenburg position and the path of the saphenous vein marked, if not already done so preoperatively. In addition, the location of the saphenofemoral junction is also marked on the skin in the groin so that the

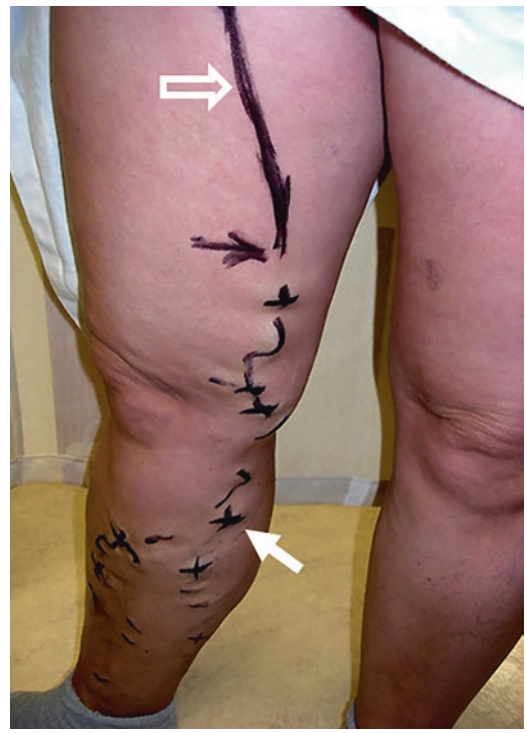

Fig. 9.2 In patients in whom stab phlebectomies are to be performed, the patient is marked preoperatively in a standing position with the location of the varicosities to be excised and marked (*white filled arrow*) as well as the course of the proximal saphenous vein to be ablated (*white unfilled arrow*) and planned percutaneous entry point of the RFA catheter (*black arrow* on skin)

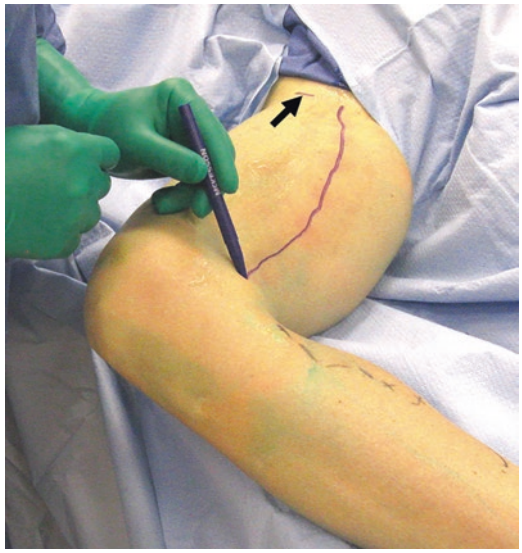

Fig. 9.3 The route of the great saphenous vein is marked intraoperatively on the skin following ultrasound-directed localization. The saphenofemoral junction (*black arrow*) is separately marked to allow proper insertion and localization of the ablation catheter tip

length of the ablation catheter that is to be inserted is estimated (Fig. 9.3). Especially in obese patients, simultaneous visualization of both the tip of the catheter and the saphenofemoral junction can be difficult. With the exception of the inadvertent catheterization and treatment of the superficial femoral artery, the worst technical and clinical complication would be heating and ablating the common femoral vein. Measuring the distance to the junction and marking that distance on the catheter with the circular white marker will help to insure that the catheter is not advanced too far into the vein.

The percutaneous entry point is selected using ultrasound, either above or below the knee for the GSV, based on easiest accessibility as determined by the size of the vein and its proximity to the surface, as well as the extent of the reflux based on the preoperative ultrasound examination. If entry into the GSV is below the knee, an attempt should be made to locate with ultrasound the site where the saphenous nerve nears the vein, and entry is made above this area to lessen the chance of thermal injury to the nerve. Lidocaine 1% without epinephrine, in order not to induce venospasm, is utilized as a local anesthetic. Similar to other vascular access procedures, we utilize a micropuncture kit with a 21 gauge needle under ultrasound guidance (Fig. 9.4). Such a small needle and its associated 0.018 in. guidewire are less likely to induce venospasm should initial entry not be successful and a repeat attempt be required. Once the guidewire is in place, a 4Fr dilator and sheath is advanced, and intravascular location is confirmed through the free flow of blood after removal of the introducer. A nick is made in the skin next to the dilator with a number 11 blade, and the sheath is upsized by advancing a 0.035 in. flexible J-tip guidewire over which the 7Fr RFA vascular sheath is now advanced (Fig. 9.5). Prior to inserting the RFA catheter, the distance to the saphenofemoral junction is measured and used as the maximal length of catheter insertion (Fig. 9.6). The catheter is thereafter flushed with normal saline and advanced under ultrasound guidance, visualizing the tip as it moves cephalad (Fig. 9.7). The echogenic tip is confirmed to be moving within the saphenous vein, rather than a branch vessel, by the characteristic transverse appearance of the circular vein within the oval saphenous fascia. In order to prevent the development of thrombus within the common femoral vein (endovenous heat-induced thrombosis, EHIT), the tip of the catheter should be distal to the entry of the superficial epigastric vein and 2.5 cm from the saphenofemoral junction (Fig. 9.8) [18]. Simultaneously visualizing both

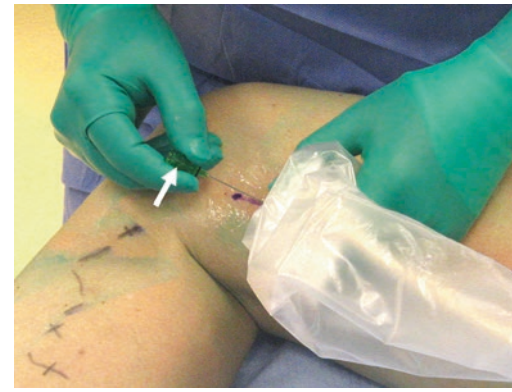

Fig. 9.4 Under ultrasound guidance, a 21 gauge micropuncture needle (*arrow*) is used to enter the saphenous vein just above the level of the knee

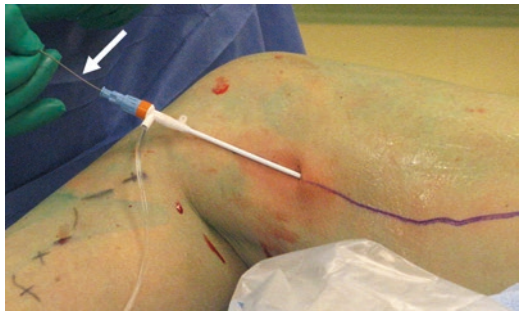

Fig. 9.5 Over a previously inserted 0.035 in. flexible J-tip guidewire (*arrow*), the 7Fr vascular dilator and sheath is inserted

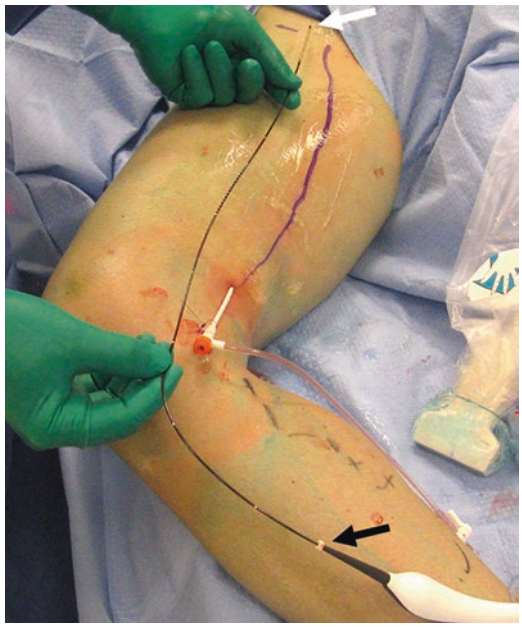

Fig. 9.6 Before insertion of the ablation catheter, the distance from the saphenofemoral junction (*white arrow*) and the exit from the sheath are measured. This distance will be marked on the catheter by advancing the associated white pledget on the catheter (*black arrow*)

the junction and the tip of the catheter in the same longitudinal plane, particularly in the obese patient, may be challenging, but a concerted effort needs to be made for the surgeon to be convinced that this safe distance is achieved. Occasionally, the catheter does not advance easily up the leg or enters a branch vessel. Most often, this difficulty can be overcome by straightening the leg and manually guiding the catheter

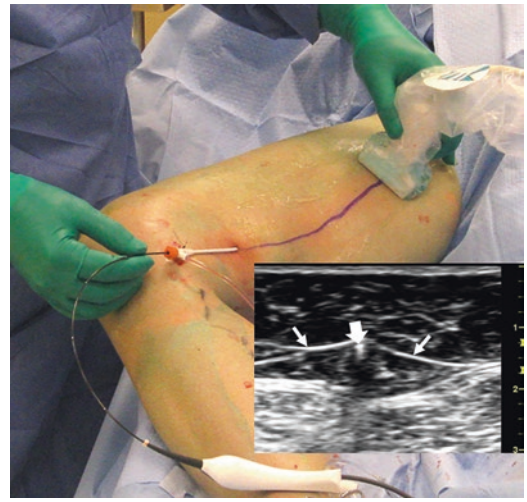

Fig. 9.7 The RFA ablation catheter is advanced up the GSV under ultrasound guidance. The catheter (*large arrow* on ultrasound image) is visualized transversely in the vein which lies within the oval saphenous fascia (*thin arrows*)

as the tip is visualized with ultrasound. On rare occasions, a 0.025 in. Glidewire (Terumo Interventional Systems, Somerset, NJ) can be used to navigate through a tortuous GSV. The tip of the guidewire, however, should not extend into the common femoral vein in order to prevent intimal injury and possible later thrombus development.

Once the ablation catheter is fixed in place, the patient is placed in a Trendelenburg position to decompress the vein in preparation for injection of tumescent anesthesia. Although formulas vary, we utilize 445 mL of 0.9% saline, 50 mL lidocaine 1% with epinephrine 1:100,000, and 5 mL of 8.4% sodium bicarbonate. The volume utilized is 10 mL per length of treated vein. It is injected circumferentially under ultrasound guidance around the great saphenous vein along its entire length from the entry point to the saphenofemoral junction. The use of the 21 gauge micropuncture needle and a motorized pump makes it less painful for the patient and allows for rapid hydrodissection around the vein (Fig. 9.9). The anesthetic agent is useful for vasoconstriction due to the epinephrine, a compressive effect due to its volume, and as a heat sink to prevent

Fig. 9.8 The tip of the catheter (*open arrow*) and the distance from the saphenofemoral junction and associate terminal valve (*white arrows*) are measured longitudinally to assure a separation distance of at least 2.5 cm

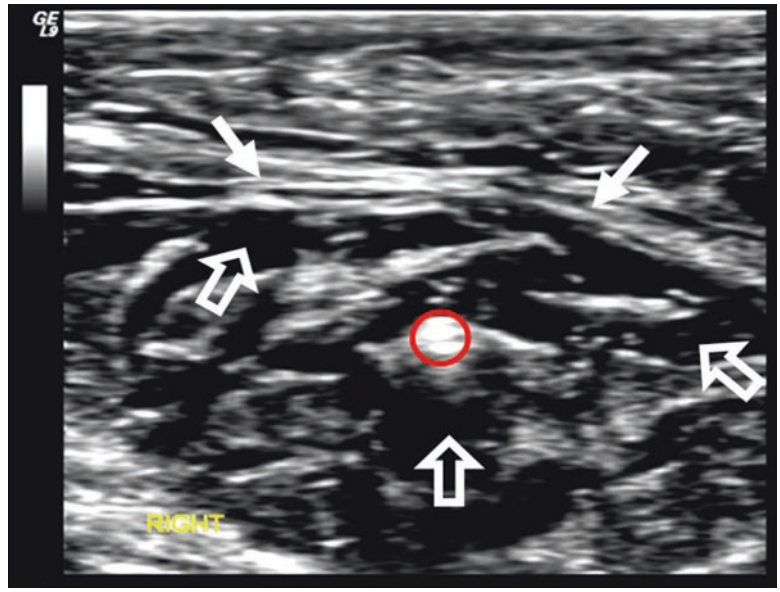

Fig. 9.9 Tumescence anesthesia is injected circumferentially around the vein. The location of the vein is best identified by the presence of the catheter within it (*red circle*), located underneath the saphenous fascia (*filled arrows*). The tumescent fluid separates the tissues and appears as anechoic areas around the vein (*open arrows*)

adjacent nerve and tissue heating. With appropriate tumescent anesthesia, the patient should not feel any pain on treatment and will have little pain postoperatively. When treating superficial veins, in thin patients, or accessory veins, sufficient tumescence should be infused to move the catheter at least 1 cm from the skin surface to prevent skin burns from the heat.

Once tumescent infiltration has been completed, treatment is begun and the electrode heated to 120°C in a 20s pulse cycle. It is important to adequately compress the vein over the full length of the heating element, either using the ultrasound probe or a rolled towel with hand compression. Failure to attain vein wall contact with the electrode may result in incomplete treatment.

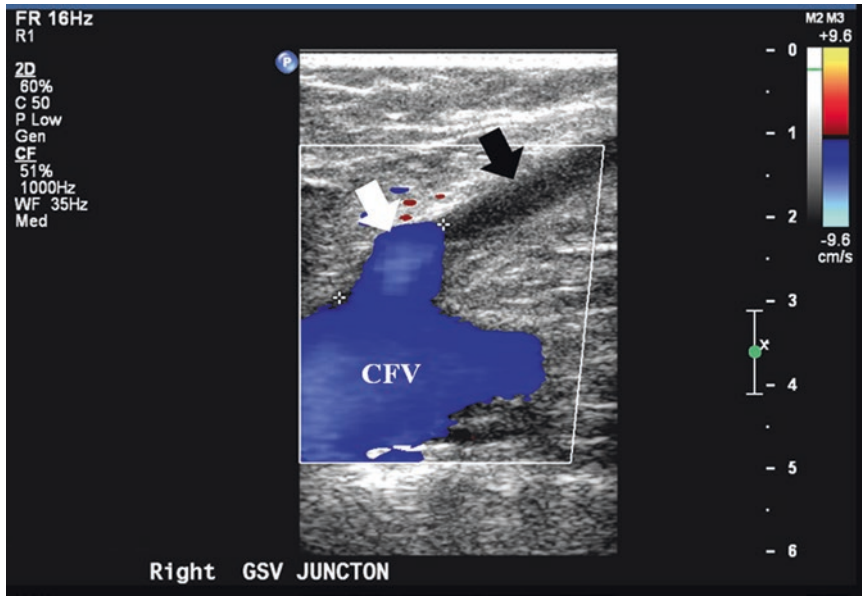

Fig. 9.10 After treatment is completed, color duplex ultrasound demonstrates continued cephalad flow and compressibility in the common femoral vein (CFV) and in the remnant patent portion of the GSV (*white arrow*). Antegrade flow in this portion of the GSV is dependent on continued patency of the superficial epigastric vein (not seen in this image). The more distant treated portion of the GSV (*black arrow*) appropriately has no flow

The proximal portion of the vein is treated with two cycles, and then the catheter is withdrawn 7 cm, according to the markings on the catheter. The remaining portion of the vein is treated segmentally in a similar manner with single cycles. If the vein is of large diameter, many practitioners will perform two cycles of heating for the entire length of the vein. The RF generator initiates power at 40 W, and it is expected that the power output needed to maintain the temperature at 120°C will drop to below 20 W within 10 s. If it does not, or if the temperature is not being maintained even at high power, it suggests insufficient compression or continuing flow within the vein that is cooling the heating element. In such cases, beyond improved compression, additional tumescent infiltration may be needed to constrict the vein. This may also occur in an aneurysmal segment where the vein wall may be thinner and less able to vasoconstrict. Treatment of the less dilated segments proximal and distal to the aneurysmal portion should lead to vein occlusion.

At the completion of treatment, the patient is returned to a supine position, and posttreatment duplex ultrasonography is done to confirm the absence of flow in the entire length of the treated vessel (Fig. 9.10). As the vein is now difficult to visualize, advantage is taken of the skin marking identifying the location of the vein that was drawn at the beginning of the procedure. This is used as a roadmap for the ultrasound probe. In addition to examining the ablated vein, continued phasic flow and compressibility in the common femoral vein needs to be demonstrated. We also make it a point to document pulsatile arterial flow in the adjacent femoral artery to confirm that there was no inadvertent vasoconstriction of the artery caused by tumescent infiltration into that vessel. With the same concern, the pedal pulses are palpated before taking the patient off the table. There is no retreatment protocol with RFA. If continued flow is seen in the vein, the catheter should not be readvanced as it may perforate the vessel and heat surrounding nerves or other tissues. The patient should instead be followed clinically, and, if needed, surgical treatment or sclerotherapy may be utilized.

There is no widespread agreement on the need or type of compression to be utilized at the end of the procedure. If no associated stab phlebectomies have been performed, many physicians will utilize compression stockings for 1 week that the patient may have been wearing before the procedure. Our present protocol is circumferential stretch bandaging (Ace) from the foot to the thigh for 48 h. This appears to be helpful symptomatically and may decrease ecchymosis. Finally, prior recommendations were for post-procedural duplex scanning at 48–72 h [4]. However, the incidence of pulmonary embolism and deep venous thrombosis is low, many clinicians have not found this practice useful, and this recommendation is now being reviewed for revision by the American Venous Forum. Our own practice at present is to do a follow-up ultrasound within a week of the procedure in order to both document successful venous closure and investigate for possible development of deep venous thrombosis or EHIT.

Outcomes

Since the introduction of RFA as a technique for ablation of refluxing veins, multiple studies have shown that short- and midterm clinical results are comparable to those achieved with surgical ligation and stripping. Several studies have shown anatomical vein occlusion rates of 90–95% with RFA [19–21]. Balint et al. [22] performed a meta-analysis on 17 studies and 1420 limbs with great saphenous vein incompetence and evaluated outcomes of EVLA, RFA, and ultrasound-guided foam sclerotherapy. Technical success rates were 89% for RFA, 85% for EVLA, and 33% for ultrasound-guided foam sclerotherapy. There were no significant differences between the three techniques regarding vein reopening or recanalization.

Another meta-analysis of seven studies with at least 2 years of follow-up showed that the overall rate of recurrent varicose veins increased with length of follow-up, but it was similar after endovenous ablation versus ligation and stripping with both being 22%. However, the cause of recurrence was different in the two groups. Neovascularization was seen more often in the surgical group, while recanalization was the most common cause of recurrence in endovenous ablations, followed by the development of anterior accessory saphenous vein incompetence and incompetent calf perforating veins [23]. These differences in cause of recurrence can affect treatment plans. Postoperative neovascularization in the groin can be more difficult to treat because of surgical scarring and the small and tortuous size of the vessels which makes percutaneous interventions much more challenging. After endovenous ablations, however, recanalized veins can be treated reasonably easily with repeat endovascular ablation or sclerotherapy.

Beyond just anatomic occlusion success, however, relief from CVI symptoms of leg pain, fatigue, and edema has been noted in most patients. Even those with recanalization remain asymptomatic in 70–80% of cases, most likely due to limited reflux as compared to their pre-interventional status.

Compared to open surgery, RFA has been found to be associated with much less morbidity, quicker recovery, and higher quality of life scores [20]. As expected, patients experience significantly less pain and analgesic usage, have no hospital stay as the procedure is performed in an outpatient setting, return to normal activities within 1 day, and have much lower total costs [24–26].

Complications

Potential complications with the RFA procedure include post-procedural pain, ecchymosis, hematoma, superficial vein phlebitis, adjacent skin burn or discoloration, DVT, and PE. The initial multicenter prospective trial reported 2.9% clinical phlebitis, 0.9% deep venous thrombosis with clot extension into the common femoral vein, one case of PE, 1.2% skin burn, and 0.2% infection at the vein access site [7]. Skin burn complications occurred primarily before the implementation of tumescent infiltration to protect the skin.

Therefore the present recommendation evolved that treatment of a vein located near the skin surface should be protected with sufficient tumescent fluid infiltration to move the vein at least 1 cm from the skin surface. The most bothersome complication is nerve injury that can occur from thermal damage to adjacent sensory nerves. Such injuries most frequently present as focal hypoesthesia and were initially observed in 12% of limbs in the first week, which dissipated with time in most patients. However, it persisted in 2.6% at 5 years. For GSV below-knee treatment the paresthesia rate was higher at 7.7% at 5 years reflecting the close location of the saphenous nerve to the great saphenous vein below the knee. On this basis, most physicians limit RFA to the proximal third of the GSV below the knee and pay special attention to identify the nerve with ultrasound and infiltrate sufficient tumescent fluid to separate the nerve from the vein. When compared to traditional surgical techniques, however, RFA has been shown to have significantly lower complication rates [27].

Endovenous heat-induced thrombosis (EHIT) is a specific complication of RFA and EVLA. EHIT is the formation of thrombus in the great saphenous vein, or proximal to the ablation site, which can extend into the deep venous system at the common femoral vein [18, 28]. The highest risk of EHIT formation is when ablation is initiated proximal and above the junction of the superficial epigastric vein. Maintaining retrograde flow in this vein allows continuing blood flow in the proximal portion of the GSV and prevention of thrombus formation (Fig. 9.10). This vein is usually located about 1 cm from the saphenofemoral junction. Present recommendations are therefore to initiate thermal ablation 2.5 cm from the junction, well away from the deep system. Although some earlier publications reported a higher rate of EHIT, the overall incidence of post-RFA thrombotic events is approximately 1% and is similar in other endovenous modalities [27, 29, 30]. Treatment of EHIT depends on the amount of clot extension into the deep system. However, because of the small number of cases reported and their mostly retrospective nature, there is little hard data on which to base treatment recommendations. If the patient does not have ongoing risk factors for DVT, observation with weekly repeat duplex imaging is not unreasonable if protrusion into the common femoral vein is less than 50% of its diameter. If extension is greater than this amount, or if the patient has ongoing risk factors, anticoagulation has been found to be successful [31]. The recent availability of oral direct-acting anti-Xa anticoagulants, without the need for intravenous bridging, makes this an appealing therapeutic option in patients who develop EHIT. In the calf, concomitant small saphenous vein ligation and stripping is a risk factor for calf-DVT [30].

There is a single case report of pulmonary embolization [32] with this rare event, estimated to occur in less than 0.02% of cases. There are also case reports of patients who developed an arteriovenous fistula following great saphenous vein RFA [33–35]. Surgical ligation and embolization are treatment options to manage this complication [36]. Finally, a multitude of nerve injuries can occur after endovenous ablation including injury to the proximal common peroneal, tibial, and distal sciatic nerves after treatment of the small saphenous vein and the common peroneal nerve associated with the vein of Giacomini [37]. A detailed understanding of the relevant anatomy and sufficient tumescent anesthesia infiltration will help prevent many such neural complications.

Treatment for Perforator Veins

The perforator veins comprise the important connection between the superficial and deep system. Physiologically, they provide a route from the superficial to the larger deep system. Pathologically, the flow is reversed, and incompetent reflux into the superficial system has been associated with CVI and ulcer development. Treatment by ligation, clipping, or ablation has been found to improve ulcer healing rates [38]. Present recommendations by the SVS-AVF guidelines support the ablation of pathologic perforating veins (those with outward flow of >500 ms duration and with a diameter of >3.5 mm

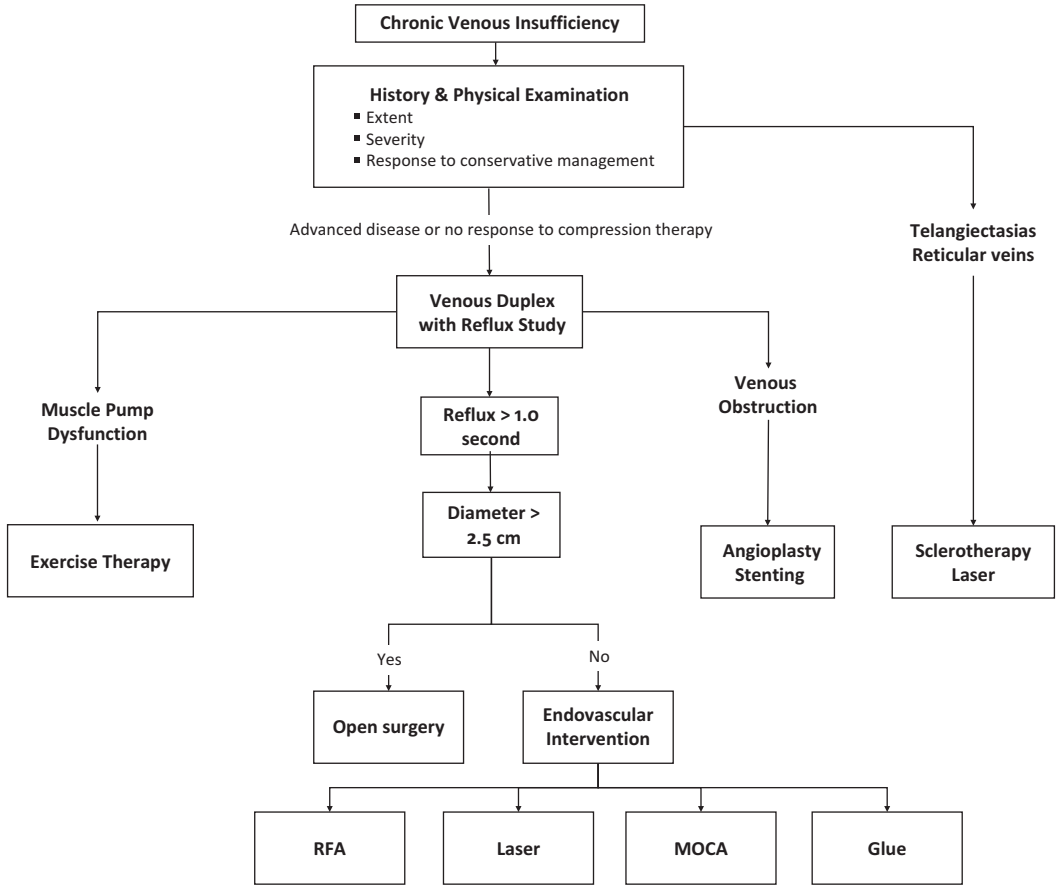

Fig. 9.11 Clinical algorithm for the evaluation and treatment of patients with venous insufficiency

located beneath or associated with an ulcer bed or skin changes) in patients with C4b, C5, and C6 disease (Guidelines 6.5, 6.6, 6.7) [6]. However, both the strength of the recommendation (grade 2) and level of evidence (C) are weak. The methodology for treatment is strongly recommended (grade 1) to be by percutaneous methods, including endovenous thermal ablation, rather than open venous perforator surgery. Treatment of incompetent perforators in the setting of C2 disease, varicose veins, is not recommended [2].

The RFA technique for the ablation of perforating veins utilizes the same RF generator but the shorter ClosureRFS stylet. It is a 6Fr system with 12 cm working length which may be inserted under ultrasound guidance either directly or over a guidewire. The tip of the stylet is inserted subfascially within the perforator but kept at least 0.5 cm away from both the deep venous system and the skin. RF energy to the vein wall is applied for 1 min each at 0°, 90°, 180°, 270° (up, right, down, left) positions then pulling back 0.5–1 cm and repeating the cycle.

RFA treatment of perforator veins is more technically challenging primarily due to the tortuous and short length of the veins and the stiff nature of the stylet. Potential complications of nerve injury and deep venous thrombosis are more likely than in treatment of the superficial venous system. Although reported occlusion rates of 80% are good, the technique is not widely utilized as sclerotherapy appears to be more widely employed for the treatment of perforators at the present time.

Table 9.1 Randomized controlled clinical trials comparing radiofrequency ablation with other modalities

Author	Year	Arms (number of patients)	Follow-up	Results
Rautio [39]	2002	– RFA (15) – Stripping (13)	8 weeks	RFA with reduced postoperative pain, shorter sick leaves, and faster return to normal activities
Lurie [20]	2003	– RFA(44) – Stripping (36)	4 months	RFA with 95% immediate success rate QOL and pain scores significantly different in favor of RFA group
Lurie [40]	2005	– RFA (36) – Stripping (29)	2 years	Comparable results of RFA with stripping Recurrence and neovascularization rates were similar in the two groups Improved QOL scores persisted through the 2-year observations in the RFA group
Perala [41]	2005	– RFA (15) – Stripping (13)	3 years	No significant difference in recurrent or residual varices in RFA or stripping group (33% vs 23.1%, $p = 0.68$)
Subramonia [42]	2010	– RFA (47) – Stripping (41)	5 weeks	RFA took longer but with less analgesic requirements, earlier return to routine activities, and higher satisfaction
Subramonia [26]	2010	– RFA (47) – Stripping (41)	N/A	Ablation took longer and was more expensive but enabled patients to return to work 1 week earlier. The increased cost of radiofrequency ablation is partly offset by a quicker return to work
Almeida [43]	2009	– RFA (46) – EVLA 980 nm (41)	1 month	Pain, ecchymosis, and tenderness were statistically lower in RFA group at 48 h, 1 week, and 2 weeks. RFA superior to EVLA for post-procedural recovery and QOL parameters
Gale [44]	2010	– RFA (59) – EVLA 810 nm (70)	1 year	Significantly more bruising occurred in the EVLA group at 1 week. At 1 year, recanalization with reflux was found in 11 RFA and 2 EVLA patients ($P = 0.002$). No difference in VCSS score was found between groups at 1 month and 1 year. Overall QOL mean score improved over time for all patients

(continued)

Table 9.1 (continued)

Author	Year	Arms (number of patients)	Follow-up	Results
Goode [19]	2010	– RFA (40) – EVLA 810 nm (39)	6 months	RFA resulted in significantly less pain and bruising than EVLA. Both RFA and EVLA resulted in similar occlusion rates (95% at 10 days)
Shepherd [45]	2010	– RFA (67) – EVLA 980 nm (64)	6 weeks	Pain scores and analgesic use were significantly higher in EVLA group. Changes in AVVQ, SF-12, and VCSS scores at 6 weeks were similar in the two groups
ElKaffas [25]	2011	– RFA (90) – Stripping (90)	2 years	RFA had an occlusion rate of 94.5%, significantly lower complication rate, shorter hospital stay, and higher cost. No significant differences in recurrence rates at 24-month follow-up
Rasmussen [46]	2011	– RFA (106) – EVLA 980 & 1470 nm bare fiber (107) – Stripping (108) – Foam sclerotherapy (107)	1 year	The technical failure (patent GSV) rate was highest after foam sclerotherapy (16.3% at 1 year). RFA and foam sclerotherapy had faster recovery and less pain than EVLA and stripping
Nordon [21]	2011	– RFA (79) – EVLA 810 nm (80)	3 months	RFA and EVLA offer comparable venous occlusion rates (>95%) at 3 months; no difference in quality of life scores was found. RFA is associated with less pain, analgesic requirement, and bruising
Dzieciuchowicz [47]	2013	60 patients randomized to: – EVLA 810 nm (with two different delivery systems) – EVLA 1470 nm radial fiber – RFA	N/A	The delivery of a working part to the SFJ was the least problematic in RFA and radial diode EVLA. The application of desired amount of energy was the easiest in RFA but visualization of the working tip at the SFJ was the most difficult in RFA. Radial diode EVLA presented the best echogenicity. In general, EVLA with radial optic fiber seems to be the easiest

(continued)

Table 9.1 (continued)

Author	Year	Arms (number of patients)	Follow-up	Results
Dzieciuchowicz [48]	2014	– RFA (13) – EVLA 810 nm (14) – Stripping (11)	10 days	Significant increase of D-dimer was seen in stripping group after 24 h. There was no significant difference in RFA and EVLA groups. PAI-1 decreased in RFA patients, did not change in EVLA, and increased in stripping group after 24 h. The highest CRP increase was observed in stripping group. At 10 days, a further significant increase of D-dimer and CRP was seen in stripping group
Mese [49]	2015	– RFA (60) – EVLA 1470 nm radial fiber (60)	6 months	Significantly less ecchymosis and edema in EVLA. 3 recanalization in RFA (5%) and none in EVLA. Significantly shorter time to return to daily activity and work in EVLA group
Morrison [50]	2015	– RFA (114) Cyanoacrylate embolization (108)	3 months	No need for tumescent anesthesia in cyanoacrylate embolization. 3-month closure rates were 99% and 96% for cyanoacrylate embolization and RFA, respectively. Pain there was mild and had similar pain score during procedures. Significantly less ecchymosis happened in embolization group
Boersma [51]	2014	– RFA (80) – Mechanochemical endovenous ablation (80)	1 year	Treatment of primary small saphenous vein insufficiency Multicenter randomized controlled trial Protocol has been published; result not published yet
Van Eekeren [52]	2014	– RFA (230) – Mechanochemical endovenous ablation (230)		Treatment of great saphenous vein incompetence Multicenter randomized controlled trial Protocol has been published; result not published yet

EVLA endovenous laser ablation, *RFA* radiofrequency ablation, *VCSS* venous clinical severity score, *AVVQ* Aberdeen Varicose Vein Questionnaire, *SF-12* short form 12, *PAI* plasminogen activator inhibitor

Comparison to Other Methods

Over the past two decades, a number of prospective randomized clinical trials have been performed (Table 9.1) which compared RFA with other procedures for the treatment of chronic venous insufficiency. These studies have provided clinicians with a scientific basis for treatment selection for these patients. Comparisons between RFA and surgical high ligation and stripping have demonstrated a comparable anatomical success rate for RFA with less pain, a shorter hospital stay, sooner return to normal activity and work, and a significantly higher quality of life [20, 26, 39, 40]. Importantly, there is no difference in recurrence rates or residual varices [41].

Several trials have compared RFA with EVLA. Most of them showed similar results in terms of technical and clinical success rates. However, confirming earlier nonrandomized reports, these comparison studies confirmed that post-interventional bruising, pain, and induration were generally higher in EVLA group [19]. This was probably due to the non-contact mechanism of heat transmission and microperforations caused by the lasers as opposed to direct contact and collagen denaturation by RFA electrodes [19, 21, 44, 45]. Newer laser fibers with jacketed and radial diode tips and longer water-specific wavelengths have shown improved results with less ecchymosis and edema [49].

There are fewer studies comparing RFA with newer methodologies, such as cyanoacrylate embolization and foam sclerotherapy, which are non-tumescent and nonthermal techniques and hold the promise for less painful alternatives in the future [24, 50]. They have shown benefits of less pain and ecchymosis, but more experience and prospective studies are needed to better evaluate their success rate and complications compared to the more established RFA and EVLA.

A recent survey has indicated that physicians' preference for a particular technique most often determines the choice of venous ablation device utilized, based on both perceived patient outcomes and previous capital investments and the costs of disposable equipment. With changes in procedural costs and reimbursement levels, physician preferences for vein ablation methodologies may change in the future [53].

Conclusions

Radiofrequency ablation of refluxing lower extremity veins has become well-established, along with laser ablation, as the standard of care in patients with varicose veins and venous insufficiency. Prospective clinical trials have documented excellent technical and clinical success rates with fewer complications and faster post-procedure recovery compared to surgical ligation and stripping. An understanding of the venous anatomy, pathophysiology, and ultrasound imaging and the technical details of the procedures are important to ensure patient safety and clinical success.

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Mechanochemical Ablation of Superficial Veins

10

Afsha Aurshina and Cassius Iyad N. Ochoa Chaar

Clinical Pearls

1. Mechanochemical ablation reduces procedural pain during superficial vein ablation.
2. The risk of nerve injury is low and treatment of the distal saphenous vein at the ankle is feasible.
3. The efficacy is comparable to thermal vein ablation methods up to 1 year in most studies.

Introduction

The Society of Vascular Surgery/American Venous Forum and the National Institute of Health and Clinical Excellence (NICE) guidelines recommend the use of endothermal ablation (ETA) in the form of endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) as the first line treatment (grade 1B evidence) for truncal venous reflux in varicose veins since 2011 and 2013, respectively [1, 2]. Endovenous thermal ablation of saphenous vein reduces the rate of postoperative complications, increases the speed of recovery resulting in faster return to work, and improves the quality of life compared to surgical ligation and stripping [3]. However, ETA requires tumescent anesthesia around the targeted vein to buffer the heat and prevent damage to the surrounding structures [4, 5].

The need for tumescent anesthesia has a few disadvantages as it prolongs the procedural time and adds to patient discomfort and constitutes the most painful part of an ablation procedure. There is also a risk of endothermal heat-induced thrombosis with thermal ablation techniques since there is no control on forward dissipation of energy [4, 6, 7]. Recent novel techniques have thus been devised to minimize these negative aspects of endothermal ablation, while incorporating its clinical benefits.

Endovenous mechanochemical ablation (MOCA) using ClariVein® (Vascular Insights, LLC, Quincy, MA) which is discussed in this chapter is a new evolving technique, which induces vein closure by a combination of mechanical injury of venous endothelium with simultaneous chemical injury using a physician-guided infusion of liquid sclerosing agent. The procedure does not involve the use of thermal energy and, therefore, does not require tumescent anesthesia.

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Mechanism of Action

MOCA produces inflammation of the vein wall and subsequent thrombosis by combining mechanical injury with chemical irritation. In a recent study, Boersma et al. conducted a prospective experimental trial using dairy animals to test the working mechanism of MOCA and provide histological analysis of its effect on targeted vein wall. The experiment revealed that the mechanical action inflicted by the device causes damage to the endothelium without signs of any histological injury to other layers of the vessel wall. The liquid sclerosant then produces irreversible damage to the cellular membrane of the endothelium resulting in fibrosis of the vein. The study thus confirmed the hypothesis that MOCA yields venous occlusion by a combination of mechanical injury of the endothelium layer and vasoconstriction, which further increases the permeability of the sclerosant and increases area of exposure into the deeper layers of the vessel wall [8]. In another recent ex vivo "vein section" study conducted by Whiteley et al., it was suggested that there was deeper penetration of the sclerosant as a result of disruption of tunica intima along with profound damage to tunica media [9].

ClariVein® Device and Technique

The ClariVein® infusion catheter (Vascular Insights, LLC, Quincy, MA) received clearance from the US Food and Drug Administration (FDA) in May 2008 for the indication of infusion of physician-specified agents (sclerosants) in the peripheral vasculature. ClariVein® device itself obtained the CE mark for the specific indication of venous occlusion of incompetent superficial veins to treat venous reflux in lower extremities in April 2010. In addition to its use in patients who do not particularly tolerate tumescent anesthesia, we have used MOCA in our practice to treat recurrent venous reflux in the distal saphenous vein. The saphenous nerve is close to the vein in that area of the leg, and there is an increased risk of nerve injury and numbness after thermal ablation. MOCA allows access at the ankle and ablation of the distal vein. In these cases, the saphenous vein is occluded at the knee and the risk of dissipation of the sclerosant to the deep veins is minimal. In fact, the sclerosant tends to dissipate to the superficial varicosities connected to the saphenous vein and can potentially increase the efficiency of the treatment by sclerosis of venous tributaries.

Device

The ClariVein® device consists of two main components: an infusion catheter with a rotating dispersion wire extending within its lumen and a motor unit/handle. The infusion catheter is a disposable plastic device which consists of a main lumen supporting the wire and a side port connection leading to the main lumen. The side port system is used as a connection to attach the syringe to flush saline as well inject sclerosant. The distal end of the ablation is angled at about 2 cm from the tip and has a small metal ball attached to the end (Fig. 10.1). This metallic ball at the tip has been designed to enhance ultrasound catheter guidance to accurately place the tip of the catheter at the targeted location and prevent vein wall perforation.

The catheter is currently available in two sizes: 45 and 65 cm length, with a white mark indicating 5 cm of the distal end. The catheter, along with the wire, is connected to a battery-motorized handle on the proximal end, which controls wire rotation. The motor has four speeds ranging from 2000 to 3500 rpm. The maximum speed is most often used as the default (Fig. 10.2). The rotating wire works by activating the coagulation pathway by instigating mechanical injury to the endothelium. Secondly, it induces vasospasm which reduces the vein diameter and increases the action of sclerosant by increasing the penetration. The rotating wire thus ensures an even distribution of the sclerosant at the vessel wall (Fig. 10.3).

The whole device can be introduced via ultrasound guidance through a micro-introducer (4–5 Fr) at the puncture site [4, 10]. Once the two units, namely, the catheter and the motor handle,

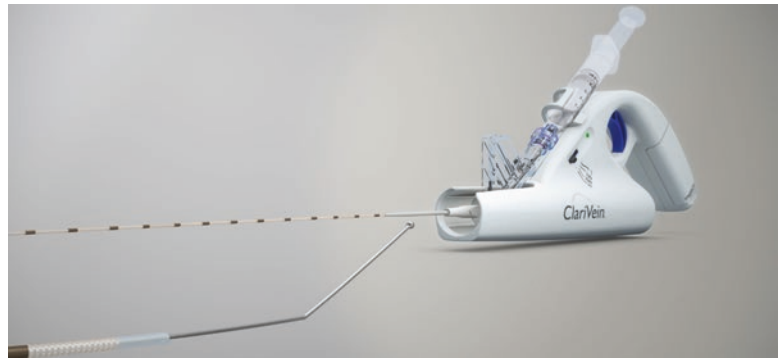

Fig. 10.1 ClariVein® infusion catheter showing the rotating tip at the end (courtesy of Vascular Insights LLC, Quincy, MA)

Fig. 10.2 ClariVein® device showing the motorized handle unit attached with a syringe holder to facilitate physician-controlled infusion of the liquid sclerosant (courtesy of Vascular Insights LLC, Quincy, MA)

have been connected, it cannot be disassembled or reused. The device is designed for single use only, easy to handle, and disposable after use.

Technique

The patient is horizontally positioned in reverse Trendelenburg based on the location of the targeted vein, and the area is prepped and draped in a sterile manner (Fig. 10.4A). Local anesthesia is infiltrated at the site of the puncture. Under ultrasound guidance, the introducer wire and catheter sheath are inserted into the vein. For treatment of below-the-knee saphenous vein reflux, access can be obtained close to the ankle (Fig. 10.4B). The ClariVein catheter is then inserted through the lumen such that the tip of the wire is placed just below the saphenofemoral junction (SFJ).

The ClariVein® catheter is then connected to the motorized handle unit, and the distal end of the dispersion wire is unsheathed to expose the dispersion tip which is then positioned 1 cm distal to the SFJ or 1 cm proximal from the "fascia" as the small saphenous vein (SSV) angles toward the saphenopopliteal junction [11]. In the case illustrated, the catheter is advanced as close as possible proximally to the segment that was ablated prior (Fig. 10.5). Since the position of the catheter is steerable only with the cartridge wing at distal end, it is important to position the catheter tip at the desired position before attaching it to the motorized handle [12].

Once the location of the catheter is confirmed by ultrasound, the catheter is attached to the handle and the 2-cm-long angled tip is exposed. A 5 mL syringe filled with 1.5% sotradecol is then connected to the handle for delivery of the

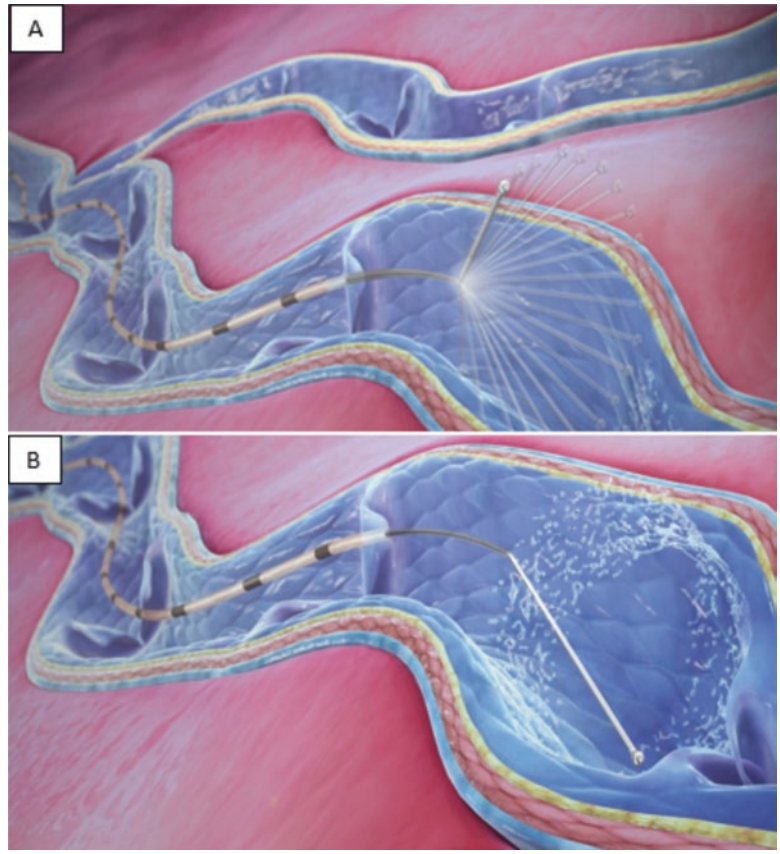

Fig. 10.3 ClariVein® device catheter with activation of the rotation mechanism of the dispersion tip (**A**). Even distribution of the sclerosant at the endothelium (**B**) (courtesy of Vascular Insights LLC, Quincy, MA)

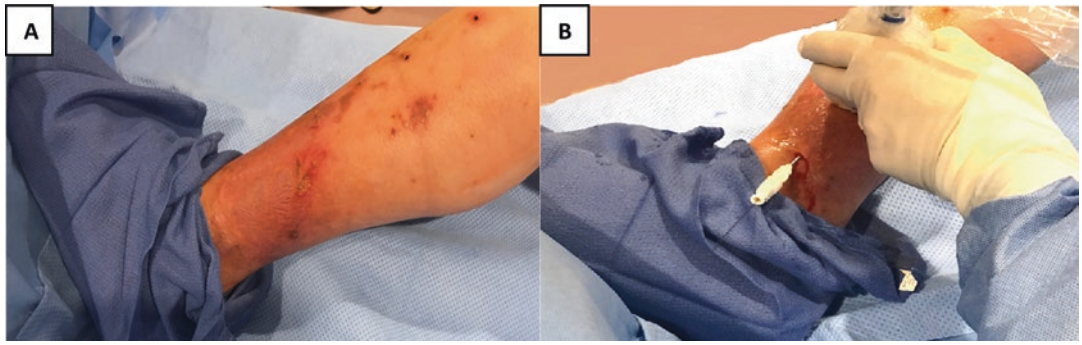

Fig. 10.4 (**A**) Pre-procedure: leg prepped below knee, positioned and draped. (**B**) After injecting local anesthesia, introducer wire and catheter sheath are introduced at the ankle under ultrasound guidance to treat GSV below knee reflux

sclerosing agent. This step comprises full assembly of the device.

The access sheath is usually removed prior to initiation of treatment to ensure a smooth, continuous, uninterrupted pullback (Fig. 10.6). The first 2–3 cm is treated only with mechanical ablation to induce vasospasm and avoids propagation of the sclerosing agent into the deep venous system. Next, the activated catheter with rotating tip is gradually withdrawn at a speed of approximately 6–7 s per cm, while the sclerosant (polidocanol/sodium tetradecyl sulfate) is injected at a rate of 0.2 mL per cm approximately. Ultrasound compression of the vein is not routinely

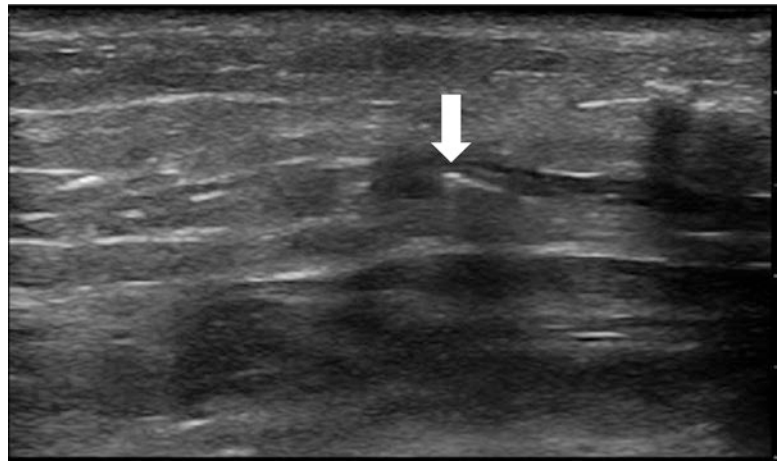

Fig. 10.5 Figure showing position of tip of ClariVein catheter (*arrow*) in the tissue, confirmed with ultrasound guidance

Fig. 10.6 The ClariVein catheter device with rotating wire is then pulled back at 7 s per cm speed while injecting sclerosant

used during treatment but is suggested for veins larger than 10 mm in diameter to enhance contact of the rotating tip with the wall of the vein. A white mark on the catheter indicates the last 5 cm of the catheter. An additional 2 cm of therapy can then be performed. The tip of the wire is re-sheathed and the catheter is withdrawn with pressure on the access site.

Immediately after procedure, an ultrasound should be performed to assess for patency of deep veins of the treated leg and examine the proximal ablation edge position, especially near the junction. The treated vein may still be compressible initially, but that does not indicate failure of treatment. Eventual thrombosis occurs subsequently with inflammation and continuous action of the sclerosing agent (Fig. 10.7).

There is a variation in the use of sclerosing agents (polidocanol/sotradecol) in terms of concentration and dosage. Some experts suggest that a higher concentration of polidocanol should be used near the junction, as it appears to be weaker than sotradecol [4]. In most cases the amount of sclerosant is calculated based on the patient's weight, and the maximum amount should not exceed the amount mentioned on the drug insert. According to Tang et al. the maximum recommended treatment dose of sotradecol for one procedure should not exceed 10 mL of 3% strength (equivalent to 15 mL of 2% sotradecol) [13]. Currently, some surgeons also suggest the dose of sclerosant used should be 2 mL, 3% polidocanol for the first 10–15 cm, and 1.5% polidocanol for the remainder of the great saphenous vein (GSV) [4, 14, 15]. There is however no standard recommendation regarding choice of sclerosant, concentration, or dosage to date.

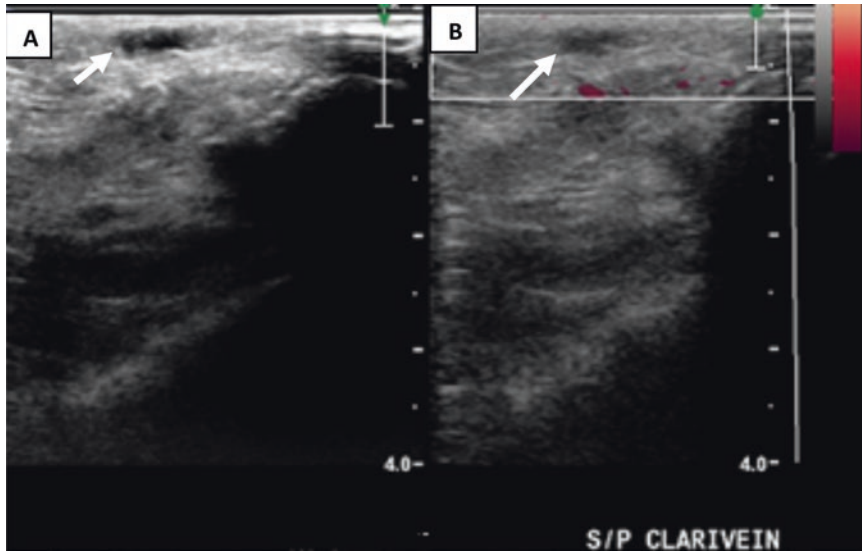

Fig. 10.7 Post-procedural venous occlusion seen after mechanochemical ablation showing ultrasound images of a treated vein without compression (**A**) and after ultrasound compression (**B**)

Post-procedural Care

- Patients can be discharged with class II thigh-high compression stockings (20–30 mm Hg) use for 48 h continuously and then during daytime for at least 2 weeks.
- Follow-up ultrasound and clinical visit should be scheduled within 1–2 weeks after procedure.
- The patients should be advised to walk immediately post-procedure for at least 10 min.
- Some studies also recommend to advice walking for at least 10 min every hour on the day of the procedure [12].

Clinical Outcomes

Ultrasound-guided foam sclerotherapy was one of the first nonthermal techniques developed but has not proved to be as effective as endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) techniques, with a 5-year success rate of 74% [16]. Furthermore, it usually requires multiple treatment sessions and is associated with a small but well-documented risk of stroke using foam sclerotherapy [17, 18].

The first human study demonstrating clinical safety and efficacy of MOCA was conducted by Elias et al. in 2012 (Table 10.1). The study included 30 incompetent GSVs in 29 patients treated for primary venous insufficiency. The primary closure rate was reported as 96.7%, with no major adverse complications [19]. Although this was the first human study conducted, it was not the first one published as in 2011; van Eekeren et al. reported their experience on clinical efficacy of MOCA. In this study, 30 GSVs in 25 patients with venous insufficiency were treated in two centers. The immediate postoperative technical success rate was 100%. After a follow-up of 6 weeks, 26 (87%) remained occluded, three veins showed partial recanalization, and one vein completely recanalized. Patient satisfaction was reported at 8.5 on a 10-point scale, and the median VCSS decreased significantly from 3 to 1 [10].

The first prospective multicenter study on efficacy of MOCA in patients with chronic venous insufficiency was described by Bishawi et al. The study included 126 patients who were noted to be significantly older and with higher BMI compared to previous studies using endothermal techniques but reported high successful closure rates in the great saphenous vein at 1 week, 3

Table 10.1 Clinical safety and efficacy studies conducted for mechanochemical ablation

Author	Year	Study sample (*n*)	Vein type	Sclerosant used	Clinical efficacy (%)	Complication rate (%)	Follow-up
van Eekeren et al. [10]	2011	25	GSV	Polidocanol (1.5%)	87	Ecchymosis (30) Phlebitis (13)	6 weeks
Elias et al. [19]	2012	29	GSV	Sotradecol (1.5%)	96.7	Ecchymosis (10)	6 months
Boersma et al. [15]	2012	50	SSV	Polidocanol proximal (2%) Distal (1.5%)	94	Ecchymosis (12) Induration (12) Phlebitis (14)	1 year
Bishawi et al. [20] (multicenter study)	2014	126	GSV	Sotradecol Polidocanol (center based)	94%	Hematoma (1) Ecchymosis (9) Phlebitis (10)	6 months
van Eekeren et al. [21]	2014	106	GSV	Polidocanol Proximal (2%) Distal (1%)	93	Phlebitis (3) Hematoma (9) Induration (12) Pigmentation (5)	1 year
Deijen et al. [14]	2016	449	GSV SSV	Polidocanol proximal (2%) Distal (1.5%)	92% 84%	Phlebitis (2) Nerve injury (0.2) Hematoma (0.2) DVT/PE (0.6)	12 weeks
Kim et al. [22]	2017	126	GSV	Sotradecol Polidocanol (1.5%)	92%	Phlebitis (10) Ecchymosis (9) Hematoma (0.7)	2 years
Tang et al. [13]	2017	300	GSV SSV	Sotradecol (2%)	97% 100%	Phlebitis (4)	8 weeks

months, and 6 months (100%, 98%, and 94%), respectively. Also, there was a significant improvement in the venous clinical severity score (VCSS) post-procedure [20]. The following year, van Eekeren et al. published 1-year results for MOCA of GSV insufficiency in 106 patients. The initial technical success rate was 99% on duplex imaging immediately after treatment. Post-procedural pain scores were reported with mean pain during the first 14 days after treatment at 7.5 mm (0–100 visual analog scale). The time to return to daily life activities was noted as 1 day. At 1-year follow-up, the clinical success rate was 93% and 88.2% of the GSV remained occluded. Twelve patients were reported to have recanalization, of which eight were partial. The venous clinical severity score (VCSS) decreased significantly from 4.0 to 1.0 at 1 year [21].

In 2013, Boersma et al. published the first report on safety and efficacy of mechanochemical ablation of small saphenous vein (SSV) insufficiency. The study included 50 consecutive patients treated with MOCA and assessed at 6 weeks and 1 year. The initial technical success rate was 100% and 94% remained occluded at 1 year. VCSS decreased significantly from 3.0 (IQR 1-3) to 1.0 (IQR 1-2) at 1 year. No major complications were noted, especially no nerve injury [15]. A recent prospective study by Tang et al. not only recommend the use of ClariVein for ablation for both great and small saphenous varicose veins (100% at 1 week and 94% at 8 weeks post-procedure) but also noted successful procedures when performed on multiple veins in the same leg or bilaterally [13]. Furthermore, MOCA has proved to be a great technique for treatment of SSV incompetence with 1-year follow-up showing 94% anatomic success rate and no major complications especially because of close proximity to sural or saphenous nerve in the distal calf [13, 15].

Another advantage of MOCA is that the procedure has proved to be painless and can be completed more rapidly compared to ETA. It can also be combined with phlebectomies during the same procedure under local anesthetic [13].

Table 10.2 Randomized clinical trials performed for mechanochemical ablation of superficial veins

Author	Year	Sample size (*n*)	Vein type	Study objective	Results	Follow-up
van Eekeren et al. [2]	2013	68	GSV	MOCA vs. RFA postoperative pain scores, early QoL	4.8 ± 9.7 mm vs. 18.6 ± 17 mm ($P < 0.001$)	14 days 6 weeks
Vun et al. [24]	2015	64 MOCA 50 RFA 40 EVLA	GSV SSV	MOCA vs. RFA/ EVLA success, medial pain scores	91% (MOCA) 93% (RFA/ EVLA) 1 vs. 5 vs. 6 ($P < 0.001$)	10 months
Bootun et al. [23]	2016	60 MOCA 59 RFA	GSV SSV	MOCA vs. RFA Mean pain scores	92% (BOTH) 13.4 ± 16 mm vs. 24.4 ± 18 mm ($P < 0.001$)	1 month
Lam et al. (dose-finding) [25]	2016	87	GSV	Polidocanol: 1% foam vs. 2% liquid vs. 3% liquid closure rate	1%: 56.5% 2%: 100% 3%: 96.4% ($P < 0.001$)	6 weeks (interim results)
Leung et al. (LAMA) [26, 27]	2016	140	GSV SSV	MOCA vs. EVLA with concomitant phlebectomies. Intra-/post-procedural pain, efficacy, cost-effectiveness	Preliminary results: MOCA 92% vs. EVLA 94%; less procedural pain with MOCA, no difference in QOL or return to work (median 7 vs. 6 days)	6 weeks 6 months (preliminary results)
Ramon et al. (MARADONA) [21]	2014	460	GSV	MOCA vs. RFA success, post-procedural pain	Ongoing trial	1 year
Boersma et al. (MESSI) [28]	2014	160	SSV	MOCA vs. RFA success, post-procedural pain	Ongoing trial	1 year
Lane et al. [29]	2016	170	GSV	MOCA vs. RFA Postoperative pain scores	VAS:15 mm vs. 34 mm ($P = 0.003$) Numeric:3 mm vs. 4 mm ($P = 0.002$)	6 months

QoL quality of life, *VAS* visual analog scale

The first randomized trial comparing MOCA and RFA was conducted by van Eekeren in 2013 in 68 patients with GSV insufficiency to compare the differences in postoperative pain and early quality of life after both procedures. Patients treated with MOCA reported significantly less postoperative pain in the first 14 days (4.8 ± 9.7 mm) compared to RFA (18.6 ± 17 mm, $P < 0.001$). The lower postoperative pain was associated with early return to daily life activities (1.2 ± 1.8 days vs. 2.4 ± 2.8 days, $P = 0.02$). At follow-up of 6 weeks, patients in both groups had an improved change in health status and quality of life [2]. In addition to similar results regarding postoperative pain scores and quality of life, Bootun et al. in 2016 noted an equivalent clinical success rate of 92% in both the groups (MOCA vs. RFA) [23] (Table 10.2).

The LAMA trial (endovenous laser ablation versus mechanochemical ablation with ClariVein) has been designed to compare the outcomes of both procedures at 1 year as well as intraprocedural

pain (n = 140 patients). Secondary outcomes for the trial include post-procedural pain, analgesic use, patient satisfaction and quality of life, and complications along with a cost-effective analysis following EVLA and MOCA [26]. The results of the trial were recently presented and showed decrease intraprocedural pain with MOCA compared to EVLA during truncal ablation. However, the overall post-procedural pain was not different since most patients underwent phlebectomy during the same procedure. The technical success rate was also comparable between MOCA (92%) and EVLA (94%). There was no difference in overall quality of life and return to work [27].

The MARADONA trial (mechanochemical endovenous ablation versus radiofrequency ablation in the treatment of primary GSV incompetence) has been designed to compare the anatomical and clinical success rate of MOCA compared to RFA at 1 year (n = 460 patients) [21]. Patients will then be followed up for 5 years to determine long-term data. The results of this study are expected in 2020. Another similar randomized clinical trial has been designed (MESSI trial) to look at anatomical and clinical success rates of MOCA and RFA for the SSV (n = 160 patients in total) [28].

Complications

Minor complications after mechanochemical ablation include mild hyperpigmentation, ecchymosis, local hematoma, and phlebitis. Transient phlebitis is the most common minor complication noted in patients treated with MOCA (4–14%) [14] (Table 10.1). The incidence of phlebitis is however lower compared to ETA techniques using radiofrequency ablation or foam/liquid sclerotherapy [17, 30]. This low incidence of superficial phlebitis with MOCA may be because of no heat being generated to occlude the vein with ClariVein compared to other alternative techniques. However, the risk of phlebitis should be explained to patients prior to procedure. Patients need to be advised to use compression/NSAIDs to treat if symptoms of phlebitis are noticed.

During venous ablation of SSV, there lies an additional risk of nerve injury due to the anatomic proximity of the sural nerve in the distal calf. A recent meta-analysis by Hirsch et al. compared the risk of nerve injury after the different known techniques for treatment of varicose veins. They concluded that the use of nonthermal endovenous techniques such as MOCA has proved to be better alternatives than ETA to avoid nerve injuries [31]. A study by Pan et al. compared open technique to endovenous and concluded that it had twice the risk of nerve injury/paresthesia compared to thermal ablation using EVLA (11.27% vs. 6.73%). Previous studies have shown transient nerve injury between 1.3 and 11% for EVLA [17, 32–34]. Dermody et al. have shown that RFA has a lower risk of nerve injury compared to EVLA (3.8 vs. 5.5%). The incidence of nerve injury with MOCA is rare and has been reported in only one study (0.2%) to date [14].

Deijen et al. have published the study with largest patient population to date (n = 449) and is the only study to have reported an incidence of deep vein thrombosis (one patient) and pulmonary emboli (two patients) [14]. There has been otherwise no case of venous thromboembolism, deep vein thrombus, or skin necrosis reported with MOCA [35, 36].

A rare complication of retrograde inversion stripping of the small saphenous vein was reported in a recent case study in 2015, where during an elective procedure, the tip of the ClariVein® catheter wire got caught into a small calcified tributary and on gradual withdrawal leading to stripping of the vein along with the device. This case illustrated the possibility of rare adverse events occurring during an elective routine procedure; however in this case, the patient suffered no recurrence or nerve injury [37].

Conclusion

The ClariVein system is the first venous ablation technique to employ a hybrid (dual energy) technique—mechanical and chemical, combined in a catheter-based device. It decreases procedural pain and discomfort related to tumescence. Most

studies have demonstrated good clinical efficacy at 1 year. Currently, there is no clear consensus on what strength and dosage of sclerosant is ideal for MOCA. This technology continues to evolve and there is an ongoing randomized clinical trial "dose-finding study" to determine the ideal sclerosant dosage to use [25, 38].

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Endovenous Sealing of Superficial Veins

11

Roshan Bootun, Tristan R.A. Lane, Ian J. Franklin, and Alun H. Davies

Clinical Pearls

1. Treatment of the saphenous vein using VenaSeal starts at 5 cm with the junction of the deep system.
2. Treatment of the saphenous vein using VariClose starts at 3 cm with the junction of the deep system.
3. Phlebitis is the most common complication with endovenous sealing of saphenous veins.

Introduction

Varicose vein disease affects approximately one third of the population [1], causing a variety of symptoms as well as negatively impacting the quality of life (QoL) of patients [2–5]. Treatment of the condition, however, has been shown to lead to improvement in patients' clinical condition and quality of life [6–8].

For a long time, such treatment took the shape of surgical ligation and stripping of the saphenous trunks. With time, though, the need for more minimally invasive interventions was felt, leading eventually to the advent of endothermal ablation, using radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). This endovenous method of treating varicose veins using thermal energy has demonstrated its merits and has been adopted as the first-line treatment option by both the American Venous Forum and the National Institute for Health and Care Excellence (NICE, UK) [9, 10].

This status has come into question with the emergence of newer methods which enable faster and more comfortable procedures. This is of particular interest as endovenous thermal ablation can be associated with patient discomfort during tumescent infiltration as well as potential injury caused by the thermal ablation process itself. These newer techniques, namely, mechanochemical ablation (MOCA) [11] and cyanoacrylate glue injection (CAE) [12], are commonly referred to as

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non-thermal, non-tumescent (NTNT) interventions. There is a suggestion that MOCA might be equivalent to the endothermal treatment [13, 14].

In this chapter, the technique and outcomes of cyanoacrylate adhesive injection are discussed.

What is Cyanoacrylate?

The chemical adhesive used in this method is N-butyl cyanoacrylate (n-BCA), which was first introduced to medical practice more than 40 years ago [15]. It is a liquid monomer, which quickly polymerises and solidifies in contact with an anionic solution (e.g. with the hydroxyl groups in blood) [16]. In the beginning, it was found to have a low tensile strength and gave rise to features suggestive of both an acute and a chronic inflammatory process [15]. The polymerisation event leads to occlusion, a marked inflammatory endothelial response, and eventually leads to fibrosis [16].

Gradually, following the addition of plasticisers and stabilisers, the material was made more flexible and less toxic [15]. This rendered the chemical more appealing and expanded its use in ophthalmology, wound closure, dentistry and gastroenterology [17]. More than 10 years of cyanoacrylate use in the endoscopic sclerotherapy of gastric variceal bleeding confirmed that the chemical was safe [17].

In endovascular surgery, cyanoacrylates have been found indispensable in the treatment of type I and II endoleaks of abdominal aortic aneurysm repairs, arteriovenous malformations (AVM), varicoceles and pelvic congestion syndrome [17].

Given the efficacy and good safety profile of cyanoacrylates in these endovascular procedures, Dr. Raabe, an interventional radiologist from Washington (USA), considered using a similar technique in the treatment of varicose veins [18]. However, as the characteristics of the cyanoacrylate in use at the time were inappropriate for leg varicose veins, a team of chemical, biochemical and product engineers were assembled to produce a chemical with more suitable properties and develop a delivery system suited for leg veins [18].

Vein Sealing Devices and Technique Used

Two vein sealing devices are currently available. They are the VenaSeal™ closure system (Medtronic, Minneapolis, Minnesota, USA) and the VariClose® vein sealing system (Biolas®, Ankara, Turkey). The technique of cyanoacrylate injection as well as the makeup of the adhesive used differs.

VenaSeal™ Closure System

The VenaSeal™ closure system was the first device available, and the technique of vein sealing involves segmental pullback. The method of cannulation is similar to other current endovenous methods: truncal vein cannulation and insertion of a 0.035 in. J-guidewire, followed by placement of a 7Fr introducer sheath/introducer [12]. A 3 mL syringe containing the cyanoacrylate adhesive is connected to the delivery catheter. This latter system possesses hydrophobic properties, thereby preventing adhesion to the vessel wall, and air-filled microchannels, which allow for better visibility when using an ultrasonic device [12]. The dispenser gun is then fired, thus priming the catheter. Each trigger pull delivers 0.1 mL of cyanoacrylate. In order to prevent premature contact between the cyanoacrylate and blood during introduction into the venous lumen, the distal 3 cm of the catheter tubing is kept empty. The catheter is then connected to the introducer sheath, and under ultrasound guidance, the tip is positioned 5 cm from the saphenofemoral junction (SFJ). With extrinsic pressure applied over the SFJ (above the tip of the catheter) using the ultrasound transducer, 0.2 mL of cyanoacrylate is delivered (two trigger pulls). The catheter is pulled back 3 cm, and pressure is applied to the treated segment for 3 min. Again, the ultrasound probe is positioned above to the tip of the catheter, 0.1 mL of CAE (one trigger pull) is injected and 30 s of pressure is applied to the vein. This cycle is repeated until the whole vein is treated. At the end, the catheter is removed and additional pressure is exerted onto the entry

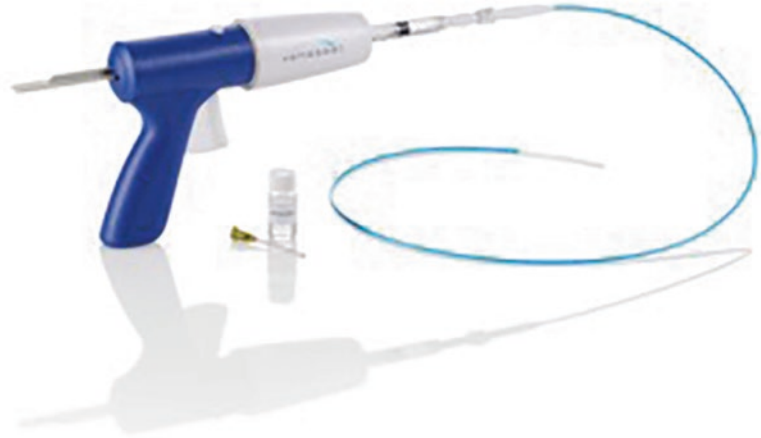

Fig. 11.1 The VenaSeal™ closure system

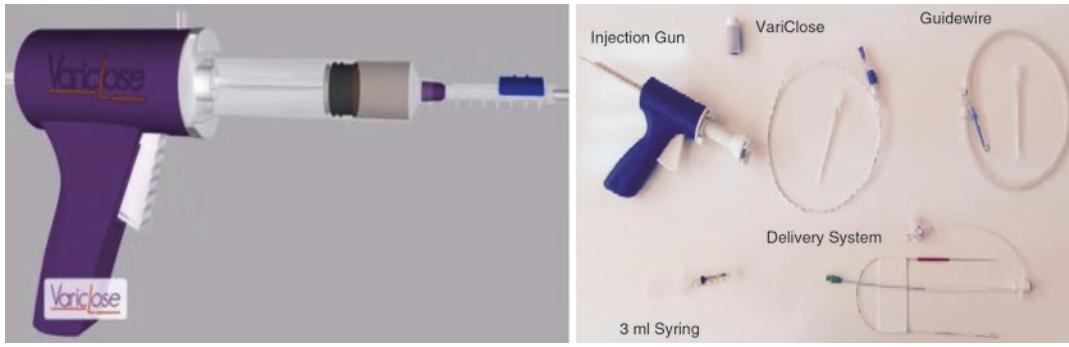

Fig. 11.2 The VariClose® vein sealing system

site. If no further treatment is necessary, a wound dressing is applied on the entry site. There is no requirement to wear compression stockings or bandaging afterwards.

Patients are discharged shortly after their treatment, with the recommendation to return to their normal activities as soon as they are able to (Fig. 11.1).

VariClose® Vein Sealing System

The VariClose® vein sealing system is similar to the VenaSeal™ closure system but uses a cyanoacrylate with a faster polymerisation rate. The process of venous access is as for other conventional endovenous methods. The delivery catheter has been designed with hydrophobic properties and features enabling easy visualisation under ultrasound. A 3 mL cyanoacrylate-containing syringe is connected to this 4Fr catheter, which is primed by slowly pulling the trigger gun over 5 s (delivering 0.3 mL of cyanoacrylate) [19]. The catheter tip is exposed and positioned 3 cm distal from the SFJ. Pressure is applied over the SFJ with the ultrasound transducer. Treatment of the saphenous vein involves injecting 0.3 mL for every 10 cm of vein length. External compression is applied for 5 s following treatment of the first 10 cm of vein. The catheter is pulled back continuously at a rate of 2 cm per second with pressure from the ultrasound probe moving down the leg at the same rate. This carries on until the full length of the vein is ablated (Fig. 11.2).

An adhesive bandage is applied over the entry site, and as for the VenaSeal™ closure system, no compression stocking or bandage is necessary. Patients are advised to return to their normal

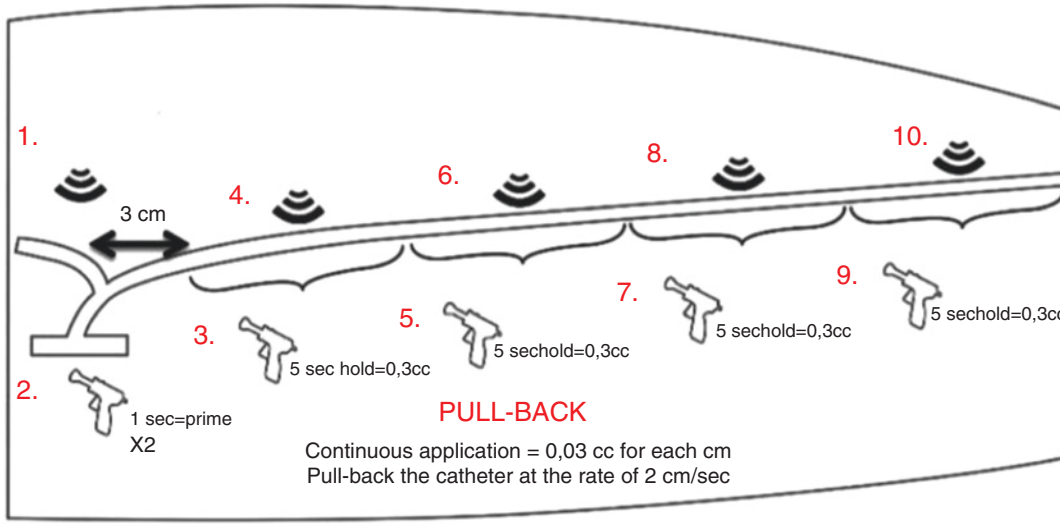

Fig. 11.3 The VariClose® vein sealing system involves positioning of the catheter 3 cm distal from the saphenofemoral junction, injection of 0.03 mL/cm of cyanoacrylate and continuous pullback of the catheter at a rate of 2 cm per second along with simultaneous application of pressure using the ultrasound probe

Table 11.1 Comparison of the VenaSeal™ closure and VariClose® vein sealing systems

	VenaSeal™	VariClose®
Country of origin	USA	Turkey
Venous access	Vein cannulation and sheath insertion	Vein cannulation and sheath insertion
Chemical used	Cyanoacrylate	Cyanoacrylate
Delivery catheter	Connected to delivery gun	Connected to delivery gun
Catheter pullback	Segmental	Continuous
External compression	Segmental	Continuous
Speed of polymerisation	Slow	Fast
Distance from SFJ	5 cm	3 cm
Post-intervention compression	None	None

activities as soon as possible but to wait until 1 day after their intervention before they start exercising (Fig. 11.3) (Tables 11.1 and 11.2).

Table 11.2 Comparison of the cyanoacrylate characteristics of the two vein sealing systems

	VenaSeal™	VariClose®
Colour	Clear	Blue
Consistency	Viscous (like 'honey')	Runny (like 'water')
Polymerisation	Slow	Fast
Texture post-polymerisation	Soft	Hard

Cyanoacrylate in the Treatment of Varicose Vein Disease

Animal Studies

A plastic and a tissue model (common carotid artery of a swine) were used to investigate the process of polymerisation of cyanoacrylates, and three distinct stages were noted [20]. An initial stage (phase I), lasting less than 10 s, showed a linear rate of increasing tensile forces, while a second stage (phase II), lasting up to 1 min, was found to have a constant strength of tensile

forces. Finally, the third and final step (phase III) follows phase II and involves complete polymerisation of the compound, characterised by an exponential rise in the tensile forces [20]. The strength of the binding forces as well as the rate of polymerisation is variable and dependent on the type and formulation of cyanoacrylate used [17, 20].

Evaluation of cyanoacrylate as a vein sealing method was conducted in the superficial epigastric veins (SEVs) in a swine model [21]. The SEVs were treated with the cyanoacrylate, and the swines were euthanised 60 days later. There were no sections of the SEVs which were patent. The segment treated was shown to be occluded with histological sections showing the presence of both inflammatory cells and fibrous tissue. This was consistent with a chronic foreign-body-type inflammatory reaction. No undesirable migration of the chemical or recanalisation of the treated veins was found.

Human Studies

VenaSeal™ Closure System

In the first clinical trial of CAE in the treatment of varicose veins, Almeida et al. (2013) recruited 38 patients [12]. They used the Sapheon closure system (Sapheon, Santa Rosa, California, USA) (eventually acquired by Medtronic, Minneapolis, Minnesota, USA) in which the catheter tip is placed 4 cm away from the SFJ. The incompetent GSV was treated, and patients were reviewed up at different time points over 24 months. Seventy-six percent of them were females, and the median age of patients was 51 years (range, 26–77 years) [12]. The mean length of GSV treated was 33.8 cm (standard deviation (SD), 9.1 cm), and the mean GSV diameter at the SFJ was 8.0 mm (SD, 2.2 mm). The complete occlusion rates were 100% at 2 days and 92.1% at the 12-month follow-up (three veins had recanalised). Using a Kaplan-Meier life table analysis, the occlusion rate was found to be 92% at the 24-month point [22]. Commonly encountered complications included post-operative thrombophlebitis (seven patients), thrombus extension into the common femoral vein (eight patients), cellulitis (one patient) and hyperpigmentation (one patient) [12].

A multicentre study in seven European centres looked at the use of CAE in the treatment of incompetent GSVs, but the distance of the catheter tip from the SFJ was modified to 5 cm [23]. This distance was thought to be more suitable as it could allow for glue propagation proximally towards the SFJ following cyanoacrylate injection and, at the same time, would provide for enough space to exert external pressure between the tip of the delivery catheter and the SFJ. As per Almeida et al. study, no compression hosiery was prescribed following treatment. In addition, no tributary treatment or reintervention was undertaken until after 3 months of post-ablation. Seventy patients were recruited in total, 78.6% of whom were females. The mean age was 48.4 years (range, 22–72 years). The mean length of GSV treated was 37.6 cm (range, 7–72 cm), and the mean GSV diameter at the SFJ was 7.8 mm (SD, 2.1 mm). The mean ablation time was 18.6 min (range, 8–74 min). At the 12-month follow-up, the complete occlusion (defined as no patent segment of more than 10 cm) rate using a life table method was 92.9% [23]. The Venous Clinical Severity Score (VCSS) improved from a mean of 4.3 at the baseline to 1.1 at the 12-month follow-up ($p < 0.0001$). The disease-specific Aberdeen Varicose Vein Questionnaire (AVVQ) also showed improvement from 16.3 at the baseline to 6.7 at 12 months ($p < 0.0001$). Phlebitis was noted in eight legs, and a single patient had thrombus extending into the common femoral vein. Treatment of this complication with 2 weeks of low molecular weight heparin led to resolution of the thrombus.

The efficacy of the VenaSeal™ device in the treatment of varicose veins was compared to endothermal ablation techniques in a multicentre randomised controlled trial (the VeClose trial), with patients randomised to receiving either radiofrequency ablation (RFA) or cyanoacrylate injection [24]. Two hundred and twenty-two patients were recruited, randomised and treated. Since the instruction for the use of RFA recommends compression stockings, these were prescribed for 7 days for all patients (3 days

continuous wear and 4 days for daytime wear only). The primary end-point was a successful closure of the entire treated vein with no discrete patent segments of more than 5 cm. The most common CEAP clinical class recorded was 2 and 3. Three months post-intervention, the occlusion rate for the cyanoacrylate group was found to be 99% compared to 96% in the RFA group [24]. Clinical scores (VCSS) and QoL (AVVQ and EQ-5D) showed significant improvement from the baseline, with no difference between treatment groups. There were more cases of phlebitis noted in the cyanoacrylate group, but this was not statistically significant. The degree of ecchymosis was found to be significantly less in the cyanoacrylate group ($p < 0.01$). The mean intra-procedural pain scores for CAE was 2.2, compared to 2.4 for RFA ($p = 0.11$). This study demonstrated that cyanoacrylate was not inferior to RFA and that it was a safe and highly effective method of varicose vein treatment.

VariClose® Vein Sealing System

Bozkurt and Yilmaz (2016) investigated the VariClose® vein sealing system, by comparing the cyanoacrylate injection device to endovenous laser ablation (EVLA) in patients attending for treatment of their GSV incompetence [19]. Three hundred and fourteen patients were recruited and followed up for 1 year. The mean age was 40.2 years for the EVLA group and 42.5 years for the CAE group. The mean GSV length was 29.7 ± 8.1 cm for EVLA and 29.8 ± 5.4 cm for CAE, and the mean vein diameter was 7.1 ± 1.6 mm and 7.2 ± 1.8 mm for EVLA and cyanoacrylate, respectively. Pain scores were recorded as 6.5 ± 2.3 for EVLA, compared to 3.1 ± 1.6 for CAE ($p < 0.001$). The procedure time was significantly faster with cyanoacrylate (15 min for CAE vs 33.2 min for EVLA; $P < 0.001$). At 12 months, the occlusion rate was found to be 95.8% for CAE and 92.2% for EVLA [19]. Both the clinical scores (using VCSS) and QoL scores (AVVQ) showed significant improvement compared to the baseline, and there were no significant differences between the two groups. Seven cases of paraesthesia were noted in the EVLA group compared to none in the cyanoacrylate group. This study, therefore, showed that both endothermal ablation and cyanoacrylate injection were equivalent.

Complications of Cyanoacrylate

The most commonly recorded complication after cyanoacrylate injection seems to be ecchymosis and phlebitis. Extension of thrombus into the common femoral vein was noted in the first human trial, and this was believed to be secondary to the catheter being placed too close from the SFJ and not providing enough room for the glue to propagate along the vein [12]. This distance was, therefore, increased in ensuing studies with a resultant improvement in the rate of this complication. The acceptable distance for the VenaSeal™ closure system catheter tip from the SFJ is now 5 cm [23, 24]. The VariClose® vein sealing system, however, still uses a distance of 3 cm, and no thrombus extension into the deep venous system has been described. Another potential problem with the technique is the possibility of the adhesive getting stuck in the delivery sheath, thereby making movement and retrieval of the catheter difficult.

Other possible complications from cyanoacrylate come from other medical usage of the chemical. In the treatment of gastric varices, CAE is at the risk of systemic embolisation. This can cause pulmonary embolism, multi-organ infarction via a patent foramen ovale, stroke and recurrent sepsis caused by the embolised cyanoacrylate glue acting as a septic focus [25]. These latter adverse events have, thus far, not been reported with cyanoacrylate use in varicose veins.

Conclusion

Varicose vein management is fast evolving with endovenous ablation now the accepted new norm. Endothermal ablation is recommended as first-line treatment by a number of venous societies, but its use is associated with complications related to the thermal ablation process as well as discomfort from tumescent infiltration. The new

non-thermal, non-tumescent methods have been launched with the aim of avoiding these undesirable effects while maintaining a high effectiveness rate. Vein sealing, using the cyanoacrylate injection devices, seems promising and has shown equivalence when compared with the endothermal methods. There is currently no set limit on the amount that can be used, and, therefore, this might be more advantageous than some of the other non-thermal interventions (e.g. the European Phlebological Societies guidelines recommend a maximum of 10 mL of foam sclerosant to be used per session [26]).

Based on available evidence, the endothermal technologies remain the favoured choice for endovenous ablation in many European centres. NICE guidelines on the use of cyanoacrylate glue occlusion for varicose veins have also highlighted that current evidence on the safety and efficacy of the technique is limited and advocates its use with special arrangements only [27]. Further randomised comparative studies will hopefully shed more light onto the longer-term efficacy of the technique.

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Sclerotherapy

12

Kathleen Gibson

Clinical Pearls

1. Hypertonic saline is the sclerosant that causes most pain.
2. Physician-compounded foam is produced by the Tessari method and combining 1:3 or 1:4 mixture of sclerosant and gas.
3. Propriety foam has smaller bubbles with narrower distribution of sizes than physician-compounded foam and is therefore more stable.

Overview

Venous insufficiency is one of the most common vascular disorders, with a prevalence of up to 63.9% in a survey of over 91,500 patients [1]. As outlined by a multidisciplinary consensus committee on chronic venous disease, the clinical severity of venous disease is wide, and patients may present with manifestations ranging from cosmetically bothersome telangiectasias to advanced disease with ulceration [2]. The use of sclerotherapy, whether liquid or foam, has a role in treating venous disease at every stage. Sclerotherapy is one of the most widely used treatments for improving the appearance of spider veins. It can be used to treat truncal saphenous incompetence, as well as incompetent tributary veins. In more advanced disease, it has been used in the treatment of pathologic perforator veins and in treating nests of abnormal dermal and subdermal veins associated with active and healed ulcers. In addition to these more common uses, sclerotherapy is also an important treatment for vascular malformations and the treatment of pelvic venous insufficiency. With the transition of venous care from the hospital to the office and the increase in the use of minimally invasive ultrasound-guided techniques, the breadth of applications of sclerotherapy in the treatment of venous disorders makes it an integral part of a vein physician's armamentarium.

History

Sclerotherapy refers to the destruction of a vein by injecting it with a substance to induce vessel injury followed by obliteration of the vessel. Zollikofer, in Switzerland, reported the first documented use of sclerotherapy in the treatment of veins in 1682. He injected a vein with acid to induce thrombosis. Since that time, multiple

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different sclerosing agents have been used including absolute alcohol, mercury compounds, sugar complexes, and hypertonic electrolyte solutions. The most commonly used sclerosing agents in use today, hypertonic saline, sodium tetradecyl sulfate (STS), and polidocanol (POL), were first described in 1926, 1946, and 1966, respectively [3].

Foam sclerotherapy is a technique that is in wide use in the United States and throughout the world [4]. Foam sclerosants are produced by mixing sclerosants in the detergent class with a gas (typically room air, CO2, O2, or a CO2/O2 mixture). The first published description of mixing air with a sclerosant was in 1944, by Orbach [5]. This technique did not become popular until some 50 years later. In 1997 two papers were published regarding the use of foam sclerosants. Juan Cabrera of Spain described his technique, utilized since the early 1990s of the creation of sclerosant foam to treat varicose veins [6]. Monfreux of France in the same year published a technique for creating a foam sclerosant using a glass syringe and a sterile plug [7]. The method of foam production that is most widely used today (the double syringe technique) was described by Lorenzo Tessari of Italy in 2000 [8].

Physician-compounded foams (PCFs) are not standardized and vary widely according to sclerosant used, gas used, and technique of production. This variability leads to differences in the physical characteristics of the foam including variation in bubble size, as well as foam stability [9]. In 2013, after 14 years of systematic pharmaceutical development, the FDA approved a standardized proprietary foam sclerosant. Marketed as Varithena™ (BTG West Conshohocken, PA), it is an injectable 1% POL foam with specific indication for treatment of incompetent great saphenous veins, accessory saphenous veins, and their branches above and below the knee [10]. Standardized commercial products provide more consistent foam characteristics (bubble size, sclerosant strength) and assured sterility [9].

Sclerosants

Destruction of the target vessel is the intended action for all sclerosing agents, but the mechanism of action differs depending on sclerosant class. Table 12.1 lists the most commonly used sclerosing agents worldwide. The main sclerosant classes are hyperosmolar agents, detergents, and corrosives. Hyperosmolar agents cause diffusion of water from the intracellular space to the extracellular, causing nonspecific cell destruction as well as hemolysis. In contrast, detergent sclerosants cause protein theft denaturation. This causes lysis of the cell wall, without hemolysis. Corrosive sclerosants have a direct cytotoxic effect on the endothelium. All sclerosants stimulate platelet aggregation. This in turn induces a dense network of platelets and fibrin that occlude the vessel, which is eventually replaced with fibrotic tissue [11].

The most widely used sclerosants in the United States are hypertonic saline, STS, and POL [4]. Both STS and POL are approved by the FDA for

Table 12.1 Sclerosing agents

Agent	Class	Trade name	Distributor	FDA/US status
Hypertonic saline	Hyperosmolar	N/A	Multiple	Off-label
Saline/propylene glycol	Hyperosmolar	Sclerodex	Omega Laboratories (Canada)	Not available
Sodium tetradecyl sulfate	Detergent	Sotradecol	Mylan	Approved
Polidocanol	Detergent	Asclera	Merz	Approved
Sodium morrhuate	Detergent	Scleromate	Glenwood, LLC	Approved
Chromated glycerin	Corrosive	Sclermo	Omega Laboratories (Canada)	Not available
Polyiodinated iodine	Corrosive	Sclerodine	Omega Laboratories (Canada)	Not available

Table 12.2 Advantages and disadvantages of sclerosing agents

Agent	Advantages	Disadvantages
Hypertonic saline	Inexpensive No real allergy potential	Painful Ulceration with extravasation Can cause hyperpigmentation
Sodium tetradecyl sulfate	Minimally painful Able to treat larger veins	Allergy less rare Ulceration more common than with POL Contraindicated with severe asthma Can cause hyperpigmentation
Polidocanol	Nearly painless Ulceration rare Allergy very rare	Limited in size of veins to treat Can cause hyperpigmentation

venous injection, but the use of hypertonic saline is considered "off-label." Specifically, STS is approved for treatment of "veins of the lower extremity," whereas POL is approved for the treatment of reticular and spider veins. Each sclerosant has different dosing, different advantages, and disadvantages as shown in Table 12.2. STS is a synthetic surfactant (soap), while POL is a non-ester local anesthetic [12]. Hypertonic saline has only a local effect and then is rapidly diluted. Detergent sclerosants are quickly deactivated by binding to circulating blood proteins, which may be a factor in the low incidence of thrombotic complications with sclerotherapy [13].

In general, while it is less expensive than other agents, hypertonic saline is more painful and has more adverse effects than detergent sclerosants [14]. STS is available in higher concentrations (stronger potency) in the United States than POL and therefore may be the agent of choice in the treatment of larger veins, venous malformations, and in the treatment of pelvic congestion syndrome [15, 16]. In other parts of the world, higher concentrations of POL are available. Most sclerotherapists would advise injecting larger vessels prior to moving on to smaller vessels: injecting feeding reticular veins, for example, prior to spider telangiectasias.

Liquid vs. Foam Sclerotherapy

Sclerosants from the detergent class can be mixed with gases to produce foam sclerosants. Upon injection, foam sclerosants displace the blood in the vessel, forming a "vapor lock," keeping the drug in contact with the vessel wall and delaying deactivation by circulated plasma proteins. The injected foam sclerosant is in contact with the vessel wall for a longer period of time, which increases the efficacy in comparison to liquid sclerotherapy. Volume and concentration of the sclerosing agent can therefore be decreased, as the active contact time is increased [17].

Advantages of foam over liquid sclerotherapy include its echogenicity with ultrasound, allowing the user to perform sclerotherapy in a precise and controlled manner. In general, foam sclerotherapy is not used for spider vein injections but is utilized for larger veins. Foam sclerotherapy is superior to liquid sclerotherapy in terms of closure rates of varicose veins and truncal veins such as the great saphenous vein (GSV). A prospective randomized trial by Hamel-Desnos and colleagues in 2003 compared foam sclerotherapy to liquid sclerotherapy (using POL) in the treatment of GSV reflux. This demonstrated that foam sclerotherapy eliminated GSV reflux in 84% and 80% of limbs at 3 weeks and 6 months, whereas liquid sclerotherapy had the same effect in 40% and 26% of limbs during the same time points [18].

Physician-Compounded Foam

Physician-compounded foam (PCF) is considered an "off-label" use of FDA-approved liquid sclerosants as the drug is fundamentally changed by mixing it with a gas. Despite the lack of

specific FDA approval, the use of PCFs in the United States, and indeed worldwide, is widespread [4]. PCFs are an effective tool in the treatment of truncal veins, tributaries/branches (replacing microphlebectomy in many cases), venous malformations, and pelvic source varicosities. Treatment is readily performed in an outpatient clinic setting and requires no procedural sedation, and patients return to normal activity levels very quickly with minimal discomfort. PCFs are produced by forcibly mixing a sclerosant of the detergent case with a gas through a small aperture, producing small sclerosant encapsulated gas bubbles. The aperture used is typically either a three-way stopcock or a "female to female" stopcock (double syringe technique). Air or physiologic gases (CO2, O2, or a mixture of both) are typical gases, while the most common choices of sclerosant include POL and STS. Figure 12.1 shows the technique as described by Tessari [19]. Typically the ratio of liquid to gas is 1:3 or 1:4 depending on whether "wet" versus "dry" foam is preferred. The stability of the foam and the size of gas bubbles in the circulation are dependent on the method of foam production, the gas chosen for use (O2 vs. CO2 vs. room air), and other factors including atmospheric pressure and temperature [20]. As the amount of nitrogen in the gas used to create foam increases, the foam is more stable, but the bubbles are also less soluble in the blood [21].

In terms of the use of PCF in the treatment of GSV incompetence, duplex closure rates are highly variable in the literature, ranging from 69 to 91%, depending on the agent used, the concentration, and the number of treatment sessions administered before assessing closure [22–26]. These variables, as well as differing patient populations and disease severities, make comparisons between studies difficult. Additionally, the evaluation of outcome assessments including venous clinical severity scores (VCSS) and quality of life (QOL) instruments is not consistent or uniform. Two more recently randomized trials did assess QOL after ablation of the GSV with ultrasound-guided PCF vs. comparator treatments. Rasmussen and colleagues randomized patients to surgical stripping, endothermal laser ablation (EVLT), radio-frequency ablation (RF), or ultrasound-guided foam sclerotherapy (UGFS). Recanalization and retreatment were most common in the UGFS group, but at 3 years, all groups showed similar improvements in VCSS and QOL [27]. A second randomized trial by van der Velden and colleagues compared EVLT and conventional surgery to UGFS. At 5 years, the GSV was obliterated in 85%, 77%, and 23% in the surgical, EVLT, and UGFS groups, respectively. In contrast to the Rasmussen study, QOL scores in the UGFS groups were inferior compared to the other groups [28]. Other studies suggest that UGFS is a cost-effective treatment for GSV reflux, especially when compared to conventional surgery [29].

Venous tributaries associated with saphenous reflux can be treated in either a staged or concomitant fashion. Choices for tributary treatment

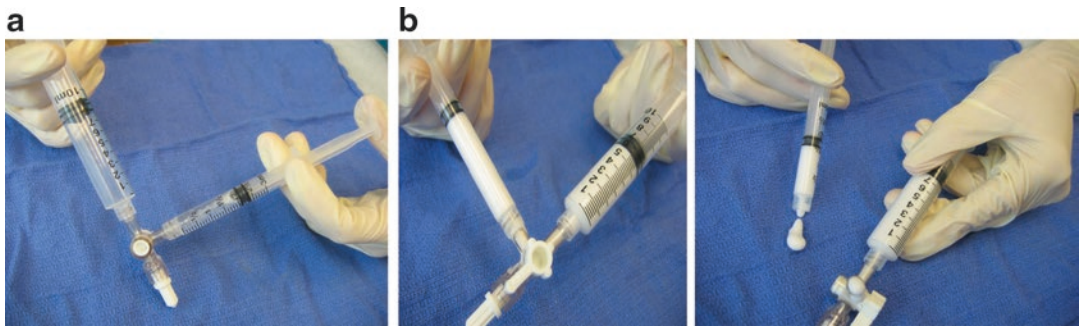

Fig. 12.1 Tessari technique for the production of physician-compounded foam. (**a**) 8 cc gas, 2 cc liquid. (**b**) Mix with three-way stopcock

include stab phlebectomy and UGFS. Recent clinical practice guidelines from the Society of Vascular Surgery and the American Venous Forum recommend either approach as an acceptable treatment (Grade 1B) [30]. Data comparing stab phlebectomy to UGFS in the treatment of tributaries is sparse, and both treatments have proponents. Considerations in treatment choice include vein size, depth, extent, and history of hypertrophic scarring or hyperpigmentation.

The use of PCF is in general thought to be safe and well tolerated; however, serious adverse events can occur. In particular, neurologic complications such as strokes and transient ischemic attacks, while rare, have been reported. In most of these reported cases, air was the gas used to produce the foam, and the patients were often found to have a structural defect such as a patent foramen ovale (PFO) or atrial septal aneurysm [31–34]. These cases have led some to advocate the use of physiologic gases (CO2 or CO2/O2) rather than air-based foams for the production of PCF [35]. While there is no firm data to support this position in terms of prevention of strokes and TIAs, there is data demonstrating fewer visual disturbances and other side effects when physiologic gases are used [36]. Physiologic gases, which have minimal nitrogen content, are biocompatible and as such are rapidly absorbed. Other than gas canister cost, there is little downside to their use. While there is minimal risk of cerebral embolization in patients without a PFO or large pulmonary shunt, a study of 221 varicose vein patients showed that 58.5% of the individuals had a right to left shunt with bubble testing: much higher than the prevalence of such shunts in the general population (est. 26%) [37]. Although individuals with right to left shunts are ostensibly at higher risk of cerebral embolization with foam sclerotherapy, the overall rarity of these events and the high prevalence of such shunts in this population make screening for shunts prior to foam sclerotherapy impractical and unnecessary. Nonetheless, foam sclerotherapy should be used with caution in patients with a known right to left defect, particularly if the patient has a history of previous events that led to the detection of the defect. The use of good quality foam (no grossly visible bubbles) and limiting injection volumes is recommended. In the case of neurologic symptoms during or after foam sclerotherapy, hyperbaric oxygen therapy has been reported to resolve intracerebral gas in the vasculature [34].

Proprietary Foam

An alternative to the use of PCF for the treatment of incompetence of the GSV, accessory saphenous veins (ASV), and their tributaries is proprietary endovenous microfoam (PEM), marketed as Varithena™. There are no head-to-head studies comparing PCF to PEM, and extrapolating results from studies of PCF are difficult due to varying study designs, endpoints, and the lack of a standard production method or technique for PCF. The sclerosant drug in PEM is 1%POL, but it is produced with a proprietary canister system containing a very low nitrogen physiologic gas. With in vitro testing in a benchtop vein model, PEM gas bubbles are overall smaller, with a narrower distribution of sizes when compared to PCF bubbles, and the stability of PEM foam is superior to PCF. Theoretically increased stability should improve foam performance in vivo, and smaller circulating bubbles could theoretically improve patient safety [37].

The neurologic safety of the use of PEM for the treatment of GSV incompetence was demonstrated in a Phase II clinical trial published in 2011. Patients with symptomatic GSV incompetence were tested with a transcranial Doppler (TCD) bubble testing for the presence of a right to left shunt. Patients who qualified for the study by virtue of a positive bubble test were then treated with PEM. During treatment, TCD monitoring showed middle cerebral artery bubbles in 61 patients. These patients had diffusion-weighted MRI testing (very sensitive to the presence of edema formation) at baseline and at 24 h and 1 month posttreatment. Patients additionally underwent visual field and neurologic testing.

None of the patients were found to have changes in MRI, visual fields, or neurologic examinations after PEM treatment [38].

In the development of PEM, following the Phase II trial, pilot studies were performed to develop a patient-reported outcome tool (PRO) and to test methods of patient blinding leading up to the pivotal Phase III trials in the United States [39]. The reliance of surrogate markers such as duplex closure of veins was deemed by the FDA to be insufficient for approval of PEM, and they required a validated PRO assessing varicose vein symptoms to be the pivotal study endpoint [40]. The VVSymQ® is the PRO instrument used in the trials. It assesses the severity of the five symptoms (heaviness, aching, throbbing, swelling, and itching) shown to be most relevant to patients with varicose veins.

The two pivotal trials, VANISH-1 (275 patients) [41] and VANISH-2 (230 patients) [42], utilized the VVSymQ® as the primary study endpoint and change in appearance of the leg as assessed by both an independent physician reviewer and the patients themselves. Patients with symptomatic GSV or ASV reflux were enrolled in the prospective single-blind randomized trials. Duplex closure was assessed, as was patient safety. Both studies compared PEM to placebo, but the VANISH-1 study randomized patients to three differing doses of POL (0.5, 1.0, and 2.0%), while VANISH-2 randomized patients to 0.5 or 1.0% POL. VANISH-2 patients were allowed to have a two treatment sessions, separated by 1 week. At 8 weeks the primary endpoint (improvement in the patient PRO) and the secondary endpoints (including improvement in appearance) were assessed. Both studies showed significant improvement in both PRO scores and appearance, and compared to placebo, these improvements were highly statistically significant ($p < 0.0001$ for both endpoints). One-year follow-up was reported for the VANISH-2 group, and symptom improvement was sustained [43]. The duplex closure rates at 8 weeks in the 1% POL groups were 80.4% for the VANISH-1 trial [41] and 86.2% for the VANISH-2 trial [42]. There were no significant adverse neurologic events in the trials, other than headache, but 5.4% of patients had superficial thrombophlebitis following the procedure, and 4.7% had a deep vein thrombosis (DVT) on follow-up duplex examination. The majority of these events were asymptomatic and detected because of study protocols requiring detailed post-procedure duplex evaluation, including imaging of all tibial vessels. There were no symptomatic pulmonary emboli, and none of the patients with a DVT later showed signs or symptoms of post-thrombotic syndrome.

Following the pivotal trials, the FDA approved Varithena for use in November of 2013 [44]. The product was released for commercial release in August of 2014. Advantages over traditional endothermal ablation techniques for truncal saphenous ablation include the avoidance of tumescent anesthesia with its attendant pain and bruising [45, 46] and the ability to treat side branch tributaries quite simply in a concomitant fashion. It can be used to treat tortuous veins and in this way can treat a broader spectrum of anatomic presentations compared to EVLT and RF. As such, it provides an attractive option for treating recurrent varicose veins and neovascularization. It does not have an indication for treatment of the small saphenous vein (SSV), so its use in this disease pattern would be considered off-label. Primary disadvantages compared to endothermal ablation include dosing limitations which may limit the number of veins that can be treated in a single session, a lower rate of duplex closure, and a higher rate of thrombotic events (DVT and superficial thrombophlebitis), when compared to historic endothermal ablation data. While data to support the safety and efficacy of PEM is robust compared to data for PCF, it is significantly more expensive.

One of the main barriers to the use of PEM at the time of this publication is the lack of a dedicated current procedural technology (CPT) code for billing. Payor coverage and reimbursement rates are variable and regional, with some insurers still considering PEM “investigational.” Over time, carrier coverage has become more widespread,

and issues of coverage and reimbursement should become more certain when a CPT code specific to PEM is approved.

Patient Workup Prior to Sclerotherapy

A thorough history and physical examination should be taken prior to treatment of either varicose veins or telangiectasias with sclerotherapy. Patients should be queried about previous treatments and response to those treatments including any adverse events they may have encountered. Special attention should be paid to the patient's goals—are they being treated for cosmetic reasons, for symptoms, or for both? It is imperative that the risks and benefits of the procedure be addressed, and the pretreatment consultation is key to avoid unrealistic expectations on the part of the patient. Multiple sclerotherapy sessions may be required for the patient to achieve their goals.

Special considerations in the pretreatment consultation include review of medications and medical history. Sclerotherapy should not be performed in pregnant women or women who are breast-feeding unless the benefit clearly outweighs the risk, which is seldom if ever the case for venous treatment. Patients who are taking minocycline should not be treated with sclerotherapy as permanent hyperpigmentation can occur [47]. If a patient has had a previous reaction to a sclerosing agent, they should not receive that agent again. Small dose skin testing with subsequent in-clinic observation can be performed and would be recommended in any patient in whom there is concern for allergic reaction. STS is contraindicated in patients with asthma. All locations where sclerotherapy is performed should have a readily available and up-to-date emergency kit in the event of an anaphylactic reaction to a sclerosant.

Prior to foam sclerotherapy with PCF or PEM, patients are queried about a known history of a structural heart defect (such as an atrial septal defect or a PFO), and if present, alternative therapies may be suggested. As sclerotherapy may cause visual disturbances or migraine headache [48], patients with a history of migraine (especially migraine with aura) are cautioned that therapy could possibly trigger symptoms. They are advised to bring any medications that they would usually take in the event of a migraine with them to their sclerotherapy session.

Techniques

STS is available in 1 and 3% concentrations, and POL is available as 1 and 0.5%. Both STS and POL have a maximum volume per session of 10 cc. Small volumes should be injected, and the concentration of sclerosant injected will depend on the vein size. Table 12.3 lists suggested sclerosant concentration by vein diameter. The lowest effective dose and concentration that will reliably achieve vessel occlusion should be used in order to minimize adverse effects such as matting, ulceration, and venous thrombosis.

Prior to sclerotherapy of either telangiectasias or varicose veins, photo documentation of the intended treatment area(s) is recommended. Photographs of the same area(s) should be repeated in follow-up to assess results and progress. Injection sites, type, and volumes of sclerosants should be documented at the time of treatment. In the author's practice, "before and after" photos are shared with the patient at every visit. With the treatment of telangiectasias in particular, the main reason for treatment may be the patient's dissatisfaction with visual appearance of the limb, making photography a necessary tool. The widespread availability of digital

Table 12.3 Sclerotherapy concentration by vein diameter

Vein diameter	Detergent	Hypertonic saline
<1 mm	STS 0.1–0.3% POL 0.3–0.5%	11.7%
1–3 mm	STS 0.5–1.0% POL 1.0%	23.4%
>3 mm	STS 1.0–3.0% POL 1.0% (or foam)	–

cameras and software programs to store medical images has simplified the use of photography in a vein practice.

Telangiectasias

Sclerotherapy of spider telangiectasias, while both safe and effective, can take a great deal of practice before mastery is obtained. The sclerotherapist should position themselves in a favorable ergonomic position in relation to the target vein. As the target vein may be a millimeter in diameter or less, any extraneous movement will dislodge the needle from the vein. When performing sclerotherapy, bracing the elbow, wrist, and hypothenar eminence of the dominant hand against a solid surface will ensure stability. The non-dominant hand is used to stretch and stabilize the skin. Such positioning is shown in Fig. 12.2. A small needle (30 or 32 gauge) and a small volume (3 cc) syringe are typically used. During injection the needle angle is very shallow with the bevel is up. Bending the needle can be helpful to facilitate shallow vein entry. The sclerosant is "dripped" into the vein with a minimal amount of pressure to avoid extravasation. There are many options to improve visualization of small veins from simple (magnification lenses, loupes) to more complex. The Syris™ system, Veinlite®, and Venoscope® are all transillumination aids, while the Veinviewer® utilizes projected near infrared light to visualize subdermal veins.

Aftercare following sclerotherapy is not standardized, and most practitioners follow nonevidence-based guidelines. There is very little data regarding exercise, bathing, and sun exposure following sclerotherapy. Compression stockings or bandaging is routinely recommended, but the level of compression and length of time stockings should be worn is highly variable. A randomized trial of 100 by Kern et al. in 2007 compared results in women treated with 3 weeks of 23–32 mm Hg compression stockings versus no stockings following sclerotherapy of telangiectasias and reticular veins. The study found no difference in adverse events between the two groups but did find a significant difference ($p = 0.026$) in favor of compression in terms of improvement in appearance as rated by blinded observers [49].

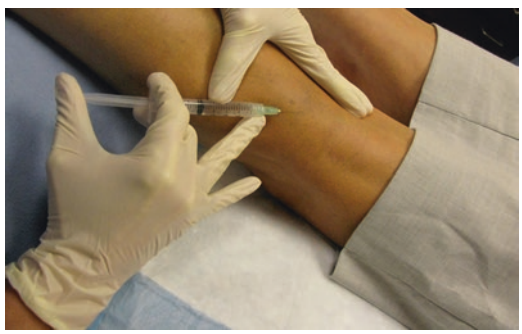

Fig. 12.2 Positioning for sclerotherapy of telangiectasias

Superficial Venous Insufficiency

PCF is commonly used for treating varicose veins [4] and is most commonly performed with UGFS. If ultrasound is not available, sclerotherapy can be performed with confirmation of needle placement with blood return. The author prefers UGFS as the ultrasound can confirm intravenous needle placement, show spasm in the treated vein, and follow the PCF as it travels through the vein. It is imperative for treating varicose veins that may be too deep to easily see. Marking the veins to be treated with an indelible pen with the patient in the standing position prior to treatment is helpful. The author typically uses a 23- or 25-gauge butterfly needle when treating varicose veins, but a standard needle can also be used. Multiple injections with small volumes are recommended, to avoid inadvertent boluses of foam into the deep system. Transit of the PCF is followed with ultrasound, and successfully treated veins should appear small, bright, and in spasm. The use of compression following treatment of PCF is not standardized in terms of strength of compression, type of compression (bandaging versus stockings), and length of time compression should be worn. The author's practice places patients in a 20–30 mm Hg stocking with or without underlying pressure pads for 2 weeks after treatment. Patients walk for 10 min

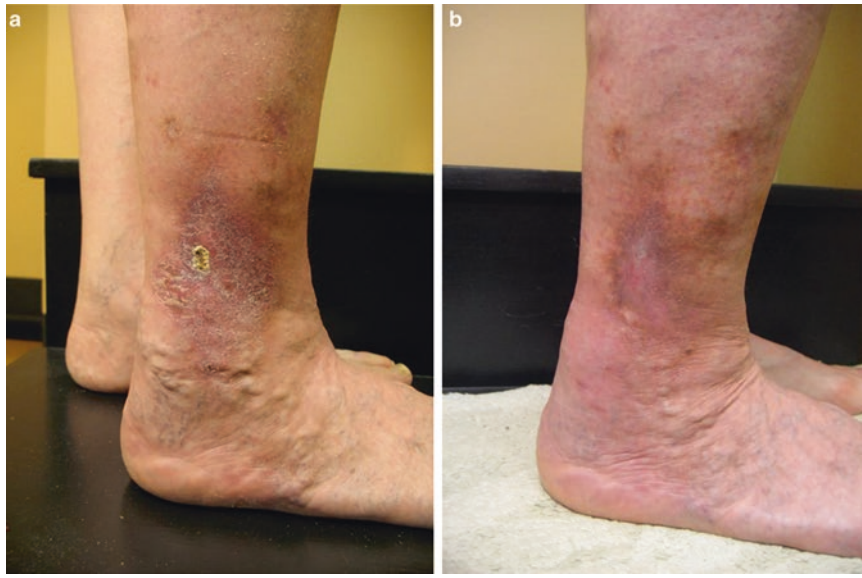

Fig. 12.3 Ultrasound-guided foam sclerotherapy in the treatment of advanced venous disease: before and after photos. (**a**) Baseline. (**b**) Three months posttreatment

post-procedure and are encouraged to walk/be physically active hourly during the first 2 weeks after treatment.

PCF has applicability in the treatment of advanced venous disease [50] as it can be readily used to inject and close nests of abnormal subdermal veins in patients with venous ulceration and lipodermatosclerosis. UGFS in these advanced cases is typically used as an adjunct to truncal ablation and compression therapy. Figure 12.3 shows before and after pictures of a patient with a lateral leg ulcer treated with UGFS and compression therapy. According to recent SVS/AVF guidelines, treatment of pathologic perforator veins (those greater than 3.5 mm in diameter with >500 ms of reflux near an open or healed ulceration) is suggested to aid in ulcer healing and prevent recurrence in patients with CEAP clinical class 5 or 6 disease [51]. UGFS can be used to treat pathologic perforator veins, and Masuda and colleagues showed a 75% improvement in patients' VCSS and venous disability scores [52]. When treating perforator veins with foam, the author recommends injection of small volumes, dorsiflexion of the foot, and pumping of the calf muscle after injection to potentially decrease volumes of foam in the deep veins.

In the author's practice, UGFS is commonly used to treat pelvic source varicose veins presenting with vulvar and inner or posterior thigh varicose veins. Pelvic venous insufficiency is a frequent source of recurrent or missed varicose veins [53]. The author uses a standard technique for treatment of veins in this region but typically has an assistant, so that one hand performs the injection, one hand holds the ultrasound probe, and two hands stretch and flatten the skin to pin the underlying veins as they tend to roll away from the needle. In the author's experience, the technique is quite successful with a low incidence of side effects; however, some patients may need multiple treatment sessions, and recurrence is not uncommon, particularly if the underlying pelvic varices are untreated. Figure 12.4 shows before and after photos of a patient with pelvic venous insufficiency manifesting as vulvar and medial thigh varices before and 3 months after UGFS.

PCF has been used extensively for both treatment of pelvic venous insufficiency on its own or as an adjunct to coil embolization of the gonadal veins [54]. It also is an essential tool for the treatment of vascular malformations [55]. Discussion of these techniques is beyond the scope of this chapter.

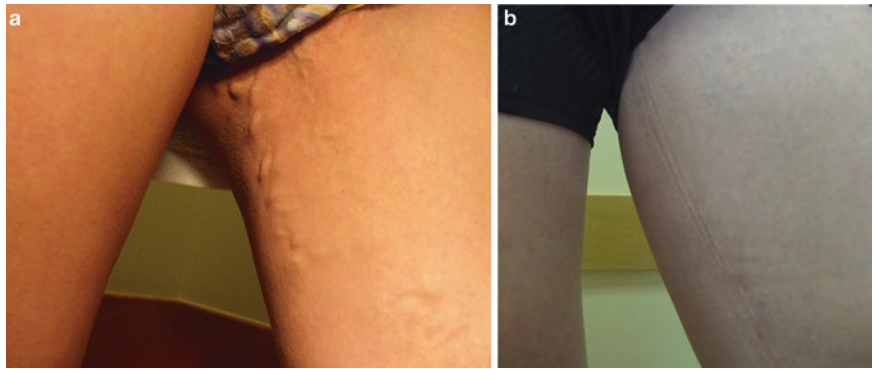

Fig. 12.4 Pelvic source varicose veins before and 3 months after ultrasound-guided foam sclerotherapy. (**a**) Baseline. (**b**) Three months

PEM

The technique for GSV or ASV ablation with PEM is standardized and outlined in its instructions for use (IFU) [56]. The technique requires two individuals—one to image the saphenofemoral junction and one to compress the SFJ once the PEM reaches this area and a second to inject PEM and hold pressure caudal to the access site. The GSV or ASV is accessed in a typical fashion with ultrasound guidance in a transverse or longitudinal view with either an angiocatheter or a micropuncture sheath with the tip of the access catheter usually positioned in the midthigh. Once venous access has been confirmed with blood return, the catheter is flushed with saline, and the limb is elevated approximately 45 degrees. The PEM is produced according to the IFU and is injected into the vein using a silicon-free syringe. During injection, the GSV or ASV caudal to the access site is compressed digitally, and an ultrasound probe is held in longitudinal view over the SFJ to await arrival of the PEM. The PEM will appear as a bright white column traveling forward through the vein as shown in Fig. 12.5. As soon as this column reaches about 2–3 cm from the SFJ, the ultrasound probe is turned into the transverse position, and the GSV or ASV is compressed to keep the PEM from entering the common femoral vein. Simultaneously, the digital pressure being held beyond the access site is released. The SFJ is compressed until the GSV or ASV is visualized with ultrasound and found to be in complete spasm along the treatment length, with no areas of patency. This may take up to 5 min. In the author's experience, a typical GSV can be treated with 4–7 cc of PEM.

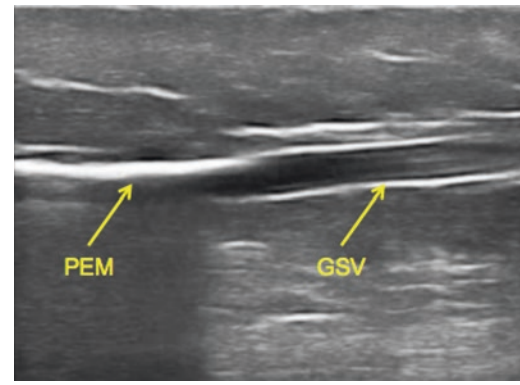

Fig. 12.5 Column of PEM in the GSV

Following treatment of the truncal vein in the thigh, it can be treated more caudally by either pulling the access catheter back slightly, compressing above the tip of the catheter and injecting retrograde through the catheter, or by accessing the vein in another location. Side branches are then accessed using a butterfly or other needle and injecting small volumes of PEM (1–2 cc per injection) while compressing any large perforator veins in associated with the side branches being treated. Up to 15 cc of PEM may be used in a treatment session. Following completion of treatment, the leg is wrapped with a short-stretch bandage, a compression pad, and a compression stocking. Patients are instructed to

walk or be active for 5–10 min out of every waking hour for the first 2 weeks after the procedure. More than one treatment session may be required for optimal results in patients with extensive branch varicosities.

Side Effects and Complications

Allergic reactions may occur with injection of any substance; however, allergy to hypertonic saline would only occur if the patient had an allergy to any additives in the solution. Allergy to both POL [57] and STS [58] has been reported, but in general, allergy is felt to be more common with STS. As stated earlier in this chapter, emergency kits should be readily available in all clinics performing sclerotherapy, with all appropriate staff trained in the treatment of anaphylaxis.

Cutaneous necrosis can occur following sclerotherapy and can be disfiguring. Ulceration is felt to be more common with hypertonic saline and STS compared to POL but can occur with any sclerosant [59]. It is more common in patients with dense telangiectasias, especially in areas of thin skin or bony prominences. Mechanisms of cutaneous necrosis include extravasation of contrast and inadvertent injection into a small arteriole or arteriovenous fistula. Figure 12.6 shows ulceration on a patient's skin following liquid sclerotherapy treatment for telangiectasias. Patient reassurance is important, as most ulcerations are small and will heal over time, although scarring may result. Large areas of cutaneous necrosis may require referral to a wound care specialist.

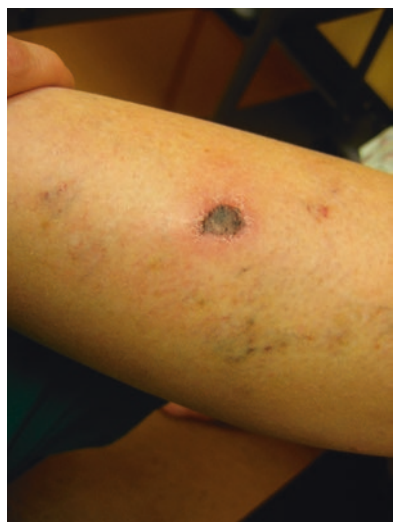

Fig. 12.6 Skin ulceration following sclerotherapy

Telangiectatic matting can occur after sclerotherapy in 10–30% of patients [59]. The etiology is not known but may be due to angiogenesis as a response to inflammation. Retrospective studies have shown a possible link to the use of oral contraceptives and increased risk of matting [60]. Compression therapy does not decrease the incidence of matting [49], and it can occur with any sclerosing agent. As with hyperpigmentation, patients should be reassured that resolution with time is typical.

Hyperpigmentation is common following sclerotherapy and will generally gradually lighten and improve over time. Spontaneous resolution will typically occur in 70% of patients by 6 months and 99% of patients by 1 year [59]. Conservative therapy with observation should be the first approach to the patient with hyperpigmentation after sclerotherapy. In the case of persistent hyperpigmentation, bleaching agents [61], topical lasers [62], and intense pulse light (IPL) therapy [63] have been suggested for treatment.

Deep vein thrombosis can occur following sclerotherapy and as referenced earlier in this chapter occurred in 4.7% of patients treated with PEM in the VANISH trials [41, 42]. Most of these patients were asymptomatic. A review of nearly 1 million subjects undergoing venous procedures from a nationwide healthcare database comprised of 40 million patients showed that the prevalence of reported DVT and PE after sclerotherapy was 0.8% and 0.2%, respectively. These rates were lower than reported rates for endothermal ablation (RFA and EVLT) and surgery [64]. Superficial phlebitis after sclerotherapy is not uncommon but is rarely dangerous. Early drainage of trapped coagula using an 18-gauge needle or a number 11 blade may provide quick relief of discomfort and decrease the extent of hyperpigmentation following sclerotherapy.

As described earlier, strokes have been reported in rare circumstances with the use of foam sclerosants. Visual disturbances and migraines are more commonly reported and can occur with the use of either liquid or foam sclerotherapy. A recent literature review estimated that the prevalence of transient visual disturbance with sclerotherapy ranged from 0.09 to 2% [65]. Proposed mechanisms for visual disturbance and migraine with sclerotherapy include gas and particle microemboli or the release of endothelin from the treated veins. Endothelin is a potent vasoconstrictor and bronchoconstrictor, and increases in endothelin-1 with foam sclerotherapy in a rat model give support to the concept that endothelin release may be responsible for side effects of migraine, visual disturbance, and cough following sclerotherapy [66].

In general, sclerotherapy is safe and well tolerated, and it is likely that the most common "adverse event" following treatment is failure to meet the patient's expectations in terms of cosmesis. One of the most important considerations in terms of patient satisfaction is educating patients in regards to realistic outcomes. Patients should be counseled that immediate improvement in appearance is not likely and that improvement is usually gradual and incremental. Multiple treatment sessions, especially for telangiectasias, may be necessary for the patient to achieve their desired results. Pre-procedural counseling should be thorough and include showing patients photographic examples of both ideal and nonideal outcomes.

Conclusions

Sclerotherapy is a versatile tool for the treatment of superficial venous insufficiency: from the treatment of unsightly telangiectasias to advanced venous disease. The availability in the United States of proprietary foam may broaden the indications for the use of sclerotherapy. Familiarity with therapeutic agents and proper techniques are imperative to for both patient safety and for obtaining good results.

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Treatment of Incompetent Perforating Veins

13

Eric S. Hager and Joyce Y. Lin

Clinical Pearls

1. The current indication to treat perforator reflux is diameter >3.5 mm with reflux >0.5 s in relation to a venous ulcer.
2. Thermal ablation is more effective than ultrasound-guided foam sclerotherapy for treatment of perforator reflux.
3. When treating a perforator with RFA stylet catheter, a drop in impedance to 150–350 Ω insures that the tip of the catheter is in the vein.

Chronic venous insufficiency is a major health problem that affects many people with devastating consequences. Venous valvular incompetence leading to venous reflux and venous hypertension is the pathophysiology of developing venous disease. Increasingly, incompetent perforator veins have been recognized as a contributor to recalcitrant or recurrent venous ulcers. Historically, surgical interruption of perforators has been performed and shown to improve healing of venous ulcers. With advances in technology and comfort in endovenous procedures, percutaneous thermal ablation and ultrasound-guided foam sclerotherapy have gained popularity in the treatment of perforating veins with good success.

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Background

Chronic venous insufficiency (CVI) is a widespread and potentially debilitating problem that affects millions of people. An estimated 23% of Americans have varicose veins including 6% with advanced venous insufficiency resulting in skin changes or ulcerations [1]. The symptoms can range from asymptomatic varicose veins to severe ulcerations. Patients with venous ulcerations are often frustrated by the high recurrence rates and constant care which requires frequent wound care visits, missed work, and social isolation. These factors contribute to significant psychosocial issues and extraordinary healthcare costs [2]. The etiology of CVI has mostly been attributed to genetic factors, but pregnancy, obesity, history of deep vein thrombosis, and jobs requiring long hours of standing have all been shown to contribute [3].

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The etiology of chronic venous insufficiency is venous hypertension. This frequently occurs from incompetent venous valves but can also arise from outflow obstruction [4]. In addition to refluxing superficial axial veins, incompetent perforating veins (IPVs) are also being increasingly recognized as a contributor to the formation and recurrence of venous ulcerations [5]. In normal limbs, perforator veins connect the superficial system with the deep system. There is typically at least one bicuspid valve within the perforator allowing unidirectional blood flow from the superficial to the deep veins. When these valves become incompetent causing venous reflux, local areas of the skin are at risk for ulcer formation [6]. Often when ulcers failed to heal or there is recurrence after successful treatment of the refluxing axial veins, one should look at IPVs as a culprit.

Historically, it was Linton who first suggested in 1938 that interruption of IPVs is a necessary adjunct in the treatment of advanced venous insufficiency. Although rarely done in contemporary practice, several modifications to the original Linton procedure have been described [7–10]. These techniques all had severe wound complications as the incisions are often lengthy and made through fragile skin that was near or at the site of the ulcer [7–10]. The high morbidity of these open procedures led to its eventual abandonment, especially with the introduction of subfascial endoscopic perforator vein surgery (SEPS) by Hauer in 1985 [11].

SEPS is a minimally invasive technique to interrupt calf perforator veins under direct vision using endoscopic instruments placed through small ports remote to the target IPV. Once the leg is insufflated, the IPV is identified and then either ablated with electrocautery or clipped and divided under direct vision [12]. Due to the decreased wound complications by having fewer incisions and away from the problematic skin, SEPS became the procedure of choice to treat IPVs between 1992 and 2008 [13, 14]. In recent years, the emergence of thermal ablations and sclerotherapy performed under ultrasound guidance has completely transformed the techniques of perforator ablation. Today, the open Linton type procedures and SEPS have become more of a historical significance and are very rarely, if ever, performed.

Societal guidelines have classified pathologic perforating veins as incompetent veins near an area of ulceration with a diameter > 3.5 mm and reflux time > 0.5 s [15]. The Society of Vascular Surgery and American Venous Forum recommend against selective treatment of perforating vein incompetence in patients with simple varicose veins (CEAP class C2) but suggest treatment of pathologic perforating veins (outward flow, >0.5-s reflux time, and vein diameter > 3.5 mm) located underneath or near healed or active ulcers (CEAP class C5–C6). The guidelines also recommend the treatment of choice be SEPS, ultrasound-guided sclerotherapy, or thermal ablation (2C recommendation) [15].

Medical Treatment

The initial treatment of patients with CVI is compression. There is good evidence that compression therapy is effective and is the basic treatment for all forms of CVI, including ulceration [16]. The types of compressive therapy range from compression stockings that are easily managed by the patients themselves to complicated medicated wraps that need to be changed by nurses or in wound clinic. Specifically, compressive therapy includes graded compression stockings, paste gauze boots (Unna boot), multilayer elastic wraps, dressings, elastic and nonelastic bandages, and nonelastic garments [16]. However, compliance with compressive therapy varies, and the results can be strikingly different. Mayberry et al. treated 113 patients with venous ulcers with local wound care and compressive therapy and found that the ulcer healing rate was 97% in compliant patients vs. 55% in non-compliant patients. In addition, they reported that ulcer recurrence was 16% in compliant patients vs. 100% in non-compliant patients [17].

The efficacy and cost-effectiveness of conservative therapy over surgical therapy have been studied in the REACTIVE trial, a randomized clinical trial that studied 246 patients with C2 disease. This trial demonstrated that surgical therapy provides more improvement in quality of life and is more cost-effective than conservative treatment alone [18]. Van Gent et al. further demonstrated

the same benefit of surgery over conservative management in advanced venous disease (C5–C6) in a prospective multicenter randomized trial [19].

Controversies often surround the need for a period of compression prior to intervention. Although most third-party payers have this requirement, there is no clinical evidence to support this practice. In reality, many patients have difficulty donning compression stockings which often leads to noncompliance.

With respect to perforator veins, it is important to understand that throughout the evaluation and treatment of IPVs, compression remains a basic and essential component of the global treatment plan, regardless of what other treatments are done concurrently or consecutively.

Percutaneous Thermal Ablation Techniques

Endovenous thermal ablation of pathological veins is a minimally invasive percutaneous technique used to cause thrombosis of the treated veins by thermal injury [20]. In order to achieve occlusion and therefore ablate the targeted vein, the laser fiber or radiofrequency-emitting catheter is placed in contact with the IPV wall in order to deliver direct thermal energy. The heat damages the endothelium of the venous walls, resulting in vasospasm and denaturation of the collagen leading to thrombosis and fibrosis of the vein [20, 21]. The two well-described thermal techniques are endovenous laser ablation (EVLA) and radiofrequency ablation (RFA). EVLA was first described in the English literature for the treatment of varicose vein by Bone in 2001 [22]. The RFA catheter, ClosureFast RF catheter (VNUS Medical Technologies, San Jose, Calif), was introduced in 2007 and has gained in popularity in the treatment of IPVs [23, 24].

Percutaneous thermal ablation of IPVs is performed under ultrasound guidance, with local anesthetic typically in an ambulatory setting. The pathological perforator is identified as one that meets reflux criteria (>3.5-mm diameter, >0.5-s reflux time) and adjacent to an active ulcer or area of recently healed ulcer. The patient is placed in reverse Trendelenburg position to cause venous distension which aids in visualization and access. Once the patient is prepped and draped and in proper position, local anesthetic is used to infiltrate the skin, and the perforator is examined with ultrasound in the longitudinal view to plan out the best angle to enter (Fig. 13.1).

Radiofrequency ablation uses a radiofrequency stylet catheter (ClosureFast radiofrequency stylet; Medtronic, Minneapolis, MN) which is inserted through the skin into the vein under ultrasound guidance. Insertion can be done directly using the stylet or using a Seldinger technique over a 0.035-inch wire. Impedance values can be measured to confirm placement and are typically between 150 and 350 Ω [3, 15]. Additional local anesthesia is used to infiltrate the tissue surrounding the stylet, the patient is then placed in trendelenburg, and treatment is initiated with the stylet placed 2–3 mm away from the deep venous system. The treatment of perforators uses a spot-welding technique where all four quadrants of the venous wall in the location of the tip of the stylet are treated for 60 s each. The stylet is then withdrawn 3–5 mm, and a second treatment is performed in the same manner. This was repeated for the length of the perforator. At the completion of the treatment, compression is applied to the treated area.

For laser treatment of perforators, a 1470-nm, 400-μm laser fiber can be used. Intraluminal access is obtained with a micropuncture needle kit using ultrasound guidance. Once the fiber is positioned, typically at or just below the level of the fascia and at 2–3 mm away from the deep venous system, local anesthetic is infiltrated into the surrounding tissues and treatment begins. The vein is treated using a pulsed technique with the generator set at 6 W, and the vein was treated with 50–100 J per 2-mm segments for the length of the perforator. At the conclusion of the laser treatment, the probe is removed, and compression therapy is applied to the site.

Ultrasound-Guided Foam Sclerotherapy

Foam sclerotherapy is a fast and relatively simple method for ablating pathologic perforating veins. It utilizes a sclerosant, typically sodium tetradecyl

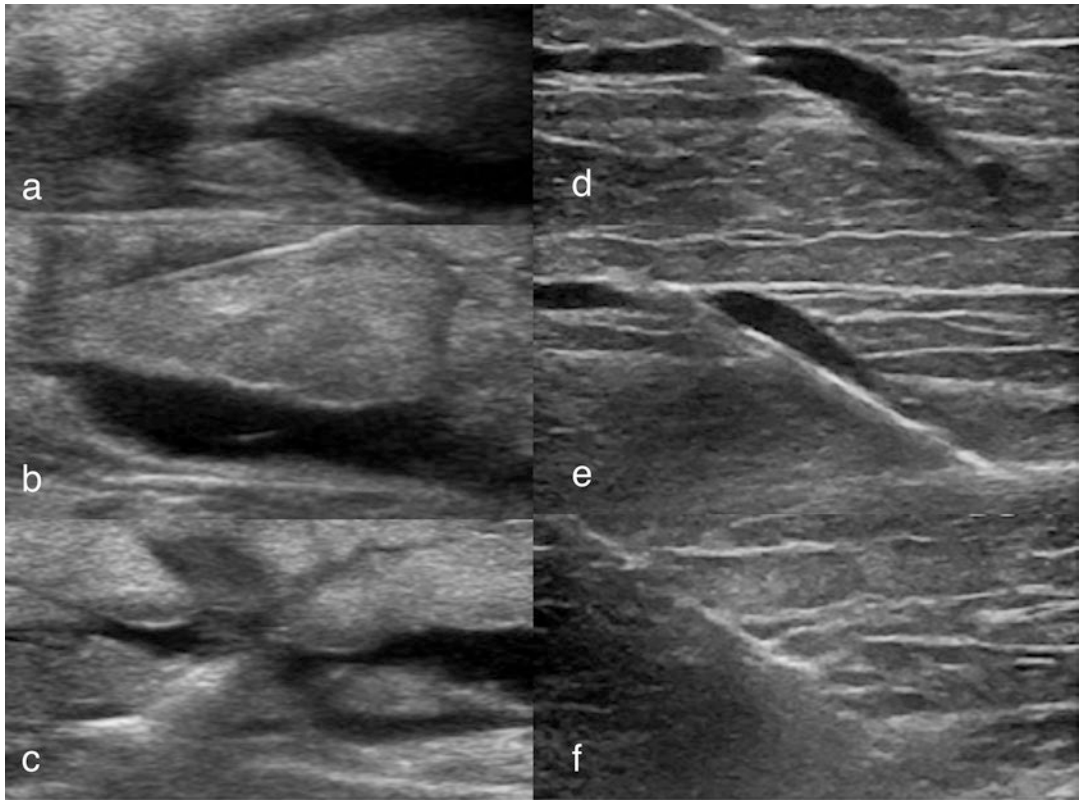

Fig. 13.1 Endovenous thermal ablation of perforators. (**a**) Duplex image showing the perforating vein before EVLT; (**b**) The EVLA fiber placed into the perforator at the level of the fascia; (**c**) duplex showing successful post-procedure ablation; (**d**) A duplex image showing the perforating vein before RFA; (**e**) The RFA images showing access of the stylet; (**f**) duplex showing successful post-procedure ablation

sulfate (STS) or polidocanol, to chemically ablate the vein. Tessari et al. describe a technique using a three-way stopcock for mixing and injecting, and this technique has been widely adopted despite lack of approval by the FDA. The technique uses two syringes connected to a stopcock, one with 1 part sclerosant and the other one with 4 parts air. The two syringes are agitated rapidly until a uniform size microbubble is formed [25].

Ultrasound is used to identify the IPV and its associated varicosities. A 25- or 30-gauge needle is typically used for cannulation of the varicosities to allow a larger volume of sclerosant to be injected. Once access is achieved, the foam is created and slowly injected. The foam is echogenic and easily visualized with duplex. Care should be taken to avoid injecting foam into the deep system. This is achieved by applying compression to the junction between the deep vein and IPV using the ultrasound probe. This allows the foam to reflux into the connecting varicosities and ablate the venous plexus. During the injection, the leg is elevated to reduce the amount of sclerosant entering the deep system. After treatment, compression is applied over the treated perforator (Fig. 13.2).

Current Data

At present, there is no compelling level 1 evidence to support the treatment of IPVs in venous ulcer healing or recurrence [15]. There are a number of small series and retrospective analysis that advocate for IPV ablation in C5 and C6 disease. One of the first studies looking at the

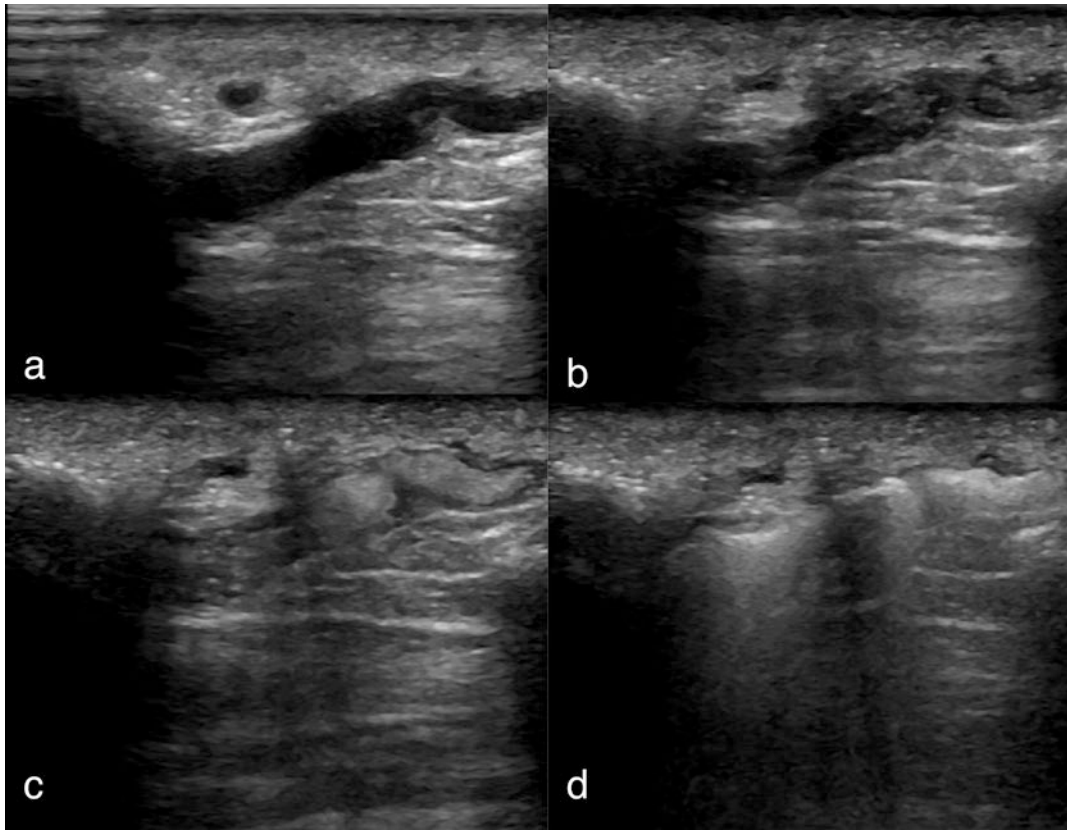

Fig. 13.2 Ultrasound-guided foam sclerotherapy of a perforator vein. (**a**) Perforator vein prior to injection. (**b**) Visualization of the sclerosant within the vein. (**c**) Partial thrombosis of the perforator vein. (**d**) Complete filling of the IPV

efficacy of EVLA in treating IPVs was published in 2010 by Hissink et al. [26]. They prospectively evaluated 58 patients with advance venous disease (C4–C6) that were successfully treated with EVLA with concomitant treatment of refluxing axial veins. They demonstrated that 80% of the ulcers healed with no major complications. Dumantepe et al. demonstrated successful 12-month closure rates approaching 90% with associated improvement in venous clinical severity score [27]. More recently, Zerweck and colleagues reported treatments of 69 IPVs concomitantly with great or small saphenous ablation with a success rate at 30 days of 96% with no reported complications [28]. In 2009, Hingorani et al. published their experience with RFA of IPVs. Their initial success rate was 88% (37 of 43), and they identified venous pulsatility as an independent risk factor for treatment failure in the cohort. Interestingly, the patients with venous pulsatility had only a 20% ablation rate [29].

In one of the larger series, Lawrence et al. enrolled 208 patients with CEAP 6 disease between 2007 and 2010 and looked at the healing of ulcers as an endpoint. All patients enrolled were treated with compression and ablation of axial veins, and after 3 months of aggressive wound care and compression, if the ulcers fail to heal, then perforator incompetence was investigated and treated with endovenous thermal ablation. Forty-five patients in this study met criteria and underwent IPV ablation. Ulcer healing was achieved in 71% at a mean of 193 days.

At 13 months, there was a 4% recurrence rate in this cohort. Interestingly, no ulcers healed without the ablation of at least one incompetent perforator [5]. Even though this study is not a randomized prospective study, it does demonstrate the existence of a subgroup of patients with ulcers that will fail to heal even with optimal compression and ablation of refluxing axial veins, and hence may benefit from perforator ablation. Harlander-Locke and colleagues looked to quantify the rate of healing using planimetry software. They demonstrated an improvement in ulcer healing rate following ablation of refluxing axial veins and perforator veins. Technical success in perforator closure was seen in 81.8%, with 76.3% of ulcers healing at a mean of 142 days. Their recurrence was 7.1% at a mean of 12-month follow-up [30]. In 2015, Shi et al. looked retrospectively at a group of 300 patients with incompetent perforator veins associated with different CEAP classes, half of which underwent ablation of the IPVs, and all of which underwent treatment of refluxing axial veins. At 1 year, 81.3% of EVLT-treated IPVs remained closed. At 1 year, 93% ulcers in the EVLT-treated IPV group healed compared to 89.8% ulcers in the untreated IPV group. Although this result is not statistically significant, the group did find that the median ulcer healing time was significantly shortened in the EVLT-treated IPV group from 3.3 to 1.4 months [31]. Masuda et al. identified and treated 80 limbs with incompetent perforator veins with ultrasound-guided sclerotherapy and reported 86.5% of ulcers healed at a mean time of 36 days. Although his ulcer recurrence rate was high at 32% with a mean of 20 months, he was able to demonstrate a statistically significant association between recurrence of ulcer and recurrence of incompetent perforators [32]. A more recent study by Kiguchi et al. showed a 54% thrombosis rate per injection in patients with venous ulceration. The patients that were successfully treated had significant improvement in ulcer healing rates (69 vs. 38% $P < 0.001$) [33]. There is currently no consensus as to the best modality to ablate IPVs because there are very few comparative studies. In 2016, Hager and colleagues published a comparative analysis between the three modalities in an effort to identify risk factors for treatment failure. They reported the results of 296 ablation procedures in 112 patients, two thirds of which suffered C5–C6 disease. Of the 296 ablations, 21% underwent RFA, 31% underwent EVLA, and the remainder underwent UGFS. They concluded that RFA was the most reliable means of closure, with 73% at 2 weeks. Closure rates were significantly lower for UGFS at 57% but improved to 85% (EVLA) or 90% (RFA) with a subsequent thermal ablation [3].

Complications

The complications of treating incompetent perforating veins are modality specific and similar to known ones previously described for the treatment of refluxing axial veins. Common complications such as paresthesia, discoloration, ecchymosis, thrombophlebitis, and pain can be seen in all three modalities [34]. Thermal burns were associated with RFA and EVLA, while TIAs or visual disturbances were more specifically seen with sclerotherapy [15]. Serious complications such as death and pulmonary embolism occur in less than 1%, as demonstrated by a systematic review of 9000 patients undergoing sclerotherapy [35]. In current literature, 1–2% had paresthesia, 1–2% had thrombophlebitis, <1% had skin discoloration, and 1–25% had pain. Although ecchymosis was included by some studies as a complication with an occurrence as high as 70%, most studies did not consider it to be a complication. More rarely were skin necrosis seen in <2% and DVTs seen in 1–5% [3, 26–28, 31, 32, 36, 37].

Conclusions

The treatment of IPVs has been shown to improve venous ulcer healing rates and reduce ulcer recurrence. A proposed algorithm for the treatment of

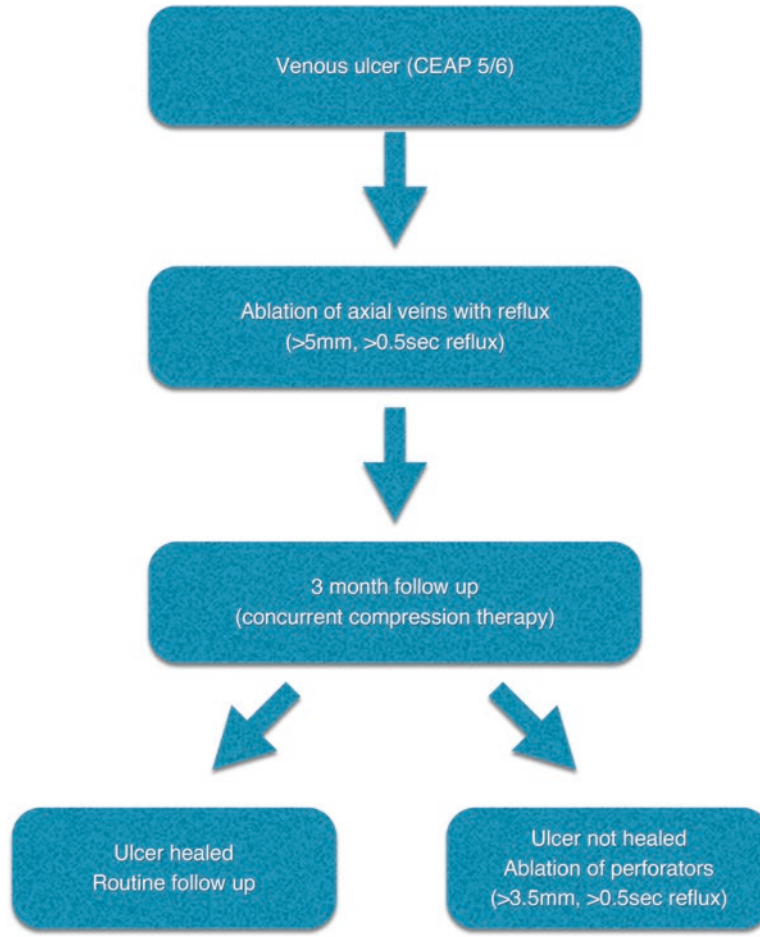

Fig. 13.3 Treatment algorithm for advanced venous insufficiency

advanced venous disease is depicted in Fig. 13.3. In modern clinical practice, the three modalities most often used are UGFS, RFA, and EVLA. These have been shown to be safe and effective although there are very few studies that compare the techniques. Venous pulsatility has been shown to lead to treatment failure in several studies, as it is typically a surrogate marker for fluid overload and severe venous hypertension [29]. Hager et al. also identified BMI >50 as a predictor of failure among all the modalities; anticoagulation and age were not significant predictors [3]. Future studies will seek to identify other risk factors for treatment failure and attempt to establish an algorithm to best treat IPVs given a patient's anatomy and comorbidities.

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Cosmetic Approach to Varicose Veins: The ASVAL Technique

14

Sylvain Chastanet and Paul Pittaluga

Clinical Pearls

1. Phlebectomy of the varicose veins (ASVAL technique) can lead in selected patients to resolution of saphenous vein reflux.
2. The ASVAL technique to treat varicose veins allows saphenous vein preservation and provides symptomatic relief and optimal cosmetic result in selected patients.
3. Saphenous vein ablation is warranted in patients with advanced varicosities and severe reflux.

Introduction

ASVAL (**A**blation **S**élective des **V**arices sous **A**nesthésie **L**ocale) is a relatively new approach for the treatment of varicose veins (VVs) which emphasizes that microphlebectomies improve the hemodynamics of the venous system and the clinical outcomes even in the presence of saphenous vein (SV) reflux [1, 2] and achieves an optimal cosmetic result. Despite some prospective studies published on this topic [3], ablation of the SV in the presence of SV reflux is still widely used without a cosmetic approach. That could be explained by the fact that the criteria for the indication of ASVAL are difficult to determine in the absence of adequate validation in the literature by randomized control trials (RCTs) and also because the technique is not routinely taught in training programs. We will explain in this chapter tips and tricks for the understanding and the performance of ASVAL in daily practice.

The Concept of ASVAL

Pathophysiology of Varicose Veins

Varicosities could develop at the level of the reticulum, stemming from the subfascial venous tributaries, which are the most superficial, the most exposed, and have thinnest walls [1]. In a standing position, the pressure is higher at the lower part of the limb reaching 90 mm Hg at the ankle when the valves are open. The subfascial veins could be the first to dilate through decompensation of their parietal weakness. Progression could initially

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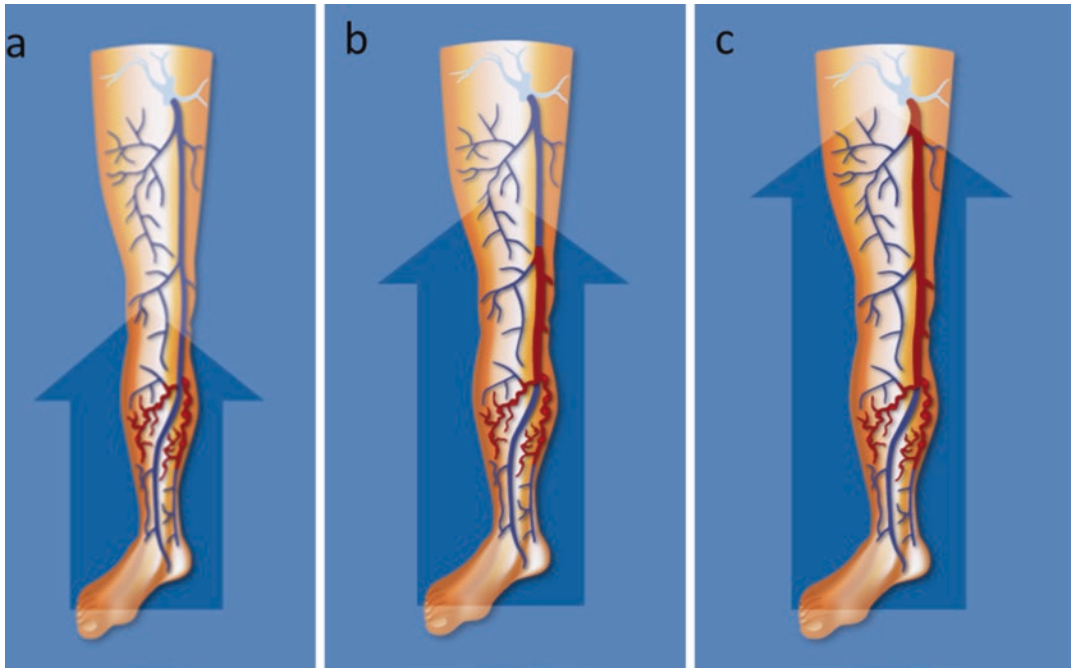

Fig. 14.1 Theory of anterograde evolution of the superficial venous insufficiency from the tributaries up to the saphenofemoral junction. The reflux starts in the tributaries (**a**). The saphenous vein is subsequently affected and becomes dilated and incompetent (**b**). The reflux eventually affects the saphenofemoral junction (**c**)

remain subfascial, creating a dilated, refluxing, or stagnant venous network. When this refluxing network becomes large enough, it could create a "filling" effect in the intrafascial SV, leading to the decompensation of the SV wall, moving cephalad to reach the saphenofemoral or popliteal junction (Fig. 14.1). The SV is the superficial vein with the thickest and most muscular wall. Furthermore, the SV is protected by the splitting of the subcutaneous fascia in which it flows. It would therefore be the last vein to experience decompensation as varicose disease progresses. Numerous publications challenge the theory of descending progression, citing the possibility of local or multifocal early distal evolution, sometimes ascending or anterograde, based on precise and detailed echo-Doppler explorations [4]. Several authors have reported that the ostial valve is frequently competent (>50%) when there is trunk reflux [5, 6].

Practical Application

This pathophysiological theory has two implications:

1. If there is no saphenous reflux, early treatment of VVs would be useful in order to prevent it spreading to the SV.
2. If there is saphenous reflux, and until a certain stage of the disease, first-line therapy should include ablation of the varicose reservoir (VR) and not elimination of the saphenous reflux which is potentially reversible (Fig. 14.2).

Saphenous stripping or ablation would only be indicated in cases where saphenous reflux seems to be irreversible. This approach therefore involves selective management of superficial venous reflux, depending on the clinical and hemodynamic context found in each case. This is the "à la carte" treatment.

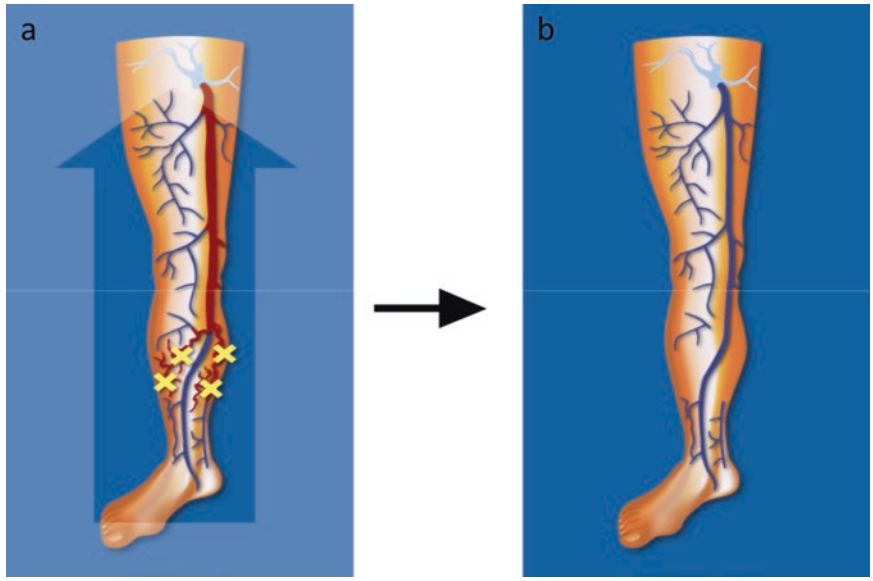

Fig. 14.2 Treatment by ASVAL surgical procedure: phlebectomy of the varicose reservoir (**a**) can lead to the resolution of the reflux in the saphenous vein (**b**)

The main argument in favor of this saphenous sparing approach is the physiological role that the SV could play in superficial drainage and its availability as revascularization conduit if needed. Moreover, literature reports the harmful effect that resection of the SV has on the long-term progression of SV insufficiency [7].

Selection of Patients Eligible for ASVAL

The ASVAL is not indicated in the more advanced stage of venous insufficiency where a saphenous ablation should be performed. Based on our experience of more than 10 years in performing ASVAL and the current published literature, we will discuss the selection process to determine the patients that would benefit from ASVAL.

Extent of the Varicosities

We have reported that the extent of the VR is a determinant factor for the hemodynamic and clinical efficiency of ASVAL [1]. The extent of the VR was evaluated according to the number of zones to be treated (NZT) by phlebectomy, with each limb divided into up to 32 zones in the preoperative clinical mapping (Fig. 14.3). Each limb was divided into four surface areas (anterior, posterior, lateral, and medial), and then each surface area was divided into eight zones: the thigh into three zones (the upper third, middle third, and lower third), the calf into three zones (the upper third, middle third, and lower third), plus one zone for the knee, and one zone for the foot. This arrangement reflects our clinical examination technique, in which we examine each lower limb in a standing position, from the front, from the back, and from each of its profiles (medial and lateral). We observed a significant linear trend between the outcomes after ASVAL and the NZT: when the NZT was above seven, an abolition of the saphenous reflux was 6.81 times more likely obtained ($P = 0.037$) and a symptom relief 2.91 times more likely achieved ($P = 0.004$).

Ultrasound Duplex Preoperative Assessment

During the ultrasound duplex assessment with the patient standing upright, the test of

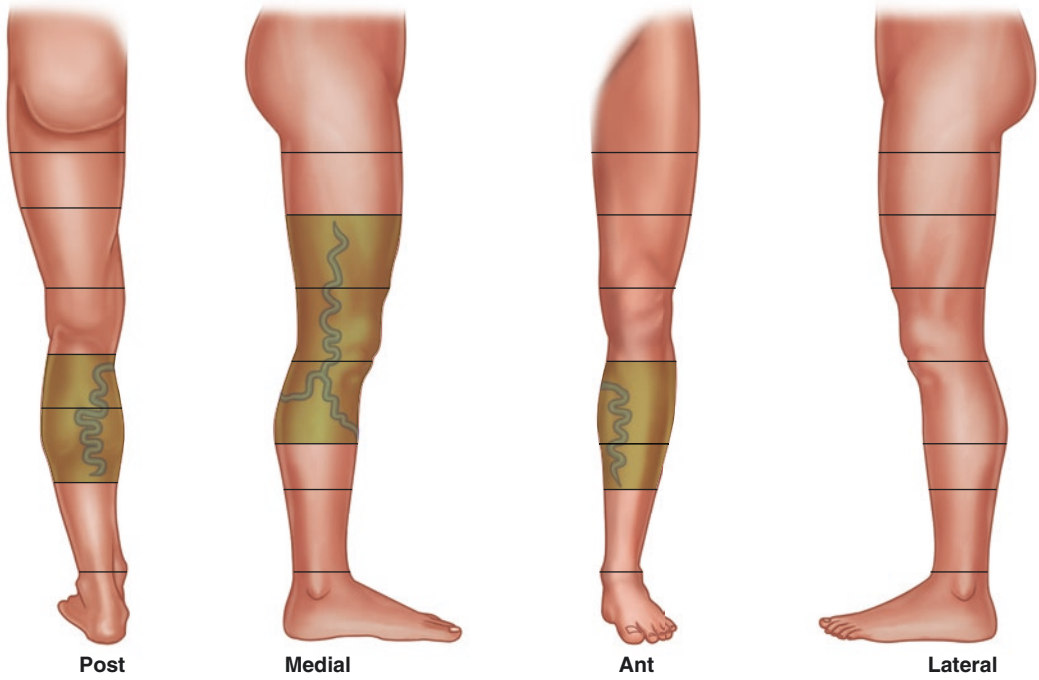

Fig. 14.3 Preoperative clinical mapping shows an example of a limb divided in seven zones for treatment of varicose veins

reversibility (TR) is considered as positive if the reflux of the SV is completely abolished by the compression of the varicose tributary with a finger at the moment of the sudden release of manual compression on the calf. We have reported the value of the TR in a study on 293 lower limbs: the positive predictive value of the TR for the abolition of reflux of the GSV was 95.7% and 94.7% at 1 and 2 years of follow-up [8]. On the other hand, the negative predictive value was weak at 36% and 14% at 1 and 2 years of follow-up, and the preoperative positivity of the TR did not have any correlation with the symptom relief or the cosmetic improvement. It means that if the positivity of the RT is a major criterion for the preservation of the SV, its negativity is not enough at the opposite to ablate the SV. Indeed, we have observed that even when the RT was negative, an abolition of the saphenous reflux, a cosmetic improvement, and/or a symptom relief can be achieved, probably because the RT is not technically feasible in the presence of multiple varicose tributaries.

Phlebectomy Reflux Elimination Success Test (PREST) Prediction Model

Biemans et al. [3] have reported a PREST prediction model including CEAP classification, number of refluxing segments, GSV diameter (above the tributary), and reflux elimination test result, in order to give a preoperative score that correlates with a probability of restoring GSV competence. For example, for patients with GSV reflux in one segment (3 points), C2 (3 points), positive reflux elimination test result (2 points), and GSV diameter of 5 mm (6 points), the model can predict that phlebectomy will be effective in 90% (total of 14 points).

Other Criteria

We have reported that a reflux reaching the malleolus was a mandatory criterion for the abolition of the SV reflux after ASVAL [1].

The nulliparity is a criterion that should be taken into account for the preservation of the SV in young women. The benefit of the ASVAL treatment for nullipara patients has been reported for the reduction of complexity, signs, and symptoms in the event of varicose vein recurrence after pregnancy [9].

The young age and the absence of symptoms with a cosmetic concern are also criteria that plead in favor of the preservation of the SV.

Technique

Skin Marking

The skin marking before the surgery is mandatory to perform a thorough ablation of the VR. We have highlighted that the removal of a large VR is one of the key to get good clinical and hemodynamic outcome after ASVAL [1]. It also diminishes the risk of lymphatic complication after VVs surgery.

Anesthesia

The administration of tumescent local anesthesia is essential for ASVAL. It is a very effective anesthesia, and it reduces dramatically the bleeding because of the subcutaneous high pressure obtained with infiltration of a large liquid volume. In addition, the volume of the mixture leads to a hydrodissection of the perivenous tissue facilitating the extraction of the vein. It gives to the surgeon an excellent comfort for removing all size of VVs. It has been reported that using isotonic bicarbonate instead of saline solution would improve further more the efficiency of the lidocaine and allow to reduce the total amount of lidocaine used, enabling to inject large volume of tumescence and therefore to treat large surface on the lower limb [10]. Since 2008, we use a mixture of 500 cc isotonic bicarbonate combined with 14 cc of 1% lidocaine and 1% epinephrine. As we are far below from the toxic doses, we don't have any restriction regarding the amount of mixture that can be infiltrated. An infiltrative pump is generally used in order to get a homogenous infiltration, but a set of syringes could also be used. The infiltration is done around the vein and parallel to the skin with a 45° angle 21 Gauge needle, making a back and forth movement to decrease the pain during the injection by decreasing the local increase of pressure. We start the injection at one side, and it progresses side by side, each new stick being done in a previously infiltrated area to avoid any pain. One can use a topical anesthetic in addition to tumescent local anesthesia to decrease the pain of the first stick, but it is not essential.

Microsurgery

The use of loops is mandatory to remove the VVs by microphlebectomy. We use a 2X350 magnification in order to be precise enough without losing the peripheral vision.

The incisions are done with a 18-gauge needle. Depending on the quality of the skin and the size of the vein, a 21- or 25-gauge needle can be used. The bevel of the needle makes a flap on the skin that facilitates the penetration of the hook through the skin and gives an excellent cosmetic result (Fig. 14.4). The purpose of the flap is also to make the skin adaptable to the vein size. If the vein size is large, the skin will enlarge easily because of the flap. As it is a tangential and irregular flap, the skin healing will be invisible contrary to a perpendicular incision performed with a blade which makes the scars more visible.

The smaller the hook is, the better the cosmetic result will be. In our experience the best tool is the Muller hook n°0. The phlebectomy should be atraumatic and with a precise skin marking that enables a micro-incision in front of the vein, avoiding scratching the subcutaneous tissues to get the veins. It is recommended to avoid leaving a piece of VVs to be as efficient as possible and in order to get the best cosmetic result since it limits the risk of staining. One important trick is to cut the fibrotic tissue around the vein. This fibrotic tissue is easily cut on the hook with a blade N°11, using the loops. The division of the fibrotic tissue facilitates the extraction of the vein and

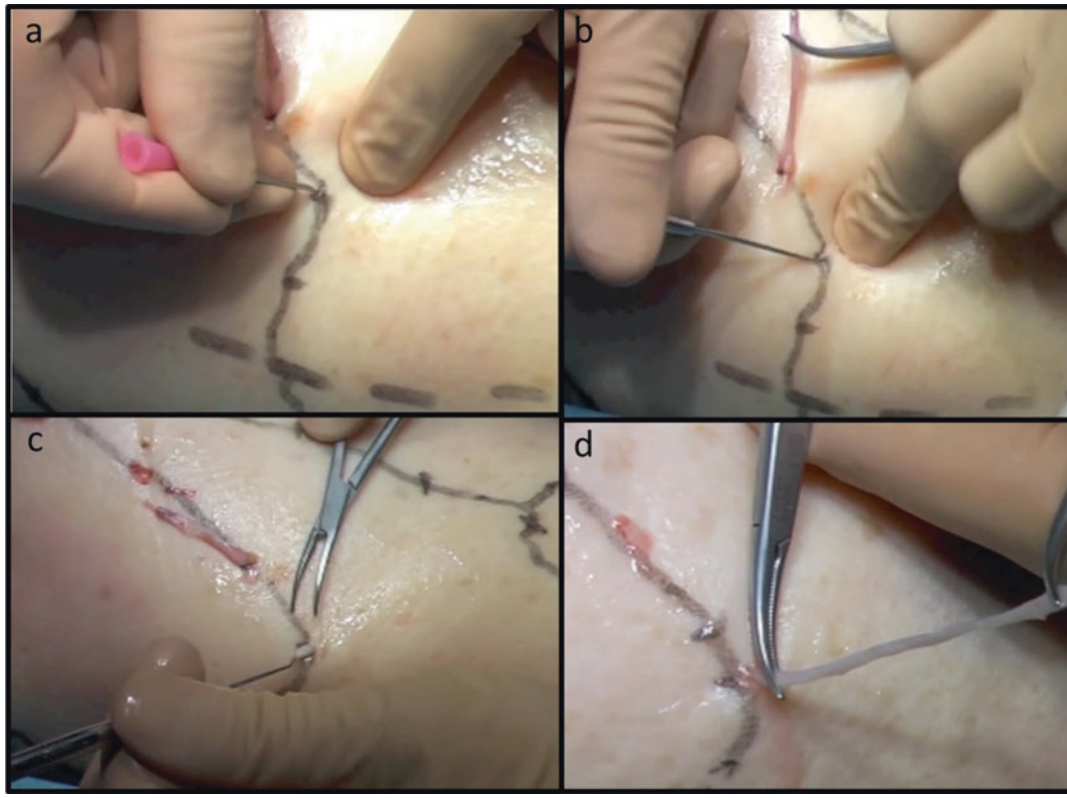

Fig. 14.4 Microphlebectomy technique. A micro-incision is made with 18-gauge needle (**a**). A hook is introduced (**b**), and the vein is exteriorized (**c**). The vein is removed with the hook and a fine clamp with attention to avoid tearing the vein (**d**)

decreases the risk of it breaking during the pullout which would prolong the procedure. Vein breaking also poses a risk of bleeding and pigmentation if a remaining piece of vein is left under the skin. The ligation of connected veins is essential to decrease the bruising and to get the best cosmetic results. Taking additional time to meticulously finish all the steps improves the quality of the healing and improves the return to daily activities.

Postoperative Management

The use of stitches is not necessary since the incisions are performed with the 18-gauge needle. The use of Steri-Strips is recommended in order to avoid blisters. The walking is immediate at the end of the procedure, and the patient could leave the hospital/office 1 h after. The patients are encouraged to walk at least 2 h on daily basis until postoperative day 8. They also can resume exercise activities the day of the surgery and swim the day after if one applies a protective film spray on the Steri-Strip. In our experience, wearing a stocking is not necessary after the first postoperative day following microphlebectomy [11].

Results

The follow-up (12, 24, 36, and 48 months) after an ASVAL procedure shows freedom of GSV reflux in 69.2%, 68.7%, 68.0%, and 66.3%, respectively, improvement of symptoms in 84.2%, 83.4%, 81.4%, and 78.0%, respectively, improvement of esthetics in 93.2%, 92.7%,

91.6%, and 89.9%, respectively, and freedom of varices recurrence in 95.5%, 94.6%, 91.5%, and 88.5%, respectively.

Conclusion

The ASVAL technique calls into question the usual approach to systematically treat the SV by high ligation and stripping or by endothermal or chemical ablation in the presence of VVs with a SV reflux. It leads at the opposite to a modern concept of an individualized "à la carte treatment" since every patient has a different clinical and hemodynamic situation of the disease at the time of treatment, which cannot match to a "one size fits all" that represents the traditional strategy. We have now at our disposal simple tools to evaluate the patients, select the good indications, and perform properly the ASVAL technique.

The microphlebectomy technique used for performing ASVAL is a mini-invasive revisited technique of phlebectomies described many years ago, with an addition of new tools, new tips and tricks, and of a new local anesthetic technique enabling to reach the highest cosmetic patient expectation.

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Strategies to Treat Venous Reflux Disease

15

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Clinical Pearls

1. Patients with severe symptoms of chronic venous disease tend to have venous obstruction in addition to reflux.
2. Thermal ablation (laser or radiofrequency) of the saphenous vein is currently considered the treatment modality of choice for superficial venous reflux.
3. Saphenous vein ablation with concomitant phlebectomy may enhance patient satisfaction compared to a staged approach.

Introduction

Chronic venous disease (CVD) is ubiquitous and it is estimated that approximately 23–30% of people in the United States have some form of venous insufficiency [1–3]. Multiple studies have shown that CVD is more prevalent in women, with an incidence as much as double that of men [4, 5]. The TAMPERE demonstrated the disparity between CVD incidence in men (18%) and women (42%), age, and parity within the female cohort [6]. Clinically, venous insufficiency has been attributed to high venous pressures in the lower extremities resulting in varicosities, skin changes, and (if left untreated or undertreated) ulcerations.

Currently, two main theories are present in the pathophysiology of venous hypertension. The descending, or "saphenocentric," theory proposes that venous insufficiency, particularly varicose veins, is secondary to a failure of the proximal superficial venous system—the valves at the saphenofemoral junction (SFJ) and/or the saphenopopliteal junction (SPJ). This valvular incompetence results in reflux extending distally through the venous system causing progressive venous distension and strain on the vein wall via dilatation, ultimately leading to varicosity formation. The ascending, or "multifocal," theory is based on the premise that the venous pressure system relies on the pressure of the right atrium and, with gravitational effects, creates a column of blood. At the base of the column, a reservoir is created in the distal limb, especially upon standing when gravitational effects are largest. This then leads to a distal to proximal distribution of venous insufficiency. This cranial ascension, in turn, will lead to proximal vein involvement that

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was not initially present. This has been supported by the presence of varicosities without the evidence of SFJ or SPJ incompetence [7].

Reflux in the great saphenous vein (GSV) is found in 70–80% of patients with CVD [8, 9]; thus interventions are geared toward removing the GSV from the circulatory system [10, 11]. Open surgery, radiofrequency ablation (RFA), endovenous laser therapy (EVLT), and ultrasound-guided foam sclerotherapy (UGFS) all abolish saphenous vein reflux. Saphenous-sparing procedures such as CHIVA and ASVAL are most popular in Europe.

There remain multiple nuances to the treatment of patients with more complex venous problems. Because limited clinical trial evidence is available for many of these, we will rely our experience of 20 years at the Miami Vein Center to support some of the treatment modalities used currently. Figure 15.1 provides a simplified overall algorithm for CVD.

Clinical Exam and Imaging

A proper history should always include a review of previous ulcers, vein surgeries (for harvest or otherwise), treatments, profession, pregnancy, hypercoagulability, trauma, family history, arteriovenous fistulas, lymphedema and risk factors for atherosclerosis. Physical exam should include inspection, palpation, auscultation, and mobility. Inspection should include the presence of any telangiectatic/reticular disease/corona phlebectactica, varicose veins, swelling, skin changes, healed ulcers, or active ulcers. Palpation is used to note any varicose dilatations, palpable cords, tenderness, thrills, or pitting edema. It is important to differentiate a venous ulcer from an arterial ulcer, and pulses should always be assessed. Maneuvers such as the Trendelenburg test to evaluate perforator and in-line valve insufficiency have been described but are rarely used now. Auscultation is particularly useful for identifying

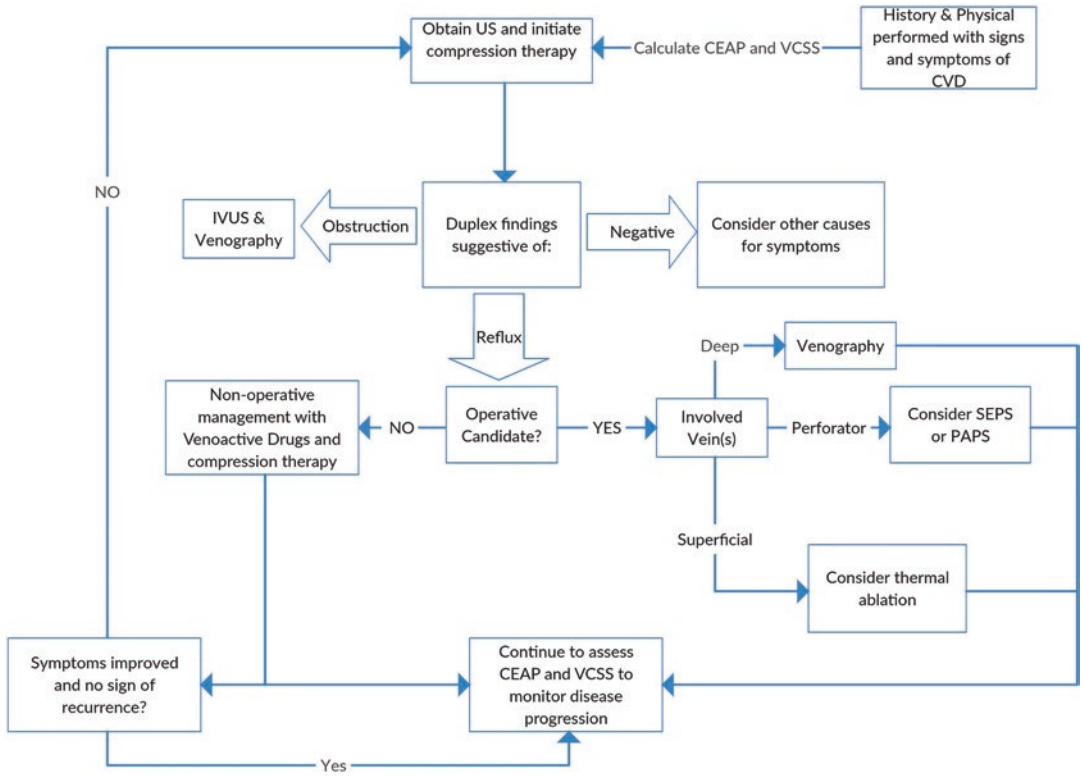

Fig. 15.1 Simplified treatment algorithm for chronic venous disease (CVD)

any bruits for arteriovenous malformations or fistulas. Decreased ankle mobility may represent more advanced CVD [8]. It is key to differentiate between primary and secondary venous insufficiency. Primary venous insufficiency occurs when a weakness of the vein wall results in valve incompetence. Secondary or acquired venous insufficiency from trauma or deep vein thrombosis can cause valvular disruption [12].

Signs and symptoms of CVD may include the five HASTI symptoms (heaviness, achiness, swelling, throbbing, itching) and pain relieved with activity or leg elevation, edema, skin changes, and ulcers [13]. Signs indicating skin damage include hyperpigmentation, stasis dermatitis, lipodermatosclerosis or subcutaneous fibrosis, atrophie blanche or hypopigmented scarring of previous ulcer sites, corona phlebectatica or visible ankle blood vessels, skin thickening, and induration.

Ultrasound

The AVF recommends a venous duplex to evaluate reflux disease and to assess for any outflow pathology [8]. Duplex ultrasound offers a high diagnostic accuracy and is safe, noninvasive, and a cost-effective tool for both diagnosis and treatment [14]. The technique for proper ultrasonography has been described by multiple authors [15–20]. Evaluation should be performed with the patient in the standing position with the leg rotated outward, the heel on the ground, and weight shifted toward the opposite limb [21]. If done in the supine position, false positive and false negatives have been reported [17]. Four components should be included in the study: (1) visibility, (2) compressibility, (3) venous flow including the presence of duration of reflux, and (4) augmentation [21]. Reflux can be elicited by either having the patient perform a Valsalva maneuver (particularly for evaluation of the saphenofemoral junction) or by manual compression and release of the limb just distal to the point of study [17]. The AVF recommends that reflux times of greater than 0.5 s be used as the cutoff for CVD of the saphenous, tibial, deep femoral, and perforator veins and 1 s be used for the femoral and popliteal veins [8].

Plethysmography

Air and strain-gauge plethysmography (APG and SPG, respectively) have also been used as a noninvasive evaluation of calf-muscle pump function, venous reflux, and outflow obstruction [19, 22, 23]. In particular, plethysmography is most useful in CVD when outflow obstruction is suspected and/or duplex scanning does not show evidence of reflux disease but patient symptoms and characteristics are suspicious for CVD. Therefore, they are recommended as complementary studies to duplex scanning. Air plethysmography in particular can reliably quantify reflux and is recommended for patients with CEAP C3–C6 disease that have not been definitively diagnosed by ultrasound [23, 24].

Venography

Contrast venography is primarily used in patients with more advanced CVD and in patients with suspected outflow obstruction such as in postthrombotic syndrome or May–Thurner syndrome [8]. CT and MR venography are less commonly used due to risks of contrast when compared to ultrasonography and are most suitable for more proximal pathology such as pelvic or iliac pathology. They may also be useful for evaluation of malformations such as Klippel–Trenaunay syndrome (KTS). For obstructive disease, intravascular ultrasound (IVUS) is crucial for diagnosis and treatment and is typically used in conjunction with contrast venography.

Classification Systems

The classification systems most widely used in practice today are the CEAP (Clinical, Etiological, Anatomical, and Pathophysiological) classification system and the VCSS (Venous Clinical Severity Score). The CEAP was first

introduced in 1994 and then revised in 2004 by the AVF and provides a basic classification of the venous insufficiency using the described components [24, 25]. The revised VCSS provides additional information from the CEAP that allows for monitoring improvement in patients within CEAP C classes. For example, C6 patients may heal their ulcer and improve to a C5 class, but they can never improve their CEAP class beyond that in spite of improved symptoms. Likewise, a C2 patient with small asymptomatic varicose veins cannot be differentiated from a C2 patient with large painful varicose veins using solely the CEAP system. Linking the VCSS to the clinical CEAP class enhances communication by adding information such as ulcer size and severity of symptoms [26]. Furthermore, the VCSS can be used to assess the broader spectrum of chronic venous disease as well as to compare patients with post-thrombotic syndrome and those subjected to different treatment modalities of saphenous venous ablation, stenting for venous obstruction, pharmacomechanical thrombolysis, and other venous interventions.

Nonoperative Management

The use of compression stockings for venous disease dates back to Ambroise Paré in the 1500s; now there are various compression therapies available including elastic wraps/bandages, Unna's boot, and pneumatic compression devices [27]. More recently, phlebotonic or vasoactive drugs have been developed but are less commonly used in practice. Table 15.1 summarizes the believed benefits and pharmacokinetics of currently used phlebotonic drugs. Among the most studied is escin, which can be found in horse chestnut seed extract (HCSE) [31–33]. A Cochrane Review of HCSE in 2012 reviewed 17 randomized clinical trials (RCTs) that compared HCSE to placebo and found a significant improvement in leg pain and reduction in leg volume. However, a comparison of HCSE with rutosides, pycnogenol, and compression stockings found no statistically significant difference between groups. Pentoxifylline used in conjunction with compression therapy may increase the likelihood of venous ulcer healing. Flavonoids such as hesperidin (found in citrus plants and peppermint) and diosmin (found in the plant *Teucrium gnaphalodes*) are used in micronized purified flavonoid fraction (MPFF) [31, 32]. Despite the development of phlebotonic drugs, the data has failed to show much benefit, and the mainstay of nonoperative management remains compression stockings (15–30 mmHg), but lifestyle modifications including weight loss, exercise, and leg elevation should also be advised.

In patients with simple varicose veins (C2 CEAP classification), Michaels et al. compared the cost-effectiveness of compression to sclerotherapy and to open high ligation and stripping (HL/S) in the REACTIV trial. They found that HL/S was significantly more cost-effective than both sclerotherapy and nonoperative management and that sclerotherapy was still significantly more cost-effective than nonoperative management alone [28]. Franks et al. [29] showed that some patient populations (particularly the obese and elderly) are unable to routinely apply the compression hosiery and that delaying surgical care costs patients in quality of life adjusted years (QALY). Additionally, Perälä et al. [30] compared perioperative and total societal costs of RFA versus HL/S and found that while RFA had higher perioperative costs, it had significantly lower total societal costs by nearly 25%. Because of the increased cost and potential delays in care, the AVF recommends that for patients with C2 disease that are candidates for operative management, compression therapy should not be the primary treatment of symptomatic varices (Table 15.2) [8].

Operative Management

Operative management for CVD has been present for over a century [10, 11]. Table 15.3 provides a general overview of the various techniques used today and their relative draw-

Table 15.1 Phlebotonic or venoactive drugs

Drug class	Drug examples	Found naturally	Effects	Mechanism of action	Pharmacokinetics
γ-Benzopyrone (flavonoids)	– MPFF[a] [38] – Hesperidin [30] – Diosmin [30, 35, 37]	*Citrus* spp., peppermint; *Rutaceae aurantiae*	– Antioxidant – Anti-inflammatory – Reduces vascular permeability – Antitumor effects – Increases venous tone – Reduces edema and lymphedema – Inhibits bone resorption – Mildly lowers blood pressure	– Reduces vascular permeability – Increases venous tone by prolonged vasoconstrictive effects of norepinephrine and decreases venous capacitance, distensibility and stasis – Improves lymphatic drainage by increased intensity and frequency of lymphatic contractions	– Poor bioavailability – $t_{1/2}$: Hesperidin, 5–8 h Diosmin, 26–43 h – Hesperidin is absorbed in the colon – Diosmin augments bioavailability of *p*-glycoprotein substrates – Metabolized by intestinal flora and liver – Mostly cleared by urine
α-Benzopyrone	Coumarin and derivatives [35, 36]	Numerous plant spp., including *Dipteryx odorata* (tonka bean); *Melilotus officinalis* (yellow sweet clover); *Hierochloe odorata* (sweet grass)	– Reduces edema and lymphedema – Relieves asthma – Improved CVD symptoms and subjective quality of life – Anticoagulation effects (i.e., Coumadin)	– Amplifies proteolysis by tissue macrophages improving lymph flow and reducing edema. – Cytotoxic – Pro-apoptotic – Tumor-destroying and antifungal effects	– Hepatic metabolism, substantial first pass effect – Cleared by urine – $t_{1/2}$: ~1.5 h
Saponosides	– Escin [30, 35] – Ruscus extract [30, 35]	Horse chestnut (*Aesculus hippocastanum*); Butcher's broom (*Ruscus aculeatus*)	– Antioxidant – Anti-inflammatory – Antithrombin – Reduces edema and lymphedema	– Prolongs vasoconstrictive effects of norepinephrine increasing venous tone and decreasing venous capacitance, distensibility, and stasis – Augments lymphatic drainage by increased intensity and frequency of lymphatic contractions – Decreases lymphatic pressure – Reduces capillary hyperpermeability and increases capillary resistance – Reduces expression of endothelial adhesion molecules and inhibits adhesion, migration, and activation of leukocytes at the capillary level	– Half-life is approximately 10–20 h – Peak plasma levels are 2–3 h after ingestion – Not well absorbed orally – Degraded by the liver, undergoes first pass effect

(continued)

Table 15.1 (continued)

Drug class	Drug examples	Found naturally	Effects	Mechanism of action	Pharmacokinetics
Other plant extracts	– Anthocyans [30, 35] – Ginkgo [30, 35] – Heptaminol [30, 35] – Troxerutin [30, 35]	– Bilberry (*Vaccinium myrtillus*) – *Ginkgo biloba*	– Antioxidant – Reduces edema – Accelerates healing of venous ulcers	– Regulates mucopolysaccharide metabolism in variceal walls – Reduces leukocyte adhesion to endothelial cells – Reduces circulating endothelial cell count	– Variable
Synthetics	Calcium dobesilate [30, 33, 34]	Synthetic	– Antioxidant – Anti-inflammatory – Reduces leg edema – Reduces blood viscosity – Augments lymphatic flow and reduces lymphedema – Improved QoL when combined with oxerutin	– Inhibits capillary permeability by serotonin, histamine, and bradykinin pathways – Inhibits synthesis of prostaglandins and thromboxanes which reduces platelet and erythrocyte aggregation as well as blood viscosity – Increases venous tone by reduced angiogenesis and VEGF expression – Regulates apoptosis and inhibits inflammatory response	– $t_{1/2}$: 2.5–15 h – Primarily cleared by urine – May cause hepatitis and agranulocytosis
	Pentoxifylline [30, 35]	Synthetic	– Healing of venous ulcers (with compression hosiery) – Decreased platelet aggregation	– Nonselective phosphodiesterase inhibitor – Inhibits platelet aggregation and leukocyte activation – Inhibits synthesis of TNF-α	– Metabolized by erythrocytes and the liver – $t_{1/2}$: 0.4–0.8 h – Primarily cleared by urine

[a]*MPFF* Micronized purified flavonoid fraction

Table 15.2 American Venous Forum recommendations for nonoperative management

Recommendation	Level of evidence[a]
We suggest venoactive drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chestnut seed extract [escin]) in addition to compression for patients with pain and swelling due to chronic venous disease, in countries where these drugs are available	2B
We suggest using pentoxifylline or micronized purified flavonoid fraction, if available, in combination with compression, to accelerate healing of venous ulcers	2B
We suggest compression therapy using moderate pressure (20–30 mmHg) for patients with symptomatic varicose veins	2C
We recommend against compression therapy as the primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation	1B
We recommend compression as the primary therapeutic modality for healing venous ulcers	1B
We recommend compression as an adjuvant treatment to superficial vein ablation for the prevention of ulcer recurrence	1A

Adapted from Gloviczki et al. [8]
[a]Grade of recommendation: 1—strong, 2—weak; level of evidence: A—high quality, B—medium quality, C—low or very low quality

Table 15.3 Summary comparison of operative procedures

Procedure	Type	Complications/drawbacks	Benefits
High ligation/ stripping [8]	Open	– Increased perioperative disability period compared to newer techniques (7–22-day average) – Increased rate of adverse events (acute DVT ~0.5–5%; PE ~0.16%) – Significant perioperative pain (17–22%), ecchymosis (19%), hemorrhage (33%), and wound infection (3–10%) – Increased paresthesia/neuralgia (2–7%, if done up to the knee, and up to 39% if done to the ankle) – Recurrence (6.6–37%)	– Improved QoL over nonoperative management – Low cost
Powered phlebectomy [8]	Open	– Increased rate of ecchymosis (4.9–95%) – High number of paresthesia/neuralgias (9.5–39%) – Increased skin complications including perforation (1.2–5%), wound infection (2.4–13%), hyperpigmentation (1.2–3.3%), and edema (5–17.5%) – Recurrence (9.1–21.2%) – Acute DVT reported in <1%	– Quicker compared to stab phlebectomy (mean operative time <20 min) – Fewer incisions compared to stab phlebectomy
Divided saphenectomy (DS) [8, 44]	Open	– Divides GSV – Ecchymosis present in ~19.7% – Not well studied	– Maintains truncal drainage despite GSV division – Low cost, no special equipment necessary
ASVAL [8, 11]	Open	– Requires detailed superficial and deep vein mapping with individualized preoperative planning – Recurrence (~11.5%) – Variable results depending on operative team and mapping	– Preserves truncal vein

(continued)

Table 15.3 (continued)

Procedure	Type	Complications/drawbacks	Benefits
CHIVA [8, 11]	Open	– Requires detailed superficial and deep vein mapping with individualized preoperative planning – Recurrence in GSV or new incompetent perforators/tributaries (Hunterian or Dodd's) – Non-truncal recurrence (~9%) – Variable results depending on operative team and mapping	– Preserves truncal vein
Sclerotherapy [8]	Endovenous	– Often requires multiple sessions – Lower success rates with larger veins – Multiple puncture sites – Documented air emboli – Higher rates of skin changes and necrosis, especially with extravasation of sclerosant	– Quick – Reduced perioperative disability – Excellent for telangiectatic and reticular vessels that are too small for catheter placement
RFA [8]	Endovenous	– Increased perioperative pain/tightness (~31%) – Recurrence (~26%) – Expensive RF equipment and ultrasound needed	Overall societal costs reduced with decreased disability time (2–8-day average) Faster than open surgery Less pain and bruising compared to EVLA
EVLA [8]	Endovenous	Perioperative pain/tightness (31%) Postoperative disability period (2–8-day average) Recurrence (26%) Expensive laser equipment and ultrasound needed	Quicker recovery period than open surgery (2–8-day average) Less wound infections Comparable closure rates without incision Less hemorrhage and ecchymoses
Mechanochemical [8]	Endovenous	– Not well studied	– Does not require local tumescent anesthesia, reducing perioperative pain
Endovenous glue [8]	Endovenous	– Not well studied	– High closure rates (95–99%) – Does not require tumescent anesthesia – Reduced perioperative ecchymoses
Steam ablation [8]	Endovenous	– Not well studied – Still requires thermal ablation but with less fluid administration	– Less perivenous tissue damage resulting in less postoperative pain

Data reviewed and summarized from Gloviczki et al. [8]

backs and benefits. Generally, endothermal ablation has become the standard first-line procedure, but many countries outside the United States and Europe still perform open procedures as the standard of care. There are no additional absolute contraindications to operative repair; however, relative contraindications may include patients who have arterial disease, deep vein insufficiency, known coagulopathy or hepatic disease, active thrombophlebitis, pregnancy, and are breastfeeding or patients that are immobile. A summary of the AVF operative guideline recommendations is available in Table 15.4 [8].

Table 15.4 American Venous Forum recommendations for surgical interventions

Recommendation	Level of evidence[a]
For treatment of the incompetent great saphenous vein, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee	2B
To reduce hematoma formation, pain, and swelling, we recommend postoperative compression. The recommended period of compression in C2 patients is 1 week	1B
For treatment of small saphenous vein incompetence, we recommend high ligation of the vein at the knee crease, about 3–5 cm distal to the saphenopopliteal junction, with selective invagination stripping of the incompetent portion of the vein	1B
To decrease recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy	1A
We suggest preservation of the saphenous vein using the ambulatory conservative hemodynamic treatment of varicose vein (CHIVA) technique only selectively in patients with varicose veins, when performed by trained venous interventionists	2B
We suggest preservation of the saphenous vein using the ambulatory selective varicose vein ablation under local anesthesia (ASVAL) procedure only selectively in patients with varicose veins	2C
We recommend ambulatory phlebectomy for treatment of varicose veins, performed with saphenous vein ablation, either during the same procedure or at a later stage. If general anesthesia is required for phlebectomy, we suggest concomitant saphenous ablation	1B
We suggest transilluminated powered phlebectomy using lower oscillation speeds and extended tumescence as an alternative to traditional phlebectomy for extensive varicose veins	2C
For treatment of recurrent varicose veins, we suggest ligation of the saphenous stump, ambulatory phlebectomy, sclerotherapy, or endovenous thermal ablation, depending on the etiology, source, location, and extent of varicosity	2C
Endovenous thermal ablations (laser and radiofrequency ablations) are safe and effective, and we recommend them for treatment of saphenous incompetence	1B
Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery	1B
We recommend liquid or foam sclerotherapy for telangiectasia, reticular veins, and varicose veins	1B
For treatment of the incompetent saphenous vein, we recommend endovenous thermal ablation over chemical ablation with foam	1B
We recommend against selective treatment of incompetent perforating veins in patients with simple varicose veins (CEAP class C2)	1B
We suggest treatment of "pathologic" perforating veins that includes those with an outward flow duration of ≥500 ms, with a diameter of ≥3.5 mm, located beneath a healed or open venous ulcer (CEAP classes C5–C6)	2B
For treatment of "pathologic" perforating veins, we suggest subfascial endoscopic perforating vein surgery, ultrasonographically guided sclerotherapy, or thermal ablations	2C

From Gloviczki et al. [8]

[a]Grade of recommendation: 1—strong, 2—weak; level of evidence: A—high quality, B—medium quality, C—low or very low quality

High Ligation and Stripping (HL/S)

The technique of HL/S can be dated back to 1884 by Madelung and has undergone multiple modifications throughout the 1900s, most notably the development of the extraluminal straight stripper by Mayo in 1906 and the flexible stripper by Myers in 1943 [11]. Classic open complete HL/S is generally only offered where endovenous methods are not available. To perform HL/S, a 3–4 cm incision in the groin is made and, once the SFJ is safely dissected out, stripped down to the level of the knee. For invagination stripping, a flexible plastic Codman stripper and a metallic Oesch

perforate-invaginate (PIN) stripper are used to invaginate the vein into the lumen and remove toward the knee. Alternatively, cryostripping may be performed which entails inserting a cryoprobe into the GSV and freezing for 2 s followed by invaginating the GSV toward the groin [35]. Stripping of the GSV should be taken down only to the level of the knee due to the increased incidence of saphenous nerve injury. Similarly, complete HL/S of the small saphenous vein (SSV) may cause sural nerve injury and is generally avoided [36].

Partial stripping, however, is still commonly used as in the hybrid procedure—laser-assisted distal saphenectomy (LADS) [9]. A superficial accessory saphenous vein (SASV) often acts as a reflux escape tributary as it exits the saphenous canal at mid-thigh, and treatment with thermal ablation is generally avoided as it may cause skin necrosis and eschar formation and leave a palpable cord. The LADS procedure involves performing endovenous thermal ablation of the proximal GSV (thereby avoiding a groin incision and associated complications) along with performing a partial stripping of the distal SASV using the sheath as the stripping tool (Fig. 15.2a, b).

Divided Saphenectomy (DS)

Divided saphenectomy (DS) is another open approach geared toward ligating the saphenous vein at multiple sites and ligating all tributaries and perforators, competent or not [37]. This is performed under local anesthesia, and the procedure entails preserving the GSV (albeit in ligated segments), ligating all perforators in the thigh, and preserving a route of venous drainage but by reducing symptoms of hemorrhage and bruising

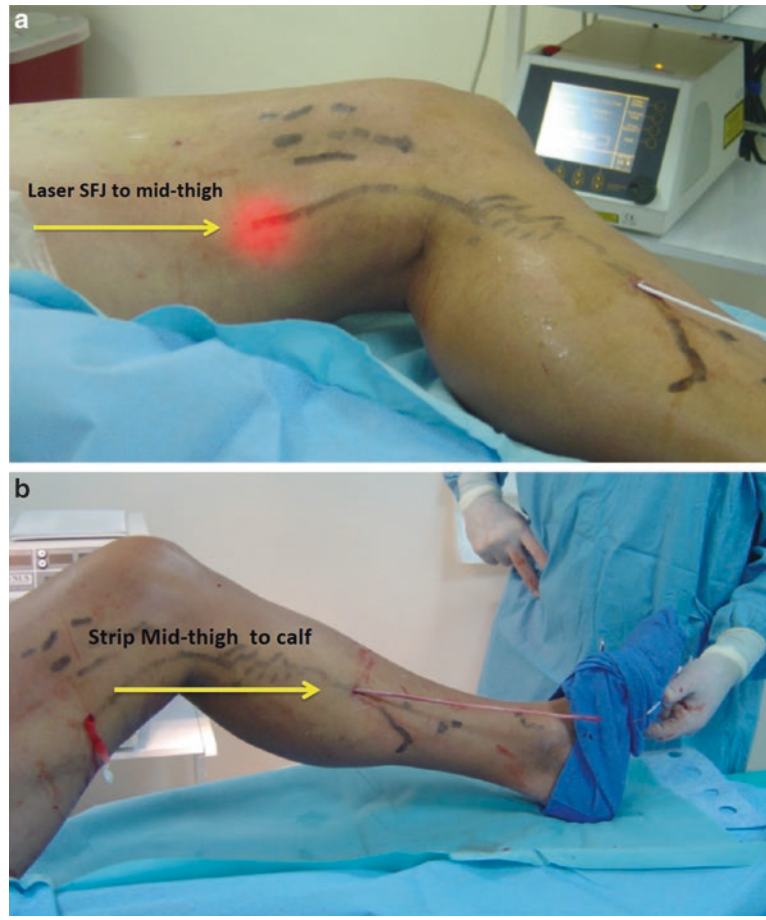

Fig. 15.2 (**a**) LADS Part 1—the laser tip is positioned at the SFJ and withdrawn to mid-thigh where the reflux escapes the GSV in the saphenous canal into the subcutaneous space as the SASV. (**b**) LADS Part 2—the SASV is exteriorized at mid-thigh and divided. The distal vein is sutured to endovenous sheath and invagination stripping performed

by ligating all tributaries using standard surgical equipment and small 1cm incisions as opposed to the larger 3–4 cm incision for HL/S.

ASVAL

The ASVAL (ambulatory selective varicose vein ablation under local anesthesia) operation is a minimally invasive technique that aims to remove varicose tributaries while preserving the saphenous trunk and reducing the GSV diameter. The combination of hemodynamic and anatomical modifications leads to a reduction in reflux volume [38].

CHIVA

First presented by Franceschi et al. in 1988, the CHIVA (ambulatory conservative hemodynamic treatment of varicose vein) procedure is targeted at maintaining the truncal venous system while promoting more efficient drainage into the deep venous system, i.e., a saphenous-sparing procedure [39]. The goal is to fragment the venous column of blood causing a redistribution of flow toward a competent deep venous system and decreasing the venous pressure. A Cochrane Review published in 2013 identified three RCTs comparing CHIVA vs saphenous stripping and one RCT comparing CHIVA vs compression. The results showed that CHIVA had reduced recurrence rates, reduced side effect profile compared to open surgery and compression, and improved QoL [40]. However, results vary tremendously depending on the user with recurrence rates (defined as reflux present in the GSV) ranging from 91% at 3 years to 18% at 10 years and are therefore not recommended for most practitioners [8].

Endovascular Treatments

Thermal Ablation

Endovenous thermal ablation has quickly become the first-line therapy for varicose veins. By causing a direct thermal injury to the vein wall, destruction of the endothelium, and collagen denaturation of the media, fibrotic and thrombotic occlusion of the vein occurs. Two methods have gained popularity in regard to endovenous thermal ablation: radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). Both therapies use electromagnetic energy converted to thermal energy to ablate the treated vein via endoluminal surface destruction. Both methods utilize local tumescent anesthesia and are performed under sonographic guidance in an ambulatory setting with similar benefits in regard to pain and postoperative recovery when compared to open procedures.

RFA gained FDA approval in 1999 and uses a catheter to direct radiofrequency energy from a dedicated generator [8, 9]. First-generation devices were slow with 15% recanalization rates; however, current devices (introduced in 2007) are more effective and the entire pullback procedure takes 3–4 min. Similarly, EVLA was first successfully performed in 1999 [41] and FDA approved in 2002 [8]. Using a diode laser, endoluminal energy delivery is transferred via thermal conversion to the vein wall (conduction and convection)—this controlled damage results in vein occlusion. Endovenous lasers are available in hemoglobin-specific and water-specific laser wavelengths, but there does not appear to be a clear superiority between one wavelength and another, and device choice is up to surgeon preference [42].

To compare RFA and EVLA, Almeida et al. [43] randomized 87 veins in 69 patients to ClosureFast or 980 nm EVL treatment of the GSV. The study was a prospective, randomized, single-blinded, multicentered study carried out at five American sites and one European site. Primary endpoints (postoperative pain, ecchymosis, tenderness, and adverse procedural sequelae) and secondary endpoints (VCSS and QoL issues) were measured at 48 h, 1 week, 2 weeks, and 1 month after treatment. The data was statistically significant favoring RFA postoperatively at the 2-week assessment; however, equalization in most recovery parameters was observed between groups at 1 month. Furthermore, Rasmussen et al. [44] randomized 500 patients (580 extremities) to

one of the three endovenous treatments (RFA, EVLA, or foam sclerotherapy) or open HL/S of the GSV. Follow-up included clinical and duplex ultrasound examinations and VCSS and QoL questionnaires. Kaplan–Meier (KM) survival analysis was used to compare the treatment arms. All treatment modalities were efficacious and resulted in a similar improvement in VCSS and QoL measures; however, more recanalization and reoperations were seen after UGFS.

In a RCT involving 798 patients with primary varicose veins at 11 different centers in the UK, Brittenden et al. [45] compared the outcomes of foam sclerotherapy, EVLA, and open surgical treatments. Using QoL measures of various scales at 6 months post-intervention, it was noted that the disease-specific QoL was slightly worse after treatment with foam than after surgery but was not statistically significant between the laser and surgical groups. The frequency of serious adverse events and clinical success measures were similar across all three groups except for the foam group having lower successful ablation rates of the main trunks of the saphenous vein when compared to laser and surgical groups.

Endovenous steam ablation (EVSA) using a catheter and generator has been introduced in Europe, but data is still lacking to fully compare its efficacy with respect to other modalities. A RCT from 2014 demonstrated non-inferiority when compared to EVLA [46], and the benefit of this modality is mostly seen in patient satisfaction from lower damage to perivenous tissue, resulting in less postoperative pain [47].

Endovenous ASVAL (eASVAL) has recently been described by Atasoy and Oğuzkurt in Turkey in 2015 [48]. This technique combines the basic concept of ASVAL (GSV sparring) and endovenous thermal ablation to treat reflux disease. The technique described uses thermal ablation of the proximal straight segments of the major tributaries connecting the symptomatic varicose veins while sparing the incompetent segment of the GSV. Then, ultrasound-guided foam sclerotherapy (UGFS) of the superficial varicose veins is performed. While the study was not completely randomized, it did show results similar to that of ASVAL with 6 of 41 patients (14.6%) having recurrent disease at a 1-year follow-up [48].

Nonthermal Ablation

The most common form of nonthermal ablation is sclerotherapy or the injection of chemicals into the vein to achieve endoluminal fibrosis and obstruction. Sclerotherapy dates back to the 1600s when a Swiss physician injected acid into a vein to induce thrombus formation, but it wasn't until 1853 that the first documented successful treatment of varicose veins by sclerotherapy was reported [49, 50]. Sclerotherapy quickly became popular, particularly in Europe, and gained favor when sodium tetradecyl sulfate (STS) was developed in the 1940s. However, in 1984, liquid sclerotherapy lost favor after a European study was published showing worse clinical outcomes when compared to open surgery [51].

Sclerotherapy was revitalized in the 1995 when Cabrera introduced the injection of small bubbles named "microfoam" which improved efficacy and visualization with ultrasound [52]. The tensioactive properties of foam obviate the dilutional effects seen with liquid by maximizing the surface area by the drug. In 1997, Tessari described a technique for foam production using a three-way stop cock to mix air and liquid sclerosant [53]. Modifications to this method now use carbon dioxide or a mixture of carbon dioxide and oxygen as the gas substrate to prevent air emboli. Multiple studies have been presented showing efficacy of foam sclerotherapy for truncal veins [54]. In 2010, polidocanol became FDA approved and is now the most commonly used sclerosant. Two placebo controlled studies (VANISH 1 and VANISH 2) have demonstrated satisfactory efficacy and tolerance of proprietary polidocanol microfoam with minimal side effects [13, 55].

Similarly, another endovenous method called mechano-chemical ablation (MOCA) uses a catheter-associated device that contains a fast-rotating thin wire tip that spins while distributing liquid sclerosant. It can be applied along the

saphenous trunk without local anesthesia and provides excellent immediate and midterm closure rates [56]. Yet another method uses a catheter system to deliver glue (proprietary *n*-butyl cyanoacrylate) endovenously. In a short-term follow-up study (3 months), closure of the target GSV was high at 99% and demonstrated noninferiority when compared to RFA [57]. These results are similar to that observed in a prior feasibility study (95%) [58] as well as in a prospective multicenter European study (96%) [59] making this a plausible future treatment modality for CVD. Because these methods are nonthermal, they have theoretical advantages—less perivenous damage and, therefore, less pain and swelling postoperatively—particularly in the case of MOCA and endovenous glue.

In most cases, combination treatment with EVLA, UGFS, and/or phlebectomy, with perivenous tumescent anesthesia, can be performed. EVLA of any straight incompetent axial venous segments deep to the skin is performed via micropuncture access. Tortuous incompetent venous segments typically do not allow the passage of guidewires; thus, UGFS is typically used for these segments. Any superficial bulging varicose veins which are palpable on the skin receive treatment with ambulatory phlebectomy. These three techniques used concomitantly yield very satisfactory results. In keeping in mind patient goals, it is also important to note that these treatments are more palliative in nature and to remind the patient that they may require a "touch-up" treatment in the future.

Common Venous Reflux Controversies

Recurrent Varicose Veins (REVAS)

Recurrent varicose veins after surgery (REVAS) continues to be a vexing problem. In 2001, Fischer et al. [60] reported a 34-year clinical follow-up performed in the United States from open surgical stripping procedures performed in the 1960s. In their publication, they noted four types of recurrence: distal vessel reflux with no saphenofemoral recurrence, junctional recurrence with multiple small vessel branchings, junctional recurrence with a single large vessel from the former site of ligation, and circumjunctional recurrence that originates from a subfascial vein other than the common femoral vein in region of former ligation.

A common REVAS scenario has been observed with duplex ultrasound imaging over the years at Miami Vein Center. Findings include neovascularity in the groin from which one or more tributary veins are found to descend down the thigh. The tributary may branch to another tributary, perforator, or remnant of the GSV in the thigh or calf. If the reflux extends into dilated tributaries of the skin, these vessels will bulge under pressure and become palpable.

Complete Occlusion (CO) and Near Complete Occlusion (NCO) Following Ablation

Follow-up of patients after ablation therapy has shed light on another group of patients that have segmental reflux. Merchant et al. [61] looked at differences in clinical outcomes in patients treated with endovenous saphenous vein obliteration in three groups of patients: (1) those with a technical outcome of complete occlusion (CO); (2) those with near complete occlusion (NCO), defined as <5 cm segment of flow in treated vein; and (3) those with recanalization (defined as >5 cm segment of flow in treated vein). They found that in patients with NCO of the GSV at follow-up, clinical outcomes were no different than those with CO, but were distinguishable from those with recanalization [61]. These results suggest that, despite the presence of reflux in the NCO cohort, the reflux is often subclinical.

Many patients with segmental reflux are asymptomatic. Normal calf-muscle pump function is dependent on adequate priming (capacitance or venous volume (VV)), compliance, and ejection volume (EV). However, because reflux is extrinsic to the calf pump mechanism, it can be a major cause of its decompensation. Increasing the EV or compliance may buffer reflux.

Similarly, increased VV can buffer reflux if EV is simultaneously increased or it can worsen the effects of reflux if EV is unchanged. Most abnormalities of the calf pump involve decreased VV, EV, compliance, or a combination.

There have been several attempts to quantify the degree of reflux in order to develop treatment strategies for this subset of patients. To quantify reflux, Raju et al. [62] used duplex ultrasound to measure several components of reflux, such as vessel size, velocity, and duration as well as the reflux volume). The takeaway message from this study is that a reflux volume of >30 cm^3 is required to overwhelm the calf pump and produce symptoms, and a GSV of at least 5.5 mm diameter is required to transmit this volume.

To further support this concept, in VANISH 2, treatment with polidocanol endovenous microfoam led to durable, clinically meaningful, and ongoing improvements at year 1 in varicose veins as measured by patient self-assessment scores regarding symptoms and appearance despite a 20% GSV segmental recanalization seen with duplex ultrasound.

At the Miami Vein Center, segmental reflux is a common finding. Based on the aforementioned information, intervention is only performed on patients with debilitating signs and symptoms.

Which Device?

Current AVF guidelines recommend endovenous thermal ablation as the primary method of treatment; however, that does not imply that nonthermal methods are inferior. Nonthermal methods have a theoretical advantage in that tumescent local anesthesia is not necessary, thereby decreasing perivenous trauma and the risk of perivenous saphenous or sural nerve damage especially below the knee. Currently in the United States, thermal ablation is the only endovenous method with Category I CPT codes for insurance reimbursement; but as reimbursements equilibrate for other modalities, the popularity of nonthermal approaches may increase and the theoretical advantages may be realized. Another factor to consider is cost. Thermal ablation (RF or laser) requires a thermal generator which may be cost prohibitive. In this case, disposable nonthermal devices require less capital outlay (no generator required).

Regarding the question of device preference in our practice, we usually prefer RFA for longer vein lengths (>30 cm length) where more venous tissues are at risk for inflammation after thermal destruction; this offers a smoother recovery during the first 2 weeks post-procedure. Conversely, for more complex anatomical challenges, such as multiple short length vein segments, laser energy can be delivered from the tip of a micropuncture access system and is our preference here. Short vein lengths (<10 cm) are more difficult with RFA catheters because the heating element that exits the sheath tip is an additional 7 cm in length, although the newer 3 cm length now available has made RFA more versatile with complex anatomy. We will see in the very near future what role the nonthermal technologies will play.

All at Once or Ablate and Wait?

The above ablative techniques are for the treatment of truncal vein incompetence; however, for varicose tributaries, ambulatory phlebectomy is usually performed. There is ongoing debate on the optimal time to perform the phlebectomy, i.e., whether during same setting as ablation or sometime thereafter.

Lane et al. [63] randomized 101 patients to either simultaneous phlebectomy or delayed varicosity treatment in the AVULS trial. The simultaneous group (n = 51) showed a significantly improved VCSS at all time points, when compared to the delayed group, and 36% of the delayed group required further treatment compared with 2% of the simultaneous group ($p < 0.001$). Carradice et al. [64] and Shekha et al. [65] reported on patients randomized to EVLA alone or EVLA with concomitant ambulatory phlebectomy. Principal outcomes were procedure duration, pain, requirement for secondary procedures, and generic QoL measures after 3 months. Median VCSS and Aberdeen Varicose VEIN Questionnaire scores at 3 months were

lower for EVLA with concomitant ambulatory phlebectomy than for EVLA alone ($p < 0.001$ and $p < 0.015$, respectively). Long-term results were not statistically significant, but the difference in initial QoL and the need for reoperation are both advantages to concomitant treatment.

On the other hand, in 2005, Monahan published a study of 222 varicose veins in 54 limbs of 45 patients treated with RFA only and followed for 6 months for the presence of recurrent varicosities [66]. He noted that only 59% required secondary intervention and argued that ablation alone may prevent the need or minimize the number of phlebectomies required. Furthermore, Nicolini et al. [67] reported in a 3-year follow-up study of RFA alone versus RFA with stab phlebectomy that there was no difference in symptom severity score or the number of asymptomatic limbs. Weiss and Weiss [68] published a comparison of RFA alone to RFA with phlebectomy; all limbs showed improvement of visible varicosities and leg pain regardless of whether a stab phlebectomy was performed. Finally, Welch [69] published a retrospective study of RFA performed on 184 limbs in 146 patients and found 63.9% of patients did not require a secondary intervention by the 9-month follow-up visit. These authors argue that GSV ablation alone (i.e., RFA alone) may allow many patients to defer stab phlebectomy and, therefore, reduce bruising, hematoma formation, skin infections, and post-procedural disability.

Ultimately, whether to do concurrent or delay phlebectomy remains up to the physician and this may differ according to patient expectations. At the Miami Vein Center, a phlebectomy, with rare exception, is always performed in conjunction with truncal vein ablation. In our experience, patient satisfaction is much higher when everything is done "all-at-once."

Deep Reflux

A common question addresses the safety and efficacy of saphenous ablation in the presence of deep vein incompetence. Walsh [70] reported on 29 limbs and Sales [71] studied 17 limbs with segmental deep venous reflux in association with saphenous incompetence. Walsh and Sales reported resolution of the deep reflux in 93% and 94%, respectively, of cases with saphenectomy [70, 71]. The experience at the Miami Vein Center, has shown that saphenous ablation in patients with axial deep venous reflux causes no notable harm. Patients with compelling venous hypertension from the superficial system incompetence typically have relief of symptoms following saphenous ablation; however, deep axial reflux does portend to a worse long-term prognosis referable to disease progression and varicose vein recurrence. In patients with a competent saphenous system presenting signs and symptoms attributable to deep reflux, confirmed by duplex imaging, treatment is usually nonoperative.

If severe symptoms do persist, various valvuloplasty techniques have been described. Data is still limited in this patient subset and most studies are retrospective in nature. However, in general, success rates after valvuloplasty are reported to be around 70% with good short-term results with competent deep veins to be noted between 35 and 100% in studies with follow-up time of up to 12 years [72].

Saphenous Reflux and Deep Obstruction

Patients with more advanced CVD (CEAP C4–C6) have a higher incidence of concurrent obstructive and reflux pathology [73]. In symptomatic patients, obstruction in combination with reflux occurs in approximately 55% of patients [72]. For these patients, there remains a debate in regard to whether the reflux symptoms or the obstructive symptoms should be treated first. To address this problem, these patients should be classified as either "reflux dominant" or "obstructive dominant" based on signs and symptoms.

Various authors have used ambulatory venous pressure (AVP) to help distinguish venous obstruction from insufficiency; unfortunately, there is conflicting data and venous hypertension

may result from either pathology [74–77]. The use of ultrasonography in addition to air plethysmography, AVP measurements, and CT or MR venography can often assist with diagnosis. In our experience in Miami, obstructive dominant patients present with unilateral leg swelling extending above the tibial plateau and grossly asymmetric lower limbs—these will likely have venous outflow obstruction. This type of edema and gross limb asymmetry cannot be produced by saphenous incompetence. Raju et al. [78, 79] along with various other groups [80, 81] have published their experiences and have shown that iliocaval stenting prior to any venous ablation may be sufficient for resolution of symptoms in these patients. On the other hand, if the patient is believed to have a reflux-dominant pathology, ablative techniques may resolve symptoms, leaving the obstructive pathology to be followed closely afterward [82]. A general guideline for treatment of obstructive versus reflux-related pathology can be seen in Fig. 15.3.

Depicted in Fig. 15.4 is a patient who presented to us with the non-healing ulcer after iliac vein stenting and split thickness skin grafting of wound at an outside facility. In this case, the patient had (1) an obstructive lesion remaining in the common iliac vein, (2) an untreated incompetent GSV refluxing in direct continuity with the ulcer bed, and (3) an incompetent tibial perforating vein located directly beneath the ulcer bed. This patient's venous hypertension was multifactorial requiring multiple interventions depicted in Fig. 15.4a, b.

Perforator Veins

Subfascial endoscopic perforator vein surgery (SEPS) was introduced in 1985 by Hauer to

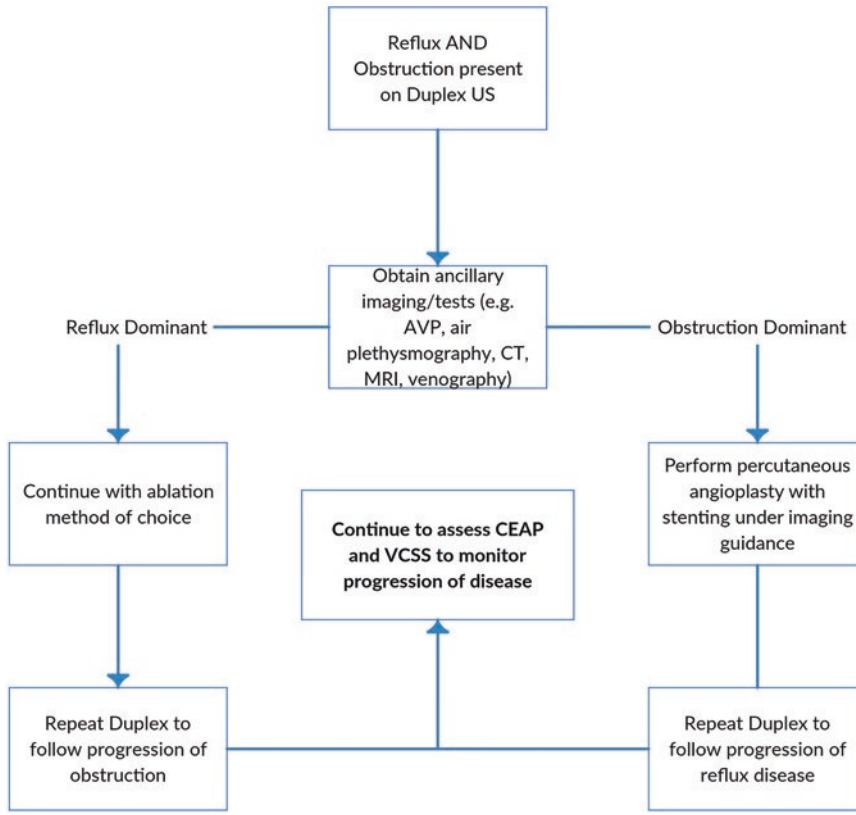

Fig. 15.3 Treatment algorithm for patients with CVD and obstruction on US

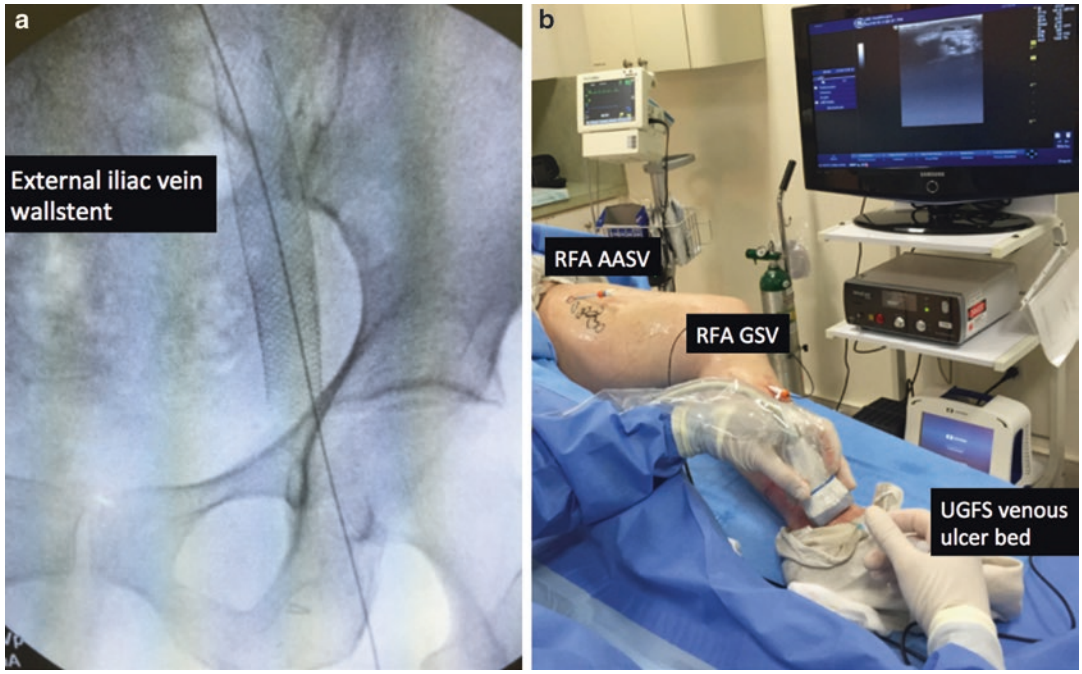

Fig. 15.4 (**a**) Venography without IVUS leads to inappropriate treatment of Iliac vein obstruction. Using IVUS, the common iliac vein lesion was correctly identified and treated with an iliocaval stent. (**b**) Correction of truncal vein incompetence with RFA (great saphenous vein, GSV, and anterior accessory saphenous vein, AASV). Concomitantly, UGFS was used to treat the subcutaneous venous network and perforators located beneath the ulcer bed

tackle the problem of perforating vein insufficiency. SEPS is generally well tolerated and was the technique of choice for the previous decade for perforator ablation before endovenous techniques became more widespread. SEPS is that it is usually performed under general or epidural anesthesia, and single or double endoscopic port techniques are used for dissection and division of medial calf perforators. Percutaneous ablation of perforators (PAPS) uses ultrasound guidance, to access the perforating vein; then either an RFA or EVLA device is used [83]. The AVF guidelines suggest treatment of "pathologic" perforating veins that includes those with outward flow of >500 ms duration, with a diameter of >3.5 mm, located beneath healed or open venous ulcer [8].

Vulvar Varices

Patients with vulvar varices (often seen with pelvic congestion syndrome) can undergo pelvic venography to identify a source of reflux. The traditional therapy for pelvic congestion syndrome has included both medical approaches (e.g., dihydroergotamine, ovarian suppression, and rheologic agents) and surgical approaches (uterine ventrosuspension, hysterectomy, ovarian vein ligation, and excision) [84]. A less invasive approach involves embolization of incompetent ovarian or internal iliac vein tributaries [85, 86]. Castenmiller et al. [87] presented a retrospective review of 44 patients with lower extremity varicosities suspected to be secondary to pelvic compression syndrome treated with selective coil embolization. They found ovarian vein insufficiency in 43 of 44 patients and complete resolution of lower extremity varicosities in 12% of patients and an improvement in CEAP classification in 31% of patients without further treatment. Of the 24 patients that presented with vulvar varices, 88% had complete resolution of varices following coil embolization.

Klippel–Trénaunay Syndrome

KTS is a congenital disorder with combined capillary-lymphatic-venous malformations without any arteriovenous fistula [88]. It is believed that the development of in utero deep vein obstruction or atresia leads to venous hypertension in the superficial and anomalous embryonic ("marginal") systems which results in the triad of port-wine stain, varicose veins, and limb hypertrophy. The lateral venous channel is present in up to 72% of KTS patients and is the focus of treatment [89]. Generally, these patients have been treated with nonoperative management unless symptoms worsen [90]. However, when performed, surgical treatments often resolve symptoms, albeit with high recurrence rates [88–91]. In 2008, Frasier et al. [91] reported performing RFA on three patients with KTS with poorly developed or absent deep systems and achieved moderate results over a short-term 6-month follow-up despite requiring multiple repeat sclerotherapy injections. More recently in 2016, Malgor et al. [92] published data on 53 limbs in 49 patients that underwent open stripping of the GSV, SASV, SSV, or lateral embryonic vein with similar results. They noted that 78% did not require subsequent treatment after 3 years, and 74% were intervention-free after 5 years.

Common Issues in Patients Evaluated for Second Opinion

Previous Phlebectomy Without GSV Stripping

We commonly see patients presenting with recurrent varicose veins previously treated with phlebectomy only, at an outside facility. These limbs, once examined with duplex ultrasound, usually have a large incompetent GSV descending from the groin and terminating ultimately in the calf at a site where large varicosities are noted. These cases do very well with routine GSV ablation using either RF or laser with concomitant ambulatory phlebectomy for associated varicosities. Having seen many of these cases over the years, a strong bias has developed against the aforementioned ASVAL technique in the senior author's opinion.

Previous Thermal Ablation Without Phlebectomy

Similarly, there are unhappy patients who present to our practice with a history of GSV ablation, which "worked temporarily." That is, the varicosities on the medial calf improved shortly after the procedure without phlebectomy, but with time, the untreated "venous reservoir" begins filling and dilating. Duplex ultrasound performed in our office usually shows successful ablation of the target GSV. However, the cluster of varicose veins in these cases has found a connection with an incompetent perforating vein. This is usually a Boyd's perforator in the upper calf. Treatment involves either ultrasound-guided sclerotherapy or thermal ablation of the perforator (function of size) and ambulatory phlebectomy of the varicose clusters.

We have also seen cases in which there are two sources of reflux in the superficial system causing venous hypertension identified, but only one source is treated. In these cases, usually only the incompetent GSV was ablated, and the incompetent anterior accessory saphenous vein (AASV) was left untreated. These patients have tended to present with temporary improvement of the varicosities that are in direct continuity with the GSV but have less or no improvement with varicosities that are not in direct continuity with the GSV. Our approach with these patients is thermal ablation of the AASV followed by concomitant ambulatory phlebectomy.

Previous GSV Ablation with No Improvement

Every so often, there will be patients that undergo successful ablation of the GSV, without improvement in symptoms. This should serve as a red flag that the patient was misdiagnosed. The majority of these cases are straightforward cases with

limbs presenting with classic SSV incompetence. Ablation of the SSV with laser or RF energy in combination with ambulatory phlebectomy will quickly rectify this problem. However, it is always important to take a proper history and physical to rule out other pathologies.

Conclusion

The CEAP and VCSS classification systems should be used to correctly identify and treat the signs and symptoms resulting from chronic venous disease. Venous specialists should familiarize themselves with the pros and cons of the available tools and techniques available for correction of venous pathophysiology. Venous specialists should also be prepared to treat an entire cadre of patients which have been treated inappropriately at outside facilities.

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Complications of the Treatment of Venous Insufficiency

16

Peter F. Lawrence

Clinical Pearls

1. Superficial phlebitis related to ablation of a superficial vein can be treated with anti-inflammatory medications and topical moist heat compression.
2. EHIT can occur with thermal and nonthermal ablation of the saphenous vein and is best avoided by starting treatment 2–3 cm away from the junction with the deep venous system.
3. Nerve injury increases with anatomical location, where the cutaneous nerves are close to the veins such as the below-knee great saphenous vein and the small saphenous vein in the mid-calf.

Introduction

Complications that occur during the treatment of chronic venous insufficiency have become less frequent since endovenous procedures have replaced surgery in most patients [1]. Therefore, many patients are treated in outpatient or office centers and discharged to home soon after a procedure [2]. However, some complications need to be prevented, diagnosed when they occur, and treated. Many are related to superficial or deep venous thrombosis, and some are related to injury to adjacent structures in the leg, such as the skin and nerve. In addition, hematoma and staining from hemosiderin pigmentation are significant concerns to patients who undergo these procedures for cosmetic, as well as other treatment goals. In addition, as with all procedures, there can be failures, which are usually termed "recurrences," but may actually be inadequate initial therapy or recanalization of veins that were initially properly treated.

Venous Thrombosis

Venous thrombosis of either superficial, perforator, or deep system is one of the greatest concerns in patients undergoing interventional treatments for venous insufficiency (Fig. 16.1). It is usually benign but can occasionally cause significant morbidity and rarely mortality.

Superficial Venous Thrombosis (SVT)

Superficial venous thrombosis comes in two forms—those close to the treated vein, whether it is a thermal or nonthermal ablation procedure, a

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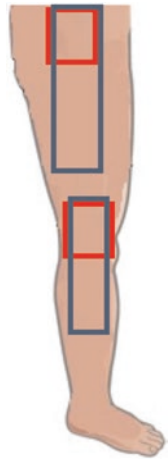

Fig. 16.1 Location of potential DVT and EHIT. EHIT occurs at the junction of superficial truncal and deep veins, while DVT can occur anywhere within the deep venous system. The *red boxes* indicate the sites of potential EHIT, where a truncal vein (great and small saphenous) joins the deep veins. The *blue boxes* are the sites of potential DVT. There is overlap between the two zones

ligation, or an excision of a superficial vein, and those unrelated to an interventional or surgical procedure. The most common is related to the procedure and occurs when there is both stagnant flow in a treated vein, due to proximal or distal ligation and injury, or when there is trapped blood within a treated vein, where the proximal and/or distal vein is ligated or thrombosed, so that the blood in between becomes stagnant and eventually thromboses.

Signs and Symptoms of SVT

SVT may be either asymptomatic or symptomatic, depending on the vein involved, the extent of inflammation within the vein, and the tissue surrounding the vein. SVT in veins that become dilated and inflamed may cause significant discomfort, and those adjacent to sensory nerves may have significant burning as well as pain, while those with minimal inflammation and swelling may be asymptomatic.

Prevention of SVT

There is little data or information on the prevention of SVT in patients undergoing venous procedures, probably because the consequences of SVT are usually not life threatening; they are usually self-limited and of little clinical consequence. The one technical principle to prevent SVT is to remove as much superficial vein as possible when performing excision and not leave large amounts of entrapped blood when performing ablation or sclerotherapy. When SVT occurs after sclerotherapy, where no vein is excised, placement of the solution in the vein is associated with spasm and inflammation of the vein being treated. Consequently, sclerotherapy of larger veins is performed with the leg elevated to collapse the vein, and after injection of the sclerosant, the leg should be compressed until the inflammatory reaction in the vein has become self-limited and the diameter of the thrombus in the vein is the smallest possible. Reducing the volume of blood in a vein with SVT reduces discomfort and later hemosiderin pigmentation related to the vein that is sclerosed [2].

Diagnosis of SVT

Clinical exam is the primary method of diagnosing SVT. Areas of SVT have localized tenderness, erythema along the vein, and firmness due to the thrombus within the vein. Localized SVT is often confused with infection. Duplex ultrasound is the primary technique to diagnose SVT and is used in cases where the cause of pain is not obvious. When there is concern about the extent of the SVT, duplex ultrasound can also easily identify the proximal and distal extent of the thrombus, determine the size of the thrombosed vein, and determine if it may be amenable to aspiration to release trapped blood.

Treatment of SVT

Treatment is dependent on the degree of patient discomfort and the anticipated cosmetic conse-

quences of untreated SVT. When a large superficial vein is thrombosed, there is considerable likelihood of long-term pigmentation, and therefore treatment may be indicated for cosmetic purposes. In addition, the degree of inflammation and pain will influence treatment. The options for treatment include symptomatic relief with anti-inflammatory medications and topical moist heat compression. When symptoms are severe or the risk of pigmentation is high, the release of entrapped blood with needle or micro-incision, followed by aspiration, usually results in rapid relief of pain and a lower likelihood of long-term pigmentation.

EHIT

Endothermal heat-induced thrombosis (EHIT) is defined as thrombus extension from a thermally treated superficial truncal vein into the deep system (Fig. 16.2). It may also occur with nonthermal techniques such as mechanochemical ablation (MOCA), foam, or glue ablation [3]. EHIT occurs at the junction between superficial and deep veins. Since the thrombus originates in the superficial vein and the thrombus extends into the deep vein without deep vein wall attachment, it is not a true DVT and it has a different natural history, unless it remains in the deep vein for a prolonged period and eventually attaches to the wall of the deep vein. In most circumstances, it is self-limited, with retraction of the thrombus back into the superficial vein within days to weeks and with no long-term consequences to the deep venous system. Consequently, the major risk of EHIT is that thrombus will break off during the time when it is unattached and/or floating in the deep venous system.

The location of the tip of a thermal catheter, when the vein is ablated, is critical in determining the likelihood of EHIT (Fig. 16.3). At least 2–3 cm from the junction is the recommended distance to prevent EHIT—the closer to the deep vein, the higher the likelihood that the thrombus will extend into the deep vein. It can occur with any thermal or nonthermal procedure that closes a large superficial axial vein at its junction with

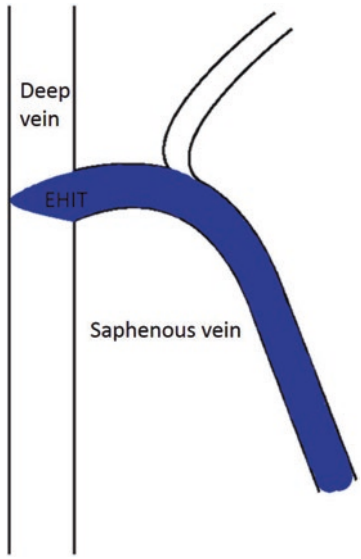

Fig. 16.2 Diagram of endovenous heat-induced thrombus (EHIT) extending into a deep vein. *Blue* represents thrombus extending from the saphenous vein into the deep venous system through the junction

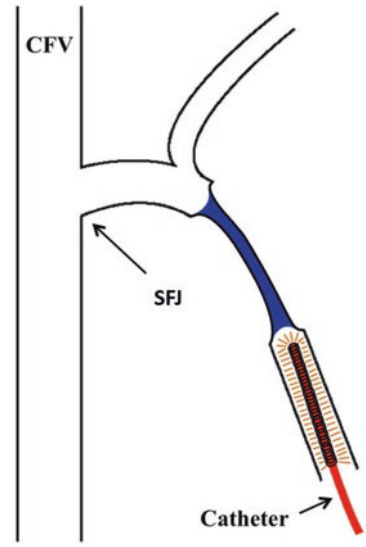

Fig. 16.3 Catheter positioned 2–3 cm from the saphenofemoral junction (SFJ) to reduce the risk of EHIT (CFV = common femoral vein)

the deep venous system. The identification of the extension into the deep system is dependent on the timing of imaging to identify EHIT.

Even though the risk of EHIT is low (<5%), it is the most common concern of the treating physician in patients who have a complication after a superficial endovenous procedure. EHIT is more common in patients with a very large truncal vein, in hypercoagulable patients, and in those patients with a prior history of DVT.

There has been no standardized and validated system of classification of EHIT, but there have been several classification systems proposed, which, although they have some differences, are similar in most ways [4–6].

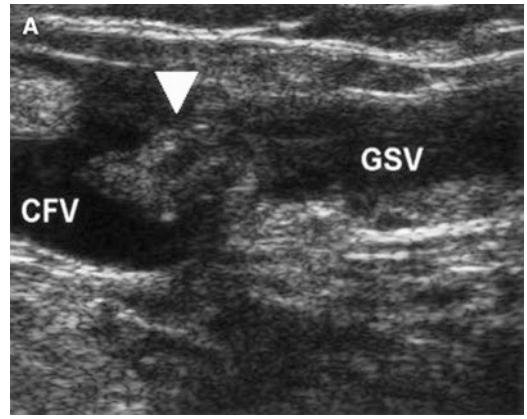

Fig. 16.4 Ultrasound appearance of EHIT, when thrombus has extended into the deep vein from the saphenous vein (GSV = great saphenous vein and CFV = common femoral vein)

Diagnosis of EHIT

Differentiating the causes of post-procedure pain and swelling is difficult, and differentiating EHIT from DVT clinically is difficult, unless duplex ultrasound is used to image the site of concern. Because there are significant differences in the natural history and treatment of EHIT and DVT, it is important to determine the etiology of post-operative complications in all patients with pain and swelling.

Duplex Ultrasound

Not all patients require a DU post-procedure to evaluate them for EHIT or DVT, but patients with significant post-op pain or swelling and those who have high risk factors for DVT and EHIT should undergo DU to assess the site of ablation, for hematoma or superficial branch or truncal vein thrombus. Both B mode and color flow, using transducers in the 2–10 MHz range, should be used for each study (Fig. 16.4). The transducer wavelength used will depend on the patient's body habitus and the depth of the superficial and deep venous system at the site of the diagnostic study. The diagnostic ultrasound should be performed in both the supine or standing position. Measurements should be taken using an electronic cursor in transverse, axial, and orthogonal positions to determine the distance and relationship between any thrombus identified and the vein wall, as well as the presence, absence, and extent of protrusion into the deep system.

Classification of EHIT

The key to the classification system is determining whether thrombus has protruded into the deep venous system, as well as the extent of protrusion [5, 6]. A simple classification system is as follows:

1. A = Closure limited to the superficial veins
2. B = Thrombus present in the deep venous system
   a. B1 = Thrombus bulging into the deep venous system but not significantly obstructing deep venous flow and not attached to the wall of the deep vein
   b. B2 = Thrombus extending into the deep venous system and occupying <½ of the deep venous diameter, as measured by cross-sectional duplex ultrasound
   c. B3 = Thrombus occupying >50% of the deep venous system at the level of protrusion, but not attached to the contralateral

deep venous wall (the thrombus can be free-floating or not free-floating)

d. B4 = Thrombus occupying the entire deep vein by cross-sectional duplex imaging and appearing similar to a short segment DVT (even though the patient does not have true DVT since all thrombus may retract)

Natural History of EHIT

The natural history of EHIT remains poorly defined, particularly when one evaluates the subgroups within an EHIT classification system. The timing of DU is critical since most thrombus that extends into the deep venous system is benign, retracts within a week, and causes no symptoms. Studies that image a patient within a few days of the procedure will identify many more patients with benign EHIT, while those that image a week to a month later will find very few cases of EHIT. The goal of all studies is to identify patients who have a risk of progressing from EHIT to DVT and treat them before they develop DVT or even pulmonary embolus.

Deep Vein Thrombosis (DVT)

DVT can occur after any interventional venous procedure, whether that procedure is performed on the superficial, perforator, or deep venous system. DVT is unrelated to the site of catheter placement and can occur in any deep vein, contiguous with the treated vein or a distance from it. In deep venous procedures such as lysis, balloon angioplasty, or stenting of the deep venous system, DVT may be related to the prior deep venous problem such as thrombosis or chronic webs and intraluminal wall changes or due to catheter, balloon, or stent manipulation within the deep venous system. It can be diagnosed by intravascular ultrasound at the time of the procedure, venography at the time of the procedure, or post-procedure duplex ultrasound, CT venography, or MR venography. Treatment is the same as DVT from any other cause.

Skin Infection

Skin infections may occur after incisions and puncture of the skin during superficial and deep venous procedures. They are most likely to occur in a patient who has a pre-existing skin infection or skin colonization, as well as situations where a hematoma occurs as part of the procedure. For those reasons, ablation of perforator veins (Fig. 16.5), when a venous ulcer is present, is among the highest risk procedures for infection, and infection may be prevented by using prophylactic antibiotics against skin and wound organisms. In addition, when multiple incisions are made in the skin to remove tributary or superficial axial veins, there is an increased risk of skin infection. It can sometimes be difficult to differentiate between infection and hematoma after venous procedures, particularly when there are pre-existing skin changes such as lipodermatosclerosis, so the prudent surgeons treat with antibiotics until the cause of the skin changes declares itself [6, 7].

Skin Necrosis

Initially, when thermal ablation procedures were first developed and reported, skin necrosis occurred directly over the site of the catheter, due to the transmission of thermal energy to

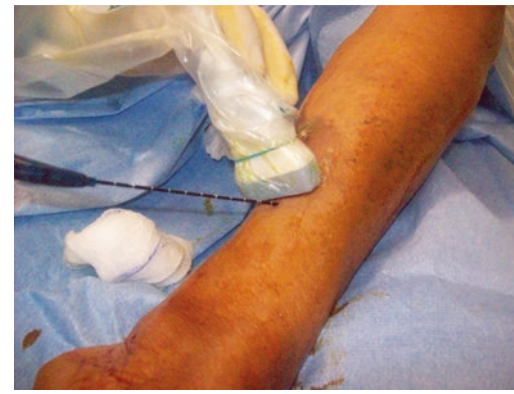

Fig. 16.5 Technique of perforator ablation which, when a venous ulcer is present in the region of the catheter, increases the risk of wound infection at the catheter puncture site

the skin. However, with new laser wavelengths, new designs of radiofrequency catheters, and tumescent techniques that separate the skin from the vein, as well as the increasing use of nonthermal devices for superficial vein closure, the frequency of skin burns has become extremely uncommon and virtually never occurs, as long as proper technique is used. The liberal use of tumescence solution around the vein to be treated with thermal energy has several purposes; it moves the vein away from the skin, moves the vein away from sensory nerves which parallel the vein, and collapses the vein to reduce the volume of intraluminal thrombus. Consequently, the current technique of thermal ablation of superficial axial veins, with the liberal use of tumescent solution, is virtually never associated with a skin burn.

Skin Pigmentation

When a truncal or superficial vein is ablated, whether with thermal or nonthermal techniques, the size of the vein at the time of closure determines the extent of pigmentation of the overlying skin. Large veins that are ablated with little reduction in their size during the ablation process often result in overlying skin pigmentation. In addition, the distance from the skin to the vein is critical, as well as whether the vein is located below the fascia. Large veins that are close to the skin require either extensive tumescence to reduce their size or nonthermal techniques to remove them. Microphlebectomy can often be used to remove very superficial truncal veins that would otherwise lead to severe pigmentation if they were ablated or closed with either a thermal or nonthermal technique. Other cosmetic concerns include the size of incisions, which may lead to scars at the site of either puncture for an interventional procedure or the sites of incisions for removal of tributary veins. Micro-incisions using an 18 gauge needle combined with a small crochet hook reduce the size of incisions so that they are nearly invisible.

Neurologic Injuries

Nerve injury may occur when a superficial sensory nerve runs adjacent to a superficial axial vein and that vein is treated with thermal energy, whether it be with a laser or radiofrequency energy. Recently, nonthermal devices have been developed that do not require heat for vein closure, and these devices have been associated with a much lower incidence of sensory nerve injury. If a thermal device must be used, the vein being treated should be separated from the surrounding tissue and sensory nerve with tumescent solution. In addition, areas of the axial vein that are adjacent to the nerve are best left alone and not treated. This includes the saphenous vein below the knee and the small saphenous vein from the mid-calf to the ankle. A commonly used approach is to first treat the proximal saphenous vein with thermal ablation and reserve treatment of the distal saphenous vein and the small saphenous vein for a nonthermal technique at a later time and only if it is needed to control symptoms or for venous ulcer healing. Ablation of the proximal small and great saphenous vein is often associated with complete resolution of symptoms and no further treatment is needed [6].

Motor nerve injury is extremely uncommon and only occurs if a catheter is placed below the fascia of the leg. This may rarely occur with small saphenous ablation, when the catheter is advanced to the popliteal vein, and during perforator ablation, if the perforating vein is treated with thermal energy below the fascia of the leg (Fig. 16.6).

Residual Symptoms

Pain occurs initially after superficial venous procedures due to skin incisions, hematomas, infection, and superficial and deep vein thrombophlebitis. A small amount of pain can be expected in every patient, due to a skin puncture (Fig. 16.7) and subcutaneous manipulation, but most mini-

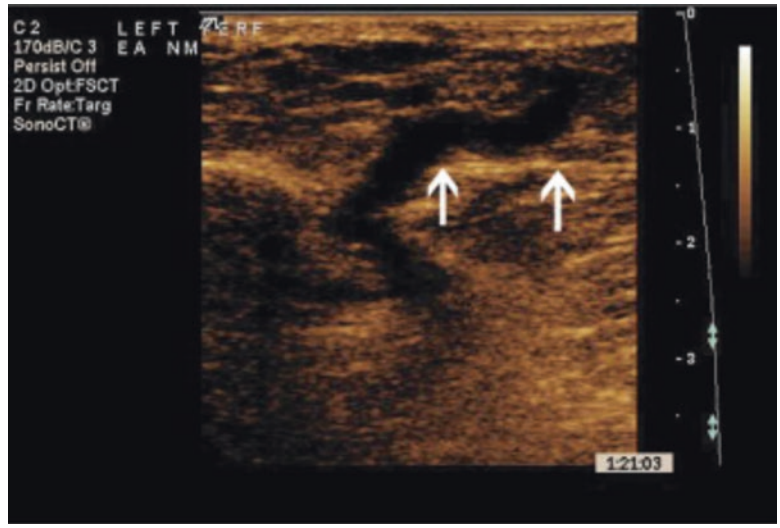

Fig. 16.6 Path of a perforator vein as it travels through the fascia. In the ankle, the perforator vein is very close to the tibial artery and motor and sensory nerves

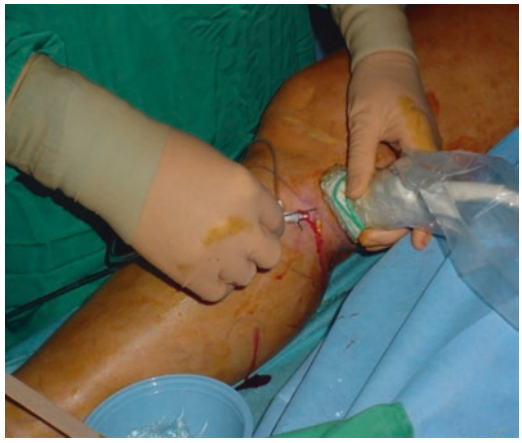

Fig. 16.7 Technique of laser or radiofrequency ablation of a truncal saphenous vein, with the puncture site being the potential site of either skin infection or superficial thrombophlebitis

mally invasive venous procedures in the modern era, where stripping is not used, are relatively pain-free. There have been comparisons of laser and radiofrequency ablation regarding postoperative pain, but it is apparent from most studies that either technique can be performed almost pain-free, as long as the catheter does not perforate the vein wall. When pain does occur, it is incumbent on the surgeon to perform a physical exam, conduct a duplex ultrasound study, and then treat, based on the findings.

Swelling

Swelling is the consequence of tissue trauma, whether it is from infection, hematoma, or superficial or deep venous thrombosis. Swelling is another indication for conducting a thorough physical exam, duplex ultrasound of the leg veins, and occasionally CT venogram and/or MR venogram, to determine the etiology of the swelling. Long-term swelling is very uncommon after superficial venous procedures and usually indicates that another problem is the cause.

Recurrence

For many patients, the most important outcome of a venous procedure is long-term success and the lack of a recurrence. Many times, what is termed a recurrence is actually incomplete removal of the offending veins or incomplete ablation of an axial or perforator vein, rather than a true recurrence. Recent reviews of recurrence have demonstrated that the frequency of recurrence is similar between

the current era and previous eras when vein stripping was the method of choice. Currently, recurrence occurs in ~5% of patients and is due to recanalization of superficial truncal veins, which can often be retreated with sclerotherapy. Neovascularization is uncommon with current minimally invasive devices, while it is more common with stripping [8].

Procedures on the deep venous system are much less commonly associated with recurrence (Fig. 16.8), although stents that occlude the contralateral iliac vein are increasingly being reported to cause contralateral leg swelling (Fig. 16.9) [9].

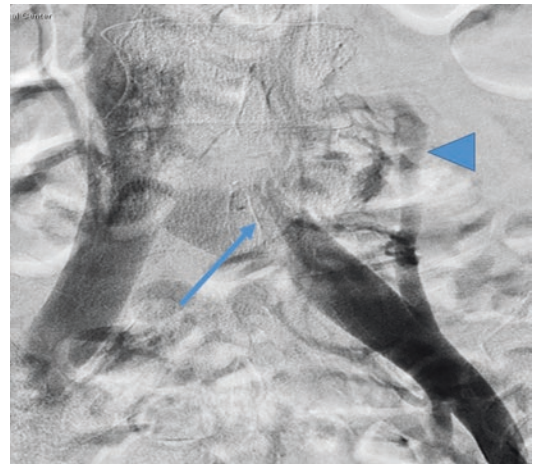

Fig. 16.8 Compression of the deep venous system (*arrow*) may lead to swelling and even DVT, when severe. Venous congestion leads to the development of large collateral veins (*arrowhead*)

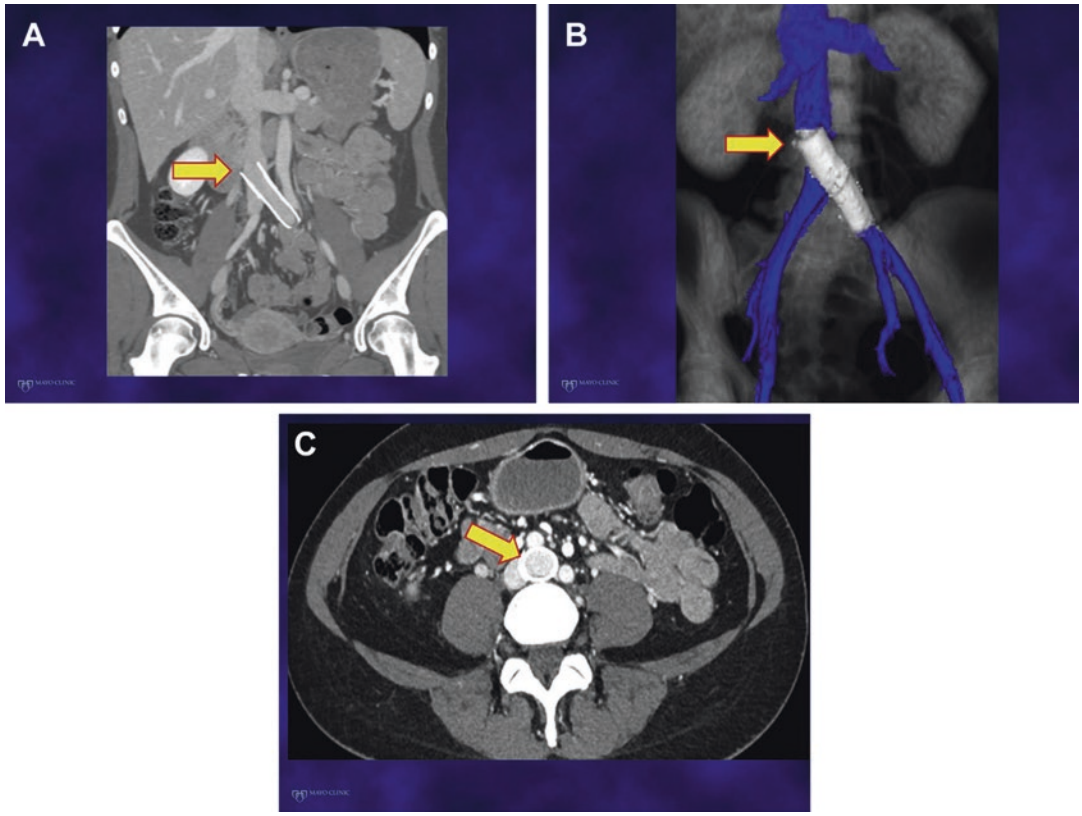

Fig. 16.9 These images show a potential complication related to iliac stent placement. The stent in the left common iliac vein (*arrow*) crosses the right iliac vein and occludes the contralateral venous outflow, potentially leading to contralateral leg swelling or DVT (**a** = frontal view, **b** = 3D reconstruction, **c** = cross-sectional view)

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Valve Reconstruction for Deep Venous Reflux

17

Oscar Maleti and Marzia Lugli

Abbreviations

AV	Axillary vein
CFV	Common femoral vein
CVI	Chronic venous insufficiency
DFV	Deep femoral vein
DUS	Duplex ultrasound
DVR	Deep venous reflux
DVS	Deep venous system
EF	Ejection fraction
FV	Femoral vein
GSV	Great saphenous vein
IVUS	Intravascular ultrasound
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PV	Popliteal vein
QoL	Quality of life
RVF	Residual volume fraction
VCSS	Venous clinical severity score
VFI	Venous filling index

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Clinical Pearls

1. Current surgical techniques for deep venous reconstruction are valvuloplasty, valve transposition, valve transplantation, and neovalve creation
2. Deep venous obstruction should be corrected before valve reconstruction
3. Neovalve creation seems to provide better valve competence after long-term follow-up compared to the other techniques for valvular reconstruction

Introduction

Deep venous reflux (DVR) is one of the main causes of chronic venous insufficiency (CVI) [1, 2]. It may be isolated or associated with other pathologies, such as deep venous obstruction; or else associated to superficial venous reflux; or reflux of the perforators [3, 4]. CVI is the consequence of venous hypertension during ambulation; it is related to high volume/low velocity blood flow, which leads to microcirculatory disorders [5]. DVR tolerance varies according to the caliber of the veins and the overall venous volume, the efficiency of the muscle pump, the age and physical activity of the patient [6–10]. DVR may be axial or segmental [11]; CVI is more frequently correlated to the presence of axial reflux [12].

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Various reflux patterns were defined at the VEIN TERM Consensus Conference [13]. Reflux is one of several determining elements in CVI [14], which also includes associated obstruction. CVI chiefly occurs in PTS, where reflux and obstruction are associated in two thirds of cases [15]. When not associated to obstruction or reflux in other districts, DVR is nevertheless a significant factor in CVI [16].

Correcting DVR must observe the principle of ensuring adequate blood flow, bearing in mind that the latter increases substantially during muscular activity. Past attempts to correct reflux, which employed ligation of the popliteal and femoral veins [17, 18], had a high failure rate because of the formation of a collateral network without valves. Failure was also reported [19] where banding was applied to reduce the vein caliber but was correlated to an increase in flow resistance. Hence, the best options would appear to be valve repair, where possible, the creation of a new valve, or a strategy to obtain a new venous axis with competent valves.

Deep Venous Reflux

On the basis of etiology, DVR can be distinguished into primary, secondary, or congenital [20–22]. Secondary reflux is by far the most frequent in that it includes post-thrombotic syndrome (PTS) valve insufficiency. Deep vein thrombosis leads to the destruction of the valve function in 40–70% of cases [23]. If rapid resolution of the thrombus occurs, the valve function may remain intact; the valve itself may present limited malfunction, and the vein wall at the thrombus site may develop simple thickening (Fig. 17.1). In other scenarios, valve destruction may be segmental; however, the valve apparatus, at sites distal or proximal, may be preserved. When the thrombotic process is not rapidly resolved and has been more extensive, valve destruction will be total and associated with axial reflux.

The term primary reflux is identified on CEAP classification [20] as a malfunction of the valve due to unknown causes, so such as to preserve the valve apparatus in a quasi-unaltered condition.

This malfunction may be due to malformations such as asymmetrical cusps or redundant leaflets which may be a congenital condition; alternatively, the malfunction might be linked to a small unrecognized venous thrombosis, thus making it in reality a secondary reflux.

Despite the fact that a congenital condition may be the cause of the malfunction, the CEAP classification currently reserves the term "congenital" to the extremely rare conditions of venous aplasia or hypoplasia [20, 22, 23]. The distinction between primary, congenital, and secondary, leaving aside etiology, in all events proves crucial since both techniques and outcomes vary widely when treating these three type of reflux [24].

Surgical Treatments

Surgical treatment of deep venous reflux essentially consists of two types of procedures: valvuloplasty or the creation of a non-refluxing segment.

Surgical Treatments in Primary DVR

Internal Valvuloplasty

As mentioned above, valvuloplasty is feasible only where the valve apparatus is intact or sufficiently preserved following the thrombotic episode. In such cases the valve malfunction presents a reflux of varying magnitude generally associated with the prolapse of one or both the free leaflets or their asymmetry or the widening of the valve annulus. The first surgical operation to correct an insufficiently functional valve was performed by Kistner in 1968 [25] and consists in stretching the leaflets, thus reducing the redundancy and the length of the free border of the leaflet itself (Fig. 17.2a, b). This first technique was subsequently modified by other authors who suggested various approaches in order to avoid direct damage to the valve apparatus during phlebotomy [26–28].

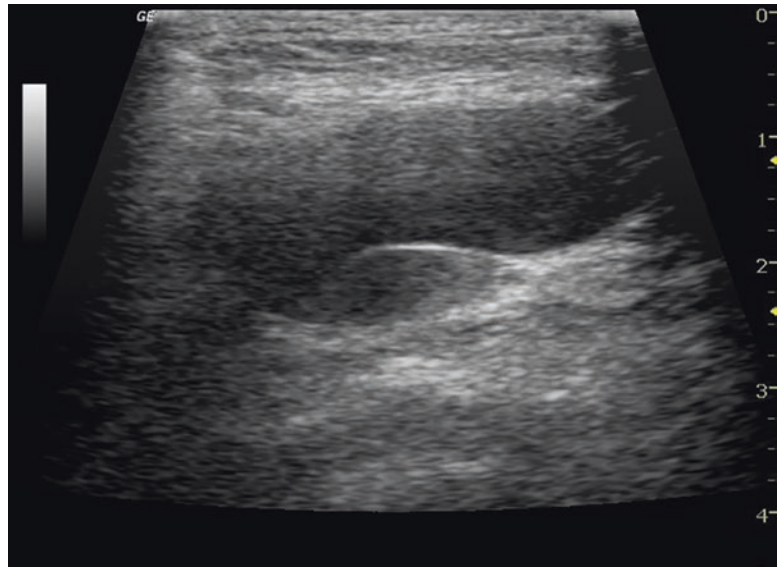

Fig. 17.1 Post-thrombotic syndrome: valve thickening

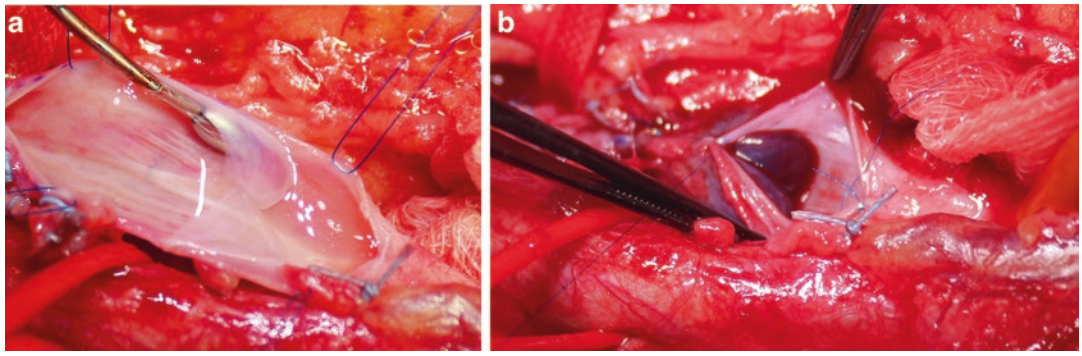

Fig. 17.2 (**a**) Primary deep venous incompetence: internal valvuloplasty. (**b**) The valve competence is checked after removing the proximal clamp

External Valvuloplasty

In order to avoid phlebotomy, external valvuloplasty was also proposed to establish valve competence by reducing the commissural angle with the application of external stitches. This technique presupposes perfect visibility of the site at which the cusps are inserted into the vein wall, but still implies the risk of damaging the valve apparatus by stretching it to excess [29–31]. The lower degree of technical precision is also associated with less satisfactory outcomes.

In view of the fact that the valve leaflets are often asymmetrical, direct frontal vision offered by phlebotomy prompts the choice of this technique. Valvuloplasty should also restore valve competence by maintaining the sail effects in the valve sinus, since the latter proves critical in ensuring correct valve function [32].

Surgical Treatments in Secondary and Congenital DVR

The surgical techniques that address secondary DVR are: vein transposition, vein transplant, neovalve, and artificial venous valve.

Vein Transposition

Where anatomical conditions permit, a devalvulated segment is relocated onto a competent valvulated segment. Transposition is normally performed at the inguinal level and was first described by Kistner in 1979 [33]. The most frequently performed version involves transposing the valvulated segment onto the deep femoral vein (DFV) or onto the great saphenous vein (GSV).

Transposition onto the DFV: Technical Details

When transposing onto the DFV, the surgeon should isolate the femoral junction in the first tract of the common femoral vein (CFV). The tract should be long enough to allow control and should extend distally toward the femoral vein (FV) and the DFV.

The most proximal and competent valve in the DFV must be identified and the FV isolated for a tract long enough to enable us to transpose the segment without creating twists and tension.

The FV is divided at the proximal insertion sited at CFV level. The residual stump is closed off with a longitudinal suture. Thereafter the femoral vein is sutured at DFV level, downstream of a previously identified competent valve.

Any trabeculae in the FV due to post-thrombotic processes should be removed. Given that the two calibers are normally incompatible, an end-to-side anastomosis is more often performed (Fig. 17.3); however, for hemodynamic reasons, where possible an end-to-end anastomosis is preferable.

DFV is a multiaxial system, which explains why hemodynamic alterations are not caused by the descending branch interruption.

Transposition onto the Saphenous Vein: Technical Details

If a competent GSV be available, the transposition of the FV onto the GSV can be performed below the sapheno-femoral junction. In view of the fact that the GSV is located at subcutaneous level, it is better to transpose the GSV itself into a subfascial location. A segment 5–10 cm long should be harvested from the proximal GSV. The FV divides just below the junction with the DFV. An end-to-end anastomosis is performed between the GSV and the FV. The FV is often distended as a result of clamping and any discrepancy in caliber will quickly diminish after restoring flow. Still, the increased blood flow through the GSV may cause dilatation and precipitate valve insufficiency. Such a scenario can be avoided by applying a cuff below the competent saphenous valve, thus preventing postoperative dilatation.

The advantages of transposition are the relative technical ease of performance when a competent GSV is available and good long-term results. On the other hand, the disadvantages are the caliber mismatch between FV and GSV or DFV; adverse anatomical conditions in DFV. Further drawbacks may be related to the competent valve being only present in distal part of DFV, requiring extensive dissection. As mentioned prior, subsequent incompetence of the DFV and GSV due to the increase in caliber is another possible problem. Finally the risk of postoperative lymphocele which can be a difficult complication to treat.

Vein Transplant

Transplant aims at inserting a segment containing a competent valve inside an incompetent axis. In the first technique described by Raju in 1979 [34], the donor segment is the axillary vein (AV); in the version proposed by Taheri in 1982 [35], it is the brachial vein.

Technical Details

The main drawback of this technique may be incompetence in the donor segment and discrepancy in caliber between the two veins. Access to the AV can be gained by longitudinal incision at the summit of the armpit; this enables removal of a segment long enough for transplantation.

Vein dissection should be performed proximally to the ribcage level and distally as far as the incision will allow. There is no need to restore anatomical continuity since collateral pathways

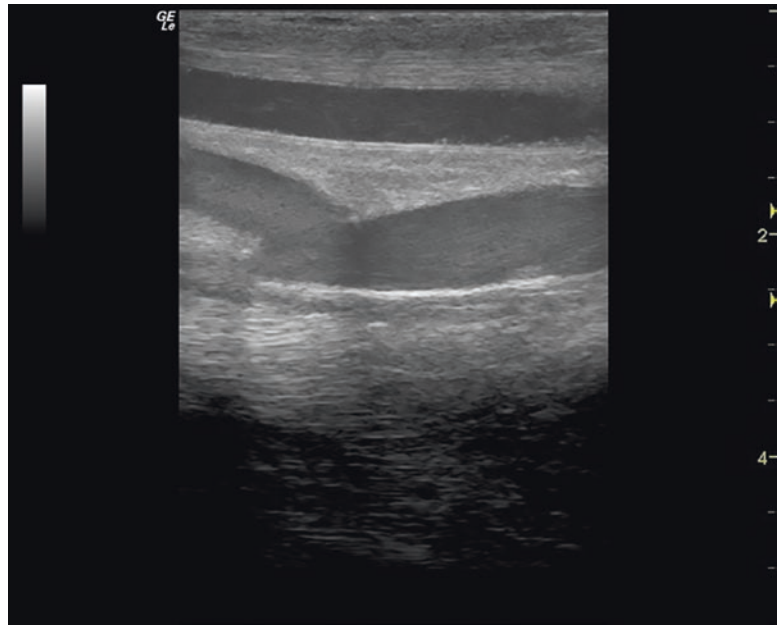

Fig. 17.3 Femoral transposition: End-to-side anastomosis between femoral vein and deep femoral vein. DUS control

ensure good drainage of blood for the arm, and therefore complications resulting from removal of the AV are rare. First, test the segment for valve competence before removing the valve (or valves). In cases of incompetence, bench reconstructive surgery can be performed, but adds significant complexity to the case.

The harvested vein segment should be kept in a heparinized saline solution. Transplantation should be performed to the most compatible recipient segment, either in the FV or popliteal vein (PV), depending on the caliber. If the PV is preferred, given its duplication sometimes, the competence of parallel veins should be verified in advance. If competence is not ascertained, the refluxing parallel veins should be ligated.

The popliteal vein can be accessed via a traditional medial incision. Posterior exposure is an option, but is technically more complex and provides limited exposure. Complexity of this technique is correlated with the double intervention (harvesting the arm vein and implantation in the lower limb).

It is essential to avoid creating twisting, tension, and stenosis at the suture site as this can predispose the vein to thrombosis. In preference to a continuous suture, an interrupted suture or two-half sutures should be performed. The proximal anastomosis should have a wider diameter than the distal one, and as large a distance as possible should be left between the valve cusps and the proximal anastomosis.

While the risks of wound complications and lymphocele are decreased by staying away from the groin area, the effectiveness of the procedure is diminished in the presence of multiple PV or DFV incompetence. It involves a surgical procedure on an unaffected a healthy upper extremity. The incidence of postoperative thrombosis is not uncommon.

Neovalve

The neovalve is a technique which uses the principle of reconstructing a new autologous valve by refashioning the patient's own vein wall. Raju and Hardy [36] proposed a *de novo* valve using a valvulated portion of the GSV or a tributary of the AV, which was inserted into the FV. They reported good results, despite a limited series. Plagnol [37] performed a neovalve in the terminal portion of the GSV; this portion of the GSV was invaginating into the CFV. Maleti [38] proposed a version in which the neovalve is obtained by dissecting the vein wall so as to fashion a flap

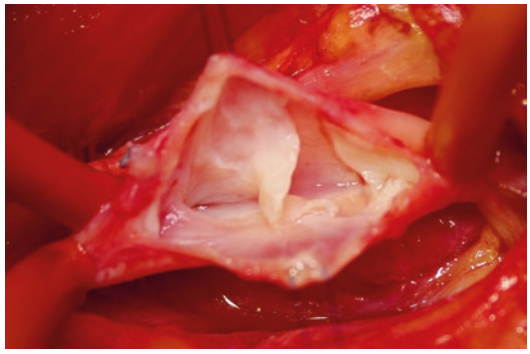

Fig. 17.4 Post-thrombotic syndrome: Neovalve according to Maleti. A posterior dissection of the wall is performed in order to create a neovalve

or leaflet (Fig. 17.4). Thanks to the characteristic thickening of vein wall tissue, the neovalve is easier to perform in PTS, and it can also be performed in cases of valve agenesis [39]. Due to the anatomical variables in the vein wall and the diversity of post-thrombotic lesions, the configuration of the Maleti neovalve is variable in each case. The choice of the neovalve site, as well as the technical variations used in constructing it, should be based on high resolution duplex ultrasound (DUS) assessment. A significant portion of the technical aspects depends on the intraoperative findings after phlebotomy.

Post-thrombotic lesions have various features: slight thickening of the vein wall; uniform or otherwise; synechiae or septa; endoluminal fibrotic tissue which forms a double channel; notable thickening of the vein wall with fibrosis occupying a large portion of the lumen.

In all but the first of these conditions, endophlebectomy should be performed. The main risk with the neovalve technique is postoperative readhesion of the leaflet at the dissection site. Specific sutures can prevent this mode of failure.

Depending on the features of the vein wall, the neovalve may be bicuspid or have a single cusp. In order to prevent leakage, a valve with a single cusp should be fashioned deeper. It is now recognized that the shape of the valve itself determines physiological valve function. As the neovalve does not fully comply with nature's model, the wash-out action performed by the sinus is lacking. The result is reduced movement in the flap, which in turn may provoke thrombosis in the valve sinus. In order to prevent this from happening, when applicable a leaflet is fashioned at the site of a tributary so as to create a competing flow.

An alternative technique has been suggested by other authors [40] whereby a portion of the vein wall is invaginated to create a flap; a PTFE patch is used to reconstruct the vein wall. The chief drawback of this technique is that, since the neovalve is open laterally, the leaflet cannot fragment the hydrostatic pressure. However, the reduced reflux volume will lead to partial functioning of the neovalve when combined with efficient ambulation.

The advantages of neovalve technique are that it creates an anti-reflux mechanism using the patient's vein wall and offers a surgical alternative where transposition and transplant are not possible. The disadvantages of the technique are that it is technically challenging and has to be individualized. It frequently requires endophlebectomy and the reconstruction site can seldom be defined preoperatively.

Artificial Venous Valve

Over the years, various attempts have been made at creating a substitute venous valve. Research is still underway, but there is no current human application.

Indication for Treatment

Patient selection for deep valve reconstruction depends on a diagnostic protocol and a thorough clinical evaluation.

The diagnostic protocol involves DUS evaluation, air plethysmography [41], venography [11], and intravascular ultrasound (IVUS) [42].

DUS is essential for defining lower-limb venous abnormalities [43]. Since DUS is not sufficient to detect proximal obstructions—frequently present and to be treated first—further investigations are needed. DUS is able to detect the reflux, except where low buffering effects are

present in the calf; in such cases the reflux can go undetected or underestimated. The reflux is not the only hemodynamic alteration correlated with valve malfunction; other features include modified volume and compliance, which may be underestimated in a standard DUS exam.

Patients with CVI should also be assessed on functional data such as calf pump efficiency [44]. Restoring valve competence at thigh level is not sufficient to maintain a low volume in the leg during ambulation if correction is not combined with efficient calf contraction.

Poor results in some series can be attributed to inappropriate patient selection.

Other parameters like VFI (venous filling index), EF (ejection fraction), RVF (residual volume fraction) are advisable in follow-up evaluation [45].

Any macrocirculatory disorders will have an impact at the microcirculatory level; correction of the same does not occur immediately following restoration of valve function. A microcirculatory evaluation is essential in monitoring the reversibility of microcirculatory lesions, and is also a key element in detecting the improvement brought about by pharmacological or compression therapy.

In patients selected for deep reflux correction, iliocaval and descending venography are indicated to rule out proximal obstruction when suspected with the use of IVUS.

The diagnostic protocol will be applied in any patient eligible for deep vein reconstruction with:

- Severely impaired Quality of Life (QoL) despite compression therapy
- Patients with C4–C6 affected by deep venous reflux
- Patients with C3 disease and no superficial insufficiency has been detected;
- Patients with C2 disease and multiple recurrences.

No further investigations and procedures are necessary [46, 47] in CVI patients who are able to maintain a good QoL and satisfactory conditions simply as a result of treatment to the superficial venous system or compression therapy.

CVI patients with malfunctioning hemodynamics in the leg, multiple recurrences in varicose veins that significantly affect QoL, but also young patients resistant to compression therapy deserve further investigation. By applying a selected and well-tolerated procedure we can considerably improve their condition [39, 48, 49].

Strategies

In primary, secondary and congenital reflux, operative treatment is important.

In primary varicose veins associated with superficial venous reflux, the competence of the deep venous system can sometimes be restored by treating the superficial system alone, thus reducing the overload of the deep system. However, the reduction of deep venous overload can restore the valve competence by reducing the diameter of the deep vein only when the valves are anatomically normal and with symmetrical, functional leaflets. Conversely, when the valves are dysplastic and present abnormal and asymmetrical leaflets, valve reconstruction should be considered since the reduction of deep venous overload is insufficient to restore the function of the valves. Thus a precise preoperative evaluation (DUS and phlebography) will allow for planning an appropriate treatment strategy.

Valve agenesis is characterized by the absence of valves throughout the deep venous system and usually manifests in young patients with severe CVI and impairment of QoL [50]. Superficial reflux and deep venous reflux due to valve agenesis are usually associated and ablation of the superficial system is usually not sufficient. In such cases, it is important to rule out any proximal venous obstruction and increase calf pump efficiency. The need to treat the deep system via a direct approach is reserved to patients in C4b–C6 and a neovalve construction is a good option.

PTS is a complex pathology characterized by two principal hemodynamic disorders: increased resistance to flow (obstruction), due to stenosis, intraluminal synechiae, rigidity of the venous wall [15] and reflux, due to valve

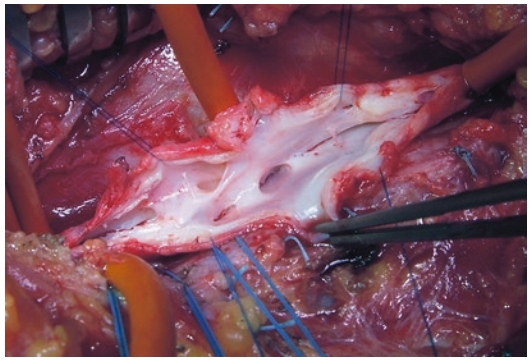

Fig. 17.5 Common femoral vein: post-thrombotic lesions

damage [12] (Fig. 17.5). Usually obstructive lesions are in the proximal iliac and common femoral vein, while reflux is in the femoral, popliteal, and tibial veins.

Operative strategy in PTS [51] involves the treatment of proximal obstruction by means of venous stenting (Fig. 17.6) as a first step since the majority of the patients can improve without corrective reflux treatment. As a second step, consider the relief of common femoral vein obstruction by means of endophlebectomy, obstructive lesions in this crucial area of the leg.

Next the femoro-popliteal veins should be evaluated as common site for hemodynamic disorders due to reflux and obstruction. As a final step, in patients who show no improvement, direct deep venous reflux correction should be considered.

The diagnostic criteria needed to decide which strategy to apply are the following:

- Presence and/or absence of proximal obstruction including occlusion.
- Presence of axial reflux below the inguinal ligament, from groin to calf, via femoropopliteal axis or by superficial or profunda transfer, as well as their combination.
- Presence and/or absence of proximal competence of the DFV.
- In the case of DFV incompetence, identify single or multiple re-entry points into the PV.
- Presence and competence of the great and small saphenous veins.
- PV features (single and multiple channels) and their competence and/or incompetence.
- Caliber of FV and PV.
- Caliber and competence of the AV.
- Presence of endoluminal fibrosis, determining double channel at femoropopliteal level.

Outcomes

The complication rate of deep venous system (DVS) treatments is particularly rare, and DVS surgery is safe [52]. The results are satisfactory, particularly in primary incompetence, despite the heterogeneity of patients. The less satisfactory results obtained treating the secondary incompetence are probably correlated with:

- Inadequate understanding of deep venous pathophysiology
- Inadequate imaging (in the past proximal obstruction was underestimated and consequently not previously treated)
- Suboptimal patient selection
- Patients with advanced CVI and non-reversible microcirculatory damage

The outcomes of deep venous reconstruction are limited to case series. Assessing the outcomes of deep vein surgery to correct reflux is complicated. Principally, we rely on the Villalta score in conjunction with VCSS. Most outcome literature to date is based on ulcer healing and pain reduction. A summary of the outcomes of each of the techniques is given in tables. Most experience has been with valvuloplasty with the internal and external techniques. The ability to achieve competent valves varies from 31.5% up to 79.8% but the clinical failure as measured by ulcer recurrence or nonhealing is 21–50% (Table 17.1). The experience with valve transposition and transplantation is more limited but has similar variability in long-term outcomes (Tables 17.2 and 17.3). There are only 3 case series with neovalve reconstruction but the outcomes seem to be relatively better with 68–100% achieving competent

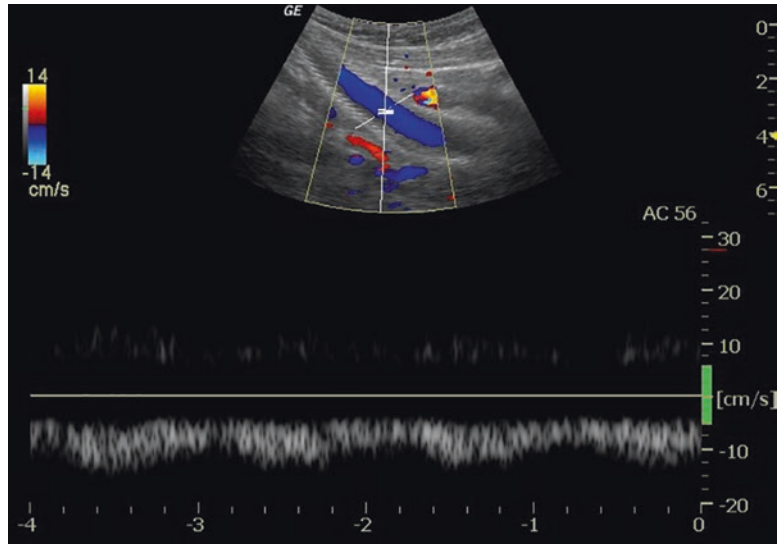

Fig. 17.6 Post-thrombotic syndrome: DUS of iliac venous stenting

Table 17.1 Valvuloplasty outcomes

Author (Year)	Technique	Number of limbs (Number of valves)	Follow-up months (mean)	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Masuda [53] (1994)	Internal	32	48–252 (127)	(28)	24/31 (77)
Raju [54] (1996)	Internal	68 (71)	12–144	16/68 (26)	30/71 (42)
Raju [54] (1996)	External	47 (111)	12–70	14/47 (30)	72/111
Sottiurai [55] (1996)	Internal	143	9–168 (81)	9/42 (21)	107/143 (75)
Raju [31] (2000)	External (Transcommisural)	141 (179)	1–42	(37)	(59)
Perrin [48] (2000)	Internal	85 (94)	12–96 (58)	10/35 (29)	72/94 (77)
Tripathi [56] (2004)	Internal	90 (144)	(24)	(32)	(79.8)
	External (Transmural)	12 (19)		(50)	(31.5)
Wang [57] (2006)	External (Transmural)	(40)	(36)	/	(91)
Rosales [58] (2006)	External (Transmural)	17 (40)	3–122 (60)	3/7 (43)	(52)
Lehtola [59] (2008)	Internal	12	24–78 (54)	/	55
	External (Transmural)	7			
	Internal + External (Transmural)	1			

valve on follow-up and only 17% experiencing nonhealing or recurrence of ulcers (Table 17.4). The Portland team [65] has developed a bioprosthetic valve. However, at one-year follow-up valve competence was not evident, and the technology is still experimental.

Conclusions

The surgical treatment of deep venous reflux is safe and effective for treatment of selected patients with advanced venous disease and ulceration.

Table 17.2 Transposition outcomes

Author (Year)	Number of limbs	Follow-up months	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Masuda [53] (1994)	14	48–252	7/14 (50)	10/13 (77)
Sottiurai [55] (1996)	20	9–149	9/16 (56)	8/20 (40)
Cardon [60] (1999)	16	24–120	4/9 (44)	12/16 (75)
Perrin [48] (2000)	17	12–168	2/8 (25)	9/17 (53)
Lehtola [59] (2008)	14	24–78	/	(43)

Table 17.3 Transplantation outcomes

Author (Year)	Number of limbs	Follow-up months (mean)	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Bry, [61] (1995)	15	15–132	3/14 (21)	7/8 (87)
Mackiewicz [62] (1995)	18	43–69	5/14 (36)	/
Raju [54] (1996)	54	12–180	/	16/44 (36)
Sottiurai [55] (1996)	18	7–144	6/9 (67)	6/18 (33)
Raju [63] (1999)	83	12–180	(40) 6 years	(38) 4 years
Perrin [48] (2000)	32	12–124 (66)	9/22 (41)	8/32 (25)
Tripathi [56] (2004)	35	(24)	(45)	(41)
Lehtola [59] (2008)	29	24–78 (54)	/	(16)
Kabbani [64] (2011)	19	(37)	6/8 (80)	8/19 (42)

Table 17.4 Neovalve outcomes

Author (Year)	Technique	Number of limbs	Follow-up months (mean)	Ulcer recurrence or nonhealed ulcer (%)	Competent valve (%)
Plagnol [37] (1999)	Bicuspid	44	6–47 (17)	3/32 (17)	38/44 (86)
Opie [40] (2008)	Monocuspid	14	(48)	0/6	13/14 (92)
Maleti-Lugli [39] (2009)	Monocuspid or Bicuspid	40 (19+21)	2–78 (28,5)	7/40 (17)	13/19 (68) 21/21 (100)

Indeed, the clinical experience in this field is confined to only a few centers around the world and studies are based on case series. Nevertheless, surgical treatment addressing the deep vein system is gaining more attention, mostly because of new procedures which can help patients suffering from severe chronic vein insufficiency. It is possible that the variability in the outcomes in early series was affected by the presence of obstructive disease that was underdiagnosed. Our enhanced understanding of the complex interactions between reflux and obstruction, as well as the interactions between the superficial and deep venous systems will continue to evolve and improve our ability to deliver better therapy to patients with venous disease.

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Pelvic Venous Insufficiency

18

Olivier Hartung

Clinical Pearls

1. Up to 30% of women with pelvic pain can have pelvic congestion syndrome.
2. Ovarian vein diameter >6 mm is highly associated with pelvic congestion syndrome.
3. Most series describing ovarian vein embolization for treatment of pelvic congestion syndrome show 70–90% improvement in symptoms.

Introduction

Pelvic venous insufficiency (PVI) refers to all the manifestations related to pelvic venous system dysfunction. Pelvic varicose veins (PVV) are the most frequent presentation of PVI. Pelvic congestion syndrome (PCS) includes all pelvic symptoms due to PVI in addition to other symptoms and clinical manifestations, mainly affecting the lower limbs. PCS was first described in 1857 by Richet [1] and given its name in 1949 by Taylor [2], but it was recognized only recently as a frequent cause of chronic pelvic pain.

Epidemiology

The incidence of pelvic varicose veins is estimated at 10% of all women. Moreover, 15% of women between the ages of 18 and 50 years suffer from pelvic pain and present with pelvic varicose veins in 60% [3]. PCS is not an uncommon source of pelvic pain: while considering 148 patients with chronic pelvic pain, Soysal noted that 30% had PCS [4]. Belenky found ovarian varicose veins in 9.9% of the general female population with 59% suffering from PCS [5]. However, because most of these symptoms can be caused by other pelvic diseases (endometriosis, uterine fibroma, pelvic cancer, etc.), initial gynecologic examinations are mandatory before reaching the diagnosis of PCS, even in the presence of pelvic varicose veins.

Moreover, PVI can cause lower limb varicose vein: 15–20% of these patients have varicose veins linked of pelvic origin [6], and this percentage can rise up to 30% in patients with recurrence of lower limb varicose veins [7].

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Anatomy of the Pelvic Venous System

The pelvic venous system is dependent on three different networks (Fig. 18.1):

- *Femoro-ilio-caval network and saphenofemoral junction*: The common femoral vein (CFV) is formed by the confluence of the femoral and the deep femoral veins. The saphenofemoral junction receives multiple branches: the superficial epigastric vein, the superficial iliac circumflex vein, and the superficial and deep external pudendal veins which drain the external genital organs. The external iliac vein (EIV) is the continuity of the CFV cephalad to the inguinal ligament. Its affluent are the inferior epigastric veins and the deep iliac circumflex veins. The common iliac vein (CIV) is formed by the junction of the EIV and the internal iliac vein (IIV). It receives the ascendant lumbar vein and the median sacral vein on the left side.
- *Gonadal network*: Ovarian and tubal veins merge to form the ovarian plexus (pampiniform plexus); it drains the upper third of the uterus, the lateral third of the infra-tubal venous arcade, and the round ligament veins. The ovarian plexus leads to the gonadal vein (ovarian vein in women) which drains into the inferior aspect of the left renal vein (LRV) on the left side and at the anterolateral side of the inferior vena cava (IVC) under the right renal vein (RRV) on the right side. Anatomic variations are found in 20% of the cases and involve the number of veins and their drainage pattern. In the middle third, only 60% on the left side and 70% on the right side have one trunk; the rest are multiple, and as many as six trunks can be found in the lower third [8]. Observations based on vaginal ultrasound have revealed that the normal average diameter of ovarian veins is less than 5 mm [9].
- *Internal iliac network*: IIV receives 12 branches on each side, which aggregate in three groups:
  - Extra-pelvic parietal group: superior and inferior gluteal veins, obturator vein, and medial pudendal vein (parietal and visceral vein). The inferior gluteal vein receives the sciatic vein, and embolization should not be performed without checking that the FV is normal.
  - Intrapelvic parietal group: ascending lumbar veins, inferior and superior lateral sacral veins.
  - Visceral group: umbilical vein, vesical vein, uterine veins, vaginal vein, and middle hemorrhoidal veins.

These veins are, in the classic anatomic description, forming two collectors, the anterior (obturator, inferior gluteal, medial pudendal, middle hemorrhoidal, uterine, umbilical, vesical, and vaginal veins) and the posterior (superior gluteal, ascending lumbar, and lateral sacral veins).

Anatomic variations of the IIV are very frequent and three main types can be found: confluence of the two collectors in one IIV (50%), separate ostia for each trunk in the iliac axis (36%), and plexiform type (14%) [10]. One frequent variation is the presence of a communication with the contralateral common iliac vein.

There are connecting networks between the branches of the internal iliac veins and the lower limbs veins that can explain the high frequency of lower limb varicose veins due to pelvic venous insufficiency through the obturator and inferior gluteal veins mainly but also by the pudendal veins.

Pathophysiology

According to Greiner [11], pelvic varicose veins can be due to three different mechanisms:

- *Type 1*: reflux secondary to pelvic vein incompetence represents the most frequent etiology. Hormonal factors contribute to varicose veins and their concentration is higher in the pelvis. Estradiol inhibits the reflex vasoconstriction of vessels and causes uterine enlargement with dilatation of the ovarian and uterine veins

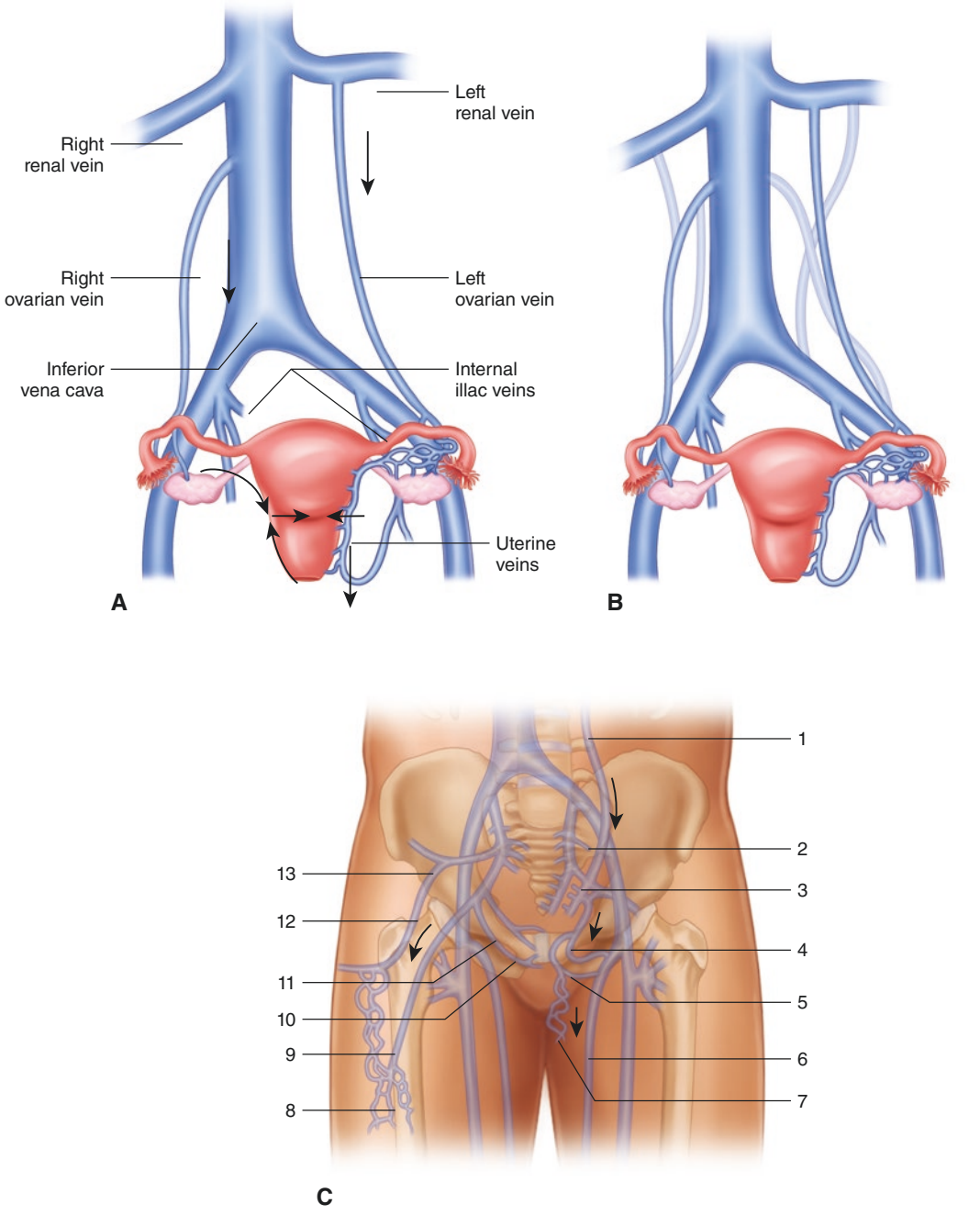

Fig. 18.1 Anatomy and reflux of the pelvic veins (*arrows* show pathologic reflux). (**A**) Anatomy. (**B**) Anatomic variations of the ovarian veins. (**C**) Internal iliac veins and their communications with the utero-ovarian plexus and thigh superficial veins: 1, ovarian vein; 2, internal iliac vein; 3, uterine vein; 4, obturator vein; 5, external pudendal vein; 6, great saphenous vein; 7, varicosity of the anteromedial aspect of the thigh; 8, varicosity of the posterolateral aspect of the thigh; 9, sciatic vein; 10, vulvar varicosity; 11, internal pudendal vein; 12, cystic and vaginal veins; 13, buttock veins

preponderantly during pregnancy [12]. Moreover a 35% decrease of pelvic veins diameter and decrease of pelvic blood flow and symptoms was found after intravenous injection of dihydroergotamine in women with pelvic congestion and pain [13]. Moreover, ovarian cyst is frequently found in patients with pelvic varicose veins [13, 14].

- *Type 2*: secondary to an obstruction of the outflow as May-Thurner syndrome [15, 16], nutcracker syndrome [16, 17] and left renal vein thrombosis, post-thrombotic disease involving the common iliac veins or the IVC (or both), and Budd-Chiari syndrome. These obstructions must always be eliminated before embolization, especially in nulliparous women.
- *Type 3*: secondary to a local extra venous phenomenon. The main cause is endometriosis, but it can also be due to tumors (benign or malignant), post-traumatic lesions.

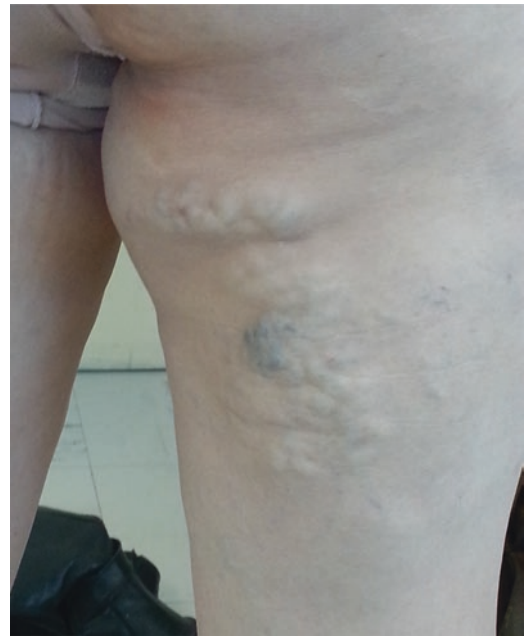

Fig. 18.2 Atypical varicose veins at the posterior aspect of the right thigh

Clinical Findings

PCI occurs mainly in young multiparous women and usually disappears after menopause [18].

The pelvic congestion syndrome (PCS) always includes chronic (up to 6 months) pelvic pain (heaviness), diffuse or localized in the iliac fossae (predominantly on the left side). It increases during the day, mostly if the patient stays sitting or standing and when lifting, and can be relieved by lying down and before menses. It can be associated with dyspareunia, dysmenorrhea, and urinary symptoms (dysuria, pollakiuria, bladder urgency). Patients should be questioned about perineal (mainly vulvar) varicose veins, past (mainly during pregnancy) and present.

On clinical examination, the combination of tenderness on abdominal palpation over the ovarian point and a history of pain after sexual activity was 94% sensitive and 77% specific for discriminating PCS from other causes of pelvic pain [18].

Perineal and lower limbs varicose veins should be searched as well as history of previous treatment. On the lower limbs, they can be located at the groin (mainly after GSV surgery), but atypical varicose veins can also be found (buttock, posterior and lateral aspect of the thigh, etc.) (Fig. 18.2).

Diagnosis

Duplex Scanning Pelvic and abdominal ultrasonography with color duplex scan should be performed with transparietal 5 MHz and transvaginal probes ideally after 3 days of a no-residue diet and with an empty stomach [15]. Pelvic varicose veins are defined as multiple dilated tubular veins around and into the pelvis with a venous blood Doppler signal and a diameter larger than 5 mm [15]. Internal iliac veins and the gonadal veins should be imaged looking for dilatation and reflux (reversed caudal flow). It can be improved by using the Valsalva maneuver. The positive predictive value of a 6 mm diameter ovarian vein for the diagnosis of PCS caused by the ovarian vein is 83.3% [19]. The obturator, sciatic, and internal pudendal veins must also be imaged.

Collateral pathways can be found. In addition, duplex scanning should evaluate the common iliac veins, IVC, and renal veins to search for venous obstruction or anatomic variations.

It can also be used to explore pelvic content looking for other causes of pelvic pain.

Lower limb duplex scan must be performed to search for varicose veins, which can be secondary to pelvic varicose veins. Superior and inferior gluteal points are highly specific of incontinence of the corresponding veins [20].

Computed Tomographic Venography (CTV) CT should be timed with a portal phase for evaluation of the genital and renal veins, and a separate imaging should be performed at a venous phase to evaluate the pelvic and iliocaval veins. According to Rozenblit, an incompetent ovarian vein is defined as a completely opacified vein during the portal phase of CT angiography and dilated if it measures 7 mm or greater at its larger diameter (Fig. 18.3a) [21]. Pelvic varices are visualized as dilated, tortuous, enhanced tubular structures around the pelvic organs (Fig. 18.3b, c). CT does not have very good visualization of the IIV network.

Magnetic Resonance Venography (MRV) Pelvic MRI is essential in the exploration of pelvic pathology. On T1-weighted MRI, pelvic varicose veins have no signal intensity because of the flow void artifact; on gradient-echo MRI, varicose veins have high signal intensity. On T2-weighted MRI, they usually appear as an area of low signal intensity, although hyperintensity or mixed signal intensity may also be noted, possibly because of the relatively slow flow through the vessels. Two- and three-dimensional, T1-weighted gradient-echo sequences performed after the intravenous administration of gadolinium are the best sequences for demonstrating pelvic varicose veins [22–24]. In order to explore completely patients in case of PVI, MRV must also analyze veins in the abdomen and assess the renal veins.

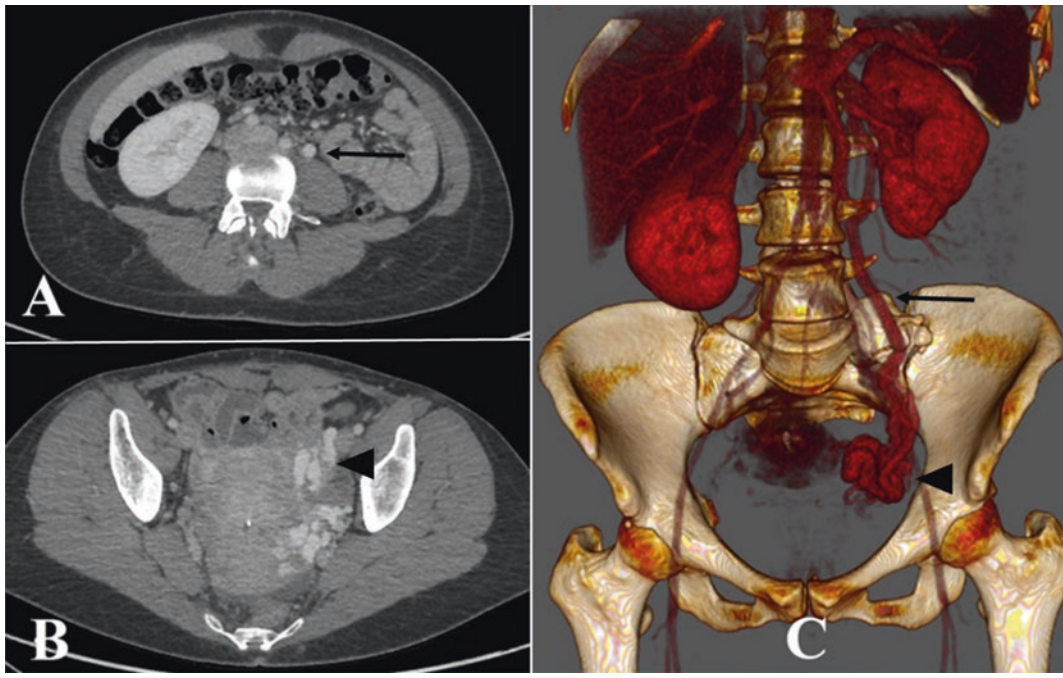

Fig. 18.3 Preoperative CTV. (**A**) Incompetent left ovarian vein (*arrow*). (**B**) Pelvic varicose veins (*arrow head*). (**C**) Three-dimensional reconstruction showing the incompetent left ovarian vein and the pelvic varicose veins

Phlebography Abdominopelvic retrograde phlebography is the "gold standard" for diagnosis [25]. It can be performed under local anesthesia via the common femoral vein (5F hydrophilic Cobra 2 catheter and Simmons catheter for the right ovarian vein) or right brachial or jugular vein (5F multipurpose catheter) approach [25, 26]. The main advantage of the jugular/brachial approach is a higher rate of right ovarian vein catheterization (18% failure for brachial approach [25] versus 58% failure through femoral approach [26]). Regardless of the approach, ultrasound-guided access should be used. Through a femoral approach the internal iliac vein can be catheterized with a Cobra 2 or a UF catheter. In case of previous left ovarian vein embolization, the left internal iliac vein can be found near the coils of the left ovarian vein.

The operator should image the four veins responsible for venous return from the pelvis: both internal iliac and gonadal veins with Valsalva manoeuver. Kim advocates the use of balloon occlusion venography to image the internal iliac veins [27]. Phlebography provides identification of the pathologic veins, their diameter, and their length. Moreover, it must explore the iliac veins, the IVC, and the LRV for obstructive disease. In the case of suspected nutcracker syndrome, the reno-caval pullback gradient must be measured (considered as significant if >3 mmHg).

Chung and Huh [28] reported criteria used for the phlebographic diagnosis of PCS caused by the ovarian vein: ovarian vein larger than 5 mm in diameter, retention of contrast medium for longer than 20 s, existence of congestion in the pelvic venous plexus or opacification of the internal iliac vein, or filling of vulvovaginal and thigh varicosities (Figs. 18.4a, b, 18.5a, b, 18.6a, b and 18.7a). Each variable is assigned a value between 1 and 3, depending on the degree of abnormality, and a venogram score of 5 or higher indicates the presence of PCS.

Differential Diagnosis

The differential diagnosis is a major concern for PCS as there are multiples causes of chronic pelvic pain (endometriosis, uterine fibroma, pelvic cancer, pudendal nerve compression, etc.). These must be eliminated before treatment because the presence of pelvic varicose veins does not necessarily mean that the cause of the pain is PCS. The diagnosis relies on analysis of the symptoms and on a thorough work-up. Laparoscopy was used till the development of MRI but is quite invasive: it can show pelvic varicose veins if performed in a feet-down position while limiting the pressure of peritoneal insufflation, and it can identify sometimes other pelvic pathologies. Pelvic ultrasound and MRI represent nowadays the imaging

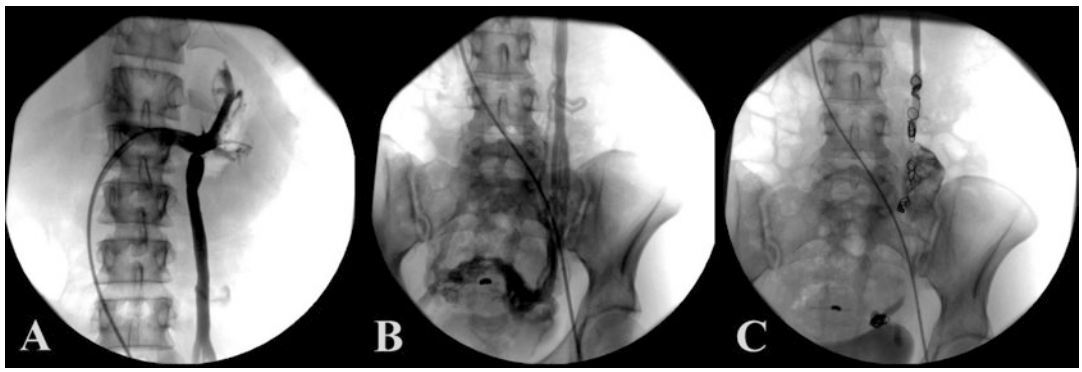

Fig. 18.4 Embolization of an incompetent left ovarian vein. (**A**) Catheterization with a Cobra (C2) catheter and angiography in the left renal vein showing absence of left renal vein compression and the presence of an incompetent left ovarian vein, (**B**) Left ovarian vein phlebography showing an incompetent vein and pelvic varicose veins. (**C**) Result after embolization using foam and coils according to the sandwich technique (multiples coils were used in the trunk of the vein due to the presence of multiple branches)

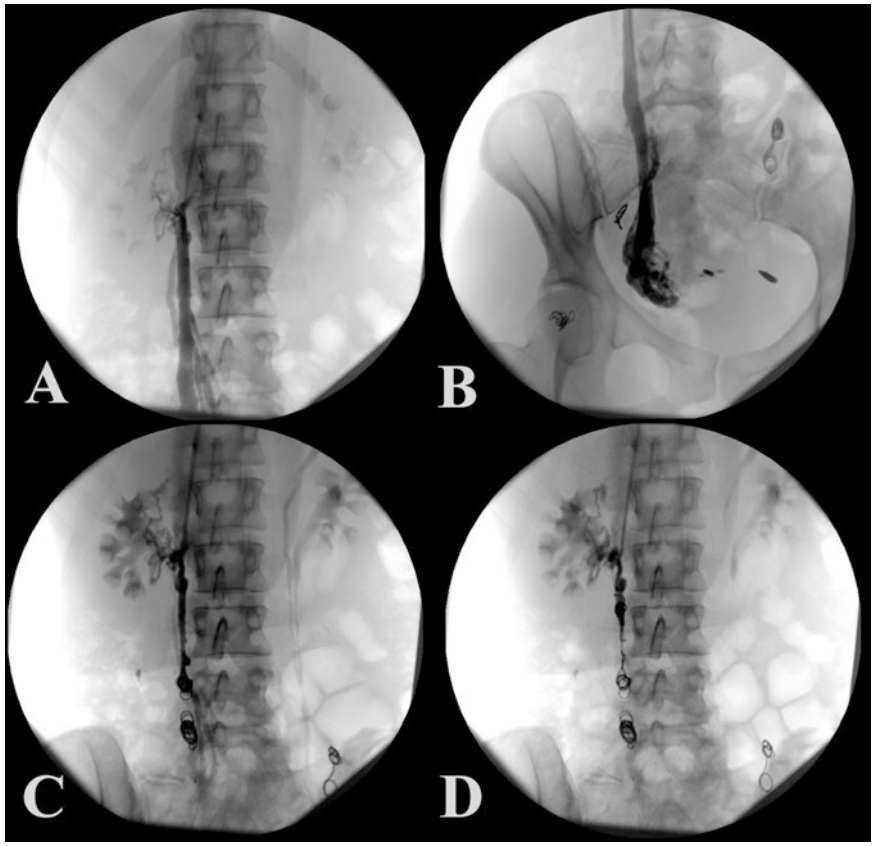

Fig. 18.5 Right ovarian vein (ROV) embolization through arm approach in a patient who previously had left ovarian vein and right inferior gluteal vein embolization. (**A**) Selective catheterization and phlebography of the ROV using a multipurpose catheter. (**B**) Phlebography of the caudal part of the ROV showing incompetence and presence of pelvic varicose veins. (**C**) Result after embolization using foam and coils according to the sandwich technique: incomplete result with persistent reflux down the ovarian vein. (**D**) Completion phlebography after deployment of another coil

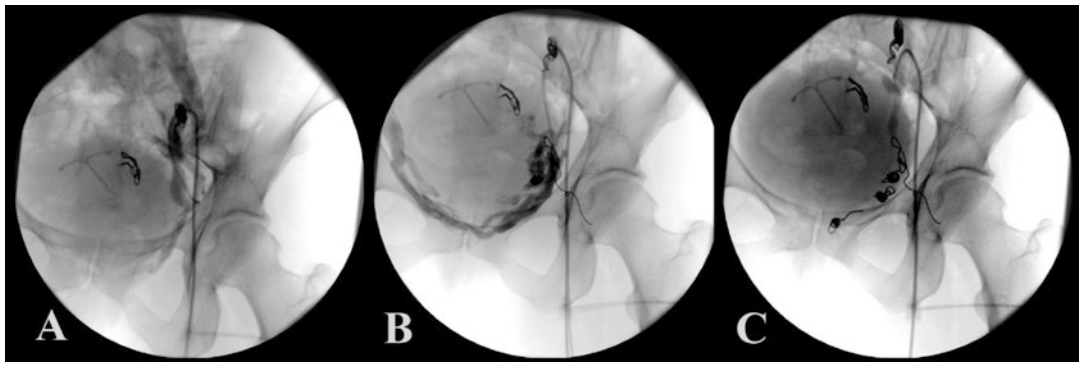

Fig. 18.6 Embolization of branches of the left internal iliac vein (LIIV) after embolization of the left ovarian vein (LOV). (**A**) Catheterization and angiography of the LIIV with a Cobra 2 catheter: the LIIV is found close to the LOV coils. (**B**) Superselective phlebography showing an incompetent vesicular vein. (**C**) Results after embolization

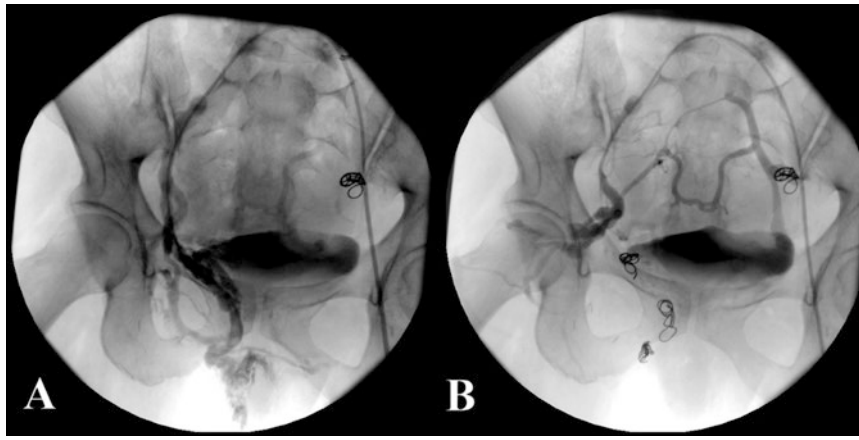

Fig. 18.7 Incompetence of the right internal iliac vein. (**A**) Selective phlebography through contralateral approach using a Cobra 2 catheter. (**B**) Result after embolization

modalities of choice for the evaluation of pelvic pain, but sometimes a more extensive evaluation is needed.

Treatment

Medical Treatment

Different drugs (medroxyprogesterone acetate, goserelin acetate, micronized purified flavonoid fraction) were shown to improve but not completely resolve the symptoms of PVI [4, 29, 30].

Surgery

Different surgical techniques have been reported for the treatment of PCS, including ovarian or internal iliac vein ligation (or both), ovarian and uterine artery and vein ligation, oophorectomy, and even total hysterectomy with bilateral salpingo-oophorectomy. Ovarian vein ligation or resection can be performed laparoscopically, but they remain invasive techniques. Despite the fact that bilateral oophorectomy combined with hysterectomy and hormone replacement therapy has been shown to be effective in patients who failed to respond to medical therapy [14], this is an invasive option that is not acceptable for women who want to become pregnant.

Embolization

The procedure can be performed under local anesthesia either together with diagnostic phlebography or as a separate procedure. After selective catheterization and contrast-enhanced study of the refluxing vein or veins, embolization is performed. In case of extensive lesions, the patient should be preoperatively counseled that multiple (two or even three) procedures may be needed.

It is mainly performed using coils (0.035 in. for 4 or 5 Fr catheter and 0.018 in. for microcatheters, pushable or detachable, fibred or not) (Figs. 18.4c, 18.5c, d, 18.6b, c and 18.7b). In case of very large veins, vascular plugs (Amplatzer®) can be used. These devices can be used in conjunction with foam in order to reduce the number of coils needed and the rate of recurrences. Foam is prepared from sodium tetradecyl sulfate (Thrombovar or Sotradecol) or polidocanol (Aetoxisclerol) according to the Tessari method and can be injected either before coiling or by using the sandwich technique (see Figs. 18.2e, 18.3b, 18.4b and 18.5b). It can use air or a 50%/50% mixture of CO2 and O2. Some teams are using glue, but their philosophy of the treatment is different: the goal is more to occlude all varicose veins rather than suppressing reflux as coils and foam do. Moreover, the use of glue is far more time consuming, painful, and expensive

than the sandwich technique. The use of sodium morrhuate together with Gelfoam has also been reported [27].

Some rules must be followed: embolization should begin the more distally possible, the main trunk of the IIV must not be embolized, and regarding the gonadal veins, embolization must be performed proximal to the last collateral in order to prevent recurrences. Regarding the right ovarian vein (ROV), even if dilated, embolization is not always necessary when the left ovarian vein (LOV) is incompetent. The incompetent LOV and branches of the IIV must be treated first and decision regarding ROV treatment will rely on its evolution. When treating branches of the IIV, Kim recommend to use balloon occlusion [27]. Moreover, the presence of significant communications between the tributaries of the IIV and the CFV and EIV must be emphasized. If not identified, it may pause a risk of coil embolization and dislodgement. Patients should be informed that in complex cases with multiple trunks incompetence embolization may need to be repeated to treat all the lesions.

Complications are rare and include hematoma at the access site, extravasation of contrast material (that excludes the use of foam), coil or glue embolization (Fig. 18.8), deep venous thrombosis and pulmonary embolism, and transient cardiac arrhythmia. In case of inadvertent coil dislodgement, it must be retrieved using a snare.

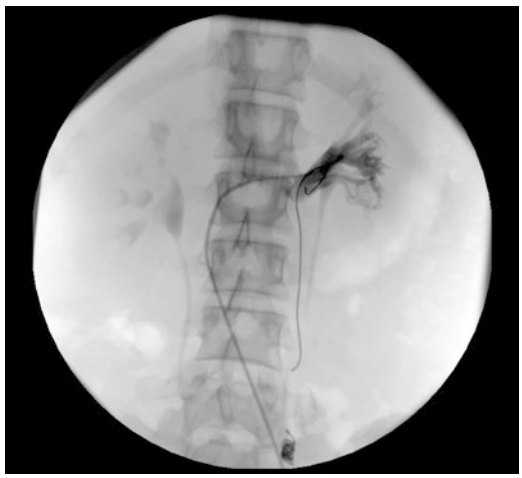

Fig. 18.8 Migration of a coil in the left renal vein during left ovarian vein embolization. It was subsequently retrieved with a snare

A review of the literature is provided in Table 18.1 [16, 24–28, 31–51]. Chung compared ovarian vein embolization, hysterectomy with bilateral oophorectomy and hormone replacement therapy, and hysterectomy with unilateral oophorectomy through a prospective randomized study of 164 women with PCS [28]: embolization was significantly more effective than the other two techniques. Asciutto showed that using embolization untreated patients had no improvement while treated patients were improved [24]. Monedero reporting on 1186 cases of embolization for recurrent lower limb varicose veins caused by PVI had better results with coils and foam using the sandwich technique than with coils alone (95.6% rate of improvement versus 76% at 6 months), thus also reducing the cost of the procedure [25]. According to the literature, better results were obtained in series reporting embolization of all incompetent veins rather than those treating ovarian veins only (Table 18.1). A review of the literature published in 2016 found 20 studies with a total of 1081 patients: technical success rate was 99%, and long-term results were good with 86.6% of improvement [52].

In case of lower limb varicose veins linked with PVI, we wait at least 3 months to take them in charge after embolization as this can reduce their volume and change the type of treatment to be used (16).

Treatment of PVI Due to Type 2 Lesions (Obstructive Lesions)

In case of obstructive lesion, the obstruction should be treated by stenting for iliocaval obstructive lesions [16, 53]. Regarding the nutcracker syndrome (NCS), either stenting or surgical procedures can be used. Embolization of the left gonadal vein must be performed only after treatment of the NCS; indeed suppressing the main collateral pathway (left gonadic vein) without treating the NCS can induce lumbar pain.

Table 18.1 Results of embolization for pelvic congestion syndrome

Series	*N*	Veins	Technique	Follow-up	Results (%)	
					Improved	Worsened
Capasso [31]	19	OV	Cyanoacrylate and/or coils	15.4M	74%	
Tarazov [32]	6	OV	Coils	24M	100%	
Machan [33]	23	OV	Coils	15M	78%	
Cordts [34]	9	OV	Coils + gelatin	13.4M	100%	
Cotroneo [35]	22	OV	Coils	3M	60%	
Richardson [36]	28	OV	Coils + foam	22.2M	SS	
Maleux [37]	41	OV	Cyanoacrylate + coils	19.9M	68.2%	
Bachar [39]	6	OV	Coils	7.7M	83%	
Pieri [40]	33	OV	3% STS	9M	61%	
Chung [28]	52	OV	Coils	26.6M	SS	
van der Vleuten [41]	21	OV	Coils	18M	62%	
Kim [27]	127	OV	Gelfoam + SM + coils	45M	83%	4
Tropeano [42]	22	OV	Foam	15M	90%	
d'Archembeau [43]	48	OV	Coils	43M	73%	
Gandini [44]	38	OV	3% STS foam	12M	100%	0
Kwon [45]	67	OV	Coils	40M	82%	
Scultetus [38]	7	OV	Coils	27M	43%	
	6	IIVT	Coils		83%	
	12	IIVT + OVR	Coils + OVR		83.4%	
Creton [26]	24	OV ± IIVT	Coils	36M	76%	
Laborda [46]	202	OV ± IIVT	Coils	89% at 60M	93%	
Nasser [47]	113	OV ± IIVT	Coils	12M	100%	0
Lasry [48]	30	OV ± IIVT	Coils	6M	90%	
Hocquelet [49]	33	OV ± IIVT	Coils + foam	23M	93%	0
Asciutto [24]	35	OV and/or IIVT	Coils	45M	Embolization >	
Monedero [25]	215	OV and/or IIVT	Coils + foam	6M	90%	
Venbrux [50]	56	OV and/or IIVT	Coils and foam	22M	SI	
Ratnam [51]	218	OV and/or IIVT	Coils	0.9M	95%	NS
Hartung [16]	78	OV and/or IIVT	Coils + foam	4M	91%	0

IIVT internal iliac vein tributaries, *OV* ovarian vein, *OVR* ovarian vein resection, *STS* sodium tetradecyl sulfate, *SM* sodium morrhuate, *SI* statistically improved

Conclusion

PVI can cause PCS involving lower limb varicose veins. Excluding obstructive diseases, its treatment should be performed by endovascular techniques that provide very good results. Recommendations were edited by the Society of Vascular Surgery and the American Venous Forum: PCS and pelvic varices due to pelvic vein incompetence should be treated using coil embolization, plugs, or transcatheter sclerotherapy, used alone or together (grade 2B) [54].

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Part III

Acute Venous Thromboembolism

Presentation and Significance of Venous Thromboembolism

19

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Clinical Pearls

1. The incidence of VTE has been stable over the past few decades despite all prophylactic measures.
2. Overall, 30% of patients with VTE die within 3 months of diagnosis.
3. Low Wells score combined with a negative D-dimer test has more than 95% negative predictive value for DVT and PE.

Epidemiology

Venous thromboembolism (VTE) is a disorder characterized by thrombus formation in the deep veins of the body and is the third most frequent vascular disease after myocardial infarction and stroke [1, 2]. Though VTE has the potential to develop in any deep vein, thrombosis of deep veins of the lower extremity and pulmonary artery (pulmonary embolism (PE)) are the most prevalent venous thrombosis. About one-half million incident and recurrent VTE events occur annually in the USA; 52% of these events are related to current or recent hospitalization (25% of hospitalization-related VTE events occur during the in-hospital stay), while 48% occur among residents with no recent hospitalization [3]. It is estimated that 1.2–1.9 per 1000 individuals are affected by an incident VTE event each year [4–8]. The incidence rate for PE is 29–78 per 100,000 person-years, while incidence rates for DVT alone range from 45 to 117 per 100,000 person-years [1]. Despite recommendation of universal anticoagulant-based DVT prophylaxis for major surgery and hospitalization for acute medical illness [9–11], the VTE incidence has remained unchanged over the last few decades [8]. This relative constant VTE incidence could reflect an increase in the population at risk (e.g., aging population) or exposure to more or new risk factors (e.g., increasing prevalence of surgery, obesity, and active cancer) [8].

Older individuals are more likely to present with VTE, as the VTE incidence rates increase with age for both men and women (Fig. 19.1) [4]. The overall incidence rates for VTE are higher in men than in women. However, women of childbearing age have higher VTE incidence compared to men of similar age, probably related to pregnancy/postpartum phase and use of oral contraceptive pills. After

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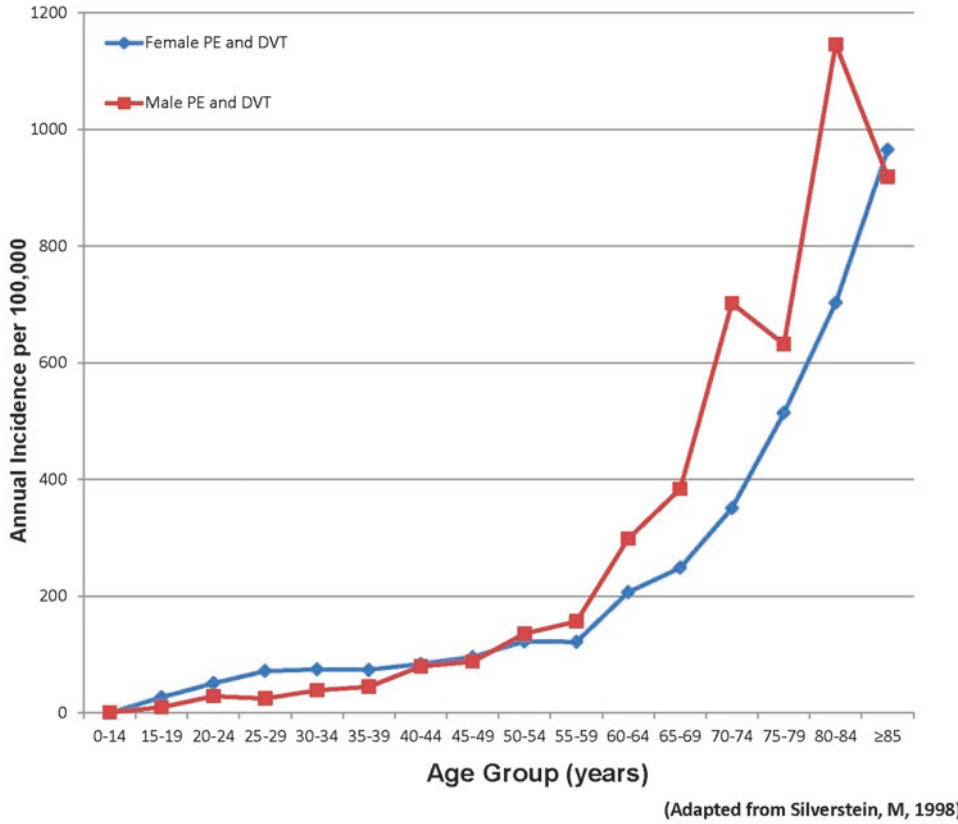

Fig. 19.1 Annual incidence of venous thromboembolism by age and sex

the age of 45, incidence rates are higher in men than women. The incidence of VTE also varies by race. Compared to whites, African-Americans have a slightly higher VTE incidence (hazard ratio [HR] 1.27), while Asian- and Native-Americans have a lower risk for VTE (HR 0.26); the incidence among Hispanics is intermediate between whites and Asian-Americans (HR 0.6) [12, 13].

VTE lends to significant morbidity and mortality within our society. The survival following VTE is significantly worse than the age- and sex-matched expected survival; the survival after PE is worse than after DVT alone [14]. Overall, up to 30% of VTE patients die within 3 months of VTE diagnosis [5, 7, 14–16]. It is estimated that there are 100,000–300,000 deaths annually that are secondary to VTE. VTE recurs frequently; about 30% of patients will develop a recurrent episode within the next 10 years [17, 18]. Post-thrombotic syndrome (PTS) is a long-term complication of DVT. Around 30–50% of patients with symptomatic DVT are likely to suffer from PTS within 2 years [17, 19–21]. Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication seen in up to 4% of PE patients, leading to significant impairment due to chronic shortness of breath and heart failure [22].

Healthcare costs related to diagnosis and management of thrombotic events and its complications are significant. In a population-based study, adjusted mean predicted costs were found to be 2.5-fold higher for patients with VTE related to current or recent hospitalization for acute illness than for hospitalized control patients that were matched for active cancer status [23]. Another study demonstrated the 5-year healthcare costs to be 1.5-fold higher for patients with VTE related to current or recent hospitalization for major

surgery than for hospitalized control patients matched for surgery and active cancer status [24]. Patients with VTE also suffer from poorer quality of life and work-related productivity. More recently, a study demonstrated a 52% higher risk for work-related disability in those with unprovoked VTE when compared with those without VTE. Further analysis indicated that associated risk for work-related disability was due to DVT and not PE [25].

Mechanisms Involved in Thrombosis

Hemostasis involves a fine balance between the endothelial wall, platelets, and proteins of the coagulation and fibrinolytic systems. Derangements in any of these components may lead to an imbalance that can either put individuals at a higher risk for bleeding or clotting. In 1856, Rudolph Virchow hypothesized that thrombosis was the result of dysregulation impacting the balance of the following three factors: integrity of the blood vessel wall, blood flow, and blood constituents. In contrast to arterial thrombosis, which is typically associated with atherosclerotic plaque rupture, venous thrombosis is usually associated with plasma hypercoagulability that can be triggered by procoagulant activity on the endothelial surfaces as a result of inflammation and/or venous stasis (Fig. 19.2) [26].

Risk Factors for VTE

Given that VTE is a result of derangements affecting the integrity of the endothelial vessel wall, blood flow, or constituents of blood, its etiology is multifactorial with interplay of genetic and environmental factors. VTE risk factors can be classified into inherited and acquired as well as nonmodifiable/persistent versus modifiable and/or intermittent factors (Table 19.1). Acquired risk factors are more common than inherited thrombophilia. Nonmodifiable, persistent risk factors include increasing age, male gender (males are more likely to suffer from VTE than females), presence of an inherited hypercoagulable state with the presence of VTE susceptibility genes, or acquired disorders such as antiphospholipid antibody syndrome.

Factor V Leiden is the most common inheritable hypercoagulable state. Other heritable mutations include prothrombin G20210A, as well as deficiencies in protein C (PC), protein S (PS), and antithrombin (AT) (Table 19.2) [27, 28]. Other nonmodifiable conditions include hematologic entities such as non-O blood group, elevated coagulation factors, sickle cell disease, and homocysteinuria. In regard to the latter, homocysteinuria is secondary to cystathionine beta-synthase deficiency and is associated with markedly elevated plasma homocysteine. It can be manifested with both arterial and venous thrombosis at a young age. Hyperhomocysteinemia, which is associated with milder elevations of

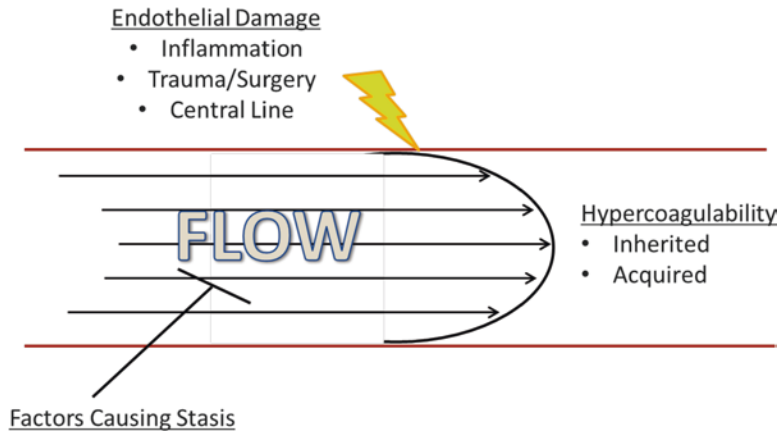

Fig. 19.2 Variables contributing to development of thrombosis

Table 19.1 Common risk factors for VTE[a]

Persistent/nonmodifiable
Age: risk increases with age
Gender
Malignancy
Higher risk: stomach, brain, pancreas, ovaries, leukemia, lymphoma, lungs, kidneys, bones
Varicose veins
Anatomic risk factors
Presence of a pacemaker
Prior VTE
CHF/respiratory failure
Hematological risk factors
Hyperhomocysteinemia/uria
Dysfibrinogenemia
Sickle cell disease
Elevated coagulation factors (VII, VIII, IX, XI)
Myeloproliferative disorders and PNH
Blood group type (non-O blood group)
Inherited thrombophilia
Factor V Leiden
Prothrombin 20210A
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Transient/modifiable
Immobility[b]
Obesity
Oral contraceptive use
Central venous catheter[b]
Postpartum/pregnancy
Hospital or nursing home inpatient status[b]
Trauma
Fracture
Spinal cord injury[b]
Surgery
Hip or knee surgery
Major general surgery
Anesthesia
General carries a greater risk than regional
Heparin-induced thrombocytopenia

[a]Modified from Heit et al. (2000)
[b]May not be transient or modifiable based on patient circumstances

plasma homocysteine, could be a genetic or an acquired abnormality and has also been associated with increased thrombotic risk, though magnitude of risk is unknown. Hyperhomocysteinemia is seen in individuals with a mutation in methylene tetrahydrofolate reductase (MTHFR) gene and who are deficient in vitamin B6, B12, or folate. Other hematologic conditions such as heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, disseminated intravascular coagulation and fibrinolysis (DIC/ICF), myeloproliferative neoplasms, and paroxysmal nocturnal hemoglobinuria also predispose individuals to an increased risk for thrombosis.

Acquired risk factors that may or may not be modifiable include immobility; neurologic disease with leg paresis; hospitalization for medical illness or surgery; trauma; pregnancy or postpartum state; presence of central venous catheters (CVC); active cancer; use of chemotherapeutic agents, oral contraceptive pills, and hormone replacement therapy; congestive heart failure; nephrotic syndrome; and inflammatory and autoimmune conditions.

Approximately 20–30% of incident VTE are cancer associated [29, 30]. Patients with cancer have a severalfold increased risk of VTE compared to the general population. It is important to note that not all malignancies carry the same risk for VTE; malignancies associated with higher risk of VTE include cancer of the brain, pancreas, lymph nodes, ovaries, colon, stomach, lungs, kidneys, and bones. In addition patients with cancer who are receiving hormonal, immunosuppressive, or cytotoxic chemotherapy, such as L-asparaginase, tamoxifen, thalidomide, or lenalidomide, are at higher risk for VTE. Several scores for predicting risk of VTE in ambulatory outpatients with malignancy have been developed. The Khorana score takes into account patient's site of primary tumor, patient's platelet, hemoglobin, and WBC count as well as patient's BMI to determine risk of VTE at the time of initiation of chemotherapy [31].

Situations causing trauma of the blood vessel wall and/or predisposing to immobility also lead to increased risk of VTE. In a population-based case control study of 625 patients in Olmsted county, the risk of VTE was 22-fold higher for patients with recent surgery, 12-fold higher for patients with recent trauma, and eightfold higher for patients confined to a hospital or nursing

home [32]. Surgeries that are associated with increased VTE include surgeries involving the abdomen and chest and those requiring at least 30 min of time under general anesthesia. The presence of CVC is associated with 9% of VTE in the community. Femoral vein located CVC are at higher risk for VTE than subclavian CVC.

Pregnancy and the postpartum period are also associated with a higher risk of VTE. Pregnant women and those in the postpartum period have a fourfold increased VTE risk compared to non-pregnant females who are not on hormone therapy. In addition to pregnancy, the use of combined oral contraceptives (OCP) and transdermal estrogen patch increases the risk of VTE by about threefold. There is controversy whether progestin-alone contraception increases the risk of VTE. In a meta-analysis assessing three retrospective cohort analysis and five case control studies, VTE incidence in women on progestin-only contraceptives was assessed, and collectively users of progestin-only contraceptives were not associated with having an increased risk of VTE compared with nonusers. A subset analysis in women only on injectable progestin did demonstrate a twofold increase VTE risk [33].

There are a multitude of studies examining VTE risk and various classes of OCPs. Though initial studies have suggested that the first- and third-generation OCPs may carry a higher risk, whether or not there are significant differences in risk between the contraceptive classes is controversial given that there are no randomized trials large enough to compare the risk of VTE in women on different types of oral contraceptives [34].

Clinical Presentation of VTE

Deep Vein Thrombosis

Clinical symptoms for DVT are nonspecific and can consist of swelling, erythema, warmth, pain, tenderness, and cramping of affected extremities which may slowly progress over several days and then suddenly accelerate [35]. Some individuals may not have any clinical signs or symptoms of DVT until after development of PE. Though most DVTs are distal, presenting in the calf and popliteal vein, iliac and common femoral vein DVT represent a specific subgroup of patients with highest risk of post-thrombotic morbidity [36].

Clinical diagnosis is based on a high index of suspicion leading to further lab and diagnostic imaging tests. Differential diagnosis for DVT include cellulitis, edema secondary to lymphedema, varicose veins, Baker's cysts, congestive heart failure, and malignancy. Individual clinical signs and symptoms such as Homans' sign have been used to guide physicians when to consider further diagnostic tests in patients; however, when used individually, these clinical signs have limited specificity and sensitivity given that they appear in only a fraction of patients. When clinical symptoms and signs are used in combination, they do have a high negative predictive value (90–95%), but positive predictive values are only in the range of 30–50%. Various scoring systems based off of clinical symptoms, signs, and risk factors have been developed to guide clinicians to determine pretest probability of VTE. The most commonly used scoring system for DVT, first proposed in 1995, is the Wells decision rule which incorporates whether or not a patient has a history of cancer, has a history of recent immobility, has localized tenderness, has leg enlargement, has collateral veins, and has a history of prior DVT and whether any other diagnosis is as likely to be the cause of patient's symptoms [37, 38]. One point is given for each factor, and the score is then stratified into low (0), moderate (1, 2), or high risk (≥3). If a patient has a low score, the likelihood of a DVT is <5%, and testing is geared toward other more likely diagnoses. If score is moderate or high, further diagnostic imaging with duplex ultrasound should be undertaken. D-dimer, a fibrin degradation product, is also utilized in clinical workup of DVT; however, high D-dimer alone is not diagnostic of a VTE given that D-dimer elevation can occur secondary to other causes, including DIC/ICF, recent surgery, active or recent bleeding, hematomas, trauma, pregnancy, liver disease, inflammation, or malignancy [39, 40]. D-dimer, however, does have a high negative predictive value, and a normal D-dimer by ELISA in conjunction with low

Table 19.2‡ Inherited thrombophilia in Caucasians (estimates)[a]

Mutation	Frequency (%) general population[b]	Frequency(%) in individuals with VTE[b]	Relative risk for thrombosis
Factor V Leiden, APC resistance	3.6–6.0	10–64	Heterozygote:3.5–8.1
			Homozygote: 24–80
Prothrombin G20210A	1.7–3.0	6.2–18	1.9–2.8
Protein C deficiency	0.14–0.5	1.4–8.0.6	3.1–3.4
Protein S deficiency	–	1.4–7.5	–
Antithrombin deficiency	0.02–0.17	0.5–4.9	5

‡Adapted from Cushman et al. (2007)
[a]Prevalence of thrombophilia varies depending on what population is being investigated. In addition, the increased in risk of thrombosis varies according other patient risk factors
[b]Adapted from Anderson and Spencer (2003)

clinical probability can be satisfactory to rule out DVT [38]. A review of 15 studies in which the Wells score was tested demonstrated that in patients in the low pretest probability category, negative predictive value for DVT of the Wells score was 72–99% and was improved to 96–100% with the presence of a negative D-dimer [41].

Pulmonary Embolism

PE is a result of a deep venous thrombus embolizing and lodging into the pulmonary circulation. Proximal lower extremity DVT, particularly those in the iliofemoral region, are at highest risk to lead to PE. Acute consequences from PE include death, pulmonary infarction, and right ventricular strain and failure.

Similar to DVT, clinical presentation of PE is quite variable and can manifest as many other diseases and thus is often known as "The Great Masquerader" [42]. Symptoms include combinations of dyspnea, chest pain, coughing, hemoptysis, and/or syncope. A patient's manifestation of symptoms from PE is dependent on their pulmonary and cardiovascular reserve as well as location and extent of clot burden. Syncope is more likely to occur in patients who have a PE that is causing a sudden obstruction of the most proximal pulmonary arteries. Similarly, patients with a more central PE are at a higher risk for hemodynamic compromise. Patients with more distal PE who have developed pulmonary infarction may present with pleuritic chest pain and hemoptysis. Patients with poor clinical baseline health status may have more severe symptoms with lower thrombus burden than those who have a high cardiovascular and pulmonary reserve. It has been estimated that in patients without a history of heart or pulmonary disease, 30–50% of pulmonary bed obstruction is necessary to develop pulmonary hypertension [43].

Characteristic signs of PE include decreased oxygen saturation, tachycardia and tachypnea. Similar to DVT, clinical signs of PE are variable but still have diagnostic utility. For example, auscultation of a pleural friction rub and decreased breath sounds may be a sign of pleural infarction. Similarly, a patient developing pulmonary hypertension as a sequela of PE may be found to have a loud P2, right sided gallop, and increased central venous pressure.

Chest X-ray, arterial blood gas (ABG), and electrocardiography (EKG) may or may not reveal abnormalities. Possible abnormal chest X-ray findings include pleural effusion, elevated hemidiaphragm, wedge-shaped atelectasis, and pulmonary consolidation [44]. EKG may indicate a right bundle branch block (complete or incomplete) and/or right ventricular strain pattern (QR in lead V1, T wave inversion in lead V1–V4, S1Q3T3 (prominent S wave in lead I, prominent Q wave, and an inverted T wave in lead III)). Classical EKG pattern is found only in about 2–15% of individuals with pulmonary embolism [45]. ABG analysis can demonstrate hypoxia ($PaO_2 < 80$ mmHg), hypocapnia, and respiratory alkalosis; however it can also be normal.

As with DVT, there are clinical scoring tools for predicting the likelihood of PE. The Wells score for PE (Table 19.3) takes into account whether patients have clinical signs of DVT, recent surgery or immobilization, patient's heart rate, prior history of PE or DVT, presentation with hemoptysis, history of malignancy, and likelihood of alternative diagnosis other than PE. Patients are stratified into low (<2)-, intermediate (2-6)-, and high (≥6)-risk groups. The negative predictive value of a low (<2) Wells score is high (96.4%) and improves further when combined with a negative D-dimer (98.5%) [46, 47]. Patients who have an intermediate or high PE risk score should then undergo a computed tomography pulmonary angiogram (CTPA) to evaluate for PE.

Table 19.3 Scoring systems for DVT and PE [37, 46, 109]

	Points	Interpretation
Wells DVT		
Active cancer[a]	+1	>2: high probability
Paralysis, paresis or recent plaster immobilization of the lower extremities	+1	1–2: moderate probability
Collateral superficial veins (non-varicose)	+1	<1: low probability
Localized tenderness along the distribution of the deep venous systems	+1	Alternative interpretation
Entire leg swollen	+1	≥2: DVT likely
Previously documented DVT	+1	< 2: DVT unlikely
Pitting edema confirmed to the asymptomatic leg	+1	
Collateral superficial veins (non-varicose)	+1	
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anesthesia	+1	
Calf swelling ≥3 cm larger than the asymptomatic side	+1	
Alternative diagnosis at least as likely as DVT	−2	
Wells PE		
Clinically suspected DVT	+3	>6: high probability
Alternate diagnosis is less likely than PE	+3	2–6: moderate probability
Tachycardia (heart rate > 100)	+1.5	<2: low probability
Immobilization (≥3 days) or surgery in the last 4 weeks	+1.5	Alternative interpretation
History of DVT or PE	+1.5	>4: PE: likely
Hemoptysis	+1	≤4: PE unlikely
Cancer[a]	+1	

[a]Treatment ongoing, within 6 months, or palliative

Severity of PE can be grouped by clinical symptom presentation into acute massive, acute sub-massive, subacute massive, and acute small PE [48]. The most severe form of PE is an acute massive PE with mortality rates exceeding 20% regardless of treatment. Hemodynamic instability with persistent hypotension and cardiogenic shock that may require the use of inotropic and vasopressor support for adequate organ perfusion is associated with severe PE presenting acutely. Patients with acute sub-massive PE are hemodynamically stable but have tachycardia and tachypnea. Mortality rates for acute sub-massive PE range from 5 to 25%. Acute small PEs have a good prognosis with a 3-month morality rate of <1%. Some patients may be asymptomatic or have tachypnea and tachycardia. In subacute massive PE, numerous small emboli form within the pulmonary bed. Symptoms, including exertional dyspnea and fatigue, take longer to develop as it takes longer for pulmonary bed obstruction to develop [49].

Though the introduction of CTPA led to an increased diagnosis of PE, it has also increased detection of small defects within the subsegmental pulmonary arteries. These defects are of questionable clinical significance. In addition to CTPA, advances in imaging techniques have increased incidental discovery of PE in patients obtaining CT of the chest for other reasons as well [50]. The incidence of unsuspected PE (UPE) is 1–5%. In a systematic review of 609 patients with UPE, 48 were localized in the subsegmental branches [51]. In another study investigating morbidity and mortality in patients with UPE, patients with UPE limited to

subsegmental arteries had a similar survival and recurrent PE rate when compared to a matched control group of symptomatic PE patients; however those with more proximal locations had increased mortality at 6 months [52]. UPE has been reported in patients with malignancy, trauma patients, and mechanically ventilated patients. In addition, UPE is reported in 50–60% of postmortem autopsy. The question still remains as to whether small subsegmental PE negatively impact patients to the point that they should be treated as having a PE. There has not been a significant decrease in PE-related mortality even though there has been an increase in the diagnosis of PE, suggesting that PE may be "overdiagnosed" [53], although this data should be interpreted with caution as it is based solely on indirect evidence.

Other Sites of DVT

Arm/Superior Vena Cava

Though DVTs are more likely to occur in lower extremities, they also occur in upper extremities, and acute upper extremity DVT (UEDVT) represents 1–4% of all DVTs [36, 54]. The lower incidence of UEDVT can be explained by considering the anatomy of the upper and lower extremities. Upper extremities are not as likely to be immobilized compared to legs, which results in less venous stasis. In addition, arm veins experience less gravitational stress and have fewer valves and therefore have fewer potential foci of thrombus [54].

UEDVT can be grouped into catheter-related and non-catheter-related UEDVT. With increasing use of central venous catheters, catheter-related UEDVT is the most common risk factor for UEDVT. Non-catheter-related UEDVT may be primary or associated with risk factors such as pregnancy, oral contraceptive use, and malignancy [55, 56].

Primary UEDVT, also known as Paget-Schroetter syndrome, differs from lower limb DVT in its pathophysiology and demographic profile and has a poor association with the usual risk factors of DVT. The etiology of primary UEDVT, which is triggered by repetitive exercise, is caused by subclavian vein compression in the narrow space of the thoracic inlet formed by the anterior aspect of the first rib, the medial clavicle, and its associated musculature. Primary UEDVT typically presents in young individuals.

UEDVT may be asymptomatic or can present with pain in the arm, neck, and shoulder regions, arm discoloration, swelling, and venous distention. It may also present with symptoms characteristic of a muscle strain [57]. Differential diagnosis includes cellulitis, lymphedema, hematoma, and superficial phlebitis. Patients could present with a complication of UEDVT including superior vena cava syndrome, PE, or gangrene of the arm [54].

The superior vena cava (SVC) is the major conduit for venous return to the heart from the upper body, and SVC syndrome which is caused by obstruction of blood flow within the SVC either by external compression or thrombosis leads to symptoms of facial, neck, and upper extremity swelling, dyspnea, and cough [58]. External compression from intrathoracic malignancies is the most common etiology of SVC syndrome, with other causes including infectious etiologies such as tuberculous mediastinitis or syphilitic aortic aneurysms [59]. Thrombosis within the SVC occurs most often in the setting of indwelling catheters or pacemakers. In addition to SVC syndrome, patients with UEDVT are also at risk for similar complications from DVT as seen with lower extremities, though patients with UEDVT, whether primary or idiopathic, are less likely to present with symptomatic PE when compared with LE DVT [60].

Inferior Vena Cava (IVC) Thrombosis

IVC thrombosis is an underrecognized and underdiagnosed entity. It is estimated that 2.6–4.0% of patients with lower extremity DVT have an IVC thrombosis [61]. The etiology of IVC thrombosis can be divided into congenital versus acquired. Most congenital IVC abnormalities remain asymptomatic due to the development of

collaterals. Acquired IVC thrombosis is associated with malignancy, endogenous intervention, placement of foreign bodies such as IVC filter, and abdominal trauma. IVC thrombosis is frequently associated with neoplastic disease, and Stein et al. reported carcinomas in 37.4% of patients diagnosed with IVC thrombosis compared to 11.4% in patients with lower extremity DVT [62]. Similar to lower extremity DVT, acquired thrombophilia and other environmental factors such as medications may also play a role in the development of thrombosis.

Clinical presentation of acute IVC thrombosis varies from an asymptomatic radiographic finding to severe hemodynamic compromise. Other symptoms, including low back or buttock pain, sciatica, and cauda equina-type symptoms, depend on the level of thrombosis and the degree of occlusion. Patients may also present with bilateral lower extremity swelling and dilation of the superficial abdominal vessels. Chronic IVC thrombosis can cause a dull aching pain in both lower limbs as well as symptoms of venous claudication. Most patients with congenital IVC anomalies have few symptoms because of collateral formation and subsequent venous compensation [63].

Unfortunately, if untreated, patients with IVC thrombosis will suffer from significant morbidity including post-thrombotic syndrome, venous claudication, and pulmonary embolism.

Renal Vein Thrombosis (RVT)

Renal vein thrombosis is used to describe the presence of thrombus in the major renal veins or their tributaries. Literature regarding presentation of RVT is limited, and RVT is extremely uncommon in patients without an underlying nephrotic syndrome or renal cancer. A prospective study of patients with nephrotic syndrome demonstrated the presence of RVT in 33% of 151 patients [64]. The largest study regarding RVT was an inception cohort analysis characterizing 218 patients at Mayo Clinic who had renal vein thrombosis (RVT) [65]. In this cohort, compared to DVT, RVT was more likely to be associated with local variables such as malignancy, nephrotic syndrome, infection, and surgery. The prevalence of malignancy was threefold higher in patients with renal vein thrombosis when compared to deep vein thrombosis, with the most common malignancy being renal cell carcinoma. Nephrotic syndrome, 87% of which was secondary to membranous nephropathy, was present in 19.7% of patients. Unlike DVT of the extremities, a personal or family history of VTE was less frequent in patients with RVT. The role of an underlying thrombotic diathesis in the pathophysiology of RVT is unclear, as thrombophilia evaluation was only carried out in a minority of patients with only 36 of 218 patients undergoing thrombophilia testing at time of diagnosis; 12 of these tested patients had a thrombotic diathesis [65].

RVT may occur unilaterally or bilaterally. In the previously discussed cohort of 218 patients, thrombosis of the left renal vein occurred in 94 patients, 73 had right renal vein involvement, and 47 patients had bilateral involvement. In addition to involvement of the renal vein, patients with RVT had involvement of the IVC, iliac vein, left gonadal vein, left adrenal vein, and extension into the right atrium in 94, 7, 1, 1, and 5 patients, respectively [65].

RVT may either present with acute symptoms or go unnoticed because of lack of symptoms. Those without symptoms may only present when they develop complications of RVT such as development of PE or renal failure. In the study by Wysokinski et al., presenting symptoms included flank pain in 73% of patients and gross hematuria in 36% of patients. Other symptoms included anorexia, nausea, and fever. On examination, asterixis was noted in nearly half of patients with RVT. Only 4% of patients had peritoneal signs. Over half of patients with RVT had laboratory evidence of renal function impairment at the time of diagnosis with 12 patients requiring dialysis therapy [65].

Reported recurrence rates are variable. In the study by Wysokinski et al., during 768 patient-years of follow-up, there were eight new lower extremity DVT and one paradoxical stroke for an event rate of 1.0/100 patient-years, although there were no recurrent renal vein thrombi [65].

Other studies, however, have reported rates ranging from 8.5 to 27%, though most of these studies occur in patients with nephrotic syndrome. Wysokinski et al. suggested that the variability regarding recurrent RVT could be due to the variability in the underlying etiology of RVT. It should be noted that patients with nephrotic syndrome are inherently more hypercoagulable given defects in the plasmatic coagulation and fibrinolysis system as well as platelet function combined with increased renal loss of the anticoagulant antithrombin [66]. Survival rates were poorer in patients with RVT than in patients with DVT; however, this was in the setting of malignancy. In the absence of malignancy, survival rates were similar to that observed in the general population [65].

Splanchnic Venous Thrombosis

Splanchnic vein thrombosis (SVT) includes portal vein thrombosis (PVT), mesenteric vein thrombosis (MVT), splenic vein thrombosis, and hepatic vein thrombosis (Budd-Chiari syndrome (BCS)). As with thrombosis in the extremities, venous thrombosis of the splanchnic veins is a result of the confluence of several risk factors. SVT can be grouped into primary or secondary depending on the presence or absence of associated local or systemic factors.

Thrombosis of the Liver Vasculature

Portal vein thrombosis (PVT) and primary Budd-Chiari syndrome (BCS) are two rare thrombotic disorders involving the liver. The portal vein is formed by convergence of the splenic and superior mesenteric veins. PVT is the most common cause of extrahepatic portal vein obstruction. Primary BCS consists of thrombosis of the hepatic veins and/or the suprahepatic inferior vena cava which results in obstruction of the hepatic venous outflow tract.

The incidence of PVT in the general population is approximately 4/1,000,000 every year. The incidence of BCS is even lower with estimates ranging from 0.1 to 0.8/1,000,000 every year and a prevalence of 1.4–2.4/1,000,000 [67]. Compared to BCS, PVT is more likely to occur in the setting of secondary local factors such as liver cirrhosis or malignancy. In patients with cirrhosis, pathophysiology of PVT is likely related to slowing of portal venous blood flow and dysregulation of hemostasis. PVT in patients with a previously healthy liver is thought to be due to acquired prothrombotic states (e.g., antiphospholipid antibody syndrome, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria).

The clinical presentation and course of BCS and PVT depend on the vein involved, extent of obstruction, and acuity of thrombus development. With low clot burden, PVT and BCS may be clinically silent and found incidentally on workup for other conditions. Conversely patients may present with acute, subacute, or chronic symptoms. Patients with subacute and chronic presentation may have formed venous collaterals, and therefore symptom presentation may be less pronounced. Other patients may have abdominal pain, either progressive or sudden, fever, abdominal distention, and signs of liver injury with jaundice, gastrointestinal bleeding, and hepatic encephalopathy. Diagnosis is made with abdominal imaging including ultrasound with Doppler, CT scan, or MRI.

Philadelphia chromosome (translocation 9;22)-negative myeloproliferative neoplasms (e.g., polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF)) are more likely associated with BCS and PVT than in DVT and PE with a prevalence of 30–50% reported in BCS and 30% reported in PVT [68]. These disorders can be associated with gain of function mutations such as JAK2V617F. Meta-analyses have been published investigating the prevalence of myeloproliferative neoplasms (MPN) and JAK2V617F mutation in patients with BCS or PVT, and of 1062 patients with BCS or PVT, MPN was present in 40.9% of patients, while 80.3% of these patients with MPN possessed the JAK2 V617F mutation [68]. Prevalence of JAK2 V617F and MPNs was higher in BCS than PVT. Of note, patients with JAK2V617F-negative MPN with CALR mutations have a significantly lower overall risk of thrombosis with an incidence of 0.8% in 944 patients [69]. Other acquired conditions associated with PVT include antiphospholipid antibody syndrome, paroxysmal nocturnal

hemoglobinuria, intra-abdominal cancers, and abdominal inflammatory conditions (infection, pancreatitis, and inflammatory bowel disease).

Both disorders can lead to lethal portal hypertension-related complications and subsequent liver failure. Recognition and early treatment for both PVT and BCS lead to improved outcomes.

Mesenteric Vein Thrombosis (MVT)

As with other SVT, MVT is a rare, potentially lethal condition that has been reported to have an incidence of 2.7 per 100,000 person-years. Though rare, the prevalence of MVT has increased in the last two decades [70, 71] and predominantly involves the superior mesenteric vein [71]. Thrombosis in mesenteric veins leads to compromise of venous return from the bowel which ultimately leads to mesenteric venous hypertension. Transmural bowel ischemia may occur if collateral circulation is unable to provide compensation and if there is concomitant arterial spasm. MVT accounts for 5–15% of all mesenteric ischemic events [71].

Presentation of MVT can be acute, subacute, or chronic. Acute MVT, which accounts for 60–80% of MVT, presents with sudden symptoms within 24–72 h of thrombus formation consisting of abdominal pain that is usually described as not being explained by physical exam findings. Other symptoms include nausea, anorexia, vomiting, and diarrhea. About 15% of patients may have hematemesis, hematochezia, or melena [72]. Occult blood is detectable in the stool in approximately 50% of patients. Acute MVT leads to increased risk of bowel infarction and peritonitis. Subacute MVT typically presents as an individual having abdominal pain for days or weeks without fulminant bowel infarction. Alternatively, patients who present with chronic MVT may present with chronic complications such as portal vein or splenic vein thrombosis or esophageal hemorrhage that occur because of formation of chronic collateral circulation. Chronic MVT is usually detected as an incidental finding on CT with radiographic evidence of sequela of portal hypertension (gastroesophageal varices and splenomegaly).

Unfortunately, given the rarity and vague, nonspecific symptoms associated with MVT presentation, diagnosis is often delayed. Ultrasound of the portomesenteric venous system can demonstrate thrombus location, burden, and degree of occlusion. Though widely available and inexpensive, ultrasound is rarely used to diagnose acute MVT as it has a poor sensitivity and specificity for the diagnosis of associated bowel ischemia. Computed tomography (CT) is the test of choice for suspected cases of mesenteric venous thrombosis, and it will establish the diagnosis in 90% of patients. CT scan is less accurate in those with early thrombosis of small mesenteric vessels.

A secondary cause for MVT can be identified in about 75% of patients with the most common causes being cancer, intra-abdominal inflammatory conditions, and the postoperative state [71]. Oral contraceptives are implicated in 9–18% of episodes.

Complications include major bleeding associated with anticoagulant therapy and recurrent thrombotic events after treatment with their rates reported as 6.9/100 person-years and 3.5/100 person-years, respectively, in the Mayo Clinic experience [73]. Mortality rates are high and are largely the result of late diagnosis and the underlying disease that may have precipitated MVT.

Splenic Vein Thrombosis

The splenic vein is positioned posterior to the pancreas. Disorders that affect the splenic vessel such as inflammation, malignancy, or trauma predispose to splenic vein thrombosis (SpleVT). In addition conditions that cause extrinsic compression of the splenic vein, thereby affecting blood flow through the vein, also predispose to SpleVT. Acute and chronic pancreatitis are the most common causes of SpleVT [74]. Pancreatic cancer and metastatic cancers causing abdominal lymphadenopathy have also been implicated. In addition, though rare, SpleVT can be seen in patients who have had splenectomy, gastrectomy, or distal splenorenal shunts [75, 76].

Thrombus in the splenic vein leads to a localized form of portal hypertension, also known as left-sided portal hypertension, which accounts for less than 5% of all patients with portal hyper-

tension. The most common cause of left-sided portal hypertension is SpleVT. In left-sided portal hypertension, collateral blood flow develops through the splenoportal or gastrohepatic systems and may lead to formation of varices in the esophagus, stomach, or colon [77], though in the absence of advanced liver disease, isolated esophageal varices are rare given normal hepatopetal flow.

Though most patients with SpleVT are asymptomatic at presentation, some presenting signs could include variceal bleeding, splenomegaly, and abdominal pain. The diagnosis of SpleVT should be considered in patients with a history of chronic pancreatitis and gastrointestinal bleeding, patients with splenomegaly (without history of portal hypertension, cirrhosis, or hematologic disease), or those patients with isolated gastric varices [76]. Ultrasound is the initial test for diagnosis of SpleVT though the accuracy may be limited by size and location of the vein. Venous phase angiography is the gold standard confirmatory test as it localizes obstruction and routes of collateralization. If timely diagnosis is not made, lack of treatment, (which includes control of variceal bleeding, variceal banding, and consideration of splenectomy for patients with bleeding varices associated with isolated SpleVT) can lead to life-threatening hemorrhage.

Cerebral Vein Thrombosis

Venous blood from the brain flows via deep cerebral veins and superficial cortical veins into the dural sinus. Cerebral vein and dural sinus thrombosis (CVT) are rare and present with a wide spectrum of symptoms and signs which can be acute, subacute, or chronic. Headache is the most frequently reported symptom and is manifested in approximately 80–90% of cases. Other symptoms include seizures and cranial nerve symptoms [78, 79].

Clinical presentation varies according to the location of the thrombosis, acuity of the event, and age of the patient. Clinical findings fall into two categories: (1) those that are related to increased intracranial pressure attributable to impaired venous draining leading to disruption of CSF absorption in the arachnoid space [80, 81] and (2) those related to focal brain injury from venous ischemia/infarction or hemorrhage. Symptoms and signs of CVT can be grouped into frequent syndromes including:

1. Isolated intracranial hypertension syndrome which consists of headache ± vomiting, papilledema, and visual changes
2. A focal syndrome demonstrating a focal deficit
3. Encephalopathy with bilateral or multifocal signs, delirium, and altered consciousness [78]

Patients who are older may be more likely to present with encephalopathy. Cavernous sinus thrombosis is more likely to present with headache orbital pain, proptosis, diplopia, and oculomotor palsies.

Diagnosis of CVT is based on clinical suspicions and imaging confirmation. With increased use of magnetic resonance imaging for investigation of patients with headaches, CVT is now being recognized with increasing frequency [78]. The most frequent risk factors for CVT are acquired or inherited prothrombotic conditions, oral contraceptives, pregnancy, infection, and malignancy. The largest study investigating CVT is the ISCVT, a multinational, multicenter, prospective observational study with 624 patients [82]. Thirty-four percent of these patients had an inherited or acquired prothrombotic condition. The most frequent genetic thrombophilias are factor V Leiden and prothrombin G20210A prothrombin mutations. Protein C, protein S, and antithrombin deficiencies have also been implicated [79]. Seventy-nine percent of patients in the ISCVT cohort recovered completely. Other meta-analyses have demonstrated an overall rate of acute death of 5.6% [83]. Prognostic factors for poor outcome include age > 37 years, male gender, Glasgow Coma Scale < 9 on admission, mental status disorder, and thrombosis of the deep venous system, intracranial hemorrhage on admission imaging, and malignancy or infection of the CNS [82]. Causes for death from acute CVT include trans-tentorial herniation secondary

to hemorrhage or edema as well as status epilepticus [84]. After the acute phase, complications include headaches, seizures, and other venous thrombotic events, the latter of which occur in about 5% of patients [78, 85]. Though most patients recover, several studies have suggested that patients with CVT suffer from long-term psychological and cognitive deterioration.

Superficial Vein Thrombosis

Superficial vein thrombosis (SupVT) is thrombosis of the superficial veins in the body and by itself has been considered to be a benign condition. However, given that patients with a previous history of SupVT have a four- to sixfold increased risk of developing PE or DVT in the future [32], recognition of this condition is important. In addition, SupVT also can present with concomitant VTE. A systemic review and meta-analysis including 22 studies suggested that DVT and PE are present in approximately 18 and 7% of patients at the time of SVT diagnosis, respectively [86].

SupVT most commonly affects the lower extremities but can also be found in other sites. The most commonly affected superficial veins are the great and short saphenous veins of the leg. It is commonly associated with varicose veins. Overall, the incidence of SupVT appears to be two- to sixfold higher than that of VTE [87]. Presenting clinical features are similar to that of DVT and can include tenderness and erythema as well as pruritus along the vein. SupVT may also present as a migratory thrombophlebitis that travels and appears in different locations over time. This presentation is known as Trousseau's sign and has a strong association with malignancy.

Unlike DVT, there are no recognized clinical scoring systems for SupVT available. Diagnosis is made on clinical grounds and with ultrasound confirmation. Studies have demonstrated that certain sonographic findings make a DVT more likely. SupVT involving the perforating veins or a SupVT < 3 cm from the saphenous femoral junction was found to significantly increase the risk of clot propagation into the deep veins.

Complications of VTE

Prognosis from DVT and PE is variable. Accurate estimates regarding morbidity and mortality are limited; however, if treated, overall mortality is estimated at 2–11% compared to up to 30% if left untreated [88]. Overall the likelihood of complications and death depends on the presence or absence of concomitant risk factors. VTE complications can be broken up into early (within the first 3 months after diagnosis of DVT and PE) and late (after the first 3 months) complications. Within the first 3 months after diagnosis of PE, largest morbidity is death due to hemodynamic compromise from PE and recurrence of PE. In patients with extreme hemodynamic compromise, shock/pulseless electrical activity is the most common cause of early death with the risk of death greatest within the first 2 h of presentation. When patients present with shock, there is a 30–50% risk of death.

Another acute complication of PE is pulmonary infarction (PI), which is caused by smaller, distally embolizing thrombi. There are no hemodynamic consequences; however, PI can lead to alveolar hemorrhage and pleuritis. Patients may present with pleuritic chest pain, cough, fever, and/or hemoptysis. Chest X-ray may demonstrate a pleural-based wedge-shaped infiltration, elevated hemidiaphragm with atelectasis or pleural effusion [44].

An uncommon but severe acute complication of DVT is phlegmasia cerulea dolens (PCD) which results from extensive thrombotic occlusion of the major as well as collateral venous drainage of an extremity. Clinical presentation consists of severe pain, swelling, cyanosis, and edema of the extremity. PCD is a life- and limb-threatening condition that can result in frank venous gangrene, pulmonary embolism, and/or death [89, 90].

Late complications of DVT and PE include VTE recurrence, post-thrombotic syndrome, and chronic thromboembolic pulmonary arterial hypertension. In addition to these above complications, treatment-related complications include major bleeding while on anticoagulation.

VTE Recurrence

VTE is a chronic disease with significant recurrence rates. The risk of recurrence is highest within the first 6–12 months from incident event. Independent predictors of recurrence include increasing patient age, male sex, idiopathic VTE event, increasing body mass index, active malignancy, and neurological disease with leg paresis [32, 91]. Following the incident VTE event, interim exposure to risk factors like major surgery, hospitalization for acute medical illness, respiratory infection, active cancer, central venous catheter, and pregnancy are associated with increased risk for VTE recurrence, whereas ongoing warfarin and aspirin use is associated with lower risk [91]. The risk of VTE recurrence may also be based on location of initial VTE. The risk of recurrence is higher in proximal DVT and PE when compared with those with distal DVT [92]. Patients who do have recurrence are significantly more likely to recur with the same event type as the incident event [93, 94].

Recurrence of VTE may have serious clinical consequences including worsening post-thrombotic syndrome and pulmonary hypertension. Furthermore, understanding VTE recurrence risk is important as it, along with the estimation of bleeding risk, helps clinicians decide on duration of anticoagulation as well as target aggressive VTE prophylaxis measures when individuals with prior history of VTE are exposed to interim VTE risk factors.

Post-thrombotic Syndrome

Post-thrombotic syndrome (PTS) is the most frequent chronic complication of acute DVT. It occurs in 20–50% of patients with DVT, and severe symptoms develop in 5–10% of these patients. In most cases PTS develops 1–2 years after acute DVT [95]. About 10% of patients will develop venous ulcers within 1–2 years [17, 19–21]. Notably, the cumulative incidence of PTS continues to increase 20 years following an incident of DVT [19], highlighting the fact that the risk of PTS persists long term.

The classic symptoms of PTS are dependent swelling and pain of the affected leg, venous ectasia, hyperpigmentation, and skin induration. Symptoms are often aggravated by standing or walking and relieved by leg elevation and resting. Severe PTS can lead to painful intractable venous leg ulcers which decrease mobility and require medical and nursing care.

There is currently no gold standard test to establish its presence, but there are several scoring systems and classifications. The Villalta scale was introduced in 1994 and was designed specifically for patients with PTS. This scale assesses five symptoms (pain, cramps, heaviness, paresthesia, pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasias, and pain on calf compression). Each variable has a four-point scale and PTS is diagnosed if the Villalta score is ≥ 5 or if a venous ulcer is present. Though other scales such as the Ginsberg measure, Brandjes score, Widmer classification, CEAP classification, and VCSS exist, the Villalta scale is the only scale that was designed specifically for patients with PTS, and the subcommittee for Control of Anticoagulation of the International Society for Thrombosis and Hemostasis has recommend it as the most appropriate method for diagnosis of PTS [96].

The main risk factors for PTS are persistent leg symptoms 1 month after acute DVT, obesity, older age, anatomically extensive DVT, and recurrent ipsilateral DVT. Approaches for prevention include use of high-pressure elastic compression stockings for at least 2 years after DVT; however, its effectiveness is debated due to the negative results of the SOX trial [97]. For patients who develop PTS, compression stockings are used to reduce edema and improve PTS symptoms. Other options include the use of intermittent pneumatic compression units. Given debilitating symptoms, PTS adversely affects quality of life and productivity, and long-term effects are costly to society [98].

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

While most patients with acute PE return to baseline functional status, some patients suffer long-term consequences. Furthermore, studies have demonstrated that up to 52% of patients have residual emboli 11 months after the sentinel event [99]. PE that fails to resolve can be remodeled into intravascular scars that cause persistent lung perfusion defects. Organizing thrombi and small vessel arteriopathy eventually causes a widespread increase in pulmonary artery resistance resulting in pulmonary hypertension. This process is known as chronic thromboembolic pulmonary hypertension (CTEPH), which is defined as the persistence of pulmonary hypertension after a single or recurrent PE [100]. Estimates for CTEPH range from 0.5 to 3.8% following acute incident PE and up to 10% in patients with recurrent PE [22, 100, 101]. CTEPH is associated with significant morbidity and mortality, and early detection is essential given that it is one of the few causes of pulmonary hypertension for which treatment is potentially curative. Risk factors for the development of CTEPH include, but are not limited to, recurrent or unprovoked PE, large perfusion defect, pulmonary artery systolic pressure >50 mmHg at time of initial PE, and persistently elevated RSVP 6 months after PE [102]. Individuals who have other comorbid chronic medical conditions including active cancer, thyroid disease, and history of splenectomy are also at increased risk [102]. Hypercoagulable states including protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin G20210A, or factor V Leiden have not been linked with CTEPH, though in patients with CTEPH, there is a high prevalence of phospholipid dependent antibodies (antiphospholipid antibodies and lupus anticoagulant) and factor VIII levels [103, 104].

Patients with CTEPH may have a "honeymoon" or asymptomatic period for many months or years after the sentinel PE. Symptoms of exertional dyspnea and exercise intolerance are the most common complaints when CTEPH manifests itself. Other symptoms include dizziness, near and/or true syncope, and exertional chest pain. Physical exam findings are similar to patients with pulmonary arterial hypertension due to other causes and include an increase in jugular venous pressure, loud split second heart sound with an increased P2, a right ventricular heave, an S4 gallop, and tricuspid regurgitation murmur. With progressive right ventricular failure, patients can develop hepatomegaly, ascites, and lower extremity edema. Right heart catheterization remains the gold standard for the diagnosis of pulmonary artery hypertension; however, other diagnostic tests such as echocardiogram, V/Q scan, and CT angiography can also be used in the diagnostic workup.

Major Bleeding While on Anticoagulation

Major bleeding during the first 3 months of anticoagulation treatment for acute VTE has been reported in 1.6–12.8% of patients and is dependent on which anticoagulant patients are being treated with (vitamin K antagonist vs heparin derivatives vs direct oral anticoagulants (DOACs)) as well as patient-specific factors. Linkins et al. performed a meta-analysis of 37 studies demonstrating that when VTE was treated with vitamin K antagonists, major bleeding was seen in 2.06% of patients during the first 3 months of treatment. After 3 months, the rate of major bleeding was approximately 2.75/100 person-years [105]. Some of the patient-specific risk factors associated with bleeding include (but not limited to) older age, history of prior bleeding, concomitant use of antiplatelet agents, severe hypertension, cancer, liver disease, and renal failure. The risk of bleeding is proportionate to the number of risk factors, and there are several bleeding risk assessment tools available for assessing bleeding risk [106]. Overall the risk of bleeding, including intracranial bleeding, fatal bleeding, and clinically relevant nonmajor bleeding, is less in patients on a DOAC than for vitamin K antagonists [107, 108].

Summary

VTE leads to significant morbidity and mortality within our society. Though DVT of the lower extremity and PE are the most common, VTE may also occur in the upper extremities, IVC, renal vein, splanchnic venous circulation, and cerebral veins. Understanding risk factors for VTE will allow us to better counsel our patients in ways to minimize risk. Furthermore, awareness of clinical signs and symptoms associated with VTE will aid in earlier recognition and treatment.

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Prevention of Venous Thromboembolism

20

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Abbreviations

ACCP	American College of Chest Physicians
DVT	Deep vein thrombosis
GCS	Graduated compression stockings
IPC	Intermittent pneumatic compression
LDUH	Low-dose unfractionated heparin
LMWH	Low-molecular-weight heparin
NICE	National Institute for Health and Care Excellence
VTE	Venous thromboembolism

Clinical Pearls

1. VTE prophylaxis should be offered to every patient based on individualized risks of bleeding and thrombosis. The prescription should be reevaluated on daily basis while the patient is in the hospital.
2. New oral anticoagulants are indicated for VTE prophylaxis after elective major hip and knee replacement for up to 35 days after surgery.
3. Aspirin is a reasonable alternative for secondary prevention after treatment with anticoagulation as it decreases the recurrence of VTE as well as major arterial vascular events compared to placebo.

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Introduction

Venous thromboembolism (VTE) is both an economic and social burden for the health-care system, resulting in significant mortality, morbidity, and cost. Therefore, identification of VTE risk factors and the use of adequate prophylaxis are major concerns for all health-care professionals. The risk of VTE and the corresponding preventive strategy depends not only on the patients' history and comorbidities but also depends highly on the acute clinical context. For example, the incidence of confirmed deep vein thrombosis (DVT) in a medical or general surgery setting varies from 10 to 40% [1, 2], whereas major orthopedic surgery is the most critical setting with up to 60% occurrence of DVT without thromboprophylaxis [3].

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Prophylaxis comprises both pharmacological and non-pharmacological methods. In this chapter, we will review the recommendations of VTE prophylaxis for each setting of patients.

Risk Assessment for Both VTE and Bleeding

Assessing the individual patient's risk for VTE and bleeding is a mandatory step before prescription of any thromboprophylaxis (Fig. 20.1). When needed, the method of thromboprophylaxis should be advised after discussion of the risk/benefit ratio. Tables 20.1 and 20.2 are adapted from the National Institute for Health and Care Excellence (NICE) clinical guideline #92 [4], respectively, describing the assessment of risk factors for VTE and bleeding.

Patients are at increased risk of VTE if they are expected to have their mobility highly reduced for ≥3 days or relatively reduced compared to their basal state, in addition to one or more of the risk factors listed in Table 20.1. In addition, surgical patients and patients with major trauma are considered at increased risk of VTE if they were admitted with an inflammatory or intra-abdominal condition or had undergone or will undergo a surgical procedure >90 min (>60 min for pelvic or lower-limb surgery).

Several risk assessment models have been developed to score the risks of VTE and bleeding, although their routine use can be cumbersome. The Padua prediction score has been evaluated in hospitalized medical patients [5]. Among a total of 11 items, the major risk factors are active cancer, previous VTE, reduced mobility, and known thrombophilic conditions (each item scores 3 points). A cumulative score ≥4 defines high risk of VTE [5].

For general surgery patients, the Rogers score evaluates 15 items, including the type of surgical procedure and some biological parameters [6]. A score above 10 correlates with a moderate risk in the vocabulary of the American College of Chest Physicians (ACCP) guidelines [1]. The Caprini score is relatively easy to use and has been adapted by the ACCP guidelines, after validation in a large retrospective study of general, vascular, and urological surgery patients [7, 8]. It also helps assess patients undergoing gynecological surgery.

For orthopedic surgery, the ACCP guidelines state that the surgery-specific risk of DVT outweighs the contribution of the patient-specific factors. Therefore, there is no validated risk assessment model, and recommendations on DVT prevention are mainly based on the type of surgery. Likewise, there is not any specific score giving a threshold for the use of anticoagulants [3].

VTE prevention starts with good hydration of the patient and encouragement to ambulate as early and as often as possible. The risk/benefit ratio and the method of thromboprophylaxis should be reassessed every 24 h for all hospitalized patients.

Mechanical Versus Pharmacological Prophylaxis

In all clinical conditions, these two modalities should be complementary rather than antagonistic.

Mechanical prophylaxis, based on graduated compression stockings (GCS) or intermittent

Fig. 20.1 (continued) peutic option and the only option when the risk of bleeding is high. Anti-embolism graduated compression stockings should be offered unless contraindicated (severe peripheral arterial disease, stroke, skin lesions, etc.). Intermittent pneumatic compression is an alternative to stockings and is recommended in many surgical settings. **5**. Pharmacological VTE prophylaxis comprises several drugs such as low-molecular-weight heparin, low-dose unfractionated heparin, and direct oral anticoagulants. The choice is guided by clinical settings, patient's comorbidities, and preferences. **6**. In all patients, tolerance of the prophylactic treatment must be monitored, with the help of monitoring of therapeutic serum levels for some regimens. Indication for VTE prophylaxis and correct dosage should be reevaluated every day during the hospital stay. **7**. At discharge, the indication for starting or continuing VTE prophylaxis should be reevaluated. If needed, the patient must leave the hospital with a detailed prescription for VTE prophylaxis, including the length of treatment and the modality of surveillance. Comprehensive information should be given to the patient and his or her helpers, in particular to his or her family practitioner in order to improve compliance and detect complications

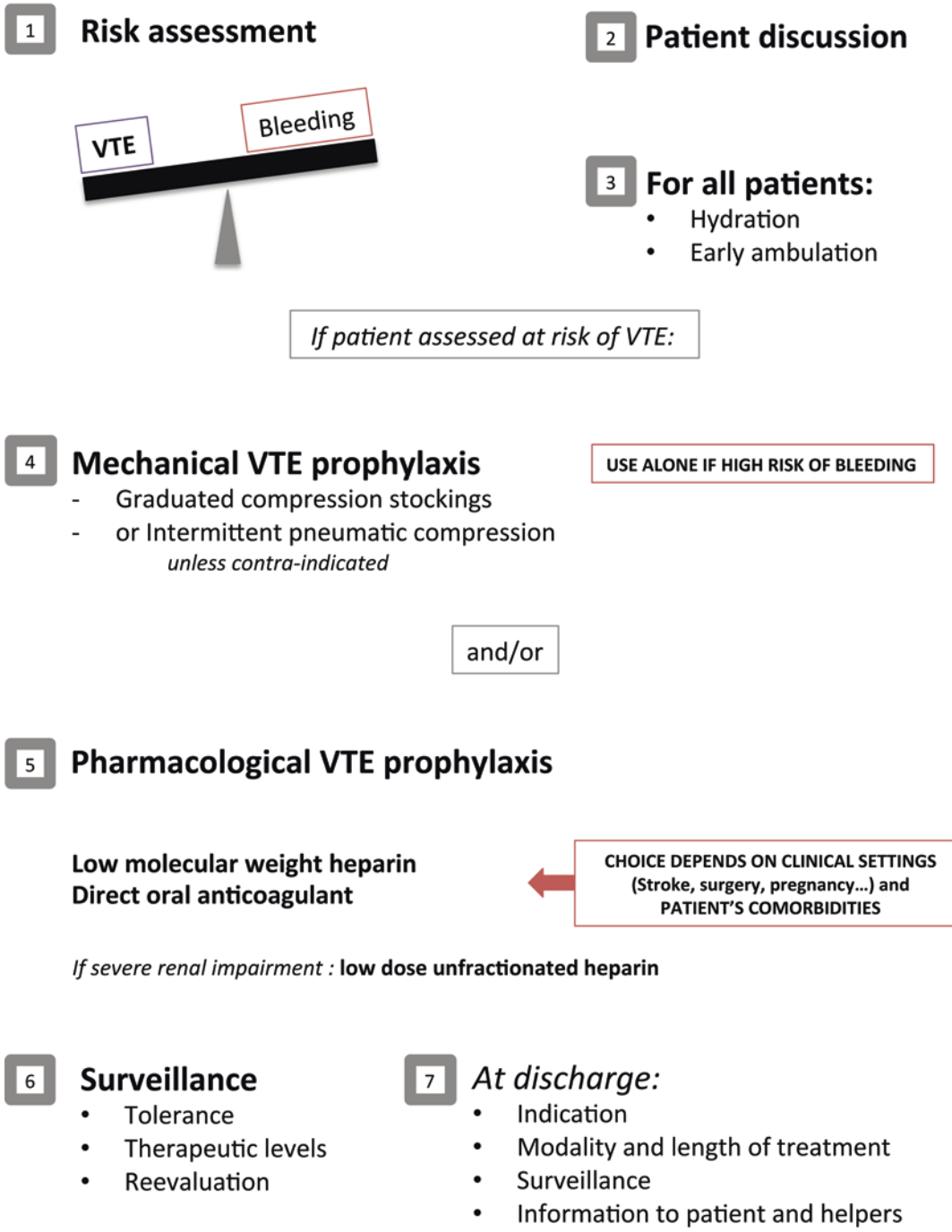

Fig. 20.1 Decision process of thromboprophylaxis in hospitalized patients. **1**. At admission, each hospitalized patient must have an assessment of his/her risks of VTE and bleeding according to the clinical settings and patient's history. Several risk assessment scores exist and can help the practitioner. **2**. Each patient must be informed of the risks of VTE and bleeding and must be offered a prophylactic treatment according to the recommendation for his or her clinical settings and his or her preferences. **3**. For all patients, VTE prophylaxis starts with a good hydration state (unless otherwise indicated for concurrent clinical settings) and early and frequent ambulation. **4**. In patients assessed to be at increased risk of VTE, mechanical VTE prophylaxis is a noninvasive and simple thera

Table 20.1 Venous thromboembolism (VTE) risk assessment

Risk factors for VTE among hospitalized patients
Constitutive variables
• Age > 60 years[a]
• Known thrombophilias
• Personal history or first-degree relative with a history of VTE
• Obesity (body mass index [BMI] over 30 kg/m^2)
• Varicose veins with phlebitis
Transient or modifiable variables
• One or more significant medical comorbidities (e.g., heart disease; metabolic, endocrine, or respiratory pathologies; acute infectious diseases; inflammatory conditions)
• The use of hormone replacement therapy or estrogen-containing contraceptive
• Critical care admission
• Dehydration

[a]French guidelines for hospitalized patients consider age >40 as a risk factor

Table 20.2 Bleeding risk assessment

Risk factors for bleeding among hospitalized patients
Constitutive variables
• Untreated inherited bleeding disorders (such as hemophilia and von Willebrand's disease)
Transient or modifiable variables
• Active bleeding
• Acquired bleeding disorders (such as acute liver failure)
• The use of anticoagulants known to increase the risk of bleeding
• Acute stroke
• Thrombocytopenia (platelets less than 75 × 10^9/l)
• Uncontrolled systolic hypertension (230/120 mmHg or higher)
• Lumbar puncture/epidural/spinal anesthesia within the previous 4 h or expected within the next 12 h

pneumatic compression (IPC), is offered as a primary prophylaxis in all patients with increased VTE risk, in particular surgical and trauma patients [4].

In patients with stroke, GCS should not be used because of an increased incidence of skin injury [9]. In other situations, GCS are an efficacious first-line measure for hospitalized patients with increased risk of VTE, as an alternative to anticoagulants when the risk of bleeding is high, or in combination with anticoagulants in patients with high risk of VTE.

Intermittent pneumatic compression (IPC) can be offered in all settings; however, good observance and efficacy are obtained only with battery-powered portable devices and sustained explanation to the patients [10–13]. IPC is a first-choice modality whenever the risk of VTE and bleeding are both high [14]. In a meta-analysis, Ho et al. showed that compared to anticoagulants, the use of IPC provides a similar level of protection against VTE (RR 0.93; $P = 0.66$) with a risk of hemorrhage decreased by 58% (RR 0.41; $P = 0.0002$) [14]. However, dual therapy, e.g., the use of pharmacological prophylaxis in addition to IPC in patients with high risk of VTE, provides increased protection when compared to IPC alone (RR 0.54; $P = 0.02$). For that reason, all guidelines recommend the use of mechanical and pharmacological prophylaxis in patients who are at high risk of VTE and low risk of bleeding [15].

Pharmacological agents used for VTE prevention comprise both antiplatelet and anticoagulant drugs. Although the role of antiplatelet drugs, in particular aspirin, remains controversial in primary prevention of VTE, it is accepted by several guidelines as a sole prophylactic agent in surgical settings [16]. Low-molecular-weight heparin (LMWH) used subcutaneously, replaced by low-dose unfractionated heparin (LDUH) in cases of renal insufficiency, has played a major role as a prophylactic agent, and can still be used in all clinical contexts excluding increased bleeding risk and allergy. Fondaparinux is a synthetic analog of the antithrombin-binding pentasaccharide found in heparins, with a more specific anti-Xa activity and a longer half-life. Because of a higher risk of bleeding, fondaparinux is not recommended over LMWH in surgical patients but is allowed for use in some settings. Recently, direct oral anticoagulants such as dabigatran (antithrombin), rivaroxaban, and apixaban (anti-Xa) have been evaluated and recommended for use in prevention of DVT in several clinical settings, mainly postsurgical, in particular after orthopedic surgery. Their use is limited to patients without

severe renal insufficiency and low risk of bleeding. Nevertheless, these agents are prescribed with increasing frequency as they are taken orally and do not need laboratory testing. The main drawback is the lack of approved antidote, although some candidates are under study.

All guidelines emphasize that the choice of either prophylactic method should take into account the patient preference [17]. Comprehensive explanations are required to expose the benefits and risks of each method to the patient. For example, some patients may prefer having injections of heparin rather than wearing IPC for 18 h a day, whereas others may prefer not receiving a drug that increases bleeding risk.

It is also very important to reassess the need for VTE prophylaxis every day and stop or change the modality according to new information as medical conditions change.

Nonsurgical Hospitalized Patients

Patients with Acute Medical Condition (Including Cancer)

All guidelines recommend the use of a pharmacologic prophylaxis as a first-line therapy in acutely ill patients, including cancer, who are at increased risk of VTE. One of several agents can be chosen including fondaparinux, low-molecular-weight heparin (LMWH), or low-dose unfractionated heparin (LDUH). The latter is specifically recommended for patients with acute or severe chronic renal insufficiency. The use of anticoagulants decreases the risk of fatal pulmonary embolism (RR 0.41; 95% CI, 0.22–0.76) and symptomatic DVT (RR 0.47; 95% CI, 0.22–1) when compared to no anticoagulants [2].

All guidelines agree that one mechanical prophylaxis, either GCS or IPC, can be used alone in acutely ill patients with increased risk of thrombosis when pharmacologic prophylaxis is contraindicated and should be substituted with anticoagulants when the bleeding risk decreases [2, 4, 18–20]. Aspirin is not recommended by any society as a sole thromboprophylactic agent in medical patients. Dual therapy (anticoagulation + mechanical prophylaxis) may improve the efficacy of VTE prevention in high-risk cancer patients [19].

The use of anticoagulants is not recommended for low-risk patients, and thromboprophylaxis should be stopped when the patient is capable of ambulation or discharged from the acute hospital stay. For example, patients who are chronically immobilized at home or institutions should not receive routine thromboprophylaxis.

Patients with Ischemic Stroke or Intracranial Hemorrhage

The ACCP guidelines recommend systematic use of thromboprophylaxis in patients with acute ischemic stroke or primary intracerebral hemorrhage with restricted mobility [21].

In acute ischemic stroke, anticoagulants and/or IPC should be started as early as possible and maintained until mobility is regained on time of discharge. Dual therapy may yield additional benefits based on studies in postoperative patients. Aspirin therapy is prescribed within 48 h but does not confer protection against VTE. LMWH is favored over LDUH.

Published after the ACCP guidelines, the CLOTS 3 trial compared IPC to no IPC in 2876 patients after stroke; the rate of DVT within 30 days was significantly lower in the treatment group (8.5%) compared to the control group (12.1%) (OR 0.65; $P = 0.001$) [9]. This study convinced the NICE guideline committee to recommend offering IPC to patients with ischemic stroke within 3 days of the event and until 30 days after the event. Contrary to the ACCP guidelines, NICE guidelines consider prophylactic doses of anticoagulants only in cases where the diagnosis of hemorrhagic stroke has been excluded and the risk of secondary hemorrhage is considered low. Both guidelines recommend against the use of GCS in these patients, since studies have shown increased risk of skin injury (RR 4.02; 95% CI, 2.34–6.91) [4, 21].

In acute primary intracerebral stroke (excluding hemorrhage due to intracerebral tumor or arteriovenous malformation), the ACCP guidelines also

recommend the use of LMWH, LDUH, or IPC to prevent VTE, started early (2–4 days) after the onset of the event [21]. Based on studies with acute stroke patients, they favor the use of LMWH over LDUH and recommend against the use of GCS.

Non-orthopedic Surgical Patients

General Surgery Patients

According to the ACCP guidelines, for general and abdominopelvic surgery (including vascular surgery), LMWH or LDUH is favored over IPC alone in patients with low or moderate risk of DVT and bleeding [1]. For patients with high risk of DVT, including during the perioperative period of cancer surgery, IPC is recommended in all cases, and dual therapy with LMWH or LDUH is recommended as soon as the risk of bleeding has decreased.

The NICE guidelines recommend the use of IPC or GCS in all surgical patients at increased risk of DVT, including cardiac, bariatric, gastrointestinal, gynecologic, cranial, spinal, vascular, and even outpatient surgery, implemented at admission and continued until the patient regains mobility [4]. Dual prophylaxis is added systematically if the risk of bleeding is low. For other surgeries, prophylaxis is proposed according to the risk of VTE.

Specific Surgical Patients

Some surgical interventions or patients require specific prophylaxis regimens. According to the ACCP guidelines, uncomplicated cardiac surgery patients should receive IPC alone over no prophylaxis or pharmacological prophylaxis, in order to minimize the risk of bleeding [1]. However, patients who underwent cardiac surgery that was complicated by a nonhemorrhagic surgical complication should receive dual prophylaxis. The same scheme is recommended after craniotomy and spinal surgery, with pharmacological prophylaxis added in high-risk patients once the risk of bleeding has diminished. Major trauma patients should receive either IPC or LMWH or LDUH, and dual therapy is recommended if they are at high risk of VTE.

The ACCP guidelines state that women at increased risk of VTE after cesarean section should receive pharmacological prophylaxis or mechanical prophylaxis if anticoagulants are contraindicated [22]. Women with very high risk should receive dual therapy. These recommendations are supported by the American College of Obstetricians and Gynecologists [23]. For the NICE guidelines, the latter category includes women who undergo surgery while pregnant or within 6 weeks after pregnancy [4].

Orthopedic Surgery

Elective Surgery

Major orthopedic surgical procedures such as total hip arthroplasty or total knee arthroplasty need robust VTE prophylaxis. Both the American Association of Orthopedic Surgeons [24] and the ACCP guidelines [3] recommend the use of at least one of the following methods: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH, vitamin K antagonist, aspirin, or IPC, for a minimum of 10–14 days after the procedure.

The ACCP favors LMWH over the other methods, but treatment should be adapted to the patient's compliance. They recommend starting the first injection either 12 h or more preoperatively or 12 h or more postoperatively. The length of the treatment should be extended until 35 days after the procedure, extending into the outpatient period [3]. Both societies recommend using dual therapy with mechanical and pharmacological prophylaxis during the hospital stay, in particular if the patient has a history of DVT.

The NICE guidelines emphasize dual therapy, recommending the use of GCS, foot pumps, or IPC at admission [4]. They also detail how and when to start pharmacological prophylaxis postoperatively, in the absence of contraindication, with one of the following drugs: dabigatran etexilate (starting 1–4 h after surgery), fondaparinux

sodium (starting 6 h after surgical closure provided hemostasis has been established), LMWH (starting 6–12 h after surgery), rivaroxaban (starting 6–10 h after surgery), or LDUH for patients with severe renal insufficiency (starting 6–12 h after surgery). Apixaban is another effective alternative but may be less cost-effective. Treatment is recommended for 28–35 days after hip replacement and 10–14 days after knee replacement. The NICE guidelines do not regard aspirin as an adequate pharmacological prophylaxis after orthopedic surgery.

Hip Fracture

Hip fracture is another common major orthopedic surgical procedure that requires careful prevention of VTE and bleeding. According to the ACCP, the same recommendations apply; however, the direct thrombin inhibitor and direct factor Xa inhibitors are not recommended in this setting [3]. NICE guidelines recommend only fondaparinux, LMWH, or LDUH for patients with severe renal insufficiency. Fondaparinux should not be used before completion of hemostasis [4].

Other Orthopedic Surgeries

For other orthopedic surgeries, the NICE guidelines recommend dual therapy with mechanical prophylaxis and either LMWH or LDUH starting 6 h after surgery, after risk assessment [4]. They recommend against the systematic use of VTE prophylaxis in upper-limb surgery, unless specific risks are present.

The ACCP guidelines recommend against the use of pharmacological prophylaxis in patients with isolated lower leg injuries requiring leg immobilization. Likewise, they recommend against the use of thromboprophylaxis in patients undergoing knee arthroscopy without previous history of VTE [3].

The use of IPC is strongly encouraged by all the guidelines in the setting of orthopedic surgery. The ACCP emphasizes that only battery-powered portable devices should be used, for 18 h of use per day, for the prophylaxis to be efficacious [3]. The NICE guidelines emphasize the need to explain the role of the device to the patient and family in order to improve compliance [4].

Prevention of VTE in Outpatient Settings

Outpatients with cancer but no additional risk factors for VTE should not receive routine prophylactic anticoagulants, even if they have an indwelling catheter. Additional risk factors for these patients include the use of angiogenesis inhibitors, thalidomide, and lenalidomide. If they present with additional risk factors and are not at high risk for bleeding, they should receive prophylactic doses of LMWH or LDUH [2].

The ACCP recommends that long-distance travelers at high risk of VTE choose an aisle seat, frequently ambulate, do calf muscle exercise, and use below-knee GCS (15–30 mmHg pressure at the ankle) during the flight [2].

Prevention of VTE Recurrence

Standard pharmacological prophylaxis for recurrent VTE includes 3–12 months of treatment with full-dose warfarin with a target international normalized ratio (INR) between 2.0 and 3.0. However, after a first episode of VTE treated with anticoagulation, a high incidence of recurrence persists, at least during the first 3 months after treatment cessation. Patients in whom the first VTE was unprovoked have a recurrence risk as high as 30% over 5 years after discontinuation of anticoagulation [25]. However, there is ongoing controversy about which prophylaxis method offers the best risk/benefit ratio.

Aspirin is a tempting drug to use for long-term prevention, because of its low cost and limited risk of hemorrhagic complications. Two large RCTs treating 1224 patients compared low-dose aspirin to placebo after an initial anticoagulant treatment (6 weeks minimum, most at least

3 months) in patients who presented with a first unprovoked VTE, either DVT or PE. The Warfarin and Aspirin (WARFASA) trial showed a 42% reduction in VTE recurrence with aspirin compared to placebo [26]. The Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial showed a nonsignificant reduction of the primary end point but a significant decrease in the rate of major vascular events, a secondary composite outcome of VTE and arterial events [27]. The design of both studies was prospectively matched, and meta-analysis showed a 32% decrease in recurrent VTE, as well as a 34% reduction in the risk of major vascular events. Aspirin was not associated with increased rates of bleeding or death in any of the trials; therefore, aspirin seems a low-risk agent for secondary prevention of venous thromboembolism, especially when compared to no prophylaxis.

Although not compared directly to aspirin, oral anticoagulation with warfarin seems to further reduce the risk of VTE recurrence. The high-quality PREVENT study reported the results of 508 patients who were randomized to either placebo or low-dose warfarin (target INR between 1.5 and 2), after the occurrence of VTE followed by proper anticoagulation for a median time of 6.5 months. Of 253 patients assigned to placebo, 37 had recurrent VTE (7.2 per 100 person-years), compared with 14 of 255 patients assigned to low-dose warfarin (2.6 per 100 person-years), a risk reduction of 64% (HR 0.36; CI 95% 0.19–0.67; $P < 0.001$) [28]. A major hemorrhage occurred in two patients treated with placebo and five treated with low-dose warfarin ($P = 0.25$). Eight patients in the placebo group and four in the warfarin group died ($P = 0.26$). Low-dose warfarin was associated with a 48% reduction in the composite end point of recurrent venous thromboembolism, major hemorrhage, or death. Low-dose warfarin was therefore considered a highly effective method of preventing recurrent venous thromboembolism and regarded as a first-choice treatment.

Recently, direct oral anticoagulants have been studied in this setting. Rivaroxaban, apixaban, and dabigatran effectively prevent recurrent VTE, with substantial risk reduction ranging between 64 and 92% compared with placebo and with acceptable risk of bleeding [25]. However, the length of treatment in these studies was quite limited, so further studies are necessary to assess the long-term risk/benefit ratio of these medications. In France, rivaroxaban is the only direct oral anticoagulant indicated for long-term prevention of VTE recurrence (starting 22 days after the occurrence, 20 mg a day or 15 mg a day if high bleeding risk or renal insufficiency).

Perspective and Conclusion

Other drugs and approaches are currently being studied in the prevention of venous thromboembolism. For example, statins have displayed a potential role in VTE prevention, especially in potential modification of aspirin effects [29]. Another molecule, sulodexide, a purified complex of glycosaminoglycans, showed effectiveness in long-term prophylaxis of VTE recurrence in a recent study, where it halved the occurrence of VTE compared to placebo [30]. However, this drug is not commercially available either in the USA or in France, and other studies are required to identify its role in VTE.

In conclusion, in patients with a transitory increased risk of VTE, low-molecular-weight heparin remains a gold standard in the prevention of VTE, as it is indicated in almost all clinical situations. It is often replaced by LDUH in patients with renal insufficiency. Mechanical prophylaxis, in particular the use of IPC, has a plain and indisputable role as a sole or adjunctive treatment for most hospitalized patients. New direct oral anticoagulants are gaining their place for thromboprophylaxis, in particular because they are very convenient to use in an outpatient setting without the burden of recurrent injections and blood analysis associated to heparins and vitamin K antagonists.

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Overview of Anticoagulation Agents

21

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Clinical Pearls

1. Direct oral anticoagulants are the current standard of care for treatment of VTE and are increasingly being used instead of vitamin K antagonists.
2. Direct oral inhibitors of factor Xa have less bleeding complication compared to coumadin.
3. Idarucizumab, ciraparantag, and andexanet alfa are specific antidotes that are undergoing clinical trials and could potentially make the use of direct oral anticoagulants safer.

Introduction

Hemostasis consists of a series of reactions that lead to the formation of fibrin and generation of an insoluble clot that strengthens the plug of platelets that halts the bleeding [1]. This process involves complex mechanisms at the cellular level (platelets) and the protein level (coagulation factors). The coagulation cascade is divided into the intrinsic, extrinsic, and the common pathways. The end product of this cascade activates thrombin which converts fibrinogen to fibrin (Fig. 21.1) [1]. Anticoagulation agents are the mainstay of prophylaxis and treatment of venous thromboembolism (VTE). The various anticoagulation agents affect hemostasis by targeting different factors of the cascade. They typically prevent formation of new clot, its propagation, and embolization. Unlike thrombolytic agents which are administered to break down the thrombus by activating plasmin, anticoagulation agents achieve various levels of delayed thrombus resolution by allowing the innate lysis mechanisms to function. This chapter gives an overview of the anticoagulation agents and is divided based on the route of administration parenteral vs oral (Table 21.1).

Parenteral Anticoagulants

Heparin

Heparins are large water soluble polysaccharides which mainly act through blocking the activated intrinsic pathway. Heparin is also referred to as unfractionated heparin (UFH) to differentiate it from other lower molecular weight derivatives

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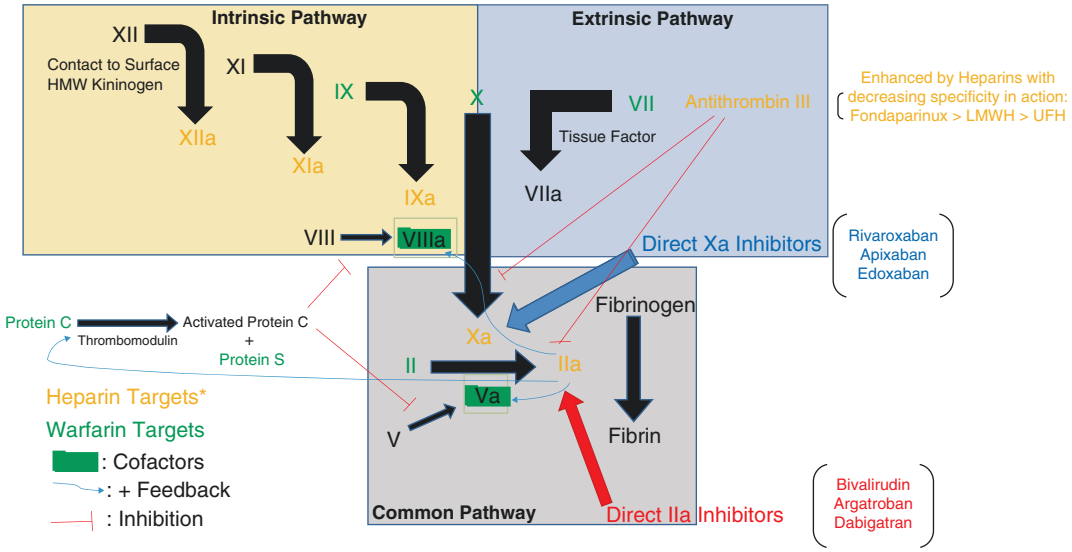

Fig. 21.1 Schematic view of the coagulation cascade and different targets of anticoagulant agents. Direct inhibitors specifically inhibit activated target coagulation factors (*red and blue arrows*), while traditional anticoagulants affect several coagulation factors indirectly (*HMW* high molecular weight, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin)

discussed below. It acts by catalyzing the binding of antithrombin III (a serine protease inhibitor) to serine protease coagulation factors (IIa, IXa, Xa, XIa, and XIIa) which results in immediate inactivation of coagulation cascade either in vivo or in vitro [2, 3]. Heparin can be administered intravenously (IV) or subcutaneously (SC). The half-life is approximately 2 h and the metabolism is through hepatic or reticuloendothelial system. The half-life is dose dependent with higher doses having longer half-life. At higher doses, the reticuloendothelial system binding sites become saturated, and clearance by hepatic metabolism is typically slower. Its use is safe without dose adjustment in patients with renal failure.

The effect is monitored through partial thromboplastin time (PTT) or activated clotting time (ACT) measurement [4, 5]. The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired. UFH is dosed to achieve a target activated PTT of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg/h. Heparins' specific structure inhibits them from placental exchange and makes them drugs of choice in pregnant patients who need anticoagulation.

Heparin is commonly used for inpatient treatment of venous and arterial thromboembolism. The main side effects are bleeding and heparin-induced thrombocytopenia (HIT), but osteoporosis and hypersensitivity have been also reported [6]. There are some important limitations in UFH use. First, it has a narrow therapeutic range window, with the risk of either bleeding or inadequate anticoagulation. This limitation was illustrated in the Enoxaparin and Thrombolysis in Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction (ExTRACT TIMI) 25 trial [7, 8]. This randomized clinical trial enrolled 20,506 patients with myocardial infarction and showed significant decrease in the composite of death, nonfatal reinfarction, or urgent revascularization in patients treated with enoxaparin compared to UFH. This difference was thought to be due partly to low predictability of dose-response and difficulty to stay in the therapeutic zone with UFH. Guervil et al. have demonstrated that aPTT monitoring

Table 21.1 Overview of anticoagulant agents

	Drug name			Half-life	Main route of elimination	Monitoring		Reversal agent
Parenteral	Heparins		*UFH*	2 h	Hepatic and reticuloendothelial	PTT ACT		Protamine sulfate
			LMWH (*enoxaparin/dalteparin/tinzaparin*)	4 h	Renal	Anti-factor Xa assay (less need as response is predictive)		Protamine sulfate (partial effect)
			Fondaparinux	17 h	Renal	Anti-factor Xa assay (usually not indicated)		–
	Parenteral DTI		*Argatroban*	40–50 min	Hepatic	PTT		–
			Bivalirudin	25 min	Proteolysis	PTT LR-ACT (in PCI)		–
Oral	Vitamin K antagonist		*Warfarin*	40 h	Renal	INR		Vitamin K FFP 4F-PCC
	Direct oral anticoagulants (DOACs)	Oral DTI	*Dabigatran*	14–17 h	Renal	Quantitative assays	Qualitative assays	Idarucizumab Ciraparantag
						HEMOCLOT dilute thrombin assay, ecarin clotting time	PTT TT ACT	
		Oral Factor Xa inhibitor	*Rivaroxaban*	5–13 h	Renal	Anti-factor Xa assay	PT	Andexanet alfa Ciraparantag
			Apixaban	12 h	Biliary			
			Edoxaban	6–11 h	Biliary			

UFH unfractionated heparin, *PTT* partial thromboplastin time, *ACT* activated clotting time, *LMWH* low molecular weight heparin, *DTI* direct thrombin inhibitor, *LR-ACT* low-range activated clotting time, *4F-PCC* 4-factor prothrombin complex concentrate, *FFP* fresh frozen plasma, *TT* thrombin time, *PT* prothrombin time, *PCI* percutaneous coronary intervention

was outside the therapeutic range in 60% of the time in patients who were receiving the UFH infusion [9].

Heparin is not suited for outpatient therapy because of the absence of an oral formulation. There is also a risk for thrombus extension during heparin therapy due to low effect on activated thrombin which has bound to factor Xa or fibrin in the formed thrombus. UFH anticoagulant effects can be reversed by protamine sulfate. Usually 1 mg of protamine sulfate is used to neutralize up to 100 units of heparin. Neutralization occurs in less than 5 min after IV administration through complexing with heparin and its inactivation [10].

Low Molecular Weight Heparins

Low molecular weight heparins (LMWHs) are fragments of UFH that exhibit less binding to plasma proteins and endothelial cells. Therefore, LMWHs have a greater bioavailability, a more predictable dose-response especially with weight-based dosing, and a longer half-life. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease. Due to their size, they are less likely but still have a significant chance of HIT. This group has more activity against factor Xa, and their levels can be monitored more efficiently by anti-factor Xa assay rather than PTT. Protamine sulfate has limited antidote effect against LMWH. Currently available LMWHs in the USA are enoxaparin, dalteparin, and tinzaparin [11]. They are different in molecular weight and manufacturing methods. Both enoxaparin and dalteparin have been used widely in VTE and share similarity in efficacy and safety profile; however drug administration can be incommodious. After initial drug selection, it is preferable not to try using different LMWHs interchangeably, since they have a different tendency to affect factor Xa versus factor IIa (enoxaparin has approximately 50% more anti-Xa effect compared to dalteparin with similar anti-IIa effect) [12].

Fondaparinux

Fondaparinux, a selective antithrombin III-mediated anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required routinely. In certain populations (renal impairment, pregnancy, obesity, children), monitoring can be achieved using anti-factor Xa assay which is currently the gold standard for monitoring LMWH and fondaparinux therapy [13]. Target anti-factor Xa levels may be different in each laboratory due to variability in the type of used assays and titration curves [10]. Target level of 0.25–0.35 units/mL was recommended for anti-Xa based on the study in patients with renal impairment due to bleeding complications associated with anti-Xa between 0.45 and 0.8 units/mL [14, 15]. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia.

Heparin-Induced Thrombocytopenia

UFH has the largest size compared to other heparins and hence most likely to cause HIT. It is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. Currently, the term HIT is used without any dividing to describe only the immune-mediated reaction [16]. It can occur in up to 5% of patients who use UFH or LMWH. Patients who develop HIT typically are noted to have more than 50% decrease in platelet count within 5–10 days after initiation of heparin without an alternative cause. They are at risk of developing a new thrombus (heparin-induced thrombocytopenia and thrombosis [HITT]). The assumption of diagnosis of HIT requires immediate discontinuation of any heparin product and initiation of alternative anticoagulants, typically a parenteral direct thrombin inhibitor [17]. Confirmation can be reached by HIT antibody testing immunoassay (ELISA) or functional assay like serotonin release assay

(SRA) [18]. HIT or HITT may be delayed and can occur up to several weeks after discontinuation of heparin [19, 20].

Direct Thrombin Inhibitors

Parenteral direct thrombin inhibitors (DTIs) block thrombin and prevent its cleaving effect on fibrinogen [21]. The drugs developed in this group are bivalirudin, argatroban, and lepirudin. Lepirudin was taken off the market in 2012. This section will focus on argatroban and bivalirudin. DTIs have no interaction with heparin platelet factor 4 (PF4) antibodies. These drugs are useful for the treatment of venous thromboembolism in the setting of HIT [22, 23]. Despite their benefits, development of this class of drugs was slower than many other classes probably due to lack of investment and research funding. One of the reasons of this disinterest is their short-term use and route of administration which results in narrow target population. On the other hand, the popularity of heparins and their high safety and efficacy profile limited the development of alternative parenteral DTIs [24]. The two main disadvantages are lack of antidote and difficulty in monitoring [25, 26]. Parenteral DTIs are also expensive and are usually reserved for patients who cannot receive heparin and LMWHs. Oral DTIs are discussed separately in this chapter.

Argatroban is commonly used for treatment of VTE in patients with HIT, whereas bivalirudin is used as an alternative to heparin in patients with acute coronary syndrome who undergo angiography and intervention [27]. Both drugs, unlike heparin, can inhibit clot-bound thrombin in addition to soluble thrombin. The relatively short half-life of parenteral DTIs necessitates precise monitoring of their level to assure effectiveness and inhibition of side effects. Bivalirudin is now commonly used in the USA as an alternative to heparin alone or heparin and GPIIb/GPIIIa inhibitor in patients with acute coronary syndrome. Compared to heparin, it has demonstrated noninferiority effect and less major bleeding and no risk of thrombocytopenia [27].

Oral Anticoagulants

Warfarin

Until recently, the vitamin K antagonists (VKAs) were the only oral anticoagulant agents available, and warfarin remains the most commonly prescribed oral anticoagulant worldwide. The main indications of warfarin use include primary and secondary prevention of VTE, prevention of systemic embolism, and stroke in patients with mechanical heart valves and atrial fibrillation (AF) [28]. Warfarin affects coagulation cascade by interfering with γ-carboxylation of vitamin K-dependent clotting factors II, VII, IX, and X. Besides anticoagulation effect, warfarin also plays a role as a procoagulant as it acts against proteins C and S. It is readily absorbed after oral administration, reaching peak concentration within 4 h. It however has significant variability in dose-response across individuals and requires maintenance in a narrow therapeutic range of international normalized ratio (INR) of 2–3 for most indications [29, 30].

The anticoagulant effect of warfarin takes several days to take action; hence concomitant bridging with other anticoagulants such as heparin or LMWH is usually done until the INR reaches therapeutic range. Then warfarin oral administration alone can be continued. Initiation with low-dose warfarin at 5mg has been found to be superior to 10 mg in patients treated with warfarin after heart valve replacement [31, 32]. Conversely, in patients with acute venous thromboembolism, initial administration of warfarin at 10 mg allowed more rapid achievement of therapeutic INR [33]. The current guidelines however suggest initiating VKA therapy with 10 mg daily for the first 2 days followed by dosing based on INR values (Grade 2C) [30].

The patient response to warfarin varies significantly because of genetic factors, comorbidities, the use of concomitant medications, as well as dietary factors, each of which can affect its metabolism. Clinical outcome and efficacy of warfarin are highly associated with patient adherence and the time for which patient's PT-INR

values are maintained within therapeutic range [34]. According to a study by De Caterina et al., patients with an average time >70% in therapeutic range are considered to be at a low risk of a major hemorrhagic or thrombotic event [35]. Patients with a low body weight [36, 37], significant congestive heart failure, liver disease, or concurrent medications with interactions may require lower doses. However, renal clearance does not play a significant role in warfarin elimination [38].

Warfarin is often initiated in the evening, so that an INR can be obtained with morning laboratory testing, allowing time in the afternoon to obtain the results and determine the next dose. This may not be however sufficient time to determine the effect of the drug. Gage suggests that INR testing needs to be done 15 or more hours after first administration [39]. It may be thus better to administer warfarin in the afternoon, if INR testing is done the following morning. The optimal frequency of INR testing to maintain patients within therapeutic range is still unclear, as patients exhibit fluctuations of INR with diet, medications, and adherence. When therapy is just initiated, INR monitoring is done every few days until it is therapeutic. The INR is then usually obtained weekly for 1–2 weeks, to verify dosing by stability of the INR within range. Commonly, testing is then obtained biweekly for one to two times. If the INR remains stable within the therapeutic range and all else remains constant, the duration between tests can be extended to 3 monthly visits. Current guidelines recommend that the frequency of testing should be scheduled to every 12 weeks (Grade 2B) [30].

The major limitation of warfarin is the interaction with drugs and dietary restrictions. Patient education and identification of factors which may lead to over or under-anticoagulation are thus necessary [40]. When combined with low-dose aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or clopidogrel, the risk of bleeding is significantly increased [41, 42]. It is recommended to avoid use of these drugs except when benefit outweighs risk of bleeding [30]. Most drug interactions affecting warfarin involve inhibition of the CYP450 enzymes. Broad-spectrum antibiotics also affect vitamin K production by intestinal flora in malnourished patients with limited stores. Chronic alcohol use can decrease activity of warfarin by increasing clearance, but the presence of concomitant liver disease can potentiate its effect. Patient education is essential to develop a diet with a relatively constant level of vitamin K and to identify foods rich in vitamin K [28].

Intracranial hemorrhage is the most feared bleeding associated with warfarin therapy. In the SPORTIF III and V clinical trials, warfarin was used for prevention of stroke in non-valvular atrial fibrillation (AF) patients and showed a rate of intracranial and subdural hematomas at 0.4%, and the rate of major bleeding was 2.5% per year [43, 44]. The DURAC trial study group in 1994 for patients with VTE concluded that 75% of INR values of their study cohort (1124 patients) were ≥2.0, and 58% were in the therapeutic range. There were eight patients with recurrent VTE (1.3 in 100 patient years; 95% CI, 0.2–1.2). Seventeen hemorrhagic events were recorded (2.8/100 patient years; 95% CI, 0.8–2.2), among which two were fatal (0.3/100 patient years; 95% CI, 0–0.4) [45]. When comparing low-dose warfarin to conventional dose of warfarin, there was no significant difference in frequency of overall bleeding between the two groups (OR, 1.3; 95% CI, 0.8–2.1), and the frequency of recurrent VTE was higher in low-dose warfarin group (OR, 2.8; 95% CI, 1.1–7) [46]. However, after conventional full-dose anticoagulation therapy for 6 months, when patients were followed with low-dose warfarin compared to placebo (PREVENT), 48% risk reduction of recurrent VTE was observed (OR, 0.36; 95% CI, 0.19–0.67) with no significant difference in major bleeding episodes [47]. In a recent meta-analysis of 11 clinical trials (41,015 patients treated for both VTE and AF), safety of warfarin in "high-risk" populations was compared. A significant association with all-cause bleeding and age>75 years (RR,1.62; 95%CI, 1.28–2.05), low body weight (RR, 1.2; 95%CI, 1.03–1.4), and those with impaired renal function (RR, 1.59; 95%CI, 1.3–1.94) was noted [48]. However, its use in patients with end-stage renal disease in a meta-analysis (56,146 patients

with ESRD and AF) showed no association with major bleeding (OR, 1.18; 95% CI, 0.82–1.69) or gastrointestinal bleeding (OR, 1.19; 95% CI, 0.81–1.76) [49].

Despite wide usage and sufficient data from clinical trials demonstrating efficacy for a variety of thrombotic and thromboembolic conditions, warfarin is becoming underutilized because its management is cumbersome for both patients and physicians. Besides hemorrhage, warfarin skin necrosis is the most serious adverse effect and is induced by a transient hypercoagulable state. It occurs with intake of warfarin in individuals with congenital or acquired protein C or S deficiency [50, 51]. Affected individuals develop skin lesions which begin as an erythematous macule and if left untreated progress to an indurated lesion before becoming necrotic.

The current guidelines for reversal established by the Ninth American College of Chest Physicians Conference on antithrombotic and thrombolytic therapy recommend [30]:

1. For patients with INR 4.5–10 and no evidence of bleeding, lower the dose or omit one or two doses as needed, monitor more frequently, and resume therapy at a lower dose when INR is in therapeutic range. Routine use of vitamin K is not recommended (Grade 2B).
2. For patients with INR >10 and no evidence of bleeding, oral vitamin K can be administered (Grade 2C).
3. In patients with major bleeding and elevated INR, hold warfarin and rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than fresh frozen plasma (Grade 2C).
4. Additional use of vitamin K (5–10 mg) administered by slow IV injection rather than reversal with coagulation factors alone is recommended (Grade 2C).

Oral vitamin K can also be used for reversal, as it was found to lower the INR rapidly in asymptomatic patients who have INR above therapeutic range [52, 53].

Direct Oral Anticoagulants

Several direct oral anticoagulants (DOACs) have been developed to overcome the limitations of heparin and coumadin. Among them, the oral direct thrombin inhibitor dabigatran etexilate (Pradaxa®) and the oral direct activated factor Xa inhibitors rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Lixiana®/Savaysa®) are currently approved for anticoagulation as prophylaxis and treatment of VTE, as well as prevention of stroke and embolic events in non-valvular atrial fibrillation.

Unlike VKA which has an indirect role in inhibition of factor synthesis, DOACs directly inhibit either thrombin or factor Xa. DOACs thus have a rapid onset and offset of action. All the DOAC agents are rapidly absorbed following oral administration and have a relatively short half-life (5–17 h). Table 21.2 illustrates the pharmacoki-

Table 21.2 Comparison of pharmacokinetics of DOAC agents [54]

DOAC	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Source	Synthetic	Synthetic	Synthetic	Synthetic
Target	Thrombin	FXa	FXa	FXa
Prodrug	Yes (etexilate)	No	No	No
Bioavailability (%)	6	80–100	50	62
T_{max}[a] (h)	0.5–2	2–4	3–4	1.5
Half-life (h)	14–17	5–13	12	6–11
Protein binding (%)	35	92–95	87	55
Renal excretion (%)	5	66	27	35
Biliary-fecal excretion (%)	95	34	56	62

[a]T_{max} time to reach maximum concentration (peak concentration), *FXa* factor Xa

Table 21.3 Summary of safety and efficacy of DOACs compared to warfarin from clinical randomized trials [67]

DOAC agent	Outcomes	Study population (*n*)	Relative effect (95% CI)
Dabigatran	All-cause mortality[a]	5107 (2 studies)	RR 1.0 (0.67–1.50)
	Recurrent VTE[a]	5107 (2 studies)	RR 1.12 (0.77–1.62)
	Major bleeding[a]	5107 (2 studies)	RR 0.73 (0.48–1.10)
Rivaroxaban	All-cause mortality[b]	8281 (2 studies)	RR 0.97 (0.73–1.27)
	Recurrent VTE[b]	8281 (2 studies)	RR 0.90 (0.68–1.20)
	Major bleeding[b]	8281 (2 studies)	RR 0.55 (0.38–0.81)[*]
Apixaban	All-cause mortality[c]	5365 (1 study)	RR 0.79 (0.53–1.19)
	Recurrent VTE[c]	5244 (1 study)	RR 0.84 (0.6–1.18)
	Major bleeding[c]	5365 (1 study)	RR 0.31 (0.17–0.55)[*]
Edoxaban	All-cause mortality[d]	8240 (1 study)	RR 1.05 (0.82–1.33)
	Recurrent VTE[d]	8240 (1 study)	RR 0.83 (0.57–1.21)
	Major bleeding[d]	8240 (1 study)	RR 0.85 (0.6–1.21)

[a]Combined analysis of Schulman et al. [59] (RE-COVER I) and Schulman et al. [68] (RE-COVER II)
[b]Combined analysis of Bauersachs et al. [69] (EINSTEIN-DVT) and Buller et al. [56] (EINSTEIN-PE) BY Prins et al. [70]
[c]Analysis from Agnelli et al. [58] (AMPLIFY)
[d]Analysis from Buller et al. [55] (Hokusai-VTE study)
[*]Statistically significant

netics of each of the DOAC agents. The disadvantages of dabigatran pharmacodynamics include low bioavailability (6%) despite the presence of prodrug etexilate to enhance its intestinal absorption, high renal clearance (85% of absorbed dose), and low metabolism (<10%, by glucuronidation). On the contrary, factor Xa inhibitors have a good oral bioavailability (>50%); lower renal clearance than dabigatran, although still significant (54–73% of absorbed dose); and high metabolism rate by mainly CYP3A4 activity (rivaroxaban), CYP3A4/CYP3A5 (apixaban), and hydrolysis (edoxaban) [54].

Since the recent shift to DOACs, four randomized clinical trials have been conducted to study the safety and efficacy of each of these agents compared with VKA therapy [55–59]. The DOACs have proven to be non-inferior to VKA in patients with venous thromboembolism (VTE) [60]. The risk of bleeding with DOACS, and particularly clinically relevant bleeding including intracranial bleeding, is less with DOACs than with VKA therapy. Dabigatran, rivaroxaban, and edoxaban tend to have higher GI bleeding compared to VKA for treatment of atrial fibrillation [61–63]. However this has not been the case in patients treated for VTE [64]. Also, the risk of bleeding may be lower with apixaban as compared with the other DOACs [65, 66]. On the other hand, the risk that a major bleeding will be fatal appears to be no higher than VKA therapy [60, 66]. Thus, based on its less bleeding tendency and greater patient convenience while providing similar or superior efficacy, DOACs are currently recommended as first choice of drugs in patients for initial and long-term treatment of VTE in patients without cancer [67] (Table 21.3).

Many patients tend to prefer DOAC over daily subcutaneous injections. DOACs however have a shorter half-life (<24 h) compared to VKA (36–42 h). Also, the anticoagulant effect declines 12–24 h after administration. Therefore, poor patient adherence to DOAC agents may leave them unprotected against VTE [71, 72]. A high level of patient compliance with these drugs is thus a must to demonstrate their efficacy. Laboratory monitoring of DOAC may help but is currently unavailable in most centers. Thus, methods like proper patient education, regular follow-up visits with physicians, and monitoring by pharmacists are necessary [73].

Close observation for food and drug interactions is necessary when initiating treatment with the DOACs or when there is change in concomitant medications as most of the patients involved are elderly with multiple comorbidities. It has

been suggested that rivaroxaban should be taken with food as there is a 39% decrease in absorption when administered without food. Also, administration of factor Xa inhibitors with P-glycoprotein, cytochrome P450 enzymes, or CYP3A4-associated drugs (azole antifungals, HIV antiproteases) is generally not recommended due to decreased activity of anticoagulation [74]. The administration of dabigatran with proton pump inhibitors decreases the absorption by 30%; however, no dose adjustment may be needed. Finally, all DOACs have pharmacodynamics correlated to antiplatelet agents and nonsteroidal anti-inflammatory drugs (NSAIDs). This is associated with increased bleeding risk and hence their combined use is discouraged.

An important advantage of DOACs is that the routine lab monitoring is not needed. This is advantageous for both patient convenience and satisfaction. However, this lack of routine monitoring could compromise assessment of anticoagulant adherence. Also, while routine monitoring is not required, physicians need to assess anticoagulation effect to make appropriate treatment decisions [75, 76]. This is especially the case in emergency trauma situations, urgent invasive procedures, major bleeding, drug overdose, renal failure, or liver failure. The activated partial thromboplastin time (aPTT) and prothrombin time (PT) are widely available tests with rapid turnaround times, but they have poor sensitivity and specificity and lack optimal dose-response relationships for monitoring DOACs. The qualitative assays can be used for monitoring but require special laboratories and thus have slower turnaround time.

The European Heart Rhythm Association (EHRA) guidelines recommend clinical assessment and non-coagulation monitoring every 1–6 months for patients taking DOACs but do not recommend any monitoring of coagulation assays [77]. The American College of Chest Physicians has not yet made a recommendation for DOAC monitoring [67, 78].

DOAC pharmacodynamics is highly dependent on renal function. Except for apixaban, these drugs are eliminated by renal clearance. Thus, the drug dosage needs to be significantly modified in case of renal impairment leading to increased bleeding risk. On the other hand, edoxaban plasma levels may be decreased with renal impairment and result in increased risk of ischemic stroke compared to warfarin [55]. Hence, creatinine clearance (CrCl) is an important measure which must be tested at initiation of treatment and at regular intervals afterward. Liver function test is another important parameter that requires frequent monitoring (Table 21.4).

Lack of availability of specific antidotes was one of the major drawbacks for DOACs initially. Recently, highly specific antidote such as idarucizumab, a humanized monoclonal antibody fragment that selectively binds dabigatran, has been approved in 2015 for clinical use in patients with fatal or uncontrolled bleeding. Idarucizumab also is useful for preprocedural anticoagulation management of dabigatran-treated patients as it provides rapid and sustainable reversibility within minutes [83]. The clinical safety and efficacy of idarucizumab are currently being studied in a Phase 3 of a trial enrolling 500 patients. Andexanet alfa is an inactive, recombinant factor Xa agent that binds factor Xa inhibitors, and ciraparantag is a synthetic agent designed to bind fractionated/unfractionated heparins and the currently used DOACs. Currently in Phase 2 clinical trials, ciraparantag (PER977) has demonstrated that a single bolus intravenous injection produces complete and sustained reversal (for 24 h) of edoxaban, 10–30 min after administration [84].

Also as all DOACs are renally excreted, adequate diuresis is another essential step in the management of drug overdose. As protein binding is low with dabigatran, hemodialysis can remove 50–60% of circulating drug. On the contrary, factor Xa inhibitors have high protein binding efficacy and hence dialysis may not help. In case of serious bleeding in a critical organ (intracerebral bleed), there is some evidence to support the role of activated prothrombin complex concentrate (aPCC) of 30–50 U/kg or nonactivated PCC at 50 U/kg to reverse anticoagulation [85]. However, with the recent development of specific reversal agents, the bleeding risk can be brought down further.

Table 21.4 Use of oral anticoagulants in special populations

	Apixaban	Rivaroxaban	Edoxaban	Warfarin
Renal impairment	Drug use recommended with CrCl <15 mL/min If S. creatinine >1.5 mg/dL: dose adjustment to 2.5 mg PO twice daily. (For non-valvular atrial fibrillation, no dose adjustment for venous thromboembolism) [79]	CrCl ≥51 mL/min: no dose adjustment needed. CrCl = 15–50 mL/min: 15 mg PO once daily with evening meal [80]	CrCl ≥51 mL/min: no dose adjustment needed. CrCl = 15–50 mL/min: 30 mg PO once daily	Drug use recommended even with severe renal impairment. No dosage adjustment is needed, as warfarin metabolism is unaffected [38]
		CrCl <15 mL/min: periodically assess renal function and adjust dose. Discontinue if patient develops acute renal failure [80]	CrCl <15 mL/min: drug use not recommended	
Hemodialysis	2.5 mg PO twice daily	Rivaroxaban is not expected to be removed by dialysis due to high protein binding	Total edoxaban exposure reduced by <7% during a 4-h dialysis session	
Hepatic impairment	Mild: no dosage adjustment needed	Mild: No adjustment needed, avoidance recommended	Mild: no dose adjustment needed	Warfarin metabolism may be increased with increased half-life; dosage adjustment is needed
	Moderate (child pugh B) Drug use not recommended			
	Severe (child pugh C) Drug use not recommended			
Geriatric	Drug concentration increased (≥65 years); however, no dose adjustment needed Avoid if CrCl <25 mL/min	Terminal half-life is increased (11–13 h) Dose reduced with CrCl, 30–50 mL/min Avoid completely if CrCl <30 mL/min or >95 mL/min[a]	Dose reduced with CrCl, 30–50 mL/min Avoid completely if CrCl <30 mL/min or >95 mL/min[a]	As age increases, lower dose of warfarin is sufficient for a therapeutic effect
Mechanical heart valves	Drug use not recommended			Maintain target INR, 2.5–3.5. Aspirin PO 75–100 mg daily is recommended
Obesity/BMI	Concentration of the drug increased in patients <50 kg compared to 65–85 kg. Concentration further decreased ≥120 kg body weight. However, dose adjustments are not needed solely based on weight	Extremes in body weight: <50 kg and >120 kg did not influence rivaroxaban exposure	Avoid use in patients with BMI >40 kg/m^2 or weight >120 kg	BMI impacts warfarin volume of distribution and clearance For each point increase in BMI, the average weekly therapeutic dose should be increased by 0.69 mg [37] Obese patients at significantly lower risk of bleeding relative to nonobese patients [36]
			Drug exposure increased by 13% in patients with low body weight (55 kg) compared to high body weight (84 kg)	

(continued)

Table 21.4 (continued)

	Apixaban	Rivaroxaban	Edoxaban	Warfarin
Pregnancy	Category B (no risk noted in animal studies, insufficient human studies)	Category C (adverse effect on fetus in animal studies)	Category C (adverse effect on fetus in animal studies)	Category X (fetal anomalies noted in animals/humans)
	Use drug during pregnancy only if the potential benefit justifies the potential risk to mother and fetus. Treatment likely to increase risk of bleeding [81]			Recognized teratogen If potential benefit justifies risk, used after 13th week and switched to LMWH close to delivery
Breast feeding	Not recommended. If anticoagulation is necessary in a nursing women, the American Academy of Pediatrics (AAP) considers warfarin to be used, as it is usually compatible with breastfeeding			Recommended for use as drug is not excreted in breast milk
Children/infant	Safety and efficacy have not yet been established for these agents			Avoid in neonates and infants <4 months age

[a]As per the American beer criteria guidelines [82]

Switching Between Anticoagulants

An appropriate INR (≥2) is necessary when switching from DOACs to VKA. It may take 5–10 days before this INR in therapeutic range is obtained. Therefore, they need to be administered concomitantly before complete switching. Close monitoring during the first months is thus recommended. When switching from VKA to DOAC, VKA should be discontinued and DOAC started when INR ≤2.5 [77].

When switching from a parenteral anticoagulant to DOAC, discontinue the parenteral and start DOAC 0–2 h before the next scheduled dose of parenteral LMWH. For transition from DOAC to parenteral anticoagulant, the first dose of parenteral is recommended at the time of next dose of DOAC intake.

Patients Undergoing Surgery or Other Invasive Procedures

Approximately 20–25% patients on DOAC require temporary cessation of anticoagulation for surgery or intervention [86, 87] (Table 21.5).

1. For procedures with low-risk bleeding in patients with normal renal function, it is recommended to discontinue DOACs at least 24 h before elective procedure [85].
2. For procedures with high-risk bleeding and normal renal function, discontinue DOAC at least 48 h before elective procedure.
3. In patients with impaired renal function, the interval needs to increase and is 24 to >48 h in low risk and 48 to >96 h in high risk.

DOACs can be resumed 6–8 h after procedures with immediate and complete hemostasis. Safety of anticoagulation with DOACs was improved; however, the efficacy remained the same when an appropriate first dose of anticoagulation is given after at least 6 h of surgery [88].

Ongoing Trials and Future Directions

The current recommendations stated above are not based on high-quality (Grade 1A) evidence. This highlights the importance for further research to guide VTE treatment decision and choice of anticoagulation. Upcoming clinical trials including VERDICT comparing apixaban with current standard therapy and RAMBLE trial comparing apixaban with rivaroxaban in VTE will further enhance our understanding and help with decision-making.

Several other anticoagulants are currently under development including factor VIII inhibitors,

Table 21.5 Direct oral anticoagulants: management of special situations [89]

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Preoperative management	Low risk of bleeding: Discontinue at least 24 h prior to intervention Moderate/high risk of bleeding: discontinue at least 48 h prior to intervention[b]	Discontinue at least 24 h prior to surgery/ intervention	Discontinue at least 24 h before surgery	Discontinue 1–2 days (CrCl[a] ≥50 mL/min) or 3–5 days (CrCl[a] ≤50 mL/min) prior to intervention. For emergency surgery/ urgent procedure, idarucizumab should be considered
Bridging	Bridging anticoagulant is generally not required if temporarily stopped for an intervention	Administer a parenteral anticoagulant and then switch to oral rivaroxaban	Administer a parenteral anticoagulant to switch to oral edoxaban	Consider another anticoagulant and restart dabigatran as soon as medically possible
Restarting DOAC	Can be restarted as soon as adequate hemostasis is achieved after procedure			Restart as soon as medically possible or 24 h after idarucizumab reversal
Red flags	Premature discontinuation increases risk of thrombotic events		Premature discontinuation increases risk of ischemic events	Premature discontinuation increases risk of thrombotic events
	Epidural/spinal hematomas may occur in patients receiving neuraxial anesthesia or spinal puncture			
	Intramuscular injections of other medications to be avoided, as there is risk of bleeding, bruising, or hematoma formation			

[a]*CrCl* creatinine clearance
[b]If surgery cannot be delayed, the risk of bleeding should be weighed against the urgency of the intervention

factor IXa inhibitors, factor XI inhibitors, factor XIIa inhibitors, thrombomodulin, polyphosphate inhibitors, protein disulfide isomerase inhibitors, and protease-activated receptor-1 antagonists.

Also, clinical development for additional anti-factor Xa-specific anticoagulant reversal agents is ongoing and may help take care of the main disadvantage of DOACs. Also, their role in the management of emergency bleeding situations and invasive procedures may become better defined. Continued better understanding of platelet aggregation and coagulation pathway of blood continues, and this knowledge can help enhance the search for better targets and safer, highly potent drug individualized for patient use.

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Superficial Thrombophlebitis

22

Anil Hingorani and Enrico Ascher

Clinical Pearls

1. Superficial thrombophlebitis affecting varicose vein tributaries can be treated with NSAIDS and warm compresses.
2. Superficial thrombophlebitis affecting the saphenous veins should be treated with prophylactic dose of anticoagulation for 6 weeks to decrease risk of DVT.
3. Migratory thrombophlebitis with no precipitating factor warrants a work-up for malignancy.

Introduction

Although superficial venous thrombophlebitis (SVT) is a relatively common disorder with a significant incidence of recurrence and has potential morbidity from extension and pulmonary embolism (PE), SVT has been considered the stepchild of deep venous thrombosis (DVT) and received limited attention in the literature. Acute SVT occurs in approximately 125,000 people in the United States per year [1]. However, the actual incidence of SVT is most likely far greater as these reported statistics may be outdated and many cases go unreported. Traditional teaching suggests that SVT is a self-limiting process of little consequence and small risk leading some physicians to dismiss these patients with the clinical diagnosis of SVT and to treat them with "benign neglect." In an attempt to dispel this misconception, this chapter will examine the more current data regarding SVT and its treatment.

Clinical Presentation

Approximately 35–46% of patients diagnosed with SVT are males with an average age of 54 years old, while the average age for females is about 58 years old [2, 3]. The most frequent predisposing risk factor for SVT is the presence of varicose veins, which occurs in 62% of patients. Other factors associated with SVT include age >60 years old, obesity, tobacco use, and history of DVT or SVT. Factors associated with extension of SVT include age >60 years old, male sex, and history of DVT.

The physical diagnosis of SVT is based on the presence of erythema and tenderness in the distribution of the superficial veins with the thrombosis identified by a palpable cord. Pain and warmth are clinically evident, and significant swelling may be present even without DVT. From time to time, a patient may present with erythema, pain,

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and tenderness as a streak along the leg with a duplex ultrasound scan revealing no DVT or SVT. In these patients, the diagnosis of cellulitis or lymphangitis needs to be considered.

Etiology

The tenet that blood flow changes, changes in the vessel walls and changes in the characteristics of the flow of blood, as cited by Virchow over 100 years ago, is recognized to play a role in the etiology of thrombosis. While stasis and trauma of the endothelium have been cited as a cause of SVT, a hypercoagulable state associated with SVT has largely been unexplored. Furthermore, since the DVT which occurs in association with SVT is often found to be noncontiguous with the SVT [2, 3], the presumed mechanism of DVT by direct extension of thrombosis from the superficial venous system to the deep venous system needs to be questioned, and systemic factors in the pathophysiology of SVT should be explored.

In order to determine whether a hypercoagulable state contributes to the development of SVT, the prevalence of deficient levels of anticoagulants was measured in a population of patients with acute SVT [4]. Twenty-nine patients with SVT were entered into the study. All patients had duplex ultrasound scans performed on both the superficial and deep venous systems. Patients solely with SVT were treated with nonsteroidal anti-inflammatory drugs, while those with DVT were treated with heparin and warfarin. All patients had a coagulation profile performed that included (1) protein C antigen and activity, (2) activated protein C (APC) resistance, (3) protein S antigen and activity, (4) antithrombin III (AT III), and (5) lupus-type anticoagulant. Twelve patients (41%) were found to have abnormal results consistent with a hypercoagulable state. Five of the patients (38%) with combined SVT and DVT and seven of the patients (44%) with SVT alone were found to be hypercoagulable. Four patients had decreased levels of AT III only, and four patients had APC resistance identified. 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 [5]. These findings suggest that patients with SVT are at an increased risk of having an underlying hypercoagulable state.

Pathology

While a great deal of literature exists describing the various changes that take place in the leukocyte-vessel wall interactions, cytokines/chemokines and various other factors involved with the development and resolution of DVT, data investigating the changes involved with SVT were not identified. Although some authors have alluded that the underlying pathology of SVT with DVT may be analogous, to date, this viewpoint remains mostly unsupported.

While the most common site of SVT is the GSV, other locations than the GSV and etiologies of SVT are discussed below.

Trauma

The most common source of trauma associated with SVT is an intravenous cannula. This SVT may result in erythema, warmth, and tenderness along its course. Treatment starts with removal of the cannula and warm compresses. The resultant lump may persist for months notwithstanding this treatment.

Suppurative

Suppurative SVT (SSVT) is also associated with the use of an intravenous cannula; however, SSVT may be lethal due to its association with septicemia. The associated signs and symptoms

of SSVT include pus at an intravenous site, fever, leukocytosis, and local intense pain [6]. Treatment begins with removal of the foreign body and intravenous antibiotics. Excision of the vein is rarely needed to clear infection.

Migratory

Migratory thrombophlebitis was first described by Jadioux in 1845 [7] as an entity characterized by repeated thrombosis developing in superficial veins at varying sites, but most commonly in the lower extremity. This entity may be associated with carcinoma and may precede diagnosis of the carcinoma by several years. Consequently, a work-up for occult malignancy may, in fact, be warranted when the diagnosis of migratory thrombophlebitis is made.

Mondor's Disease

Mondor's disease is defined as thrombophlebitis of the thoracoepigastric vein of the breast and chest wall. This diagnosis is thought to be associated with breast carcinoma or hypercoagulable state, although cases have been reported with no identifiable cause [8]. The term has also been applied to SVT of the dorsal vein of the penis [9]. Treatment consists of conservative measures with warm compresses and nonsteroidal anti-inflammatory drugs.

Small Saphenous Vein (SSV) SVT

While the bulk of attention has been focused on SVT of the great saphenous vein (GSV), SVT of the SSV is also of clinical importance. SSV SVT had been demonstrated to progress into popliteal DVT. In a group of 56 patients with SSV SVT, 16% suffered from PE or DVT [2]. Therefore, patients with SSV SVT must be treated similarly to those diagnosed with GSV SVT, employing the same careful duplex examination, follow-up, and anticoagulation or ligation if the SVT approaches the popliteal vein.

SVT with Varicose Vein Disease

Only 3–20% of SVT patients with varicose veins will develop DVT, as compared to 44–60% without varicose veins [10, 11, 21]. Therefore, patients with varicose veins may have a different pathophysiology as compared to 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 the SVT patients with and without associated varicose veins should be thought of as separate classifications remains ambiguous.

Conversely, addressing those patients with SVT involving only varicose veins is essential. This type of SVT may remain localized to the cluster of tributary varicosities or may, from time to time, extend into GSV [2]. SVT of varicose veins themselves may occur without antecedent trauma. SVT is frequently found in varicose veins surrounding venous stasis ulcers. This diagnosis should be confirmed by duplex ultrasound scan as the degree of the SVT may be much greater than that based solely on clinical examination. Treatment consists of conservative therapy of warm compresses and nonsteroidal anti-inflammatory drugs.

Upper Extremity SVT

Although very little appears in the literature, upper extremity SVT is believed to be the result of intravenous cannulation and infusion of caustic substances that damage the endothelium. Interestingly, the extension of upper extremity SVT into upper extremity DVT or PE is a very rare occurrence as compared to lower extremity SVT 12. Initial treatment of upper extremity SVT is catheter removal followed by conservative measures, such as warm compresses and nonsteroidal anti-inflammatory medications. While there is relatively little literature that examines treatment of catheter-associated SVT, recent data has suggested removal of the catheter and

conservative treatment with warm compresses and nonsteroidal drugs if symptomatic.

Diagnosis

It is supposed by a few authors that SVT is a benign common process that requires no further work-up unless symptoms fail to resolve quickly on their own [13]. This belief is despite the findings that indicate DVT associated with SVT may not be clinically apparent [2].

Duplex ultrasound scanning has become the initial test of choice for the diagnosis of DVT and the evaluation of SVT since first introduced by Talbot in 1982. The availability of reliable duplex ultrasonography of the deep and superficial venous systems has made routine determination of the location and incidence of DVT in association with SVT accurate and practical. Furthermore, the extent of involvement of the deep and superficial venous systems can be more accurately assessed utilizing this modality as routine clinical examination may not be able to precisely evaluate the proximal extent of involvement of the deep or superficial systems. Duplex ultrasound imaging also offers the advantage of being inexpensive and noninvasive and can be repeated for follow-up examination. As venography may contribute to the onset of phlebitis and duplex imaging affords an accurate diagnosis, venography is not recommended as an initial diagnostic modality. Duplex imaging of patients with SVT has revealed the concomitant DVT to range from 5 to 40% [2, 14–16, 22]. It is important to note that up to 25% of these patients' DVTs may not be contiguous with the SVT or may be even in the contralateral lower extremity [2].

Treatment

The location of the SVT determines the course of treatment. The therapy may be altered should the SVT involve tributaries of the GSV, distal GSV or GSV of the proximal thigh, and SSV near the junction with the popliteal vein. Traditional treatment for SVT localized in tributaries of the GSV and the distal GSV has consisted of ambulation, warm soaks, and nonsteroidal anti-inflammatory drugs [1, 17, 18]. Surgical excision may play a role in the rare case of recurrent bouts of thrombophlebitis in spite of maximal medical management. However, this type of management does not address the possibilities of clot extension or attendant DVT associated with proximal GSV SVT.

The progression of isolated SVT to DVT has been evaluated [19]. In one study, patients with thrombosis isolated to the lower extremity superficial veins by duplex ultrasound examination were assessed by follow-up duplex ultrasonography to determine the incidence of disease progression into the deep veins. Initial and follow-up duplex scans evaluated the femoropopliteal and deep calf veins in their entirety with follow-up studies performed at an average of 6.3 days. Two hundred sixty-three patients were identified with isolated superficial venous thrombosis. Thirty (11%) patients had documented progression to deep venous involvement. The most common site of deep vein involvement was the progression of disease from the GSV in the thigh into the common femoral vein (21 patients), with 18 of these extensions noted to be nonocclusive and 12 having a free-floating component. Three patients had extended above-knee saphenous vein thrombi through thigh perforators to occlude the femoral vein in the thigh. Three patients had extended below-knee saphenous SVT into the popliteal vein, and three patients had extended below-knee thrombi into the tibioperoneal veins with calf perforators. At the time of the follow-up examination, all 30 patients were being treated without anticoagulation. As a result of this type of experience, we recommend repeat duplex scanning for SVT of the GSV or SSV after 48 h to assess for progression [20].

For SVT within 1 cm of the saphenofemoral junction, management with high saphenous ligation with or without saphenous vein stripping has been suggested to be the treatment of choice due to the recognized potential for extension into the deep system and embolization [21–25]. In a

series of 43 patients who underwent ligation of the saphenofemoral junction with and without local CFV thrombectomy and stripping of the GSV, 2 patients had postoperative contralateral DVT, 1 of whom had a PE [3]. Eighty-six percent of the patients were discharged within 3 days. Four patients developed a wound cellulitis that were treated with antibiotics. One patient had a wound hematoma requiring no treatment. While satisfactory results were noted in these instances, several issues still remain unresolved. The question of whether or not to strip the GSV in addition to high ligation is not clearly addressed, although these patients do seem to experience less pain once the SVT is removed. Ligation was initially proposed to avert the development of DVT by preventing extension via the saphenofemoral junction. Since issues of noncontiguous DVT and post-ligation DVT with PE are not addressed by this therapy, alternative treatment options need to be explored.

A prospective nonrandomized study was conducted to evaluate the efficacy of a nonoperative approach of anticoagulation therapy to manage saphenofemoral junction thrombophlebitis (SFJT) [22]. Over a 2-year period between January 1993 and January 1995, 20 consecutive patients with SFJT were entered into the study. These patients were hospitalized and given a full course of heparin treatment. Duplex ultrasonography was performed before admission, both to establish the diagnosis and to evaluate the deep venous system. Two to 4 days after admission, a follow-up duplex ultrasound scan was performed to assess resolution of SFJT and to reexamine the deep venous system. Patients with SFJT alone and resolution of SFJT as documented by duplex ultrasound scans were maintained on warfarin for 6 weeks. Those patients with SFJT and DVT were maintained on warfarin for 6 months. The incidence of concurrent DVT and its location were noted. The efficacy of anticoagulation therapy was evaluated by measuring SFJT resolution, recurrent episodes of SFJT, and occurrence of PE.

A 40% incidence (8 of 20 patients) of concurrent DVT with SFJT was found. Of these eight patients, four had unilateral DVT, two had bilateral DVT, and two had development of DVT with anticoagulation. DVT was contiguous with SFJT in five patients and noncontiguous in three patients. Seven out of 13 duplex ultrasound scans obtained at 2–8 months follow-up demonstrated partial resolution of SFJT, five had complete resolution, and one demonstrated no resolution. There were no episodes of PE, recurrences, nor anticoagulation complications at maximum follow-up of 14 months. Anticoagulation therapy to manage SFJT was effective in achieving resolution, preventing recurrence, and preventing PE within the follow-up period. The high incidence of DVT associated with SFJT suggests that careful evaluation of the deep venous system during the course of management is necessary [26]. Note that the short-term effect of anticoagulation on progression to DVT or long-term effect on local recurrence of SVT had not been evaluated.

When comparing these two types of therapy, one group suggested that high ligation for SFJT would be more cost-effective than systemic anticoagulation for 6 months [3]. The question as to whether patients with SVT need to be treated for a 6-month period remains uncertain. Our treatment course of anticoagulation spans a period of 6 weeks and, over the last 20 years, we have noted no incidence of PE or complications of anticoagulation. Furthermore, significant cost savings could be realized if the low-molecular-weight heparins or the directoral anticoagulants are used in an outpatient setting instead of unfractionated intravenous heparin. In addition, since the surgical options do not address the hypercoagulable state of these patients and may create injury to the endothelium at the saphenofemoral junction, the surgical options seem to be less appealing, at least on a theoretical basis.

This issue of anticoagulation versus surgical therapy was addressed in a prospective study consisting of 444 patients randomized to six different treatment plans (compression only, early surgery [with and without stripping], low-dose

subcutaneous heparin, low-molecular-weight heparin, and oral anticoagulant treatment) in the management of SVT [27]. Patients presenting with SVT and large varicose veins without any suspected/documented systemic disorder were included in this study. The criteria for inclusion were as follows: venous incompetence (by duplex); a tender, indurated cord along a superficial vein; and redness and heat in the affected area. Exclusion criteria were obesity, cardiovascular or neoplastic diseases, non-ambulatory status, bone/joint disease, problems requiring immobilization, age >70 years, and patients with SVT without varicose veins. Color duplex ultrasound scans were used to detect concomitant DVT and to evaluate the extension or reduction of SVT at 3 and 6 months.

The incidence of SVT extension was higher in the elastic compression and in the saphenous ligation groups ($p < 0.05$) after 3 and 6 months. No significant difference in DVT incidence existed at 3 months among the treatment groups. Stripping of the affected veins was associated with the lowest incidence of thrombus extension. The cost for compression solely was found to be the lowest, and the treatment arm including LMWH was found to be the most expensive. The highest social cost (lost working days, inactivity) was observed in subjects treated with stockings alone.

However, careful examination reveals that the results of this study are difficult to evaluate, as the details of the treatment protocols were not specifically identified. Furthermore, the exclusion criteria would eliminate many of the patients diagnosed with SVT in a clinical practice and the inclusion of almost any patient presenting with SVT, regardless of its location makes the remaining groups quite variable.

In an attempt to further clarify some of these issues, one group attempted to perform a meta-analysis of surgical versus medical therapy for isolated above-knee SVT. However, a formal meta-analysis was not possible due to the paucity of comparable data between the two groups. This review suggested that medical management with anticoagulants is somewhat superior for minimizing complications and preventing subsequent DVT and PE. Ligation with stripping allows superior symptomatic relief from pain [28]. Based on these data, the authors suggest that anticoagulation is appropriate in patients without contraindication.

In a randomized, double-blind trial, 3002 patients with acute lower extremity superficial thrombophlebitis received either fondaparinux, administered subcutaneously at a dose of 2.5 mg once daily (prophylactic dose), or placebo for 45 days. All patients were diagnosed with duplex scans. Only 7% of these cases did not involve the GSV. After a follow-up of 77 days, the rate of pulmonary embolism or deep-vein thrombosis was reduced by 85% in the fondaparinux group as compared to the placebo group. Fondaparinux also decreased the rate of extension to the saphenofemoral junction by 90%. While these data demonstrated the safety and efficacy of fondaparinux for treatment of acute SVT, direct oral anticoagulants would be probably be used as an alternative today. While this study examined some important issues, the study did not stratify which specific of location of SVTs may benefit from this type of anticoagulation [29]. Our current treatment algorithm for SVT is illustrated in Fig. 22.1.

Although proximal thigh GSV SVT and SSV SVT approaching the popliteal vein occurs not infrequently, the best treatment regimen based on its underlying pathophysiology and resolution rate remains controversial. More recent investigations do offer some guidelines. While anticoagulation has become the mainstay of treatment for SVT involving these two locations, care should be exercised by the physician in diagnosing SVT to avoid the complications that may ensue due to the nature of the SVT. Further examination of the unresolved issues involving SVT is fundamental.

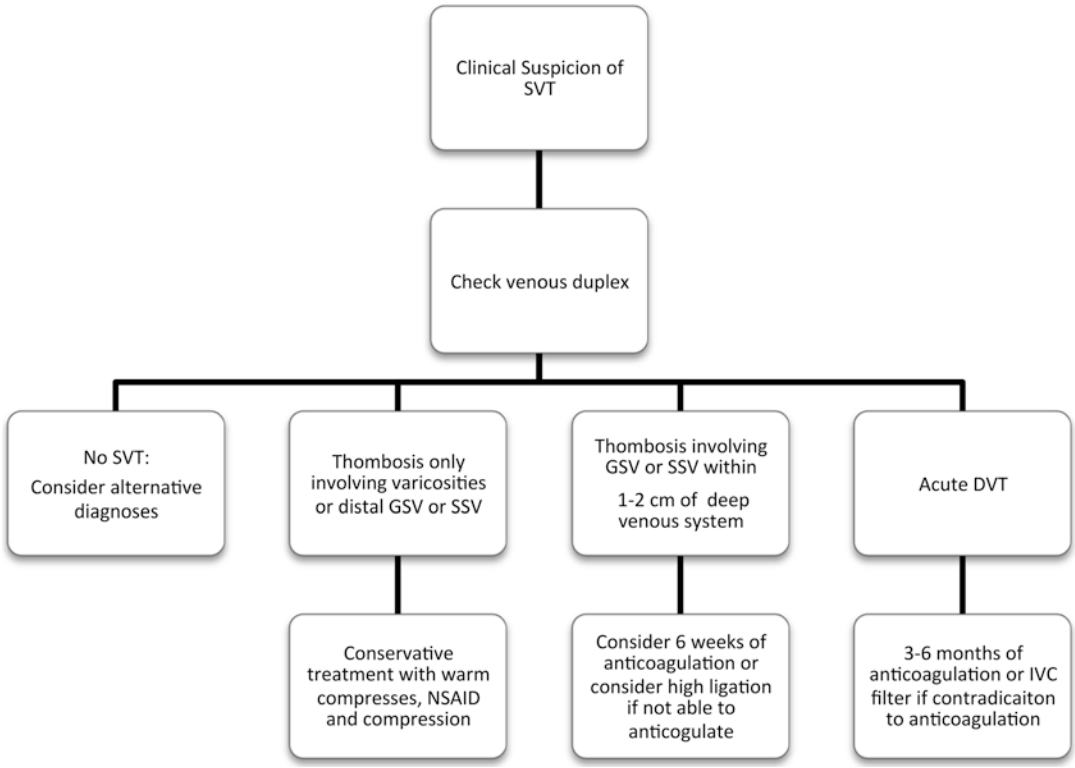

Fig. 22.1 Algorithm for treatment of SVT

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Anticoagulation for Proximal Deep Vein Thrombosis

23

Alfred Ian Lee and Eun-Ju Lee

Clinical Pearls

1. Proximal lower extremity DVT should be treated with at least 3 months of anticoagulation with consideration for extended therapy for unprovoked DVTs with high risk of recurrence and low risk of bleeding.
2. Low-molecular weight heparin is the agent of choice for anticoagulation in cancer-associated DVT.
3. Older age, male sex, and elevated D-dimer after initial anticoagulation are risk factors associated with increased recurrence of VTE based on multiple risk models for prediction.

Background

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolus (PE), affects an estimated 1–2 of 1000 individuals per year. Incidence of first VTE is similar among men and women, and rates in both genders rise significantly with advancing age [1–4]. Ethnicity impacts VTE risk, for unclear reasons; Asians, Pacific Islanders, and Hispanics have a lower incidence of VTE compared to Caucasians, while African–Americans have the highest rates of VTE and subsequent mortality [5, 6].

VTE is a significant public health concern, with a 30-day case fatality of 6–14% and a 1-year mortality of up to 30% [1, 3, 6]. DVT is associated with substantial morbidity, as thrombosis-induced damage to venous valves leads to postthrombotic syndrome (PTS) in 20–50% of patients. Risk factors for PTS include recurrent DVT and subtherapeutic anticoagulation, with symptoms ranging from mild leg swelling to painful, non-healing venous ulcers [7–10]. PTS increases healthcare expenditure and decreases patient-reported quality of life [11, 12]. These adverse consequences of VTE emphasize the importance of optimizing treatment for and preventing recurrences of VTE.

Proximal DVT occurs in veins proximal to and including the popliteal vein (i.e., the iliac, femoral, and popliteal veins). Isolated distal DVT (IDDVT) occurs in the infra-popliteal veins, including veins of the deep (anterior tibial, posterior tibial, peroneal) and muscular (gastrocnemius and soleus) calf. The prognosis and treatment of IDDVT differ from that of proximal

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Table 23.1 Provoking factors for VTE

Strong risk factors
• Recent surgery
• Recent trauma or fracture
• Immobilization/bedbound >1 week
Minor risk factors
• Estrogen therapy
• Pregnancy or within 3 months postpartum
• Prolonged travel

Adapted using information from [30, 49, 103]

DVT, with the former demonstrating lower risks of proximal extension, PE, recurrent VTE, and PTS in general [13–17]. Because of the strong association of proximal DVT with PE, anticoagulation management in both conditions is similar and will be the focus of the remainder of this chapter. Thrombolysis in treatment of proximal DVT will not be addressed in detail here.

VTE events may be categorized as provoked or unprovoked. Provoked DVT and PE occur because of specific factors that transiently and reversibly increase thrombotic risk, while VTEs arising in the absence of strong, identifiable risk factors are considered unprovoked or idiopathic (Table 23.1). Treatment considerations and long-term clinical outcomes vary substantially between provoked and unprovoked VTE (Fig. 23.1).

The Role of Anticoagulation

The goals of anticoagulation are twofold: first, to stop the acute thrombotic period to block extension of the existing thrombus and improve symptoms and, second, to prevent the formation of new clots outside the initial thrombotic phase. Active treatment, which addresses the first goal, describes the time period from initiation of anticoagulation to inactivation of the acute thrombus, during which time pharmacologic anticoagulation protects from further clot deposition while endogenous systems stabilize and dissolve the existing thrombus [18]. This is a slow process, with about 50% of patients demonstrating persistent venous impairment at 6 months post-diagnosis and treatment. Surgically provoked clots resolve faster, while patients with cancer-associated thrombosis and those with larger clot burdens have slower clot dissolution [15, 19]. Following completion of active anticoagulant treatment, secondary prevention in the form of extended anticoagulation may follow if the risk of recurrent thrombosis after discontinuation of anticoagulation is deemed sufficiently high.

In patients unable to safely receive systemic anticoagulation, including those with absolute contraindications such as active hemorrhage (involving the central nervous system, gastrointestinal tract, or retroperitoneum), massive hemoptysis, severe thrombocytopenia, head trauma, or a history of life-threatening bleeding while on anticoagulation, inferior vena cava (IVC) filters are an alternative therapeutic consideration [20]. IVC filters may prevent PE and decrease short-term mortality but are associated with increased risks of recurrent DVT and long-term complications including filter fracture and migration and IVC thrombosis [21–23]. If placed, retrievable filters should be removed after anticoagulation can be safely initiated [23].

The choice of anticoagulant agent is guided by numerous clinical parameters including age, renal function, coexisting medical conditions (e.g., cancer, pregnancy), and patient preference. Unfractionated heparin (UFH), low-molecular weight heparin (LMWH), vitamin K antagonists (VKA), and direct oral anticoagulants (DOAC) are all acceptable treatment options; descriptions and dosing of these anticoagulants are summarized in Tables 23.2 and 23.3. In the acute setting, hemodynamically stable patients, who are reliable, in secure social situations, and without severe symptoms, renal impairment, or high bleeding risk, may be treated safely on an outpatient basis [24]. Those with massive DVT (as defined by limb ischemia, thrombosis of the iliofemoral veins or IVC, or swelling of the entire limb), concomitant symptomatic PE, a high bleeding risk, or other select comorbidities limiting safe administration of anticoagulant therapy in the outpatient setting are suitable candidates for hospitalization [25].

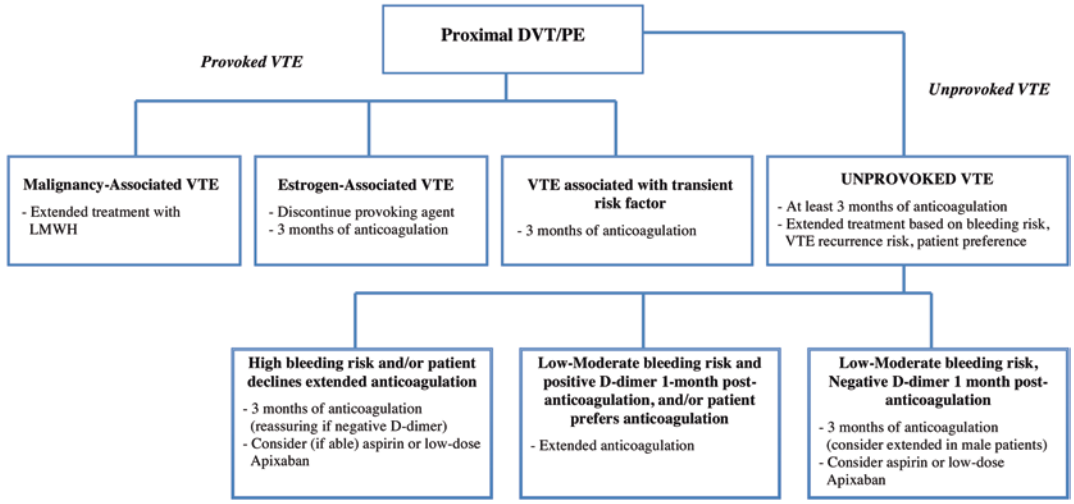

Fig. 23.1 Algorithm for treatment of VTE

Anticoagulation for Proximal DVT Due to a Strong Provoking Risk Factor

VTE caused by a reversible risk factor has a lower risk of recurrence than unprovoked VTE. The actual risk of clot recurrence varies according to the type of provoking factor. Patients with VTE after major surgery or trauma carry a very low risk of recurrence, with less than 1% of such patients experiencing a recurrent thrombotic event in the year following completion of anticoagulation and 3% having recurrent thrombosis at 5 years [26–28]. Based on these numbers, patients with a proximal DVT due to a "strong" provoking risk factor such as surgery, trauma, or profound immobilization are anticoagulated for a defined period of 3 months (Fig. 23.1) [29, 30]. The duration of anticoagulation in such patients is generally independent of any additional factors, including body mass index, patient comorbidities, or massive or life-threatening VTE. An exception is DVT patients with persistence of an otherwise reversible major thrombotic risk factor, in whom extended anticoagulation may be considered as long as the risk factor remains [31]. Patients with DVT arising in the context of spinal cord injury are usually given therapeutic anticoagulation for at least 3–6 months, with consideration of prophylactic-dose anticoagulation afterwards [32].

Anticoagulation for Proximal DVT Due to a Minor Provoking Risk Factor

Patients with VTE associated with a minor, non-surgical thrombotic risk factor such as exogenous estrogen exposure or prolonged travel have a higher risk of recurrent thrombosis (6–8% clot recurrence at 1 year, 15% at 5 years) than those with VTE due to a strong thrombotic risk factor [26–28]. Because the recurrence rates for DVT and PE due to minor thrombotic risk factors are still lower than those observed for unprovoked thrombosis, such patients are usually anticoagulated for 3 months [30]. In many cases, however, additional factors may weigh into this decision, including age-appropriate and symptom-directed cancer screening, D-dimer testing, gender, thrombophilia testing, and thrombotic risk recurrence scores, like patients with unprovoked VTE (Fig. 23.1 and discussed further below).

DVT Associated with Exogenous Estrogen

Combined oral contraceptive pills (OCP), hormone replacement therapy (HRT), and selective estrogen receptor modulators (SERM) are associated with a two- to fourfold increased risk of

Table 23.2 Common anticoagulation agents for outpatient VTE treatment

Anticoagulant	Mechanism of action	Half-life (time to peak)[a]	FDA approved indications	Specific reversal agent
Dabigatran (Pradaxa®)	Direct thrombin inhibitor	14–17 h (2–4 h)	• Stroke prevention in non-valvular atrial fibrillation • Acute and extended treatment of DVT/PE[b]	Idarucizumab (Praxbind®)
Rivaroxaban (Xarelto®)	Factor Xa inhibitor	7–11 h (2–4 h)	• Stroke prevention in non-valvular atrial fibrillation • Acute and extended treatment of DVT/PE • DVT prophylaxis post hip/knee surgery	*Andexanet alfa*[c]
Apixaban (Eliquis®)	Factor Xa inhibitor	8–15 h (0.5–2 h)	• Stroke prevention in non-valvular atrial fibrillation • Acute and extended treatment of DVT/PE • DVT prophylaxis post hip/knee surgery	*Andexanet alfa*[b]
Edoxaban (Savaysa®)	Factor Xa inhibitor	10–12 h (1–2 h)	• Stroke prevention in non-valvular atrial fibrillation • Treatment of DVT/PE acute	
Warfarin (Coumadin®)	Vitamin K antagonist	2–5 days[d] (72–96 h)[e]	• Prophylaxis and acute and extended treatment of DVT/PE • Prophylaxis for thromboembolic complications associated with atrial fibrillation, cardiac valve replacement • Post myocardial infarction	Vitamin K, prothrombin complex concentrate, fresh frozen plasma
Enoxaparin (Lovenox®)	Binds to antithrombin leading to FXa, FII inactivation[f]	4.5–7 h (3–5 h)	• DVT prophylaxis in abdominal and orthopedic surgeries or in mobility limited hospitalized patients during acute illness • Treatment of DVT/PE • Unstable angina, non Q wave myocardial infarction • Treatment of ST-elevation myocardial infarction	Protamine sulfate (reverses about 60% of the anti-Xa activity) [131]

[a]Half-life values in non-elderly patients with intact renal function are shown
[b]Acute: initial 3–6 months of anticoagulation for diagnosed VTE; extended, secondary prevention after acute treatment for VTE
[c]Not yet FDA approved, but promising results have been demonstrated in healthy, older adults [132]
[d]Duration of warfarin effect 2–5 days, effective half-life 20–60 h
[e]Time to peak of the anticoagulant effect is modulated by the long half-lives of prothrombin and FX, increases in INR can be seen within 24 h due to the short half-life of FVII
[f]FII inhibited to a far lesser degree than FXa, degree of FII inhibition varies by LMWH formulation

thrombosis [33–37]. Such hormone exposure modulates levels of fibrinogen, antithrombin, proteins C and S, and numerous coagulation factors (including factors II, VII, and VIII), leading to an increased propensity toward thrombosis [34, 38–40]. For combined OCPs, thrombotic risk varies according to the specific types and doses of estrogen and progesterone components,

Table 23.3 Anticoagulant dosing for VTE treatment

Anticoagulant	Dosing for acute treatment	Dosing for extended treatment
Dabigatran (Pradaxa®)	• Initial treatment with a parenteral anticoagulant (LMWH, UFH) for 5–10 days • CrCl >30 mL/min: 150 mg twice daily • CrCl <30 mL/min: contraindicated	• CrCl >30 mL/min: 150 mg twice daily • CrCl <30 mL/min: contraindicated
Rivaroxaban (Xarelto®)	• CrCl >30 mL/min: 15 mg twice daily with food × 21 days, then 20 mg daily with food • CrCl <30 mL/min: contraindicated	• CrCl >30 mL/min: 20 mg daily with food • CrCl <30 mL/min: contraindicated
Apixaban (Eliquis®)	• 10 mg twice daily × 7 days, then 5 mg twice daily[a]	• 2.5 mg twice daily[a]
Edoxaban (Savaysa®)	• Initial treatment with a parenteral anticoagulant (LMWH, UFH) for 5–10 days • CrCl >50 mL/min: 60 mg daily • CrCl 15–50 mL/min or weight ≤60 kg: 30 mg daily	*Not applicable*
Warfarin (Coumadin®)	• Overlap with LMWH or UFH for 4–5 days *and* until attainment of target INR • Adjust dose for goal INR 2–3	• Adjust dose for goal INR 2–3
Enoxaparin (Lovenox®)	• 1 mg/kg SC every 12 h or 1.5 mg/kg SC once daily[b] • CrCl <30 mL/min: 1 mg/kg SC once daily	• 1 mg/kg SC every 12 h or 1.5 mg/kg SC once daily[b] • CrCl <30 mL/min: 1 mg/kg SC once daily

Abbreviations: *CrCl* creatinine clearance, *mL* milliliter, *min* minute, *mg* milligram, *kg* kilogram, *LMWH* low-molecular weight heparin, *UFH* unfractionated heparin, *INR* international normalized ratio, *SC* subcutaneous

[a]Per FDA package insert for apixaban, renal dose adjustments are made only if treating for atrial fibrillation. But in general practice, not prescribed for CrCl <30 mL/min

[b]Maximum dose of Lovenox is 150 mg SC every 12 h

with "total estrogenicity" (defined by the ratio of estrogen and progesterone) being of greater thrombotic significance than absolute dosage amounts [33, 34, 40]. Certain progesterone-only options are safer alternatives from a thrombotic standpoint, as studies report no significant increase in thrombosis for progesterone-only oral pills and intrauterine devices, although injectable depot progesterone may pose some thrombotic risk [41, 42]. For HRT, hormonal formulation may also affect thrombotic risk although debate remains as to which modes of delivery are safest, as some studies indicate increased risk with oral estrogen [35, 43] while others suggest a higher risk with the transdermal form [44].

Older literature suggested that women with OCP- or HRT-associated thrombosis had similar rates of recurrent VTE as those whose thrombosis was unprovoked [45–47]. More recent data, however, report a low risk of clot recurrence, similar to DVT and PE due to strong thrombotic risk factors [48]. Based on this, current guidelines recommend 3 months of anticoagulation in patients with estrogen-associated VTE [30, 49], although many clinicians, including those at our institution, opt to pursue age-appropriate and symptom-directed cancer screening in such patients as well [50].

DVT Associated with Pregnancy

The incidence of VTE in pregnancy is estimated at about 1–2 cases per 1000 women, about 5–10

times higher than nonpregnant women, with the highest risk during the 6–12 weeks following delivery, at which time the risk rises to 15 to 35-fold [51–56]. In women with acute DVT or PE during pregnancy, anticoagulation with UFH or LMWH, neither of which crosses the placenta, is recommended from the time VTE is diagnosed until 6 weeks postpartum, for a minimum total duration of 3 months [54, 57, 58].

Women without active DVT or PE but with a history of prior estrogen-associated VTE should receive antepartum and postpartum prophylactic anticoagulation to mitigate risk of another event, due to a 6–9% chance of a recurrent VTE during pregnancy [52, 57]; postpartum thromboprophylaxis typically continues to 6 weeks after delivery. Postpartum prophylactic anticoagulation may also be indicated in pregnant women with other thrombotic risk factors; antepartum thromboprophylaxis is sometimes given as well, although recent data have called into question its utility [59].

DVT Associated with Prolonged Travel

The risk of DVT due to prolonged travel is very small [60]. For unclear reasons, such DVT, when it occurs, tends to involve the distal rather than proximal leg [14, 61]. As with estrogen-associated DVT, patients with travel-related DVT are typically anticoagulated for 3 months [30], with many clinicians also recommending cancer screening.

For patients without active thrombosis but with thrombotic risk factors (e.g., prior VTE, obesity, recent surgery, OCP or HRT use, pregnancy, cancer, heritable thrombophilia), graduated compression stockings may be beneficial in reducing the risk of DVT [62]. Prophylactic anticoagulation is also increasingly being given to such patients, although data for this is less strong [63].

May–Thurner Syndrome

May–Thurner syndrome (compression of the left common iliac vein by the overlying right iliac artery) is an anatomic abnormality commonly affecting young women in their third through fifth decades. Risk factors include pregnancy, exogenous estrogen exposure, obesity, or heritable thrombophilia. Because the DVT arises from vascular compression, treatment typically involves a combination of catheter-directed thrombolysis, stent placement, and anticoagulation; the latter of which may last a year or longer, depending on stent patency and the presence or absence of PTS [64].

Anticoagulation for Unprovoked DVT

Unprovoked VTE occurs in the absence of identifiable thrombotic risk factors (Table 23.1). The risk of clot recurrence is 2- to 2.5-fold higher for unprovoked than for provoked VTE, with 10% of patients experiencing a recurrent VTE after 1 year and at least 30% having recurrent thrombosis at 5 years [27, 65]. Consensus guidelines therefore recommend a minimum of 3 months of anticoagulation in patients with unprovoked DVT or PE, with consideration of extended or indefinite anticoagulation in those with an acceptable bleeding risk (Fig. 23.1) [30]. Several additional clinical and laboratory factors should be considered when weighing the risks and benefits of extended anticoagulant therapy.

Bleeding Risk

Extended anticoagulation with VKA effectively reduces risk of thrombosis recurrence by about 90%, with similar results seen in extended treatment using LMWH and TSOACs (Dabigatran, Apixaban, Rivaroxaban) [29, 66–69], but at a cost of a two to threefold increased risk of bleeding [28]. Patients on extended anticoagulation have an annual major bleeding risk of about 1–3%, which rises to 4–5% in older individuals [66, 70, 71]. Factors associated with increased bleeding include advanced age (greater than 65 years old), cancer, previous bleeding, thrombocytopenia, renal or liver failure, concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs, recent surgery, or frequent falls [30].

Bleeding risk assessment tools such as the HAS-BLED score have been developed for patients on chronic VKA for atrial fibrillation. While these scores have not been validated in VTE, some data suggests that they might be an accurate predictor of early bleeding risk in such patients [72].

Case fatality rates, defined as the percentages of fatal events among patients with a particular disease, offer an additional tool to weigh the potential risks and benefits of long-term anticoagulation [73, 74]. In VTE patients on anticoagulation, case fatality rates due to recurrent VTE and bleeding are similar during the first 3 months of anticoagulant therapy, following which the case fatality rate for recurrent VTE drops significantly [73, 74]. The case fatality rates for recurrent DVT are half that of recurrent PE and one-third that of major hemorrhage, so in order to benefit from long-term anticoagulation, the estimated rate of recurrent DVT in an individual patient must be three times that of major hemorrhage [73, 75].

In patients with unprovoked VTE who have a high long-term risk of bleeding, where the risk of serious hemorrhage outweighs the projected benefit of ongoing anticoagulation, anticoagulant therapy is usually discontinued after 3 months [29, 75]. For patients with low to moderate bleeding risk, discussions regarding extended vs. short-term anticoagulation are more complicated and highly individualized. This is an area of active investigation, and in hopes of individualizing recommendations, many studies have focused on identifying factors that separate patients with the highest risk of recurrent thrombosis, who have the most to gain from extended treatment, from those with lower recurrence risk, in whom extended anticoagulation may reasonably be avoided.

Estimating Recurrent VTE Risk

- *D-dimer*: D-dimer is a by-product of fibrinolysis and is used for diagnostic purposes as a non-invasive marker to exclude VTE [76, 77]. In the multicenter prospective PROLONG trial, D-dimer levels were measured before and 1 month after stopping anticoagulation in 608 patients with unprovoked VTE (the vast majority of whom had proximal limb DVT without PE) who completed at least 3 months of VKA therapy [78]; those with D-dimers within normal range remained off treatment, whereas those with elevated values after cessation of anticoagulation were randomized to either resume anticoagulation or remain off it for the next 18 months. The highest recurrence rate (15%) occurred in patients with elevated D-dimer levels who remained off anticoagulation, compared to those with abnormal D-dimers who resumed anticoagulation (2.9%) and those with normal D-dimers (6.2%). On extended follow-up, patients with negative D-dimers continued to have lower risks of VTE recurrence compared to those with positive D-dimers (estimated annual risk, 3.5% vs. 8.9%, respectively) [79, 80]. Surveillance monitoring of D-dimers in patients who have stopped anticoagulation may also have utility [81].
- *Gender*: Men with unprovoked VTE have a 1.5–2.5 times higher risk of recurrent VTE than women [29, 30, 45, 82, 83]. The increase in recurrent thrombotic risk attributed to gender is independent of D-dimer status [84, 85]. Men with unprovoked VTE who have a negative D-dimer after stopping anticoagulation have a higher risk of clot recurrence than women (9.7% vs. 5.4% per patient year, respectively), indicating that a negative D-dimer is not as reassuring in men as it may be for women [85].
- *Surveillance ultrasonography*: Although commonly performed, a role for surveillance ultrasonography in assessing clot recurrence risk in patients with DVT has not been established. In most prospective studies and meta-analyses, residual vein occlusion following an initial period of anticoagulation either was not associated with increased VTE recurrence or demonstrated only a minor association [86–89], while a positive D-dimer appeared to be a stronger predictor [88, 89]
- *Thrombophilia testing*: Five major thrombophilias have been described: factor V Leiden

(FVL), prothrombin gene mutation, and deficiencies of antithrombin, protein C, and protein S [90]. Minor thrombophilias include elevations in other coagulation factors, such as factor VIII, von Willebrand factor, or plasminogen activator inhibitor [91–93]. The most common among these is FVL, present in about 5% of Caucasians and associated with DVT more than PE (the so-called "FVL paradox" [94]).While heritable thrombophilias increase the overall lifetime risk of VTE, they exert at most only a minor effect on recurrent VTE in patients with an unprovoked DVT or PE [26, 47, 95], although such effects may be amplified when present in combination [96]. Consensus guidelines advise against thrombophilia testing in patients with provoked DVT or PE but are uncertain as to its role in those with unprovoked VTE [90, 97, 98], as such testing has not been shown to change outcomes [99].

- *Other factors*: Several other factors may be associated with an increased risk of recurrent thrombosis, including older age, PTS, and obesity [29, 47, 93, 100–103]. None of these on an individual level play strongly into decisions about duration of anticoagulation.
- *Risk assessment models*: Several multivariable risk assessment models have been developed to aid in estimation of recurrent thrombosis risk in patients with unprovoked DVT and PE [71, 104–106]. The goal of all of these models is to aid clinicians in identifying patients with projected recurrence risks low enough to justify stopping anticoagulation. Male gender and abnormal D-dimers are the only variables identified in all risk assessment models as adverse predictors of VTE recurrence risk. In the absence of sufficient external validation studies in diverse patient populations (the risk models described below were derived from predominantly Caucasian populations) and prospective studies assessing the clinical impact of management decisions using these scores, it remains unclear how to best utilize these tools [24, 106].
  - The *Vienna prediction model* was derived from a study of 929 Austrian patients with unprovoked thrombosis who were treated with at least 3 months of anticoagulation [104]. Patients with cancer, estrogen-associated VTE, or inherited thrombophilias were excluded. Three variables—male gender, location of clot (proximal DVT vs. PE), and elevated D-dimer measured 3 weeks after discontinuation of anticoagulation—were significantly associated with an increased rate of recurrent VTE and compiled to estimate an individual patient's risk of recurrence at 12 and 60 months (Table 23.4). An updated version was published in 2014 enabling ongoing risk assessments based on serial D-dimer measurements up to 15 months post-anticoagulation [107]. The original Vienna prediction model was externally validated in a large cohort of 904 patients [65], although the updated model failed to predict recurrent VTE rates in a multicenter study of older adults [108].
  - The *DASH score* was derived from a study of 1818 patients with unprovoked VTE who completed at least 3 months of VKA therapy. Four factors predicted clot recurrence: an abnormal D-dimer (measured 3–5 weeks after stopping treatment), age less than 50 years, male sex, and VTE not associated with hormonal therapy (Table 23.4). The DASH score has not been externally validated.
  - The *men continue and HERDOO2* rule was derived from a multicenter prospective study of 646 patients with unprovoked VTE, which found that upon discontinuation of anticoagulation, men faced a 13.7% annual risk of recurrent VTE with no identifiable low-risk group compared to a 5.5% annual risk for women [105]. Clinical predictors were identified to stratify women into low- and high-risk groups, including signs of venous stasis (*h*yperpigmentation, *e*dema, or *r*edness of either leg), *D*-dimer ≥250 μg/L while on warfarin, *o*besity (body mass index ≥30 kg/m^2), and age 65 years or *o*lder (Table 23.4). Preliminary results from the REVERSE II trial pre-

Table 23.4 Proposed risk prediction tools

Vienna prediction model[a]	
Risk variables	
• Sex (male > female)	
• Location (PE > proximal DVT > distal DVT)	
• D-dimer μg/L (higher levels > lower levels)	
DASH score[b]	
Risk variables	
• Post-anticoagulation D-dimer (abnormal)	
• Age ≤50 years	
• Male sex	
• Hormone use at time of VTE (women)	
Men continue and HERDOO2[c]	
Risk variables	
• Signs of venous stasis (hyperpigmentation, edema, redness) in either leg	
• BMI ≥30 kg/m^2	
• Age ≥65 years	
• D-dimer ≥250 μg/L while on anticoagulation	
DAMOVES score[d]	
Risk variables	
• D-dimer on anticoagulation (abnormal > normal)	
• Age (older > younger)	
• Genetic thrombophilia (presence > absence)[e]	
• Obesity (presence > absence)	
• Varicose veins (presence > absence)	
• Factor VIII level (higher > lower)	
• Sex (male > female)	

[a]More points assigned to factors associated with greater VTE risk: male gender, PE, greater D-dimer levels. Predicts cumulative recurrence rates at 12 and 60 months [104, 107]. Web-based risk calculator for the updated Vienna prediction model: http://www.meduniwien.ac.at/user/georg.heinze/dvpm/

[b]DASH scores ≤1 with low recurrence rate of 3.1% [71]

[c]Clinical predictors only apply to women. Women with scores ≤1 with predicted to have a <3% annual recurrence risk [105]

[d]More points assigned to factors associated with greater VTE risk: abnormal D-dimer, advanced age, the presence of genetic thrombophilia, obesity, the presence of varicose veins, elevated factor VIII levels, male gender. Low-recurrence risk (<5%) predicted with a score <11.5 [133]

[e]Factor V Leiden, prothrombin G20210A mutation

sented at the European Society of Cardiology meeting in 2016 validate the HERDOO2 rule [109].

– The *DAMOVES score* was derived from a prospective study of 398 Spanish patients with unprovoked VTE 124. Among preselected variables, the authors found that abnormal *D*-dimer (while on anticoagulation), advanced *a*ge, inherited thrombophilic mutation (FVL, prothrombin G20210A mutation), *o*besity, the presence of *v*aricose veins, elevated factor VIII (*e*ight), and male *s*ex were associated with increased VTE risk (Table 23.4). A limitation of this model is its reliance on a single factor VIII level, which may fluctuate in inflammatory states.

Anticoagulation in Cancer-Associated Thrombosis

Patients with malignancy-associated VTE experience considerably greater thrombosis recurrence rates than those with VTE not associated with cancer, despite active anticoagulation [110]. They also have a greater than 10% risk of VTE recurrence within a year of stopping anticoagulation [111] and a higher risk of bleeding than non-cancer patients [112]. Guidelines recommend extended anticoagulation for those with cancer-associated thrombosis who have active cancer, are undergoing cancer treatment, or have ongoing risk factors for thrombosis, provided that bleeding risk remains manageable (Table 23.1) [30, 113–115]. Patients with cancer-associated thrombosis and early-stage cancer who are cured of their malignancy may stop anticoagulation after a 3–6 month course. The Ottawa score was developed as a risk stratification tool to predict VTE recurrence risk and guide decisions regarding anticoagulation in patients with cancer VTE [116, 117], although its utility has not been established in clinical care.

LMWH is the preferred anticoagulant in cancer-associated VTE based on the landmark CLOT trial, which demonstrated superior efficacy of LMWH over VKA in these patients

[118]. Additional studies confirmed the superiority of LMWH compared to VKA in terms of recurrent VTE and bleeding risks [119–121]. Increasingly, DOACs are being used in select patients with cancer-associated VTE [122–124] and there is also data to support transitioning from LMWH to VKA after an initial 6-month period of anticoagulation [125].

One rare but potentially devastating complication of cancer-associated DVT is limb gangrene, which occurs in patients with acute DVT who are being transitioned from UFH to VKA and develop phlegmasia cerulea dolens of the affected leg despite having a supratherapeutic INR [126]. The condition arises from perturbations in coagulation factors and natural anticoagulants, leading to an acquired protein C deficiency. Parenteral anticoagulation with UFH or LMWH and anti-Xa monitoring is the primary treatment, with administration of vitamin K to reverse any VKA effects and consideration of thrombolysis as appropriate.

Additional Long-Term Pharmacologic Interventions to Reduce VTE Recurrence

Following completion of the initial 3-month period of anticoagulation, in patients for whom extended anticoagulation is not indicated, there are three options besides complete discontinuation of anticoagulant therapy.

Low-Dose VKA

Two studies evaluated the efficacy of low-dose VKA therapy, targeting an INR of 1.5–2, in patients who completed an initial period of full-dose VKA. These studies led to slightly different conclusions. The PREVENT study, which compared low-dose VKA to placebo, showed a mild reduction in VTE with low-dose VKA, with no significant increase in bleeding [127]. The extended low-intensity anticoagulation for thromboembolism study compared low-dose and full-dose VKA and showed improved VTE recurrence with full-dose anticoagulation, with no reduction in bleeding risk observed for low-dose VKA [128]. Based on these studies, at present the use of low-dose VKA therapy remains provider dependent.

Low-Dose Aspirin

Two studies, ASPIRE and WARFASA, evaluated the use of daily low-dose aspirin (100 mg) in patients who completed an initial course of therapeutic anticoagulation. In the WARFASA study, low-dose aspirin reduced the rate of recurrent VTE by about 30% compared to placebo without an associated significant increase in bleeding events, although the effectiveness of aspirin in reducing recurrent VTE was substantially less than that seen with extended anticoagulation with VKA or DOAC therapy (90% risk reduction) [129]. In the ASPIRE study, aspirin conferred no benefit in terms of VTE reduction but showed a 34% reduction in rate of major vascular events [129, 130]. The conclusion from these two studies is that low-dose aspirin may have minor efficacy in preventing VTE recurrence in select patients but is less effective than extended anticoagulant therapy.

Low-Dose Apixaban

The safety and efficacy of low-dose apixaban (2.5 mg twice daily) was explored in the AMPLIFY-EXT study, which compared low-dose apixaban, full-dose (5 mg twice-daily) apixaban, and placebo in patients with unprovoked VTE who completed at least 6 months of full-dose anticoagulation [69]. Both low-dose and full-dose apixaban substantially decreased risk of recurrent VTE at similar rates compared to placebo; moreover, low-dose apixaban showed no significant increase in bleeding rate compared to placebo. Further data will be needed regarding long-term outcomes beyond a year and outcomes in specific populations including patients older than 75 years, those with impaired renal function, and those with small body weights.

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Controversies in the Diagnosis and Management of Distal Deep Vein Thrombosis

24

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Clinical Pearls

1. Distal DVT constitutes approximately 50% of all lower extremity DVTs.
2. Isolated distal DVT in patients with high risk of propagation should be treated with 3 months of anticoagulation.
3. Isolated distal DVT in low-risk patients can be managed by serial ultrasound, and data from the CACTUS trial suggest an increased risk of bleeding with low molecular weight heparin with no difference in recurrent VTE compared to placebo.

Introduction

Isolated distal deep vein thrombosis (DVT), i.e., infrapopliteal DVT without extension to proximal veins (popliteal vein or above) or pulmonary embolism (PE), also known as calf DVT, is frequent and represents 30–50% of all lower limb DVT diagnosed on ultrasound series [1–3]. Unlike proximal DVT and PE, which have been extensively studied and for which management is well standardized and the subject of high-level evidence and recommendations, much less is known on the optimal management of isolated distal DVT [4].

The rate of extension to the proximal veins, as well as the rate of PE associated with distal DVT, is highly variable from one study to the other. As a result, there is significant variation in diagnostic and therapeutic practices across centers [1, 5–8]. In some centers, both the proximal veins and the calf veins are imaged in all patients with suspected DVT, and patients diagnosed with isolated calf DVT are treated with anticoagulant therapy [9]. Other centers rely on serial imaging of the proximal veins only and thus do not diagnose or treat calf DVT [10]. In the latter strategy, in case of a negative proximal ultrasound, the test is often repeated 1 week later to rule out extension of a calf DVT to proximal veins. Comparisons between these two diagnostic strategies have shown that the proportion of patients diagnosed with DVT and thus treated with anticoagulants was higher when using whole-leg imaging as compared with serial proximal imaging. Nevertheless, diagnosing and treating distal DVT were not associated with better overall safety for patients. Indeed, the 3-month venous thromboembolism (VTE) risk was equivalent in patients left without treatment based on either strategy [11, 12]. These results thus question the need to

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systematically diagnose and treat all calf DVT with anticoagulants, particularly in patients free of any of the major strong identified predictors of DVT extension/recurrence (inpatients, patients with history of previous VTE or with cancer), who represent the majority of calf DVT patients [4, 13, 14].

The aim of this chapter is to discuss current controversies in the therapeutic management of symptomatic isolated distal DVT. Because of lack of extensive data on this specific subject, and in order to better understand some important issues, the natural history of distal DVT will be first presented. Then, the limitations in the accuracy of distal DVT diagnosis and the impact of different diagnostic strategies used in patients with suspected DVT will be discussed in detail. Finally, the most recent available studies on distal DVT treatment as well as the evolution of international recommendations are presented and discussed in detail.

Epidemiology and Natural History of Distal DVT

In studies including inpatients, 80% of all diagnosed DVT are proximal DVT, and 20% are calf DVT [15–17]. However, some studies including outpatients diagnosed with DVT by compression ultrasound (CUS) report a proportion of calf DVT as high as 60–70%, underlining the potential relevance of the problem in everyday clinical practice [18, 19].

The natural history of DVT seems to be, in the vast majority of cases, the development of a thrombus in the distal veins of the calf that extends proximally, the so-called ascending pattern of thrombus extension [17]. Whereas the embolic potential of proximal DVT is unanimously recognized, distal clots appear to have a much lower embolic potential, although data remain limited [20]. Therefore, the rate of extension of distal DVT to the proximal veins as well as the rate of PE are crucial issues as they largely determine the clinical significance of distal DVT in terms of patients' outcomes and hence in terms of need for treatment.

Risk of Proximal Extension of Distal DVT Without Treatment

Performing a thorough estimation of the risk of extension of distal DVT to proximal DVT and/or PE remains difficult. Indeed, the rate of extension among different studies is highly variable due to high heterogeneity in patients' population, clinical settings, and diagnostic strategies [2, 21]. Comparison between studies is also limited by disparity in treatment regimens as well as major differences in the follow-up and definition of outcomes (symptomatic extension vs extension diagnosed on systematic testing).

An interesting approach to assess the rate of extension of distal DVT to the proximal veins is to use data arising from diagnostic studies based on serial proximal CUS (described in detail in the next section). These studies show a low rate of proximal DVT (1–5.7%) detected by the repeated proximal CUS in patients left untreated after a first negative CUS limited to proximal veins (Table 24.1) [10, 22–26]. Of note, these studies mainly include outpatients with suspected DVT, so the rather low reported rates of extension to proximal veins could reflect the natural history of untreated calf DVT in a group of "low-risk" patients.

Clinical Outcomes of Patients Treated with Anticoagulants for Distal DVT

Two registry-based analyses aimed to assess patients' outcomes after a symptomatic distal DVT and identified 933 and 1885 eligible patients, respectively. As the vast majority of patients included in these French (OPTIMEV) [3] and international (RIETE) [27] registries received therapeutic anticoagulation (97% and 89%, respectively), these studies could not add knowledge on the true natural history of distal DVT. Nevertheless, they revealed interesting findings on some differences between patients treated for distal and proximal DVT. The 3-month VTE rate was similar in distal and proximal DVT patients. However, mortality was significantly higher in patients with proximal DVT vs distal DVT in both studies (8% vs 4.4% in OPTIMEV

Table 24.1 Performances and safety of proximal compression ultrasonography for diagnosing DVT in outcome management studies

Source, year	Patients (*n*)	Prevalence of DVT (%)	Proportion of proximal DVTs detected by the second CUS % (95% CI)	Three-month thromboembolic risk, % (95% CI)[a]
Birdwell et al. [22], 1998	405	16	2 (0.8–4.2)	0.6 (0.1–2.1)
Cogo et al. [10], 1998	1702	24	0.9 (0.3–1.2)	0.7 (0.3–1.2)
Bernardi et al. [23], 1998	946	28	5.7 (1.9–12.8)	0.4 (0–0.9)
Wells et al. [24], 1997	593	16	1.8 (0.3–5.2)	0.6 (0.1–1.8)
Perrier et al. [25], 1999	474	24	N.A.*	2.6 (0.2–4.9)
Kraaijenhagen et al. [26], 2002	1756	22	3 (1.9–5.2)	0.7 (0.3–1.6)
Pooled estimate	5876	23	N.A.	0.6 (0.4–0.9)

Distal DVTs were not searched for in these studies

DVT deep vein thrombosis, *CUS* compression ultrasonography, *N.A.* not applicable

N.A.*: In the study by Perrier et al., only one CUS limited to proximal veins was realized in patients with a positive ELISA D-dimer measurement

[a]During 3-month follow-up in patients left untreated after normal proximal compression ultrasonography

and 7.5% vs 2.7% in RIETE). In distal DVT patients, mortality was non-VTE related in the majority of cases. Interestingly, distal DVT was found to be more often associated with transient risk factors (such as recent travel, hospitalization, and recent surgery) than proximal DVT.

The long-term outcome after stopping treatment in patients prescribed therapeutic anticoagulation for distal DVT was analyzed in two recent prospective observational studies. The first study consisted of a 3-year follow-up of patients included in the OPTIMEV registry. It showed that after treatment cessation, patients with distal DVT ($n = 490$) had a lower annual rate of overall VTE recurrence compared to patients with proximal DVT (2.7% vs 5.2%, $p = 0.02$), but a similar rate of PE (0.9% vs 1%, $p = 0.83$). Some predictors of recurrence in patients with index distal DVT were identified: age > 50 years, unprovoked event, and multiple distal vein involvement [13]. The second study was a single-center small study ($n = 90$) assessing 2-year outcomes after stopping therapeutic anticoagulation for distal DVT. Treatment duration was of 30 days and 3 months in patients with provoked and unprovoked distal DVT, respectively. In this study, male sex and the presence of cancer were associated with higher VTE recurrence rates after treatment cessation, whereas location and the provoked character of the index distal DVT were not [28].

Comparison of Patients' Outcomes Between Treated and Untreated Patients

Variations in study design and target populations are too large to allow a clinically relevant pooled estimate to compare the proportion of patients with distal DVT who extend to proximal DVT between treated and untreated patients. Nevertheless, a systematic review published in 2006 reported an estimated rate of extension of 10% (95% CI, 7–12%) in untreated patients and of 4% (95% CI, 3–6%) in treated patients [2].

A recent systematic review published this year, including prospective cohort studies and some of the most recent randomized studies, reported an overall proximal extension rate varying between 0 and 35%, corresponding to a mean extension rate of 9%. Although the true signification of a mean value in view of the large heterogeneity of studies can be debated, it helps to give a rough idea of the potential range of extension rate. The reported rate of PE ranged from 0 to

5.8% with a mean rate of 1.4%. None of the available studies found that anticoagulant treatment was associated with a reduction in adverse outcomes. In terms of bleeding, the major bleeding rate (excluding an older study which showed a high major bleeding rate of 7%) was of 0–2.1% in patients treated with anticoagulants, whereas no major bleeding was reported in patients who did not receive anticoagulant treatment [21].

All these elements highlight the uncertainty about the natural history of distal DVT, its clinical significance, and the need for its treatment and modality and duration of treatment. The increasing occurrence of this medical condition since the implementation in many vascular laboratories of systematic whole-leg compression ultrasound in all patients with suspected DVT has led to considerable efforts over the last 10–15 years to answer the question on the need for its treatment with anticoagulants, without any definitive conclusion but with some important data on the potential necessity to stratify the risk of extension in patients with distal DVT to guide decision on treatment. In view of the uncertainty regarding the necessity to treat distal DVT, the question of the necessity to diagnose distal DVT can be raised. As the diagnostic management of distal DVT varies as widely as its therapeutic management among centers, this issue is discussed first in detail the next section. Then, the most recent studies comparing outcomes between treated and untreated patients will be discussed in a dedicated section.

Venous Ultrasonography for the Diagnosis of DVT

Venous compression ultrasound using B-mode imaging was first reported in 1986 and is currently the main ultrasonographic method used to diagnose DVT [29]. This technique allows a two-dimensional imaging of the lower extremity veins. With the patient in the supine position and a slight external rotation of the leg, deep veins can be visualized starting from the common femoral vein at the inguinal level and then followed down along the femoral vein (formerly called superficial femoral vein although this vein is part of the deep venous system). The popliteal and calf veins are better assessed in sitting position. Normal veins collapse completely under pressure applied by the transducer. When a thrombus is present, compression of the vein is impossible. Inability to compress the vein, also called noncompressibility, is the most reliable criterion for DVT diagnosis [30]. This technique is illustrated in Figs. 24.1 and 24.2.

Other criteria for the diagnosis of acute DVT are reported in the literature and are summarized in Table 24.2. Direct thrombus visualization using B-mode imaging has variable accuracy, since visibility of the clot may depend on its age. Fresh thrombus usually appears anechoic and can be missed [32]. Enlargement of the occluded vein is another criterion for acute thrombosis. Doppler studies (color flow imaging or spectral Doppler) are used to assess venous blood flow. Color flow imaging can assist in the characterization of the thrombus as obstructive or partially obstructive. These diagnostic criteria have not been shown to improve diagnostic accuracy for DVT and should not be used without the noncompressibility criterion to confirm DVT [33]. However, it is important to point out that the examination of the Doppler signal at the level of the common femoral vein can give indirect evidence of iliac and inferior vena cava patency [30].

Different Protocols of Compression Ultrasound (CUS)

Depending on the extent of lower limb venous system examination, two main types of protocols using compression maneuvers are described in the literature [34]. The proximal CUS (two-point or extended CUS) limits ultrasonographic examination to the proximal deep veins, whereas the whole-leg or complete CUS assesses both proximal and distal deep veins of the leg. These technical distinctions are important to discuss in detail as the applied diagnostic protocol has a direct impact on the rate of diagnosis (± treatment) of distal DVT.

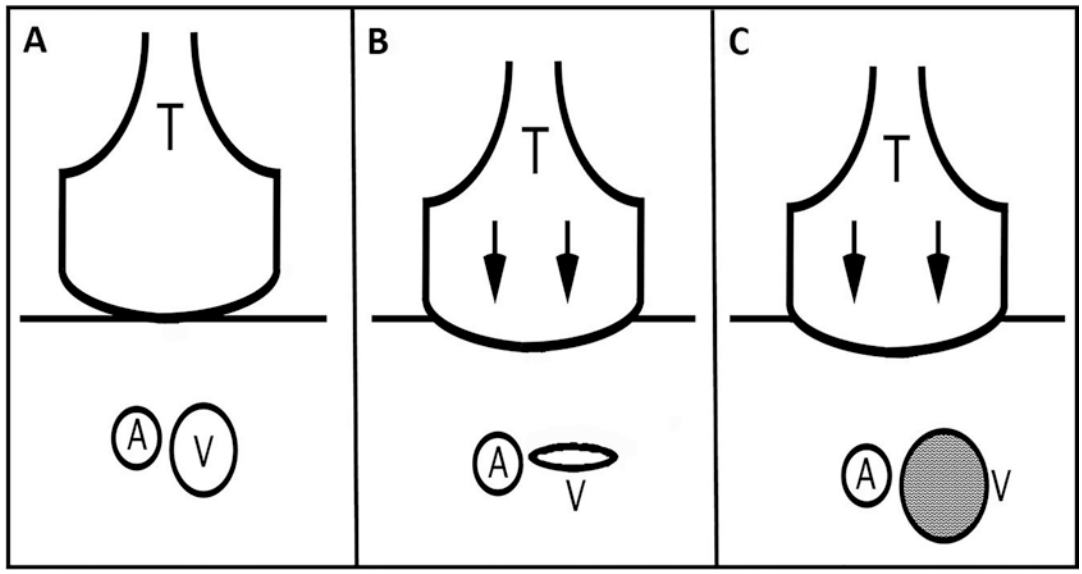

Fig. 24.1 Schematic representations of compression testing using the ultrasound probe. Adapted from reference [31]. A normal compression test is depicted in (**a**) and (**b**). The third schematic image depicts incompressibility of the vein, the most reliable and validated criterion for DVT diagnosis (**c**) (*A* artery, *V* vein, *T* transducer ultrasound probe)

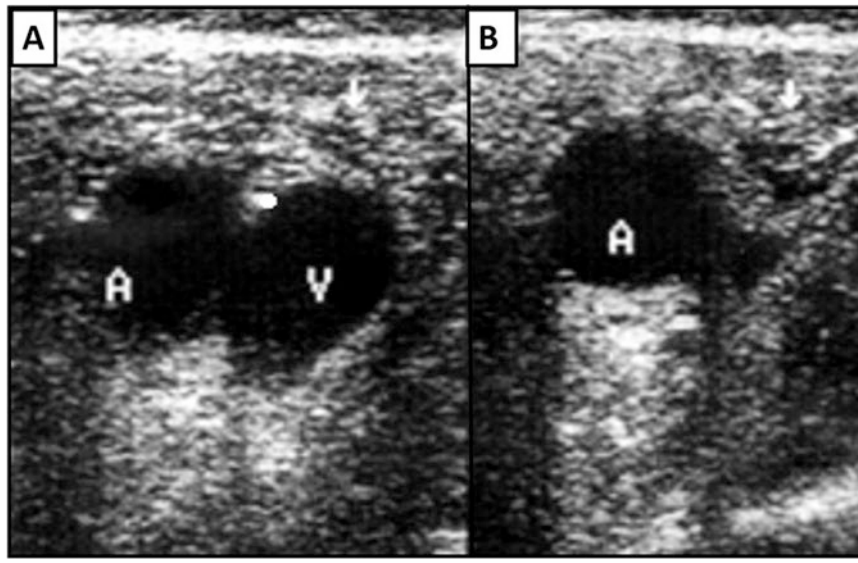

Fig. 24.2 Ultrasound images of compression testing of a normal vein. Vein seen before compression. (**a**) Under compression (image on the *right side*), the vein is not seen any more as it is fully compressed. (**b**) Adapted from reference [31] (*A* artery, *V* vein)

Proximal CUS

The so-called two-point proximal CUS is limited to the assessment of compressibility limited to the common femoral and popliteal veins in transverse plane with a linear probe. With the patient in supine position, the common femoral vein is first identified at the level of inguinal ligament by using the laterally situated common femoral

Table 24.2 Ultrasonographic diagnostic criteria for acute lower limb deep vein thrombosis

Primary diagnostic criterion	Secondary diagnostic criteria
Vein noncompressibility[a]	Echogenic thrombus within the lumen of the vein[b]
	Vein distention
	Absence of pulsed wave or color Doppler signal within the vein lumen
	Loss of venous flow phasic pattern (associated with breathing) and/or response to Valsalva's maneuver

Adapted from Tapson et al. [30]
[a]Noncompressibility is the most reliable sign of acute deep vein thrombosis
[b]Risk of false negative (an acute clot is not always echogenic) or false positive (any intraluminal echogenic structure is not necessarily a thrombus) results if this criteria is used without the primary diagnostic criterion

artery as a reference point. The popliteal vein is scanned with the patient in seated or lateral decubitus position and the transducer placed posteriorly in the popliteal fossa. The popliteal vein is generally located above the popliteal artery. This protocol was first described by Lensing et al. in 1989 [35]. The rationale to restrict the examination to these two "points" is based on phlebographic studies which showed the extreme rarity of isolated DVT of the femoral vein between these two points [17]. However, CUS protocols are not always identical between studies using serial proximal CUS (see below). For example, Perrier et al. [25] used a two-point examination (as described above), while Wells et al. [10] also imaged the femoral vein along the thigh. Cogo et al., Kraaijenhagen et al., and Bernardi et al. performed a two-point CUS but extended the popliteal imaging to the calf trifurcation [11, 26, 36]. Finally, Birdwell et al. tried to define more precisely to which extent the popliteal area was imaged, by describing that veins were imaged down to 10 cm under the patella [22].

Management studies using repeat proximal CUS performed at 1-week interval ("serial" testing) have been reported to be safe regardless of the exact proximal imaging protocol used (Table 24.1) [22–26, 36]. However, these differences in diagnostic protocols at the popliteal level highlight the limitations in the ability to provide an exact definition of a distal DVT (vs a proximal DVT) which is thus quite variable. The complexity and variations in the anatomy of the popliteal division render this task even more difficult. Nonetheless, DVTs located near the popliteal vein are generally considered as proximal DVTs and, in the abovementioned studies, received anticoagulation as prescribed for all proximal DVTs.

Single Complete (Proximal and Distal) or Whole-Leg CUS

The ultrasonography protocols described above do not take into account distal veins. Consequently, other authors proposed standardized protocols that assessed the whole leg: all proximal veins (common femoral, femoral, and popliteal veins) and calf veins (posterior tibial, peroneal, and calf muscle veins) are examined. This kind of ultrasound examination has been called whole-leg or complete CUS. Of note, most authors agree that examination of anterior tibial veins is not mandatory as isolated anterior tibial vein DVT is exceptionally rare [37]. Whole-leg CUS as a single diagnostic test in ambulatory patients with suspected symptomatic DVT has been validated in six prospective cohort studies (Table 24.3) and one randomized control trial [11, 37–42].

Detailed Comparison and Respective Limitations of Ultrasound Strategies for Suspected DVT

The sensitivity and specificity of CUS for proximal DVT are high (97 and 98%, respectively) [43], and the necessity of treating proximal DVT by anticoagulants is widely accepted [44]. On the other hand, the sensitivity and specificity of CUS for distal DVT are lower [15, 43]. A meta-analysis by Kearon et al. reported sensitivity of 50–75% and specificity of 90–95% [43]. Even if another more recent meta-analysis published in 2005 suggested similar values for ultrasound accuracy for calf thrombosis [45], one must take into account that some studies in the hands of highly skilled ultrasonographers using the best

Table 24.3 Performances and safety of a single complete (proximal and distal) compression ultrasonography for diagnosing DVT in management outcome studies

Source, year	Patients (*n*)	Prevalence of all DVT *n* (%)	Distribution of DVT level *n* (%)		Three-month thromboembolic risk % (95% CI)[a]
		All	Proximal	Distal	Single proximal and distal CUS
Elias et al. [37], 2003	623	204 (33)	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong et al. [38], 2003	1646	275 (17)	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens et al. [39], 2004	445	61 (14)	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam et al. [40], 2005	526	113 (22)	49 (43)	64 (57)	0.2 (0.01–1.3)
Bernardi et al. [11], 2008	1053	278 (26)	213 (76)	65 (24)	1.2 (0.5–2.2)
Sevestre et al. [41], 2009	3871	1023 (26)	454 (44)	569 (56)	0.6 (0.3–1.2)
Sevestre et al. [42], 2010	1926	395 (21)	155 (39)	240 (61)	0.6 (0.1–1.7)
Pooled estimate	10,090	2349 (23)	1146 (49)	1203 (51)	0.6 (0.3–0.9)

[a]During 3-month follow-up in patients left untreated after a normal complete (proximal and distal) compression ultrasonography. *N.A.* not applicable, *DVT* deep vein thrombosis

ultrasound machines reported much higher values of sensitivity and specificity at the calf level [37]. The improvement in ultrasound technology and increased experience in the field have led to a quite reliable diagnosis of distal DVT in experienced hands when the most reliable diagnostic criterion is used, i.e., the lack of compressibility of a venous segment. However, despite such technologic improvements, some other limitations are still present at the calf level. For example, the rate of inconclusive diagnostic tests has been reported to be as high as 50% in some series (Table 24.4) [46–49]. This rate might not be true for outpatients in whom calf examination is usually easier but seems to reflect the reality of inpatients, especially after orthopedic surgery or in the intensive care unit setting.

Table 24.4 Rate of indeterminate calf ultrasound examinations

First author	Study type	Frequency of indeterminate examinations %, (*n*/*n*)
Rose et al. [46], 1990	Prospective	42% (21/50)
Simons et al. [47], 1995	Prospective	29% (16/56)
Atri et al. [48], 1996	Prospective	9.3% (10/108)
Gottlieb et al. [49], 1999	Retrospective	82.7% (8206/249)
Pooled total		54.6% (253/453)

Adapted from reference [49]

Serial Proximal CUS in Outcome Studies

The limited performances of distal venous examination reported in some studies may explain why many centers use only proximal CUS, i.e., limited to the popliteal and supra-popliteal veins. Since such protocols do not search for distal DVT (that if present could potentially extend to the proximal veins with a significant risk of PE), the standard diagnostic approach consists of performing a second CUS limited to the proximal veins at day 7, the so-called serial proximal CUS strategy. Patients with a proximal DVT on the initial CUS are treated with anticoagulants. When the initial examination is negative, patients are not given anticoagulants, and a second proximal

CUS is repeated 1 week later to detect the possible extension of distal DVT. Patients with a second normal CUS are considered as definitely not having a DVT and are not anticoagulated.

Many prospective well-designed outcome studies have shown the safety of proximal CUS integrated in diagnostic strategies (Table 24.1). The six studies used CUS limited to proximal veins [10, 22–26]. Five of these studies used the classic serial proximal CUS, and one used a single proximal CUS included in a strategy associating pretest clinical probability and D-dimer measurement [25].

The pooled estimate of the 3-month thromboembolic risk of these prospective management studies using CUS limited to proximal veins was 0.6% (95% CI, 0.4–0.9%). There was no significant difference in the 3-month thromboembolic risk between these six studies. If one considers each study individually, the 3-month thromboembolic risk in patients with a negative proximal CUS was low: it was lower than 1% in the studies using serial proximal CUS [10, 22–24, 26] (CUS repeated after 1 week in patients with an initially negative CUS) and 2.6% (95% CI, 0.2–4.9%) in the one study that used clinical probability, D-dimer, and a single proximal CUS (Table 24.1) [25]. This compares favorably with the 3-month thromboembolic risk in patients with clinically suspected DVT left untreated after a negative venogram (the gold standard), which was found to be 1.9% (95% CI, 0.4–5.4%) [50].

Even if serial proximal CUS is very safe, its main limitation is the need for a second ultrasound examination, which is cumbersome and costly and has a very low yield as it reveals a proximal DVT in only 1–5.7% of patients (Table 24.1).

Single Complete (Proximal and Distal) CUS in Outcome Studies

Seven prospective outcome studies using a single complete (i.e., proximal and distal) CUS have been published (Table 24.3) [11, 37–42]. Patients were treated if CUS showed a proximal or distal DVT and were left untreated if proximal and distal veins were normal, without any further testing. These studies showed that extending the ultrasonographic examination to distal veins without repeating the CUS at 1 week is very safe. Indeed, the pooled estimate of the 3-month thromboembolic risk performed in a systematic review and meta-analysis is 0.6% (95% CI, 0.3–0.9%) [9].

However, despite their diagnostic safety, these studies point to some important problems. First, such an approach is costly and time-consuming as complete CUS is proposed to all patients with suspected DVT. Indeed, in outpatients with clinically suspected DVT, a normal enzyme-linked immunosorbent assay (ELISA) D-dimer test allows to withhold anticoagulation without further testing in about one third of outpatients at a much lesser expense and with a similar safety [25]. Second, the pooled estimate of the 3-month thromboembolic risk of these studies is similar to that computed for studies using a strategy including proximal CUS only (Tables 24.1 and 24.3). This means that detecting calf DVT may actually be deleterious: it does not reduce the 3-month thromboembolic risk, and it entails a risk of unnecessary anticoagulant treatment in patients who would have fared well without anticoagulant treatment. Moreover, because of the limitations in the diagnostic performance of CUS at the calf level, some of the positive findings might even be false positives, rendering the potentially unnecessary exposure to bleeding risk associated with anticoagulation even more unacceptable. To give an idea of the potential extent of this issue, a pooled analysis of the studies performing complete CUS shows that among a total of 10,090 included patients, 1203/2343 (51%) of diagnosed DVT were distal DVT (Table 24.3). This signifies that in half of patients with suspected DVT undergoing complete CUS with a final positive diagnosis of DVT, there is no clear benefit for diagnosing the (distal) DVT.

Serial Proximal vs Single Complete CUS in Suspected DVT

The next logical step was obviously to perform a direct comparison between serial proximal CUS and single complete CUS diagnostic strategies

Table 24.5 Main results of the randomized trial comparing serial proximal CUS with a single complete CUS in patients with suspected DVT [11]

	Serial proximal CUS	Single complete CUS
Patients (*n*)	1045	1053
DVT (*n* (%))	231 (22.1)	278 (26.4)
Proximal (*n*)	231	213
Distal (*n*)	0	65
Three-months VTE risk (% (95% CI))	0.9 (0.3–1.8)	1.2 (0.5–2.2)

Adapted from Bernardi et al. [11]
CUS compression ultrasound, *DVT* deep vein thrombosis

Table 24.6 Advantages and disadvantages of serial proximal CUS and of single complete CUS

	Advantages	Disadvantages
Serial proximal CUS	Safety in terms of 3-month VTE risk	Repeated testing
	No risk of overtreatment	
	Easy to perform	
	Short (3–4 min)	
	Few inconclusive tests	
Single complete CUS	Safety in terms of 3-month VTE risk	Risk of overtreatment
		More difficult to perform
		Longer (12–14 min) to perform
	Stand-alone test	More inconclusive tests in inpatients
		Lower diagnostic performances

for DVT. This was performed in three studies, with very similar results [11, 12, 51]. Therefore, only the most robust study in terms of methodology will be discussed here [11].

In this prospective randomized multicenter trial, a strategy including serial two-point (femoral and popliteal) proximal CUS associated with D-dimer testing was compared to a single whole-leg CUS strategy in more than 2000 outpatients with a clinical suspicion of DVT (Table 24.5) [11]. In the proximal CUS arm, patients with a normal two-point CUS underwent qualitative D-dimer testing (SimpliRED®, Agen Biomedical, Australia). Patient with negative D-dimer were spared further investigations and not treated with anticoagulants. Only patients with abnormal D-dimer levels underwent the repeat CUS at 1 week. Both strategies reported similar 3-month rate of VTE: 0.9% (95% CI, 0.3–1.8%) for the two-point proximal CUS and D-dimer arm vs 1.2% (95% CI, 0.5–2.2%) for the complete single CUS arm. The safety of both strategies was therefore similar. It should be noted that 23% (65/278) of patients with confirmed DVT in the complete CUS arm were treated with an anticoagulant for a distal DVT, without decreasing the 3-month thromboembolic risk. Authors thus concluded that detecting isolated distal DVT might not be as relevant as previously believed and that the search for distal DVT might even expose patients to the harm of unnecessary anticoagulant treatment. The advantages and disadvantages of using serial proximal CUS vs a single complete CUS are summarized in Table 24.6.

To decrease the number of patients undergoing a distal vein examination, a new diagnostic strategy was recently evaluated in a prospective outcome study. All patients with suspected DVT had a clinical probability assessment. Patients with suspected DVT had a whole-leg CUS (i.e., proximal and distal) only in case of both a likely clinical probability *and* a positive D-dimer measurement. Patients with an unlikely probability and negative D-dimer did not undergo CUS and were left untreated. All other patients with positive D-dimer result had a single proximal CUS only. The overall prevalence of DVT was of 18% in the whole cohort. Among all confirmed DVTs, 39% were isolated distal DVT, which is lower than the pooled estimate of 51% in studies including complete CUS for all patients (Table 24.3). In spite of a lower rate of detection of distal DVT, this strategy revealed to be safe, with a 3-month thromboembolic risk of 0.9% (95% CI, 0.44–1.70) [52].

D-Dimers in the Diagnosis of Calf DVT

The safety and the cost-effectiveness of D-Dimer measurement in the diagnosis of patients with suspected DVT have been extensively studied. D-dimer measurement has been proven to be highly sensitive but not very specific for the presence of venous thromboembolism and to be associated with a very high negative predictive value for DVT in different patient populations [25, 53, 54].

D-dimer seems to have a lower sensitivity and a lower negative predictive value for calf DVT than for proximal DVT. For example, Jennersjö and coworkers reported that as many as 35% of patients with calf DVT may have normal D-dimer levels, suggesting a limited sensitivity of the test to rule out distal DVT [55]. However, some other studies reported much higher values of sensitivities [56, 57], rendering a robust evaluation of D-dimer sensitivity for distal DVT quite difficult. Nevertheless, a meta-analysis showed that all D-dimer assays had a higher sensitivity for proximal than distal DVT: 98% vs 86% for ELISA test, 94% vs 79% for latex agglutination, and 84% vs 64% for whole-blood agglutination tests [58]. A more recent study reported that the area under the curve (AUC) of the receiving operating characteristic (ROC) analysis for D-dimer and calf DVT was of 0.72 [59].

Altogether, these data suggest that D-dimer is indeed less sensitive at the distal than at the proximal level and that some patients may have a distal DVT and D-dimer levels below the usual cut-off value set at 500 ng/ml. However, one should rather keep in mind that in terms of patients' outcomes, many prospective outcome studies including several thousands of patients have clearly shown that patients with suspected PE or suspected DVT have a very low 3-month thromboembolic rate (<1%) when left untreated on the basis of a negative D-dimer test [60]. Another important point is that in the studies assessing the accuracy of D-dimer for distal DVT, the reference diagnosis test was ultrasound. Due to the imperfect accuracy of CUS itself at the distal level, some of the detected thrombi might also have been false positive results of ultrasound testing rather than false negative results of D-dimer, limiting a thorough assessment of D-dimer performance in diagnosing distal DVT. Therefore, we still believe the fear of calf DVT should not alter the full confidence in a normal D-dimer test result to identify patients who will have very favorable outcomes without anticoagulant treatment. Interestingly, a similar discussion may also be held for isolated subsegmental PE. Indeed, whereas D-dimer sensitivity is estimated at around 75% for subsegmental PE even for highly sensitive tests [61], a negative D-dimer test result has been shown to be very safe to exclude PE in outcome studies by identifying patients at very low risk of 3-month thromboembolic events without treatment.

As a general consideration, the uneventful outcome of patients left untreated after a negative D-dimer, even though small clots (distal DVT or subsegmental PE) may be "missed" by such a test, further advocates for the doubt about the necessity to treat all distal DVTs.

Recent Trials and Recommendations for Therapeutic Management of Distal DVT

The First Randomized Trials Assessing the Need for Anticoagulant Treatment

To date and to our knowledge, only five randomized trials have assessed the need for anticoagulant treatment in patients with calf DVT [14, 62–65], four of which have been published to date and will be discussed here. The results of the fifth study, the only double-blind randomized placebo-controlled study in this field, will be presented and discussed in detail in a dedicated section.

The first study was published more than 30 years ago by Lagerstedt and coworkers [63]. Through the landmark study in the field, it was a small, open-label study with many methodological limitations. After a 10-day course of therapeutic heparin, 51 patients were randomized to

receive either therapeutic warfarin (target INR 2–3) or no warfarin. During the 3-month follow-up, no patient in the warfarin arm had a recurrent event, while 19/28 patients who did not receive warfarin had recurrent VTE events. However, recurrent events were assessed by physical examination and serial isotopic tests, which were later abandoned due to their limited sensitivity. It is therefore quite difficult to rely on this single study to recommend systematic anticoagulation for all distal DVTs. Nevertheless, it is interesting to point out that on the basis of this single trial and due to the absence of other randomized data, the 2008 ACCP consensus still recommended to treat all calf DVTs with a 3-month course of anticoagulant treatment (Grade 2C) [66].

In another open-label, randomized trial, Pinede et al. compared a 6-week against a 12-week course of oral anticoagulant treatment in patients with symptomatic DVT [64]. Among the group of patients with distal DVT (n = 197 patients), those who received 6 weeks of treatment had both less recurrent events (2.0% vs 3.4%, relative risk 0.58 (95% CI, 0.1–3.36)) and less major bleedings (1.0% vs 3.4%, relative risk 0.29 (0.03–2.72)) compared to those who received 12 weeks of treatment. Despite an open-label design, the study suggested that 6 weeks of treatment are probably enough for distal DVT.

One randomized study focused on patients with calf muscle vein thrombosis only, i.e., soleus or gastrocnemius vein thrombosis [65]. This study, which was not placebo controlled, randomized patients to receive either 10 days of subcutaneous injections of therapeutic dose of the low molecular weight heparin (LMWH) nadroparin associated with elastic compression or elastic compression alone. The study did not show significant differences in the rate of extension to proximal veins nor in the recanalization rate of affected venous segments between the two groups.

A fourth randomized open-label feasibility study compared therapeutic anticoagulation with the LMWH dalteparin followed by warfarin to a conservative treatment (nonsteroidal anti-inflammatory drugs and/or paracetamol) in patients with calf DVT [62]. A total of 70 patients were randomized, and while no patients in the anticoagulation arm had a VTE event, 4 out of 35 patients (11.4%) of those in the conservative treatment arm had a thromboembolic event. However, the small sample size and the open-label design limit the robustness of conclusions that could be drawn from this study.

Altogether, the analysis of these available randomized data shows a high disparity between reported results and does not allow drawing firm conclusions.

Evolving International Recommendations for the Treatment of Distal DVT

Nevertheless, some reassuring data published in these randomized trials and in nonrandomized trials has probably had some impact on the recommendations included in international expert consensus guidelines such as those established by the American College of Chest Physicians (ACCP). As an example, a cohort study published in 2010 including 431 nonconsecutive outpatients in two Italian centers showed a low rate of proximal extension or thromboembolic events in patients left untreated for a distal DVT [67]. In a more recent study, 171 patients diagnosed with distal DVT were treated with twice-daily administration of therapeutic LMWH for 1 week, followed by half-dose LMWH for another 3 weeks [68]. During the treatment period, five patients (2.9%) had a proximal extension. Further recurrences during the rest of 3-month observation period occurred in only four patients, three of whom in patients with an index unprovoked event, suggesting that prolonged full-dose therapeutic treatment might not be necessary for all patients with calf DVT.

All these rather reassuring data had probably some impact on the last ACCP recommendations [4, 69] that contrary to the suggestions of 2008 now suggest that serial imaging of the deep veins for 2 weeks could be proposed over

Table 24.7 Risk factors for calf DVT extension warranting anticoagulation according to ACCP recommendations [4, 69]

Positive D-dimer
Extensive thrombosis or close to the proximal veins (>5 cm in length, involves multiple veins; >7 mm in maximum diameter)
No reversible provoking factor for DVT
Active cancer
History of VTE
Inpatient status

initial anticoagulation in patients without severe symptoms or risk factors for extension. The presence of the risk factors listed in Table 24.7 should warrant therapeutic anticoagulation per these recommendations.

Is It Necessary to Treat All Distal DVTs in Low-Risk Patients?

The next step to improve the management of distal DVT was probably to assess the safety of not giving anticoagulant treatment to selected patients with distal DVT at low risk of proximal extension and of thromboembolic events. This was the basis to draft the CACTUS trial, which is the only randomized placebo-controlled study in the field of distal DVT [14]. In the CACTUS trial, 259 outpatients without active cancer or previous VTE were assigned to receive once-daily subcutaneous injections of either the LMWH nadroparin, at the dose of 171 UI/kg, or placebo for 6 weeks. The primary efficacy outcome measure was the composite of extension of calf DVT to proximal veins, contralateral proximal DVT, or PE at 6 weeks. The primary safety outcome measure was major or clinically relevant nonmajor bleeding at 6 weeks. All patients were also prescribed elastic compression stockings for 6 weeks and followed for 90 days.

The primary efficacy outcome occurred in 4 of 122 patients (3.3%) in the nadroparin arm and in 7 of 130 patients (5.4%) in the placebo arm ($p = 0.54$; risk difference −2.1% (95% CI, −7.8 to +3.5%)). Major or clinically relevant nonmajor bleeding occurred in 5 of 122 patients (4.1%) in the nadroparin arm and in 0 of 130 patients (0.0%) in the placebo arm ($p = 0.03$; risk difference +4.1 (95% CI, +0.4 to +9.2%)) (Table 24.8). In the nadroparin arm, one patient died from metastatic cancer, and one patient was diagnosed with type II heparin-induced thrombocytopenia. The main conclusions of the study were that the use of therapeutic doses of nadroparin for 6 weeks in low-risk outpatients with symptomatic calf DVT was not superior to placebo in reducing the risk of proximal extension or thromboembolic events but was associated with a significantly higher risk of bleeding. The main limitation of the study is that the target sample size was not reached, resulting in limited statistical power.

In a recent monocentric nonrandomized study including 384 patients with calf DVT, in which the decision to give anticoagulant treatment was retrospectively analyzed by the investigators, 243 patients were treated with anticoagulants and 141 patients were not. Interestingly, anticoagulation was associated with a nonsignificant reduced adjusted odds ratio (OR) of developing PE 0.37 (95% CI, 0.09–1.45), which were mainly lobar or segmental. However, anticoagulant treatment was associated with a 4.87 (95% CI, 1.37–17.39) adjusted OR to develop bleeding. Of note, a high proportion of these patients were inpatients (71% in the non-treated group and 49% in the treated group). So even though the OR has been adjusted for age, sex, care setting at the time of calf DVT, existing cancer, and history of DVT to compare treated and untreated patients, the overall population is a rather high-risk population of patients [70].

Altogether, these studies question the necessity to treat all calf DVT with therapeutic anticoagulation. Due to the frequency of distal DVT (calf DVT represents approximately half of all diagnosed DVTs in ultrasound series), avoiding systematic anticoagulation could have a significant impact for the individual patient and from a public health perspective.

Table 24.8 Major efficacy and safety outcomes at day 42 in the CACTUS trial [14]

	Therapeutic nadroparin (n = 122)	Placebo (n = 130)	Absolute risk difference, %, (95% CI)	p value
Primary outcome by day 42	4 (3.3%)	7 (5.4%)	−2.1 (−7.8 to +3.5)	0.54
Proximal DVT	2 (1.6%)	7 (5.4%)	–	–
Pulmonary embolism	2 (1.6%)	0 (0.0%)	–	–
Major bleeding or nonmajor clinically relevant bleeding	5 (4.1%)	0 (0.0%)	+4.1 (+0.4 to +9.2)	0.03
Major bleeding	1 (0.8%)	0 (0.0%)	–	–
Nonmajor clinically relevant bleeding	4 (3.3%)	0 (0.0%)	–	–

Conclusions

Whether calf DVT requires anticoagulant therapy is currently one of the most debated issues in the field of venous thromboembolism. Although calf DVT is a very common medical condition, only few randomized controlled trials have addressed its treatment to date. Moreover, results of these trials are discordant, half of them suggesting that therapeutic anticoagulation should be prescribed, while some of them do not report a clear benefit of therapeutic anticoagulation. Three of these trials were open label and had many methodological limitations, while the only placebo-controlled trial was hampered by a limited statistical power.

Nevertheless, existing evidence suggests that not all calf DVTs deserve therapeutic anticoagulation. As shown in the randomized placebo-controlled trial, the risk-benefit ratio of anticoagulation is highly debatable in low-risk patients, as treatment is associated with a non-statistically significant decrease of symptomatic thromboembolic events but at the expense of a statistically significant increase in the rate of major or nonmajor clinically relevant bleedings. Therefore, it is quite possible that low-risk patients (e.g., patients without active cancer, outpatients, and patients without previous VTE) are better served without therapeutic anticoagulation and should undergo ultrasound surveillance.

This latter point supports the current ACCP guidelines, which suggest that low-risk patients with symptomatic calf DVT, such as patients without a previous DVT or active malignancy, could safely be managed with serial ultrasound testing and no anticoagulant therapy [4, 69]. Moreover, not treating with anticoagulants all calf DVT could be an important cost-saving strategy, as calf DVT represents half of diagnosed DVT [9].

Recent approval of the direct oral anticoagulants (DOACs) could also impact future strategies. Until recently, the use of anticoagulants in patients with calf DVT was limited by the cost and especially the invasive nature of daily LMWH injections or the cumbersome initiation and management of warfarin therapy. The risk-benefit balance of DOACs has not been evaluated for this indication yet, and large prospective trials are needed. The use of a prophylactic dose of anticoagulants could also represent another alternative in the future as it could potentially reduce the symptomatic VTE rate and decrease the bleeding rate when compared to therapeutic treatment. In patients with superficial vein thrombosis, a prophylactic dose was shown to be associated with a reduction in the rate of thromboembolic complications, without any increase in the risk of bleeding [71]. However, no formal validation of this attitude is nowadays available for thrombosis involving the deep venous system. Whether a prophylactic dose of anticoagulants could be an alternative for distal DVT remains to be determined.

In conclusion, low-risk patients with symptomatic distal DVT may benefit more from

elastic compression stockings and ultrasound monitoring rather than therapeutic anticoagulant treatment. At the moment and despite the lack of clear data, it seems wise to still give therapeutic anticoagulation to patients with active cancer, to patients with previous VTE, to patients with unprovoked distal DVT, and maybe to inpatients not at high bleeding risk, but this may be challenged by future studies.

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Endovascular Treatment of Deep Vein Thrombosis

25

Raja S. Ramaswamy and Suresh Vedantham

Clinical Pearls

1. Patients with acute extensive iliofemoral DVT with severe symptoms and low risk for bleeding are most likely to benefit from catheter-directed thrombolysis.
2. Avoid full anticoagulation at the time of thrombolysis to decrease risk of bleeding.
3. Using pharmacomechanical thrombectomy techniques in the first session can decrease the length of infusion therapy and sometimes allow for single-session treatment.

Introduction

Venous thromboembolic disease (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major health problem in the United States and worldwide. The United States Surgeon General has estimated that approximately 350,000–600,000 cases of symptomatic lower extremity DVT/PE occur each year, causing over 100,000 deaths, and named PE as the most preventable cause of death in hospitalized patients [1].

Lower extremity DVT is a serious medical condition with short- and long-term complications that can result in major disability as a result of pulmonary embolism, postthrombotic syndrome, paradoxical embolization, and/or limb amputation. Although anticoagulation is the mainstay, first-line treatment, the last two decades have seen increased use of catheter-based methods to treat acute deep venous thrombosis. The purpose of this chapter is to highlight the rationale, safety profile, evidence, and clinical outcomes that are achieved utilizing endovascular methods for the treatment of acute DVT.

Rationale for Thromboreductive Strategies

Acute DVT has the potential to lead to major short- and long- term health consequences. In the short-term or acute phase, DVT may present as pulmonary embolism (PE), phlegmasia cerulea dolens, and/or paradoxical embolization. DVT resulting in pulmonary embolism (PE) represents one-third of the presentation of venous thromboembolic cases [2]. DVT may also manifest clinically as phlegmasia cerulea dolens, a rare condition in

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which DVT leads to massive swelling of the entire extremity with resultant arterial insufficiency, compartment syndrome, venous gangrene, and/or potentially limb amputation. Paradoxical embolization is another potential manifestation of DVT. Paradoxical embolization is rare and occurs when thrombus in the venous system passes through an intracardiac shunt to enter the arterial circulation. Paradoxical embolization may lead to systemic embolization and cerebrovascular ischemia [3].

Late or long-term complications of PE may arise despite the use of anticoagulant or endovascular therapy including recurrent venous thromboembolic disease, chronic thromboembolic pulmonary hypertension, and postthrombotic syndrome (PTS) [4, 5]. Anywhere from 25 to 50% of patients with a first episode of proximal lower extremity DVT may develop PTS [2]. PTS is a chronic condition that develops in the affected lower extremity (or extremities) months to years following an episode of DVT. Patients with PTS have symptoms and signs including daily limb pain, aching, fatigue, heaviness, and swelling that worsen in an upright position or with activity. Other potential manifestations of PTS include stasis dermatitis, skin changes (hyperpigmentation and/or subcutaneous fibrosis), and skin ulceration [6]. PTS significantly affects quality of life and poses a major economic burden due to the associated treatment costs [7, 8].

Factors that predict the development of PTS are not entirely understood. Recurrent ipsilateral DVT increases the risk of PTS by 2–6 times [3]. The quality of anticoagulant therapy, specifically if subtherapeutic, is associated with development of PTS [9]. Despite adequate anticoagulant therapy, a large subset of patients progress to the development of PTS. Other factors that may influence the development of PTS include increased age, increased BMI, and female gender [4]. Anatomic extent is another important factor in the development of PTS. Patients presenting with proximal DVT develop PTS at higher rates than those that present with distal DVT. Patients with DVT in the iliac venous system and/or common femoral vein experience PTS rates that exceed 50% despite appropriate therapy and have much higher rates of recurrent VTE [7, 10, 11]. Physicians should regard iliofemoral DVT as a high-risk condition for which efficient and effective therapy should be administered.

Early Thrombus Removal: The Open Vein Hypothesis and Proof of Concept

Although the pathogenesis of PTS is poorly understood, the physiologic parameters leading to its development are valvular reflux and venous obstruction. The "open vein" theory hypothesizes that rapid thrombus elimination and restoration of unobstructed deep venous flow in patients with acute DVT may prevent PTS [12]. PTS is found to develop more frequently in proximal DVT patients who have residual venous thrombus or valvular reflux [13]. A meta-analysis of randomized DVT treatment trials found a correlation between quantity of residual thrombus after anticoagulant therapy and the subsequent incidence of VTE which is associated with PTS [14]. Further, small randomized trials have shown the use of surgical venous thrombectomy and systemic thrombolysis to be associated with reduced rates of PTS in comparison with anticoagulation alone [14–17].

Systemic thrombolysis is no longer recommended for the treatment of acute DVT as the thrombolytic agent does not reach the area of thrombus in optimal concentrations and poses an unacceptably high rate of major bleeding [18–21]. However, multiple studies regarding the use of systemic thrombolysis have been performed which have led to observations that provide current rationale for the use of endovascular therapy in the treatment of acute DVT. In one study, the use of streptokinase provided complete thrombus lysis in 45% with acute DVT and partial lysis in 65%, while the use of anticoagulation alone had complete clot lysis in less than 5% and partial lysis in 20% [22, 23]. A significant finding from systemic thrombolysis studies is that clot lysis occurred more frequently in patients with nonocclusive thrombi as opposed to occlusive thrombi [24]. These findings led to

the development of catheters that could be embedded into thrombus for complete treatment. Systemic thrombolysis and surgical thrombectomy inherently carry risks including excess bleeding and invasiveness, respectively; for this reason, systemic thrombolysis is not used for DVT in current practice, and surgical thrombectomy is reserved for severely affected patients with contraindications to endovascular therapy [19].

Indications for Endovascular Intervention

Per the Society of Interventional Radiology quality improvement guidelines, most patients undergoing endovascular thrombus removal for lower extremity DVT should have imaging-proven symptomatic DVT in the IVC or iliac, common femoral, and/or femoral vein in a recently ambulatory patient with DVT symptoms for <28 days or in whom there is a strong clinical suspicion for recently formed (<28 days) DVT [25–27].

Likelihood of Successful Catheter-Directed Thrombolysis

Catheter-directed therapy is more likely to be successful in patients in which symptoms have been less in the acute phase or less than 2 weeks. A careful history should be performed to detail if patients have had acute symptoms (<2 weeks) or chronic symptoms (>4 weeks). If chronic DVT alone is suspected, thrombolytic therapy is not likely to be effective, and there are other endovascular treatment options that may better serve the patient [21, 25].

Patient Selection for Catheter-Directed Thrombolysis

A detailed history and physical exam should be performed prior to selecting patients for catheter-directed therapy. Current evidence in the literature favors the use of CDT along with anticoagulation in patients with acute DVT that includes severe manifestations of DVT (progressive IVC thrombosis or phlegmasia cerulea dolens) or rapid extension of DVT or its clinical manifestations despite anticoagulation. CDT may be used as a first-line treatment option for thrombus that includes the iliac and/or common femoral veins based on the additional risk of recurrent DVT and PTS, but it should be recognized that definitive randomized trials have not yet been completed to validate a favorable benefit-to-risk ratio for this approach. Concurrently, patient selection also depends on a tailored individual approach assessing the projected risk of bleeding, clinical severity of DVT, anatomic extent of DVT, life expectancy/ambulatory capacity, and the patient's personal preference.

Patients selected to undergo CDT should be assessed for the projected risk of bleeding which includes current active bleeding, recent major surgery, recent gastrointestinal bleeding, pregnancy, history of stroke within the previous 3 months, recent intracranial/intraspinal trauma or surgery, recent internal eye surgery or hemorrhage, intracranial/intraspinal mass or other lesions, thrombocytopenia, or other bleeding diatheses (Table 25.1) [25, 27].

Clinical severity and anatomic extent should be taken into account with previously published data when deciding if CDT is necessary. Patients can be categorized into groups based on clinical severity of DVT. Group A comprises of patients in which urgent thrombolysis is indicated to prevent life- or limb-threatening complications of acute DVT. Group A includes those patients with progressive IVC thrombosis or phlegmasia cerulea dolens or if IVC thrombosis presents increased risk of fatal PE or renal failure. Group B includes patients where initial anticoagulation failed to achieve therapeutic objectives including DVT progression and worsening of clinical severity/symptoms. Group C is reserved for patients with symptomatic DVT for which anticoagulation is administered with the purpose of preventing PTS. Aggressive therapy should be pursued for patients in Group A. A low threshold for exclusion should be applied for patients in Group B or

Table 25.1 Indications and contraindications to catheter-directed thrombolysis for lower extremity DVT

Indications
• Imaging-proven symptomatic DVT in the IVC, iliac, common femoral, and/or femoral vein in a recently ambulatory patient with DVT symptoms for less than 28 days or in whom there is strong clinical suspicion for recently formed (less than 28 days) DVT
Contraindications
• Active internal bleeding or disseminated intravascular coagulation
• Recent cerebrovascular event (including TIA), neurosurgery (intracranial, spinal), or intracranial trauma (<3 months)
• Contraindication to anticoagulation
• Recent cardiopulmonary resuscitation, major surgery, obstetrical delivery, organ biopsy, major trauma, or cataract surgery (<7–10 days)
• Intracranial tumor or other intracranial lesion
• Uncontrolled hypertension: systolic BP >180 mmHg, diastolic BP >100 mmHg
• Recent major GI bleeding (<3 months)
• Serious allergic reaction to thrombolytic agent, anticoagulant, or contrast media
• Severe thrombocytopenia
• Known right to left cardiac or pulmonary shunt or left heart thrombus
• Inability to tolerate procedure due to severe dyspnea or acute medical condition
• Suspicion for infected venous thrombus
• Moderate-to-severe renal failure
• Pregnancy or lactation
• Severe hepatic dysfunction
• Bacterial endocarditis
• Diabetic hemorrhagic retinopathy

BP blood pressure, *DVT* deep vein thrombosis, *GFR* glomerular filtration rate, *TIA* transient ischemic attack

C particularly if there is a significant risk for complications [26, 28, 29].

Anatomic extent of DVT is an important consideration in appropriately selecting patients for CDT. Historically, *proximal DVT* refers to thrombus within the popliteal, femoral, deep femoral, common femoral, or iliac veins or the IVC. Patients with DVT in the iliac vein or common femoral vein, also referred to as *iliofemoral DVT*, experience much more clinical severity and experience higher rates of recurrent VTE. *Distal or isolated calf DVT* is confined in the calf veins below the popliteal vein (Table 25.2).

Table 25.2 CDT decision criteria based on clinical presentation

	Bleeding risk		
Clinical presentation	Low	Moderate	High
Acute limb threat	Yes	Yes	Surgery
Extensive IVC thrombosis	Yes	Yes	No
Iliofemoral DVT with progression of symptoms or anatomic extent despite anticoagulation (second-line therapy)	Yes	No	No
Iliofemoral DVT to prevent PTS (first-line therapy)	Maybe	No	No
Femoropopliteal or isolated calf DVT to prevent PTS	No	No	No

CDT should generally not be pursued in patients where the extent of the DVT does not include the IVC, iliac vein, or common femoral vein given the risks of therapy and the paucity of data showing a compelling benefit. Patients presenting with an iliofemoral DVT and low bleeding risk are the group that is most likely to achieve clinical benefit (Fig. 25.1). Patients with asymptomatic or isolated calf DVT are not candidates for endovascular therapy [27]. Patients that have a short life expectancy or are unable to ambulate are not likely to benefit from CDT. Additionally, given the risk/benefit profile and inconveniences, fully functional patients may decline aggressive therapy. Regardless, the benefits versus risks and treatment alternatives should be thoroughly discussed [4, 30, 31].

Interventional Options for Acute Deep Vein Thrombosis

Technological advances in catheter technology and device development coupled with literature-supporting minimally invasive interventional techniques have led to an aggressive approach in the treatment of acute DVT. Advances in noninvasive imaging modalities including Duplex ultrasound, CT, and MRI have provide enhanced

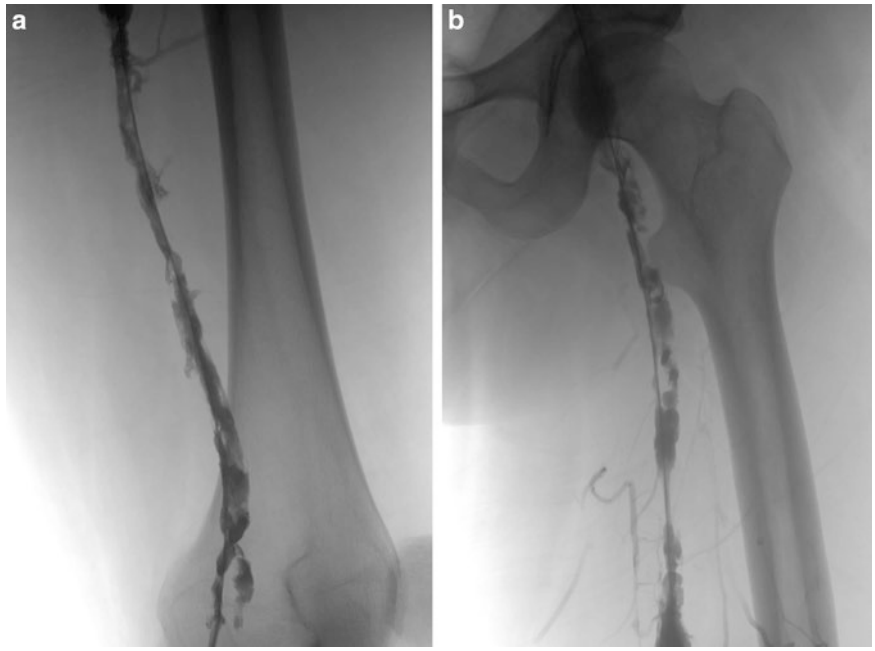

Fig. 25.1 Twenty-four-year-old male status post trauma to the right knee presented to the emergency department with right lower extremity swelling. Access was obtained via the right popliteal vein. Venogram performed via the right popliteal vein demonstrates multiple filling defects and venous expansion (**a**, **b**) in the right popliteal, right femoral, and right common femoral veins compatible with acute thrombus formation. Catheter-directed thrombolysis was not pursued because the patient had a recent spinal surgery, and iliofemoral veins were patent and without evidence of thrombus (not shown). The patient was managed with therapeutic anticoagulation

characterization of the extent of thrombus particularly in the IVC and iliac venous system. Improvements in catheter-based delivery systems have been made such that intrathrombus drug delivery is more efficient. Device development including but not limited to the AngioJet (Boston Scientific, Marlborough, MA), Arrow-Trerotola percutaneous thrombolytic device (Arrow, Reading, PA), and AngioVac (Angiodynamics, Latham, NY) has served a significant adjunctive tool to acute thrombus removal.

Multiple endovascular techniques have evolved for the treatment of acute thrombus. Current endovascular techniques used include catheter-directed thrombolysis (CDT), percutaneous mechanical thrombectomy (PMT), and percutaneous catheter-directed thrombolysis (PCDT). PCDT can then be further subdivided into first- and second-generation techniques which will be discussed in the following sections.

Catheter-Directed Thrombolysis (CDT)

Catheter-directed thrombolysis refers to the delivery of thrombolytic drug directly into thrombus using a catheter or catheter-based device that is embedded within the thrombus using imaging guidance [32]. This was the first endovascular method utilized for treatment of acute DVT. CDT achieves a higher intrathrombus drug concentration and reduced systemic drug concentration which allows thrombolytics to penetrate into a completely occlusive thrombus [33]. Additional benefits include reduced overall thrombolytic agent dose systemically, treatment time, and complication rates. Further, adjunctive techniques can be utilized to evaluate and treat venous abnormalities that may have provoked the initial thrombotic event.

Access is gained via either an internal jugular vein, popliteal vein, or other veins of the affected

extremity. Ideally a non-obstructed, non-thrombosed vein is accessed. The popliteal vein serves as a convenient access point owing to its ease for achieving hemostasis through manual compression following intervention. The jugular vein serves as a good access site as well; however, wire and catheter manipulation are against the direction of the venous valves. The jugular venous access site requires longer wires and catheters. Serial venograms and/or intravascular ultrasound (IVUS) is used and obtained to evaluate the extent of thrombus. Next, a multi-side hole infusion catheter is placed within the thrombus, and a fibrinolytic drug is infused. The most commonly used fibrinolytic drug is recombinant tissue plasminogen activator (rt-PA, Genentech, San Francisco, CA). Although this drug is not FDA-approved for DVT therapy, suggested dosing of rt-PA is weight-based and is 0.01 mg/kg/h for up to a maximum of 1.0 mg/h for approximately 6–24 h. While infusing lytics, the patient is continuously monitored in a high-acuity bed, and a CBC, fibrinogen, and PTT are drawn every 6 h. If laboratory parameters deviate from expected ranges, infusion is temporarily or permanently discontinued. After infusion serial venograms are obtained to determine if further lysis needs to be performed or if the catheter needs repositioning. Serial venograms also serve to identify any venous anatomic lesion that needs further treatment with balloon venoplasty and/or stent placement (Fig. 25.2).

Stent placement is typically reserved for the common iliac and external iliac anatomic abnormalities. At times it is necessary to extent stent placement into the common femoral vein. Currently, there are no venous stents that have FDA approval. If stent placement is necessary, an uncovered, self-expandable bare metal stent is favored because they have sufficient hoop strength and allow inflow from venous tributaries. Drawbacks or limitations to CDT are its long infusion times required to obtain complete thrombus treatment, the risk of major bleeding (see below), and hospital resources utilized. Following catheter-directed thrombolysis, patients should be anticoagulated and monitored closely (Table 25.3).

Percutaneous Mechanical Thrombectomy

Percutaneous mechanical thrombectomy (PMT) devices provide mechanical clot debulking by macerating and removing thrombus fragments from the vascular lumen. PMT increases the surface area of the vessel which may improve endogenous thrombolytic action. Mechanisms of action include rheolytic/high-velocity water jets (AngioJet Rheolytic Thrombectomy System; Boston Scientific, Marlborough, MA) [34] or rotational mechanical devices (Arrow-Trerotola percutaneous thrombolytic device; Arrow, Reading, PA) [35]. Potential disadvantages of PMT devices include venous valvular damage and potential for embolizing thrombus with mechanical manipulation. Additional disadvantages when using AngioJet are the potential for bradycardia and hemoglobinuria secondary to red blood cell hemolysis. As a stand-alone technique, PMT using percutaneous devices is rarely sufficient to treat a large thrombus burden [36].

AngioVac (Angiodynamics, Latham, NY) is an aspiration thrombectomy device capable of removing large amounts of thrombus via a large bore (22 Fr) suction catheter. The AngioVac device utilizes a recirculation circuit (and hence, a second large sheath) and is primarily considered in those with a significant amount of thrombus in the right atrium or vena cava and a contraindication to thrombolysis. Early results are promising for the ability of AngioVac to remove thrombus, but there are no completed prospective studies evaluating this device [37].

Pharmacomechanical Catheter-Directed Thrombolysis (PCDT)

Pharmacomechanical catheter-directed thrombolysis combines the use of CDT and PMT. CDT dissolves fragments that may otherwise have led to a PE. PMT removes thrombus and thus increases the surface area which allows for faster dispersion of thrombolytic drug. PCDT therefore reduces the required lytic dose and infusion time and may therefore reduce bleeding complications. Different permutations of drugs and devices may

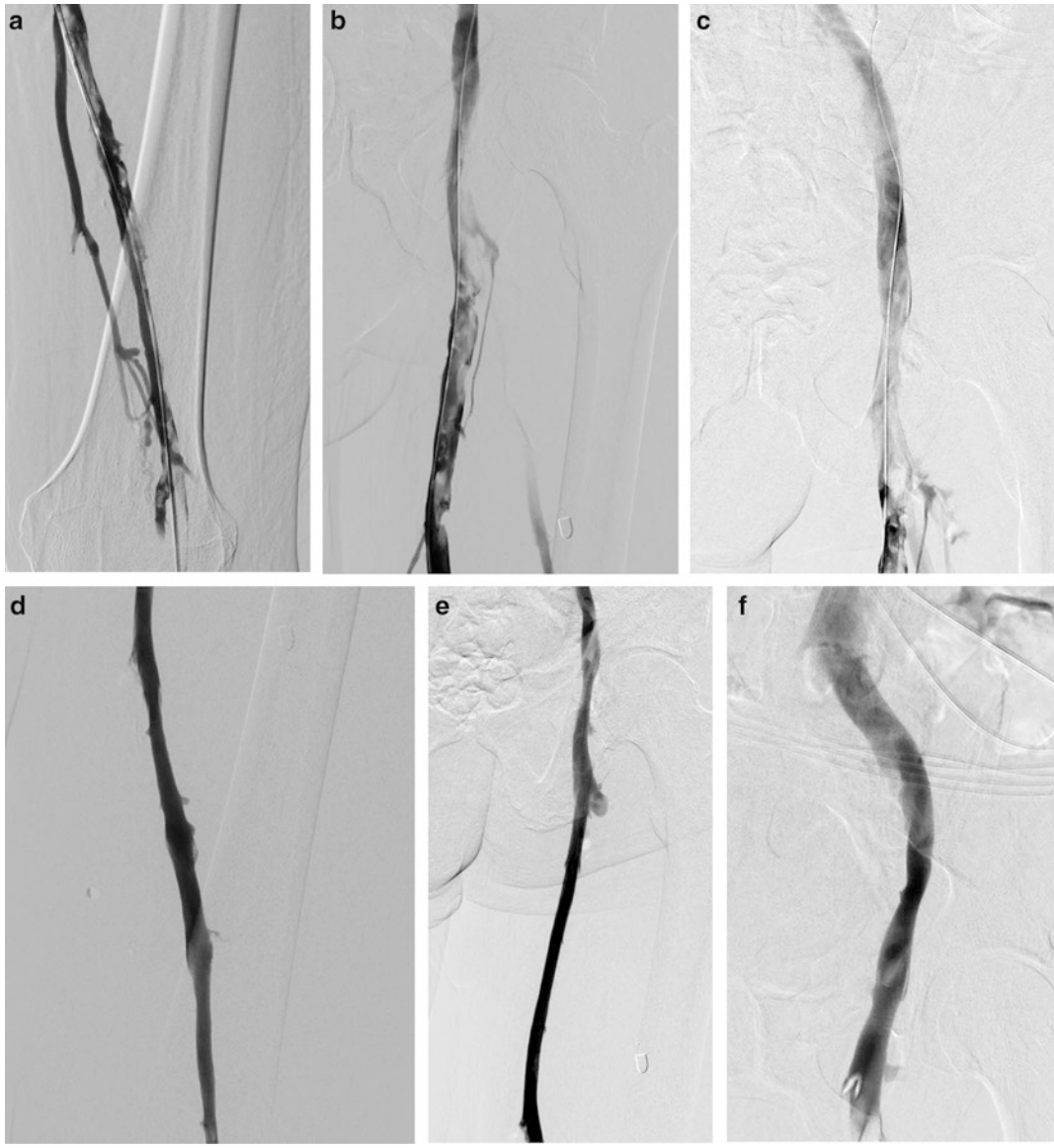

Fig. 25.2 Sixty-three-year-old male with history of previous right lower extremity below the knee amputation with acute onset of left lower extremity pain and swelling. Duplex ultrasound (not shown) demonstrated acute thrombus in the left popliteal, left femoral, and left common femoral veins. Due to concern for thrombus extending into the iliofemoral system, a venogram was pursued. Vascular access was obtained in the left popliteal vein. Digital subtracted contrast venograms were obtained demonstrating acute thrombus extending from the left popliteal/femoral vein (**a**, **b**) into the left common femoral and left iliac vein (**c**). An infusion catheter was placed into the thrombus, and rt-PA was administered at a rate of 0.01 mg/kg/h for a total of 12 h. The patient returned for a repeat venogram. Percutaneous mechanical thrombectomy was performed in addition to catheter-directed thrombolysis with follow-up venograms showing resolution and clearing of the thrombus burden (**d**–**f**)

be used; however, no single technique has been proved superior. There are two general categories of PCDT methods: "first-generation PCDT" and "single-session PCDT."

With first-generation PCDT, the proceduralist may initially use CDT infusion with subsequent use of PMT with either an aspirating or nonaspirating device to macerate and remove residual

Table 25.3 Technical considerations in performing catheter-directed thrombolysis

– Apply rigorous clinical evaluation to identify patients with major clinical manifestations of DVT, major anatomic thrombus extent, and a very low risk of bleeding
– Ensure that the effect of oral anticoagulants or long-acting (e.g., once daily) parenteral anticoagulants is subtherapeutic before thrombolysis is initiated
– Routinely use ultrasound guidance for venous access, to prevent bleeding from inadvertent arterial punctures
– Use infusion CDT when the popliteal vein has poor inflow, to optimize thrombus removal from the non-axial veins; consider single-session pharmacomechanical therapy when there is good popliteal venous inflow
– Use weight-based TPA infusions at 0.01 mg/kg/h, not to exceed 1.0 mg/h
– Keep TPA infusion durations to a minimum, ideally less than 24–30 h
– Target unfractionated heparin to the subtherapeutic range during thrombolysis, to avoid overshoot which could cause bleeding
– Ensure that iliac vein obstructive lesions (e.g., May-Thurner syndrome) are treated
– Closely monitor anticoagulant therapy during the weeks after CDT to avoid preventable cases of re-thrombosis. If possible, utilize LMWH for 1–3 months after CDT
– Avoid routine placement of IVC filters for CDT, but if a filter is placed, be sure to remove it in a timely fashion (assuming the patient can still be anticoagulated)

thrombus. Retrospective comparative studies suggest that these methods offer a safety profile at least as good as traditional CDT, with up to 50% reduction in drug dose and treatment time, reduced hospital stay, intensive care unit utilization, and hospital costs [38].

Single-session PCDT obviates the need for extended drug infusions or monitoring in the ICU. An example of single-session PCDT would be to first use the AngioJet catheter with the power-pulse technique to infuse thrombolytic into the thrombus. After a dwelling period of 30 min, the AngioJet catheter is used to aspirate residual thrombus (Fig. 25.3). The effects of PCDT on the development of postthrombotic syndrome are still unknown at this point. The major disadvantage to both first-generation and single-session PCDT is longer procedure duration [27].

Complications

The proceduralist should be aware of complications that may potentially arise from CDT and related methods. The risk of major endovascular thrombolytic complications is between 2 and 4%. In a review of major studies, major bleeding was the most frequent major complication at approximately 2.8%. Intracranial bleeding, symptomatic pulmonary embolism, and death are the most feared complications of catheter-directed thrombolytic therapy; however, they are rare and occur at a rate of <1% based on existing studies.

Outcomes

Multiple published studies have validated the ability of catheter-directed therapy to rapidly remove thrombus and restore venous flow in more than 85–90% of patients who are treated for acute DVT. However, most CDT studies had major design limitations [39–41]. The CaVenT trial, published in 2012, randomized patients with iliac or upper femoral vein DVT to receive either CDT and anticoagulation or anticoagulation alone (both groups also received elastic compression stockings). At 2-year follow-up, the relative risk of PTS was reduced by 26% in those that received CDT (41.1 versus 56.6%, $p = 0.047$) [11]. At 5-year follow-up, CDT resulted in persistent and increased clinical benefit in terms of PTS reduction; however, CDT did not lead to improved quality of life (QOL) in that study [42].

The ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) is an ongoing, NIH-sponsored, multicenter randomized controlled trial. In the ATTRACT trial, 692 patients have been randomized to receive PCDT plus standard DVT therapy or standard DVT therapy alone (anticoagulant therapy and elastic compression stockings). Patients are followed for 2 years with assessment of PTS, health-related QOL, relief of initial leg pain and swelling, safety, and costs. The results of the ATTRACT trial are forthcoming in 2017 [29].

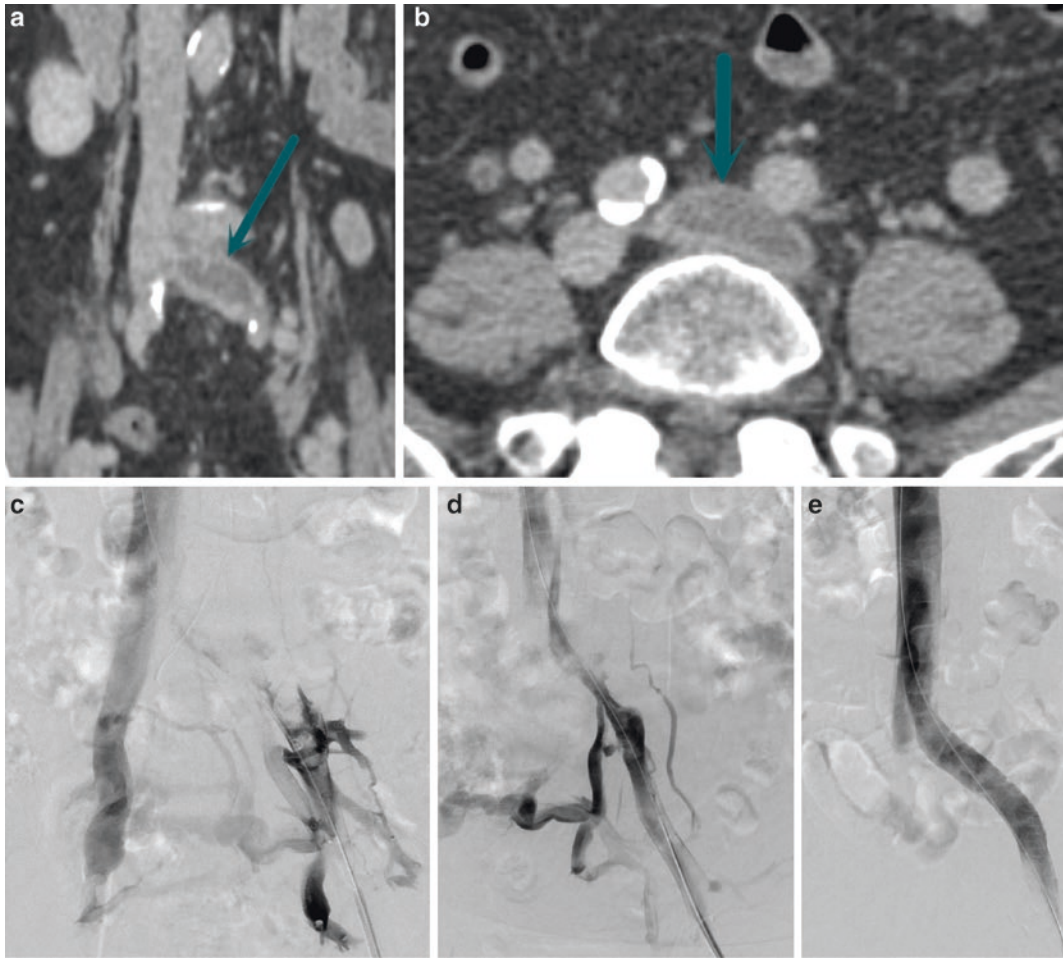

Fig. 25.3 Seventy-three-year-old female presented with an acute onset of left lower extremity pain and swelling. CT scan of the abdomen and pelvis with intravenous contrast demonstrated thrombus within the left common iliac vein (**a**, **b**). The patient was referred for a catheter-directed venogram and treatment. Contrast venogram via the left common femoral vein demonstrated thrombus within the left common iliac vein (**c**). Single-session percutaneous catheter-directed thrombolysis was performed. First, rt-PA was infused through a multi-side hole catheter and allowed to dwell for 30 min. Next, the Angiojet thrombectomy device was used to remove additional thrombus. Angioplasty (**d**) and a stent was placed in the left common iliac vein. Final venogram shows a widely patent left common iliac vein with resolved venous collaterals and flow into the inferior vena cava (**e**)

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Surgical Thrombectomy for Deep Vein Thrombosis

26

Faisal Aziz and Emelia Bittenbinder

Clinical Pearls

1. Open venous thrombectomy is an effective modality for thrombus removal and can be used in patients with contraindication to thrombolysis.
2. Infrainguinal thrombectomy is performed in the direction of flow and requires a counter incision over the calf to pass Fogarty catheter.
3. Thrombectomy of the iliac veins should be performed under fluoroscopy with protection of the IVC from embolization.

Introduction

Presentation of deep venous thrombosis (DVT) can encompass a wide range of clinical presentations ranging from mild calf swelling to severe, painful swelling of the entire lower extremity [1]. While tibial vein DVT can have a fairly benign clinical course, acute obstruction of the iliofemoral venous system may lead to development of phlegmasia cerulea dolens and venous gangrene. Patients with iliofemoral DVT who do not develop phlegmasia cerulea dolens in the acute phase and are not treated surgically are at a substantially higher risk for developing postthrombotic syndrome long term. Postthrombotic syndrome is associated with significant reduction in the quality of life [2, 3]. This is attributed to the fact that the common femoral vein, external iliac vein, and common iliac vein form the main venous outflow channel from the lower extremity [4]. Postthrombotic syndrome is caused by ambulatory hypertension, which is defined by elevated venous pressure during exercise [1]. Ambulatory hypertension is directly correlated with changes of chronic venous disease such as swelling, venous hyperpigmentation, and ulceration. Valvular incompetence and obstruction contribute to ambulatory hypertension. Early removal of thrombus burden can significantly decrease the long-term sequelae of postthrombotic syndrome by removing obstruction and preserving valve function.

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Patient Evaluation and Selection

For any thrombus removal strategy to be successful, it is imperative to have adequate imaging of the proximal and distal extent of thrombus. Venous duplex is usually a useful study to determine the distal extent of the DVT. Determination of the proximal extent of thrombus may necessitate the use of CT scan with contrast. CT of the chest has additional benefit of identification of pulmonary embolism, which is found in approximately 50% of these patients [1]. CT scans also allow for identification of other pathologies that may be contributing to thrombus formation, such as malignancy. The Society for Vascular Surgery and the American Venous Forum states that the indication for early thrombus removal includes a patient with the following criteria (grade 2C) [5]:

1. First episode of acute iliofemoral deep venous thrombosis
2. Symptoms less than 14 days in duration
3. A low risk of bleeding
4. Ambulatory with good functional capacity and an acceptable life expectancy

The evidence is limited by lack of randomization, loss to follow-up, and inability to compare studies; however, it does suggest that early thrombus removal is associated with decreased severity of postthrombotic syndrome and improvement in valvular competence. There is grade 1A evidence for early thrombus removal in patients with limb-threatening venous ischemia (phlegmasia cerulea dolens).

The guidelines suggest utilizing open surgical venous thrombectomy in patients who are candidates for anticoagulation, but in whom thrombolytic therapy is contraindicated (grade 2C) [5]. Surgical venous thrombectomy has the potential to offer patients a quick resolution of extensive iliofemoral DVT and significantly reduces the postthrombotic morbidity. A small prospectively randomized study [6] demonstrated that patients with iliofemoral DVT in the surgical group had less severe sequelae with improved patency and milder postthrombotic symptoms ($p < 0.05$) as compared to patients treated medically with anticoagulation only. In another study, compartment pressures were measured before and after venous thrombectomy. The data demonstrated pathologically high compartment pressures preoperatively and normal pressure postoperatively [7]. The surgical modalities available for thrombus removal include endovascular management and open surgical thrombectomy. Endovascular management has been described in the previous chapter. This chapter will focus on the open surgical treatment of iliocaval DVT.

Surgical Venous Thrombectomy Operative Technique

Comerota et al. have described contemporary venous thrombectomy in detail [1]. This technique differs from traditional operative thrombectomy in many ways. These include the following:

1. Obtaining a pretreatment imaging study, including venous duplex to demonstrate the level of venous occlusion
2. Utilizing Fogarty thrombectomy catheter
3. Utilizing intraoperative venograms
4. Correcting iliac vein stenosis by stenting
5. Creating an arteriovenous (AV) fistula
6. Performing infrainguinal thrombectomy
7. Placing the patient on full postoperative anticoagulation
8. Utilizing catheter-directed anticoagulation postoperatively
9. Utilizing postoperative intermittent pneumatic compression devices

The main objectives of open venous thrombectomy include identification of the extent of the thrombus, comprehensive removal of as much clot as possible, construction of an AV fistula to improve outflow velocities, and early and long-term anticoagulation. The technique is described below:

The procedure should be done in a room with access to fluoroscopy, whether that is fixed or with portable C-arm. As a precaution, an auto-

transfusion device should be available during the procedure. After induction with general anesthesia, a longitudinal groin incision is made to expose the common femoral vein. The confluence of the profunda vein and femoral vein into the common femoral vein should be identified and controlled with silastic vessel loops. A longitudinal venotomy is made in the common femoral vein at approximately the level of the saphenofemoral junction (Fig. 26.1a). Upon completion of thrombectomy, the venotomy can be closed with monofilament suture without significant compromise to the lumen of the common femoral vein. In cases, where primary closure may create significant narrowing of the venous lumen, a vein patch (or bovine pericardial patch) angioplasty should be performed. Basic principles of vascular surgery should be followed: securing inflow is the most critical aspect of any thrombectomy operation. The infrainguinal venous system is the inflow for iliofemoral veins. Infrainguinal thrombus is addressed first by elevating and wrapping the leg from toes proximally with tightly wound rubber bandage. The foot is dorsiflexed; the leg is squeezed to milk thrombus from below. The thrombus is then retrieved from femoral venotomy site. Good venous back bleeding usually indicates that significant burden of venous thrombus has been successfully removed.

Lack of decent venous back bleeding indicates presence of significant thrombus in the infrainguinal venous system. To address this, medial incision is made in the lower leg to expose the posterior tibial vein. After obtaining proximal and distal control, a longitudinal venotomy is performed on the posterior tibial vein (Fig. 26.1c). A #3 Fogarty balloon is passed from the posterior tibial vein proximally to the common femoral vein and brought out through the proximal femoral vein venotomy (Fig. 26.1a). A silastic IV catheter is used to connect the #3 Fogarty to another #4 Fogarty balloon. Pressure is applied to both balloons to secure them in the silastic tubing, and both are passed distally to the posterior tibial vein venotomy. This allows for atraumatic passage through the valves and clotted vein (Fig. 26.1b). The #3 Fogarty and the silastic tubing are removed. The #4 Fogarty is inflated and utilized to complete the infrainguinal thrombectomy (Fig. 26.1d). The inflated Fogarty catheter is passed with the direction of flow in the vein to avoid getting stuck on valves, and the thrombus is removed from the femoral incision (Fig. 26.1e). This process can be repeated with a bigger Fogarty in the place of the #4 Fogarty until no further thrombus is extracted.

An alternative to the abovementioned technique is introducing over the wire Fogarty catheter from the posterior tibial vein. At its exit from common femoral vein, a guidewire is inserted into the tip of the catheter and advanced, till it comes out of the catheter's hub (Fig. 26.2a). Now, the catheter can be removed and introduced over the wire, from the common femoral venotomy side and advanced till it exits the posterior tibial vein. The Fogarty catheter is then inflated and thrombus removed when the catheter is withdrawn from the common femoral venotomy site (Fig. 26.2b). This process can be repeated multiple times till good venous back bleeding is achieved.

Once infrainguinal thrombectomy is completed, a large diameter red rubber catheter is inserted into the posterior tibial vein and is flushed with a bulb syringe. This hydraulically removes any remaining thrombus from the deep venous system (Fig. 26.3). Infrainguinal deep venous system can now be instilled with dilute plasminogen activator solution. Comerota et al. recommend 4–6 mg recombinant tissue plasminogen activator in 200 mL of saline. This solution will remain in the infrainguinal veins until completion of the procedure. If infrainguinal thrombectomy is unsuccessful due to chronic thrombus in the femoral vein, the femoral vein is ligated below the level of the profunda femoris vein. The patency of the profunda femoris has to be ensured to allow for adequate inflow. Attention is then directed to the proximal thrombus. A #8 or #10 Fogarty catheter is passed several times into the iliac veins to remove the bulk of the thrombus. Then it is passed into the vena cava. This part of the procedure should be performed under fluoroscopy. Saline should be mixed with contrast to inflate the balloon. In cases in which caval clot exists, thrombectomy can be performed in the

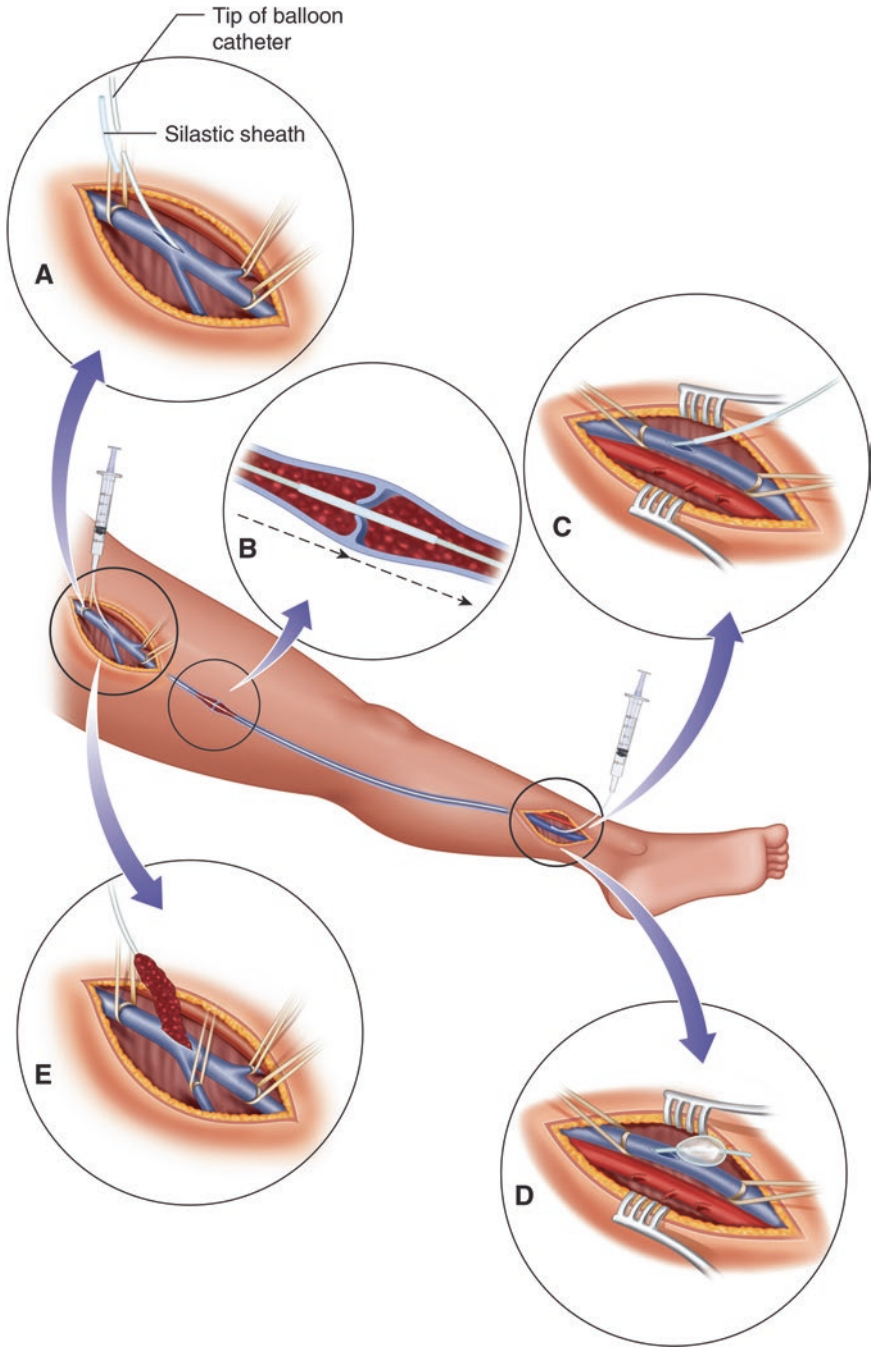

Fig. 26.1 Open thrombectomy of infrainguinal veins. The femoral veins (**a**) and the posterior tibial vein (**c**) are controlled via separate incisions. The Fogarty balloon is introduced from the tibial vein into the femoral vein with the direction of the valve. A silastic sheath is used to connect two Fogarty balloons together (**a**) to allow the passage of the balloon catheter with the direction of the valves (**b**) into the calf incision (**c**). The balloon is inflated (**d**) and pulled back to perform thrombectomy in the direction of flow and remove thrombus from the femoral vein (**e**)

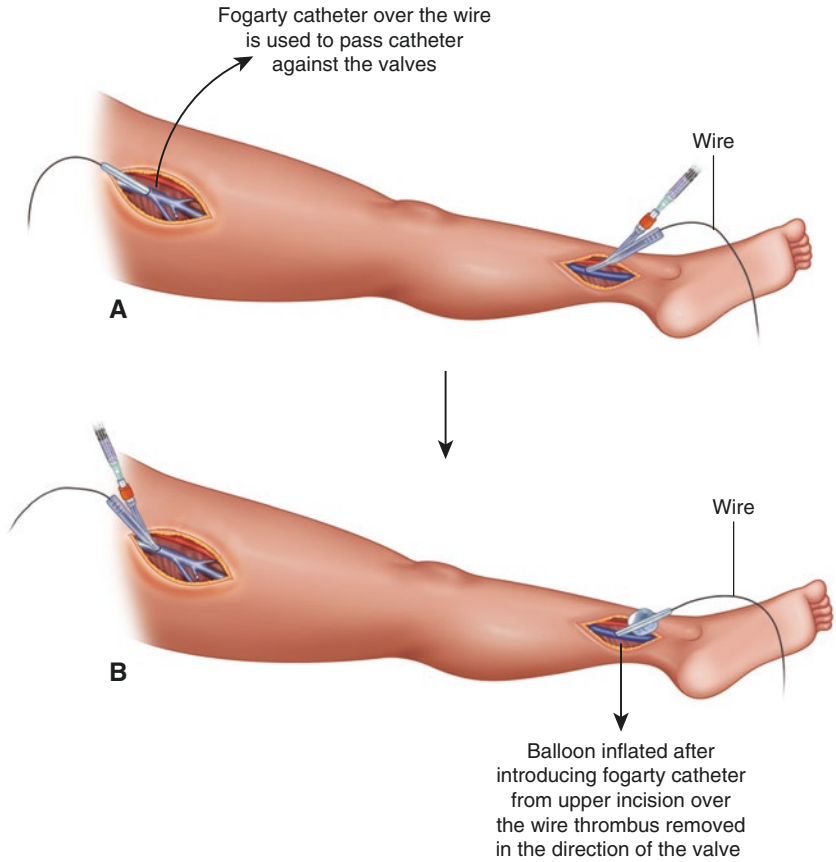

Fig. 26.2 Open thrombectomy of infrainguinal veins using over the wire Fogarty balloon. A Fogarty balloon is used as a directional catheter, and guidewire is passed from the posterior tibial vein into the femoral vein with the direction of flow (**a**). Next the catheter is withdrawn, while the wire is kept in the vein protruding from the body from both incisions. The Fogarty catheter is subsequently introduced from the groin incision over the wire. The wire allows the deflated balloon catheter to be advanced against the valves into the calf incision. The balloon is subsequently inflated and thrombectomy performed (**b**), while an assistant pins the wire next the calf incision. Having the wire in situ facilitates reintroduction of the catheter over the wire as needed until a "clean pass" is achieved

presence of a protective balloon. Another Fogarty balloon is inserted into the vena cava through the contralateral femoral vein and is inflated above the level of the clot to prevent pulmonary embolism. It is imperative that these steps be performed under fluoroscopic guidance. Once the iliofemoral venous thrombectomy is completed, fluoroscopy is used to evaluate the iliofemoral venous system to ensure drainage into the inferior vena cava. Any residual stenosis should be addressed with balloon angioplasty. If there is continued recoil, then an appropriately sized stent should be utilized. It is recommended to use at least a 12–14 mm stent for external iliac veins and 14–16 mm stent for common iliac veins. The common femoral venotomy is closed with a fine monofilament suture. Next an AV fistula is created between the superficial femoral artery and the end of the saphenous vein. A large branch of the saphenous vein can also be utilized for the fistula (Fig. 26.4a). The anastomosis of the fistula should be between 3.5 and 4 mm in diameter. The patency of the saphenous vein needs to be verified, and commonly thrombectomy needs to be performed. The AV fistula should be marked with suture with clips to guide future dissection if the AV fistula needs to be ligated in the future. The fistula can be closed using endovascular coils, and clips can be useful to determine the site of fistula under fluoroscopy. Most of these fistulas

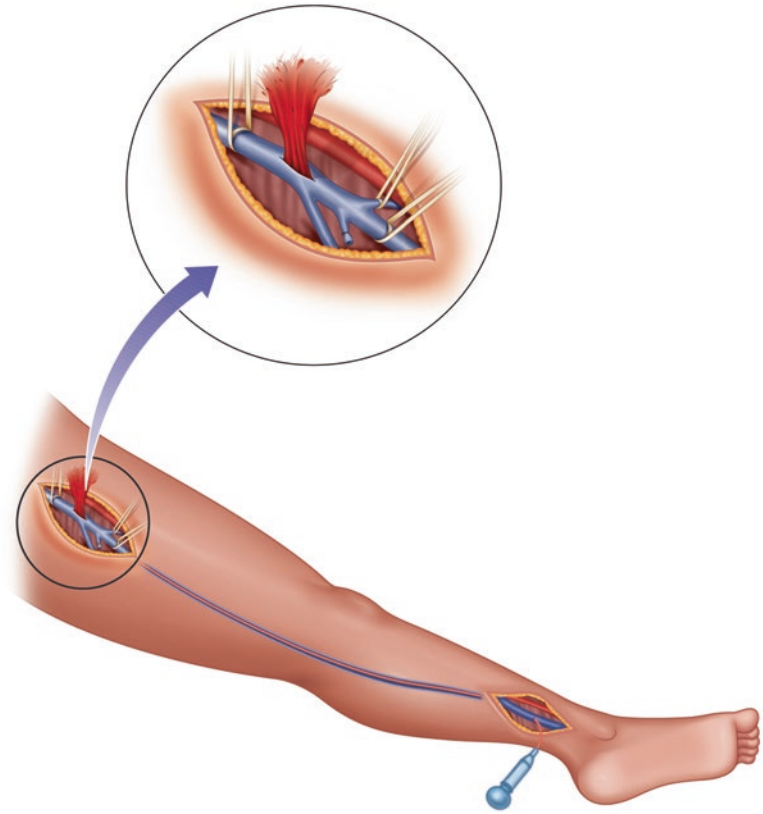

Fig. 26.3 After thrombectomy is performed, red rubber catheter and bulb syringe with heparinized saline are used to mechanically flush any residual thrombus in the venous system

do not need future ligation. Some surgeons recommend using a piece of synthetic PTFE graft to encircle the fistula in order to facilitate later dissection and ligation.

Measurements of the pressure in the common femoral vein should be taken before and after the AV fistula is opened. The pressure should not increase after placement of fistula. If the pressure gradient is more than 10 mmHg, the proximal vein should be evaluated for residual stenosis. This can be done with intravenous ultrasound. If residual stenosis is identified, then it should be corrected. If the pressure continues to be elevated, the AV fistula is banded to decrease flow and normalize the pressure. A closed suction drain is placed in the wound to collect any serous drainage or blood accumulation. The drain should exit through a separate incision that is adjacent to the incision. The wound is then closed in layers with running absorbable suture.

Next, closure of the calf incision is performed. The posterior tibial vein distal to the venotomy is ligated. An infusion catheter is placed in the distal posterior tibial vein and brought out through a separate stab incision. This is used to infuse heparin postoperatively and as access for future venograms. This allow for direct infusion of heparin in the affected veins. Suture is looped around the posterior tibial vein and infusion catheter, and both ends exit the skin. The ends are passed through a sterile button and secured snugly to the skin (Fig. 26.4b). This will occlude the posterior vein and decrease the risk of bleeding after the infusion catheter is removed.

Antibiotic ointment is applied to the groin incision, the sterile dressings are placed over the incisions, and the leg is wrapped in gauze and elastic bandages from toes to groin. This elastic bandage should be wrapped snugly around the leg. The infusion catheter will exit between the layers of the elastic bandage and can be connected to an infusion pump for heparin infusion. Full anticoagulation is continued postoperatively with unfractionated heparin via the posterior tib-

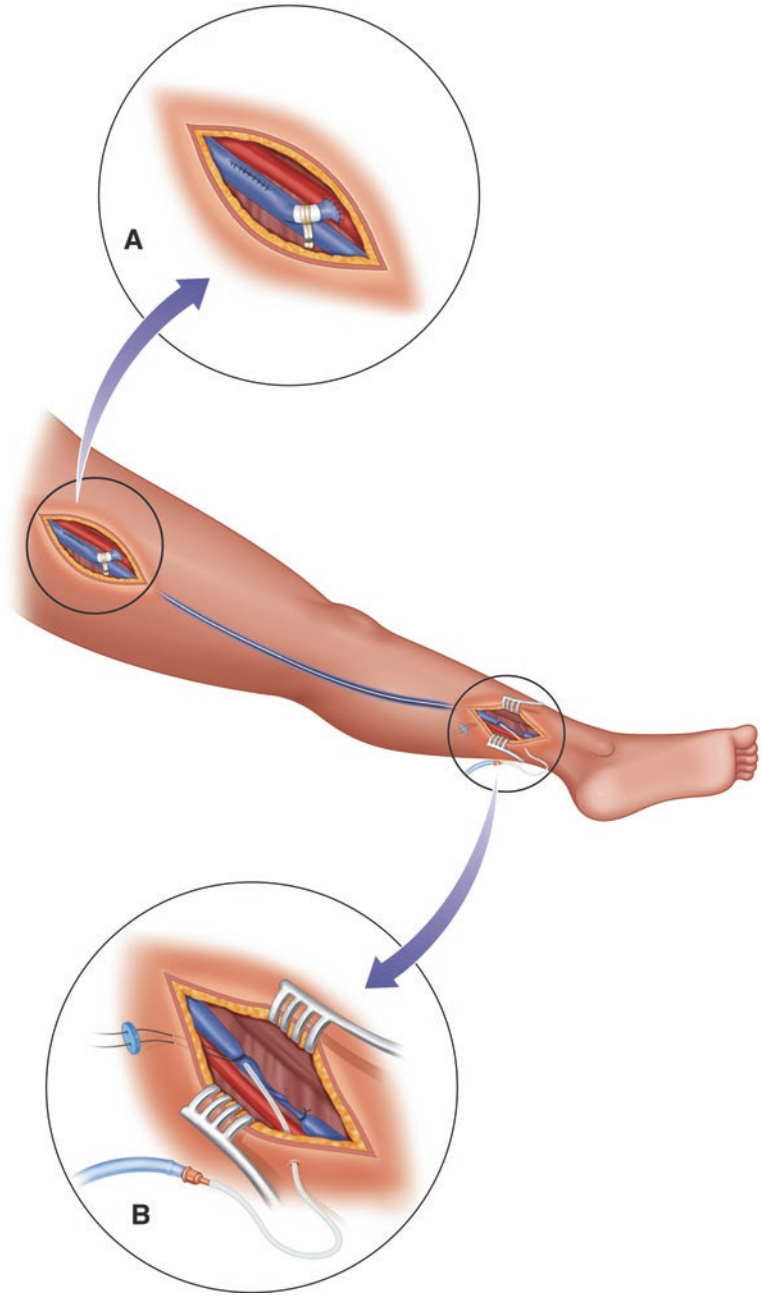

Fig. 26.4 An arteriovenous fistula is created between the CFA and the femoral vein to improve flow through the venous system (**a**). A silastic catheter is inserted in the posterior tibial vein and secured with a purse-string suture to the vein for immediate delivery of heparin drip into the veins after surgery (**b**)

ial vein infusion catheter. Oral anticoagulation is initiated when the patient is awake and taking in oral intake. The heparin drip should overlap the oral anticoagulation for 5 days and until the international normalized ratio is therapeutic between 2 and 3. The patient is encouraged to ambulate postoperatively. Intermittent pneumatic compression garments are used on both limbs during the postoperative period when the patient is not ambulating. These garments can be placed on top of compression stockings or dressings. Prior to removing the posterior tibial infusion catheter, a venogram should be obtained to evaluate for femoral-popliteal and iliofemoral venous system.

It is important to remember that the arteriovenous fistula can cause significant washout of contrast once it reaches the common femoral vein. If there is any significant stenosis seen in the iliofemoral segments, it should be corrected to maintain unobstructed drainage to the inferior vena cava. Oral anticoagulation should be continued for a prolonged period of time, at least a year. At discharge, the patient should be prescribed 30–40 mmHg compression stockings and advised to wear them from the time they awaken until the time they go to bed every day.

Outcomes

Operative venous thrombectomy is a surgical operation which was initially largely abandoned by surgeons in the United States because of two early reports, reporting non-favorable outcomes. A Scandinavian randomized trial [8] randomized patients with iliofemoral deep venous thrombosis into two arms: surgical thrombectomy with arteriovenous fistula versus anticoagulation alone. Five-year outcomes showed improved iliac vein patency, asymptomatic status, and ambulatory venous pressures in surgical group as compared to nonsurgical group. With the advancements in endovascular technologies, more and more iliofemoral deep venous thrombosis cases are treated with minimally invasive strategy, however, technique of open surgical thrombectomy part of the armamentarium of vascular surgeons. When used for appropriate indications, it can prove to be a beneficial technique in patients with massive iliofemoral deep venous thrombosis.

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Upper Extremity Deep Vein Thrombosis

27

Suzanne M. Bleker, Noémie Kraaijpoel, and Harry R. Büller

Abbreviations

CI	Confidence interval
CT	Computed tomography
CVC	Central venous catheter
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
LMWH	Low-molecular-weight heparin
OR	Odds ratio
PE	Pulmonary embolism
PTS	Post-thrombotic syndrome
TOS	Thoracic outlet syndrome
UEDVT	Upper extremity deep vein thrombosis
UFH	Unfractionated heparin
VCF	Vena cava filter
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

Clinical Pearls

1. Cancer and central venous catheters are the most important risk factors for UEDVT.
2. The risk of PE after UEDVT is estimated 3–12% and is less than with lower extremity DVT estimated at 30%.
3. Central venous catheters that are functioning and needed should not be removed because of UEDVT. Patients should receive anticoagulation as long as the catheter is in situ.

Introduction

Upper extremity deep vein thrombosis (UEDVT) is a disease which was first described in the late nineteenth century by Paget and von Schroetter [1, 2]. The condition accounts for approximately 4–10% of all deep vein thrombosis, with an estimated incidence of 3.6/100,000 patient-years [3]. UEDVT is an increasingly frequent clinical problem, mainly due to the widespread use of central venous catheters (CVCs) which carry a substantial risk of thrombosis [3, 4]. It may involve the radial, ulnar, brachial, axillary, subclavian, internal jugular, and brachiocephalic veins but most often occurs in the subclavian or axillary veins;

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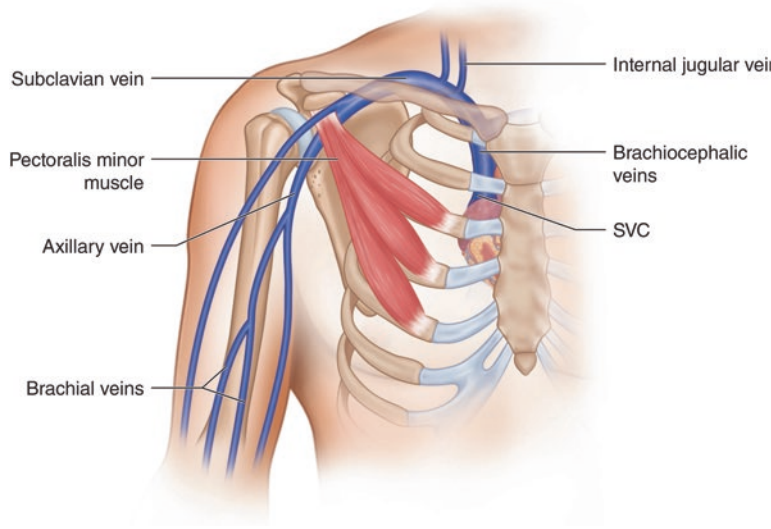


Fig. 27.1 Deep veins that may be involved in upper extremity deep vein thrombosis (SVC, superior vena cava)

frequently more than one venous segment is affected (Fig. 27.1) [5–11]. The cephalic and basilic veins are superficial veins and common site of insertion of peripherally inserted central catheters (PICC). Isolated thrombus in those two veins is not considered UEDVT. Deep vein thrombosis (DVT) of the radial, ulnar, and brachial veins are considered distal UEDVT, whereas DVT in the axillary or more proximally located veins is referred to as proximal UEDVT. As UEDVT may lead to loss of venous access or pulmonary embolism (PE) in the acute phase and is associated with serious long-term complications such as the post-thrombotic syndrome (PTS), prompt diagnosis and treatment are warranted. At present, objective imaging is the cornerstone of diagnosis despite its moderate efficiency. Several strategies to improve diagnostic efficacy have been proposed and tested, but which strategy can most safely and effectively exclude UEDVT remains to be determined.

In the absence of direct evidence, current treatment recommendations are largely extrapolated from studies on lower extremity DVT, since for UEDVT only small, observational studies are available. In this chapter the current understanding on the clinical characteristics, risk factors, diagnosis, management, prognosis, and prevention of UEDVT will be discussed..

Symptoms and Signs

Patients with UEDVT most often present with unilateral swelling and discomfort or localized pain [4, 8, 12–14]. Other symptoms and signs that have been described are weakness, paresthesia, heaviness, low-grade fever, visible collateral veins, erythema, a palpable cord, cyanosis, and warmth (Table 27.1) [8, 12, 16–19]. The majority of UEDVT associated with a CVC or pacemaker remains subclinical, as most cases are discovered during the work-up of a dysfunctional catheter or PE [20–22]. Concomitant symptomatic PE is present in 3–12% of all patients with UEDVT [6, 7, 23–28], which is less than in patients with lower extremity DVT, in which prevalences of around 30% have been reported [23, 28].

Risk Factors

UEDVT is subdivided into primary and secondary UEDVT, based on the pathogenesis. Primary UEDVT represents 20–50% of all cases and includes effort-related thrombosis (also known as the Paget-Schroetter syndrome) in combination with the thoracic outlet syndrome (TOS) and idiopathic thrombosis. The majority of UEDVT is secondary to a predisposing risk factor [3, 9, 29–32].

Table 27.1 Possible symptoms and signs of upper extremity deep vein thrombosis

Symptoms	Prevalence in patients with UEDVT
Unilateral edema or swelling	70–100%[a] [4, 8, 12, 13, 15]
Discomfort or localized pain	34–83%[a] [4, 8, 12, 13, 15]
Weakness	NR
Paresthesia	NR
Heaviness	NR
Signs	
Cyanosis	77% [15]
Warmth	36–52% [12]
Erythema or skin color change	3–47%[a] [4, 13]
Visible collateral veins	20–34%[a] [12]
Palpable cord	3–12%[a] [8]
Low-grade fever	5%[a]
No symptoms or signs	5% [4]

UEDVT upper extremity deep vein thrombosis, *NR* not reported

[a]Including own data from a cohort of 104 consecutive patients with confirmed UEDVT, previously enrolled in a prospective diagnostic management study [7]

The risk factors most strongly associated with UEDVT are cancer and the presence of a CVC. Other risk factors include pacemakers, previous venous thromboembolism (VTE), a positive family history of VTE, arm surgery or trauma, immobilization, the use of estrogens, and thrombophilia (Table 27.2).

The Paget-Schroetter Syndrome

The Paget-Schroetter syndrome accounts for 10–20% of all UEDVT and mainly occurs in young, otherwise healthy individuals who encounter repetitive or strenuous arm movements [10, 32, 38, 39]. It has been mostly associated with sports activities such as baseball, swimming, weight lifting, and wrestling [40, 41] but also with playing the violin for prolonged periods of time. The pathogenesis of the Paget-Schroetter syndrome is not entirely elicited, but it is thought that venous TOS plays a key role. Venous TOS is characterized by compression of the subclavian vein, usually caused by either congenital or acquired variations in the bone and muscle anatomy [42, 43]. This renders the subclavian vein more susceptible to trauma. Repeated trauma then leads to intimal hyperplasia, inflammation, and perivascular fibrosis, which may eventually cause venous thrombosis [44].

Table 27.2 Risk factors for upper extremity deep vein thrombosis

Parameter	Odds ratio (compared to healthy controls)
Cancer	18.1 [29]
Surgery of the upper extremity	13.1 [29]
Central venous catheter	9.7 [4]
Immobilization (plaster cast)	7.0 [29]
Family history of VTE	2.8 [29]
Thrombophilia	2.6–4.2 [29, 33–35]
Trauma of the upper extremity	2.1 [29]
Any surgery lasting more than 1 h	1.7 [36]
Oral contraceptives	1.2–2.9 [29, 34, 37]

VTE venous thromboembolism

Central Venous Catheters

Common indications for CVC placement are the administration of chemotherapy, parenteral nutrition, and prolonged intravenous antibiotic treatment. It is estimated that over 5 million CVCs are inserted annually in the United States [45]. CVC-related UEDVT accounts for up to 70% of all secondary UEDVT [8, 25, 32]. The high risk of CVC-associated UEDVT is mainly due to vessel wall damage following insertion and infusion of irritating substances and to impeded blood flow through the vein across the catheter. The incidence of symptomatic and asymptomatic CVC-related UEDVT lies around 2–6% and 11–19%, respectively [18, 46]. Baseline factors that increase the UEDVT risk are subclavian vein insertion, improper positioning of the catheter tip, and multiple lumen catheters (Table 27.3)

Table 27.3 Central venous catheter-specific risk factors for upper extremity deep vein thrombosis

Parameter	Odds ratio (95% CI)[a]
Type of catheter	
• PICC	1[b]
• Implanted port	0.4 [47]
Number of lumina	
• Single lumen	1[b]
• Double lumen	1.3–7.5 [36, 47, 48]
• Triple lumen	3.3–19.5 [36, 47, 48]
Multiple insertion attempts	1.1[c] [48]
Insertion site	
• Upper arm veins	1[b]
• Subclavian vein	2.2 [47]
• Internal jugular vein	1.6[c] [47]
Catheter tip positioning	
• Proper positioning	1[b]
• Improper positioning	1.9 [47]

CI confidence interval, *PICC* peripherally inserted central catheter
[a]Unadjusted for other risk factors
[b]Reference category
[c]Confidence interval crosses 1

[47]. Peripherally inserted central catheters are associated with a higher UEDVT risk than implanted ports (odds ratio [OR] 2.55, 95% confidence interval [CI] 1.54–3.24), especially in critically ill (incidence 13.9%, 95% CI 7.7–20.1) and cancer patients (incidence 6.7%, 95% CI 4.7–8.6) [47, 48].

Cancer

Approximately 40% of all patients with UEDVT have active cancer; it is one of the strongest risk factors for the development of UEDVT (adjusted OR 18.1, 95% CI 9.4–35.1). The presence of distant metastases increases the risk even further, for an OR of 11.5 (95% CI 1.6–80.2) compared to cancer patients without metastases. Cancer and CVCs often coincide [23], as a substantial proportion of cancer patients require a CVC for the administration of chemotherapy [46]. The presence of a CVC increases the UEDVT risk in patients with active cancer approximately twofold (OR 43.6, 95% CI 25.5–74.6) [29].

Diagnosis

An accurate diagnosis of UEDVT is important, as appropriate treatment can reduce the clinical burden and prevent complications in the acute phase, such as PE. The prevalence of UEDVT in patients with a clinical suspicion of UEDVT varies from 10 to 45% in several cohort studies, which might be explained by differences in study design and the proportions of cancer patients, CVCs, and the number of inpatients (Table 27.4) [7, 12, 49, 50]. In patients with a CVC, the prevalence of UEDVT was 53% in one study [7], compared to only 18% in patients without a CVC ($p < 0.01$). These figures were 31 and 23% for cancer and non-cancer patients, respectively ($p = 0.07$, manuscript under revision).

Venography is the gold standard to diagnose UEDVT, as it visualizes the entire deep vein system of the upper extremity, but it is invasive, expensive, and involves the use of contrast, which may cause complications including renal failure and allergic reactions. Due to these disadvantages, venography has been largely replaced in clinical practice by compression ultrasonography, which is noninvasive, relatively cheap, and easy to perform [19]. In a systematic review, identifying nine studies on the role of compression ultrasonography in the diagnosis of UEDVT, the overall sensitivity was 97% (95% CI 90–100%), with a specificity of 96% (95% CI 87–100%) [51]. The presence of the clavicle may hinder evaluation of the middle part of the subclavian vein, and in case of indeterminate compression ultrasonography results, venography may provide a definitive answer. Other diagnostic options include computed tomography (CT) angiography and magnetic resonance angiography (MRA), which are both noninvasive. However, both have only been evaluated in studies with very few patients with a clinical suspicion of UEDVT, and the diagnostic performance of both modalities is therefore unclear [52, 53].

Several attempts have been made to improve the diagnostic process in patients with a clinical suspicion of UEDVT. Constans and colleagues developed a clinical decision rule, incorporating

Table 27.4 Prevalence of upper extremity deep vein thrombosis and associated risk factors in consecutive patients with a clinical suspicion of upper extremity deep vein thrombosis

	Constans [12]			Armour [7]	Sartori [49, 50]	
	Cohort 1	Cohort 2	Cohort 3		Cohort 1	Cohort 2
Patients, n	140	103	214	406	239	483
UEDVT confirmed, n (%)	50 [42]	46 [51]	65 [31]	103 [26]	24 [10]	64 [13]
Study design	Single center			Multicenter	Single center	
Cancer (%)	52	54	NR	34	16	13
CVC (%)	61	65	12	35	6	17
Inpatient (%)	100	100	53	20	0	0

UEDVT upper extremity deep vein thrombosis, *CVC* central venous catheter, *NR* not reported

Table 27.5 Constans clinical decision score [12]

Item	Count
Venous material present[a]	+1
Localized pain	+1
Unilateral edema	+1
Other diagnosis at least as plausible	−1

If the total score is ≤1, upper extremity deep vein thrombosis is unlikely; if the total score is ≥2, upper extremity deep vein thrombosis is likely

[a]Central venous catheter or pacemaker thread

four items (Table 27.5) [12]. If the total score is one or less, UEDVT is deemed unlikely, whereas if the total score is two or higher, the diagnosis is likely. The prediction of UEDVT based on this score was consistent in three study samples, with prevalences of 64–70% in patients with a total score indicating "UEDVT likely" and 9–13% in those with a total score indicating "UEDVT unlikely," suggesting that this score can be a valuable tool in a diagnostic algorithm [12].

The diagnostic value of D-dimer has been tested in 2 studies, 1 including 52 patients of whom 15 (29%) had UEDVT, and the other including 239 patients of whom 24 (10%) were diagnosed with UEDVT [49, 54]. Both studies applied a cutoff value of 500 ng/mL. The sensitivity was high in both studies with 100% (95% CI 78–100%) and 92% (95% CI 73–99%), respectively, whereas the specificity was low (14%, 95% CI 4–29% and 60%, 95% CI 52–67%, respectively). These figures were similar for cancer patients and patients with a CVC [49, 54].

Recently, a multicenter, international, prospective diagnostic management study evaluated an algorithm consisting of the Constans score, D-dimer testing, and compression ultrasonography in consecutive patients with a clinical suspicion of UEDVT [7]. In total, 406 patients were included, and the algorithm was feasible in 390 (96%). UEDVT was confirmed in 103 patients (25%). In 87 patients (21%; 95% CI 17–25%), ultrasonography could be withheld. One patient, in which UEDVT was initially excluded, developed a UEDVT during 3-month follow-up, for an overall failure rate of the algorithm of 0.4% (95% CI 0–2.2%). In another study, 483 patients with a clinical suspicion of UEDVT all underwent immediate compression ultrasonography and were followed for 3 months prospectively. The failure rate, defined as the rate of recurrent VTE, was 0.6% (95% CI 0.2–2.2%) for single ultrasonography and 0.2% (95% CI 0.1–1.7%) for serial ultrasonography. Of note, the prevalence of UEDVT was relatively low in this cohort (13%) [50].

While there have been important improvements in the field, the best diagnostic strategy in patients with a clinical suspicion of UEDVT remains to be determined. Hence, at present, objective imaging remains the cornerstone of UEDVT diagnosis. D-dimer testing may help to reduce the number of patients who require imaging, although the efficiency of the test appears moderate in this population with high prevalences of cancer and CVCs. The use of an algorithm has been shown to be efficient and safe but

needs to be validated prospectively before it can be implemented in clinical practice. Furthermore, improvement of the algorithm appears to be desirable, for example, by applying age-adjusted D-dimer cutoff values (van Es, in press). In patients with a CVC and a suspicion of UEDVT, direct imaging seems justified, as only two examinations must be performed to detect one UEDVT.

Treatment

In the acute phase of UEDVT, the goal is to relieve acute symptoms and prevent complications, such as the loss of venous access or development of PE. The long-term goals of treatment are mainly the prevention of recurrent VTE, including fatal PE, and the development of PTS. Treatment of UEDVT is based on anticoagulation predominantly with selective use of thrombolytic therapy, mechanical catheter interventions, first rib resection, and vena cava filter (VCF) placement. No randomized controlled trials have evaluated any of these therapies in patients with UEDVT. Therefore, treatment recommendations by the major guidelines are largely extrapolated from studies on DVT of the leg and are only based on small observational studies in UEDVT patients [55].

Anticoagulant Therapy

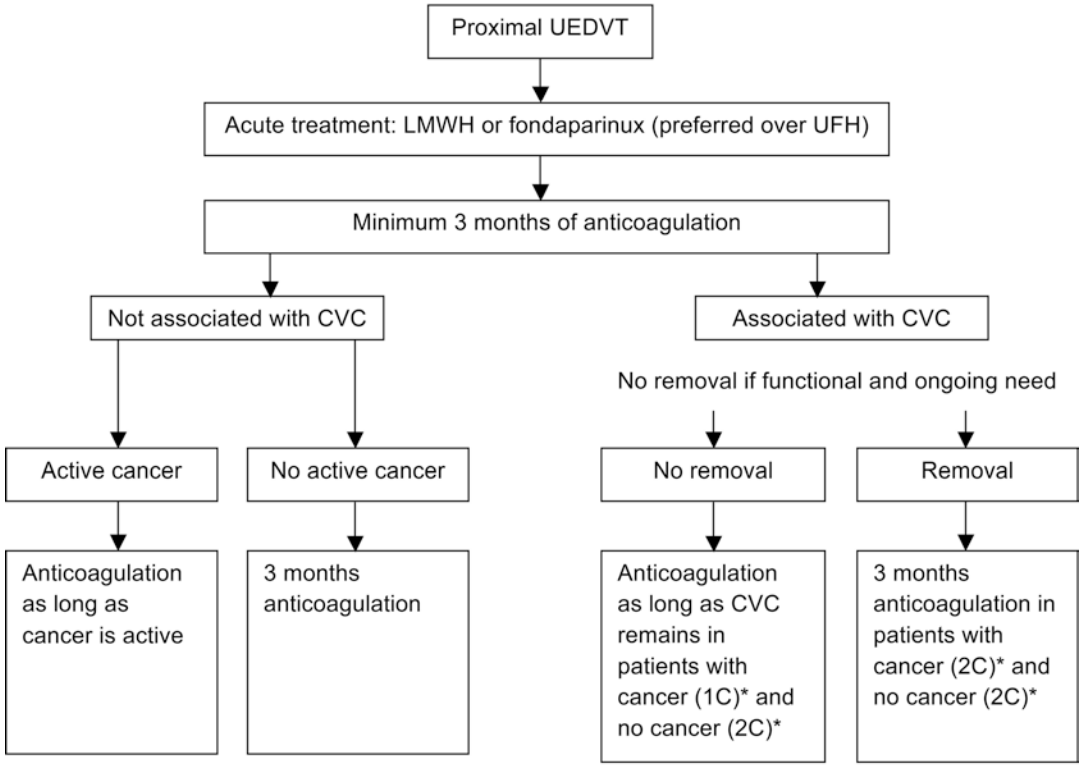
In patients with lower extremity DVT, low-molecular-weight heparin (LMWH) has a superior efficacy and better safety compared to unfractionated heparin (UFH) for the initial period of treatment (i.e., the first 5–10 days) [56]. In addition, 4 observational studies that included a total of 209 patients with UEDVT receiving LMWH reported low recurrence and major bleeding rates [27, 57–59]. Based on these data, LMWH is the preferred anticoagulant for the initial phase of UEDVT treatment (Fig. 27.2). UFH is reserved for patients with contraindications to LMWH such as severe renal failure [55].

For the long-term treatment of UEDVT, i.e., after the initial phase of 5–10 days, treatment options besides LMWH are vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs). VKA have been the standard method of anticoagulation for decades, but the use of DOACs is emerging since large trials have shown that they are as effective as VKA for the treatment of acute symptomatic lower extremity DVT and PE, with a significant reduction in major bleeding events [60]. Extrapolating from trials investigating these drugs for the treatment of DVT of the leg or PE, both can be considered for long-term UEDVT treatment. LMWH may be prescribed, but the daily injections are cumbersome and painful for many patients, and hypersensitivity skin reactions are often seen. Despite these disadvantages, the cornerstone of treatment in cancer patients is LMWH, based on a superior efficacy and similar safety profile compared to VKA in cancer patients with lower extremity DVT and PE [61, 62].

Treatment Duration

All patients with proximal UEDVT (i.e., DVT of the axillary or more proximally located veins) are recommended to be treated with a therapeutic dose of anticoagulants for at least 3 months (Fig. 27.2). If UEDVT is not associated with a CVC but is associated with active cancer, patients should receive anticoagulation as long as cancer is active or the patient is receiving chemotherapy. In non-cancer patients with non-CVC-associated UEDVT, 3 months of treatment is recommended.

If the UEDVT is CVC associated, the CVC should not be removed if it is functioning well and there is an ongoing need for it. This recommendation is in part based on the fact that many patients still require central venous access and insertion of another CVC will increase the thrombotic risk as well. Furthermore, an observational study showed no benefit of CVC removal in 58 of 112 patients (52%) with symptomatic CVC-related thrombosis. In total, four patients failed to show resolution of their presenting symptoms, all of whom had their CVC removed at the time of UEDVT [63]. In another, prospective study including 74 patients with acute symptomatic



UEDVT: upper extremity deep vein thrombosis; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; CVC: central venous catheter
* Grading of Recommendations Assessment, Development and Evaluation (GRADE); 1C: strong recommendation based on low-quality evidence, 2C: weak recommendation based on low-quality evidence

Fig. 27.2 Treatment recommendations for upper extremity deep vein thrombosis [55]

CVC-related UEDVT in which the catheter remained in place, there were no recurrent VTE during 3 months of anticoagulant therapy [57]. According to the ACCP guideline, anticoagulation should be given as long as the CVC remains in place. This is similar for cancer and non-cancer patients. If the CVC is removed, only 3 months of treatment is recommended, regardless of the presence of cancer. There are no data to guide whether CVC removal should be preceded by anticoagulant therapy [55]. There is some debate on the safety of cessation of therapy in patients in whom the CVC is removed but who still have active cancer after 3 months. In a recent retrospective study, the cumulative probability of recurrent VTE was 22.2% in patients with active cancer after cessation of anticoagulant therapy, compared to 2.3% in those in remission ($p = 0.02$) [64]. Another study reported a recurrent VTE rate after 3 months of 7.7% in cancer patients with CVC-related UEDVT, compared to 4.4% in cancer patients with non-CVC-related UEDVT [23]. These data suggest that patients with active cancer with CVC-related UEDVT in whom the CVC is removed may benefit from anticoagulation beyond 3 months.

For distal UEDVT, there is significant uncertainty on the benefits of anticoagulation, as it is thought that complications occur less often and are less severe in case of distal UEDVT as compared to proximal UEDVT. Therefore, conservative treatment with close surveillance to detect UEDVT

extension, a prophylactic dose of anticoagulation, or a shorter course of treatment are options alternative to full therapeutic anticoagulation. If distal UEDVT is symptomatic, associated with a CVC (with the CVC remaining in situ) or with cancer, 3 months of therapeutic dose anticoagulation is favored, unless there is a high bleeding risk [55].

Thrombolytic Therapy

Thrombolytic therapy may improve early and late venous patency in patients with UEDVT [65–69], but whether it lowers the risk of recurrent VTE or development of PTS remains unknown. The American College of Chest Physicians (ACCP) guideline suggests that thrombolysis is considered only in patients with severe symptoms for less than 14 days with a good functional status, a life expectancy of at least 1 year, and a low risk of bleeding [55]. Data on the use of thrombolytic therapy for UEDVT is limited but suggests a high risk of major bleeding of up to 17% when systemically administered [66, 68, 69]. Therefore, if thrombolysis is applied, catheter-directed thrombolysis is recommended over systemic thrombolysis, based on the assumption that this is associated with lower bleeding risk [55].

Mechanical Catheter Interventions

Mechanical interventions include clot aspiration, fragmentation, thrombectomy, percutaneous transluminal angioplasty, and stent placement. These techniques are mostly used in combination with catheter-directed thrombolysis. Stents have been associated with high rates of complications such as stent fracture and rethrombosis in the presence of TOS [70, 71].

First Rib Resection

In patients with UEDVT and TOS, surgical decompression through first rib resection has been advocated [55]. No randomized trials have evaluated the efficacy and safety of first rib resection in the resolution of acute complaints and prevention of long-term sequelae such a recurrent VTE and PTS. The indications for first rib resection will be discussed in a separate chapter.

Vena Cava Filter

In patients with a contraindication for anticoagulant therapy, placement of a VCF may be considered. In a review, reporting on a total of 209 superior VCF placements in patients with UEDVT, complications occurred in 3.8% of the cases, including cardiac tamponade, aortic perforations, and a pneumothorax [72]. The use of VCF should be limited to experienced centers in selected cases.

Other Therapies

The use of compression stockings to prevent PTS after UEDVT has not been investigated, and the ACCP suggests against its routine use [55].

Prognosis

On the long term, UEDVT can be complicated by recurrent VTE, PTS, bleeding during anticoagulation, and death. To date, mostly small studies with methodological shortcomings have evaluated the long-term clinical outcome of UEDVT. A systematic review of all available studies on this topic reported an average incidence of recurrent VTE of 3–4% during anticoagulant therapy. After cessation of treatment, the annual incidence of recurrence lies around 4% [73]. PTS after UEDVT seems to occur infrequently, and complaints are mostly mild [32, 74]. Compared to DVT of the leg, the incidences of recurrent VTE and of PTS after UEDVT seem relatively low [27, 28, 32, 74, 75].

The recurrence risk in patients with CVC-related UEDVT was reported in two prospective studies; one observed an incidence of 7 per 100 patient-years during anticoagulant therapy, which decreased to 3.4 per 100 patient-years after cessation of treatment [76]. Another study observed recurrent VTE in 4.4% of the patients during

3 months of anticoagulant therapy [23]. Of note, in both studies no information was available on catheter removal. Cancer patients with UEDVT appear to have a twofold higher risk of recurrent VTE compared to non-cancer patients [23, 32, 73], which is comparable to findings from studies on DVT of the leg or PE [77, 78].

In patients receiving a therapeutic dose of anticoagulants, the cumulative incidence of major bleeding is approximately 4% after half a year of treatment [23, 32, 59, 73, 79]. The mortality rate in patients with UEDVT is high and reflects the high prevalence of underlying cancer. To which extent fatal PE adds to this risk is unclear.

Prevention

The prevention of UEDVT has mainly been investigated in patients with indwelling CVCs. A total of six meta-analyses evaluating the efficacy and safety of VKA in the prevention of CVC-related thrombosis showed no overall benefit on the occurrence of symptomatic thrombosis compared to placebo or no treatment [80]. Six randomized studies in cancer patients with CVCs found no increased risk of bleeding with LMWH thromboprophylaxis but also no benefit in preventing CVC-related thrombosis. Routine anticoagulant thromboprophylaxis is therefore not recommended in patients with a CVC by the major international guidelines [55, 80]. The role of UFH, thrombolytics, and heparin-bonded catheters in the prevention of CVC-related thrombosis remains uncertain [47, 80]. CVCs should only be placed in carefully selected patients in whom the benefits outweigh the risks. As mentioned before, several catheter-specific factors increase the risk of UEDVT and should be taken into account when placing a CVC (Table 27.3).

Future Directions

Several aspects related to UEDVT remain unresolved. Future studies need to evaluate what the most effective and safe diagnostic strategy is to confirm or refute UEDVT. Furthermore, in cancer patients with CVC-related UEDVT in whom the CVC is removed, the efficacy and safety of 3 months of anticoagulant therapy versus prolonged treatment should be assessed. Ideally, future studies would include the use of DOACs for the treatment of UEDVT.

More research is warranted to identify those patients with a CVC in whom the benefits of pharmacological thromboprophylaxis exceed the associated harms, for example, by risk stratification. Also, new regimens that are possibly effective and safe in preventing CVC-associated UEDVT, including prophylactic doses of DOACs, should be explored.

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Venous Thoracic Outlet Syndrome

28

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Clinical Pearls

1. Venous TOS constitutes 3–5% of call cases of TOS.
2. First rib resection and anterior scalenectomy are currently considered the standard of care for treatment.
3. Venography after first rib resection is recommended to optimize patency of the vein using balloon angioplasty and very rarely stenting.

Introduction

Venous thoracic outlet syndrome (vTOS) occurs when there is compression of the axillo-subclavian vein while traversing the small dynamic space of the thoracic outlet. It has taken many names over the last century including effort thrombosis, Paget-Schroetter syndrome, and McCleary syndrome. Occurring frequently in the youth, it is one of the few reasons for adolescents to be evaluated by a vascular surgeon.

Etiology

The axillary vein becomes the subclavian vein at the lateral border of the first thoracic rib. This transition occurs at the thoracic outlet which is anatomically defined as the location between the first thoracic rib, first thoracic vertebra, and sternum (Fig. 28.1). The low-pressure system within the thin-walled vessel is easily compressed, especially between the bony clavicle and first rib. The subclavius muscle is closely associated with the clavicle in this location and contributes to the compression. Already a small space, the volume of the thoracic outlet is quite dynamic, changing with position, activity, and respiration. This is then further complicated by frequent anomalous fibrocartilaginous bands and ligaments [1]. Cervical ribs can also be present causing further crowding.

Chronic compression of the venous system at the thoracic outlet is thought to lead to cyclical inflammation and quiescence. This eventually can generate endothelial injury and perivenous fibrosis which then prompts stasis and thrombosis of the axillo-subclavian vein [2].

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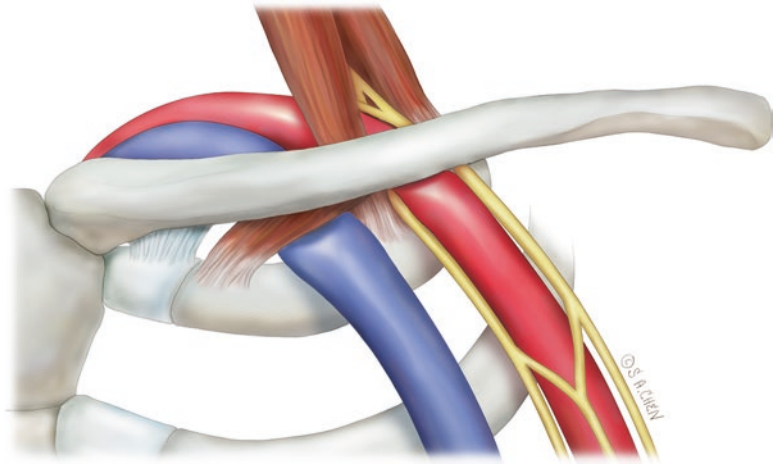

Fig. 28.1 Anatomy of the thoracic outlet

Venous thoracic outlet syndrome must be differentiated from secondary venous thrombosis. Secondary upper-extremity deep venous thrombosis (DVT), an increasing problem, occurs in association with intravenous catheters for dialysis, chemotherapy, central intravenous access, and bone marrow transplantation.

Epidemiology

The true incidence of all thoracic outlet syndrome (including arterial and neurogenic) is debated. Venous TOS generally comprises 3–5% of all thoracic outlet cases. Primary upper-extremity DVT occurs in 2/100,000 individuals [3].

Clinical Presentation

Patients with venous thoracic outlet syndrome most commonly present with thrombosis, although some with McCleary syndrome (compression without thrombosis) may simply complain of intermittent swelling and color changes which resolve with adduction. Venous thrombosis can be occlusive or partially obstructive, acute, or chronic. The affected upper extremity can become suddenly blue-purple or even red and markedly edematous in the acute process. These patients become alarmed and will frequently present to the emergency room. Chronically, patients may be seen in the office with swelling that does not seem to resolve. They will often exhibit signs of collateralization with dilated superficial veins over the neck, chest, shoulder, back, and neck (Fig. 28.2). Dull aching or heaviness in the recumbent position is customary.

Venous TOS is regularly associated with repetitive upper-extremity activity and trauma. Patients who are athletes or professionally participate in arm motion can develop substantial muscle mass of the shoulder and the scalene triangle. Because of this, vTOS can present in adolescents [4].

Diagnosis

Diagnosing vTOS is a combination of clinical presentation, imaging, and ruling out other causes. Patients with unprovoked upper-extremity DVT need to be evaluated for an underlying hematologic etiology including oncological as well as hypercoagulable conditions. Secondary thrombosis with chronic indwelling catheters or pacemakers occurs more frequently than vTOS.

Maneuvers

Many physical exam maneuvers have been employed in the diagnosis of TOS. These are noninvasive, free, and performed in the office.

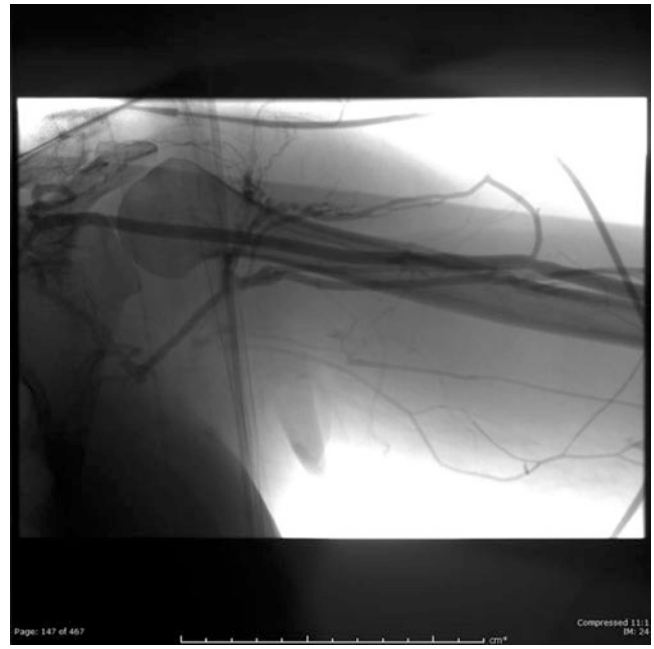

Fig. 28.2 Venogram showing extensive superficial collateralization

They are more directed at the arterial and neurogenic components of the thoracic outlet syndrome; however, they remain an important part of the overall evaluation. Because some patients can have compression of all three elements of TOS, these exercises should be completed for all patients being considered for TOS as some patients will have mixed components. The Adson test is most popular and utilized maneuver. The patient is requested to take a deep breath, rotate, and extend their head toward the unaffected side. The affected arm is then abducted with the elbow flexed while palpating the radial pulse. A positive test will obliterate the ipsilateral pulse. One should be cautious as the Adson test can produce false positives in many cases. The elevated arm stress test (EAST) or Roos Test is more sensitive. The patient is asked to abduct both shoulders to 90° again with the elbows flexed. With the hands facing forward, they alternately open/close their hands for a period of 3 min. A positive test occurs when this induces or exacerbates their symptoms.

Imaging

Routine imaging to diagnose vTOS primarily consists of ultrasound. A complete evaluation by duplex ultrasound is essential, using both gray-scale and Doppler spectral waveform analysis. Maneuvers by abducting and adducting can be helpful although many ultrasonographers are hesitant in the setting of acute upper-extremity DVT for fear of clot embolization. Dampening of the waveform and marked decrease in velocities in the abducted position are nearly always present in vTOS. The presence and severity of venous thrombosis are also important to document. Sonographic imaging has been found accurate in the diagnosis of upper-extremity DVT with a sensitivity of 78–100% and a specificity of 82–100% [5].

Magnetic resonance venography (MRV) and computed tomographic venography (CTV) have been utilized to diagnose vTOS with increasing frequency. Results have shown high concordance with duplex ultrasound, but the cost for these

tests can be unnecessarily burdensome in acute vTOS. They may have more of a role in chronic cases where extensive collaterals may affect the approach for surgical treatment.

Invasive venography has traditionally been the "gold standard" in diagnosis; however, catheter-based imaging is generally reserved for patients who need an initial intervention such as thrombolysis. Post-resection venography has become routine (see Treatment).

Treatment

Initial therapy for venous thoracic outlet syndrome is anticoagulation and arm elevation; however, definitive treatment remains surgical. Recurrent thrombosis without surgical decompression can occur in up to 70% of patients [6]. Additionally, 40% of patients treated with thrombolysis and anticoagulation alone will eventually undergo rib resection because of symptom recurrence [7]. To date, first rib resection and anterior scalenectomy (FRRS) is the standard of care.

Patients will naturally present in various stages of chronicity or even treatment. Once the diagnosis is reached, first rib resection and anterior scalenectomy for decompression should be scheduled. The sooner patients can be decompressed, the sooner they may come off anticoagulation. Our routine is to hold anticoagulation on the day of surgery and restart it at postoperative day 3. The patient then returns for a post-resection venogram at 2 weeks to assess for persistent stenosis and/or thrombosis (Fig. 28.3). Routine preoperative thrombolysis and venoplasty have not been shown to improve vein patency [8]. However, if the patient is found to be without stenosis or thrombosis at the postoperative venogram, anticoagulation may be safely stopped. This shortened length of anticoagulation is invaluable in the adolescent patient. Should a balloon venoplasty be required, anticoagulation should be continued for 1–2 months, and prior to stopping it, a duplex scan should demonstrate vein patency in abduction and adduction. If the vein cannot be reopened due to scarring or residual thrombus, anticoagulation is generally continued for an additional 6 months where >90% of the veins will reopen due to the removal of the extrinsic compression by the first rib, anterior scalene muscle, and subclavius tendon.

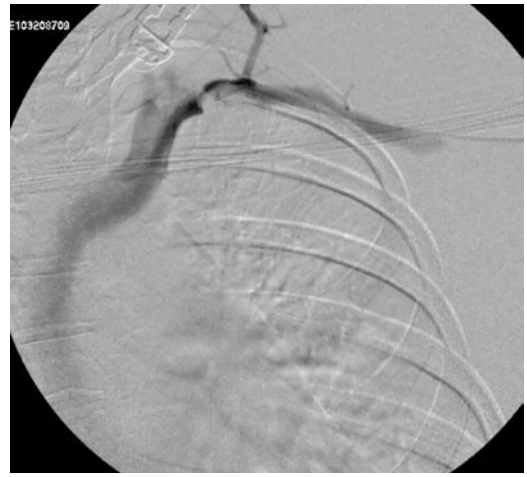

Fig. 28.3 Postoperative venogram showing filling defect within left axillo-subclavian vein

Patients should also undergo postoperative physical therapy as the rib resection does cause the shoulder to anteriorly rotate, and strengthening exercise prior to the patient resuming their normal activity is important to prevent other injuries such as a rotator cuff tear.

First Rib Resection and Anterior Scalenectomy: Transaxillary

The transaxillary approach is quickly becoming the favored approach for surgical decompression of the thoracic outlet. The procedure is performed under general anesthesia with avoidance of any long-acting paralytics for intraoperative nerve identification and monitoring. Appropriate positioning and adequate retraction are vital for a safe and complete resection. Using a bean bag, the patient is placed laterally with ample padding to protect pressure points (Fig. 28.4). The axilla and arm are prepped circumferentially to the wrist and placed into a Machleder retractor.

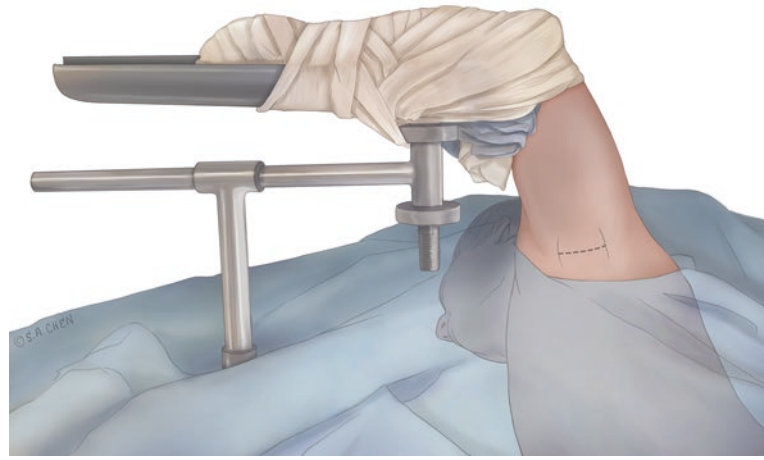

Fig. 28.4 Patient arm positioned within the Machleder retractor

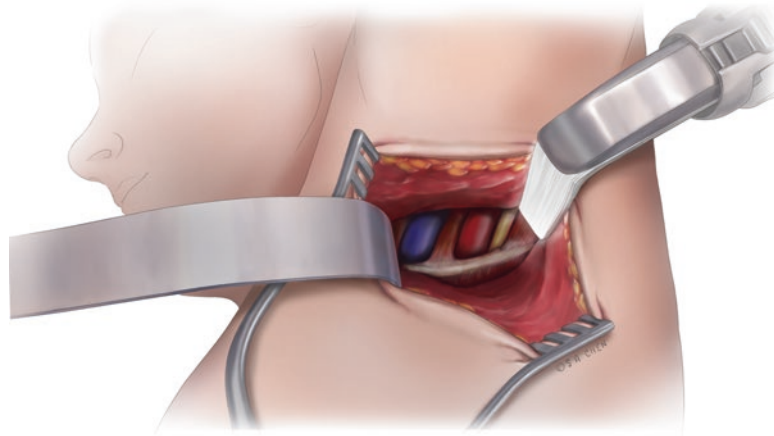

Fig. 28.5 Exposure of thoracic outlet with handheld lighted retractors

Additional lighted handheld retractors are also advantageous (Fig. 28.5). A transverse incision is made between the borders of the latissimus dorsi muscle and pectoralis major muscle. Electrocautery is used to dissect down to the chest wall. This is done in a direct fashion so as to avoid disturbing the axillary lymphatic bed. Blunt dissection is then utilized in order to expose the axilla and first rib. The first rib is identified by locating the anterior scalenus muscle insertion. The subclavian vein is found anteriorly, associated with the subclavius muscle. The vein is separated from the subclavian artery by the anterior scalenus muscle which must be carefully and cleanly divided by exposing it with a right angle (Fig. 28.6). The artery is closely accompanied by the brachial plexus. The inferior edge of the first rib is cleared of intercostal muscles with a sharp periosteal elevator. Once mobile, the underlying pleura is gently peeled away which can be difficult in patients with extensive scarring. Prior to dividing the rib anteriorly, the small but tense subclavius muscle must be excised. The rib is then cut anterior to the vein; this is critical to ensure complete decompression of the vein. Posteriorly, we recommend dividing the rib at the brachial plexus and then carefully pursuing further resection gradually with a rongeur (Fig. 28.7). Once the rib is removed, the vein is closely inspected. If perivenous scarring and fibrosis is noted, this is carefully lysed with a Metzenbaum scissors.

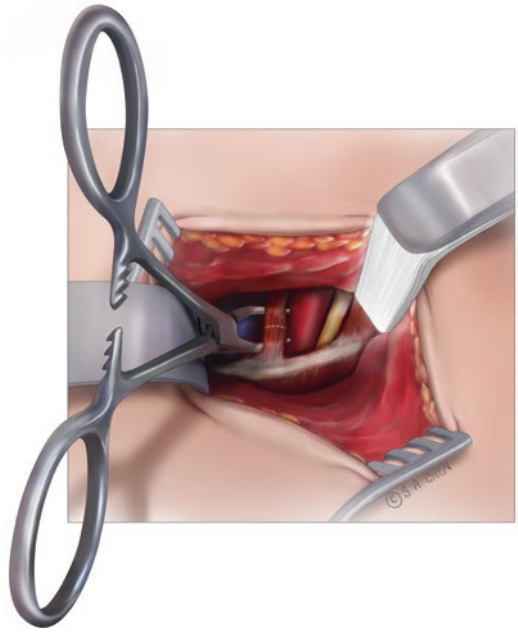

Fig. 28.6 Exposure of anterior scalenus muscle for division

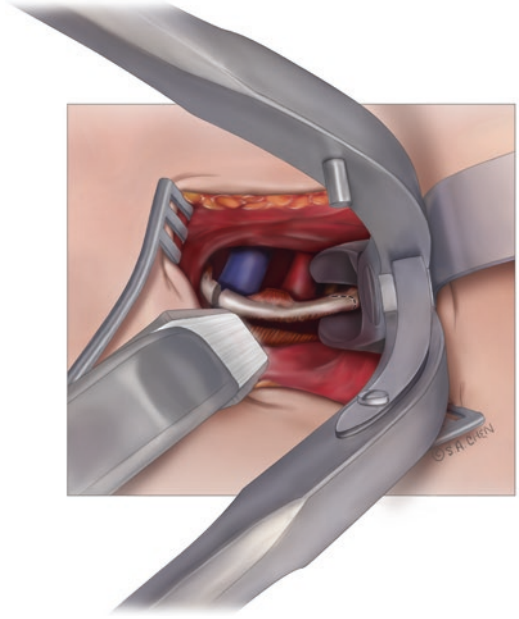

Fig. 28.7 Division of the first thoracic rib

First Rib Resection and Anterior Scalenectomy: Supraclavicular Approach

Also performed under general anesthesia and avoidance of long-acting paralytics, patients are positioned supine with an intrascapular bump during this approach. The head is turned to the contralateral side, and a generous transverse incision is made just 2 cm above the clavicle starting 2 cm lateral from the sternal notch. The platysma is divided with bipolar cautery, and then monopolar is favored for the remainder of the procedure. Supraclavicular nerves located just beneath the platysma are preserved if possible. Subplatysmal flaps are created superiorly and inferiorly. The clavicular head of the sternocleidomastoid muscle (SCM) is marked with silk sutures for future reapproximation and then divided. The omohyoid is impartially transected. The scalene fat pad is then mobilized laterally, taking care to tie small lymphatics to avoid a lymph leak. If the left rib is being removed, one is cognizant of the thoracic duct which should be doubly ligated and divided. Once the fat pad is mobilized, the underlying anterior scalene muscle is evaluated for the phrenic nerve traversing medially. The phrenic nerve is protected and should not be mobilized in any way. The anterior scalene muscle is then divided sequentially with bipolar cautery taking care of the posterior subclavian artery and the brachial plexus at the interscalene position. The middle scalene is often partially transected to allow full access to the first thoracic rib underneath. This is done slowly and sequentially because although the long thoracic nerve is generally on the lateral border, it can also travel within the muscle belly itself. The upper, middle, and lower trunks of the brachial plexus are easily visualized and can be gently retracted. The first rib is cleared of its intercostals with a periosteal elevated and transected where it is easily visible. The rib is then further resected both anteriorly and posteriorly with a rongeur. Again it is vital to

resect this rib anterior to the vein in order to achieve complete decompression. This may require anterior retraction of the clavicle or even a small infraclavicular incision during this approach. Once the rib is removed, the vein is closely inspected. If perivenous scarring and fibrosis are noted, this is carefully lysed with a Metzenbaum scissors. The fat pad is tacked back medially to the sternal head of the SCM. The clavicular head of the SCM is also reconstructed.

Post-resection Venography

This is performed under light sedation and local anesthetic. The ipsilateral basilic vein is accessed with a micropuncture needle under ultrasound guidance. This small sheath is generally enough to proceed with diagnostic venogram under voluntary apnea. The entire axillo-subclavian vein as well as the central veins should be evaluated. If there is persistent stenosis, then exchange for a larger sheath is performed and balloon venoplasty pursued. If the axillo-subclavian vein remains completely thrombosed, recanalization should be attempted. Generous sizing of the balloons is safe and can deliver improved results. We do not recommend stenting of the subclavian vein at the first postoperative intervention. If symptoms persist despite surgical decompression and balloon angioplasty, rarely intravenous stenting may be considered; however, spontaneous recanalization on anticoagulation after first rib resection and anterior scalenectomy has been reported [9, 10].

Results

Although there are no randomized control trials, abundant evidence has shown excellent results with thoracic outlet decompression for venous TOS. In 2007, Molina et al. experienced 100% clinical success and 100% secondary patency in 97 patients [11]. Similarly, long-term patency exceeded 90% in the Chang et al. series [9].

Recent Developments and Future Research

Modern experience indicates that a comprehensive approach to TOS can expedite treatment and improve outcomes. Centers of excellence have been established which utilize a multidisciplinary yet uniformed process to work up and treat TOS patients [12]. Nurses, administrators, and especially ultrasonographers who are experienced with the disease process can greatly assist patients as they progress through preoperative and postoperative course.

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Medical Management of Pulmonary Embolism

29

Stefano Barco and Stavros V. Konstantinides

Clinical Pearls

1. Workup of patients with PE should include chemical as well as imaging evaluation of early right heart strain for better stratification into treatment algorithm.
2. Systemic thrombolysis is indicated for high-risk, massive PE in patients with acceptable bleeding risk. Catheter-directed thrombolysis is becoming more popular in centers with adequate expertise.
3. New oral anticoagulants are the agents of choice for anticoagulation.

Impact of Pulmonary Embolism

Acute pulmonary embolism (PE) (Fig. 29.1) is the third most frequent acute cardiovascular syndrome after acute myocardial infarction and stroke, and consequently a major cause of acute and long-term morbidity and mortality worldwide. Depending on clinical severity, and particularly the presence of hemodynamic instability at presentation, up to 30% of patients with acute PE may die within the first 30 days [1], and as many as 30% of survivors will later develop potentially life-threatening recurrent venous thromboembolism (VTE) or some sort of chronic disabling symptoms [2]. Moreover, a variable proportion of PE patients ranging between 1 and 9% are at risk of presenting, over the long term, with a devastating complication termed chronic thromboembolic pulmonary hypertension (CTEPH) [2, 3]. Apart from their relevance for the life and well-being for patients, these numbers point to the substantial economic burden imposed by PE on healthcare systems. In fact, direct costs related to acute PE have been estimated to be at least twice as high as those for management of deep vein thrombosis, and spending virtually "explodes" when it comes to the management of patients with CTEPH [4, 5]. Finally, it is certain that the impact of PE will continue to increase in the future, since the risk of VTE approximately doubles with each decade after the age of 40, and thus an increasing number of individuals in aging societies will suffer from the disease and its sequelae in the years to come.

Clinical Severity and Risk of Early Death Determine Initial Management

Current international guidelines emphasize that the appropriate management of patients with confirmed acute PE requires their stratification

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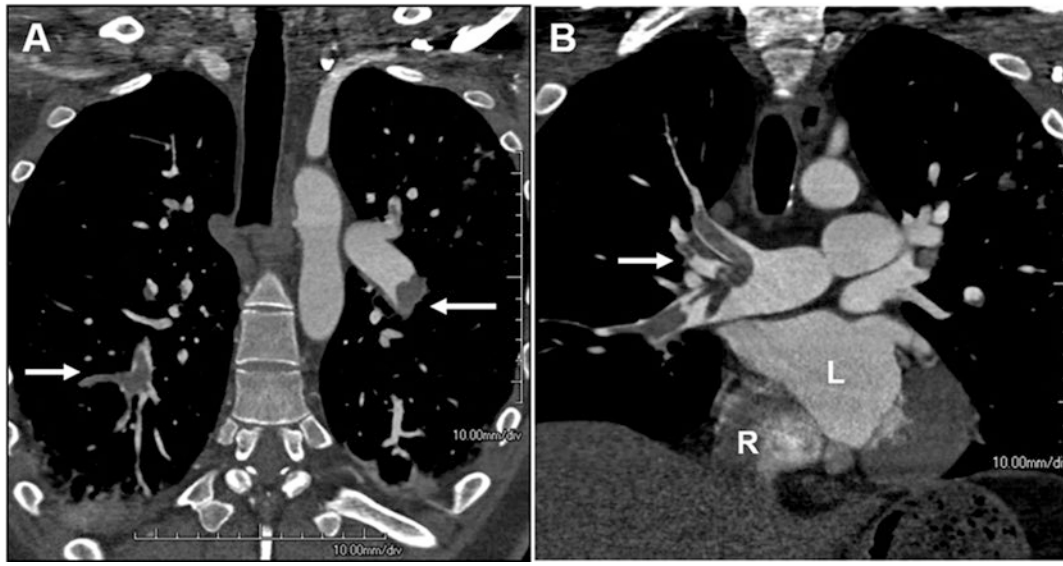

Fig. 29.1 Computed tomographic pulmonary angiogram demonstrating bilateral filling defects in the branches of the pulmonary arteries (*white arrows*), which are diagnostic of acute pulmonary embolism. (**a**) A "four-chamber view" in the transverse plane, which allows a first assessment of right ventricular size, more specifically of the right-to-left (R/L) ventricular diameter ratio at the tricuspid/mitral annulus level (**b**)

into classes of disease severity in order to create an algorithm which adjusts the modalities of medical, surgical, or interventional treatment to the early death or complication risk (Fig. 29.2) [6]. Patients with clinically overt right ventricular failure on admission, which results in reduced cardiac output and manifests as persistent hypotension accompanied by signs of end-organ hypoperfusion (i.e., frank cardiogenic shock), are classified into the high-risk (or "massive") PE category. These patients undoubtedly constitute the most challenging subgroup, exhibiting 30-day fatality rates of 20–40% or even higher, and they are in need of immediate treatment of acute right heart failure in addition to medical or pharmacomechanical reperfusion.

The high-risk group represents only 5% or even less of all PE patients [1, 7]. Outside this emergency situation, normotensive, "not-high-risk PE" patients should further be stratified into intermediate versus low risk using two categories of tools or modalities: (1) the Pulmonary Embolism Severity Index (PESI), or its simplified form (sPESI), reflecting clinical severity and comorbidity, and (2) imaging and/or laboratory tests detecting subclinical right ventricular dysfunction or myocardial injury [6]. While PESI and sPESI primarily serve to identify low-risk patients who may be eligible for early discharge and home treatment, echocardiographic (or computed tomographic) or biochemical markers of right ventricular (RV) dysfunction represent the key tool for defining the groups of "intermediate-low risk" (with *either* evidence of RV dysfunction *or* elevated biochemical markers) or "intermediate-high risk" (with RV dysfunction *combined* with elevated biochemical markers) (Table 29.1). This advanced classification on the basis of the functional status of the right ventricle helps to determine the need for and duration of hemodynamic monitoring as well as the need for (rescue) reperfusion treatment (Fig. 29.2). It may also be helpful for the choice of the initial anticoagulant regimen, as will be explained below.

Management of Acute Right Heart Failure

The principles of acute right heart failure management were recently reviewed in a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and

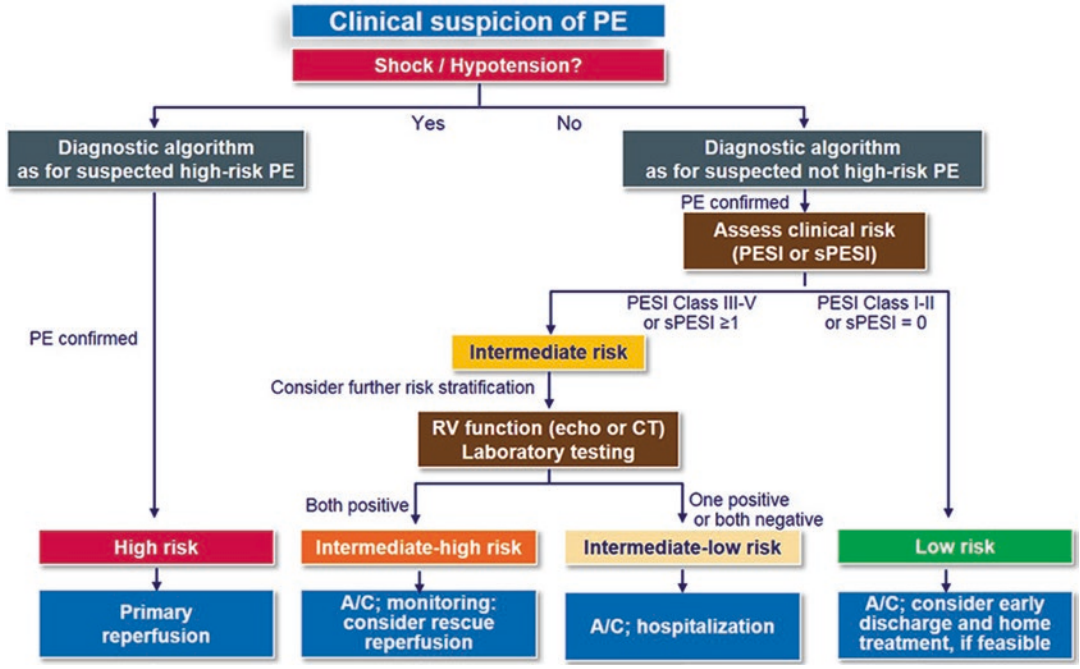

Fig. 29.2 Integrated risk-adjusted management algorithm for acute pulmonary embolism (adapted from [6] *A/C* = anticoagulation, *CT* = computed tomographic, *PE* = pulmonary embolism, *PESI* = Pulmonary Embolism Severity Index, *RV* = right ventricular, *sPESI* = simplified Pulmonary Embolism Severity Index)

Table 29.1 Risk categories in patients with acute pulmonary embolism

		Risk parameters and scores			
Early mortality risk		Shock or hypotension	PESI class III–V or sPESI ≥1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate	Intermediate-high	–	(+)[a]	Both positive	
	Intermediate-low	–	(+)[a]	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

From the 2014 European Society of Cardiology Guidelines on the Diagnosis and Management of Pulmonary Embolism, updated [8]

PESI = Pulmonary Embolism Severity Index, *RV* = right ventricular

[a]Current guidelines do not routinely recommend further assessment in patients belonging to the PESI class I–II or with a sPESI of 0. Nevertheless, some of these patients have been reported to exhibit RV dysfunction on imaging tests and/or elevated biomarker levels. If any doubts persist regarding the severity of PE upon clinical evaluation of the patient, even in the presence of a formally low PESI or a sPESI of 0, the functional status of the RV should be assessed. If RV dysfunction is then detected, the patients' risk should be classified based on the imaging and biochemical tests

Right Ventricular Function of the European Society of Cardiology [9]; an overview of the current treatment options for acute RV failure is provided and briefly discussed in Table 29.2.

Acute RV failure principally responds to changes in preload. Importantly, however, excessive volume loading may increase wall tension, decrease contractility, impair left ventricular filling, and ultimately further reduce systemic cardiac output and tissue perfusion. Cautious volume loading guided by central venous pressure monitoring and aimed at reaching and maintaining pressures of 5–10 mmHg is the most reasonable approach.

Table 29.2 Medical and device treatment of overt right heart failure in patients with acute high-risk pulmonary embolism

Strategy, drug, or device	Dosage	Properties and instructions	Caveats
Volume optimization			
Volume loading with saline or ringer lactate	At least 200 mL over 15–30 min	Consider patients with decompensated RV failure, normal central venous pressure, and low arterial pressure	Volume overloading may further distend the ventricles, worsen ventricular interdependence, and reduce cardiac output
Vasopressors and inotropes			
Norepinephrine	0.2–1.0 μg/kg/min	Increases RV inotropy, systemic blood pressure, promotes positive ventricular interactions, restores coronary perfusion gradient	Excessive vasoconstriction may further reduce tissue perfusion
Dobutamine	2–20 μg/kg/min	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor, especially if left heart failure coexists
Levosimendan	0.1–0.2 μg/kg/min (6–12 μg/kg bolus over 10 min optional and not recommended if SBP <90 mmHg) Infusion can be decreased to 0.05 or increased to 0.2 μg/kg/min	Combines RV inotropy and pulmonary vasodilation; favorably effects right ventricular-arterial uncoupling	May aggravate arterial hypotension
Mechanical circulatory support			
ECMO/ECLS	–	Short-term support, cost-effective, rapid; oxygenator can be added	Complications with use over longer periods (>5–10 days)
Percutaneous catheter-mounted micro-axial pumps	–	–	Limited pump capacity; ECLS preferred in severe cardiogenic shock or if high pump flow required
Paracorporeal RVAD	–	Appropriate for longer-term use (e.g., weeks or months); can be combined with oxygenators when pulmonary support also needed	–

The table is based on the recent recommendations by the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology [9]
ECLS = extracorporeal life support, *ECMO* = extracorporeal membrane oxygenation, *RV* = right ventricle/ventricular, *RVAD* = right ventricular assist device(s), *SBP* = systolic blood pressure

Vasopressors, particularly noradrenaline, are preferred in shock since they restore blood pressure and improve cerebral, coronary, and other organ perfusion, without disproportionately increasing pulmonary vascular resistance. By combining RV inotropy and pulmonary vasodilation, levosimendan appears to have a favorable hemodynamic profile, even though the evidence to support its use in precapillary RV failure (i.e., not due to left heart disease) is not very strong

yet. Phosphodiesterase III inhibitors are also expected to exert positive inotropic effects on the RV without increasing pulmonary vascular resistance; however, like dobutamine, they may aggravate arterial hypotension and should therefore be combined with noradrenaline if used. Finally, mechanical circulatory support of the RV, including extracorporeal membrane oxygenation (ECMO) or life support (ECLS), may be required in acute high-risk PE. Timely implantation is critical to avoid irreversible organ damage, and thus early transfer of the patient to an expert referral center is essential.

Thrombolysis and Pharmacomechanical (Interventional) Reperfusion Therapy

Systemic Intravenous Thrombolysis

Thrombolytic agents have been used for the treatment of acute PE since the late 1960s [10]. Today, immediate systemic reperfusion treatment with intravenous thrombolysis continues to be the mainstay of therapy for high-risk (or massive) PE [6, 11, 12]. This recommendation is partly supported by meta-analyses of randomized trials which enrolled, in total, more than 2000 patients with acute PE and suggested that thrombolysis may reduce, by approximately two thirds, early mortality or hemodynamic decompensation requiring further "rescue" treatment (odds ratio [OR] 0.34, 95% CI: 0.22–0.52) [13]. Of course, this benefit is to be viewed against the risk of major bleeding which occurs much more frequently than under anticoagulation alone (OR 2.91, 95% CI: 1.95–4.36), particularly when fatal or intracranial hemorrhage is considered (OR 3.18, 95% CI: 1.25–8.11) [13]. In light of this delicate balance, current evidence-based guidelines point out that intermediate- or low-risk patients with acute PE are not likely to benefit from the routine use of systemic thrombolysis and that this treatment should therefore only be used as rescue treatment in case of hemodynamic decompensation under anticoagulation alone [6, 12]. The basis for this recommendation has been provided by the results of the Pulmonary Embolism Thrombolysis (PEITHO) trial, which compared a single bolus of tenecteplase (plus heparin) with placebo (plus heparin) in 1006 patients with acute PE and RV dysfunction plus myocardial injury detected by imaging and a positive cardiac troponin test; in this intermediate-high-risk group (Table 29.1), the clinical benefits of thrombolysis were counterbalanced by the intracranial and other major bleeding risks [14].

Emerging approaches to reperfusion treatment of PE might help to achieve comparable efficacy while minimizing the bleeding risk associated with systemic (intravenous) full-dose thrombolysis. Preliminary evidence from small studies suggests that reduced-dose systemic thrombolysis might represent an option for improving safety while maintaining efficacy of this treatment. In a prematurely terminated trial of 118 patients, half-dose recombinant tissue-type plasminogen activator (alteplase) was comparable to the full dose in terms of efficacy and possibly associated with improved safety [15]; in another study of 121 patients with (rather arbitrarily defined) "moderate PE," reduced-dose rtPA appeared to be safe and effective over a follow-up period of more than 2 years (Table 29.3) [16]. However, until the hypothesis generated by these data is confirmed by larger, appropriately designed trials with standardized selection criteria and outcomes, the use of "low-dose" thrombolytic regimens cannot, at the moment, be proposed as an alternative to the dosage approved for systemic intravenous use.

Pharmacomechanical, Catheter-Directed Reperfusion

Catheter-directed pharmacomechanical reperfusion with low-dose local thrombolysis has been developed as an option for clearing pulmonary emboli from larger arteries [22]; this procedure is an alternative to operative embolectomy if systemic thrombolysis is contraindicated or the bleeding risk is high [8]. A phase 2 randomized multicenter trial enrolled patients with acute PE and a right-to-left ventricular dimension ratio

Table 29.3 Functional and hemodynamic outcomes[a] in patients receiving thrombolysis for acute pulmonary embolism: overview of randomized trials and prospective cohort studies

Author and reference	Study population[a]	Groups[a]	Outcome[b]	Follow-up	Thrombolysis group	Control group	Comparison between groups
Kline et al. [17]	Intermediate-risk or submassive PE (n = 83)	Tenecteplase vs placebo	NYHA class III–IV	3 months	5.4%	20.5%	p = n.s
			RV dilation or hypokinesis		33.3%	37.8%	p = n.s
			6-min walking distance <330 m		16%	28%	p = n.s
			Composite functional outcome		85%	63%	p = 0.017
Becattini et al. [18]	Intermediate-risk PE (n = 58)	Tenecteplase vs placebo	Δ RV/LV ratio	7 days	0.47 ± 0.07	0.34 ± 0.05	p = n.s.
Sharifi et al. [16]	"Moderate" PE (n = 121)	Half-dose tPA vs anticoagulant alone	Mean SPAP (mmHg)	6 months	31 ± 6	49 ± 8	p <0.001
			SPAP ≥40 mmHg	28 months	16%	57%	p <0.001
			Mean SPAP (mmHg)		28 ± 7	43 ± 6	p <0.001
			Death		1.6%	5.0%	p = n.s.
Wang et al. [15]	High- and intermediate-risk PE (n = 118)	Half-dose tPA 50 mg vs tPA 100 mg	Δ RVED/LVED; Δ RVWM; Δ SPAP; lung perfusion defects and obstruction score	24 h and 14 days	No differences between groups reported		
Kuo et al. [19]	Massive or submassive PE (n = 101)	All treated with CDT	SPAP	Pre- vs post-CDT	51.2 ± 14.1 → 37.2 ± 15.8		p <0.001
			RV strain (Bowker test of symmetry)		89.1% (95%CI: 76.8%–94.4%) with vs 10.9% with no improvement		p <0.001

Kucher et al. [20]	Intermediate-risk PE ($n = 59$)	CDT vs anticoagulant alone	Δ RV/ LV ratio	24 h	0.30 ± 0.20	0.03 ± 0.16	$p < 0.001$
			Δ RV/RA pressure gradient (mmHg)		9.8 ± 9.9	0.3 ± 10.9	$p = 0.03$
			Δ TAPSE (mm)		−3.1 ± 4.4	0.9 ± 4.9	$p = 0.02$
			Δ RV/LV ratio	90 days	0.35 ± 0.22	0.24 ± 0.19	p = n.s.
			Δ RV/RA pressure gradient (mmHg)		12.3 ± 12.8	11.6 ± 15.1	p = n.s.
			Δ TAPSE (mm)		−6.1 ± 4.6	−3.4 ± 5.4	p = n.s.
Piazza et al. [21]	Intermediate- or high-risk PE ($n = 150$)	All treated with CDT, low-dose thrombolysis	Mean RV/LV ratio	Pre- vs post-CDT (48 h)	1.55 ± 0.39 → 1.13 ± 0.2		$p < 0.001$
			Mean SPAP (mmHg)		51.4 ± 16 → 36.9 ± 14.9		$p < 0.001$
			Modified Miller index		22.5 ± 5.7 → 15.8 ± 5.9		$p < 0.001$

AC = anticoagulant, *CDT* = catheter-directed thrombolysis, Δ = difference (at follow-up versus baseline), *NYHA* = New York Heart Association, *PE* = pulmonary embolism, *RA* = right atrium, *RV/LV* = right-to-left ventricular ratio, *RVED/LVED* = right-to-left ventricular end-diastolic diameter ratio, *RVWM* = right ventricular wall motion, *SPAP* = systolic pulmonary artery pressure, *TAPSE* = tricuspid annular plane systolic excursion, *tPA* = tissue-type plasminogen activator, *WD* = walking distance

[a]The size of the study population displayed in the table refers to the total number of patients included in each study and may be higher than the number of patients considered in the (often secondary) analyses of functional or hemodynamic outcomes

[b]This table focuses on surrogate, i.e., functional and imaging (echocardiographic, computed tomographic) parameters at follow-up, which were not included in the meta-analysis by Marti et al. (discussed in the text)

>1.0, comparing unfractionated heparin plus a 15-h catheter-directed, ultrasound-assisted regimen of 10–20 mg rtPA versus heparin alone [20]. Catheter-directed treatment led to significant recovery of RV function at 24 h, with no increased risk of major hemorrhage [20]. The efficacy and safety of the pharmacomechanical approach using low-dose local thrombolysis were more recently supported by the results of a prospective, single-arm multicenter trial [21], and those of a registry, both including patients with massive or submassive PE [19] (Table 29.3).

Like any other interventional procedures, catheter-directed pharmacomechanical reperfusion requires adequate operator expertise and institutional volume. Furthermore, it remains to be determined whether the speed of thrombus removal, and consequently of the relief of the RV from pressure overload, is adequately high in patients with overt or imminent hemodynamic decompensation and whether the use of ultrasound is really necessary for obtaining maximum efficacy [20].

Impact of Thrombolysis on Late Outcomes After Pulmonary Embolism

Cohort studies with long-term follow-up suggest that a substantial proportion of patients who have survived an acute PE episode may complain of persistent functional limitation and/or reduced quality of life for long periods after the index event [2]. Moreover, some degree of persistent pulmonary hypertension or RV dysfunction was observed in as many as 40% of survivors followed over 6 months to 1 year after acute PE [23]. These data are to be interpreted with caution as the number of patients followed in observational studies performed so far was rather small, echocardiographic parameters of RV dysfunction were not standardized, and a correlation of ultrasound findings with the severity of patients' symptoms or the degree of functional limitation could not be established [24]. Similarly, the broad range of the reported CTEPH incidence rates after symptomatic PE (0.1–9.1% of the patients within the first 2 years [3]) is probably due to referral bias, absence of early symptoms, and the occasional difficulty in differentiating truly acute PE at baseline from an acute episode superimposed on pre-existing CTEPH [25].

Early thrombolysis might exert favorably prolonged effects on the patients' clinical and hemodynamic course after PE. Two small randomized trials suggested that thrombolysis might improve, compared to anticoagulation alone, functional capacity at 3 months [17], or the persistence (or development) of pulmonary hypertension at 28 months (Table 29.3) [16]. These data are to be viewed as preliminary and hypothesis generating at present: in the former study, the small difference in favor of thrombolysis on long-term outcomes was mainly driven by the patients' subjective perception of wellness based on the SF36 survey [17], while in the latter study, surprisingly many (57%) patients in the control group were reported to have an estimated systolic pressure higher than 40 mmHg [16]. In fact, the 2-year follow-up of intermediate-risk patients randomized to tenecteplase plus anticoagulation versus anticoagulation alone in the PEITHO trial [14] revealed no impact of thrombolytic therapy on overall survival rates after acute PE (unpublished preliminary data under review).

Anticoagulation for Acute Treatment and Secondary Prophylaxis

Shift Toward New Oral Anticoagulants as the Standard of Care

In all patients with acute PE, anticoagulation treatment should be initiated immediately to reduce the risk of recurrence and fatal thromboembolic events. In fact, the first dose of anticoagulant treatment, preferably one subcutaneous injection of low-molecular-weight heparin or fondaparinux, should be given *already during the diagnostic workup* in patients having an intermediate or high clinical "pretest" probability of PE, i.e., even before the disease is confirmed by an imaging test [8]. High-risk individuals with

hemodynamic instability, or in whom clinical decompensation is considered imminent, may be candidates for thrombolytic or other reperfusion treatments and should therefore initially receive an intravenous agent with a shorter half-life (unfractionated heparin) and the possibility of a laboratory monitoring of the anticoagulant levels.

For many years, parenteral anticoagulant agents (heparins or the synthetic pentasaccharide fondaparinux) followed by vitamin K antagonists (VKA) represented the gold standard for the anticoagulant treatment of VTE. The standard regimen consisted of parenteral anticoagulation and VKA co-administration for the first 5–10 days, until the INR values reached the target therapeutic range (between 2.0 and 3.0) for at least 2 consecutive days; then heparin was discontinued. This strategy is still valid and included in the guideline recommendations; however, in the past decade, two classes of direct, non-vitamin K-dependent oral anticoagulants (NOACs) were approved for the treatment and secondary prophylaxis of acute PE: three direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and one direct thrombin inhibitor (dabigatran etexilate). These drugs exhibit similarly short half-lives (7–13 h) and a predictable anticoagulant effect allowing fixed dose administration with no need for routine monitoring. Large phase 3 trials showed that these drugs were non-inferior to the "standard" treatment mentioned above with respect to efficacy outcomes, while their safety profile was overall superior to that of the comparator arm, particularly in terms of bleeding severity [26, 27]. As a consequence, NOACs are increasingly being used in the treatment of VTE, and this progressive shift to a new standard of care in anticoagulation is supported, at least in part, by current guideline recommendations [12].

Table 29.4 summarizes the approved regimens of the NOACs for the initial, long-term, and extended management of acute PE; Table 29.5

Table 29.4 Overview of non-vitamin K-dependent oral anticoagulants in the acute-phase treatment and secondary prevention of venous thromboembolism

Anticoagulant	Dosage and anticoagulation period			Not recommended or contraindicated[a]
	Initial	Long-term	Extended	
Rivaroxaban	15 mg twice daily for 21 days	20 mg once daily with food (15 mg once daily in selected patients[b])		• CrCl <30 mL/min (FDA), CrCl <15 mL/min (EMA)
				• Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy
				• Concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers
Dabigatran etexilate	Initial therapy with parenteral anticoagulation for 5–10 days	150 mg twice daily (110 mg twice daily in selected patients[c])		• CrCl <30 mL/min
				• Elevated liver enzymes >2× upper limit of normal or with liver disease expected to have an impact on survival
				• Concomitant treatment with P-gp inhibitors in patients with CrCl <50 mL/min or with P-gp inducers (i.e., rifampin)

(continued)

Table 29.4 (continued)

Anticoagulant	Dosage and anticoagulation period			Not recommended or contraindicated[a]
	Initial	Long-term	Extended	
Apixaban	10 mg twice daily for 7 days	5 mg twice daily	2.5 mg twice daily after at least 6 months of treatment	• CrCl <15 mL/min • Severe hepatic impairment (Child-Pugh C), or hepatic disease associated with coagulopathy • Strong dual inhibitors or inducers of CYP3A4 and P-gp
Edoxaban[d]	Initial therapy with parenteral anticoagulation for 5–10 days	60 mg once daily (30 mg once daily in selected patients[d])		• CrCl <15 mL/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant treatment with rifampin

The table is adapted from [28]. *CrCl* = creatinine clearance, *CYP3A4* = cytochrome P450-3A4, *EMA* = European Medicines Agency, *FDA* = Food and Drug Administration (United States), *NSAID* = nonsteroidal anti-inflammatory drug(s), *P-gp* = P-glycoprotein, *VTE* = venous thromboembolism

[a]All mentioned anticoagulant agents should also be avoided in patients: (1) for whom thrombolysis or pulmonary embolectomy may be required, (2) requiring dialysis, (3) at significant risk of bleeding, (4) receiving a concomitant anticoagulant, (5) with known hypersensitivity to the agent, and (6) during pregnancy or breastfeeding

[b]According to the EMA product information, rivaroxaban 15 mg should be considered for the long-term phase if the patient's assessed risk for bleeding outweighs the risk for recurrent venous thromboembolism. In the European Union, rivaroxaban is contraindicated in patients with CrCl <15 mL/min and should be used with caution in patients with CrCl 15–30 mL/min

[c]According to the EMA product information, dabigatran 110 mg twice daily is recommended in patients aged 80 years or above and in those receiving concomitant verapamil, while it can be considered in patients between 75 and 80 years, with moderate renal impairment, with gastritis, esophagitis or gastroesophageal reflux, or in other subjects at increased risk of bleeding

[d]Although a separate extension trial was not conducted for edoxaban, more than 40% of patients included in the Hokusai-VTE study received treatment with edoxaban for up to 12 months. The reduced daily dose (30 mg) should be considered in patients with ≥1 of the following: CrCl 15–50 mL/min, body weight ≤60 kg, concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole

displays a list of major ongoing NOAC trials on specific patient populations, treatment duration, and possible new or extended indications. The duration of anticoagulation after a first episode of VTE should cover a minimum of 3 months, but it remains largely undetermined beyond that time and must be individualized on a case-by-case basis [6, 12]. In this regard, some important facts need to be pointed out [28]:

(a) There is persisting uncertainty on the influence and relative "weight" of individual baseline or follow-up parameters as predictors of recurrence risk.
(b) There is lack of robust, externally validated recurrence scores for VTE patients.
(c) The VTE recurrence risk begins to rise as soon as anticoagulation is discontinued, regardless of its previous duration.
(d) There have also been no dedicated and validated bleeding scores for VTE patients under chronic anticoagulation, although a recently developed, relatively simple score (Table 29.6) appears to be promising in this regard; as a result, the question on how to define risk categories and the "net clinical benefit" of anticoagulation over the long term has, until now, remained unresolved.

Table 29.5 Ongoing trials on specific patient populations and possible new or extended indications of NOACs for the treatment or secondary prevention of deep vein thrombosis or pulmonary embolism

Study identifier	Population	Intervention	Comparator	Primary clinical outcome(s)	Follow-up	Sample size	Study	Estimated completion date
EINSTEIN CHOICE (NCT02064439)	Secondary VTE prevention	Rivaroxaban 10 mg or 20 mg once daily	Aspirin 100 mg once daily	Recurrent VTE, major bleeding	12 months	3399	Phase 3b	October 2016
HoT-PE (2013–001657–28)	Outpatient management of acute PE	Rivaroxaban standard therapeutic dose	–	Recurrent VTE- or PE-related death	3 months	1100	Phase 4	January 2018
RIDTS (NCT02722447)	Isolated distal DVT	Rivaroxaban standard therapeutic dose for 6 weeks after an initial course of 6-week treatment	Placebo	Recurrent VTE	3 months	1100	Phase 3b	June 2020
Hokusai-VTE cancer (NCT02073682)	Cancer patients with acute VTE	Edoxaban standard dose	Dalteparin standard therapeutic dose	Recurrent VTE, clinically relevant bleeding	6 months	1000	Phase 3b	December 2017
VERDICT (NCT02664155)	Acute VTE in patients with moderate or severe renal dysfunction	Apixaban standard therapeutic dose for 7 days followed by 2.5 mg twice daily, or rivaroxaban standard therapeutic dose for 21 days followed by 15 mg once daily	Standard of care (heparin, INR-adjusted VKA)	Net clinical benefit (recurrent VTE, major bleeding)	3 months	800	Phase 3b	March 2019
PEITHO-2 (NCT02596555)	Intermediate-risk PE	LMWH standard therapeutic dose for 72 h followed by dabigatran standard therapeutic dose	–	Recurrent VTE- or PE-related death	6 months	700	Phase 4	August 2019
TRAPS (NCT02157272)	Antiphospholipid syndrome	Rivaroxaban standard therapeutic dose	INR-adjusted warfarin	Recurrent thrombosis major bleeding, death	4 years	536	Phase 3b	December 2018

(continued)

Table 29.5 (continued)

Study identifier	Population	Intervention	Comparator	Primary clinical outcome(s)	Follow-up	Sample size	Study	Estimated completion date
SELECT-D (2012-005589-37)	Cancer patients with acute VTE	Rivaroxaban standard therapeutic dose for 6 months	Dalteparin 200 IU/kg daily for 1 month followed by 150 IU/kg during months 2–6	Recurrent VTE- or PE-related death	6 + 6 months	530	Phase 3b	December 2018
		Rivaroxaban standard therapeutic dose for further 6 months	Placebo (6 months)					
Apixaban: VTE treatment in cancer (NCT02585713)	Cancer patients with acute VTE	Apixaban standard therapeutic dose	Dalteparin standard therapeutic dose	Major bleeding	6 months	315	Phase 3b	December 2020
RAMBLE (NCT02761044)	Treatment of VTE in young women	Rivaroxaban standard therapeutic dose	Apixaban standard therapeutic dose	Patient reported menstrual bleeding	3 months	308	Phase 3b	May 2019
CAP (NCT02581176)	Cancer patients with acute VTE	Apixaban standard therapeutic dose for 6 months followed by 2.5 mg twice daily	–	Recurrent VTE, major or clinically relevant nonmajor bleeding	6 months	300	Phase 4	January 2021
CASTA-DIVA (NCT02746185)	Cancer patients with acute VTE	Rivaroxaban standard therapeutic dose	Dalteparin standard therapeutic dose	Recurrent VTE	6 months	200	Phase 3b	May 2017
ASTRO-APS (NCT02295475)	Antiphospholipid syndrome	Apixaban 5 mg twice daily	INR-adjusted warfarin	Recurrent thrombosis major and nonmajor bleeding	13 months	200	Phase 3b	December 2017

MERCURY PE (NCT02584660)	Outpatient management of acute PE	Rivaroxaban standard therapeutic dose	Standard of care	Major bleeding, days of hospitalization	3 months	120	Phase 3b	March 2017
RIVASVT-100 (NCT02627053)	Treatment of acute portal, mesenteric, or splenic vein thrombosis	Rivaroxaban standard therapeutic dose	–	Major bleeding	3 months	100	Phase 4	December 2018

DVT = deep vein thrombosis, *NOAC* = non-vitamin K-dependent oral anticoagulant(s), *PE* = pulmonary embolism, *VTE* = venous thromboembolism
Study acronyms (where available): *ASTRO-APS* = Apixaban for the Secondary prevention of ThROmboembolism among patients with the AntiPhospholipid Syndrome, *CASTA-DIVA* = Cancer ASsociated Thrombosis, A pilot treatment stuDy using rIVAroxaban, *HoT-PE* = Home Treatment of patients with low-risk Pulmonary Embolism, *MERCURY PE* = MulticEnter trial of Rivaroxaban for early disCharge of pUlmonaRY embolism from the Emergency Department, *PEITHO-2* = Pulmonary Embolism International Trial-2, *RAMBLE* = Rivaroxaban vs Apixaban on Menstrual Blood Loss, *RIDTS* = RIvaroxaban for the treatment of symptomatic Isolated Distal Deep vein ThrombosiS, *RIVASVT-100* = RIVAroxaban for the treatment of Splanchnic Vein Thrombosis, *SELECT-D* = Anticoagulation therapy in SELECTeD cancer patients at risk of recurrence of venous thromboembolism, *TRAPS* = Trial on Rivaroxaban in high risk patients with AntiPhospholipid Syndrome, *VERDICT* = VEnous thromboembolism in Renally impaired patients and DIreCT oral anticoagulants

Table 29.6 The VTE-BLEED score for prediction of major bleeding events during stable anticoagulation after VTE

Baseline variable	Score
Active cancer[a]	2
Male patient with uncontrolled arterial hypertension[b]	1
Anemia[c]	1.5
History of bleeding[d]	1.5
Age ≥60 years old	1.5
Renal dysfunction[e]	1.5
Classification of bleeding risk[f]	
Low risk	Total score <2
High risk	Total score ≥2

eGFR = estimated glomerular filtration rate. *VTE* = venous thromboembolism

Definition of score variables in the derivation population [29, 30]

[a]Cancer diagnosed within 6 months before diagnosis of VTE (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer, or any cancer that required anticancer treatment within 6 months before the VTE was diagnosed

[b]Uncontrolled arterial hypertension defined as systolic blood pressure ≥140 mmHg at baseline

[c]Hemoglobin <13 g/dL in men or <12 g/dL in women

[d]Including prior major or nonmajor clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or hematuria

[e]eGFR <60 mL/min at baseline, calculated using with the Cockcroft-Gault formula which accounts for serum creatinine, age, and body weight

[f]Refers to the risk of major or clinically relevant nonmajor bleeding [29]

(e) Extended (beyond the first 6 months) anticoagulation treatment with NOACs, but also with contemporary VKA-based regimens, has exhibited a satisfactory efficacy and safety profile.

(f) Accumulating "real-world" data appears to confirm the results of the large phase 3 trials regarding the efficacy and safety of NOACs [31].

In view of all these considerations, we are already observing a trend toward increasingly longer or "indefinite" anticoagulation periods for secondary VTE prophylaxis.

Although NOACs are generally associated with less frequent life-threatening complications compared to vitamin K antagonists, bleeding management under any anticoagulant drug remains a major challenge. Idarucizumab, a reversal agent ("antidote") for the direct thrombin inhibitor dabigatran, has already been approved and is available for clinical use; this agent has been integrated in recently updated bleeding management algorithms [32]. Andexanet, a reversal agent against the direct oral factor Xa inhibitors apixaban and rivaroxaban (and possibly also against edoxaban as well the as the low-molecular-weight heparin enoxaparin as an indirect parenteral Xa inhibitor), has yielded promising results in an ongoing phase 3 clinical trial [33] and will probably also be approved in the future. Ciraparantag, a synthetic cationic small molecule and "universal" antidote, is at an earlier stage of development. In view of the concerns regarding the potential for overuse or misuse of antidotes in clinical practice, the International Society on Thrombosis and Haemostasis (ISTH) has issued recommendations regarding their indications and contraindications together with handling instructions [34]; these are summarized in Table 29.7.

Specific Patient Groups and Indications for Anticoagulation

Table 29.5 summarizes the major ongoing trials on the use of NOACs in specific patient populations. For example, a prospective multicenter management trial is focusing on the safety and efficacy of dabigatran in the treatment of patients with acute intermediate-risk PE defined by imaging (echocardiographic or CT) and laboratory (circulating levels of cardiac troponins and natriuretic peptides) parameters and their combinations. At the low end of the PE severity spectrum, a prospective multicenter management trial has set out to determine whether early discharge and out-of-hospital treatment of patients with "low-risk" PE (on the basis of clinical criteria combined with the exclusion of right ventricular dysfunction and intracardiac thrombi) with rivaroxaban is feasible and safe; the trial will also obtain health economic variables as the basis for description of resource utilization [35].

Table 29.7 Instructions on NOAC reversal in emergency situations

Indications for use of NOAC reversal agents	• Life-threatening bleeding (i.e., intracranial hemorrhage)
	• Bleeding in a closed space or critical organ (intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome)
	• Major bleeding not responsive to local hemostatic measures or risk of recurrent bleeding because of delayed NOAC clearance or NOAC overdose
	• Need for emergency surgery or intervention that is associated with a high risk of bleeding
	• Emergency surgery or intervention in patients at high risk for procedural bleeding: neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgeries
Potential indication for the use of NOAC reversal agents	• Need for urgent surgery or intervention in patients with acute renal failure
Reversal agents not indicated	• Elective surgery
	• Gastrointestinal bleeds that respond to supportive measures
	• High drug levels or excessive anticoagulation without associated bleeding
	• Need for surgery or intervention that can be delayed long enough to permit drug clearance
Handling	• Institutional protocol for management of bleeding in patients taking anticoagulants
	• Dedicated logistics for storage and timely administration of the antidote
	• Team approach to manage bleeding complications in anticoagulated patients

This table is in accordance with the recent recommendations issued by the International Society on Thrombosis and Haemostasis [34]

The pathophysiological, epidemiological, and clinical relevance of the association between VTE and cancer is well documented. The consensus that weight-adjusted subcutaneous low-molecular-weight heparin should be considered for the first 3–6 months instead of oral anticoagulants for patients with PE and cancer has remained unchanged in the past years [6, 12]. Post hoc analysis of the patients with active cancer or history of cancer included in the phase 3 rivaroxaban trials [36] as well as a meta-analysis of the cancer patients included in all phase 3 NOAC trials on the treatment of VTE [37] suggested a good efficacy and safety profile for target-specific oral anticoagulants as compared to VKA. However, further data, including a comparison between NOACs and low-molecular-weight heparins, are needed to determine the optimal anticoagulation strategy in this patient population. Ongoing controlled trials (included in Table 29.5) are aiming to evaluate whether oral factor Xa inhibitors are non-inferior to low-molecular-weight heparin for treating acute VTE in cancer patients.

Conclusion

Pulmonary embolism is a significant contributor to acute and chronic mortality and morbidity. Beyond pharmacological and, if necessary, mechanical circulatory support of the failing right ventricle, systemic thrombolysis remains the mainstay of treatment for hemodynamically unstable patients with “high-risk” PE. On the other hand, the (intracranial) bleeding risks of full-dose thrombolysis outweigh its potential clinical benefits in normotensive patients. Catheter-directed, possibly ultrasound-accelerated low-dose local thrombolysis has emerged as a promising option for minimizing major bleeding risk while maintaining reperfusion efficacy. Non-vitamin K-dependent oral anticoagulants directly inhibiting factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran) are evolving into the new standard of care in VTE treatment and secondary prophylaxis, as they can simplify initial and long-term anticoagulation after PE while reducing major bleeding risk.

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Catheter-Directed Thrombolysis of Pulmonary Embolism

30

Adham Abou Ali, Efthymios D. Avgerinos, and Rabih A. Chaer

Clinical Pearls

1. Catheter-directed thrombolysis for submassive/massive PE improves right ventricular function with a smaller dose of thrombolytic agent compared to systemic lysis and therefore decreases the risk of bleeding.
2. Catheter-directed thrombolysis for submassive/massive PE has been shown in multiple series to achieve 85–100% clinical success.
3. A variety of suction thrombectomy devices are available for treatment of patients with massive PE and absolute contraindication to thrombolysis, but the data supporting it is limited.

Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death after myocardial infarction and stroke [1]. The annual incidence of PE is approximated to be between 75 and 300 cases per 100,000 individuals, even reaching 700/100,000 cases in the elderly population (>70 years of age). PE incidence has increased over the past two decades due to better diagnostic modalities and the aging population and remains the most common preventable cause of in-hospital death with approximately 5–10% of cases [2]. This has driven research and contemporary practice toward novel treatment strategies. Catheter-directed interventions (CDIs) have recently emerged for the treatment of high-risk PE, and their increased use has been attributed to their potentially lower complication rates compared to systemic thrombolysis, mainly due to the lower thrombolytic dose used [3]. This chapter summarizes the contemporary practice of CDI: evidence, indications, types of CDI, associated complications, and short- and long-term outcomes.

Clinical Presentation and Diagnosis of PE

The clinical presentation of PE depends on the clot burden and the underlying cardiopulmonary status of the patient. It can range from the incidentally diagnosed asymptomatic presentation to shock and sudden death. The most common symptomatic presentation of PE is dyspnea followed by pleuritic chest pain and cough [4].

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Additional signs include tachypnea, tachycardia, jugular venous distention, decreased breath sounds, and even syncope. PEs presenting as shock occur in <10% of cases but are critical to recognize as they are associated with high mortality rates. Chronic thromboembolic pulmonary hypertension (CTEPH) is a late manifestation of acute PE. Progressive dyspnea and exercise intolerance are common symptoms with this entity. Many patients have a history of PE or deep venous thrombosis; however, it is worth noting that up to 40% of patients deny a history of venous thromboembolism [5].

The nonspecific presentation of PE has led to the adoption of laboratory markers, imaging modalities, and clinical prediction algorithms. This is especially true given that several diagnoses present in a similar fashion such as acute coronary syndrome, aortic dissection, pneumonia, pneumothorax, and arrhythmia to name a few.

Among laboratory markers, the plasma D-dimer level at a 500 ng/mL cutoff has a high sensitivity in the diagnosis of PE. This is useful in patients presenting with a low to intermediate probability of PE as it obviates the need for further testing and radiation exposure. Patients with a high probability of PE do not require D-dimer testing and proceed directly to other confirmatory imaging modalities. Older age and several pathologies such as inflammation, cancer, bleeding, trauma, and surgery increase D-dimer levels making it a nonspecific finding.

Biomarkers such as cardiac troponins (TnT or TnI), brain natriuretic peptide (BNP), and its precursor NT-BNP levels are helpful in risk stratification [6–8]. Although standard cutoff values exist for TnT, TnI, and BNP (0.1, 0.4 ng/mL, and 90 pg/mL, respectively), age-adjusted values appear to be better predictors [8].

Electrocardiographic changes are neither sensitive nor specific. The S1Q3T3 pattern (prominent S wave in lead I, Q wave and inverted T wave in lead III) frequently described with PE appears in less than 20% of cases. And while this pattern reflects right ventricular (RV) strain, echocardiography and computed tomography angiography (CTA) are better assessors of RV function. ECG is mainly used to rule out myocardial infarcts.

Transthoracic echocardiography (TTE) is frequently used to assist in the diagnosis and prognosis of PE; however, it cannot be used to confirm the diagnosis of PE. RV dysfunction is a common sign accompanying intermediate- to high-risk PE and is associated with an increased risk of death [9]. Although other pulmonary pathologies such as pulmonary hypertension can have associated RV dysfunction, TTE is a useful tool in the setting of a clinical suspicion of PE. RV dysfunction signs on TTE include RV dilatation, RV to left ventricular (LV) end diastolic diameter ratio (RV/LV) >0.9, McConnell sign (depressed contractility of RV wall compared to RV apex), reduced tricuspid annular plane systolic excursion (TAPSE), interventricular septal flattening, and thrombus in the right atrium or RV (thrombus in transit) [9–11]. TTE use is reserved for unstable patients who cannot undergo a CTA and may justify the use of emergent thrombolytic therapy [12]. Right ventricular hypokinesis on echocardiography has been identified as a significant prognostic factor in determining overall crude mortality at 3 months [13].

The gold standard for PE diagnosis is computed tomographic pulmonary arteriography (CTPA). Given CTPA's sensitivity of 83% and specificity of 96%, this modality has been suggested as a stand-alone diagnostic tool to exclude or diagnose PE [14–18]. The addition of CT venography (CTV) enhances the sensitivity while having a similar specificity compared to CTA alone. CTA is also a prognostic tool that detects RV enlargement and allows for the calculation of the RV/LV ratio. A ratio ≥0.9 is used as a marker of RV dysfunction (similar to echocardiography) [19].

Risk Stratification

PE risk stratification is based on its mortality risk; it is not based on the degree of pulmonary vasculature obstruction. The angiographic burden of a pulmonary embolus (Miller index) has been abandoned as a risk stratification tool due to

its poor correlation with mortality risk [20]. PE is classified into low-, intermediate (submassive)-, and high (massive)-risk types based on the expected 30-day mortality rate. The terms "massive" and "submassive" were introduced when the Miller index was used, so "intermediate" and "high risk" seem to be more appropriate in today's practice. This classification guides major treatment decisions in accordance with treatment guidelines [12, 21, 22].

Societal guidelines define PE types as follows:

1. Low risk: hemodynamically stable PE patients without evidence of RV dysfunction on echocardiography and without elevated cardiac biomarkers such as troponin and BNP. Those patients have the lowest mortality rate around 1–2% [21, 23].
2. Intermediate risk: hemodynamically stable PE with evidence of RV dysfunction on echocardiography and/or with elevated cardiac biomarkers. These patients have a mortality rate ranging between 3 and 15% [13, 24, 25]. Intermediate-risk patients are subclassified into intermediate-low risk and intermediate-high risk depending on the simplified pulmonary embolism severity index (sPESI), cardiac biomarkers, and imaging findings [26].
3. High risk: hemodynamically unstable PE patients with sustained hypotension (<90 mmHg) for at least 15 min or requiring vasopressors or experiencing a cardiac arrest. These patients have an in-hospital mortality rate reaching up to 30% [13, 25, 27, 28].

The pulmonary embolism severity index (PESI) is one of several scoring systems for risk stratification [29]. The PESI and sPESI scores are validated tools correlating clinical patient risk factors with mortality outcomes, whereby a PESI class I or II (sPESI = 0) has a 30-day mortality rate of around 3% and a PESI class III or V (sPESI $\geq$ 1) has a mortality rate ranging between 10 and 25% [30–32]. A combination of risk scores, cardiac biomarkers, and imaging modalities identifies the high-risk patient that would benefit from invasive interventions and treatments (intermediate-high-risk and high-risk PE patients) [33].

Treatment

The primary goal of PE treatment is the prevention of mortality and secondarily the prevention of late-onset chronic thromboembolic pulmonary hypertension [3, 12, 34, 35]. Anticoagulation remains the standard of care for low-risk PE, and therapy is escalated to the use of thrombolytics or surgical thrombectomy for selected intermediate- and high-risk PE. The patient's clinical presentation, PESI scores, cardiac biomarkers, and imaging findings allow risk stratification which along with local resources will guide treatment escalation [21, 22].

Systemic Thrombolysis

Systemic thrombolytics have proven to be highly effective with early hemodynamic recovery, but their high complication rate particularly intracranial bleeding limited their widespread use not only for intermediate-risk but even for high-risk PE [22, 36, 37]. A recent meta-analysis showed that systemic thrombolytics for PE are associated with a 47% mortality risk reduction but this came at the cost of a 9.2% major bleeding rate and a 1.5% stroke rate. As a result, only 30% of patients eligible for systemic thrombolytics end up receiving the treatment [38]. The Pulmonary Embolism International Thrombolysis (PEITHO) trial demonstrated the efficacy of thrombolytics in reducing the primary end point of all-cause mortality and hemodynamic decompensation compared to anticoagulation alone for patients with intermediate-risk PE (5.6 vs. 2.6%) [39]. This came at the expense of increased extracranial major bleeding rates (6.3 vs. 1.2%) including intracranial hemorrhage (2.0 vs. 0.2%) [39]. It is important to note that the main driver for a reduction in the combined primary end point (with systemic thrombolysis compared to anticoagulation) was hemodynamic decompensation and not all-cause mortality. As such, the absence of a

mortality difference along with a high complication rate for thrombolytics could not justify their use in intermediate-risk PE patients up until CDI appeared on the market.

Catheter-Directed Interventions

CDIs have been increasingly utilized for both intermediate- and high-risk PE in an attempt to reduce the complication rates of systemic thrombolytics [40–47]. The rationale behind CDI use was providing the same treatment benefit while decreasing complication rates compared to systemic thrombolytics [48, 49]. CDIs have been available for almost two decades, and the techniques have evolved from the insertion of large bulky sheaths through a femoral cutdown to lower-profile sheaths and catheters [50]. The modern CDI era employs thrombolytic infusion catheters at the clot site with or without ultrasound technology, mechanical fragmentation, and aspiration/suction thrombectomy devices (Fig. 30.1). These techniques lack robust evidence supporting them, and yet their use has been exponentially growing over the past 2 years [48]. Rheolytic (pharmacomechanical) thrombectomy is not used anymore after a series of associated adverse events and deaths.

Summary of Evidence

The Ultrasound-Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial is the only randomized controlled trial to compare CDI and anticoagulation vs. anticoagulation alone for intermediate-risk PE. The trial's conclusion was that CDI improves RV systolic function compared to anticoagulation alone at 24 h and 90 days

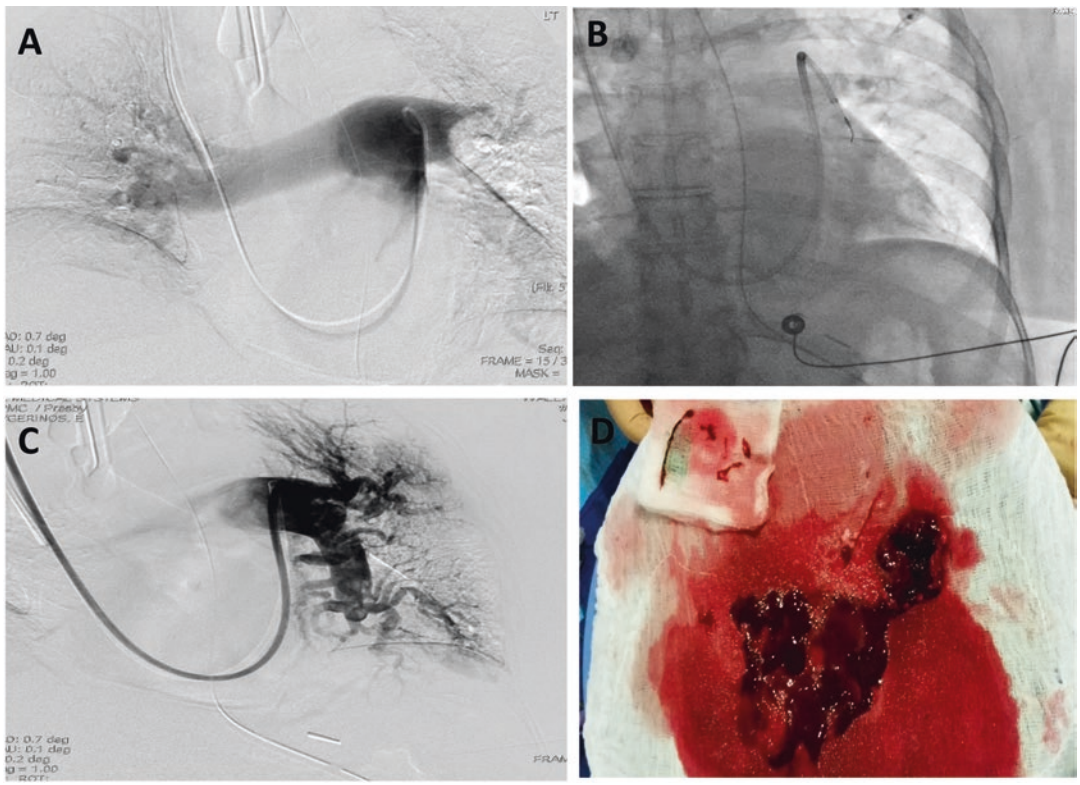

Fig. 30.1 (**a**) Pulmonary angiogram showing a left main pulmonary artery thrombus. (**b**) Placement of suction thrombectomy catheter (Indigo catheter) through left main pulmonary artery clot. (**c**) Pulmonary angiogram showing resolution of the clot. (**d**) Evacuated clot

[49]. The results are in agreement with our experience comparing CDI and anticoagulation alone for intermediate-risk PE; it showed improved early right ventricular function and shorter ICU length of stay at the expense of potentially higher major complication rates with no difference in 30-day mortality or decompensation rates between the two groups [51].

Few studies have compared CDI to systemic thrombolytics for intermediate- and high-risk PE. The recent National Inpatient Sample (NIS) study compared the two treatment modalities in a propensity-matched comparison with in-hospital mortality as the primary outcome. Both in-hospital mortality and intracranial hemorrhage rates were lower for the CDI group compared to the systemic thrombolysis group, but CDI had a higher cost of hospitalization [48]. The study (and the database) was limited by the absence of confounding variables such as PE type, vasopressor use, thrombolytic dose, and anticoagulation regimens. Our recent experience comparing those two groups (CDI and systemic thrombolysis) reveals equivalent clinical and echocardiographic (RV/LV ratio) 30-day outcomes at a potentially lower major bleeding and stroke rates. Randomized studies comparing the two treatment modalities have some ethical and methodological concerns given the data suggesting a lower complication rate for CDI and the large sample size needed to show a clinically significant mortality difference between the two groups, if any.

Several non-comparative studies including the Prospective, Single-arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (SEATTLE II); the Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT) registry; and multiple case series have presented their favorable results with CDI use [19, 40, 41, 45, 47, 50–53]. CDI clinical success rates, defined as treatment completion without major bleeding, stroke, or other major treatment-related events, decompensation, or in-hospital death, have been consistently high across studies ranging between 85 and 100% (Table 30.1).

Yet, despite the data about the efficacy and relative safety of CDI, they should not be portrayed as risk-free procedures [59, 60]. Death, major bleeding, and procedural-related complications such as coronary sinus rupture, cardiac tamponade, tricuspid valve rupture, arrhythmias, and acute renal failure requiring hemodialysis have been reported [50, 54]. Apart from the randomized ULTIMA trial and the PERFECT registry reporting a major bleeding rate of 0%, real-life experience with CDI has revealed a major bleeding rate ranging between 3 and 10%, which still compares favorably against systemic lysis with a range between 0 and 33%; a recent meta-analysis reported a major bleeding rate of around 9% associated with systemic thrombolysis [19, 38, 48–50, 54]. Different major bleeding criteria have led to variabilities and discrepancies in the reporting of major bleeding rates [46, 60]. As a result, pooled analyses of CDI complication rates remain statistically and clinically heterogeneous due to differences in patient selection and study design. The true complication rate of these interventions is difficult to obtain. Using the Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) criteria, we performed a meta-analysis on bleeding outcomes for CDI and obtained a pooled major bleeding rate of 3.5% [60]. Our experience with CDI has revealed a failure rate (major adverse event or no improvement) of around 15% and a major bleeding rate of around 7% [51, 54, 60]. Predictors of CDI failure and complications included PE type, older age, and major contraindications to thrombolytics. While CDIs can be used in patients with relative contraindications to systemic thrombolytics, a major contraindication remains a prohibitive factor for the use of thrombolytics with CDI. However, the near 0% stroke rate of CDIs compared to the 2% stroke rate of systemic thrombolytics has been the major drive toward increased CDI [19, 48–50, 52].

Cost-effectiveness is another aspect to consider in the comparison between CDI and anticoagulation or systemic thrombolysis. Data from the NIS revealed higher hospitalization costs associated with CDI compared to systemic thrombolysis [48]. The added cost with CDI will

Table 30.1 Clinical success and complication rates of CDI for acute PE across studies

Study	PE type	Number of patients	CDI clinical success N (%)	Death N (%)	Bleed major N (%)	Bleed minor N (%)	Stroke N (%)
Avgerinos et al. [54]	Mixed	102	87 (85.3%)[a]	4 (3.9%)	7 (6.9%)	10 (9.8%)	1 (1%)
Patel et al. [48]	Mixed	352	(86.1%)[c]	(10.2%)	(3.7%)	–	(0.3%)
SEATTLE II [19]	Mixed	150	–	4 (2.7%)	15 (10%)	–	0 (0%)
PERFECT [52]	Mixed	101	95 (94.1%)[c]	6 (5.9%)	0 (0%)	13 (12.9%)	0 (0%)
George et al. [55]	Mixed	32	–	(6.3%)	(3.1%)	–	0 (0%)
Bagla et al. [56]	Submassive	45	43 (95.6%)[c]	0 (0%)	2 (4.4%)	4 (8.8%)	0 (0%)
McCabe et al. [57]	Submassive	53	53 (100%)[c]	0 (0%)	0 (0%)	5 (9.4%)	0 (0%)
Dumantepe et al. [41]	Mixed	22	21 (95.5%)[c]	1 (4.5%)	0 (0%)	2 (9.0%)	0 (0%)
ULTIMA [49]	Submassive	30	30 (100%)[c]	0 (0%)	0 (0%)	3 (10%)	0 (0%)
Engelberger et al. [43]	Mixed	52	–	2 (3.8%)	2 (3.8%)	11 (21%)	0 (0%)
Kennedy et al. [44]	Mixed	60	57 (95%)[c]	3 (5%)	1 (1.7%)	1 (1.7%)	0 (0%)
Engelhardt et al. [58]	Mixed	24	20 (83.3%)[c]	0 (0%)	4 (16.7%)	2 (8.3%)	0 (0%)
Kuo et al. [50]	Massive	594	(86.5%)[b]	5 (–)	19 (–)	21 (–)	1 (–)
Lin et al. [45]	Massive	25	–	3 (12%)	3 (12%)	0 (0%)	0 (0%)
Chamsuddin et al. [40]	Massive	10	10 (100%)[c]	0 (0%)	0 (0%)	2 (20%)	0 (0%)

[a]Clinical success was defined as treatment completion without major bleeding, stroke, or other major treatment-related events, decompensation, or in-hospital death

[b]Clinical success was calculated by determining the number of treatment completions without in-hospital death or major bleeding events

[c]Clinical success was defined as stabilization of hemodynamics, resolution of hypoxia, and survival to hospital discharge

need to be justified by superior short- and long-term clinical outcomes or a superior quality of life, if any.

Enrolling randomized clinical trials comparing standard vs. ultrasound-assisted CDI for submassive PE [SUNSET sPE] and studying the optimal duration and dose of thrombolytics for submassive PE [OPTALYSE PE] are currently under way to allow a better understanding and standardization of the various CDI techniques and protocols [61].

The most recent American College of Chest Physician (ACCP) and European Society of Cardiology guidelines recommend systemic thrombolysis over CDI for high-risk acute PE patients and selected intermediate-risk PE patients who fail to improve or deteriorate with anticoagulation. CDIs are suggested over systemic thrombolysis if the patient has a high risk of bleeding, and local expertise and resources are available [12, 22].

Types and Techniques

The contemporary use of CDI has expanded to include catheter interventions with or without thrombolytics. The latter may involve thrombus fragmentation and/or aspiration/suction thrombectomy techniques; both have been described and used in patients with major contraindications to thrombolysis. However, their safety and effi-

Table 30.2 Available and most commonly used CDI for acute PE

CDI types	Device name	Technique	Use
Standard catheter thrombolysis	Cragg-McNamara (Boston Scientific, Marlborough, Mass)	4–5F non-FDA-approved multiside hole catheter introduced across heaviest clot burden	Ultrasound-assisted thrombolysis has most of the literature supporting its use for intermediate-risk and high-risk PE; however, there is no evidence of superiority for ultrasound-assisted over standard catheter-directed thrombolysis
	UniFuse (AngioDynamics, Latham, NY)		
Ultrasound-assisted catheter thrombolysis	EkoSonic™ catheter (EKOS® Corp, Bothell, Washington)	6F FDA-approved multiside hole catheter with ultrasound microtranducers introduced within clot	
Aspiration/suction thrombectomy	*Small-bore aspiration catheters*:	9–14F catheter using manual aspiration with a syringe	Aspiration/suction thrombectomy devices have been used in intermediate-risk and high-risk PE patients with contraindications to thrombolytics. While there is no evidence supporting one device over the other, local resources and expertise guide the use of these devices. To note, none of these devices are FDA approved for acute PE
	Pronto XL (Vascular Solutions, Minneapolis, MN)	Handheld mechanical aspirator connected to any catheter	
	Aspire (Control Medical Technology, Park City, UT)		
	Large-bore suction devices:	22F catheter (through a 26F sheath) employing extracorporeal bypass circuits	
	AngioVac (AngioDynamics, Inc., Latham, N.Y.)	8F catheter using vacuum-assisted aspiration	
	Indigo (Penumbra Inc., Alameda, CA)	20F catheter employing three spiral wires for capture and aspiration of clot	
	FlowTriever (Inari Medical, Irvine, CA)		

cacy remain controversial [3, 50, 62]. Depending on patient factors, contraindications to thrombolytics, and physician preference, the appropriate CDI technique is selected (Table 30.2).

The usual technique irrespective of catheter use involves ultrasound-guided vein access through a transjugular or transfemoral approach. Two single-lumen sheaths (two access sites) or single dual-lumen sheaths are used for bilateral PEs. An inferior vena cava (IVC) filter is placed prior to pulmonary arteriograms, if deemed necessary. A standard J wire is guided through the right atrium toward the right ventricle and then to the main pulmonary artery. When large devices are planned to be used, care should be taken at this step to prevent tricuspid valve injury (if the wire goes through the chordae tendineae). To avoid this, a pigtail catheter can be used to cross the valve or an inflated Swan-Ganz catheter. Once the pigtail is within the main pulmonary artery, an arteriogram is done to locate the clot and initiate thrombolysis by directing the lytic catheters toward the clot or suction thrombectomy by introducing the suction system.

Standard and Ultrasound-Assisted Thrombolysis

Standard CDI use involves a 5 or 10 cm non-Food and Drug Administration (FDA)-approved multiside hole infusion catheter placed unilaterally or bilaterally in the pulmonary arteries across the heaviest clot burden. While there is no standardized protocol, our protocol uses a 2–4 mg of on-table thrombolytic infusion followed by the initiation of thrombolytic at a 0.5–1 mg/h per catheter. The catheter side holes allow for the local infusion of thrombolytics into the surrounding thrombus (Fig. 30.2a). A modification of this standard catheter system is the ultrasound-assisted thrombolysis. The EkoSonic

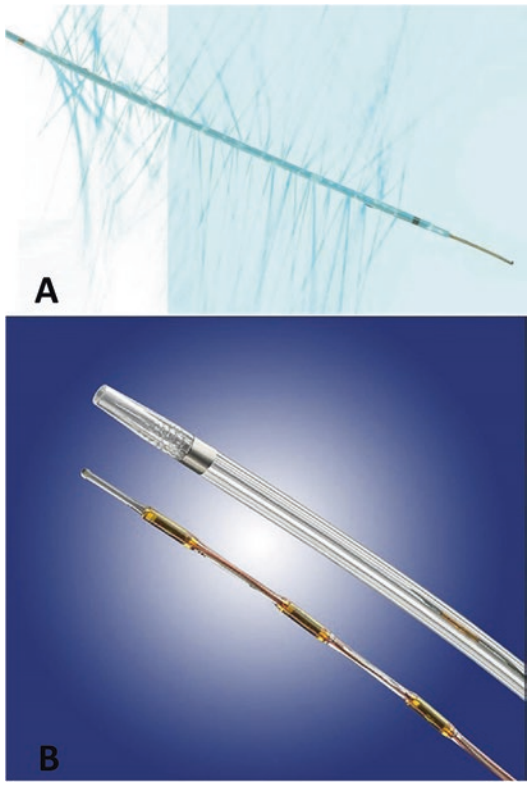

Fig. 30.2 Standard and ultrasound-assisted catheter-directed thrombolysis. (**a**) Standard multiside hole infusion catheter. (**b**) EkoSonic catheter (EKOS® Corp, Bothell, Washington)

Endovascular System (EKOS Corporation, Bothell, WA, USA) is an example of a FDA-approved setup that combines the standard CDI catheter with an ultrasound-emitting core (Fig. 30.2b). Ultrasound transducers are placed along a wire that is introduced on the infusion catheters with the proposed benefit of faster thrombus resolution compared to the standard CDI technique. Ultrasound energy loosens the thrombus' fibrin strands and allows for more contact of the lytic agent with the thrombus [63]. Despite the theoretical advantage, the clinical superiority of ultrasound-assisted CDI over standard CDI remains to be proven [52, 64].

The optimal dose of thrombolytic has not been established and ranges between 15 and 25 mg across studies, which is substantially lower than the 100 mg standard systemic dose. The indication to stop lysis has not been established; however, clinical parameters such as heart rate, blood pressure, and oxygen requirement frequently guide the management of PE patients and the decision on termination of lysis. Other adjuncts contributing to the decision of lysis termination include invasive cardiac monitoring or echocardiographic parameters such as the right ventricle to left ventricle ratio. The OPTALYSE PE trial is currently randomizing submassive PE patients to one of four treatment arms with thrombolytic doses ranging between 4 and 24 mg and infusion times ranging between 2 and 6 h to determine the optimal treatment strategy for submassive PE.

The rate of heparin infusion during lytic administration is a controversial issue. While some recommend minimal heparin (500 units/h) to prevent bleeding complications, our group has agreed on a low-dose heparin protocol (atrial fibrillation protocol) with a target activated partial thromboplastin time (aPTT) between 60 and 80 s, to prevent further clot formation.

Suction Thrombectomy

Major contraindications to thrombolytics have contributed to the advancements seen with catheter interventions. Hemodynamically unstable PE patients with a major contraindication such as a recent stroke or surgery can be attended to using several adjuncts to CDI. Rotating pigtail and balloon embolectomy catheters have been used as thrombus fragmentation CDI techniques [65]. At present, mechanical thrombus fragmentation is combined with aspiration/suction thrombectomy to prevent distal embolization of clot fragments, provide rapid clot resolution, and avoid the use of thrombolytics. Suction thrombectomy devices break down into two groups, small- and large-bore suction thrombectomy catheters, none of which are FDA approved for acute PE.

Small-Bore Suction Thrombectomy Catheters

Practically any catheter attached to a large syringe can serve as a thrombectomy system. The current small-bore suction thrombectomy cathe-

Fig. 30.3 Small-bore aspiration thrombectomy device: Aspire catheter (Control Medical Technology, Park City, UT)

ters being marketed include the Aspire (Control Medical Technology, Park City, UT) and Pronto XL (Vascular Solutions, Minneapolis, MN) catheters. The 14F Pronto XL catheter employs a 60 mL lockable syringe through which manual aspiration is performed. The catheter is rotated under suction which is controlled and modified using a roller clamp near the syringe [66] (Fig. 30.3a). The Aspire handheld mechanical aspirator can be connected to any catheter to allow forceful aspiration of the clot (Fig. 30.3b).

Large-Bore Suction Thrombectomy Catheters

Large-bore suction devices such as the Vortex AngioVac System (AngioDynamics, Latham, NY) have recently entered the market and involve en bloc removal of emboli. The 18F suction device makes use of an extracorporeal veno-venous bypass circuit which drains, filters, and reinfuses the blood (cleared from clot) for up to 6 h. This FDA-approved technique (though not for PE) has been successful in small case series, but more evidence is needed [67]. The primary drawback is the rigidity of the catheter, which makes positioning and advancing the catheter in and beyond the pulmonary artery quite challenging (Fig. 30.4a). Other aspiration devices currently being assessed include the Indigo System CAT8 aspiration catheter (Penumbra Inc., Alameda, CA) and the FlowTriever (Inari Medical, Irvine, CA) (Table 30.2). The 20F FlowTriever device uses three expanding spiral wires to envelop portions of the clot, after which retraction and aspiration are simultaneously applied to capture most of the clot within the spiral wires [68] (Fig. 30.4b). The FlowTriever pulmonary embolectomy clinical study (FLARE) trial will help define the successes and failures of this device. The 8F Indigo catheter uses a powerful vacuum aspiration mechanism along with a separator wire that continuously breaks down the clot for constant aspiration. Its major drawback is aspirating a large volume of blood in the process (Fig. 30.4c). Both Indigo and FlowTriever catheters are relatively new; apart from a case report describing the FlowTriever mechanisms, the literature lacks evidence supporting either catheter and data about the safety of these devices is still absent [68].

The AngioJet Rheolytic Thrombectomy System (Boston Scientific, Marlborough, MA) is a pharmacomechanical system implementing a high-velocity jet to remove intravascular thrombus. The catheters have been used in the past for massive PEs; however, the FDA has recently issued a black box warning regarding their use after a series of adverse events and deaths [69, 70]. Therefore, it is currently best if this device is avoided.

The evidence from suction thrombectomy devices (small and large bore) comes from case series and reports. We are limited in drawing solid conclusions about the efficacy and safety of throm-

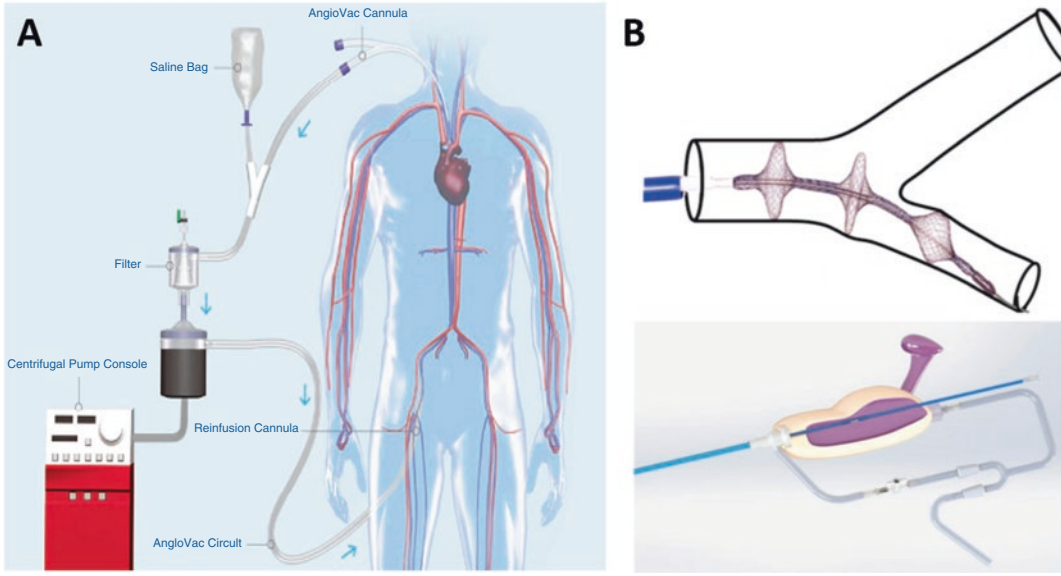

Fig. 30.4 Large-bore suction thrombectomy devices. (**A**) AngioVac (AngioDynamics Inc., Latham, NY). (**B**) FlowTriever (Inari Medical, Irvine, CA)

bectomy techniques; however, these devices remain the only option for high-risk PE patients with a high risk of bleeding. Recent guidelines suggest the use of suction thrombectomy devices in massive PE patients with high bleeding risks if appropriate expertise and resources are available [22].

Surgical Thrombectomy

Surgical pulmonary thrombectomy is reserved for patients with absolute contraindications or those who have failed systemic thrombolysis. But given the advancements in CDI, these patients are now being treated using aspiration/suction thrombectomy devices. In contemporary practice, surgical pulmonary thrombectomy is viewed as a last resort option given the significant morbidity and mortality associated with the procedure [71].

Treatment Strategy

Implementing a multidisciplinary approach in the management of acute PE is gradually becoming the standard. At our institution, a pulmonary embolism response team (PERT) represents this approach and has a unified algorithm for the treatment of acute PE (Fig. 30.5). PERT members include pulmonary, critical care physicians, cardiologists, and vascular and cardiothoracic surgeons. The most important factor in determining management is hemodynamic stability and secondarily the bleeding risk. Hemodynamically unstable patients require immediate revascularization, and systemic thrombolysis is their most common treatment strategy, unless the bleeding risk is high at which we consider a catheter intervention. Hemodynamically stable patients are risk stratified into intermediate- or low-risk PE based on PESI score, laboratory markers, and imaging findings. Low-risk PE patients receive anticoagulation alone. Intermediate-risk PE patients are further stratified into intermediate-low- and intermediate-high-risk PE which in turn determines the treatment strategy. It is always prudent to assess the risk-benefit ratio of our interventions or treatments by assessing the bleeding risk. Given the lack of randomized trials comparing CDI techniques with anticoagulation and/or systemic thrombolysis, patient selection

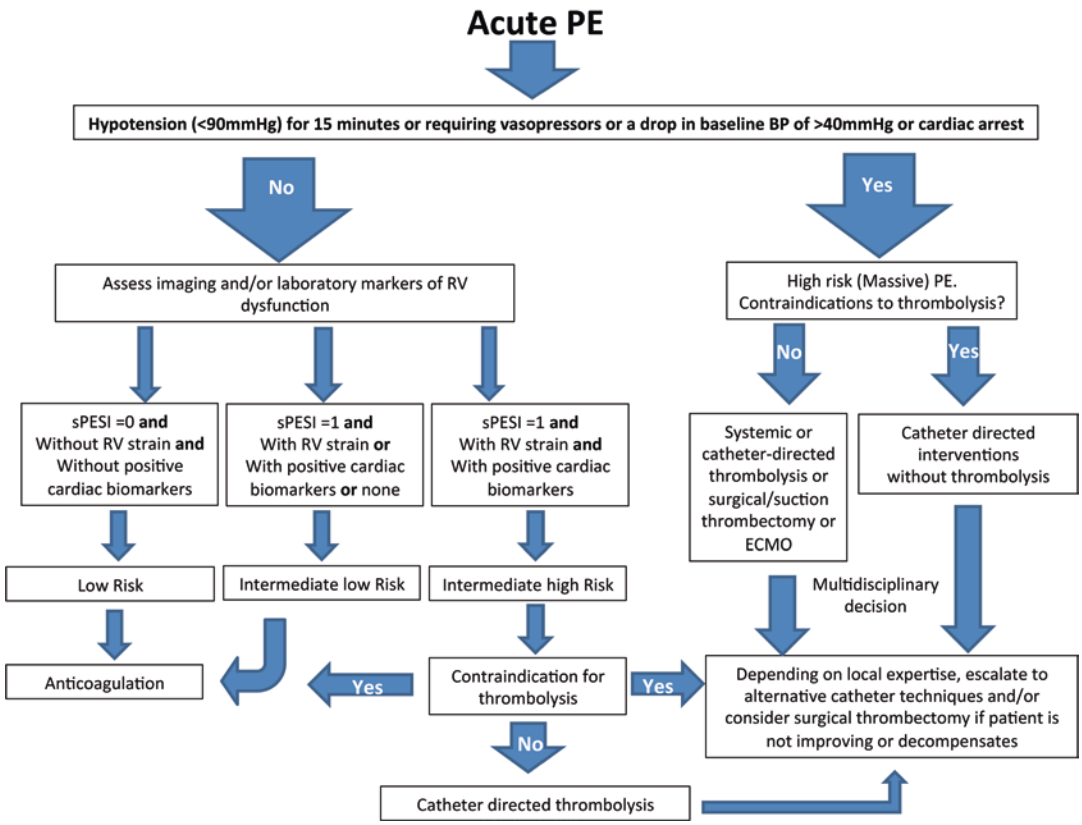

Fig. 30.5 Treatment algorithm for the management of acute PE

and multidisciplinary communication are of utmost importance to achieve better outcomes.

Inferior Vena Cava Filter

IVC filters are deployed in patients with acute PE and an absolute contraindication to anticoagulation, in patients with recurrent PE despite therapeutic anticoagulation, or in patients with complications from anticoagulation. IVC filter use in acute PE patients is independent of whether or not the patient has a concomitant acute deep vein thrombosis (DVT). The Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption 2 (PREPIC-2) trial recently concluded that IVC filter use is not recommended in patients that can be adequately anticoagulated. There was no difference at 3 and 6 months of recurrent PE and mortality rates between IVC filter and anticoagulation and anticoagulation alone in acute PE patients [72]. Current guidelines recommend against IVC filters in acute PE patients who can be adequately anticoagulated [22]. In patients with poor cardiopulmonary reserve, the risk-benefit ratio may favor IVC filter insertion [21]. Follow-up should include plans for filter retrieval once the indication for its placement no longer applies.

Long-Term Outcomes

Chronic thromboembolic pulmonary hypertension (CTEPH) is a feared long-term sequela of PE. Its incidence ranges between less than 1 and 4% in most series [73, 74]. Those patients are likely to develop progressive lung disease and

subsequent right ventricular failure leading to death. CTEPH is defined as having a mean pulmonary artery pressure greater than 25 mmHg persisting 6 months after the PE. Recent evidence suggests that thrombolysis might reduce CTEPH occurrence and improve exercise tolerance and quality of life [75, 76]. Long-term follow-up investigating the incidence of CTEPH post CDI is lacking. Future studies will target whether or not CDI reduces the incidence of CTEPH and improves quality of life compared to anticoagulation and systemic thrombolysis.

Conclusions

PE treatment strategies have evolved in an attempt to reduce the high mortality rates, long-term pulmonary hypertension, and quality of life. CDIs have been on the forefront of the technological advances in the management of PE. The wide array of catheter interventions being used places significant pressure on the scientific body to provide reliable evidence on the efficacy, safety, and long-term outcomes of these techniques. These interventions appear to hold great promise in select patients; however, generalizing the current low-quality evidence about CDI places patients at risk of complications. At present, multidisciplinary approaches are essential to share the expertise and better identify the intermediate-high- and high-risk patients that might benefit from these invasive interventions.

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Surgical Management of Pulmonary Embolism

31

Jeenah Jung and Pramod Bonde

Abbreviations

BNP	Brain natriuretic peptide
CTEPH	Chronic thromboembolic pulmonary hypertension
DVT	Deep vein thrombosis
ECG	Electrocardiography
ECMO	Extracorporeal membrane oxygenation
ICOPER	International Cooperative Pulmonary Embolism Registry
IVC	Inferior vena cava
LMWH	Low-molecular-weight heparin
LV	Left ventricle
MI	Myocardial ischemia
NYHA	New York Heart Association
PA	Pulmonary artery
PAH	Pulmonary artery hypertension
PAP	Pulmonary artery pressure
PE	Pulmonary embolism
PERC	Pulmonary embolism rule-out criteria
PFO	Patent foramen ovale
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PVR	Pulmonary vascular resistance
RV	Right ventricle
SVC	Superior vena cava
TEE	Transesophageal echocardiography
V/Q	Ventilation/perfusion
VTE	Venous thromboembolism

Clinical Pearls

1. Open thrombectomy of PE is an option for patients who fail or have contraindication to lytic therapy.
2. Hemodynamically unstable patients after open thrombectomy may require ECMO as a bridge to stabilization and resuscitation.
3. Pulmonary thrombectomy is performed via median sternotomy and often requires circulatory arrest.

History of Pulmonary Embolectomy

In 1908, Friedrich Trendelenburg presented a new procedure for treating acute pulmonary embolism (PE) in Leipzig, Germany. He was motivated by the observation that most pulmonary emboli were not immediately fatal, offering an opportunity for surgical intervention. The main

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pulmonary artery (PA) was exposed through a small left anterior thoracotomy, and the embolus was extracted with forceps through a small arteriotomy that was sutured closed under a clamp. Although this procedure was completed in less than 6 min, the patient died of hemorrhage from the posterior aspect of the pulmonary artery. His two subsequent efforts also were not successful. The first successful Trendelenburg procedure was not performed until 1924 by his trainee, Martin Kirschner, proving that the hemodynamic insult of a massive PE can be reversed by surgical removal of the emboli [1].

In 1934, Edward Churchill noted diminished enthusiasm for Trendelenburg procedure after ten consecutive failures. Even then, the timing of the procedure was controversial. He endorsed postponing the procedure until the patient was nearing death but cautioned that unnecessary delay would decrease the chance of success [2]. However, the Trendelenburg procedure was not widely applied until 1958, after the development of cardiopulmonary bypass in the 1950s.

In 1930, John Gibbon, a research fellow at Massachusetts General Hospital, was assigned to monitor the vital signs of a female patient with a massive PE, who decompensated. An emergent Trendelenburg procedure was performed unsuccessfully. This loss inspired Gibbon to spend 23 years developing a heart-lung machine that would support the patient's cardiopulmonary functions, while the embolism could be surgically removed.

The Trendelenburg procedure underwent multiple modifications in the 1950s, including addition of hypothermia or intermittent normothermic venous inflow occlusion. Although these modifications improved the initial procedure, they salvaged only 30–40% of mortality and used only when the cardiopulmonary bypass was not immediately available.

In 1961, Denton Cooley and Edward Sharp independently performed the first pulmonary embolectomy under cardiopulmonary bypass. Their pulmonary embolectomy involved establishing cardiopulmonary bypass, pulmonary arteriotomy, complete evacuation of emboli under direct vision, and consideration of vena caval interruption. Their success inspired pulmonary embolectomy to be performed in multiple centers, despite the mortality rate of 40–60%. At the time, such a high mortality rate was considered acceptable considering near-fatal Trendelenburg procedure and the lack of alternative treatments for massive PE.

By the late 1960s and early 1970s, the basic techniques of embolectomy on cardiopulmonary bypass were well established [1]. It began with peripheral partial bypass under local anesthesia and was established between the jugular vein and iliac artery or femoral artery and vein. The peripheral bypass was considered to avert severe circulatory collapse and hypoxic myocardial damage secondary to induction of anesthesia before going on total bypass for embolectomy. Sudden death from pulmonary embolism was treated with external cardiac compression, which was thought to break up the thrombus and to allow pulmonary blood flow.

Under general anesthesia, the patient was placed under the cardiopulmonary bypass. The main pulmonary artery was opened longitudinally, and the emboli were removed. To completely clear the pulmonary arterial tree, a suction catheter was used into the pulmonary arteries with irrigation and bilateral intrapleural pulmonary massage from the periphery to the center as described by Cooley, Beall, and Alexander in 1961 [3]. The occlusion of subsegmental tributaries was cleared by applying retrograde flushing of the pulmonary arterial tree by injecting saline in temporarily clamped pulmonary veins. Brisk back-bleeding of bright-red blood was considered successful removal.

The high incidence of recurrence following pulmonary embolectomy motivated the surgeons to consider inferior vena cava plication or ligation below the renal veins mandatory as a part of the same operative procedure. If the patient's condition permitted, they considered preferable to precede embolectomy by the Spencer's method of plicating the inferior vena cava. In female patients, the ovarian veins were also often ligated. If cardiopulmonary bypass was not available, the Trendelenburg procedure was performed under hypothermia or using normothermic venous inflow occlusion. Unilateral pulmonary embolectomy was frequently performed without the cardiopulmonary bypass [4].

Although the fundamentals of this procedure have remained unchanged, there are a few key differences in how the embolectomy is performed now. The techniques for clot extraction, such as massaging the lungs, blind passage of instruments into the periphery, or retrograde perfusion of the lungs through the pulmonary veins, have been considered excessively traumatic. With medical prophylaxis for thrombosis, inferior vena cava or ovarian vein plication or ligation is no longer considered. Bronchoscopy is often used to assess the completeness of the embolectomy, instead of assessing the blood return.

Epidemiology of VTE

With no national surveillance for venous thromboembolism (VTE), the exact incidence is unknown. Based on clinical administrative databases and studies, the annual incidence of VTE in the USA is about 350,000–600,000 [5], which is likely under-reported [6, 7] and increasing [8]. Of these VTE cases, about one-third presents with PE, while the other two-third present with deep vein thrombosis (DVT) [9].

The incidence of VTE varies by age, race, and gender. The incidence is higher in those aged more than 80 years (1 per 100) than the young (1 per 100,000). The overall rate is higher among African Americans compared to whites. Men have a small but significantly higher incidence than women. However, women have a slight increase during the reproductive years [9].

Following the Virchow's triad of risk for thrombosis, certain acquired and genetic risk factors that affect hemostasis, venous injury, and hypercoagulability increase the likelihood of VTE. Acute medical illness and reduced mobility in hospitalized patients leave them vulnerable to VTE. In a 5-year retrospective study of all autopsy reports in a general hospital, 24% of PE patients who died had undergone surgery 6.9 days before, on average [8]. Total hip and knee replacement, surgery for hip fracture, surgery for cancer, trauma, and spinal cord injury are associated with high risks [10]. Prolonged sitting during air or ground travel [11] or as a part of a sedentary lifestyle and occupations have been shown to increase risks [12].

Disorders and medications have been shown to increase risks for thrombosis. In cancer, the procoagulant effects of the tumor or its treatments may increase the risk of VTE. Also, venous obstruction by the tumor, reduced mobility, chemotherapy, and lines for its delivery may contribute to higher risks [11, 13]. Prothrombotic states associated with antiphospholipid antibody syndrome and polycythemia vera make VTE more likely. The use of hormone replacement therapy and oral contraception also increases thrombotic risks [14].

There are numerous hereditary factors that promote coagulation and contribute to thromboembolism. Deficiencies in antithrombin, protein C, and protein S induce thrombosis. Factor V Leiden, which leads to activated protein C resistance, is the most common genetic risk factor for thrombophilia. Activated protein C resistance without factor V Leiden, prothrombin gene mutation, dysfibrinogenemia, and plasminogen deficiency are less frequent genetic disorders that result in increased thrombosis. In young patients with unprovoked thromboembolism or in patients with thrombosis in uncommon places, such as cerebral, mesenteric, portal, or hepatic veins, these disorders should be considered [14] (Table 31.1).

Table 31.1 Risk factors for VTE consist of demographic characteristics, behavior, disorders, and medical treatments

Age, race, gender	Behavior	Disorders	Treatments
Old > young	Prolonged travel	Cancer	Surgery
Blacks > whites	Sedentary lifestyle	Antiphospholipid antibody syndrome	Chemotherapy
Men > women	–	Polycythemia vera	Hormone therapy
–	–	Genetic mutations	–

Studies of autopsy data estimate that 10–30% of VTE cases are fatal within 30 days. PE is the primary cause of mortality in those with VTE. Approximately 20–25% of all PE cases present as sudden death [14–17]. It is considered a common cause of death in hospitalized patients (15% of total in-hospital mortality) that may be prevented with timely diagnosis and appropriate use of prophylaxis [5, 8, 13]. Considering that PE is fatal in only about 6.5% posttreatment [17], missing its diagnosis in the setting of rapid deterioration may contribute to poor prognosis.

Timely restoration of hemodynamic stability has been shown to prevent mortality. In the International Cooperative Pulmonary Embolism Registry (ICOPER), the 90-day mortality rate for patients with acute PE and cardiogenic shock at presentation (108 patients) was 52.4% versus 14.7% for the hemodynamically stable [18]. Consistently, the Germany-based Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET, 1001 patients) showed the in-hospital mortality was 25% for those presenting with cardiogenic shock, 65% for those requiring cardiopulmonary resuscitation, and 8.1% for hemodynamically stable patients [19].

Pathophysiology of VTE

PE and DVT lie in the spectrum of VTE. Thrombi form in the deep veins of extremities, such as the calf, and then propagate into the proximal veins, where they likely embolize [7] (Fig. 31.1). Lower-extremity DVT is found in 79% of PE patients, and if not found, it likely has embolized [14]. Because of the circulation arising from both pulmonary and bronchial arteries, pulmonary infarct is uncommon.

Acute right-sided heart failure due to increased pulmonary vascular resistance (PVR) is the main cause of death in PE [20]. The rapid increase in afterload causes right ventricle (RV) dilatation, which in the setting of systemic hypotension diminishes the coronary perfusion, resulting in cardiac ischemia. The septal shift resulting from right ventricle dilatation further reduces left ventricular (LV) preload and output, and the patient enters a worsening cycle of acute right-sided heart failure and cardiogenic shock [21] (Fig. 31.2).

Although it has been thought that PVR increase was due to the mechanical obstruction of the pulmonary vasculature, studies have not found a correlation between the mechanical obstruction and the hemodynamic derangement associated with PE. This finding has been con-

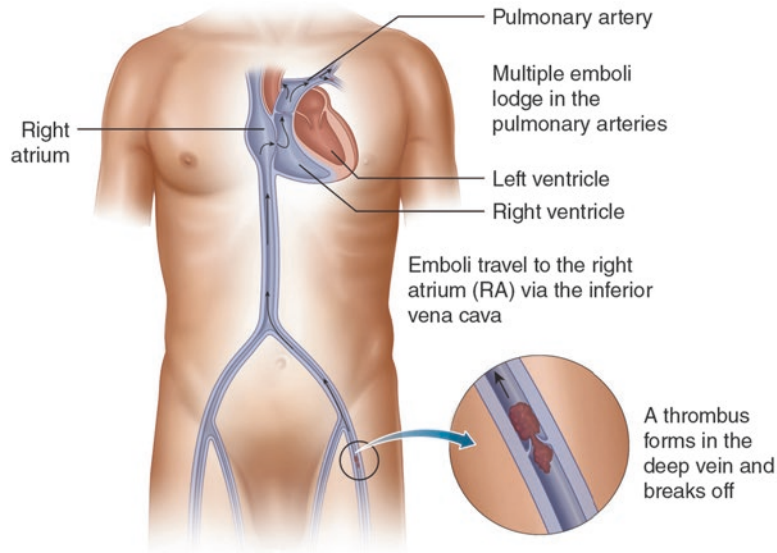

Fig. 31.1 A thrombus forms in the deep vein and embolizes to the pulmonary arteries

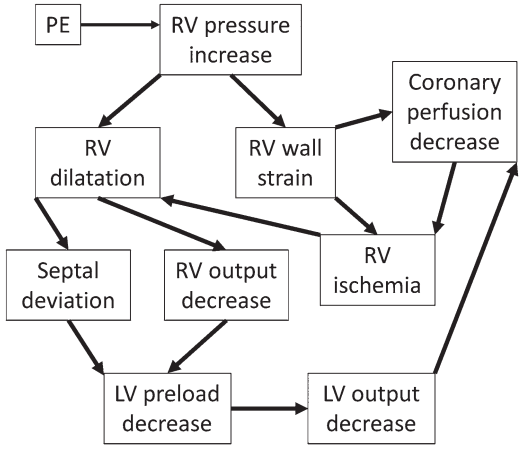

Fig. 31.2 The pathophysiology of right heart failure and cardiogenic shock due to PE

firmed by only a small, insignificant rise in the pulmonary artery pressure (PAP) after cross-clamping the left or right pulmonary artery during a surgical procedure or by unilateral balloon occlusion. The increase in PAP is never enough to cause right-sided heart failure [20].

Interestingly, PE often obstructs only about 25% of the pulmonary vasculature but causes significant pulmonary hypertension and heart failure [22]. Vasoconstriction induced by PE is likely the main cause. In symptomatic, non-heparinized PE patients, stellate ganglion blockade that prevents pulmonary vasoconstriction [23] has been shown to reduce cyanosis, dyspnea, and cardiac shock [24].

PE has been characterized as massive, submassive, and non-massive based on the hemodynamic burden of the emboli. This classification is useful for guiding medical and interventional treatment decisions. Massive PE has been described as acute PE with loss of pulse, persistent bradycardia, or sustained hypotension (systolic blood pressure less than 90 mmHg for at least 15 min or requiring inotropic support). The hypotension cannot be caused by other factors, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction. Submassive PE is acute PE without systemic hypotension (systolic blood pressure greater than or equal to 90 mmHg) but with either RV dysfunction with RV dilation or myocardial ischemia (MI). Non-massive or low-risk PE is acute PE that lacks symptoms of massive or submassive PE [25]. Surgical or catheter-based intervention should be considered for patients with massive or submassive PE whose hemodynamic decompensation appears imminent (Table 31.2).

Table 31.2 Massive, submassive, and low-risk PE

Massive PE	Submassive PE	Low-risk PE
Prolonged hypotension	No systemic hypotension	No sign of massive or submassive PE
No pulse or bradycardia	RV dysfunction or MI	

Diagnosis of PE

Patients with PE present with a variety of symptoms. They often have dyspnea or chest pain, which may be sudden or evolving over days to weeks. Many patients with PE may also have DVT symptoms, such as leg pain, warmth, or swelling in the extremities. Pleuritic chest pain and hemoptysis occur more often in those with pulmonary infarction, which is characterized by smaller, more peripheral emboli and a pleural rub. Cough, palpitations, light-headedness, fever, wheezing, and rales may result from PE or concomitant illnesses. Tachypnea and tachycardia are common but nonspecific findings.

Pulmonary hypertension due to PE may present as elevated neck veins, a loud second heart sound (S2), a right-sided extra heart sound (S3, S4), systolic murmur in the left sternal edge, a right ventricular lift, and, less frequently, hepatomegaly. These symptoms are suggestive but neither sensitive nor specific [26]. Patients with these symptoms often do not have the disease. However, PE is often unlikely in those without either chest pain or acute or worsening shortness of breath [27].

The arterial blood gas analysis often suggests hypoxia and hypocapnia. Chest radiography results are nonspecific; it is common for PE patients to have normal chest X-ray. However, an elevated hemidiaphragm, unilateral pleural effusion, and atelectasis may be seen occasionally. Chest radiography is usually useful for

Table 31.3 Diagnostic criteria for PE

Wells	PERC	Geneva	Charlotte
DVT	Unilateral leg swelling	Unilateral leg pain	Age >50 or HR/SBP >1
Previous DVT/PE	Previous DVT/PE	Previous DVT/PE	Unilateral leg swelling
Tachycardia	Tachycardia	Heart rate >74	Surgery in <1 month
Active malignancy or palliative	Trauma/surgery <1 month	Surgery/leg fracture <1 month	Unexplained hypoxemia
Surgery <1 month	Age >49	Age >65	Hemoptysis
Hemoptysis	Hemoptysis	Hemoptysis	D-dimer assay, if PE unlikely
>2-day immobilization	Exogenous estrogen	Active malignancy	Imaging, if PE likely
PE most likely	O_2 sat in RA <95%	–	–

ruling out alternative diagnosis with more obvious findings.

With PE, the electrocardiography (ECG) may show tachycardia, nonspecific T wave and ST changes in the precordial leads, the S1Q3/S1Q3T3 pattern, or a right bundle branch block. These findings also are uncommon and nonspecific [27]. RV dysfunction may be reflected in elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP. Myocardial infarction due to RV dysfunction may elevate troponin.

Due to the difficulty diagnosing PE based on clinical findings, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) highlighted the need for determining the pretest probability to influence the posttest probability [27]. This was confirmed by Wells et al. as the Wells scoring system and application of D-dimer [28, 29]. They demonstrated a scoring system based on DVT symptoms, no alternative diagnosis, tachycardia, and risk factors, such as recent immobilization or surgery, malignancy, hemoptysis, and previous VTE [29].

Currently, in addition to the Wells criteria, there are the pulmonary embolism rule-out criteria (PERC), the Geneva score, and the Charlotte rule for estimating the probability of PE. No difference in the rate of missed PE was observed comparing these systems [27] (Table 31.3). PE may be effectively excluded based on these assessment systems and D-dimer levels, a plasmin-derived fibrin degradation product that is highly sensitive but not specific for VTE [28].

Once a patient is suspected of PE based on these exclusion criteria, computed tomography (CT) pulmonary angiography is commonly used to diagnose PE (Fig. 31.3). For the patients with renal failure or contrast dye allergy, who cannot undergo a CT angiography, ventilation/perfusion (V/Q) scanning may be considered, at the cost of lower sensitivity [29]. To evaluate the RV dysfunction or stress due to PE, transthoracic echocardiography may be employed.

Management of PE

Patients with PE and no contraindications for anticoagulation should be given subcutaneous low-molecular-weight heparin (LMWH), intravenous or subcutaneous unfractionated heparin, or subcutaneous fondaparinux. For those with heparin-induced thrombocytopenia, a non-heparin-based anticoagulant, such as lepirudin, argatroban, or bivalirudin, may be employed. For those with high probability of PE, they should be given anticoagulant during the diagnostic work-up.

Thrombolytic medications, streptokinase, urokinase, and alteplase, promote the hydrolysis of fibrin molecules, breaking down the thrombus. They are enzymes that convert the native circulating plasminogen into plasmin, a serine protease that cleaves fibrinogen and releases fibrin or D-dimer fragments. These medications have been FDA approved for treatment of massive/submassive PE and compared to heparin, offer faster alleviation of symptoms and stabilization of cardiovascular function.

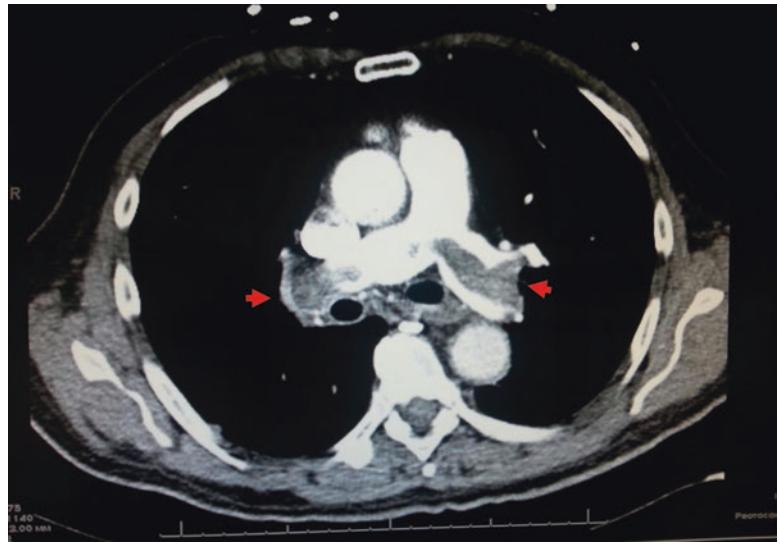

Fig. 31.3 Computed tomography pulmonary angiography of a patient with emboli in the left and right pulmonary arteries (*red arrows*)

At 24 h after starting treatment, heparin resulted in no significant improvement in pulmonary blood flow, but addition of fibrinolysis improved the total perfusion by 30–35%. By day 7, the blood flow increased significantly with 65–70% improvement [25]. Thus, thrombolysis is effective in cases with a larger clot burden. However, they are contraindicated in patients with bleeding risks, such as previous hemorrhagic stroke, recent major surgery, or trauma, and may result in minor to fatal hemorrhage. Therefore, they are not recommended for patients with low-risk PE or submassive PE with minor symptoms (Fig. 31.4).

With hemodynamic instability or RV dysfunction, removal of the embolus surgically or using a catheter-based intervention is an effective alternative to fibrinolysis in patients with high bleeding risks or inadequate time to infuse thrombolytic agents. Surgical embolectomy is suited for acute PE patients with a right atrial thrombus or paradoxical embolism as well as those that are refractory to thrombolysis [30].

Although surgical embolectomy is one of the oldest cardiac procedures, its application in PE treatment has not been studied adequately, largely limited by small patient cohorts. For example, in the ICOPER, 33 patients were treated with fibrinolysis, 1 underwent surgical embolectomy, and 1 had catheter-based intervention [18]. While

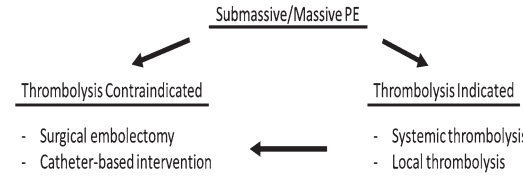

Fig. 31.4 For submassive/massive PE, surgical or catheter-based embolectomy may be considered for patients, who are contraindicated or refractory to thrombolysis

high inpatient mortality (27.2%) was associated with surgical embolectomy, in a recent review, the cumulative operative mortality for surgical embolectomy improved significantly from 30–35% before 1999 to 19% thereafter [31]. Recent studies have reported 92–96% clinical success in patients, including critically ill patients receiving inotropic support. A greater comorbidity burden and black race were identified as independent predictors of operative mortality [32].

Catheter interventions may be considered when emergency surgical embolectomy is unavailable or contraindicated. They are applicable when fibrinolysis failed to restore the RV function or hemodynamic stability. In a systematic review of 348 patients, clinical success with percutaneous therapy with acute massive/submassive PE was 81 and 95% when combined with local infusion of thrombolysis. There are four catheter-based interventions: aspiration

thrombectomy, thrombus fragmentation, rheolytic thrombectomy, and rotational embolectomy.

Aspiration thrombectomy removes the centrally located embolus by applying negative pressure to the tip using manual sustained suction with a large syringe (10Fr Greenfield suction embolectomy catheter, Medi-Tech/Boston Scientific, MA) or using a centrifuge pump, filter, and reinfusion cannula for venous drainage while on an extracorporeal bypass (22Fr AngioVac, AngioDynamics, NY). It requires the retrieval of the device and the thrombus as a unit via surgical venotomy due to the large, stiff lumen catheter (Fig. 31.5). Thrombus fragmentation involves mechanical disruption of the thrombus into smaller fragments with distal embolization, using manual rotation of a pigtail rotational catheter (Cook – Europe, the Netherlands) or a peripheral Fogarty arterial balloon embolectomy catheter (Edwards Lifesciences Corp., CA). Most patients undergoing fragmentation also receive local thrombolysis; therefore, it is unknown if fragmentation without local thrombolysis is effective. The main disadvantage is the risk of distal embolization and continued deterioration of RV function.

Rheolytic thrombectomy removes intravascular thrombus by applying a high-velocity jet using the AngioJet (MEDRAD, PA), Hydrolyser (Cordis, FL), or Oasis (Medi-Tech/Boston Scientific, MA). The high-velocity saline jet fragments thrombus by creating a Venturi effect and removing the debris into an evacuation lumen. The main disadvantage is that it was not designed for use in the large main pulmonary arteries. Rheolysis can lead to fatal arrhythmias and small vessel perforations. Rotational embolectomy involves aspiration, maceration, and removal of pulmonary artery thrombus using a

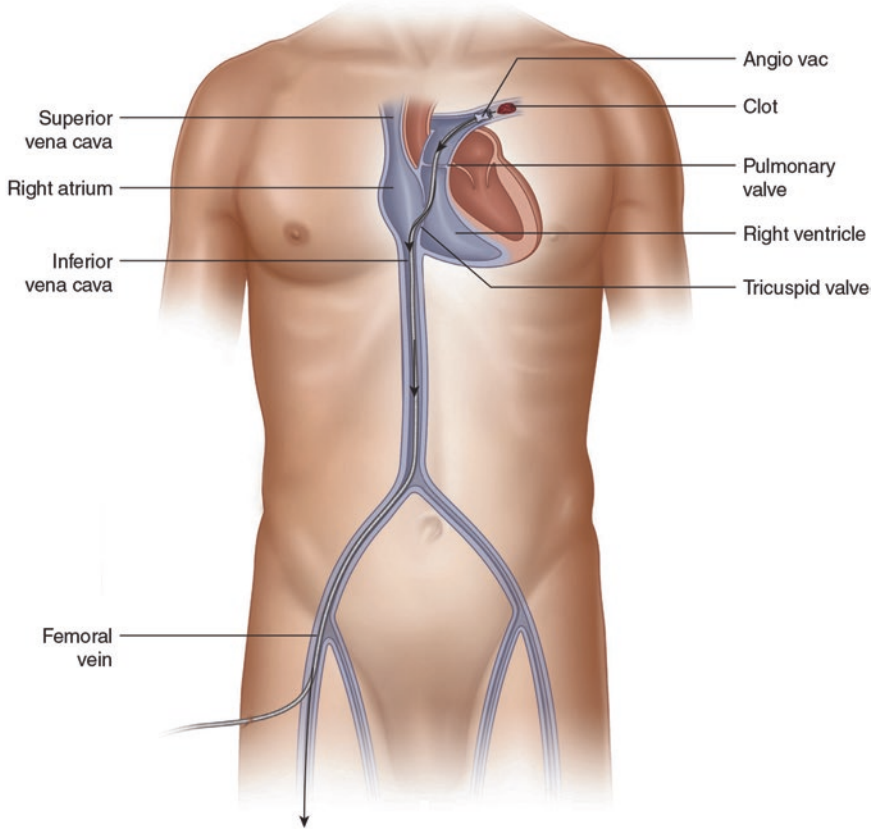

Fig. 31.5 Aspiration thrombectomy removes the centrally located embolus by applying negative pressure to the tip

high-speed rotational coil within the catheter body that creates negative pressure through an L-shaped aspiration port at the catheter tip. This combines the benefits of fine thrombus fragmentation with aspiration. But aspiration may cause hemodynamic instability with acute blood loss [33] (Table 31.4).

Hybrid therapy (catheter-directed thrombolysis and ultrasound-accelerated thrombolysis) that includes both catheter-based clot removal and local thrombolysis is an emerging strategy. The decision to proceed with catheter-based versus surgical embolectomy requires a discussion between the surgeon and the interventionalist and an assessment of the local expertise.

Inferior vena cava (IVC) filters may be useful in patients with contraindications to anticoagulation or with active bleeding complications. The PREPIC trial with randomized 400 patients with proximal DVT at high risk for PE showed that while IVC filters may prevent recurrent PE, they are associated with increased incidence of recurrent DVT (21%) with no effect on overall mortality [34]. Because of the risk for recurrent DVT, permanent or retrievable IVC filters require anticoagulation as soon as the contraindication or bleeding risk has resolved. Retrievable filters should be removed within the retrieval window [33].

Extracorporeal membrane oxygenation (ECMO) may be considered temporarily to stabilize patients who are not hemodynamically stable enough to undergo surgical or catheter-based intervention or who are unstable post-op. After treatment of the acute PE, patients should be managed with anticoagulation to prevent VTE (Fig. 31.6).

Surgical Techniques

After full median sternotomy, pericardiotomy, and full heparinization (Fig. 31.7), cardiopulmonary bypass can be established with bicaval cannulation and high ascending aortic cannulation (Fig. 31.8). A temporary vent may be placed through the main PA 1–2 cm distal to the pulmonary valve. The insertion site can then be used for the left pulmonary arteriotomy. With vacuum-assisted venous drainage, the right atrium can be explored without separately controlling the vena cava.

Although aortic cross-clamping and cardioplegic or fibrillatory arrest may be employed, they are not necessary and possibly detrimental. Pulmonary embolectomy and right heart exploration can be performed with the heart beating under normothermic conditions. Performing the operation on the unloaded, well-perfused, beating heart avoids ischemic injuries to the stunned right ventricle and provides the heart to recover and restore its perfusion.

If the intraoperative transesophageal echocardiography (TEE) shows thromboemboli in the right atrium or right ventricle, exploration of these chambers is necessary before embolectomy.

Once cardiopulmonary bypass is established, the actual embolectomy begins with a longitudinal incision over the main pulmonary artery at about 2 cm distal to the pulmonary valve (Fig. 31.8, 31.9). The incision can be extended onto the proximal left PA. The clot can be removed completely, avoiding fragmentation, under direct vision using simple gallbladder stone forceps (Fig. 31.10).

Table 31.4 Advantages (A) and disadvantages (D) of catheter-based interventions

	Aspiration	Fragmentation	Rheolysis	Rotational
A	Established application	–	–	Combines fragmentation and aspiration
D	Uses a large, stiff catheter that is difficult to manipulate and requires venotomy	Risk of distal embolization	Cannot use on the main PA. High risk of arrhythmias and small vessel perforation	Aspiration can cause acute blood loss and hemodynamic instability

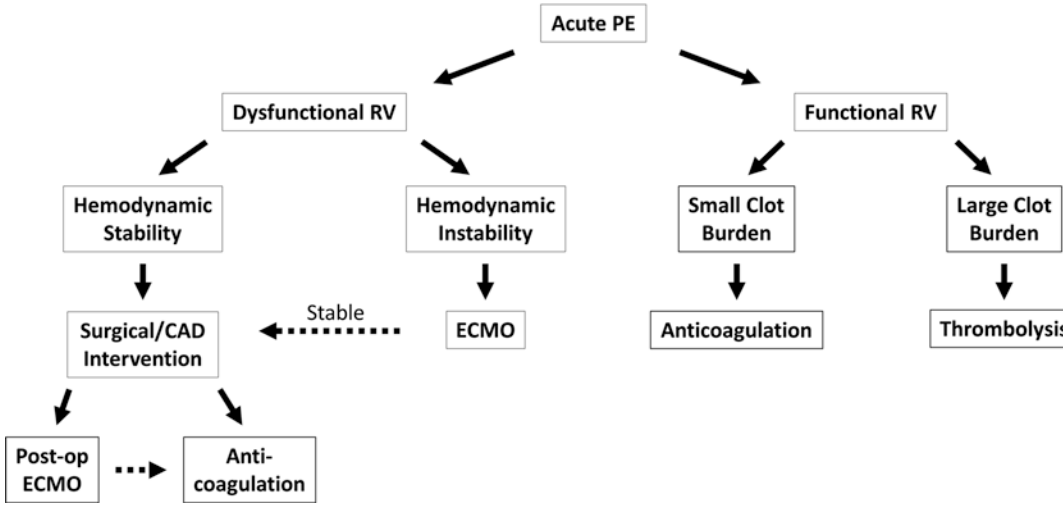

Fig. 31.6 Management of acute PE

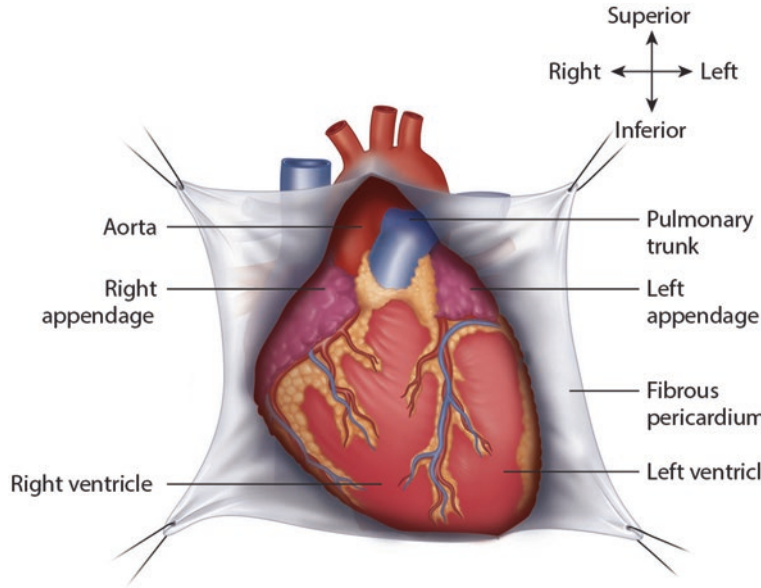

Fig. 31.7 Median sternotomy allows for visualization of the right appendage, aorta, pulmonary trunk, right ventricle, and left ventricle, allowing both the left and right pulmonary artery to be accessed

The right PA can be opened longitudinally between the superior vena cava (SVC) and the aorta for additional exposure. Inserting a cerebellar retractor between the SVC and aorta may allow visualization of right PA branches (Fig. 31.11).

The pulmonary arteries are fragile; therefore, aggressive clot extraction should be avoided. Excessive extraction maneuvers may cause pulmonary hemorrhage, which is usually fatal. Extraction of all visible central and distal clots will result in nearly complete restoration of pulmonary artery pressures. Clots that are not visible due to their small size or distal location will be cleared by the pulmonary vasculature eventually. A bronchoscope may be used to assess the completeness of the embolectomy.

The main concern when weaning cardiopulmonary bypass after embolectomy is the right heart function. Most patients will demonstrate

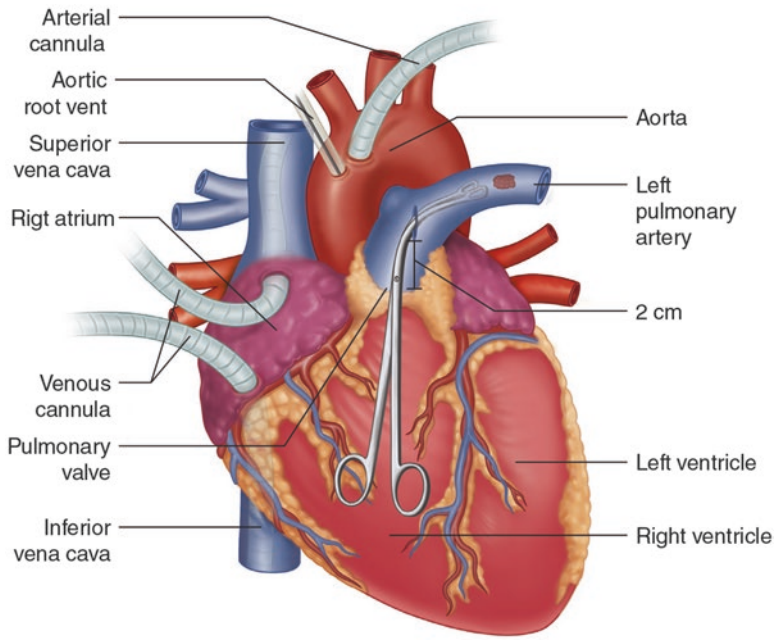

Fig. 31.8 Cardiopulmonary bypass can be established with bicaval venous cannulation, aortic arterial cannulation, and aortic vent. Clots can be removed under direct visualization using simple gallbladder stone forceps

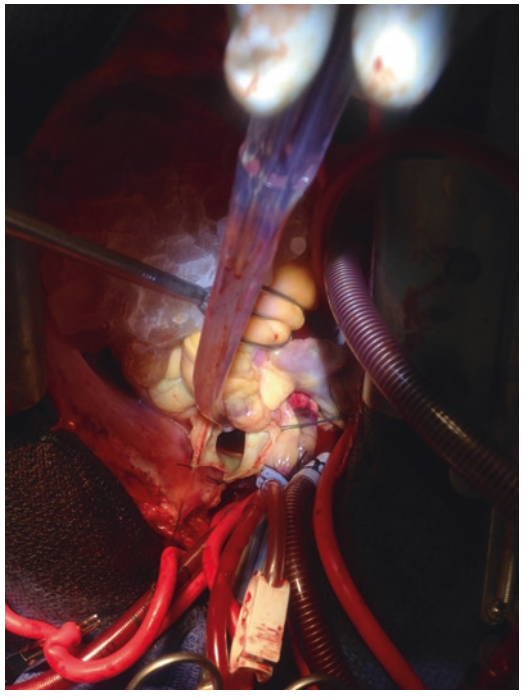

Fig. 31.9 A longitudinal incision over the main pulmonary artery at about 2 cm distal to the pulmonary valve. The incision can be extended onto the proximal left PA. The clot can be removed completely, avoiding fragmentation, under direct vision

Fig. 31.10 Surgical specimen removed from right and left pulmonary arteries during pulmonary embolectomy. Fresh clots are *dark red*

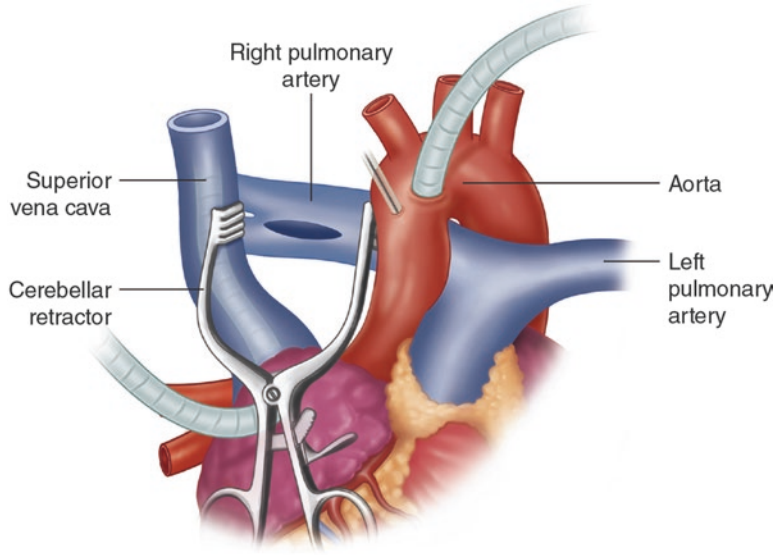

Fig. 31.11 A cerebellar retractor is used to expose the pulmonary artery between the aorta and the SVC. An incision is made in the right pulmonary artery at the center of the vessel from beneath the ascending aorta under the SVC and entering the lower lobe branch of the pulmonary artery immediately distal to the takeoff of the middle lobe artery

immediate improvements, but some residual RV stunning is common. TEE is helpful in assessing the right atrial and pulmonary artery pressures. Volume loading and inotropic support may be needed in short term. Persistently high pulmonary artery pressure should be evaluated and treated.

Right heart function may take several days to recover and aggressive support may be needed. Right atrial and pulmonary artery pressure and cardiac output should be monitored post-operation. Adequate ventilation and oxygenation are crucial to avoid pulmonary vasoconstriction. Inotropes should be weaned slowly. If needed, adding milrinone may allow catecholamines to be weaned. If an IVC filter has been placed, heparin can be delayed for 24–48 h and started to partial thromboplastin time goal of 50–60 s. When the patient can tolerate oral medications, warfarin can be initiated with a target international normalized ratio (INR) goal of 2–2.5. Long-term anticoagulation is usually continued for 6 months. The patient can be followed biannually with echocardiogram to monitor right heart function and V/Q scan to resolution of any perfusion defects [1].

Paradoxical Embolization

Paradoxical embolization can occur in patients with massive PE and can increase morbidity and mortality. A patent foramen ovale (PFO) in PE patients increases the risk of death, ischemic stroke, peripheral arterial embolism, and a complicated hospital course. Hence, it's important to include a bubble study to routine transthoracic echocardiography in imaging studies for PE patients. Patients with PFO should undergo surgical embolectomy for additional PFO closure and for decreased rate of stroke compared to thrombolysis and catheter-based intervention [1].

Conclusion

PE is underdiagnosed and carries poor prognosis. PE has a variety of possible treatments from anticoagulation, thrombolysis, and catheter-based intervention to pulmonary embolectomy, which individually target reduction or removal of the emboli in varying degrees. Still, for submassive and massive PE, pulmonary embolectomy has shown to be an effective intervention in addition to the

medical therapy or for patients refractory to or with contraindication to thrombolysis. Pulmonary embolectomy has evolved in the last four decades with significantly improved outcomes. However, it fails to target the key component of pathophysiology, acute vasoconstriction, or vasculopathy resulting in right heart failure. Understanding the different interventions available and their limitations provides opportunities for optimizing treatments for these debilitating and possibly fatal diseases.

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Vena Cava Interruption

32

John E. Rectenwald

Clinical Pearls

1. The indications for IVC filter placement are contraindications to anticoagulation or failure of anticoagulation in the setting of VTE. Relative/prophylactic indications should be individualized and likely discussed in a multidisciplinary fashion.
2. During IVC filter placement, a venogram is important to rule out anatomic variation and get accurate sizing of the cava.
3. The PREPIC trials demonstrated that IVC filters decrease the risk of PE but increase the risk of DVT. Treating high-risk patients with retrievable IVC filters in addition to anticoagulation does not improve their outcomes compared to anticoagulation alone.

Introduction

Deep venous thrombosis (DVT) and pulmonary embolism (PE), together comprising venous thromboembolic disease (VTE), occur with an annual incidence of 1 per 1000 adults. In the United States, an estimated 350,000–600,000 individuals develop VTE and 100,000–180,000 people die of PE each year. With the population aging, an increased disease burden is expected as VTE rates are approximately 13-fold higher in octogenarians. Moreover, elderly individuals are more susceptible to adverse outcomes associated with VTE, highlighting the importance of both management and prevention of this disease. Although anticoagulation with Lovenox, Coumadin, or more recently developed novel oral agents remains the mainstay of therapy, situations arise when these medications are contraindicated or inadequate. It is in these instances that inferior vena cava filters are indicated 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.

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Indications for Filter Placement

It is well established that the first-line therapy for treatment of VTE is anticoagulation [1, 2]. 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 make intuitive sense. These indications include the presence of VTE and one of the following: a baseline contraindication to anticoagulation, a complication from anticoagulation, and recurrent 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).

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 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 later. This scenario is cited as a rational for the increased use of retrievable IVC filters.

Complications secondary to anticoagulation include bleeding or, in rare cases, an adverse reaction to the anticoagulant used. Five to ten percent of patients treated with intravenous heparin will develop a bleeding complication during 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 [3, 4]. In addition to bleeding complications, heparin-induced thrombocytopenia develops in 1.1–2.9% of patients receiving unfractionated heparin [5]. Should this occur, all heparin must be discontinued, even that used for flushing lines and catheters as the condition responds to cessation of therapy. 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 INR are more likely to develop major hemorrhagic complications than those with mildly elevated levels [6]. 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. It 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 [7].

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 confirmed 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 h. For low molecular weight heparin, patients become therapeutic with an appropriate weight-based dose. Nomograms have been developed to ensure that therapeutic levels of anticoagulation are achieved [8, 9]. 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 have been developed for treatment of VTE. These novel oral anticoagulants (NOACs) include the direct thrombin inhibitors and the direct anti-Xa inhibitors. The increasing use of NOACs for 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 if 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 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 treatment of VTE, future guidelines may require failure of multiple pharmacologic modalities prior to use of an IVC filter.

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, such as demonstrated poor adherence to medications or those with ataxia or a high fall risk. Additionally, patients with a high periprocedural 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 [2]. 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 very strict indication for IVC filters with recommendation to place only if the patient has VTE and cannot receive anticoagulation [1]. 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 absolute, relative, and prophylactic indications.

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 placement of an IVC filter even in the absence of DVT.

Trauma patients may be at excessively high risk of DVT and thus are possible candidates for prophylactic IVC filters [10]. 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 [11, 12]. 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 treat existing DVT. There are also concerns about increased health-care costs and procedural morbidity/mortality [13].

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 as 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 [14]. The rate of PE after spinal surgery is reportedly as high as 13%; thus, this patient population may benefit from preoperative prophylactic IVC filter placement. Several small retrospective studies support this contention [15, 16]; however, the quality of evidence remains 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 [17]. Two studies have estimated the risks of PE in cancer patients to be approximately 3.6-fold higher than in patients without malignancy [18, 19]. These same patients that are at increased risk for VTE also appear to be at increased risk of bleeding while receiving anticoagulation therapy [20–22]. Debate regarding the use of IVC filters in the setting of malignancy has persisted since the 1990s. Despite the 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 mobility leading to a 4.9-fold increased risk of PE [23]. 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 the risk of intracerebral hemorrhage, cannot receive anticoagulation. There is limited data demonstrating 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 [24].

Table 32.1 highlights the indications for filter placement. Although seemingly straightforward, the decision to place a vena cava filter should be thoughtfully considered as their use has recently fallen under intense scrutiny by the US Food and Drug Administration (FDA) because of increased reports of filter complications: filter fracture, migration, penetration of the inferior vena cava and adjacent structures, and embolization to the heart or lungs. At the same time, the occurrence of perioperative VTE has become a measure of quality, and well-intended attempts at risk mitigation may influence the decision to place a filter using more lenient or extended criteria. Nevertheless, in 2013 the FDA issued a position statement advocating that the prophylactic use of inferior vena cava filters in patients without pulmonary embolism is off-label. Despite this recommendation, off-label, or prophylactic, use has increased in prevalent as clinicians recognize that certain subsets of patients, including those with multisystem trauma, bariatric patients, immobile patients, and cancer patients, all have increased

Table 32.1 Indications for vena cava filter placement

1. Absolute indications
VTE with
(a) Contraindication to anticoagulation
(b) Recurrent thromboembolic disease despite adequate anticoagulation therapy
(c) Significant bleeding complications of anticoagulation therapy
2. Relative indications
VTE with
(a) Large, free-floating iliocaval thrombus (greater than 6 cm in length)
(b) Pre- or postpulmonary thromboembolectomy
(c) Thromboembolic disease with limited cardiopulmonary reserve
(d) Poor compliance with medications
(e) Thrombolysis of iliocaval thrombus
(f) Patients with ataxia or significant fall risk
3. Extended indications
(No requirement for VTE)
(a) High-risk trauma patients
Head or spine injury
Spine, pelvis, or long bone fracture
(b) Bariatric surgery
(c) Preoperative patients with multiple risk factors for VTE
(d) High-risk immobilized patients

risk for VTE and are not easily anticoagulated for prophylaxis.

Patients with absolute and relative indications for filter placement both have existing thromboembolic disease and either a contraindication to anticoagulation, complications arising from anticoagulation, or overt failure of anticoagulation. Placing filters utilizing extended criteria, by definition in patients without existing DVT, should be tailored to each individual patient after thorough discussion of the risks and benefits of the procedure and with the understanding that off-label use may pose a liability risk to the physician. In addition, every attempt should be made to remove these filters when the risk of VTE has decreased or the patient can be safely anticoagulated to reduce the risk of long-term complications associated with retrievable filters and off-label use.

The only absolute contraindications to filter placement are complete thrombosis of the IVC and lack of caval access due to extensive thrombosis. Caution is advised in the setting of coagulopathy and in children and pregnant patients. In the case of female patient of childbearing age, physicians should consider placement of retrievable filters or a permanent IVC filter in the suprarenal position to avoid compression of the IVC filter by the gravid uterus.

Types of Available Vena Cava Filters

The stainless steel Greenfield filter (Fig. 32.1), introduced in 1972 and deployed using an open venotomy and 24 French sheath, was the first successful endoluminal caval interruption device. Although the Mobin–Udin filter preceded the Greenfield filter, it was plagued by IVC thrombosis and its use was abandoned [25]. The Greenfield IVC filter consists of a cone of six steel wires ending in tethering, recurved hooks. The conical design of the Greenfield filter allows for two-thirds of the filter cone could be filled with thrombus while leaving 50% of the caval diameter patent [26]. This allows for a large amount of thrombus to be captured within the filter without impeding flow through the caval and around the captured thrombus and promotes the native fibrinolytic system to lyse the clot. Percutaneous introduction techniques evolved 12 years later, followed by a proliferation of other devices including deviations from the conical filter design, lower-profile devices, and ultimately retrievable filters.

An ideal filter would be securely fixed within the vena cava, biocompatible, non-thrombogenic, low profile, easy to deploy and retrieve, and have a low complication rate. While newer devices have some of these characteristics, the perfect filter does not exist. Retrievable devices must be less secure than permanent filters. Access-related complications persist, despite lower-profile deployment systems. Caval thrombosis, recurrent PE, and fracture are still major concerns to be dealt with. Table 32.2 depicts features of an ideal IVC filter.

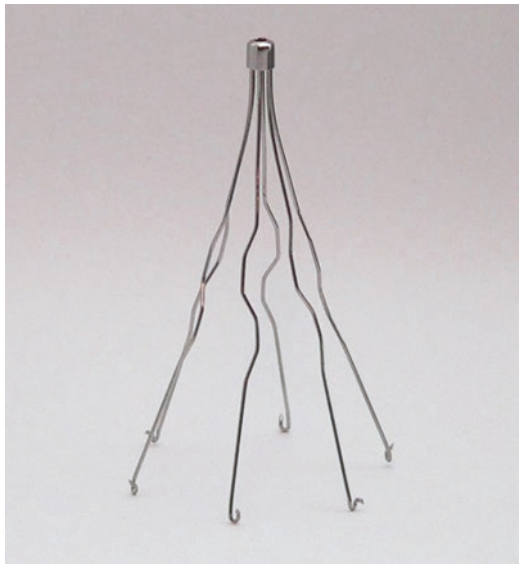

Fig. 32.1 Stainless steel over-the-wire Greenfield inferior vena cava filter

Table 32.2 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; low cost
4. Ideal biomechanical property: biocompatible, non-thrombogenic, MRI compatible
5. Ideal delivery system: small caliber, easy deployment with ability to reposition
6. Safe retrievability when no longer needed

Preprocedure Evaluation

Once indications are confirmed and the decision made to place a filter, preparation includes a thorough physical exam, review of basic laboratory data, and evaluation of pertinent imaging. With few exceptions, inferior vena cava filters should be placed with the intent for removal; however, all currently available temporary filters carry approval for permanent use. Access for an infrarenal filter is most easily obtained via the right common femoral vein, as this provides the most direct route for device deployment and comfort for the operator. If right common femoral venous access is precluded, the right internal jugular vein is a reasonable second choice. The left common femoral vein, although feasible, is less desirable as the left common iliac vein drains into the IVC via an acute angle which may direct the filter delivery system into the right lateral wall of the inferior vena cava, causing the filter to tilt. Lab data, including creatinine and a coagulation profile, should be obtained. Anticoagulation should be held for 2–4 h prior to the procedure. Imaging, including venous duplex studies, CT venogram, or MRV, should be reviewed with specific attention focused on determining patency of the iliofemoral veins and vena cava. If computed tomography or magnetic resonance imaging is available in the preoperative period, these studies may help delineate anatomic features of the inferior vena cava which may alter the surgical plan by identifying the location of the renal veins, caval diameter, the presence of a circumaortic or retroaortic left renal vein, or duplicated IVC.

Anatomic Variations of the IVC Affecting Filter Placement

The IVC develops between the 6th and 8th week of gestation from growth and regression of three paired cardinal veins. Anatomic variants arise due to abnormalities in the process and become relevant in patients requiring a filter as their presence may necessitate alteration of the surgical plan in up to 3–15% of cases.

Duplication of the IVC

With an incidence of 0.2–3%, duplication of the IVC occurs when the right and left supracardinal veins persist, leading to a double IVC to the level of the left renal vein. The left IVC drains into the left renal vein, which subsequently drains into the right IVC. Filter placement in one side, while leaving the other uninterrupted, is inadequate prophylaxis for PE. To rule out this anomaly, during venography through a flush catheter, one should visualize contrast refluxing into the contralateral common iliac vein. In the absence of this finding, duplicated IVC should be suspected and confirmed by accessing the contralateral side

and performing venography to identify contrast filling the left renal vein. Additional clues hinting at the presence of a duplicated IVC would be a diminutive right IVC or a high volume of non-opacified blood filling the right IVC above the level of the left renal vein.

Circumaortic and Retroaortic Left Renal Vein

Circumaortic renal veins occur in 1.6–14.0% of the population and carry significance for filter placement as the hilar junction of these veins with the IVC may be quite large, allowing for an alternative pathway for thrombi to escape the filter. To mitigate this risk, filters should be placed inferior to the entire circumaortic venous complex, where the overall diameter of the IVC is smaller, or in the suprarenal inferior vena cava. The presence of a retroaortic left renal vein should be noted but does not carry an increased risk of embolism.

Left IVC

Persistence of the left supracardinal vein and regression of the right supracardinal vein results in a left-sided inferior vena cava in 0.2–0.5% of the population. In this situation, the infrarenal IVC lies on left, and the suprarenal IVC lies on the right. Generally, the left IVC crosses anterior to the aorta to join the right at the level of the renal veins; however, retroaortic left IVC has also been described. With left IVC, venous anatomy may be reversed, whereby the left gonadal and adrenal veins drain directly into the IVC and the right gonadal and adrenal veins drain into the right renal vein. Additionally, patients with a left IVC frequently have multiple renal veins. In this situation, a suprarenal filter may be necessary.

Megacava

Megacava, defined as an inferior vena cava diameter of greater than 28 mm, is an important entity to identify prior to placing a filter. Currently, all commercially available devices can be used with caval diameters up to 28 mm; however, only a few (the Gunther Tulip/Celect, the TrapEase/OptEase, and the Option filter) can be used for diameters up to 30 mm, and only one device (the Bird's Nest filter) is approved for megacava up to 40 mm. Alternatively, two IVC filters can be placed in both iliac veins, or a single suprarenal IVC filter can be positioned in the suprarenal cava if it is of appropriate diameter. Filters are secured in place either with lateral force exerted by the legs, active fixation via tethering hooks, or a combination of both. As caval diameters increase, the legs of an undersized filter may not exert enough force on the wall to maintain position or sink the hooks, thereby resulting in migration. Obtaining accurate measurements, either with contrast venography or intravascular ultrasound, is critical when choosing a device of appropriate size.

Fluoroscopically Guided Inferior Vena Cava Filter Placement

The common femoral vein is identified using ultrasound. Obtaining access over the femoral head is critical to facilitate gentle manual compression at the conclusion of the case. Overaggressive compression of the femoral vein has been cited as one possible cause for perioperative venous thrombosis. Appropriate position is confirmed by placing a clamp at the intended access site and shooting a spot view under fluoroscopy. The groin is then anesthetized, and a 2–3 mm skin incision is made with an 11-blade scalpel. The common femoral vein is percutaneously cannulated with a double-wall needle, and a soft wire (Glidewire, Bentson, or J-wire) is advanced into the IVC under continuous fluoroscopic guidance. A 10 cm No. 5 French sheath is then advanced over the wire, into the common femoral vein, using Seldinger's technique. A flush catheter is then advanced over the wire and an iliocavogram obtained (Fig. 32.2). At this point, the surgeon should take note of several key factors:

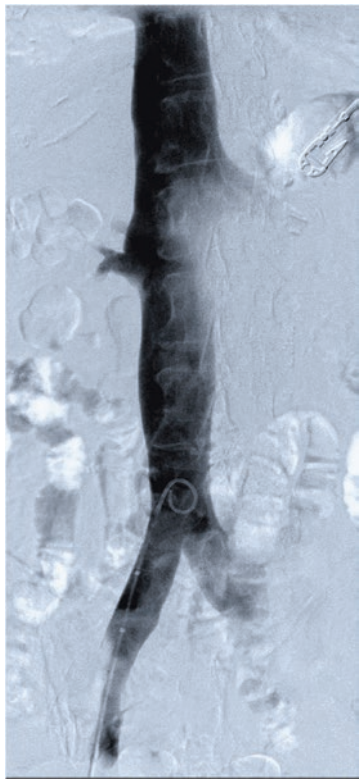

Fig. 32.2 Inferior venacavogram demonstrating both common iliac veins and the location of both right and left renal veins. There is no evidence of thrombus or aberrant caval anatomy on this study

1. The presence of iliac and vena cava thrombus should be ruled out. Distal IVC thrombus generally necessitates jugular access.
2. Anomalous venous anatomy should be noted, and the surgical plan altered as necessary.
3. The location of the renal veins (particularly the lowest renal vein) should be documented.
4. The diameter of the infrarenal IVC should be determined. If megacava, with diameters between 30 and 40 mm, is identified, either a Bird's Nest, bilateral iliac vein filters, or a suprarenal IVC filter may be required.
5. The distance between the lowest renal vein and the confluence of iliac veins should be documented.

Occasionally, venacavogram may fail to clearly identify the renal veins. In this instance, the renal veins should be selectively catheterized and injected to eliminate any ambiguity in their location. Most available filters are 60 mm in length or shorter. The exception is the Bird's Nest filter which is 80 mm in length.

Once the anatomy is confirmed and appropriate measurements are made, the device is opened and placed through the long delivery sheath which accompanies each filter. Although most IVC filters have similar deployment systems, each device has its own idiosyncrasies which the surgeon must consider. Deployment typically involves advancing the delivery sheath, under fluoroscopic guidance, to a point just below the lowest renal vein. Deploying the device as close to the renal veins as possible is important to avoid creating a low-flow zone above the filter and below the vein which could create a nidus for thrombosis outside the filter. The dilator and wire are then removed while precisely maintaining sheath position in the IVC. The filter is then inserted into the delivery sheath and advanced to the end of the sheath under fluoroscopic surveillance. To deploy the filter, the delivery system is immobilized with one hand, while the other pulls the sheath back. Most filters deploy fully with this technique, but some have additional steps to facilitate more precise delivery and to avoid tilting and uncontrolled forward advancement of the filter. Once deployed, completion venography is performed to document the final position and ensure patency of the IVC and renal veins (Fig. 32.3). The device delivery system is removed from the access point and manual compression is held to achieve hemostasis. A completion spot film is then obtained to document the final position of the IVC filter for future reference if needed.

Ultrasound-Guided Inferior Vena Cava Filter Placement

Some patients may be poor candidates for fluoroscopically guided IVC filter placement due to clinical instability and inability to transfer to an operating room or have prohibitively elevated creatinine levels precluding the use of contrast media. Under such circumstances, placing an

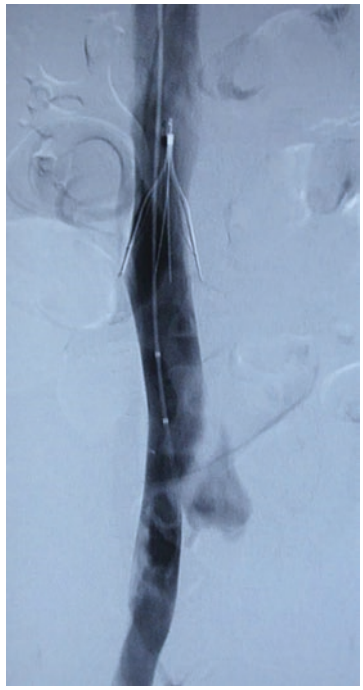

Fig. 32.3 A completion inferior venacavogram from the right internal jugular approach demonstrating correct position of the inferior vena cava filter below the renal veins with minimal tilt of the filter and continued patency of the inferior vena cava

IVC filter is still possible with the aid of a portable intravascular ultrasound (IVUS) system brought to the bedside. IVUS allows for precise device deployment without the use of contrast, and data suggest that intravascular ultrasound measurements are more accurate than those obtained with traditional contrast venography, which tends to overestimate IVC diameter. Despite these advantages, there are several caveats to this technique. The learning curve is steep and rates of filter malposition range from 2 to 8%, attributable primarily to inexperience leading to misidentification of normal anatomy and failure to appreciate abnormal anatomy [27]. Familiarity with basic wires and IVUS interpretation is a prerequisite to any attempt at IVUS-guided IVC filter placement.

The first IVUS-guided filter was placed in 1999, but the technique was initially met with some resistance as bilateral access was required to maintain real-time ultrasound imaging during deployment. The IVUS catheter was advanced into the IVC via one common femoral vein, and the delivery device was placed via the contralateral side. With both the IVUS catheter and delivery system in the IVC, deployment is directly observable. An alternative technique, utilizing a single puncture, involved mapping the IVC with IVUS, measuring the distance from the puncture site to the renal vein, removing the IVUS catheter, and then advancing and deploying the filter blindly.

With this technique, common femoral access is obtained, and the delivery sheath for the filter is advanced a few centimeters into the vein over a wire. An 8 French sheath and an IVUS catheter are then inserted and advanced with the wire to the level of the heart, verified by visualizing cardiac motion. The IVUS catheter is then withdrawn to map the anatomy of the entire IVC. Renal vein identification is aided by noting the location of the right renal artery posterior to the vena cava just below the level of the renal veins. Once the IVUS catheter is in position below the renal vein, the 8 French sheath is advanced until its tip just overshadows the IVUS probe. The wire and IVUS catheter are then removed, maintaining sheath position. The filter is then loaded with its obturator through the 8 French sheath and advanced until the shaft reaches the level of sheath diaphragm. The filter is now at the end of the sheath, ready for deployment. The obturator is then removed using a "pin-and-pull" technique to deploy the filter. Position can be confirmed either with an abdominal plain film or by reinserting the IVUS catheter over a wire and evaluating the IVC directly.

Single puncture methods involving the use of transabdominal ultrasound for real-time guidance during deployment have been described in the literature and appear to be a promising technique.

Suprarenal and Superior Vena Cava Filter Placement

Placing a filter in an infrarenal location is preferable whenever possible, but situations do arise which require placement in the suprarenal vena cava. Heavy thrombus burden in the IVC, thrombus

extending to the renal veins, renal or gonadal vein thrombosis, pregnancy, and a duplicated IVC may all necessitate a suprarenal filter. The suprarenal IVC tends to have a larger diameter than the infrarenal IVC; thus, filters may be more prone to migration in this segment, and care must be taken in measurement of the diameter of the suprarenal IVC. In a recent publication, 70 patients with suprarenal filters were followed for 20 years, and no occurrences of caval thrombosis were noted. Three patients had CT evidence of thrombus in the filter, there was one incidence of filter fracture, and asymptomatic filter penetration of the IVC wall occurred in two patients. Post-filter PE was suspected in ten patients (11.5%), eight of whom underwent CT, but only one of those patients had radiographic evidence of a new PE. They concluded that the safety and efficacy of suprarenal IVC filters is comparable to that of filters placed below the renal veins [28].

If a superior vena cava filter is to be placed for the prevention of PE from upper-extremity DVT, placement proceeds following the steps described for the IVC filter. The ideal location is immediately proximal to the innominate vein. It is important to remember that, in this case, the orientation of the filter must be reversed in comparison to a standard IVC filter. Therefore, a femoral IVC filter kit must be used from a jugular approach or, more commonly, a jugular kit from the femoral approach. Care must be taken to avoid extension of the IVC filter into the right atrium.

The PREPIC Trials

To date, there has only been one long-term randomized study evaluating the roll of IVC filters in the prevention of pulmonary embolism. The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) study, whose initial 2-year results were published in 1998 [29] and whose 8-year long-term follow-up results were published in 2005 [30], randomized 400 patients with proximal DVT to treatment with anticoagulation alone (with low molecular weight heparin for 8–12 days, followed by a vitamin K antagonist for a minimum of 3 months) versus anticoagulation and a permanent vena cava filter. At 12 days, two pulmonary emboli occurred in the filter group (1.1%) versus 9 PEs in the nonfilter group (4.8%) (P = 0.03). At 2 years, there were 6 PEs (3.4%) in the filter cohort and 12 PEs (6.3%) (P = 0.16) in the nonfilter group. Recurrent DVT occurred in 37 (20.8%) patients in the filter group and 21 (11.6%) patients in the nonfilter group (P = 0.02). The 2-year results suggest that inferior vena cava filters provide significant short-term protection from pulmonary embolism compared with anticoagulation alone, but this benefit wanes over time and that filters are associated with an increased risk of recurrent DVT.

Eight-year results of the PREPIC trial demonstrated 9 PEs in the filter group (6.2%) versus 24 PEs in the nonfilter group (15.1%) (P = 0.08). The filter group had 57 patients with DVT (35.7%) versus 41 (27.5%) in the nonfilter group (P = 0.042). Postthrombotic syndrome (PTS) occurred at similar rates in both groups and was found in 109 (70.3%) patients in the filter group and 107 (69.7%) in the nonfilter group. This rate is substantially higher than other rates reported in the literature; however, it should be noted that 24% of patients in the PREPIC trial had PTS at the time of inclusion in the study. Mortality rates between the groups did not differ as there were 98 (48.1%) deaths in the filter group and 103 (51.0%) deaths in the nonfilter group. Of note, the predominant cause of death was cancer (in 49 patients), followed by cardiovascular-related mortality (32 patients), cardiac disease (22 patients), and bleeding (17 patients).

PREPIC results suggest that at 8 years, vena cava filters reduce the risk of PE but increase the incidence of DVT. Inferior vena cava filters have no effect on the incidence of postthrombotic syndrome or on survival.

The results of the PREPIC 2 trial were recently published [31]. This extension of the PREPIC trial looked at the effect of routine placement of IVC filters on rates of recurrent PE in high-risk patients compared to anticoagulation alone. This multicenter, controlled trial randomized 399 patients to IVC filter (n = 200) and anticoagulation or anticoagulation alone (n = 199) at 17 centers in France from 2006 to 2012. Follow-up was

at 3 and 6 months and the primary outcome was recurrent symptomatic PE at 3 months. The study reported rates of symptomatic or fatal recurrent PE were 3% in the IVC filter group versus 1.5% in the group with anticoagulation alone (RR 1.4, $P = 0.29$). Recurrent PE at 6 months was similar (3.5% filter group versus 2% anticoagulation alone, RR 1.75, $P = 0.54$). There was no difference in all-cause mortality or major bleeding events between both groups at any time point. The PREPIC 2 study suggests that in patients with pulmonary embolism, at high risk of recurrence, the routine placement of IVC filters does not reduce the risk of recurrent PE when compared to anticoagulation alone.

Despite their longstanding and widespread use, long-term data on the safety and efficacy of vena cava filters is lacking. The PRESERVE trial (Predicting the Safety and Effectiveness of Inferior Vena Cava Filters), a joint venture between the Society for Vascular Surgery, the Society of Interventional Radiology, and the FDA, began enrolling patients in 2015 in the first large-scale multispecialty prospective study designed to evaluate the use of IVC filters and follow-up. The trial aims to evaluate 2100 patients at 60 centers in the United States, with 300 patients enrolled from each of the major filter manufacturers. Results will likely be available in the years to come and may answer many of the questions about IVC filter use and performance in the real practice.

Retrievable Filters

The intent of a retrievable filter is risk mitigation for patients with a transiently increased risk of PE. However, when retrievable filters are placed prophylactically in a patient without a DVT or PE, it is considered off-label use of the device. The FDA estimates that nearly 50% of filters are placed using extended criteria. Retrievable filters are placed in a manner identical to permanent filters but have design features allowing for recapture and removal during a second procedure from a jugular approach. Ironically, key features of the filter which allow for recapture may also lower the safety profile of these devices, promoting fracture or migration. Ease of retrieval requires less secure fixation, more shallow or flexible anchoring hooks, and reduced endothelialization of the anchoring portion of the filter (Fig. 32.4). Nevertheless, all currently available retrievable filters carry dual FDA approval for either temporary placement or permanent use. Although the option of retrieval is appealing at face value, in real-world clinical practice, there are no defined follow-up criteria and only a paucity of these devices gets ever removed.

The development of retrievable filters was spurred by several factors. Data obtained from the PREPIC trial suggested that IVC filters, left in place long-term, increase the risk of recurrent DVT. Second, physicians across multiple specialties are implanting ever-increasing numbers of filters using off-label extended criteria as certain subsets of patients were perceived to have an increased risk of thromboembolism in temporal relation to their condition or procedure and a relative contraindication to standard primary VTE chemoprophylaxis. Multisystem trauma patients, orthopedic patients, bariatric patients, and pregnant patients all represent higher-risk cohorts for

Fig. 32.4 The Gunther Tulip retrievable IVC filter. Note the presence of a hook on the apex of the filter to facilitate removal by an internal jugular approach

Table 32.3 Factors to consider before discontinuing a retrievable filter

1. No indication for a permanent filter
2. Expected period of increased VTE risk has passed, and the patient will not return to a high-risk state
3. Risk of PE is low
4. Life expectancy is long enough for the patient to derive benefit from removal
5. Filter retrieval is safe and technically feasible

whom these filters are used in an off-label prophylactic fashion.

Currently available retrievable filters have a window of time during which they can safely be removed, and retrieval times may vary between filter designs. There are no strict criteria to guide the decision-making process for removal, but several factors should be considered (Table 32.3). Well-controlled clinical trials evaluating the impact of retrieval versus permanence are lacking; however, mathematical modeling suggests an optimal time frame for removal lies between 29 and 54 days after the VTE risk subsides [32].

Complications

Although a myriad of filter-related complications (Table 32.4) have been described, major adverse events are fortunately rare and are related to the length of time the filter stays inside the IVC [33]. During the procedure or immediately thereafter, filter malposition, migration, access site hematoma, and femoral vein thrombosis are most frequent. New femoral vein thrombosis on the side ipsilateral to the procedure and after insertion is common, occurring in up to 20–40% of patients by 1–2 weeks in some series. In general, however, less than half of these new DVTs are symptomatic. Disappointingly, new lower-profile devices have not been shown to lower this rate. Recurrent PE, perhaps the most important measure of a filter's efficacy, occurs in some estimated 2–5% of patients. However, this data may underreport the true incidence as the number of asymptomatic recurrences is difficult to quantify.

Table 32.4 Complications of IVC filter placement

	Incidence (%)
1. Procedure related complications	4–11
• Puncture site complications: bleeding, infection, thrombosis, air embolism	
• Delivery system complications, filter malposition, tilting, or incomplete opening	
• IVC wall penetration	
• Death	
2. Filter migration—to renal vein, heart or pulmonary artery	3–69
3. Filter fracture	<1
4. New or worsened DVT	6–30
5. IVC thrombosis	6–30
6. Recurrent PE/fatal PE	2–5
7. Venous insufficiency	10–30

Asymptomatic perforation of the IVC with a chronically indwelling filter is one of the most common findings observed in patients who undergo abdominal imaging for other indications. In a retrospective series of 50 patients with either the Gunther Tulip or Celect filters and who had abdominal CT scans obtained between 1 and 880 days after insertion, 43 (86%) of these filters had at least 1 component perforating the vena cava. By 71 days, all filters imaged demonstrated some degree of caval perforation. Isolated reports of filters perforating the vena cava and injuring surrounding organs, including the aorta, duodenum, or small bowel, have been reported, but the true incidence of these rare events is unknown [34].

Filter fracture and embolization are common events, the incidence of which increases with longer dwell time, but whose clinical significance remains unclear. Data suggest that between 6 and 25% of filters left in place longer than 2 years will fracture. But the clinical consequences when a portion of a filter dislodges are highly variable, ranging from asymptomatic to immediately life-threatening. Most embolized fragments lodge harmlessly in distal pulmonary arteries. However, a minority of events have led to lethal cardiac arrhythmias and cardiac tamponade.

The importance of removal of retrievable IVC filter has recently been underscored by two safety

alert communications from the FDA. Currently, very few retrievable IVC filters are actually removed with published retrieval rates ranging from as low as 13 to 18%. In 2009, a review of the FDA's Manufacturer and User Facility Device Experience (MAUDE) database, the FDA noted 951 IVC filter complications over a 5-year period documented in the database and that a significant majority of these were occurring with retrievable IVC filters [35]. This resulted in an FDA alert communication in August of 2010 recommending "that implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection from PE is no longer needed." This communication was followed by a second update on the original safety alert in May of 2014 "encouraging all physicians involved in the treatment and follow up of patients receiving IVC filter to consider the risk and benefits of filter removal for each patient. A patient should be referred for IVC filter removal when the risk/benefit profile favors removal and the procedure is feasible given the patient' health status." According to a decision analysis published by representatives of the FDA, patients without pulmonary embolism should have their filters removed between 29 and 54 days after the time their filters were placed as the transient risk of PE has passes and the benefit/risk profile favors filter removal [32].

Conclusion

Inferior vena cava filters are lifesaving devices when placed for traditional indications. However, with the interpretation of the data from the PREPIC study and the development of retrievable IVC filters, the numbers of IVC filter placed over the past decade have increased dramatically, especially for extended criteria (prophylactic) indications. Ironically, while there has been an explosion in the use of retrievable IVC filters, there has also been an increasing and acute awareness of the numbers and types of complications associated with the placement of these filters. Data from studies such as the PRESERVE trail will be pivotal to understanding the true rates of complications associated with filters and identifying patients that are most likely to benefit from the presence of an IVC filter.

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Retrieval of Inferior Vena Cava Filters

33

Anand Brahmandam, Afsha Aurshina, and Cassius Iyad Ochoa Chaar

Clinical Pearls

1. IVC filter tilt, hook to the wall apposition, and prolonged dwell time increase the technical difficulty of IVC filter removal.
2. In our experience, using a loop-snare technique and a large (16F) sheath can retrieve most of IVC filters with challenging configuration.
3. Open surgical removal is an option and should be considered in cases where endovascular retrieval is impossible or deemed not safe.

Introduction

In 2003, the Food and Drug Administration (FDA) approved modification of two permanent inferior vena cava (IVC) filters, allowing for their removal after the period of protection elapsed. The Günther-Tulip filter (Cook Medical Inc., Bloomington, IN) and Recovery filter (CR Bard, Tempe, AZ) were the first retrievable filters available in the USA. Shortly after in 2004, the OptEase (Cordis Endovascular, Warren, NJ) was made available. Prior to this, IVC filters were available for permanent interruption of the IVC only [1, 2]. There are currently seven optional IVC filters approved by the FDA in the USA (Table 33.1). The introduction of temporary IVC filters has increased the popularity for treatment of venous thromboembolism (VTE) as a "safe" modality since the IVC filter can be removed when patients resume anticoagulation. The placement of IVC filters significantly rose, while the reported retrieval rates remained low [3–5]. Despite increasing reports of adverse events, the national retrieval rates range between 12 and 45% (mean 34%) for a variety of factors [6]. Retrieval of an IVC filter is a technically simple procedure performed with a snare and a long sheath. However, prolonged dwell time, filter migration and tilt, filter fracture, and IVC penetration make the procedure challenging in 15–17% of the cases [7–9]. In these scenarios, a myriad of advanced endovascular techniques and, in certain complex scenarios, open surgical removal has been described to achieve success. Although no single technique is ideal for the variety of complex retrievals encountered in real world, this chapter will provide a comprehensive

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Table 33.1 Retrievable IVC filters

Filter	Maximal IVC diameter (mm)	Material	Mean duration of implantation (range)[a]
Denali (Bard Peripheral Vascular, Tempe, AZ)	28	Nitinol	140 days (5–454 days)
Günther-Tulip (Cook Medical Inc., Bloomington, IN)	30	Conichrome	11 days (2–20 days)
Celect (Cook Medical, Inc., Bloomington, IN)	30	Conichrome	354 days (7–469 days)
ALN (ALN, Bormes-les-Mimosas, France)	28	Stainless steel	93 days (78–108 days)
Option Elite (Argon Medical Devices, Inc., Plano, TX)	30	Nitinol	Within 175 days
OptEase vena cava filter (Cordis Corporation, Bridgewater, New Jersey)	30	Nitinol	Up to 12 days
Vena Tech Convertible Filter (B. Braun, Bethlehem, PA)	28	Cobalt chromium	130 days (15–391 days)

[a]As recommended in device-specific instructions for use (IFU)

overview of tools and techniques described for IVC filter retrieval.

Timing of Filter Retrieval

The timing for safe and uncomplicated retrieval of an IVC filter cannot be universally determined. However, in the setting of increasing reports of device-related adverse events, the FDA issued an alert in 2010, urging physicians responsible to retrieve the filter as soon as protection from pulmonary embolism (PE) was no longer needed. This alert was updated with a quantitative decision analysis model by Morales et al. in 2014 [10]. The model showed the risk of complications began to outweigh protective benefits of the filter at day 35 from implantation. Based on a sensitivity analysis, the authors suggested an ideal retrieval time between 29 and 54 days from implantation. In practice, several patient- and physician-related factors can delay significantly the timing of retrieval. Some patients have prolonged complicated hospital course and need for repeat surgeries especially after multi-trauma accidents [11]. Vascular specialists placing IVC filters may not have established algorithms for continuity of care resulting in loss to follow up. The creation of institutional mechanisms to capture patients after IVC filter placement has significantly improved and expedited their removal [12, 13]. In a recent survey of vascular specialists, 45% of responders who place IVC filters would not offer IVC filter removal after a dwell time of 2 years [14]. On the other hand, several case reports have described retrieval of IVC filters after extended periods from 3 years and up to 16 years from the time of placement [15–17]. Prolonged dwell time increases failure and complications of filter removal [8, 9]. Therefore, the decision of IVC filter removal and the technical strategy should be individualized based on patient's symptoms, risk of recurrent VTE/bleeding, and local expertise.

Patient Evaluation

Prior to retrieval of the IVC filter, patients are evaluated to assess for risk of recurrent VTE. This evaluation involves a focused history and physical, routine laboratory investigations focusing on renal function and coagulation profiles. The presence of signs and symptoms suggestive of new or recurrent VTE requires a full workup prior to IVC filter removal. The ambulatory status of the patient must be assessed prior to retrieval. In our practice, we do not remove IVC filters routinely

from patients who are immobilized because of increased risk of VTE. The presence of DVT must be ruled out by obtaining venous duplex of the lower extremities prior to consideration for filter retrieval. If imaging performed reveals new or progressive VTE, filter retrieval must be deferred to a later date. However, these patients should be reevaluated for filter retrieval, upon completion of the appropriate anticoagulation regimen. We follow a modified version of the algorithm provided by the Society for Interventional Radiology (Fig. 33.1) [18]. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast is warranted for patients with a filter dwell time over 1 year. Additionally, in our practice we routinely obtain CT scan of the abdomen and pelvis with intravenous contrast for retrieval of IVC filters that were placed at outside institution and referred for retrieval. Cross-sectional imaging is useful to determine the configuration and integrity of the filter, the presence of thrombus within the filter, and the location of the hook as well as penetration into surrounding structures. A grading system has been devised to better define the extent of strut penetration into the IVC wall [19] (Table 33.2). Filter tilt is measured as the angle between the axis of the filter and the axis of the IVC. The tilt is deemed significant when this angle is greater than 15° from long axis [20]. Filter migration can also be determined and is defined as a 2 cm or greater superior or inferior movement from initial placement location [20].

Standard Technique

Standard retrieval of an IVC filter is commonly performed via right internal jugular vein access under ultrasound guidance. First, a venogram is performed to ensure that there is no thrombus trapped in the IVC filter. If more than a third of

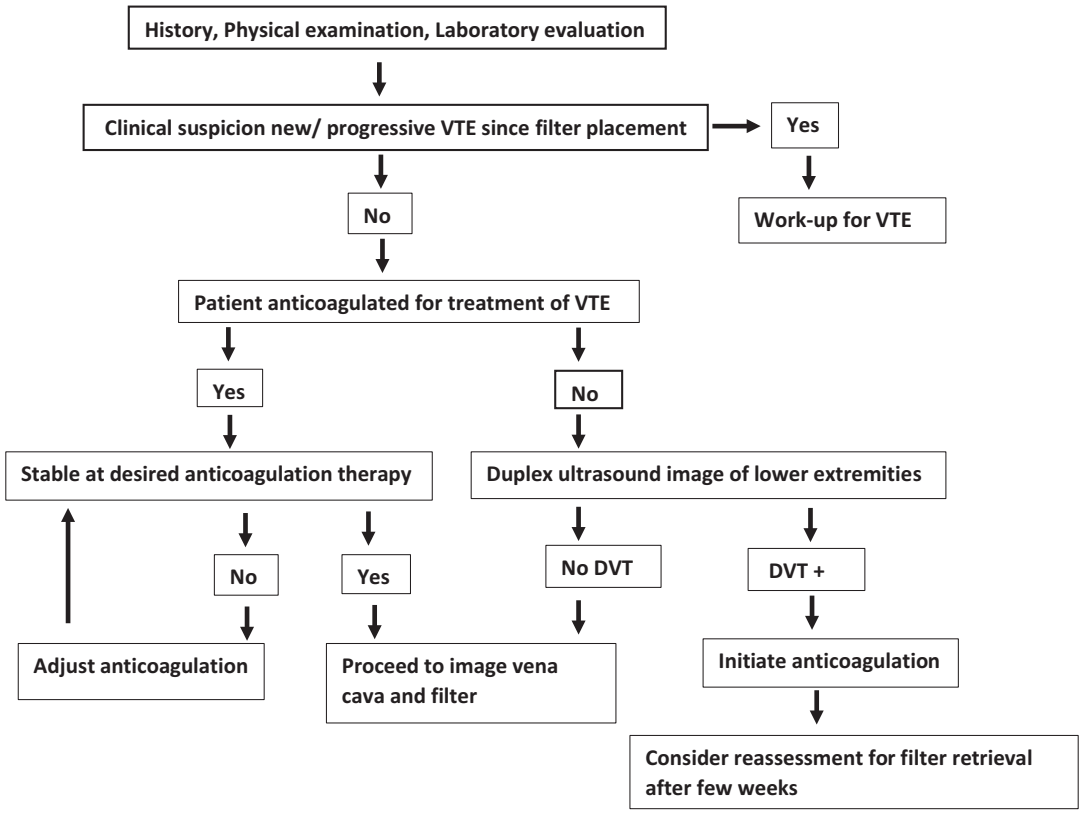

Fig. 33.1 Algorithm for patient evaluation before vena cava filter retrieval

Table 33.2 Grading system for strut penetration of IVC wall

Grade	Extent of strut penetration into IVC wall	Retrieval technique
Grade 0	All struts being confined within the IVC	Standard filter retrieval technique employed
Grade 1	Filter struts that tent the caval wall	Standard filter retrieval technique with/without modifications
Grade 2	Filter struts penetrating the retroperitoneum	Advanced retrieval techniques often required
Grade 3	Filter struts penetrate adjacent organs	

the cone has thrombus, we leave the IVC filter in situ to avoid "squeezing" and embolization of the clot to the lungs. A vascular snare or a retrieval cone system is introduced to grasp the hook of the filter. This is followed by advancing a vascular sheath over the snared filter to disengage the struts and collapse the filter (Fig. 33.2). Most filters have the apex or the "cone" directed cephalad and can be retrieved via a transjugular approach. However, certain filters have the hook placed caudally, requiring a transfemoral approach for retrieval. There are various kits and tools commercially available such as Recovery Cone Removal System (Bard Peripheral Vascular, Tempe, AZ), Günther-Tulip retrieval kit (Cook Medical Inc., Bloomington, IN), and ALN Optional Vena Cava Filter Extraction Kit (ALN Implants Chirurgicaux, Ghisonaccia, France). Filter retrieval can be performed with local anesthesia and sedation as outpatient procedure. When performed in a timely fashion after placement, successful retrieval can be achieved in 93% of the time as demonstrated in a recent randomized trial [21].

Challenges

Filter removal involves two maneuvers: first, securing the filter and aligning it with the sheath and, second, collapsing it and freeing its tines from the IVC wall. As simple as it may seem, these two steps can be fraud with significant challenges transforming a simple procedure to a vascular specialist's worst nightmare. Increased dwell time, filter tilt, and filter to caval wall apposition have been shown to be associated with failure of retrieval and increased complexity [8, 9]. Filter tilt without apposition to the wall of the cava typically does not prevent removal but makes it more challenging. The commercially available kits contain straight linear tools with inability to tilt or aim in a specific direction. Posterior tilt can be particularly deceiving, as the filter may appear to be centered on the anteroposterior fluoroscopy image. The operator can spend some time trying to capture the hook of the device without success. Oblique views are needed to visualize the tilt and direct the operator. Apposition of the filter to the wall makes the hook inaccessible, but erosion of the hook through the wall makes safe endovascular retrieval even more challenging (Fig. 33.3). Moreover, severe fibrosis around the tines of the filter can make the removal very hard. Significant force is needed sometimes that surpasses the maximal stress that the material of the filter or the retrieval device can tolerate before failure. Figure 33.4 illustrates a retrieval sheath that is accordioned from excess pressure while pulling on the filter and pushing the sheath (Fig. 33.4a). The filter was captured, but a tine was stuck and eroded through the sheath at the deformed zone (Fig. 33.4b). Filter and sheath had to be removed together. The filter was confirmed to be intact after cutting the sheath open and visualizing the filter (Fig. 33.4c). In another example, one of the tines was stuck in a lumbar vein and could not be disengaged easily. The force applied was excessive, resulting in a complete straightening of the filter hook (Fig. 33.5). The case was aborted because of patient discomfort. The filter was subsequently removed successfully during a second attempt under general anesthesia with dual access and wire-loop technique. These challenges led to significant creativity in the vascular community to use available tools, sometimes in an off-label fashion, for endovascular IVC filter removal. These methods will be referred to as advanced endovascular techniques and will be summarized in the next section.

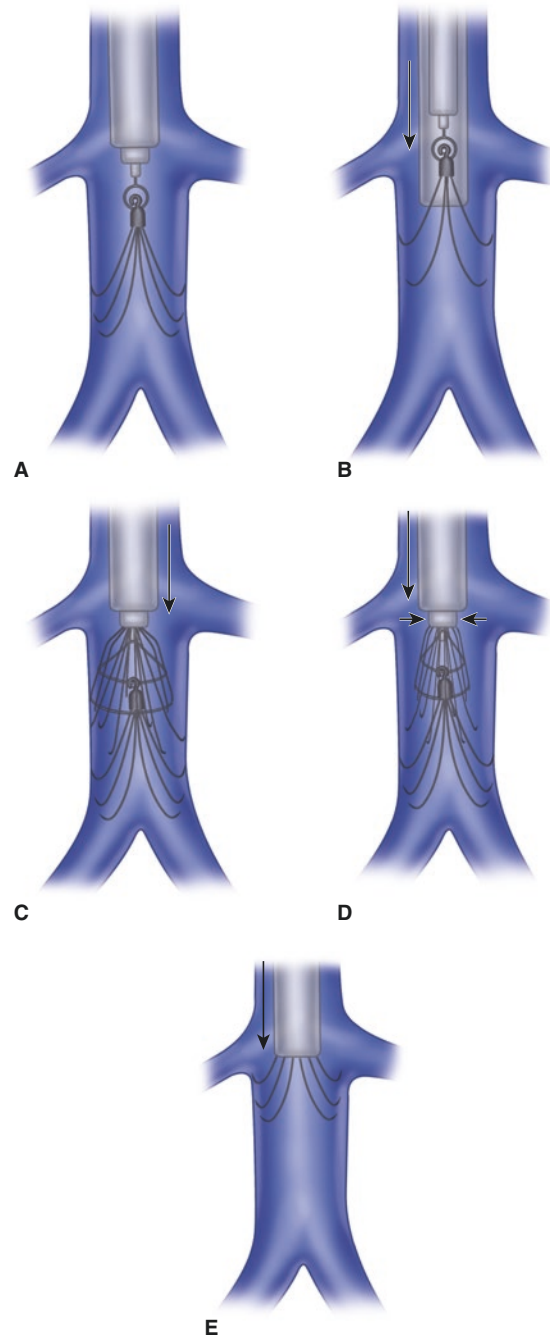

Fig. 33.2 Standard retrieval of an IVC filter. (**a**) The filter hook is grasped by a vascular snare. (**b**) Subsequently, the vascular sheath is advanced and the filter is collapsed into the sheath. (**c**) A retrieval cone system is advanced over the filter hook. (**d**) Filter hook is engaged by the retrieval cone. (**e**) The vascular sheath is advanced over the filter, which is then collapsed and retrieved

Advanced Endovascular Techniques

In up to 20% of cases, standard endovascular retrieval is unsuccessful [7–9]. Over the years, numerous advanced techniques have been described for filter retrieval, in these complex scenarios [22–24]. The simplest modification of standard retrieval is when the sheath is upsized to a large-bore sheath (16 French), increasing the rigidity of the retrieval apparatus. Additionally,

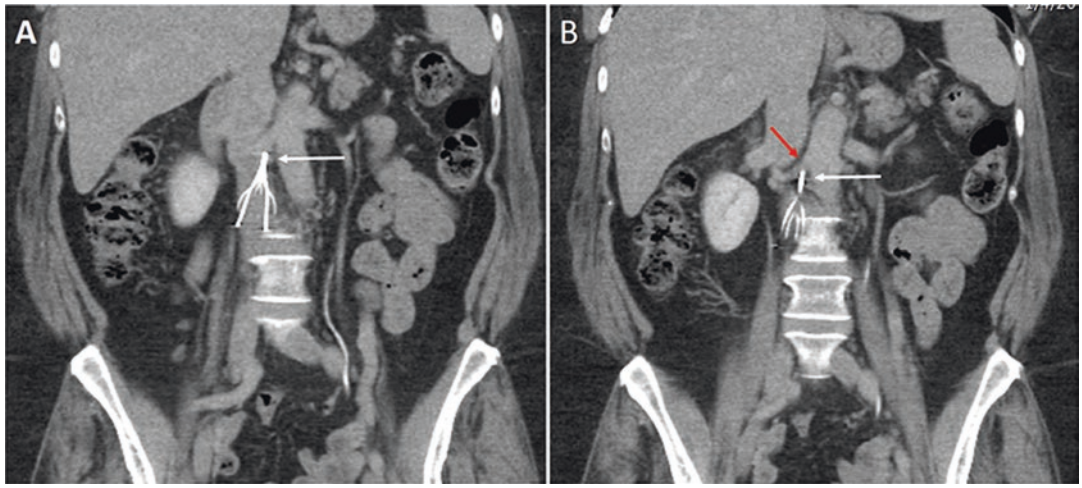

Fig. 33.3 Coronal reconstruction of CT scan demonstrating a tilted IVC filter with the hook (*white arrow*) eroding through the wall of the cava. (**a**) The next CT cut shows the hook of the filter abutting the origin of left renal artery (*red arrow*) (**b**)

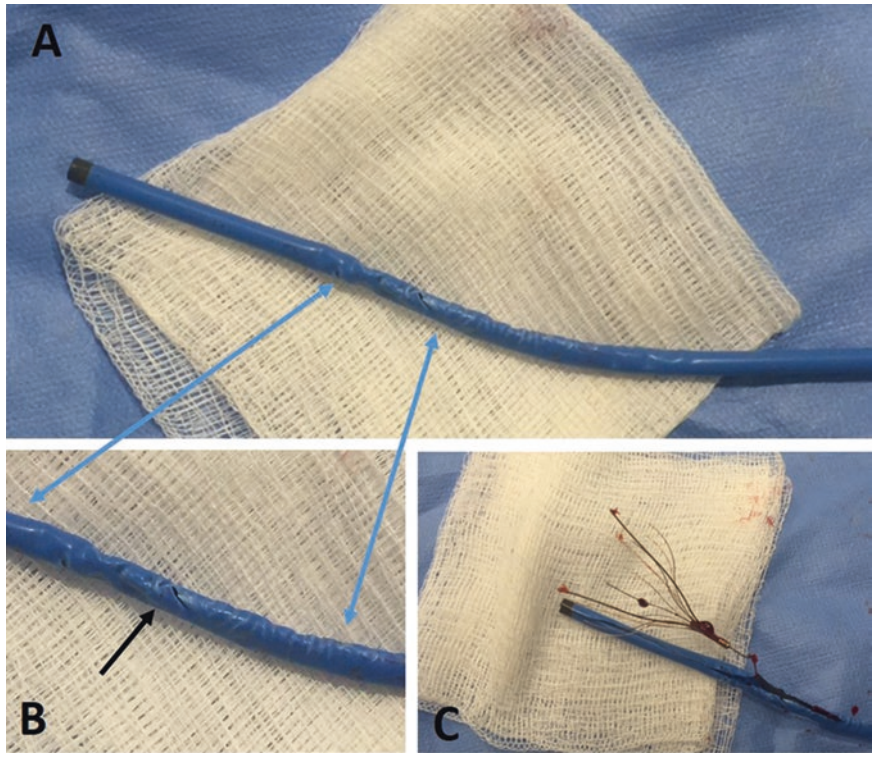

Fig. 33.4 Retrieval sheath deformed from excessive force. (**a**) Magnified view of the segment that "accordioned" (*blue arrows*) demonstrating the tip of a tine that eroded through the sheath and caused the filter to be stuck in the sheath. (**b**) The sheath was cut open and the IVC filter was confirmed to be retrieved intact (**c**)

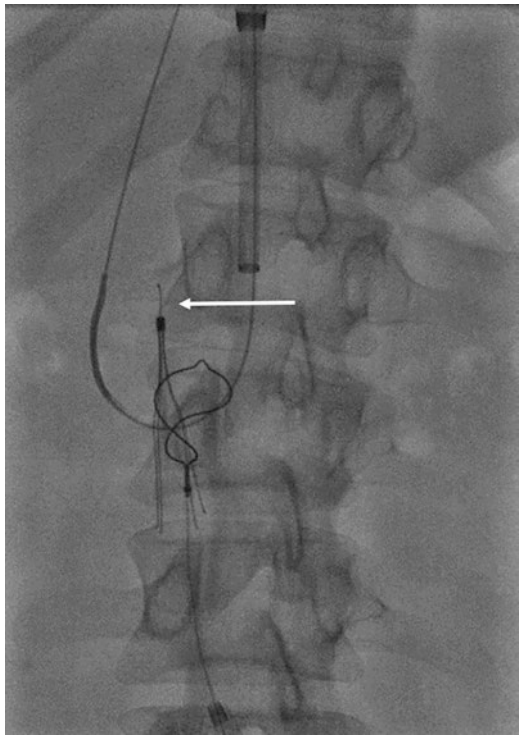

Fig. 33.5 IVC filter with hook becoming "straight" (*white*) from excessive tension during attempted retrieval

the snare can be introduced through an angled catheter, in cases with significant filter tilt. This simple maneuver permits for easy engagement of the apex in these situations.

These techniques incorporate the use of multiple wires, snares, and sheaths to engage the hook of filter and mechanically disrupt embedded struts of the filter. It is important to note that the characteristics of optional filters render them a higher risk for filter deformity, strut fracture, and strut migration. Hence, careful vigilance must be used while incorporating these techniques.

Wire Displacement Technique

In certain cases, where the filter is tilted >15°, engaging the hook becomes challenging. The hook of the filter can be deflected into or "centered" in the IVC using a tip-deflecting wire. Alternatively, a straight wire can be passed between the IVC wall and the filter hook, attempting to dislodge the hook (Fig. 33.6). Once the hook is "centered" in the IVC, it can be grasped by a snare or a retrieval cone and collapsed into the sheath. In scenarios where the hook is embedded in the wall, a retrieval cone or a snare can be advanced over the wire.

In some situations, both the wire and the filter apex can be grasped using a snare or a cone and subsequently collapsed into a sheath. The sheath is then removed from the IVC in total.

Wire and Snare with Dual Access

When the wire displacement technique fails, a dual access wire and snare technique can be utilized to free the apex from the IVC wall. In this technique, long sheaths are passed via transjugular and transfemoral access. A stiff wire, introduced through one end, is passed between IVC wall and filter hook. A snare passed through the other end is used to grasp the wire. This wire and snare system is used to provide a through and through distraction force to dislodge the hook from the IVC wall (Fig. 33.7). This technique relies on the principle of traction and countertraction applied on the wire and snare system from both the jugular and femoral ends. Once the filter is "centered," it is grasped by a snare or collapsed into a sheath using a cone and subsequently extracted. Iliescu et al. cautioned vascular specialists incorporating this technique, to ensure that the wire is adequately protected in a long sheath during the process of "flossing," thus preventing lacerations of pelvic veins.

Loop-Snare Technique

This technique has been described with great success in cases where filter tilt, embedded hook, and strut penetration have led to failure of standard retrieval. The basic principle incorporated forming a loop handle around the filter. A reverse curve catheter is placed below the filter

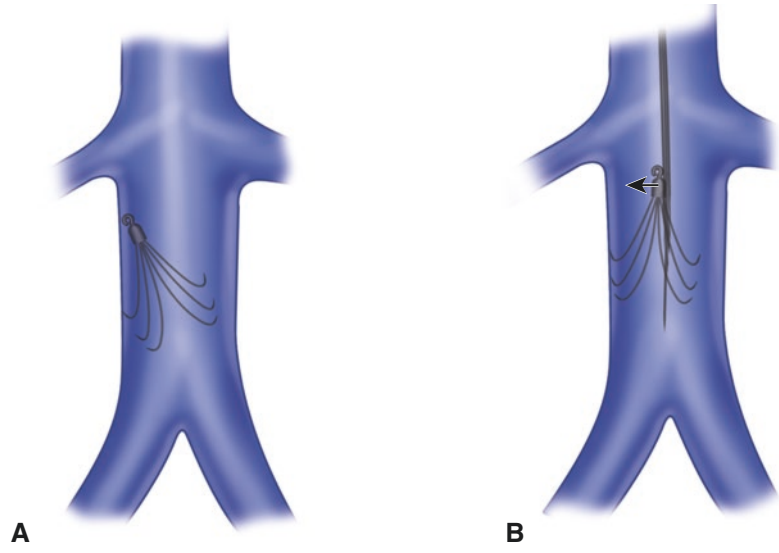

Fig. 33.6 Wire displacement technique. The filter is tilted with the hook apposed to the IVC wall. A stiff wire is passed between the caval wall and filter, attempting to "center" the filter. Once the hook is freed from the caval wall, it can be retrieved in a standard fashion

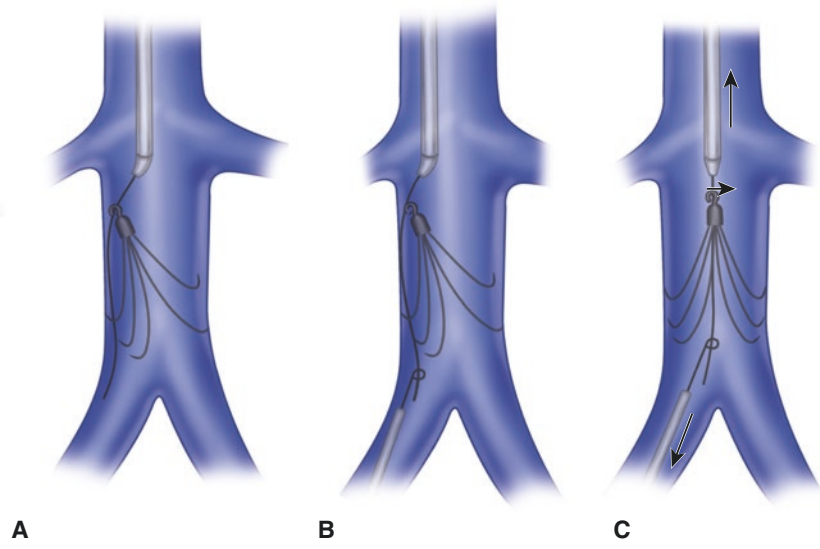

Fig. 33.7 Wire and snare with dual access through jugular access a guide catheter, and a wire is passed between the IVC wall and the filter. (**a**) The wire is grasped by a snare introduced from a femoral access. (**b**) The wire and snare system provides a distraction force, freeing the filter hook from the IVC wall. Once the hook is freed from the caval wall, it can be retrieved in a standard fashion (**c**)

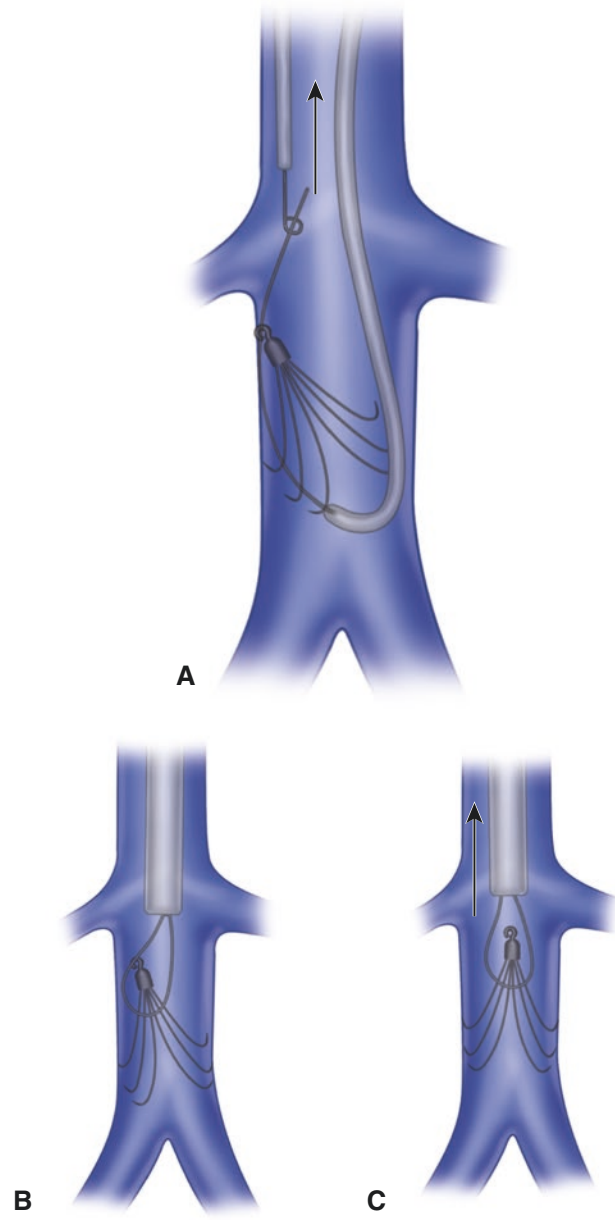

Fig. 33.8 Loop-snare technique is a guide catheter that is passed beyond the position of the filter, and through this catheter, a wire is passed retrograde between the filter and the caval wall. (**a**) The wire is then grasped by a vascular snare. (**b**) This loop is tightened such that the filter hook is "grasped" and the filter "centered." (**c**) The filter is collapsed into the sheath and retrieved

apex, through which a guidewire is directed backwards, such that a loop is formed around the filter. The guidewire is then grasped by a snare forming a loop handle, and the sheath is advanced to collapse the filter (Fig. 33.8). Iliescu et al. recommend a nitinol-based wire for the loop, given its kink resistance and elastic properties. Foley et al. describe a 94% (32/34) success rate using a Bentson wire (0.035 in., Cook Medical), EnSnare device (Merit medical

systems, South Jordan, Utah) for the loop handle, and an 18 French sheath to collapse the filter. They did not report any complications [25]. Etkin et al. describe 76% (42/55) with this technique [23]. In some situations, they noted the 18 French sheath to "accordion" over itself. To address this, they incorporated the use of coaxial sheaths to collapse the filter, an 18 French inner sheath and a 22 French outer sheath. They reported four complications in their series; one filter strut was fractured and embedded in the caval wall, and three struts had migrated to the right atrium or pulmonary artery. Lynch et al. describe a modification of the loop-snare technique where they passed a metal that guides from a liver access and biopsy kit (Cook) over the loop handle to forcefully close it around the filter, prior to collapsing the filter in a sheath. They rationalize that this permitted operators to incorporate a large amount of force collapsing the filter, without causing the sheath to "accordion" on itself [26].

Balloon Displacement Technique

This technique incorporates an angioplasty balloon between the IVC wall and the embedded hook or struts. The balloon is then inflated to "dissect" the filter elements off the IVC wall (Fig. 33.9). Following this, the filter can be retrieved in a standard fashion [27].

Parallel Wire Technique

This technique was originally described by Owens et al. in 2002 for the retrieval of a misplaced Hickman catheter (Bard, Salt Lake City, Utah) [28]. In this "double-wire restraining" technique, jugular and femoral access are obtained with long sheaths. Subsequently, two guidewires are passed on either side of the filter such that the filter and its components are entrapped by the parallel wires. These wires are directed by guide catheters. Both jugular and femoral sheaths are then advanced such that direct traction is applied on the filter (Fig. 33.10). This may be repeated until filter hook or struts are freed from the IVC wall [29].

Bronchoscopy Forceps

Certain filters are embedded to thick fibrous tissue and intractable to retrieval by the techniques mentioned above. In these scenarios, the use of endobronchial forceps has been described for dissecting the filter and its elements off the IVC wall [30–33]. Via jugular access and a coaxial system of sheaths (12 French and 14 French), the endobronchial forceps are introduced to the top of the filter. The filter hook is grasped by the forceps, dissecting it free from the IVC wall and withdrawing the filter into the sheath (Fig. 33.11). Endobronchial forceps aided retrieval have reported high success rates up to 96% (109 of 114 filters) [34]. The mean implantation was 465 days in their series. They reported four complications, two IVC pseudoaneurysms—one requiring balloon tamponade and overnight admission and one self-limiting—and two cases of filter strut fracture and embolization to the pulmonary artery. In both cases, the embolized struts were retrieved.

Endoscopy and Laparoscopy Forceps

There are reports of successful filter retrieval using endoscopic forceps [35, 36]. Just as the bronchoscopy forceps, the success rate and rate of complications are dependent on operator's experience. Johnston et al. describe a dual access technique using endoscopy forceps via the right IJV and the right common femoral vein (CFV). Via the right IJV, large-bore sheaths are placed, and then a wire is looped around the filter struts to provide traction. Following this, via the right CFV, the endoscopy forceps are used to dissect the tissue embedding the filter [35]. Kwolek et al. describe using a laparoscopic alligator grasper to free the filter from the IVC via femoral access, while a snare was used to grasp the filter from a jugular access [37].

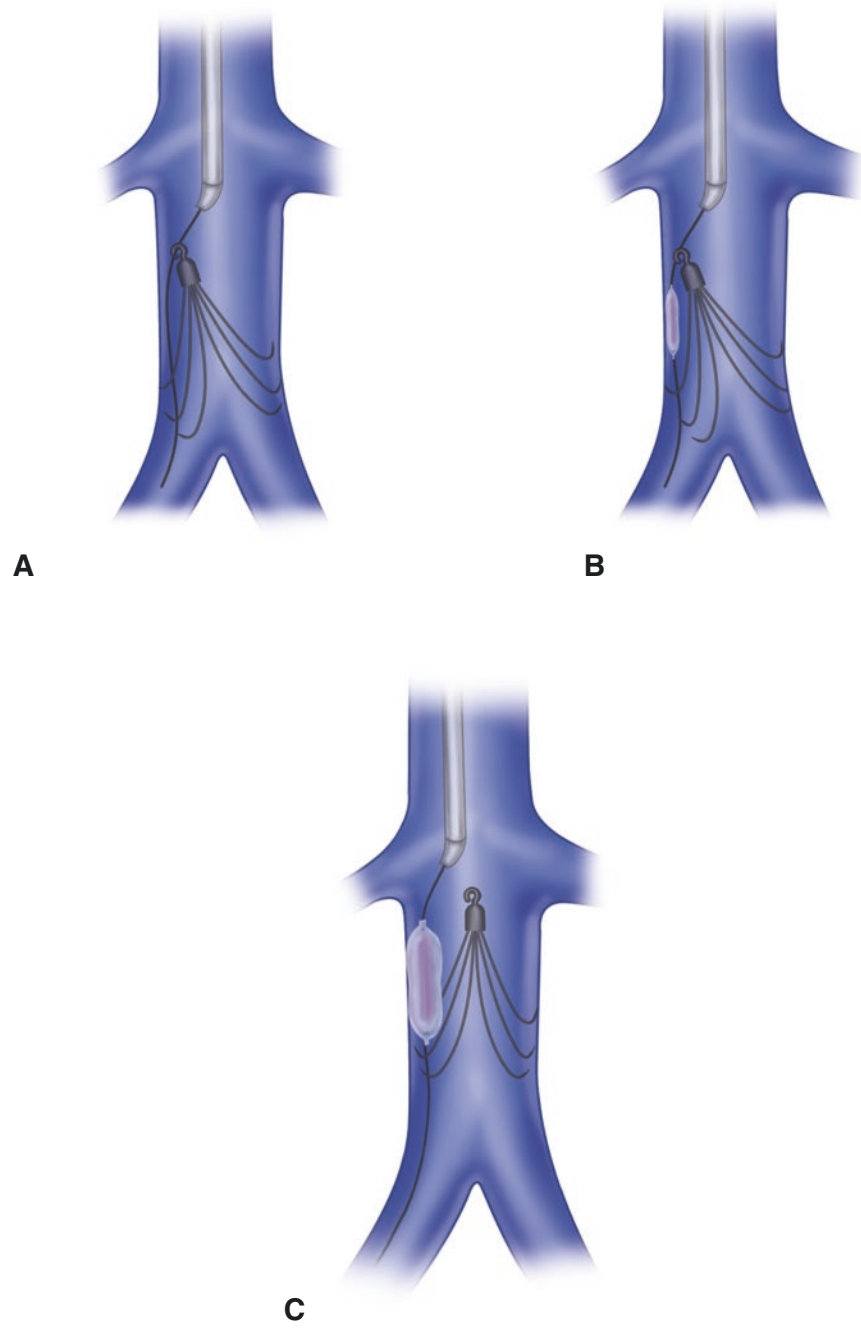

Fig. 33.9 Balloon displacement technique using a guide catheter. A wire is passed between the IVC wall and the filter. (**a**) An angioplasty balloon is advanced over the wire. (**b**) The balloon is inflated such that the filter hook is disengaged. (**c**) Once the hook is freed from the caval wall, it can be retrieved in a standard fashion

Laser Sheath

Similarly, Kuo et al. described the safe use of an endovascular laser sheath as a tool for thermal dissection to free embedded filters by circumferential ablation of dense fibrotic tissue [38, 39]. They reported successful retrieval for 24/25 filters (96%) using photothermal ablation and

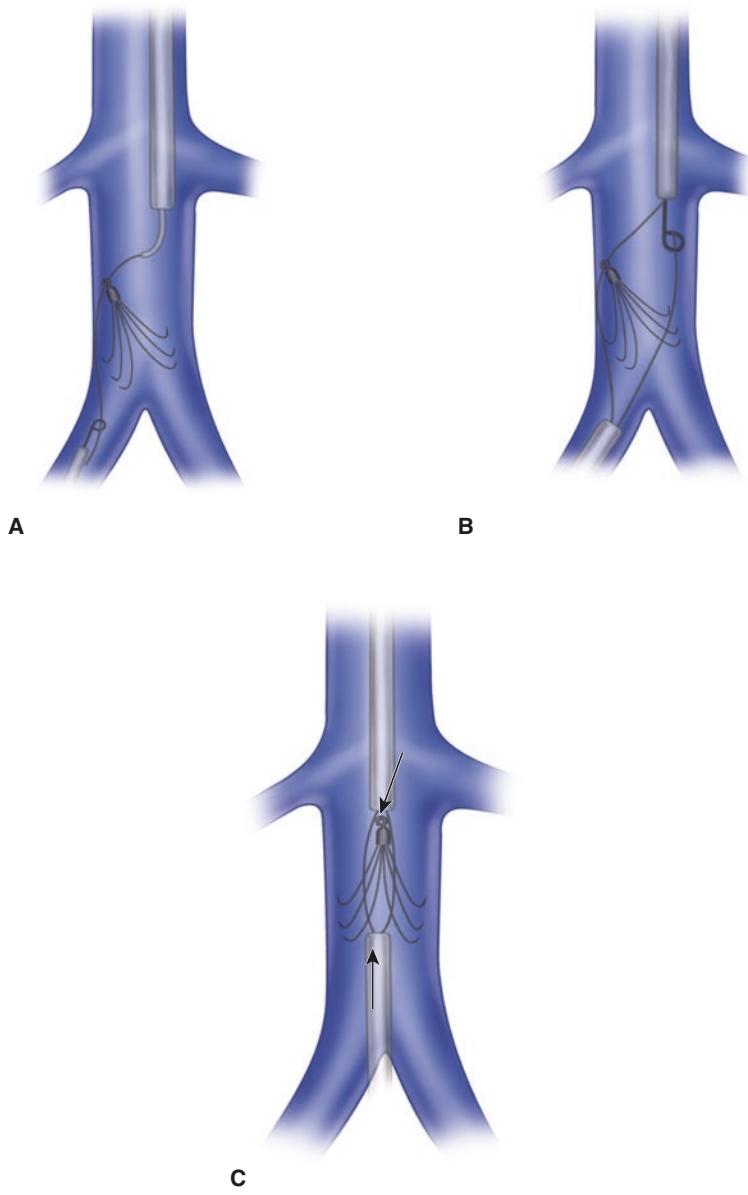

Fig. 33.10 Parallel wire technique. A wire is guided between the filter hook and caval wall from a jugular access. The wire is grasped by a vascular snare introduced from a femoral access. (**a**) Another wire is introduced from a femoral access, around the medial end of the filter, and grasped by a snare from the jugular sheath forming a "double-wire restraint" around the filter. (**b**) Both femoral and jugular sheaths are advanced providing traction on the embedded hook. (**c**) Once the hook is freed from the caval wall, it can be retrieved in a standard fashion

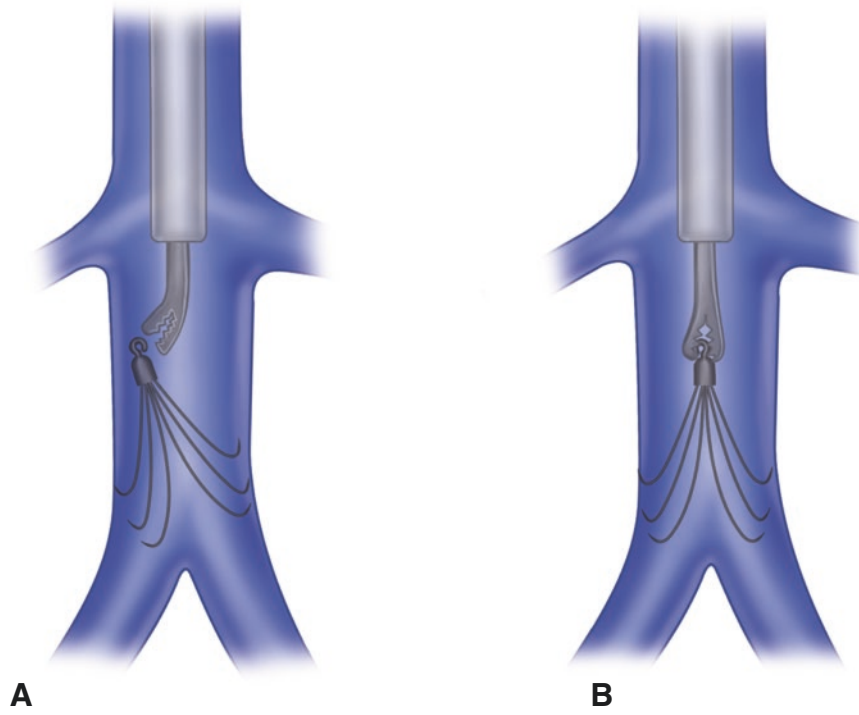

Fig. 33.11 Dissection with bronchoscopy forceps endobronchial forceps is advanced through the vascular sheath, and fibrous capsule around the filter hook is dissected. The hook of the filter is grasped with the bronchial forceps and collapsed into the sheath

reduced risk for caval injury or perforation by decreasing traction forces (Fig. 33.12). In a recent 5-year study of laser-assisted filter removal, Kuo et al. reported success rate of 98% (249 of 251 filters) with a mean implantation of 979 days. Of the 251 filters, 236 had digital force assessments, and these filters had failed high force attempts (mean force 6.7 lbs). They reported a major complication rate of 1.6% (n = 4/251) and a minor complication rate of 11.1% (n = 28/251). Major complications were acute caval injury in two cases causing hypotension and requiring endovascular stent placement. Minor complications were development of pseudoaneurysms and focal hemorrhage [40]. Equipment availability, operator training, and cost have restricted wide implementation.

It must also be noted that the abovementioned techniques of laser sheath excision and dissection using laparoscopy/endoscopy/bronchoscopy forceps are considered "off-label" usage of these devices by the FDA. In a survey of vascular specialists practice patterns regarding IVC filter retrievals, we noted that 65% (n = 168/259) and 82% (n = 212/259) of the respondents were not comfortable using bronchoscopy forceps and laser sheath for IVC filter retrieval, respectively [14].

Complications of Advanced Endovascular Techniques

Advanced endovascular retrieval techniques are very successful with filter retrieval, where standard techniques are not. The success rates range from 65 to 96% and are operator dependent in real-world practice [41, 42]. However, the high success rate comes at a cost of higher associated complications. Al-Hakim et al., in their review of 231 IVC filter retrievals, noted a higher rate of complications among those that underwent advanced endovascular retrieval (5.3%, advanced, vs 0.4%, standard) [9].

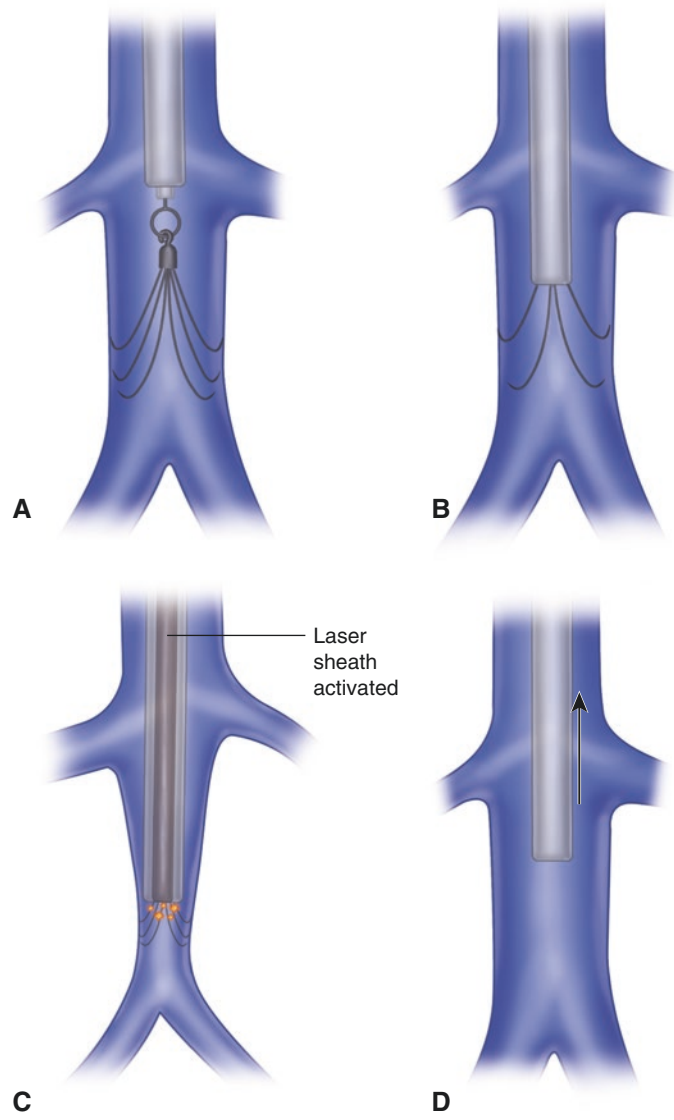

Fig. 33.12 Laser sheath excision. The hook of the filter is engaged in a standard fashion. A vascular sheath is advanced over the filter, attempting to disengage the struts. Laser sheath is activated and embedded struts are disengaged by thermal dissection. Next, the IVC filter is collapsed into the sheath and removed

Complications reported in their series are caval injury, as evidenced by contrast extravasation, severe IVC stenosis requiring balloon angioplasty, and IVC intussusception. The IVC stenosis was caused since the filter legs were coapted. These advanced endovascular procedures also have a prolonged fluoroscopy time (~34 min, advanced, vs ~5–8 min, standard), placing both the patient and operator at a higher risk of radiation exposure [41, 43]. Moreover, review of the costs of advanced endovascular techniques at our center showed that the cost of retrieval of IVC filter using advanced endovascular techniques compared to standard retrievals increase procedural cost by 91% based on billing data [43].

Open Surgery for IVC Filter Retrieval

Sometimes advanced endovascular retrieval of filters fails. In these cases, open surgical removal of the IVC filter has been described. Open surgery must be considered as an option when there is penetration of adjacent structures such as small intestine, aorta, renal veins, lumbar veins, or vertebral bodies [44]. Operations can be performed via a right subcostal incision or a midline incision, and the IVC can be exposed via kocherization of the duodenum. Connolly et al. describe two surgical techniques for open retrieval in their series of five patients (four with duodenal penetration, one with colonic penetration, and one with aortic penetration) [45]. In the first technique, filter retrieval was achieved by an IVC venotomy with appropriate proximal and distal control, and the venotomy was closed with running sutures. The second technique is used in cases where the apex of the filter is embedded in the wall of the vena cava. A purse-string stitch is secured around the IVC, allowing for hemostasis. Following this, an incision is made over the vena cava, small enough to deliver the apex of the filter, which is secured with a 0 silk tie. The silk tie is run through a 9Fr sheath, which is advanced into the IVC, capturing the filter. To facilitate ease at retrieval, penetrating filter struts must be clipped and removed flush to the IVC. The caveat to the latter technique is being a more extensive dissection and potential ligation of lumbar veins when the filter apex is embedded in the posterior caval wall. They did not report any complications or follow up outcomes in their series. In a series of six patients, Rana et al. report retrieval of two permanent TrapEase filters (Cordis Corporation, Hialeah, Fl) and four optional filters. The permanent filters were retrieved via longitudinal cavotomies. For the optional filters, a purse-string suture can be placed on the IVC wall, around the hook. The ends of the purse-string stitch are run through a 14Fr rubber tube (Argyle Vascular Tourniquet Kit, Sherwood Medical, St. Louis, MO) to provide a "Rummel tourniquet." This tourniquet can be used to apply pressure and the filter can be delivered via a stab incision. If the apex of the filter is migrated to a lumbar vein, distal control is obtained with a vessel loop, and the proximal end of the lumbar vein is ligated. The apex of the filter can be grasped with a blunt forceps via a stab incision of the vessel. In their series, Rana et al. reported IVC thrombus in one of six patients. The patient received anticoagulation for 12 months. The mean hospital stay was 3.6 days with no mortality, major complication, or PE at discharge and at a mean postoperative follow-up of 1.3 years. Manzur et al., in a series of five complex retrievals, report four open surgical and one advanced endovascular. There were two retroperitoneal and two transperitoneal approaches and one patient also required a sternotomy with cardiopulmonary bypass [46]. The mean length of hospital stay was 7 days, with four complications in three patients. One patient developed pulmonary complications requiring reintubation and subsequently developed an ileus, one patient developed acute kidney injury, and one patient had propagation of thrombus in the IVC. At 30-day postoperative follow-up, all the patients had resolution of presenting symptoms.

There are increasing reports of filter migration and strut fracture to the heart requiring midline sternotomy and cardiopulmonary bypass for extraction of the struts [46–50].

Overall, open surgery for retrieval of IVC filters is a safe option and should be offered for patients specially when endovascular retrieval is not possible. However, the recovery time and risk of complications such as bleeding, postoperative ileus, acute kidney injury, and IVC thrombus are higher, akin to that of any open surgery.

Minimally Invasive Surgery for IVC Filter Retrieval

Benrashid et al. describe a case of laparoscopic IVC filter retrieval, after two failed endovascular attempts [51]. Peritoneal access was achieved via a Veress needle (Covidien, Dublin, Ireland), and 5-mm laparoscopic ports were placed in the left upper and lower quadrants, right lower quadrant, epigastric region, and periumbilical region. Additionally, a 12-mm port must be placed in the right upper quadrant for removal of the IVC filter.

The IVC is exposed by kocherizing the duodenum. After the filter hook is visualized, a snare device can be passed through the 12-mm port to grasp the hook and a 12Fr sheath to collapse the filter. Via common femoral vein access, a vascular sheath can be placed, and a balloon is inflated under fluoroscopic guidance to assist in hemostasis.

Robotic IVC Filter Retrieval

Davila et al. reported success with IVC filter retrieval using a Da Vinci robot (Intuitive Surgical Inc., Sunnyvale, CA) in three patients. All three patients underwent at least two prior endovascular attempts, without success. After obtaining appropriate proximal and distal control, a cavotomy is performed to retrieve the filter. Filter struts that are penetrating through the wall of the IVC can be clipped. The filter is retrieved through the largest port, and the venotomy is closed in a standard running fashion [52]. Owji et al. describe an alternate robotic-assisted endovascular retrieval technique using the Magellan Robot (Hansen Medical, Mountain View, CA). In this technique, standard jugular access is obtained, and a 9Fr robotic sheath is advanced into the IVC and positioned just proximal to the filter. The filter is then captured with a snare and retrieved through the sheath [53]. The authors state that the steerability and flexibility of the robot facilitate ease at navigation of the snare and capture of the filter, compared to conventional endovascular tools.

Conclusion

The decision to retrieve an IVC filter from a patient should be individualized taking into consideration risks of VTE, bleeding, and potential difficulty of procedure. It is possible via endovascular approach in most cases. Open surgical, laparoscopic, and robotic removals have been reported, and their use relies on local expertise. The development of a dedicated tool for advanced endovascular removal may increase the effectiveness and predictability and lower the costs associated with the procedure.

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Part IV

Chronic Venous Obstruction

Wound Care Management for Venous Ulcers

34

Sheena K. Harris, Dale G. Wilson, and Robert B. McLafferty

Clinical Pearls

1. Peripheral arterial disease is present in 15–25% of patients with venous ulcers and needs to be addressed to optimize wound healing.
2. A multilayer elastic compression wrap is the first line of treatment for newly diagnosed venous ulcers.
3. Obtaining a swab culture when infection is suspected should be done after debridement is performed.

Introduction

Of the 25 million Americans with chronic venous disease, about 20% will develop a venous ulcer [1]. These ulcers can be painful and can take years to heal [2]. The result can be a profound decrease in quality of life [3] and functional status. An estimated two million working days and three billion dollars per year can be attributed to the cost of venous ulcers [4]. The cause of chronic venous ulcers results from a complex physiological cascade and requires a multimodal approach to diagnosis and management.

Venous ulcers are the consequence of untreated chronic venous hypertension. This leads to chronic edema of the lower leg with the development of dilated perforating veins and venules. The resultant alteration in microcirculation leads to leukocyte trapping and activation near the skin surface that results in tissue inflammation, destruction, and ultimately ulceration [5]. In this chapter, we review techniques for evaluation and treatment of chronic venous ulcers.

Initial Assessment

Patients with a venous ulcer should undergo a thorough history and physical examination. In brief, the history should include onset, chronicity, pain location, pain level, and whether the patient has had a lower extremity deep venous thrombo-

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Table 34.1 CEAP clinical classification showing the progression of chronic venous disease

C0: No visible or palpable signs of venous disease
C1: Telangiectases or reticular veins
C2: Varicose veins
C3: Edema
C4a: Pigmentation and eczema
C4b: Lipodermatosclerosis and atrophie blanche
C5: Healed venous ulcer
C6: Active venous ulcer

sis or trauma. Inspection of the both extremities in the supine and standing position should evaluate for signs of chronic venous disease. These include varicose veins, edema, eczema, hyperpigmentation, lipodermatosclerosis, atrophie blanche, areas of healed ulcers, and active ulcers. Wound dimensions and depth as well as the presence of eschar or fibrinous exudate should be noted [6]. Classification of chronic venous disease has been standardized using the comprehensive classification system (CEAP) (Table 34.1) [7].

Confirming Adequate Arterial Perfusion

Concomitant peripheral arterial disease in patients with venous leg ulcers has been reported to be between 15 and 25% [8, 9]. The identification of arterial occlusive disease prior to starting treatment of venous ulcers remains paramount to obtaining healing. All patients should have a thorough evaluation of their lower extremity arterial circulation. Knowing the risk factors for peripheral arterial disease, such as hypertension, diabetes mellitus, obesity, and tobacco use, will help to identify those at risk. While a pulse examination is important, it can be misleading due to signs of edema and lipodermatosclerosis. In addition, a palpable pulse does not equate to presumed normal circulation. Therefore, all patients should have a lower extremity ankle-brachial index (ABI) [9]. If ulcers on the ankle prevent cuff placement or the arteries in the lower extremity are non-compressible, then toe pressures are necessary. Patients who have a chronic venous ulcer and an ABI in the range of 0.80–1.20 (or toe pressure greater than 50 mmHg) do not need revascularization and may proceed with the next stage of therapy. Patients with an ABI <0.50 (or a toe pressure of <30 mmHg) should undergo further evaluation for peripheral artery disease and, if possible, will require some form of revascularization prior to the next stage of therapy. For those patients with ABI between 0.50 and 0.80 (or toe pressures between 30 and 50 mmHg), selective revascularization may be necessary depending on such factors as initial ulcer size (i.e., greater than 25 cm^2), chronicity of the ulcer (present greater than 1 year), whether the ulcer is recurrent, and whether an ulcer fails to show 50% healing with the next phases of therapy over 4–6 weeks [9]. The reason that revascularization must occur in those selected patients is for fear that compression therapy will worsen the ulcer due to decreasing the capillary perfusion pressure and worsening ischemia.

Eliminating Edema

Compression therapy is the cornerstone for the prevention and treatment of venous hypertension, a crucial step to healing venous ulcers [6]. The external pressure provided by compression therapy reduces venous hypertension and improves calf muscle pump performance [10]. Compression on the superficial venous system also allows for a larger volume of blood to return to the deep venous system, furthering the action of the calf muscle pump [11].

Narrowing of the venous lumen begins at a median pressure of 30–40 mmHg when the patient is sitting or standing [12]. Strength of compression is grouped into three main categories: low, or class 1, comprised of pressures less than 20 mmHg; medium, or class 2, comprised of pressures 20–30 mmHg; high, or class 3, comprised of pressures greater than 30 mmHg [13].

Compression therapy of any kind has been shown to reduce the time of venous ulcer healing compared to no compression therapy; however, compression therapy varies in type and effective-

ness. Compression wrap therapy uses layers of fabric to create increased pressure. The number of layers can range from two to four and has some degree of stretch—elastic bandages are referred to as long stretch, and inelastic bandages are referred to as short stretch. In a Cochrane analysis, multicomponent compression systems with elastic were found to be more effective than those comprised of inelastic components. The number of layers does not seem to coincide with higher pressures in that two-layer wraps have been shown to be just as effective as four-component wraps [14].

Compression stockings (considered long stretch) have been used since the 1950s to prevent and treat venous ulcers [15]. They have been shown to be more effective in healing ulcers than inelastic wraps [14]; however, no data is available on the effectiveness of compression stockings versus multicomponent compression wrap therapy with elastic. One small cohort study demonstrated, when combined with debridement and dressing changes, compression stocking therapy achieved a 97% ulcer healing rate with a median healing time of 5 months [11]. Generally, when a new active venous ulcer appears, a multilayer compression wrap is used for the first line of therapy. When the ulcer gets close to healing, the transition to compression stockings is made. For obese patients or patients who do not have the strength or means to put on a compression stocking, a short-stretch compression device, such as a CircAid (Fig. 34.1), may work well to prevent recurrence.

The usage of compression therapy by both providers and patients can vary. One German study showed that among patients with venous ulcers, compression therapy was used in only 40% [16]. Compliance, once prescribed, is also variable, with some estimated 26–41% of patients adhering to therapy [17]. Increasing use of compression therapy includes education at the provider level as well as increasing patient awareness to the importance to compliance. Patient adherence may be increased by aiding patients in donning compression therapy independently, either by education or through assist devices [18].

Fig. 34.1 CircAid

Treating Infection

Infection in chronic venous ulcers leads to an inability in wound healing which may cause enlargement of the ulcer and/or lead to systemic illness. Increased risk of infection also stems from the presence of lower extremity edema, hemosiderin deposits, and a weakened skin barrier secondary to chronic dermatitis [19]. Patient-related risk factors for infection include obesity, diabetes mellitus, immunosuppression, tobacco use, and PAD [19–21]. Infection should be suspected in the presence of frank purulence, increasing pain, erythema, foul smell, and/or an increasingly wet or weeping wound [9, 19]. Ulcer debridement to remove necrotic tissue and excessive bioburden should be performed [1]. When clinical signs of infection are present, a swab or tissue culture should be performed. If no clinical signs of infection are present, routine culture and antibiotic therapy are not warranted [9, 21]. If

performing a swab or tissue culture, it should be done after the debridement of the ulcer. Identification of colonized bacteria by routine culture has been shown to be unhelpful in guiding treatment [22–24]. Systemic antibiotic choice, which may be given intravenously or orally, should be guided by patient presentation and local antimicrobial susceptibility patterns. A large Cochrane review in 2013 found limited evidence to support both systemic and local antibiotic therapy [25]. Additionally, there was limited evidence to support the use of povidone-iodine, peroxide-based preparations, and other tropical antibiotics and antiseptics in the treatment of venous ulcers [25]. There was no evidence supporting the use of honey- or silver-based preparations in treating chronic venous ulcers. There was evidence to support the use of cadexomer iodine compared with standard therapy (compression) in terms of improved healing time [25]. Nherera et al. recently examined the use of cadexomer iodine with and without standard care, defined as multilayer compression bandaging and debridement. The results found the addition of cadexomer iodine resulted in more wounds healed at decreased cost [26]. However, when compared to silver-based preparations, hydrocolloid or paraffin dressings, there were no differences.

Venous Reflux

One of the main causes of venous hypertension is venous valvular incompetence. Valvular incompetence can be primary or secondary. Primary valvular incompetence has been associated with factors such as obesity, female gender, prolonged standing, and family history [27]. Secondary valvular incompetence can be from postthrombotic syndrome or proximal venous obstruction such as May-Thurner syndrome. Secondary valve incompetence, or postthrombotic syndrome (PTS), occurs in about one-third of patients after acute deep venous thrombosis [28].

Venous reflux is objectively diagnosed using a duplex ultrasound. Lower extremity axial veins (superficial and deep) are examined with the patient in the standing position. A cuff is placed distal to the venous segment that is undergoing duplex insonation. With rapid deflation of the cuff, venous valves should close quickly, and reversal of flow should be less than 500 ms. If reversal of flow is greater than 500 ms, then valvular incompetence is present in that segment [28].

Initial treatment of chronic venous ulcers from venous insufficiency consists of compression therapy. If there is failure of the venous ulcer to heal approximately 50% within 4–6 weeks, then venous reflux testing should be performed. Other relative indications to perform venous reflux testing include a large ulcer (>25 cm^2), a recurrent ulcer, or an ulcer that has been present for more than 1 year. When these clinical scenarios exist and superficial axial valvular reflux is present (in great saphenous vein, accessory saphenous vein, and/or small saphenous vein), operative stripping or thermal ablation in combination with phlebectomy or sclerotherapy (for branch varicosities) should be performed [6]. In a prospective randomized controlled trial comparing compression alone to high ligation and stripping plus compression, venous ulcer recurrence was found to be significantly lower in patients who underwent surgery at 1 year (12% versus 28%) [29].

Catheter-based percutaneous ablation of superficial axial venous reflux has gradually replaced open surgery as the procedure of choice. Endovenous laser ablation uses laser light that causes either water or hemoglobin absorption which then results in heat energy damage to the endothelium and closure of the vein [30]. Radiofrequency ablation uses an electrical current that, when in contact with the venous wall, causes thermal energy and resultant endothelial destruction and closure [31]. Compared to open surgery, hematoma and infection rates are significantly lower, and recovery time is shorter [32]. In a meta-analysis of randomized controlled trials, endovenous ablation has been shown to be as effective as open surgery in treatment of great saphenous varicose veins [33]. In several small cohort studies [34–36], endovenous ablation has been shown to prevent ulcer recurrence. There have been no randomized controlled trials com-

paring endovenous thermal ablation to open surgery or compression therapy on ulcer healing or recurrence [37]. Treatment with either endovenous laser or radiofrequency ablation appears to be nearly equivalent. Endovenous ablation by radiofrequency was shown in one small randomized controlled trial to have lower post-procedure pain and bruising, but there were no significant differences in patient satisfaction, adverse effects, or recurrence at 1 year [38].

Venous Obstruction

Proximal venous obstruction impeding venous return from the lower extremities can also cause venous hypertension in the deep and superficial axial veins. As with venous valvular incompetency, this can result in distension of the capillary walls, inflammation, and leakage of macromolecules into the subcutaneous tissues and dermis leading to ulcer formation [9, 20]. The most common cause of venous obstruction is postthrombotic syndrome which can arise after a past history of deep vein thrombosis (DVT) [39]. Early treatment of DVT is recommended to improve functional outcomes and decrease sequelae of postthrombotic syndrome [40]. A recent review found that catheter-directed thrombolysis plus anticoagulation improved venous patency, decreased venous obstruction, and decreased incidence of postthrombotic syndrome [41]. Interestingly, there was no benefit in reducing mortality, pulmonary embolism, or recurrent DVT [42]. The ATTRACT trial represents a large multicenter prospective randomized trial that is currently in progress and addresses the question of postthrombotic severity in patients with DVT above and below the inguinal ligament [43].

May-Thurner syndrome represents another form of venous obstruction, whereby the right common iliac artery compresses the left common iliac vein. The true incidence of May-Thurner syndrome is not known; however, approximately 50–60% of left-sided iliofemoral DVTs are secondary to right iliac artery compression of the left common iliac vein [39]. Not all people with May-Thurner syndrome will develop a DVT; however, the stenosis can cause venous hypertension. Duplex ultrasound can be useful in diagnosing the presence of May-Thurner syndrome if there is lack of respiratory phasicity in the ipsilateral common femoral vein. When considering stenting of a left common iliac vein stenosis due to May-Thurner syndrome, intravascular ultrasound is necessary to make the diagnosis because venography may be falsely negative due to compression causing "pancaking" of the vein. Patients with venous ulcers who fail to show healing of approximately 50% with compression after 4–6 weeks should have computed tomographic or magnetic resonant venography to evaluate for May-Thurner syndrome [44]. If demonstrated and then confirmed with intravascular ultrasound, venous stenting is indicated [45, 46]. Other indications in making the diagnosis for May-Thurner include presenting initially with large ulcer (>25 cm^2), having an ulcer for greater than 1 year, and having a recurrent ulcer.

Reducing Impact of Host Risk Factors

Risk factors for development of venous ulcers include age, female gender, family history [47], pregnancy, and prior lower extremity trauma. Modifiable risk factors that can improve healing and prevent recurrence include treatment of postthrombotic syndrome, obesity, calf muscle pump dysfunction, smoking, prolonged standing, and nutrition [48].

Postthrombotic Syndrome

Proximal deep venous thrombosis (iliofemoral DVT) can lead to more severe postthrombotic syndrome and usually occurs within the first 2 years [49]. About one-third of patients with venous ulcers have had a history of DVT. More importantly, early compression therapy can reduce incidence of PTS, and for proximal DVT, thrombolysis followed by stenting that is able to restore patency will reduce incidence of PTS by one-third [49].

Obesity

The incidence of varicose veins has been shown to be higher in obese individuals [50]. The increased intra-abdominal pressure which accompanies obesity may play a role in transmitting pressure to the deep venous system and causing venous hypertension. Femoral venous pressure has been found to correlate to intra-abdominal pressure as measured by bladder pressure [51]. Chronic venous disease has been shown to improve after successful weight-loss reduction surgery [52].

Calf Muscle Pump Dysfunction

Calf muscle pump dysfunction can be a critical component of venous hypertension and contribute or be the primary cause of a venous ulcer [53]. The calf muscle pump functionally attenuates with prolonged standing and progressively deteriorates with a sedentary lifestyle. Venous ulcers occurring in the presence of calf muscle pump dysfunction are typically larger and take longer to heal [54]. Calf muscle pump dysfunction can be assessed by using air plethysmography. In a small randomized controlled trial, it was shown that structured exercise improved calf muscle pump function in patients with moderate to severe chronic venous disease [55]. Patients who have evidence of calf muscle dysfunction should be encouraged to increase physical activity, and a structured physical therapy program may be indicated. Another option includes the use of a sequential leg pumping device.

Smoking

Smoking has several deleterious effects on wound healing, including decreased tissue oxygenation, decreased fibroblast activity, lymphocyte function, and epithelialization [56]. Patients with venous ulcers should be counseled on the importance of smoking cessation and offered access to support groups as well as pharmaceutical treatment.

Prolonged Standing

Prolonged standing contributes to venous hypertension by keeping the calf muscle pump static and increasing hydrostatic pressure. The number of hours standing has been shown to be a significant correlate to the development of chronic venous disease [57], particularly in women, though some smaller trials have also shown this in men [58]. Recommendations for modifying this risk factor include alternating standing periods with sitting, calf exercises, and use of compression therapy.

Nutrition

There is increasing interest in assessing nutritional status in patients with venous ulcers, as positive correlations have been made with the presence of malnutrition [59]. Deficiencies in protein [60], vitamin D [61], and vitamin C [62] have been shown to be prevalent among patients with venous ulcers. However, targeted supplementation has not shown reliable results in stimulating improved healing or prevention of recurrence. A meta-analysis of several small trials failed to show improvement with oral zinc [63], a mineral that when depleted can be associated with reduction in wound healing. Until reliable supplementation data emerges, patients with venous ulcers should be screened by history and physical exam for malnutrition. If confirmed after laboratory testing, standard nutritional supplementation should be prescribed.

Wound Care Centers

The sharp rise in the number of wound care centers over the past 25 years has brought more needed attention to the challenges of healing venous ulcers. Generally, wound care centers have better outcomes due to the entire patient workflow and experience directly center around healing the chronic wound. Multidisciplinary teams can more effectively manage the patients on a weekly basis, and services including such

things as advanced compression therapy, wider array of bandage and dressing supplies, skin substitutes, and ability to debride are readily available. This multidisciplinary approach to wound care has been shown to improve outcomes, decrease amputations, and heal wounds faster [64–66]. Wound care centers also have been shown to be more cost-effective [67]. Surgeons and in particular vascular surgeons can play a pivotal role given their unique skill set in managing chronic venous disease. A recent review looking at the establishment of wound care centers suggests that the core makeup of the physician team should include vascular, plastic, and podiatric/orthopedic surgery [66].

Conclusion

Venous ulcers are a prevalent and debilitating condition that significantly affects quality of life. Diagnosis includes a thorough history and physical examination as well as identifying venous reflux and obstruction and investigating host factors. Treatment includes assuring adequate arterial perfusion, eliminating edema, treating infection, debridement, addressing venous valvular reflux and obstruction, and optimizing host risk factors. The cornerstone of treatment remains compression therapy, and failure warrants further investigation and possible surgical or catheter-based endovenous treatment. Due to the multifaceted etiology and chronicity of venous ulcers, wound care centers can offer a better setting to provide multidisciplinary, specialized care and improve outcomes.

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May-Thurner Syndrome: Diagnosis and Management

35

Brian DeRubertis and Rhusheet Patel

Clinical Pearls

1. May-Thurner syndrome should be suspected in patients with unilateral venous symptoms specially left sided and with a negative venous ultrasound study.
2. Intravascular ultrasound is the modality of choice to diagnose and guide the treatment of MTS.
3. Iliac vein stenting is effective treatment for MTS with patency of 80–90% up to 5 years. Non-thrombotic lesions have superior patency compared to thrombotic lesions.

Introduction

Since its original description in the seminal 1957 manuscript by May and Thurner, May-Thurner syndrome (MTS) has become increasingly recognized as a pathophysiologic variant of normal anatomy in which the left common iliac vein and caval confluence are compressed by the overlying aortic bifurcation and right common iliac artery, leading to physiologic venous outflow obstruction, intraluminal venous wall abnormalities, and ultimately deep venous thrombosis due to these aberrations. While venous compression of the left common iliac vein is commonly seen as an incidental finding on contemporary axial imaging, most persons with this compression are asymptomatic and only a small percentage go on to develop symptoms associated with MTS. Of those that are affected, however, the symptoms can be significant and range from unilateral leg swelling to iliofemoral deep venous thrombosis. Both recognition of this entity and options for treatment have expanded in recent years, largely due to the role of endovascular therapy, which has virtually replaced open surgical options for this uncommon clinical entity.

Historical Perspective

In their landmark manuscript in 1957, Robert May and Josef Thurner not only confirmed earlier observations that lower extremity deep venous thrombosis occurred with a "sinistral," or left-sided, predominance but also offered pathologic basis for this clinically observed phenomenon [1]. Over 100 years before this report, Virchow had first observed and reported that iliofemoral DVT was five times more likely to occur in the left leg than the right [2]. Additionally, a prior report by McMurrich in 1908 had described the presence of intraluminal webs in the iliac veins, noting them in 33 of 107 unselected autopsy specimens, and sug-

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gested this finding as an etiologic factor in deep venous thrombosis [3]. In "The Cause of the Predominantly Sinistral Occurrence of Thrombosis of the Pelvic Veins," May and Thurner attributed this risk of left-sided laterality of deep venous thrombosis to "venous spurs" which resulted to as an inflammatory response to the chronic overlying pulsations from the right common iliac artery [1]. In 1967, Cockett further validated and expanded upon the findings in May and Thurner's original manuscript with the observation that 65% of patients with iliofemoral deep venous thrombosis (DVT) had evidence of left common iliac vein (LCIV) compression on venography and that the left leg was affected in 83% of unilateral cases [4]. Importantly, he also noted multiple anatomical variations that accounted for compression of the LCIV, vena cava, left external iliac vein, and right common iliac vein—clinical entities that are even less common than May-Thurner syndrome but are being increasingly recognized due to modern imaging techniques. Most of these variations, as well as May-Thurner syndrome itself, remained poorly recognized and largely untreated for many decades, until contemporary imaging techniques demonstrated these findings with increasing frequency and endovascular therapy began offering effective treatment associated with minimal morbidity.

Prevalence

The incidence of patients presenting with unilateral leg swelling due to May-Thurner syndrome in the general population is unknown, in large part due to the uncommon nature of this condition. However, based on axial imaging of normal individuals or patients undergoing imaging for nonvascular reasons, there is growing evidence that asymptomatic compression of the left common iliac vein is quite common. In a study of consecutive patients undergoing computed tomography scans for non-venous complaints, left common iliac vein compression resulting in at least 25% luminal compromise was found to occur in 66%, while greater than 50% compression was seen in 24% [5].

Considering the purported causative link between deep venous thrombosis and iliac venous compression or intraluminal webs and spurs, it is not surprising that patients with left iliofemoral deep venous thrombosis have a relatively high incidence of left iliac venous compression consistent with a diagnosis of May-Thurner syndrome [4, 6]. The true incidence of LCIV compression in iliofemoral DVT is likely underreported, as most patients with acute deep venous thrombosis historically have had this diagnosis confirmed by duplex ultrasonography without other imaging modalities. This notion is supported by at least one study of patients with left iliofemoral DVT, in which those patients who had more extensive imaging than duplex ultrasound alone were frequently found to have LCIV stenosis, occurring in up to 55% of cases [6]. Because venous compression syndromes can exist in both genders and all age groups, patients with extensive iliofemoral deep venous thrombosis, especially those with unprovoked thrombosis, generally warrant pelvic imaging to assess for the possibility of correctable causes of the deep venous thrombosis and rule out lesions putting them at heightened risk of recurrent thromboembolic events.

In addition to playing a direct role in unilateral left leg swelling and acute left iliofemoral deep venous thrombosis, iliac venous compression likely has an important role in the heterogenous group of patients with chronic venous disease. In a recent large series of 1000 patients with venous disease of all CEAP classifications who underwent intravascular ultrasound (IVUS) imaging, non-thrombotic compression of the common iliac vein was noted in 53% of cases and postthrombotic stenosis in 40% [7]. When looking specifically at patients with symptoms and physical exam findings consistent with postthrombotic syndrome in conjunction with deep and superficial axial vein reflux, there appears to be a high likelihood of iliac vein compression, and correction of this compression and other postthrombotic lesions may allow for resolution of symptoms of chronic venous disease. In 2010, Raju and colleagues reported a series of 504 patients with chronic venous insufficiency suffering from

lipodermatosclerosis and venous ulcers who underwent iliac vein stenting for either iliac vein compression or postthrombotic lesions without concomitant treatment of superficial axial vein reflux. With iliac stenting alone, the ulcer healing rate and freedom from ulcer recurrence at 5 years in CEAP class 5 limbs were 54% and 88%, respectively, and symptom improvement occurred in 55% of patients presenting with leg swelling [8]. These data suggest that while the classic presentation of MTS with unilateral left leg swelling is an uncommon clinical entity, pathologic compression of the left common iliac vein occurs frequently across a wide spectrum of venous disease.

Pathophysiology

Although there are several anatomic variants of May-Thurner syndrome, this condition is traditionally defined as compression of the left common iliac vein against the fifth lumbar vertebral body by the right common iliac artery as the artery crosses in front of the vein. The exact point of maximal compression can vary from patient to patient, sometimes affecting solely the left common iliac vein but other times leading to significant compression of the caval confluence as well.

In addition to the venous flow abnormalities intuitively attributed to the significant compression of these structures, chronic compression can also lead to structural changes within the vein. Chronic pulsation of the artery is thought to cause a significant inflammatory response within the vein, ultimately leading to elastin and collagen deposition intraluminally and resulting in intimal fibrosis and the formation of venous spurs and webs as originally described by May, Thurner, and McMurrich [1, 3]. These pathologic changes can ultimately result in significant luminal narrowing leading to development of unilateral chronic leg swelling and contributing to venous thrombosis. External compression of the iliac vein is therefore a ubiquitous finding but not the only contributing factor.

Still, the clinical significance of MTS in chronic venous disease remains a matter of debate, as up to 50% of asymptomatic patients have findings of LCIV compression on axial imaging or IVUS. What makes these lesions symptomatic in some and silent in others is not well understood. MTS may be thought of as a "permissive" condition that predisposes a person to thrombosis when a "second hit" occurs, such as initiation of oral contraceptives, prolonged immobility, malignancy, or hypercoagulable state. The presence of intraluminal webs and external compression may contribute to increased morbidity from conditions such as new distal DVT, heart failure, saphenous vein valvular incompetence, cellulitis, and lymphedema. Recognition of the role that venous compression syndromes can play in any patient with leg swelling or iliofemoral DVT should therefore not be neglected.

Additional anatomic variants can produce compression at the IVC, right common iliac vein, and left external iliac vein by the right common iliac artery or left hypogastric artery as it crosses over the vein into the pelvis. Similarly, the right hypogastric artery can sometimes lead to pathologic venous compression of the right external iliac vein by the same mechanism.

Clinical Presentation

Previously considered to be primarily a disease of women and isolated to the left leg, more recent studies have found that venous compression syndromes occur in both men and women and can also involve the right leg. In one study of asymptomatic individuals, venous compressive lesions were found as frequently in men, but women were found to have higher degrees of stenosis [5]. In a large modern series of symptomatic patients with MTS without reflux, the female to male ratio was 4.7:1, with a left to right preponderance of 3:1 [9].

May-Thurner syndrome most commonly presents in the second to fourth decade of life and may manifest with either of two classic presentations: (1) unilateral leg swelling or (2) acute iliofemoral deep venous thrombosis. Roughly half of patients treated at our institution presented with chronic unilateral leg swelling. The severity of

this swelling can range considerably, from barely noticeable asymmetry due to trace left leg edema to severe swelling involving the entire lower leg and thigh. Most patients presenting with unilateral leg swelling report a duration of symptoms of many months, but on careful questioning, many of these patients have been aware of asymmetry between their right and left legs for years, even noting lifelong differences in the way their shoes fit on the left and right feet. The degree of disability these symptoms cause is also quite variable, with some patients noting only cosmetic concerns but most reporting chronic symptoms of heaviness, aching, and vague discomfort that is typical of patients with venous reflux as well. In severe cases the swelling is associated with venous claudication, in which the leg becomes full or tight with exercise due to the venous outflow obstruction and resultant engorgement of left leg veins. Most patients will report the need to elevate the affected leg periodically to relieve symptoms, and many have previously been prescribed compression therapy at some point in their lives, but seldom have they complied with a full trial of daily stocking usage in our experience.

May-Thurner patients who present with acute deep venous iliofemoral thrombosis also tend to present between the second and fourth decade of life but also can present at older ages, especially in conjunction with another prothrombotic risk factor, such as oral contraceptive use or a period of prolonged immobility. In the acute presentation, accounting for between 18 and 49% of cases, patients typically present with sudden onset of leg pain, swelling, and edema [10], and the diagnosis of deep venous thrombosis is typically confirmed by duplex ultrasound. While the deep venous thrombosis in these cases can be isolated to the iliac venous system, most commonly patients with thrombotic MTS suffer relatively extensive deep venous thrombosis involving the iliac and femoral segments, and symptoms seem to be more severe than patients presenting with acute deep venous thrombosis in the absence of compression syndromes. Because disease occurs as a result of compression against the lumbar vertebrae, patients with scoliosis and dilated perimedullary veins should be suspected of having MTS [11]. Spontaneous iliac vein rupture and retroperitoneal hematoma have also been reported as a rare but life-threatening acute presentation of MTS.

While the classic presentation of May-Thurner syndrome includes either unilateral leg swelling or acute left iliofemoral deep venous thrombosis, there is growing evidence that a certain percentage of patients with chronic venous occlusive disease and postthrombotic syndrome are patients whose initial thrombotic event was due to May-Thurner compression of the iliac vein, and this diagnosis had gone unrecognized at the time. These patients may exhibit a range of clinical findings, including chronic leg pain and other symptoms associated with deep system valvular incompetence, varicose veins, recurrent superficial vein thrombophlebitis, lower leg hyperpigmentation, lipodermatosclerosis, and even venous ulceration (which usually localize to the "gaiter" distribution above the medial malleolus). While the contribution of May-Thurner compression of the left common iliac vein in these patients was previously thought to be insignificant, modern imaging and endovascular treatment options have led to an increased recognition of this diagnosis in this patient population. Patients with these conditions, especially when unilateral, should therefore undergo evaluation of the iliac system to assess for the contribution of these compression syndromes to their chronic venous disease.

Diagnostic Imaging

Appropriate diagnostic testing should be considered in all patients with unilateral leg swelling and/or unilateral DVT as routine history and physical exam cannot rule out May-Thurner pathology. Upon initial evaluation of patients presenting with unilateral leg swelling, duplex ultrasonography is also performed to rule out deep venous thrombosis, superficial or deep venous reflux, and other venous pathology. Ultrasound is

significantly limited in the case of identifying iliac venous pathology, as the position of iliac veins deep in the pelvis makes them difficult to adequately visualize in most patients. However, evaluation of venous waveforms, including comparison between the right and left common femoral waveforms, can provide evidence of unilateral venous outflow obstruction. In cases of severe compression or occlusion of the left common iliac vein, continuous waveforms without respiratory phasicity can often be appreciated.

Axial computed tomographic venography (CTV) or magnetic resonance venography (MRV) is highly sensitive and specific for detecting venous compression syndromes and pelvic or lower extremity deep venous thrombosis. They also have the advantage of being noninvasive and operator independent. These modalities can rule out other intra-abdominal or pelvic pathology, such as malignant compression of the venous system, and can delineate congenital venous abnormalities that can mimic May-Thurner syndrome. These modalities are widely available and, in the case of MR venography, can be performed without the need for ionizing radiation. However, the static nature of these imaging techniques does not allow for assessment of the physiologic impact of iliac vein compression because they do not show real-time flow patterns.

The authors therefore favor the use of detailed contrast venography in conjunction with intravascular ultrasound (IVUS) to reliably identify abnormal venous flow patterns and precisely pinpoint the location and degree of maximal compression. Venography in only an anteroposterior view will show flattening and widening of the left CIV but will not demonstrate an actual narrowing of the vein in the majority of cases. Therefore, venography in the left anterior oblique and cranial caudal views is necessary to visualize the narrowing. Venogram findings that suggest a pathological degree of compression of the left common iliac vein are those that suggest outflow obstruction at the level of the junction between the left common iliac vein and the caval confluence and include (1) contrast stagnation in the left iliac venous system compared to the right, (2) contralateral cross-filling to the right iliac venous system via hypogastric collateral system (Fig. 35.1), and (3) extensive retroperitoneal and pelvic collateralization (Fig. 35.2). Any of these findings suggest a pathophysiologic degree of compression of the left common iliac vein and tend to predict successful improvement or complete amelioration of symptoms following stenting. The best determinant of the degree of compression of the vein by the overlying artery is provided by IVUS, which allows for intraluminal measurement of vein diameters and cross-sectional area and allows for demonstrating the precise location of the area of maximal compression, and thus is helpful at guiding accurate stent placement. Some have proposed stenting of the left common iliac vein based on a finding of >50% reduction in cross-sectional area at the region of compression, although we believe optimal assurance of improvement with stenting occurs in patients with both this cross-sectional area reduction and the venogram findings described above. Venography and IVUS typically require only local anesthesia and should be done safely on an outpatient basis.

Treatment

While MTS and its sequelae were historically treated with open surgical bypass procedures (albeit rarely), the current treatment choice is minimally invasive, venography- and IVUS-guided, endovascular stenting. Beginning with the development of lytic techniques in the early 1990s, the use of catheter-directed thrombolysis and venography for the treatment of iliofemoral DVT frequently identified compression of the left CIV and simultaneously offered the ability to treat the underlying conditions with iliocaval stenting. With the widespread adoption of advanced endovascular techniques, iliac vein stenting for symptomatic MTS leading to acute iliofemoral deep venous thrombosis, as well as a host of other chronic venous occlusive lesions, has now become standard practice in most centers.

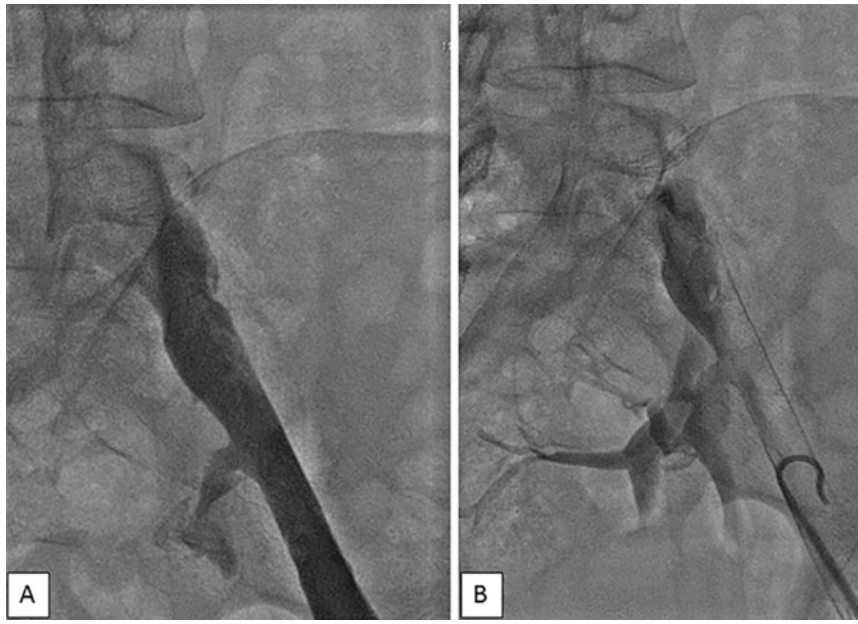

Fig. 35.1 Venogram showing slow flow of contrast across the origin of the left CIV (**A**) and delayed filling of transpelvic collaterals (**B**)

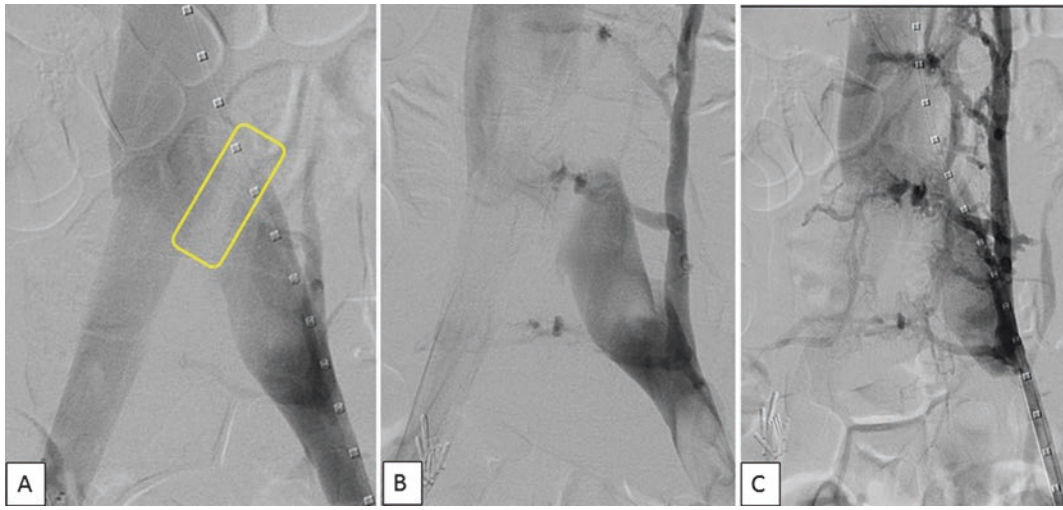

Fig. 35.2 Pelvic venogram demonstrating brisk filling and washout on the right side but slow flow on the left related to compression (**A**—*yellow rectangle*). Contrast in the left iliac veins fills retrograde into paravertebral ascending network of veins (**B**). There is persistent contrast in the left CIV that is slowly washing through the collaterals back into the IVC beyond the lesion, while contrast washed immediately from the right iliac veins into the IVC (**C**)

Any treatment should be preceded by thorough history and physical exam that subsequently guides appropriate diagnostic imaging. Hypercoagulable workup should be done when any underlying coagulopathy may be suspected, as genetic thrombophilias can dictate anticoagulation management in some patients undergoing stenting for MTS.

For those patients with non-thrombotic MTS presenting with symptoms of mild unilateral left leg swelling, a trial period of daily compression stocking use, exercise program, weight loss, and other conservative measures is appropriate and should be considered first-line therapy after initial evaluation with duplex ultrasonography. Daily use of stockings can control many of the symptoms and may eliminate the need for stent implantation in compliant patients. Patients with severe or debilitating symptoms, or those that have failed a trial of compression therapy, should undergo venography and IVUS assessment of the iliac venous system, often with the intention of stenting at the same setting if appropriate.

Venography and IVUS can be performed under local anesthesia in an outpatient setting, although conscious sedation can be helpful if stenting is planned due to the associated back pain that often accompanies stent placement. Access for therapeutic interventions is guided by duplex ultrasound, which is used to identify a non-diseased segment of femoral or common femoral vein. For non-thrombotic MTS with unilateral leg swelling, antegrade duplex-guided access is generally performed at the common femoral vein, although patients with previously unrecognized deep venous thrombosis may have common femoral vein or femoral vein scarring that necessitates puncture of the femoral vein at the mid-thigh level or popliteal level. In anticipation of stent implantation, the puncture should be done below all diseased segments to allow for stenting of all diseased segments of vein, including across the inguinal ligament if necessary.

Initial venograms are obtained after venous access is achieved, observing for the venogram findings described above, including iliac vein contrast stagnation, extensive collateralization, and contralateral cross-filling to the right iliac circulation. Our practice includes selective catheterization of the contralateral right iliofemoral venous system via left femoral access, followed by simultaneous contrast injection within the diagnostic catheter in the right iliac circulation and the left femoral sheath to compare flow patterns bilaterally (Fig. 35.3). Next, wire access is established across the left common iliac vein into the inferior vena cava, and IVUS is used to assess cross-sectional area of the left iliac system and to identify the point of maximal compression of the left common iliac vein. If proceeding with stent implantation, the sheath is upsized to an appropriately large sheath for stent delivery (generally 10Fr for braided stainless steel stents), and the patient is anticoagulated with 100 units/kg of intravenous heparin.

Choosing the proper stent size is based upon IVUS diameter measurements of the compressed vein and also the proximal vein segment, which is an important anchor point for the stent. Oversizing 10–20% is appropriate, and undersizing should be avoided as it may lead to stent migration or embolization. In patients with isolated compression of the distal left CIV and no evidence of postthrombotic scarring, stents are placed from the normal-appearing proximal segment of the left common iliac vein to the caval confluence. It is critical to extend the stent at least 1–2 cm beyond the point of maximal compression, as determined by IVUS. This generally includes extension of the stent into the inferior vena cava by at least 1 cm, which is rarely of any consequence to the flow through the right iliac system. Our group exclusively uses braided stainless steel stents, typically in diameters of 16–20 mm, for iliac vein stenting. These stents perform well in this location but have reduced radial force at the ends, thus the requirement to extend the stent into the vena cava (Fig. 35.4). While there are self-expanding nitinol stents specifically designed for venous stenting under investigation in the USA, these are not yet commercially available. In patients found to have postthrombotic scarring of portions of the iliac or common femoral veins, it is generally recommended that all diseased areas be stented to avoid stent thrombosis due to poor venous blood flow. Following stent implantation, balloon angioplasty is used to help stent expansion and achieve adequate wall apposition (Fig. 35.5). Completion venography and IVUS imaging should be performed subsequently to evaluate luminal gain and stent apposition to the vein wall (Fig. 35.6).

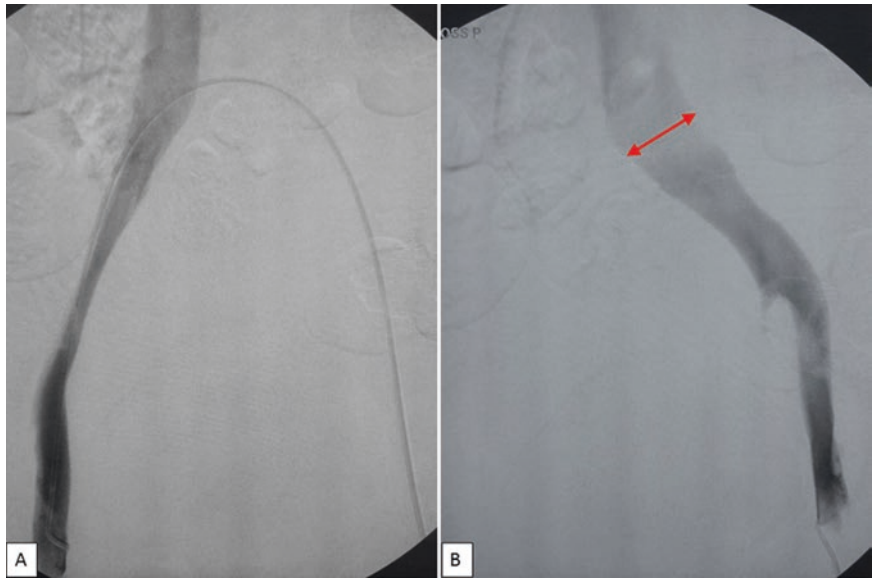

Fig. 35.3 Diagnostic venogram technique for evaluation asymmetry in venous flow patterns between the right and left iliac veins. Left common femoral access with selective cannulation of the contralateral right iliac system (**A**) allows comparison of flow rates by simultaneous contrast injection through the catheter in the right iliac system (**A**) and the left femoral sheath (**B**). While there is some flattening and widening of the left common iliac vein (**B**, *red arrows*) consistent with compression of the vein, there were symmetric flow patterns in both iliac systems and absence of significant pelvic collaterals in this patient

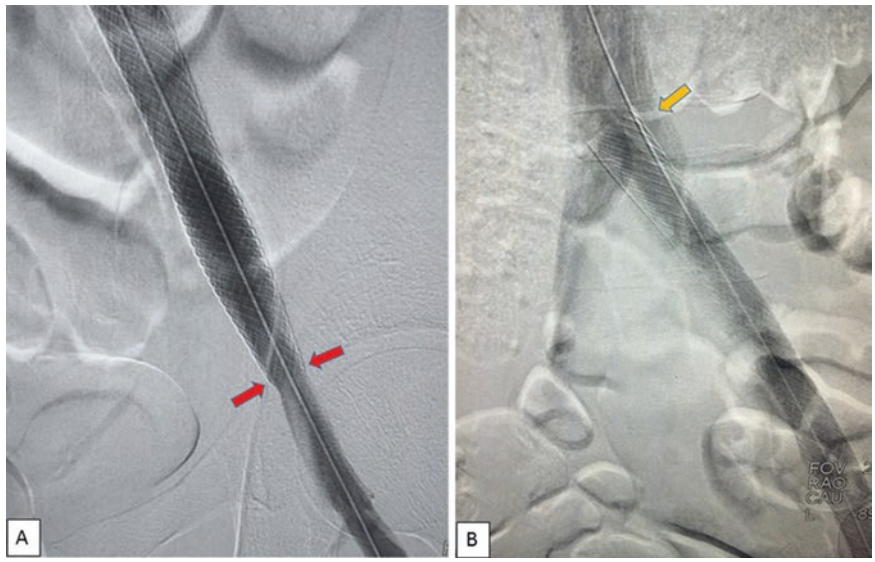

Fig. 35.4 Iliac vein stenting into the iliac femoral vein junction (**A**—*red arrows*). Stent protruding into the IVC beyond the lesion centrally (**B**—*yellow arrow*)

In thrombotic May-Thurner patients presenting with acute iliofemoral DVT, lysis or pharmacomechanical thrombectomy is required prior to treatment of the underlying venous compression pathology. Venous access in these cases is typically via the popliteal vein with the patient

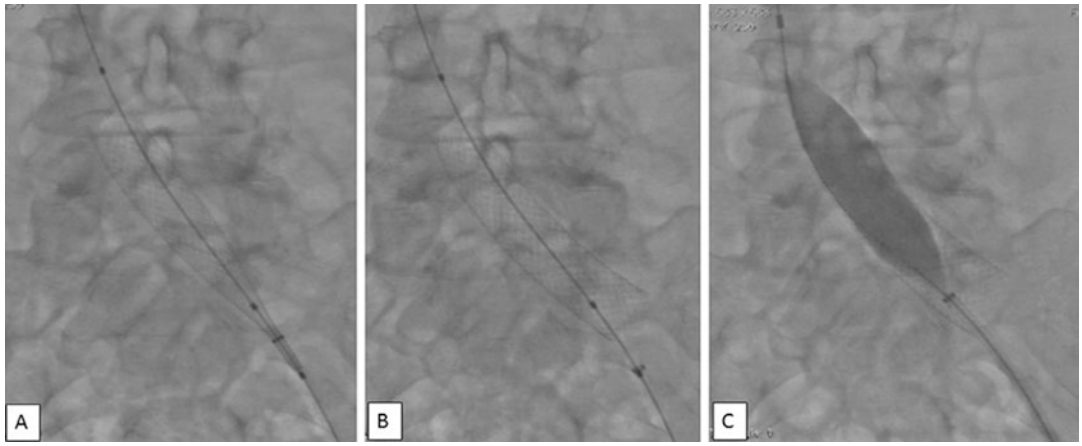

Fig. 35.5 Deployment of self-expanding stent into the left CIV (**A**, **B**). Balloon post dilatation (**C**)

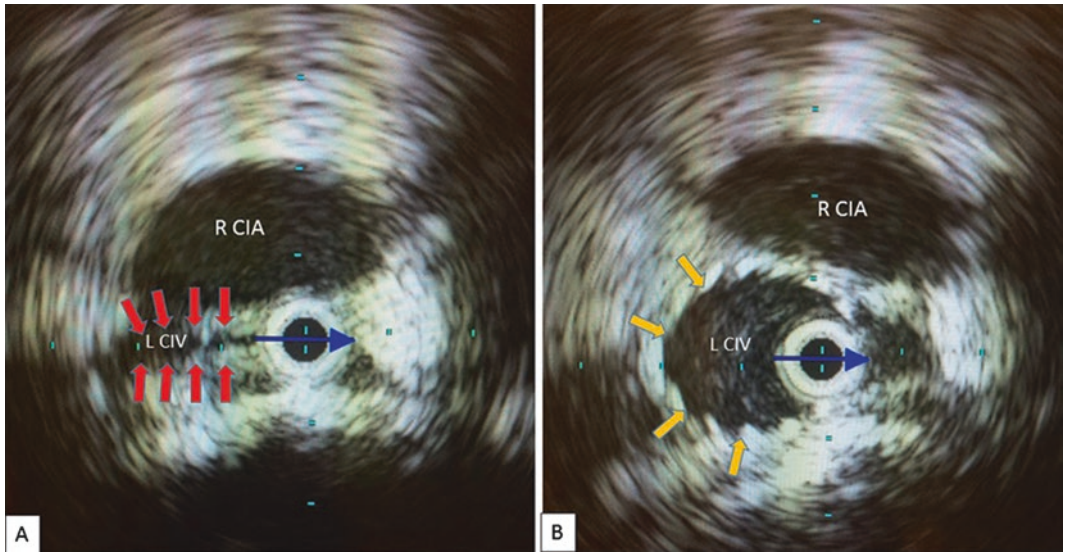

Fig. 35.6 Intravascular ultrasound (*blue arrow*) demonstrating left CIV compression (**A**—*red arrows*) by the overlying R CIA. The lesion is expanded after stenting (**B**—*yellow arrows*). L CIV = left common iliac vein; R CIA = right common iliac artery

in the prone position to access the venous system below the lower extent of the thrombus burden. For patients with acute deep venous thrombosis and symptoms of less than 1-week duration, an attempt of a single-session clearance of the thrombus with pharmacomechanical thrombectomy is reasonable, generally utilizing the AngioJet system (Boston Scientific, Minneapolis, MN) in the "power pulse" mode in which the thrombus is laced with 10 mg of tissue plasminogen activator, followed by aspiration of the lysed thrombus after a 10–20-min dwell time. For patients with a longer interval between initial symptom onset and treatment, we have noted less success with single-session thrombus clearance attempts and therefore recommend overnight catheter-directed thrombolysis, typically at tissue plasminogen activator drip rates of 0.5–1.0 mg/h. Following clearance of thrombus, venographic and IVUS evaluation for May-Thurner compression

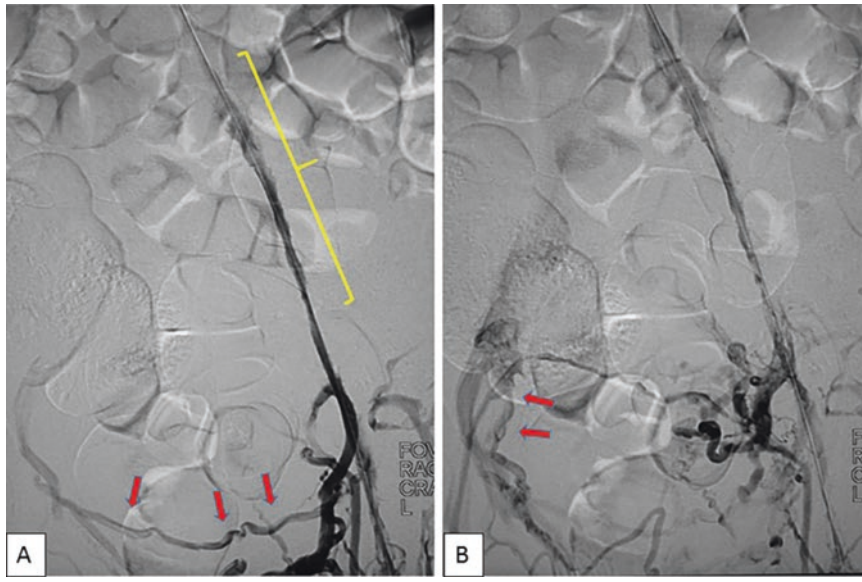

Fig. 35.7 Pelvic venogram demonstrating chronically collapsed and atretic left iliac venous system (*yellow bar*) with trans-pelvic collaterals (**A**—*red arrows*). The trans-pelvic collaterals fill the contralateral right iliac veins (**B**—*red arrows*)

of the left common iliac vein is nearly identical to that discussed for non-thrombotic May-Thurner patients, with the caveat that these patients are more likely to have additional postthrombotic occlusive lesions, and these lesions from the common femoral vein (even below the inguinal ligament) up to the caval confluence should be stented if they are flow limiting (Figs. 35.7 and 35.8).

Anticoagulation with heparin is performed intra-procedurally, with activated clotting times (ACT) of 250–300 desired prior to stent implantation. Postoperatively, aspirin 81 mg daily and clopidogrel 75 mg daily are prescribed to all stented patients for a period of 3 months, at which point we favor single antiplatelet therapy with aspirin alone. In patients with a history of hypercoagulable state or those treated with lysis for acute DVT before correction of the MTS lesions, appropriate systemic anticoagulation is continued according to national guidelines. Oral opioid analgesics and muscle relaxants are prescribed perioperatively for pain control, as oftentimes patients complain of lower back pain within the first 1–2 weeks after stent implantation.

Perioperative complications are infrequent, with the most common being back pain that can be managed with oral analgesics and muscle relaxants as noted above. Access site complications, including puncture site hematomas, may occur in the setting of full anticoagulation and antiplatelet therapy, although these are uncommon complications that require no treatment in most cases. The rate of complications has been reported to be as low as 0.3% in large series of iliac vein stenting [12].

Post-intervention, patients are imaged with duplex US to confirm patency of the iliac venous system within 2 weeks, as our experience suggests that patients that lose patency tend to do so in the early postoperative period due to technical factors, and if these are identified early, the patient can undergo lysis and correction of the inciting issue. Thereafter, patients are followed at 6 months and then yearly with duplex ultrasonography and assessment of residual symptoms. Patients generally experience significant improvement shortly after stenting, but ongoing clinical improvement can continue to be seen for up to 1 year.

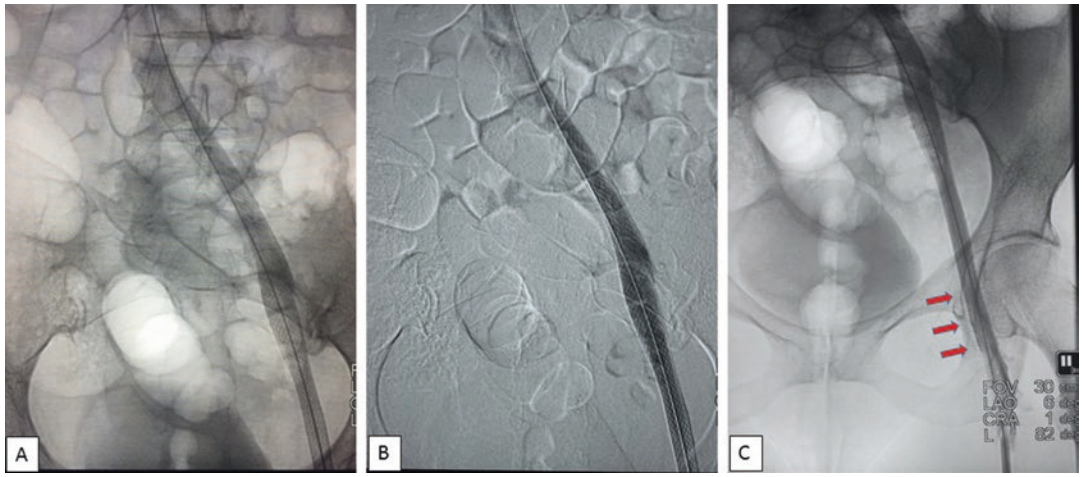

Fig. 35.8 Iliac vein stents with brisk flow into the IVC and resolution of collaterals (**A**, **B**). Stent extends into the common femoral vein (**C**—*red arrows*)

Outcomes Following Iliac Vein Stenting for May-Thurner Syndrome

The paradigm shift toward endovascular treatment of May-Turner patients is now a decade and a half old, with a growing library of evidence to support not only acute endovascular thrombus clearance strategies in thrombotic May-Thurner syndrome but also the effectiveness of stenting as a definitive treatment of iliofemoral compression.

Raju and Neglen have published widely on iliofemoral stenting for a broad range of obstructive venous lesions, beginning with a publication on their early experience in 2000, establishing the technique's safety and good short-term outcomes. The study of 77 patients showed a technical success rate of 97% and primary and secondary patency rates of 82% and 92%, respectively, at 1 year [13]. Followed further to an average of 30 months by the same group, a cohort of 610 limbs stented for nonmalignant obstructive lesions of the iliofemoral and caval venous system had an overall primary patency rate of 67%, assisted primary patency rate of 89%, and secondary cumulative primary patency rate of 93% at 6 years [12].

In congruence with the publication of these encouraging results, Baron and colleagues first described iliac vein stenting as a safe and effective method of treating May-Thurner syndrome specifically [14]. Since that time, multiple studies have demonstrated the efficacy of endovascular intervention in May-Thurner syndrome, establishing percutaneous stenting as the primary mode of treatment for these patients. A series of 36 patients undergoing iliac venous stenting from the Cleveland Clinic in 2011, in fact, showed that patients stented for a diagnosis of May-Thurner syndrome had higher patency rates than those stented for malignant compression, thrombophilia, or other causes of iliac vein disease. In the 15 patients for whom May-Thurner syndrome was identified as the etiology of iliac vein obstruction, there was 100% primary patency at 24 months compared to 78% for the entire group [15].

A relatively large retrospective review from the University of Pittsburg again demonstrated favorable stent patency rates and further demonstrated persistent symptom resolution in May-Thurner syndrome patients treated endovascularly. Seventy patients (77 interventions) with May-Thurner syndrome were evaluated as two separate groups: postthrombotic patients (56 interventions) and de novo leg swelling patients

without acute DVT (21 interventions). At a median follow-up of approximately 2 years, symptom resolution persisted in 93% of patients in the postthrombotic group and 96% of patients in the de novo leg swelling group. Primary and secondary patency was 91% and 98% at 3 years in postthrombotic patients and 91% and 91% in de novo leg swelling patients. In both groups, patients experienced symptomatic relief that mirrored stent patency, underlying the importance of long-term stent patency for durable treatment [16].

Further analysis of endovascular treatment in cases presenting without acute DVT reveals high technical success rates and few complications; however, permanent symptomatic relief may be variable between patients. A study of 34 patients from the University of Chicago in 2016 showed a 100% technical success rate with no major complications and 100% stent patency at 1 year. Even with these results, only 62% of patients with edema and 88% of patients with pelvic pain experienced clinical improvement. Two patients with edema, who had initially reported improvement, subsequently returned to their baseline level of swelling within 1 month [17]. Dr. Raju published similar results as part of a larger series, in which 196 patients underwent stenting for chronic venous disease attributed to non-thrombotic May-Thurner physiology. Stent patency at 5 years was 82%, and significant improvement of pain and swelling was 78% and 55%, respectively [8]. While other series have reported higher response rates in patients treated for non-thrombotic May-Thurner syndrome, this data certainly suggests that clinical outcomes can be variable and may be dependent on patient presentation and symptom chronicity, although the overall results of endovascular treatment of May-Thurner syndrome appear quite favorable.

As discussed previously, in the case of thrombotic MTS presenting with acute iliofemoral DVT, patients must first undergo acute thrombus removal. Although no studies have compared catheter-directed thrombolysis (CDT) versus pharmacomechanical thrombectomy (PMT) specifically in the setting of MTS, both techniques have been shown to have similar rates of thrombus removal. In a 2006 study of 98 interventions at Baylor College of Medicine, complete thrombus removal occurred in 70% and 75% of the CDT and PMT groups, respectively. Minor access site complications were observed in two patients in both groups. Notably, CDT was associated with longer ICU stay and greater overall cost to the hospital, and thus PMT may have some potential advantages over CDT, at least in patients whose duration between symptom onset and interventional management is short [18].

Following thrombus removal and stenting in the thrombotic May-Thurner syndrome patients, recent studies demonstrate both long-term stent patency and symptom relief. A 2014 study of 61 patients showed one 1- and 6-month and 1-, 2-, 3-, and 5-year primary patency rates to be 96.7%, 95.1%, 91.8%, 90.2%, 88.5%, and 85.2%, respectively. Stent occlusion occurred on average 1 year after the procedure. Although the incidence of postthrombotic syndrome was 11.5%, no patients reported venous claudication, discoloration, varicosities, or ulcerations, and only 4 (6.5%) patients reported persistent limb swelling [19]. Similar results were reported in a series of 51 patients who underwent thrombolysis and iliac vein stenting following acute DVT due to MTS. Primary patency was 84.3% after 2 years, and at a median follow-up of 16 months, only 8% of patients had recurrent thrombotic occlusions [20]. Postthrombotic syndrome and recurrence of thrombo-occlusive disease certainly remain a concern in patients treated endovascularly, as recurrent thrombosis may range from 4% to 11% [19–21]. However, the great majority of these patients, between 81 and 92%, have complete or partial symptomatic relief of their lower extremity edema [16, 19, 22].

Overall, despite differences in treatment modalities and underlying disease in the published literature, both thrombotic and non-thrombotic patients appear to benefit from high stent patency rates and a high degree of symptom amelioration following iliac vein stenting. A summary of stent patency in the largest studies of endovascular intervention for MTS is presented in Table 35.1 [16, 17, 19–24].

Table 35.1 Patency rates of iliocaval stenting for thrombotic and non-thrombotic May-Thurner syndrome from large contemporary series

Author	Year	Thrombotic/ non-thrombotic	No. of interventions	Median follow-up	Primary patency (%)	Secondary patency (%)
Xue	2014	Thrombotic	68	5 years	85.2	
Park	2014	Thrombotic	51	2 years	84.3	
Zhu	2014	Thrombotic	26	1.5 year	96	100
Igari	2014	Thrombotic	8	1.33 year	75	87
Ahmed	2016	Non-thrombotic	34	1 year	100	
Hager	2013	Both	70	3 years	91	95/91
Liu	2014	Both	48	1 year	93	
Goldman	2016	Both	16	3 years	79	89

When looking at the differences between patients with thrombotic and non-thrombotic May-Thurner syndrome, a few common themes emerge in the published literature. While both groups do well with endovascular treatment, stent patency rates tend to be lower and recurrent thromboembolic events tend to be higher in the thrombotic May-Thurner patients compared to those non-thrombotic May-Thurner patients presenting with leg swelling. Considering that a significant proportion of thrombotic May-Thurner patients have additional contributing factors to their thromboembolic events, this finding is not surprising. Hypercoagulability is not an uncommon diagnosis in this patient population, and it is reasonable to consider that inappropriate management of this risk factor will leave these patients at greater risk of thrombotic complications [15–17]. Additionally, patients who suffer a deep venous thrombosis are sometimes left with postthrombotic lesions in the iliocaval and infrainguinal femoral venous circulation, and these residual lesions indicate a larger volume of disease that may portend toward recurrent events and loss of patency.

When looking specifically at complete resolution of leg swelling, data in the literature are somewhat inconsistent but seem to suggest that patients with thrombotic MTS may have a higher likelihood of complete symptom resolution after treatment compared to non-thrombotic patients. In the studies detailed above, between 55% and 62% of non-thrombotic May-Thurner patients presenting with leg swelling had complete resolution of swelling following intervention. Conversely, 81–92% of patients who presented with acute iliofemoral DVT had resolution of their lower extremity swelling. While some of these differences could be explained by differing patient expectations and definitions of success, it is also not surprising that complete resolution of swelling is more likely in patients whose swelling is sudden and related to acute thrombotic occlusion of the iliocaval and femoral veins, compared to the non-thrombotic May-Thurner patients who generally have suffered years of chronic venous hypertension in the affected leg.

One special circumstance worth considering is the pregnant patient with MTS. The displacement of the pelvic anatomy by the gravid uterus during pregnancy can exacerbate iliac vein compression, thus leading to worsening left leg swelling and predisposing to venous thrombosis while simultaneously presenting unique challenges to treatment. Pregnant women with unilateral leg swelling thought to be due to MTS are almost always treated conservatively with stenting deferred until after delivery if swelling persists. On the contrary, pregnant patients with MTS who develop acute deep venous thrombosis obviously require treatment of their DVT, and traditionally these patients are managed with anticoagulation (with fractionated heparin) with or without IVC filter placement, as pregnancy is a relative contraindication to the use of pharmacologic catheter-directed thrombolysis due to the concern for placental abruption. However, these patients are at significant risk for developing postthrombotic sequela and generally tend to be quite symptomatic from their venous thrombosis. Although no

large retrospective data has yet been published, there is limited evidence for the safe of use of pharmacomechanical catheter-directed thrombolysis in this patient population [25, 26]. The largest study of 11 patients with extensive iliofemoral DVT and persistent pain and edema on anticoagulation reported 100% successful thrombolysis and rapid clinical improvement without any pregnancy or postpartum-related complications. Thrombolysis was done with a combination of catheter-directed and pharmacomechanical techniques, and patients were not stented until the postpartum period. At a mean follow-up of 1.3 years, 85% of patients had normal Villalta scores [27]. Undoubtedly, further studies are still required to establish the role of thrombolysis and/or stenting in pregnant patients with presentation of thrombotic May-Thurner syndrome.

Conclusion

May-Thurner syndrome is an increasingly recognized clinical entity resulting in chronic unilateral leg swelling in non-thrombotic patients and acute iliofemoral deep venous thrombosis in thrombotic patients. Chronic left common iliac vein compression by the overlying right common iliac artery is the hallmark of this syndrome and is likely a contributing pathologic factor in many patients with chronic venous disease not formally diagnosed with May-Thurner syndrome. Increasing awareness of these conditions, coupled with advancements in endovascular technology and techniques, has allowed for improvement in the quality of life for many patients with this disease process. The published results of iliac venous stenting for MTS are quite favorable, with high stent patency rates and significant symptom resolution in most patients.

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Endovascular Recanalization of Chronic Venous Obstruction

36

David L. Gillespie and Micheal Toma Ayad

Clinical Pearls

1. Recanalization of chronic iliofemoral venous occlusion can be accomplished with a hydrophilic wire and catheter most of the time.
2. It is best to avoid common femoral vein access for iliofemoral vein recanalization and use alternative access such as the jugular vein, popliteal vein, or femoral vein in the upper thigh.
3. "Sharp recanalization" has been described using TIPS needle, transseptal needle, and arterial reentry devices in challenging cases. These techniques are off label and can lead to fatal complications.

Introduction

Deep venous thrombosis (DVT) is the most common cause of venous outflow obstruction. Venous outflow obstruction can be non-thrombotic or thrombotic, either acute or chronic. Non-thrombotic venous obstruction of the vena cava or left common iliac vein may occur from abnormal reaction to the overlying right common iliac artery (May-Thurner syndrome) with resultant intravenous web formation. Intravascular ultrasound technology enabled the identification of non-thrombotic iliac vein lesions (NIVL) and demonstrated that they can occur anywhere throughout the entire venous outflow tract. Patients with acute DVT usually present with sudden onset of unilateral leg swelling. This is often painful, associated with cyanosis of the extremity, and often after prolonged immobilization. Chronic venous outflow obstruction usually occurs months to years after an initial DVT. In symptomatic patients, recanalization of thrombosed veins is incomplete, and the collateral circulation is inadequate. The proximal obstruction results in distal venous hypertension, lower extremity swelling, and pain worsened after ambulation. Although venous outflow obstruction of the lower extremity may involve the entire venous system, current endovascular techniques are most effective in treating thrombosis of the largest veins—namely, the inferior vena cava (IVC), common iliac vein, and external iliac veins [1–5]. Thrombotic venous outflow obstruc-

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tion may be associated with thrombophilia. Less commonly, it may be associated with IVC filter thrombosis resulting in caval occlusion [6].

Access Technique

There are several options for access used in venous stenting. In general, one should avoid placing a sheath in the common femoral vein as this is usually the inflow to the iliofemoral venous system and may need to be stented to insure adequate inflow [1, 6–9]. As such access for venous stenting is usually obtained in the mid-femoral vein to facilitate this. As an alternative option, a jugular approach has been popularized by Kolbel [10] and Gillespie [11]. It is the authors' preference to place a 12 Fr 35 cm sheath into the right internal jugular vein extending into the retrohepatic vena cava. This allows access to both right and left iliofemoral venous systems and prevents prolapse of catheters into the right ventricle during these procedures.

Retrograde and antegrade approaches to iliocaval venous stenting have been described. Benefits of a jugular approach include ease of access to either iliac vein, whereas disadvantages include limited catheter lengths needed to deliver venous stents. The antegrade approach involves ipsilateral cannulation of the femoral vein. Low thigh access is necessary to allow stent deployment up to and below the inguinal ligament without being impeded by the sheath. Popliteal vein access is rarely used and often not possible due to segmental occlusion of the proximal femoral vein. We use ultrasound guidance to avoid inadvertent arterial puncture. Ultrasound guidance also aids in femoral vein location, which can be variable in the posterolateral or posteromedial location compared to the femoral artery. The use of regional or general anesthesia should be based on both patient and physician preference. Chronic cases can often be long, and general anesthesia has its benefits. However, sedation with local anesthesia is a viable option. Heavy intravenous sedation or general anesthesia is useful because many patients will experience some discomfort when undergoing angioplasty of tight or long venous lesions. Without this, clinicians are usually limited in the diameter to which patients will tolerate percutaneous transluminal angioplasty. We use IVUS to assess the vein before and after stent placement and look for adequate recanalized vein lumen diameter, apposition of the stent against the vein wall, need for further stenting, and any thrombotic debris that might need to be treated.

Crossing Chronic Total Venous Occlusions

Crossing venous chronic total occlusions (CTOs) can be quite challenging. In general, the use of standard Glidewire and glide catheter techniques works well. Most cases can be crossed using 0.035 size wires. Using a torque device attached to the wire and quick spinning or drilling movements, the Glidewire will often maneuver through the chronic venous trabeculations and eventually cross into a nonoccluded segment. The interventionist should be cautioned to verify the path of the Glidewire using orthogonal imaging and venography. Great caution should be exercised to avoid balloon angioplasty and vessel injury of smaller collateral veins such as paraspinal veins, hemiazygous veins, or other unnamed veins.

As an alternative to 0.035 Glidewire and glide catheter, one could use smaller 0.018 or 0.014 platforms. These systems offer occasional advantage in negotiating the small tracks within the venous trabeculations. In the 0.018 platform, the V-18 (Boston Scientific, Marlborough, MA) floppy tip wire or a 0.018 hydrophilic Glidewire (Terumo Medical Corporation, Somerset, NJ) is commonly used. Either wire works well especially when combined with the corresponding size Quick-Cross catheter (Spectranetics Corp, Broomfield, CO). In addition, the Quick-Cross Select (Spectranetics Corp, Broomfield, CO) catheter has an angled tip that provides additional steerability to this system. In the 0.014 platform, the operator can choose the stiffness of the wire tip from a 12.5 g wire with moderate flexibility to the 25 g CTO stiff wires that are very rigid.

Again, combining these different wires with a corresponding Quick-Cross catheter allows directional steerability that is very powerful. Once the lesion is crossed using these smaller profile catheters and wires, the operator can upsize to larger stiffer wires to facilitate the more forceful pushability to cross these lesions with larger profile balloons and stents. This is facilitated by passing an 0.035 Quick-Cross catheter (Spectranetics Corp, Broomfield, CO) over the 0.014 or 0.018 wires and then exchanging them with a stiffer 0.035 guidewire such as Amplatz Super Stiff (Boston Scientific, Marlborough, MA), Glidewire Advantage (Terumo Medical Corporation, Somerset, NJ), or Lunderquist Extra-Stiff Wire Guide (Cook Medical, Bloomington, Indiana). These very stiff wires allow for the most trackability and pushability that are available currently. The only more forceful method of gaining pushability is to incorporate these wires into a body floss technique (described below).

A ready system incorporating the best features of all the above tools is the TriForce Peripheral Crossing Set (Cook Medical, Bloomington, Indiana) (Fig. 36.1). This 5 Fr sheath (flexor sheath) tapers to a 4 Fr support catheter (CXI) that is introduced over a 0.035 in. wire which allows the system to act as a guide for an uninterrupted transition. A tungsten-loaded tip aids pushability and adds to radiopacity as it goes through venous lesions, and the hydrophilic coating on both the CXI and the Flexor sheath enhances trackability.

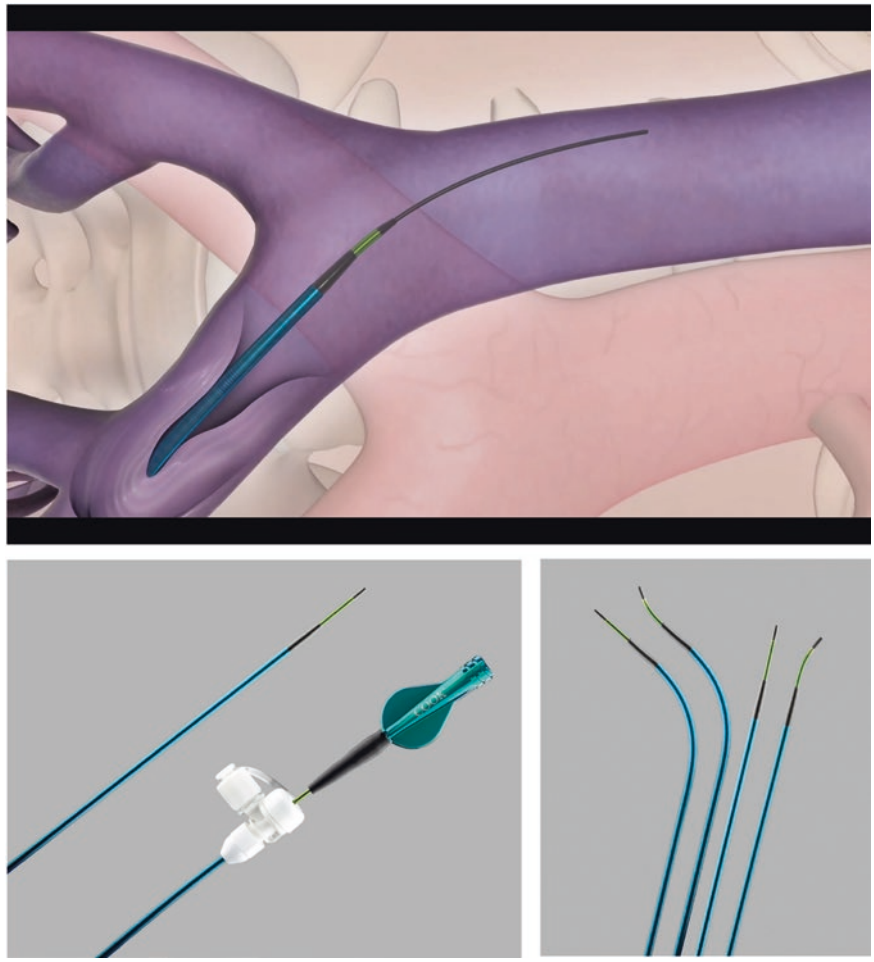

Fig. 36.1 The TriForce Peripheral Crossing Set (Cook Medical, Bloomington, Indiana)

An advanced adjunctive technique that can be used to increase the trackability of balloons and stents across chronically occluded venous lesions is the "body floss technique" [12]. Once the lesion is crossed, an appropriate sized snare is used to capture this wire and bring it out of the body through a second venous access typically incorporating both a jugular and a femoral venous access. Once the wire is brought out of the sheath, the operator has a "floss" through and through the body. With traction placed on both ends of the wire simultaneously while advancing a balloon, the operator can achieve additional pushability in crossing very scarred CTOs to perform the initial balloon angioplasty. Usually once this is performed, all other catheters, balloons, and stents track across the wire more easily.

Once across the CTO, intraluminal position is confirmed using intravascular ultrasound (IVUS) Volcano catheter (Philips, Andover, MA) introduced over 0.035 wire. In these cases, IVUS is used to size the normal inflow and outflow to the stent and the length of the segment needing to be stented. It is not used to size the chronically occluded segment, as these are usually very small and not reflective of any sized stent that would be useful to treat the patient.

Advanced Methods of Crossing Chronic Total Venous Occlusions

There are several other "off-label" techniques that can be considered in more challenging chronic total venous occlusions. The use of a transjugular intrahepatic portosystemic shunt (TIPS) kit also known as the Rösch-Uchida Transjugular liver access set (Cook Medical, Bloomington, Indiana) (Fig. 36.2) has been reported to be a useful method of "sharp" recanalization [13, 14]. The curved 0.038 in. flexible catheter is used to orient the tip and allow the placement of a sharp trocar stylet. Using orthogonal fluoroscopic views, the trocar is then used to cross the CTO and then allow the passage of a Glidewire into the true lumen. In the report by Dou et al., the authors identified nine cases that required the use of a transjugular liver access cannula as a guiding instrument. The transjugular liver access cannula was used to traverse chronic occlusions in both the upper and lower central venous systems in these patients. The technical success rate was 100%. There were no clinically significant complications. One patient was lost to follow-up. Of the remaining eight patients, seven experienced symptomatic relief within 1 month of recanalization. The authors stated that the use of this TIPS needle technique may serve as a useful adjunctive tool during difficult venous recanalizations, especially when traditional guidewire and catheter techniques fail. Other authors have reported on using the cardiac Brockenbrough septal puncture needle (Medtronic, Dublin, Ireland) [15, 16] or Chiba Biopsy Needles (Cook Medical, Bloomington, Indiana) [17] to cross venous CTOs of the brachiocephalic veins. The *Brockenbrough* needle (Medtronic, Dublin, Ireland) (Fig. 36.3b) is a hollow tube which is 18 gauge tapering to 21 gauge. The proximal end has a flange with an arrow that points toward the needle tip. The Mullins sheath (Fig. 36.3a) is the most commonly used sheath used with the Brockenbrough needle. This is an 8 French 60 cm sheath that can be introduced over a 0.032 J-tipped guidewire.

The other needles available are the BRK, BRK-1, BRK-2, and BRK-XS needles, which are marketed by St. Jude Medical (St. Jude Medical, St. Paul, MN). The BRK is the standard needle with slight angulation between the tip and the shaft (19 F), which can be useful in directing the needle in any direction. The BRK-1 needle has a greater angulation between the shaft and the tip (53 degrees). The needle is available in two lengths (71 or 89 cm) [18]. The Chiba needle (Fig. 36.4) is straight and comes in 10, 15, and 20 cm length, which may limit its use to crossing shorter total occlusions in the common femoral or external iliac veins. To further facilitate this sharp recanalization technique, the interventionist can consider placing an open loop snare (10 mm) on the central side of the occlusion to use as a target to aim for with the needle or wire [19].

Another advanced technique reported has been the use of a radiofrequency guidewire [20–

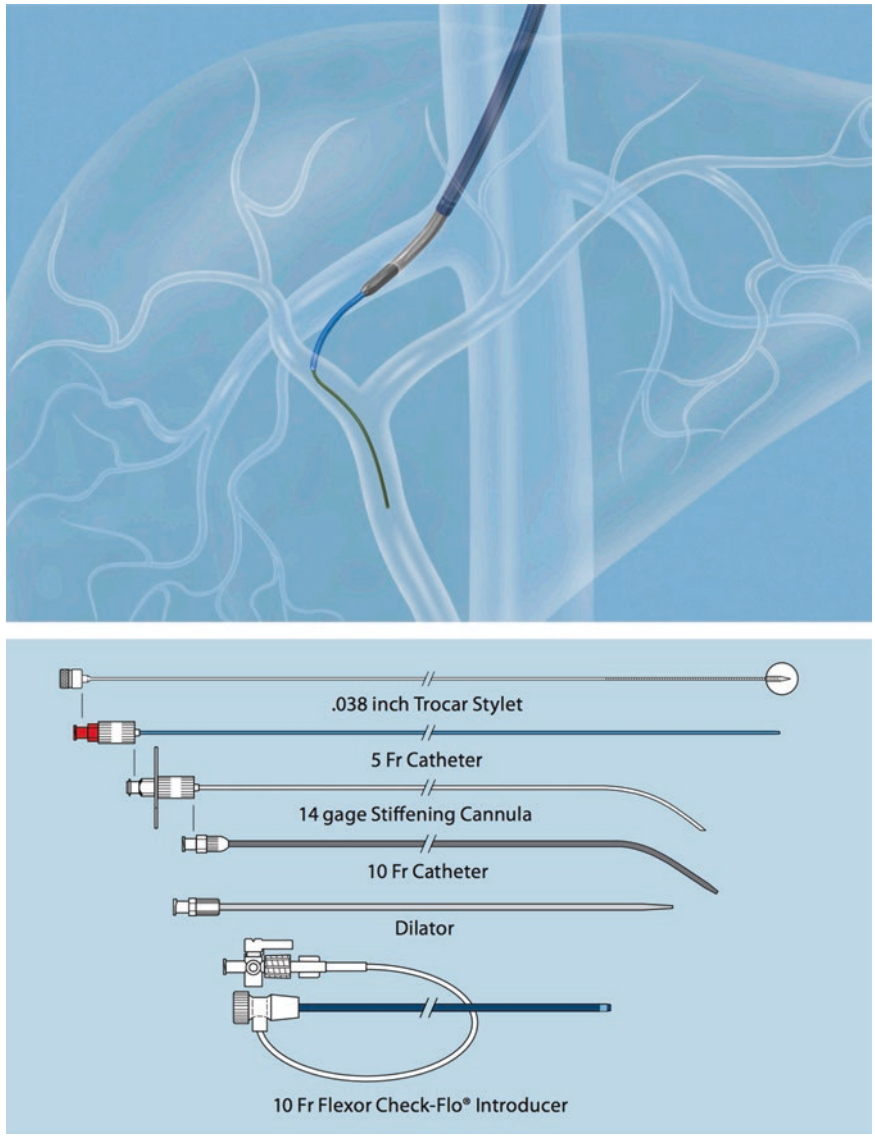

Fig. 36.2 Rösch-Uchida Transjugular liver access set (Cook Medical, Bloomington, Indiana)

22]. In the report by Iafrati et al., the author discusses three patients with complicated central venous occlusions in whom conventional catheter and guidewire techniques were not successful and who were successfully treated using the PowerWire™ Radiofrequency Guidewire (Baylis Medical, Montreal, Canada). Occlusions were traversed using the radiofrequency wire, followed by angioplasty and stenting. The average length recanalized was 8.2 ± 3.6 cm. One patient required repeat angioplasty at 4 months. All stents were patent at 12–15 months. The radiofrequency wire is valuable in the management of patients with refractory central venous occlusions. It is a 4 Fr 0.035 compatible system that is 250 cm in length. The PowerWire™ has various straight and angled-tip models to adjust the wire trajectory to anatomical geography. Once across the lesion, it can be used as the guidewire on which to pass venoplasty balloons. It has an atraumatic radiopaque tip that delivers radiofrequency (RF) energy to vaporize a channel through

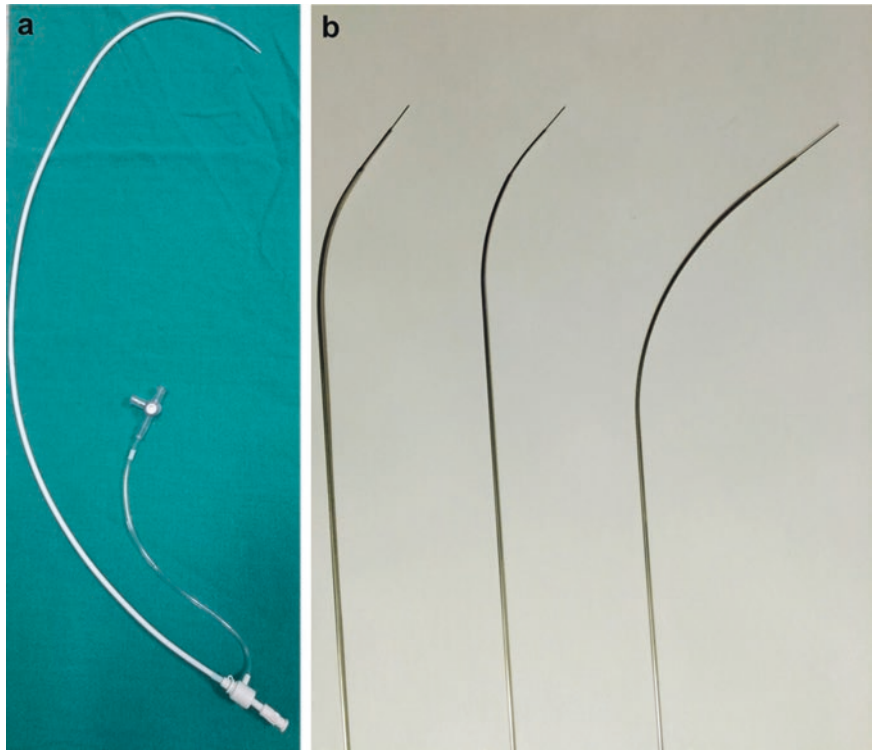

Fig. 36.3 Mullins sheath (**a**). Brockenbrough transseptal needle (**b**). Reproduced with permission of Medtronic, Inc

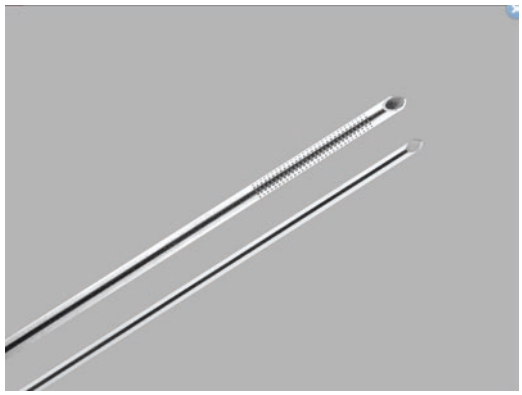

Fig. 36.4 The Chiba needle

lesions with minimal trauma to surrounding tissue. The PowerWire™ RF Guidewire has a torqueable, stiff proximal shaft with a smooth transition to a more flexible distal end. However, there have been reported complications attributed to this technique when used for the treatment of upper extremity central venous occlusions [23]. In this report, one of twelve patients treated using this technique (8.3%) experienced a major complication with tracheal perforation by the RF wire leading to the patient's death.

Several different devices have been developed for the use of crossing arterial CTO. These devices have rarely been reported to be used off label for crossing venous CTO. The Wildcat catheter (Avinger, Redwood City, CA) is one such rotational atherectomy device. It is a 6 Fr 0.035 system that has a 110 cm working length and a 2 mm crossing profile. The device can be used in a passive mode rotating the catheter counterclockwise to cross softer lesions. In the active mode, the device deploys wedges at the tip, which corkscrew through tougher lesions. Once the lesion is crossed, a 0.035 guidewire can be passed into the true vessel lumen. A recent article by Smeds et al. reported on the use of a Wildcat catheter to cross an occluded iliac vein stent originally placed for deep venous thrombosis and May-Thurner syndrome [24]. The patient presented with complaints of left lower extremity

pain and swelling. Multiple previous attempts had been made to cross this lesion with guidewire and catheter techniques without success. The authors reported crossing the lesion using the Wildcat catheter and then used directional laser atherectomy followed by balloon angioplasty and stenting with successful recanalization of the stent and resolution of the patient's symptoms.

The Outback reentry catheter (Cordis, Milpitas, CA) is a 6 Fr compatible device designed for reentry in arterial chronic total occlusions (Fig. 36.5). In 2015, Adam et al. described using the Outback reentry catheter for endovascular stent reconstruction of a chronic total occlusion of the inferior vena cava [25]. In this report, the authors were successful in using bidirectional wire access and a balloon puncture utilizing the Outback reentry device. The device has visible markers, which help practitioners orient the reentry cannula toward the true lumen. An "L"-shaped radiopaque marker (visualized from 90° orthogonal view) provides confirmation of the desired alignment at the reentry site. Once across the lesion, the reentry needle is deployed into the true lumen allowing the passage of a 0.014 wire.

Fig. 36.5 Outback reentry catheter

Stenting Venous Stenoses

Once the CTO is crossed, predilation is usually necessary in order to allow delivery of the larger stents that are required to reestablish venous outflow. Unlike the artery, the vein tolerates extensive dilation without rupture. We use standard noncompliant angioplasty balloons for venous dilation. For angioplasty before stent delivery, we use small diameter balloons (e.g., 3–4 mm × 10 cm). After this, we place the stents. Stents are placed well into the inferior vena cava to avoid migration and early restenosis. Insertion of a large diameter stent is recommended with stent sizes: 18–24 mm for the cava, 16–18 mm for common iliac veins, and 14–16 mm for external iliac veins. Currently, we use the Wallstent (Boston Scientific, Marlborough, MA) to accommodate this range of sizes. Stents are delivered distally first in the external iliac and build proximally to and into the inferior vena cava. After delivery of the most distal stent, post-dilation is recommended before delivery of the next stent due to the foreshortening that occurs as lumen diameter increases. It should be noted that the disease is often more extensive than venography would suggest. It is essential that the entire diseased segment is treated as outlined by IVUS. Inadequate stenting has been shown to be the most common cause of restenosis. It is important to avoid short skip segments (<5 cm) in between two stents because they are also prone to secondary stenosis. Long-term patency rates of iliocaval stents have been reported in many series. In 2004, Neglen and Raju reported on their series of 324 iliac vein stents. In this large series, primary, primary-assisted, and secondary patency was 75%, 92%, and 93% at 3 years, respectively. Restenosis of iliocaval stents was a major cause of stent failure. At 3.5 years, more than 75% had some degree of in-stent restenosis with the highest in patients with post-thrombotic syndrome [26]. The reported early thrombosis rate (<

30 days) with iliocaval stenting is 11–15%, which is lowest in patients with chronic venous obstruction. Factors associated with early thrombosis may include patients with thrombophilia, stent length, extension below the inguinal ligament, and complete occlusions. In their retrospective analysis, Knipp et al. did find long stent length to be a significant risk factor for thrombosis in univariate analysis, as was thrombophilia; in multivariate analysis, however, neither was independently associated with decreased stent patency [27]. Inadequate stent dilation, inadequate inflow, and failure to stent entire diseased vein are the most common causes of stent thrombosis. Currently, there is no data comparing a single iliac vein stent to the use of multiple stents across the bifurcation of the iliac veins into the vena cava. In our experience, restenosis or stent thrombosis occurs commonly because of failure to stent across the lesion and into the inferior vena cava adequately. In these cases, salvage can be achieved using standard pharmacomechanical thrombolysis (PMT) to open an acutely thrombosed stent followed by restenting across the lesion and into the inferior vena cava. Due to poor experience with placing stents across joints, extension of venous stents below the inguinal ligament has long been avoided. However, Neglen et al. found no effect on patency rate or stent fracture when stenting across the inguinal ligament with the braided stainless steel Wallstent (Boston Scientific, Marlborough, MA) [9].

Posttreatment therapeutic anticoagulation is usually recommended in thrombotic patients to prevent recurrent thrombosis. Anticoagulation should be continued indefinitely in patients with underlying hypercoagulable states. The duration of anticoagulation recommended in other patients is not agreed upon but should be individualized for each patient. The use of dual therapy with anticoagulants and antiplatelet agents is based on extrapolation from treatment strategy in arterial stenting and the pathophysiology of the disease process. Nonetheless, there is no substantial body of evidence to support this treatment strategy. Langwieser et al. reported on short-term follow-up after 10 venous stenting procedures in 9 patients maintained on rivaroxaban and clopidogrel for 6 months. Their report noted that under dual treatment strategy, none of the patients experienced in-stent restenosis, stent occlusion, or major bleeding at median follow-up of 14 months (range 6–26 months) [29].

Treatment of Stent Thrombosis

One of the most difficult venous lesions to treat is stent thrombosis. In general, if a thrombosed stent is discovered within 14 days, standard methods described above work well for crossing these lesions. Once crossed successfully, the use of usual techniques of thrombolysis followed by angioplasty with or without stenting is usually effective to restore patency. In a report, Strijkers et al. reported on the use of EKOS ultrasound-assisted thrombolysis (BTG Interventional Medicine, London, UK) in 18 patients treated for acutely occluded venous stents [28]. Technical success was achieved in 11/18 (61%) patients. Primary patency in 8/11 patients was 73% at last follow-up (median follow-up 14 months [range 0–41 months]). Additional treatments after successful lysis were restenting (seven patients) and creation of an arteriovenous fistula (six patients). As reported by Neglen and Raju, thrombosis after venous stenting is usually due to missed lesions inadequately treated of either the inflow or outflow. This can be reassessed using venography and IVUS and treated accordingly.

Chronically occluded venous stents seem however to behave very differently. While not reported often, the success rate of crossing chronically occluded venous stents is felt to be extremely low. As stated previously in this chapter, some of the newer techniques at crossing CTOs have been tried off label [24].

Conclusion

Recent advancements in the endovascular treatment of venous outflow obstruction have improved the care of patients with chronic venous disease. Advances in crossing venous CTO have the potential for further exploding

this field. Despite these advances, however, numerous questions remain. Only through the careful application of these techniques, close follow-up, and critical analyses of outcomes will treatment improve.

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The Venous Stent: Is It Primetime Yet?

37

Arjun Jayaraj and Seshadri Raju

Clinical Pearls

1. Assessment of the iliac venous system for outflow obstruction involves utilization of IVUS and determination of reduction in diameter/area of the vein.
2. Angioplasty alone is usually not sufficient to treat venous stenosis because of recoil.
3. In stent restenosis should be suspected in patients who develop recurrent symptoms and can be confirmed with IVUS and treated with balloon angioplasty.

Introduction

Utilization of stents in the venous system has been done for over 30 years. Venous stents are routinely used currently to correct pathology in the central venous system and dialysis access in addition to the femoro-ilio-caval system (off-label use). Endovenous management of chronic venous disease (CVD) relating to deep veins of the lower extremity and pelvis involves accurate diagnosis of venous pathology and treatment with angioplasty and stenting. There is no role for angioplasty alone given the recoil encountered in the fibrotic diseased vein. This chapter provides an overview of endovascular management of deep venous disease of the leg and explores the future of such therapy.

Diagnosis

Manifestations of CVD include lower extremity venous claudication, orthostatic pain, swelling, skin changes (hyperpigmentation, eczema, dermatitis, lipodermatosclerosis), and ulceration(s) typically in the "gaiter" area. The goal of preoperative evaluation of CVD is to determine etiology of obstruction and status of inflow and outflow through the involved segment. Diagnostic studies include venous duplex ultrasound, air plethysmography, cross-sectional imaging (computerized tomographic venogram [CTV]/magnetic resonance venogram [MRV]), as well as venography with intravascular ultrasound (IVUS). Duplex ultrasound serves as a screening tool and helps determine the extent of femoro-ilio-caval obstruction in addition to providing information on valvular function. The reference normal luminal diameter minima used for the common femoral vein (CFV), external iliac vein (EIV), and the common iliac vein (CIV) are 12, 14, and 16 mm, respectively (Table 37.1). Air plethysmography appraises calf pump function. CTV/MRV elucidates individual venous anatomy, stenosis/

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Table 37.1 Cutoff sizes and luminal areas of iliofemoral veins

Vein	Luminal area (mm^2)	Diameter (mm)
CFV	125	12
EIV	150	14
CIV	200	16

CFV common femoral vein, *EIV* external iliac vein, *CIV* common iliac vein

occlusion, and collateral circulation. Additionally, specific pathology (thrombotic/non-thrombotic) can also be evaluated by such cross-sectional imaging. Supplemental information on segmental inflow and outflow is provided by venography. IVUS enables more accurate determination of etiology and extent of disease than is possible with venography alone. Luminal areas obtained with IVUS planimetry are used to assess severity of stenosis by comparison to reference areas (Table 37.1).

Treatment

Endovascular Intervention

Reconstruction of the obstructed femoro-iliocaval segment is done by using an endovascular approach. Open approach is reserved for patients who are not candidates for or who have failed an endovascular approach. The procedure is performed under general anesthesia given the frequent severe intraoperative pain/discomfort associated with balloon angioplasty. Access to the mid-thigh femoral vein is attained under ultrasound guidance. This allows angioplasty/stenting of the common femoral vein if needed without being impeded by the sheath. A 0.035 Glidewire (Terumo Medical Corp, Somerset, NJ) is passed into the inferior vena cava and a short (10 cm) 11 Fr sheath is placed. An ascending venogram is performed, renal function permitting, of the iliofemoral segments and inferior vena cava. Intravascular ultrasound (IVUS) [Volcano, San Diego, CA] is then performed using the 0.035″/7 Fr catheter and planimetric measurements of the luminal areas of the common femoral vein (CFV), external iliac vein (EIV), and common iliac vein (CIV) made. Normal luminal areas of 125, 150, and 200 mm^2 are used as cutoffs in the CFV, EIV, and CIV, respectively. Any decrease in luminal areas below these reference values in a symptomatic patient is considered abnormal meriting angioplasty and stenting. A threshold value of 70% stenosis for correction, often used in arterial stenosis, does not apply because there is no correlation to venous pressure with grade of stenosis. Even minor stenosis of 30–40% can significantly elevate venous pressure in postthrombotic limbs. Venous hypertension is the basis of chronic venous disease; the aim of venous stenting is to relieve the venous hypertension. Predilation of the stenosis is performed using an 18 × 60 mm Atlas angioplasty balloon (Bard Peripheral Vascular, Tempe, AZ). Stenting is then carried out using 18–20 mm Wallstents (Boston Scientific, Marlborough, MA) with landing zones determined by IVUS and defined bony landmarks. The proximal landing zone is typically 1–2 cm above the iliac confluence that can be related to the corresponding vertebral body (upper, middle, or lower border). The distal landing zone is an area of adequate inflow in the CFV and can be related to a body landmark of the pubic ramus, femoral head, or lesser trochanter. Careful attention must be paid to the vein at the level of the inguinal ligament since this is often an area of compression. Stenting across the inguinal ligament must be performed in these cases and can be done with good results (Fig. 37.1) [1]. Given the decreased radial strength of the Wallstent, a Gianturco stent (Cook Medical, Bloomington, Indiana) is used to provide additional strength across the confluence with an extension of the Gianturco stent beyond the Wallstent proximally into the inferior vena cava (IVC). The Gianturco stent should be oversized relative to the Wallstent with an overlap of the lower half of the Z stent within the Wallstent to prevent stent embolization. An overlap of 3 cm or so between each Wallstent in the stack is required to compensate for foreshortening during post-dilation. Post-dilation is performed using

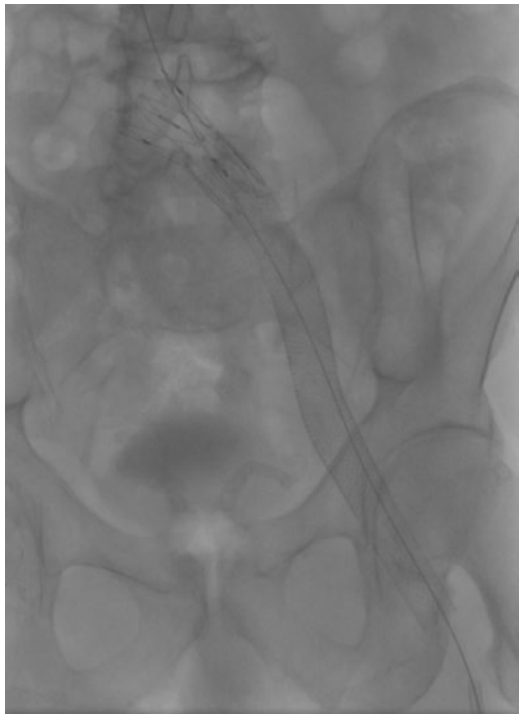

Fig. 37.1 Stenting across the inguinal ligament

the 18 × 60 mm angioplasty balloon. Completion IVUS is performed to ensure adequacy of luminal area. Any residual narrowing on IVUS interrogation is overcome by repeat dilation using a larger caliber angioplasty balloon taking into account the rated stent size deployed. Completion venogram is then performed. The 11 Fr sheath is subsequently withdrawn to just outside the vein, and a Surgicel Fibrillar patch (Ethicon, Somerville, NJ) is introduced via the sheath to aid in local hemostasis. Manual pressure is held to compliment the hemostatic effect. Kurklinsky et al. reported the Mayo Clinic group's experience with stenting 91 postthrombotic iliac or iliofemoral veins. Primary, primary-assisted, and secondary patencies at 3 years were 71%, 90%, and 95%, respectively [2]. A recently published systematic review of deep venous stenting for CVD supported consideration of stenting as a treatment option given promising results and safety profile [3]. Graaf et al. reported their experience with stenting across the ilio-caval confluence and noted primary, primary-assisted, and secondary patency of 70, 73, and 78% at 36 months for self-expanding stents and 100% short-term (~5 months) patency for balloon expandable stents [4]. The largest published single institutional experience of 982 stents for chronic nonmalignant obstructive lesions of the ilio-caval-femoral vein segments with 6-year follow-up demonstrated a primary, primary-assisted, and secondary patency rates of 79, 100, and 100% for non-thrombotic lesions and 57, 80, and 86% for postthrombotic lesions, respectively. Risk factors for restenosis/stent occlusion after venous stenting were the presence and severity of postthrombotic disease [5].

Chronic Total Occlusion (CTO)

Recanalization of CTOs is most commonly done through the use of a 0.035″ Glidecath (Terumo Medical Corp, Somerset, NJ) and 0.035″ Glidewire. A mid-thigh femoral vein approach is satisfactory in most instances with a short entry to lesion length allowing greater pushability. Right internal jugular vein approach is sometimes necessary when the antegrade approach fails. A body floss technique may be occasionally necessary as described by Kolbel and colleagues [6]. Other devices used for recanalization of CTO lesions include Quick-Cross support catheter (Spectranetics Corp, Colorado Springs, CO) and the TriForce Peripheral Crossing Set (Cook Medical, Bloomington, IN). Generally, a single-step dilation of the wire tract to the desired final size is safe and saves supplies. Serial angioplasty with sequentially larger balloons may have to be performed in some cases to create an appropriate recanalization tract. Rupture/hemorrhage from this maneuver is extremely rare. Angioplasty is carried out caudal to cranial (femoral access) or cranial to caudal (jugular access) as this enables easier retrieval of the angioplasty balloon if it disrupts. The likelihood of the latter happening is higher in CTO than in stenotic lesions. Use of stents, post-dilation, IVUS interrogation, and venogram are all performed as previously described. Raju et al. described their experience in 120 patients with chronic obstruction of the IVC

and reported cumulative stent patency at 2 years of 82%. With regard to symptom relief, the group noted relief of pain and swelling of 74% and 51%, respectively, at 42-month follow-up. Additionally, the cumulative rate of complete ulcer healing at 2 years was 63% [7]. Fatima et al. reported 90% 2-year patency rate and 80% symptom-free survival in a series of 28 patients undergoing IVC stenting for occlusion/high-grade stenosis. Freedom from reintervention in this group, which included 13 patients with IVC filters at the 24-month mark, was 84% [8].

Stenting Across Inferior Vena Cava Filters

IVC filters can over time serve as a nidus for a fibrotic reaction that leads to IVC stenosis/occlusion. Trapped embolus may start the process in some instances. The occluded filter and IVC segment have to be recanalized to provide adequate outflow. This can be accomplished by removal of the filter if possible (usually not in chronic occlusions) or crushing the filter and stenting across it. A 24 mm Wallstent is typically used in the IVC/across IVC filters and has had good results (Fig. 37.2). Patients should be coun-

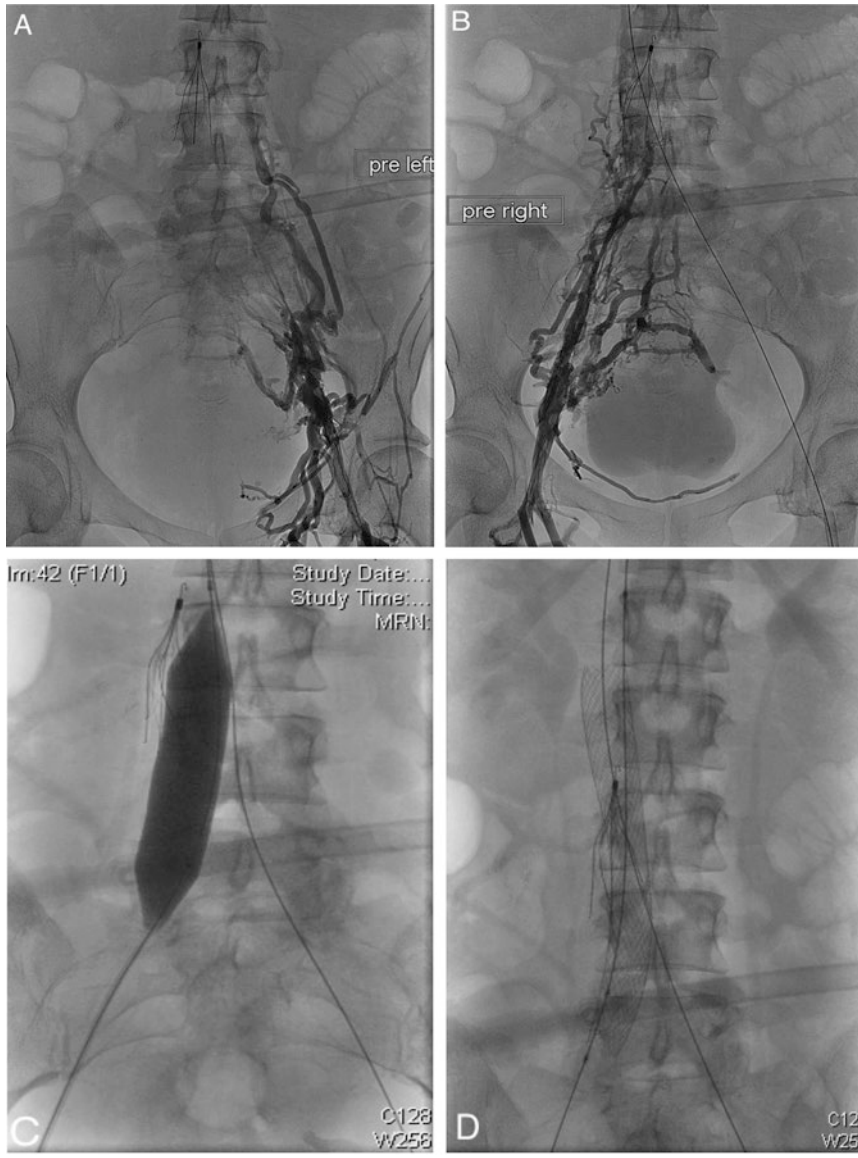

Fig. 37.2 Recanalization—Ilio-caval occlusion with IVC filter. Venogram showing total occlusion of the *left* (**A**) and *right* (**B**) iliac veins with extensive collaterals. Balloon angioplasty (**C**) and stenting (**D**) across the IVC filter.

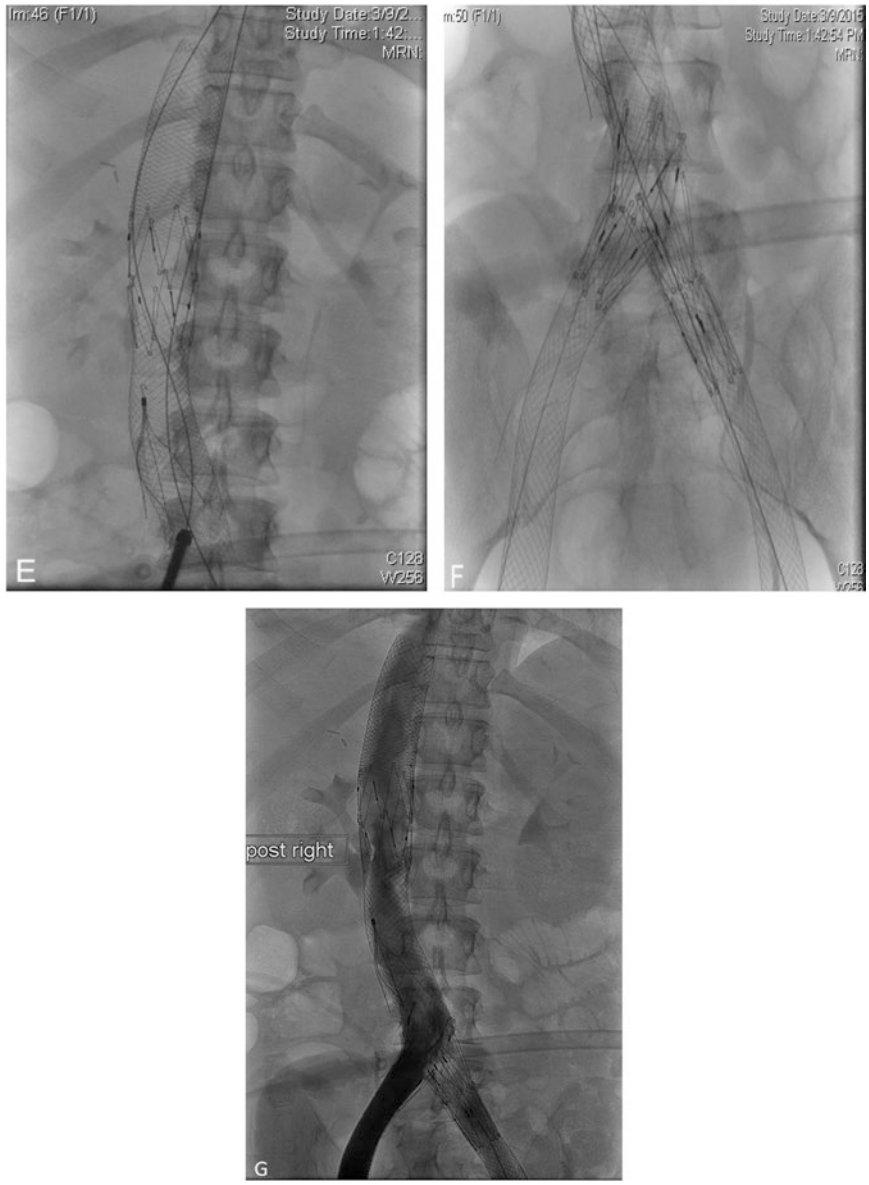

Fig. 37.2 (continued) Extension of the stents into the suprarenal IVC (**E**) and the external iliac veins (**F**). Completion venogram showing flow in the stents (**G**)

seled about loss of filter protection for pulmonary embolism consequent to such procedures. In a review of 121 limbs that underwent stenting for postthrombotic ilio-caval occlusions, limbs stented for recanalized occlusions with ($n = 23$) and without IVC filters ($n = 92$) showing no difference in patency rates. Cumulative primary and secondary patency rates were 30% and 35% ($p = 0.9678$) and 71% and 73% ($p = 0.9319$), respectively. The primary factor, the authors conclude, affecting stent patency in such patients was severity of postthrombotic disease and not presence of a filter [9].

Bilateral Ilio-caval Stenting

Contemporarily, there is limited role for simultaneous bilateral femoro-ilio-caval stenting, save for bilateral recanalization procedures. Typically, the worse leg is stented giving adequate time for the less affected leg to improve from off-loading of cross collaterals. In patients with persistent symptoms in the contralateral lower extremity, contralateral stenting can be pursued. In the presence of a prior Z stent, the flowering technique is used wherein the nylon suture of the new Gianturco stent is cut in order to allow the struts to flower out and allow it to mesh with the older contralateral Z stent (Fig. 37.3). If the contralateral stent is a Wallstent, then a fenestrum needs to be created by wire access across the wall stent interstice and dilation of the same using an 18 × 60 mm angioplasty balloon. Stenting across this fenestrum uses a combination of Wallstent and Gianturco "crown" as previously described. The wide struts of the Z stent lining the fenestrum allow free flow in the contralateral stent across the fenestrum (Fig. 37.4). Raju et al. reported 24-month cumulative primary and secondary patency of 69% and 93%, respectively, using the fenestral technique [10].

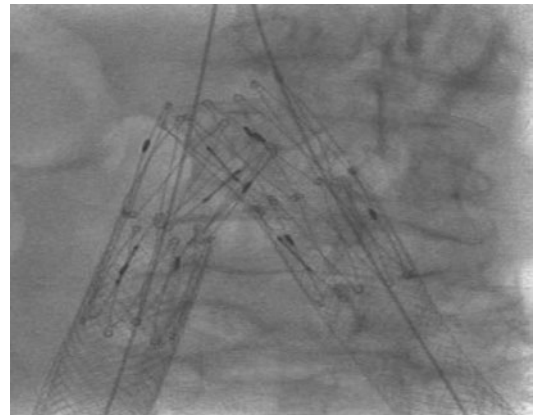

Fig. 37.3 Bilateral iliac stenting with Z stent deployment

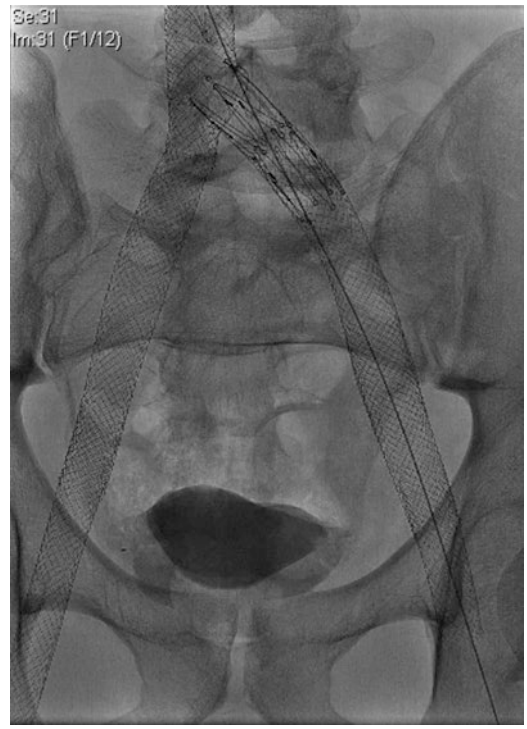

Fig. 37.4 Bilateral stenting using fenestration technique

Management of Stent Complications

Stent Compression/In Stent Restenosis

In previously stented patients who develop recurrent symptoms, IVUS interrogation is merited. Such patients could have stent compression and/or instent restenosis and can be managed by *hyperdilation* (Fig. 37.5). This involves use of an angioplasty balloon larger than the rated size of the stent used (e.g., for a 20 mm stent, we can use a 22–24 mm angioplasty balloon). *Isodilation*, on the other hand is dilation with use of an angioplasty balloon of the same rated diameter as the stent. Hyperdilation of a freshly deployed Wallstent is not possible as the braided strands of wire without cross-links recoil immediately. After the stent, has been incorporated in the vein wall following residence for 8 weeks or more, hyperdilation with little recoil becomes possible. Stent compression is unique to the venous system and results from perivenous fibrotic/scar tissue build up. Raju et al. noted a reintervention rate of 13% following femoro-ilio-caval stenting in 1085 limbs. Median time to reintervention after the initial procedure was 15 months. Post reintervention, the group reported cumulative improvement in pain and swelling of 67% and 72%, respectively, at 18-month follow-up. Complete

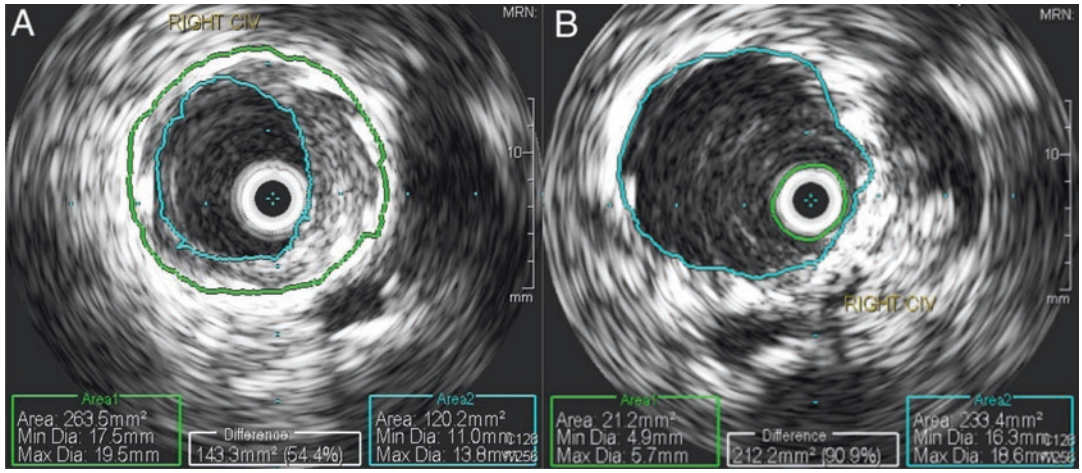

Fig. 37.5 Severe in-stent restenosis in the common iliac vein (**a**). Improved lumen area post hyperdilation (**b**)

Table 37.2 Venous stents undergoing trials

Stent type	Material	Diameter (mm)	Length (mm)	Cell technology
Vici venous[a]	Nitinol	12–16	60–120	Closed
Sinus[b]	Nitinol	10–36	30–160	Open/closed
Zilver vena[c]	Nitinol	14–16	60–140	Open
Venovo[d]	Nitinol	10–20	40–160	Open

[a]Veniti Inc. (St. Louis, MO, USA)
[b]Optimed Medizinische Instrumente GmbH (Ettlingen, Germany)
[c]Cook Medical (Bloomington, IN, USA)
[d]Bard Peripheral Vascular (Tempe, AZ, USA)

cumulative healing of venous dermatitis/ulcer at 12 months post reintervention was 90% [11].

Stent Occlusion

For acute/subacute occlusions, treatment is with pharmacomechanical thrombectomy ± balloon maceration (no pulmonary embolisms in our experience). For more chronic occlusions (CTO), recanalization can be pursued as earlier described. Acceptable results have been noted in both situations. Laser recanalization has also been used as a last resort in occluded stents with modest success.

Morbidity

Venous stenting has proven to be a low-risk procedure in an evidence summary of worldwide experience. Morbidity and mortality have been negligible [12].

Venous Stents

Currently in the United States, the most commonly used venous stent is the Wallstent. Other stents designed exclusively for the venous system and in use elsewhere are available here only as part of a trial. These include the Veniti, Optimed, Cook, Bard, and Medtronic stents (Table 37.2). Long-term data is not available on these stents to compare with the Wallstent. Given that one of the most common problems encountered in the venous stent is instent restenosis, there might be a role for drug-eluting stents/drug-coated balloons of a caliber suited for the venous system. Bioabsorbable stent is another potential prospect. With regard to stent compression, a condition exclusively seen in the venous system, the balance between radial force and crush resistance needs to be taken into account while constructing a venous stent. The future is an exciting one for

management of deep venous disease and venous stenting in particular. A tremendous amount of work however remains to be done. So, it is certainly prime time for the venous stent!

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Open Reconstruction for Chronic Venous Obstruction

38

Arjun Jayaraj and Peter Gloviczki

Clinical Pearls

1. Open surgical reconstruction is an option for patients with advanced venous symptoms who are not candidates for or who have failed endovascular therapy.
2. Vein bypass should be performed with a concomitant temporary arteriovenous fistula to increase flow and prevent thrombosis.
3. Perioperative anticoagulation has an important role in venous bypass surgery with utilization of low dose subtherapeutic heparin drip in the immediate post operative period.

Introduction

Patients with obstructed iliofemoral vein or the inferior vena cava (IVC) due to nonmalignant disease usually present with pelvic or lower extremity chronic venous insufficiency (CVI) following a previous deep vein thrombosis. Chronic non-thrombotic iliac vein occlusion (NIVO) like May–Thurner syndrome (MTS) is responsible for symptoms in up to 60% of patients with chronic venous disease [1]. Endovascular intervention with stenting is the treatment of choice of benign iliac, iliofemoral, or iliocaval venous obstructions in patients who fail conservative compression therapy. Open surgical and hybrid reconstructions are used in those symptomatic patients who are not candidates for or who have failed endovascular reconstructions. In this chapter, we discuss technique and results of open surgical reconstructions for nonmalignant IVC and iliofemoral venous obstructions.

Etiology

Chronic venous obstruction is usually the result of a previous acute deep venous thrombosis (DVT) leading to postthrombotic syndrome (PTS). PTS develops in 20–50% of patients who develop DVT [2]. MTS where compression of the left common iliac vein by the overriding right common iliac artery occurs has been recognized now as the most frequent cause of left iliofemoral

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venous thrombosis [3, 4]. Acute symptoms generally are more common (73%) in patients with MTS [5]. Compression of the left iliac vein without concomitant DVT is an important etiology of symptomatic chronic venous outflow obstruction. In a series of 982 patients who underwent venous stenting, 53% of the IVC and iliofemoral lesions were of non-PTS etiology [6]. Since compression of the iliac veins may occur on the right side and in areas other than the proximal left common iliac vein, described by May and Thurner, the more general non-thrombotic iliac vein obstruction (NIVO) term has been proposed to include all non-thrombotic iliac vein obstructions. Other etiologies for iliofemoral or IVC obstructions include retroperitoneal fibrosis, blunt–penetrating trauma, congenital venous anomalies, benign or malignant tumors, and, rarely, congenital suprarenal inferior vena cava occlusion (webs or caval coarctation).

Pathophysiology

During the acute phase of DVT, the inflammatory cascade that is stimulated in response to thrombus also promotes partial lysis of the thrombus. This process that leads to recanalization of the vein is also responsible for damage to the vein wall and venous valves leading to chronic obstruction and valvular incompetence. If collateral venous circulation in iliofemoral venous occlusion is inadequate, ambulatory venous hypertension develops due to a functional venous outflow obstruction. The iliac venous system is more prone to lack of collateral flow channel development than the femoral segment. An additional contributor is infrainguinal deep reflux and concomitant obstruction of multiple venous segments seen in postthrombotic syndrome.

Diagnosis

Signs and symptoms of CVI in patients with chronic iliofemoral and iliocaval obstructions include pigmentation, skin and subcutaneous inflammatory changes, varicosity, swelling, and pelvic, thigh, or hip pain that frequently develops after exercise. In the Mayo Clinic experience, patients who underwent open venous reconstruction had a mean duration of symptoms for 6 years with 94% having swelling, 90% with venous claudication, and 84% had both. With respect to ulcers, 19% had active, and 12% had healed ulceration [7].

Evaluation of CVI must focus on confirming the cause of chronic iliofemoral and iliocaval venous obstruction and establishing the presence and significance of poor venous outflow due to such obstruction. It is imperative to pay careful attention to both inflow and outflow during workup. Additionally, the physician must exclude any abdominal or pelvic malignancy and consider MTS or other NIVOs as the cause of benign left iliac vein obstruction. Tests include an initial venous duplex scan to help define the location, cause, and severity of the underlying venous pathology. Duplex scanning will diagnose both valvular incompetence and venous obstruction. Typical appearance of a postthrombotic vein at duplex scanning is that of a thickened, hardly compressible vessel with damaged, incompetent valves in the femoropopliteal and tibial veins and variable degrees of venous flow due to partial recanalization. Air or strain gauge plethysmography is designed to evaluate the global leg hemodynamics by measuring reflux, obstruction, and calf pump function. Decreased vein wall compliance in patients with PTS may interfere with proper evaluation of calf muscle pump function. Cross-sectional imaging like computed tomography venography (CTV) and magnetic resonance venography (MRV) will identify any obstructing mass or tumor and provides sufficient information in most patients about venous anatomy, collateral circulation, occlusion, or stenosis. Contrast venography is useful in some patients before open surgical deep venous reconstructions, and it is routinely done in those who have endovascular intervention. Venography is a useful adjunct, especially in PTS patients. Ascending venography provides the anatomic layout of veins of the limb, besides defining sites of obstruction, collateral venous circulation, and the patterns of preferential flow. It is typically done by cannula-

tion of the dorsal vein of the foot to assess the veins of the leg and through separate access of the common femoral vein to assess the iliocaval system. Descending venography under fluoroscopy permits evaluation of sites of reflux in the saphenous and deep system. Contrast venography is combined with direct venous pressure measurement to document a pressure difference between the femoral vein and the vena cava. A resting pressure differential of 5 mmHg or greater is considered evidence for significant obstruction. A lower pressure at rest but an increase to 10 mmHg after exercise is also a sign of functional obstruction. Exercise consists of 10 dorsiflexions of the ankle or 20 isometric contractions of the calf muscle. Ambulatory venous pressure measurement by venous cannulation in the foot will help quantify venous hypertension and guide follow-up post intervention. Intravascular ultrasound is helpful in patients with NIVO, if there is no complete obstruction, but in postthrombotic patients with complete venous obstructions, it is seldom helpful.

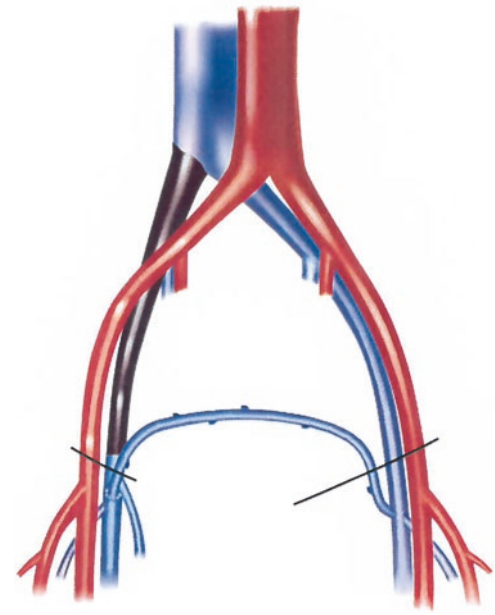

Fig. 38.1 Right-to-left femoral vein bypass of the left great saphenous vein (Palma procedure) (Reproduced with permission from the Mayo Foundation)

Open Reconstruction

Patients who are not candidates for or who failed endovascular reconstructions can be treated with venous bypasses to relieve symptomatic venous outflow obstruction. Venous reconstruction is also performed in those patients who undergo excision of malignant tumors invading the vena cava or iliac veins, although treatment of malignant tumors with invasion of large vein is not the topic of this chapter (refer to Chap. 42).

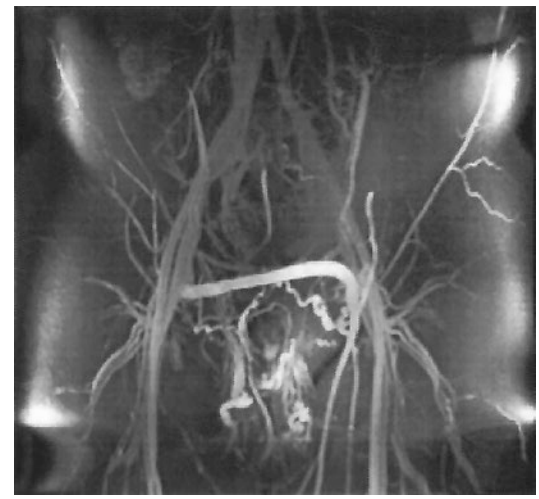

Fig. 38.2 Magnetic resonance angiography at 9 months after a Palma procedure performed for left iliac vein occlusion (Reproduced with permission from the Mayo Foundation)

Crossover Saphenous Vein Transposition (Palma Procedure)

Patients with symptomatic unilateral iliac vein obstruction are candidates for saphenous vein transposition (Palma procedure) (Figs. 38.1, 38.2). With this technique, the contralateral saphenous vein is used for a crossover bypass to decompress venous congestion in the affected limb. The common femoral vein on the affected side is exposed first through a 6- to 8-cm-long longitudinal groin incision. The collateral veins should be preserved if possible. The great saphenous vein of the contralateral leg is dis-

sected through a 3- to 5-cm incision made in the groin crease, starting just medial to the femoral artery pulse. Tributaries of the saphenous vein are ligated and divided, and the saphenous vein is mobilized in a length of about 10–12 cm. A short second upper-thigh incision is made to dissect a 20- to 25-cm-long portion of the saphenous vein. Distally the vein is ligated, and proximal to the ligature, it is divided and pulled up to the groin incision. Alternatively, endoscopic harvesting of the saphenous vein can also be performed. It is essential to free up the saphenofemoral junction completely and dissect at least the anterior wall of the common femoral vein around the saphenous vein so that there is no kink or buckle when the saphenous vein is pulled into the suprapubic tunnel. In some patients with a low saphenofemoral junction, a kink is unavoidable. Excision of the saphenous vein with a 2-mm cuff from the common femoral vein and reanastomosis to the femoral vein with running 6-0 polypropylene suture, after turning the junction upward 180°, can solve this problem. Before tunneling, a small Satinsky clamp is placed on the common femoral vein to allow distention of the saphenous vein and the saphenofemoral junction under gentle pressure using heparinized papaverine–saline solution. The vein is then tunneled subcutaneously in the suprapubic space over to the contralateral side using an aortic clamp to ensure a large tunnel without any constriction of the graft whatsoever. The common femoral vein is cross-clamped with small vascular clamps or bulldogs, and the vein is opened longitudinally in a length of about 2 cm. The anastomosis between the saphenous vein and the femoral vein is performed with running 6-0 polypropylene suture. A vein at least 5 mm in diameter is required to achieve a satisfactory result and provide adequate venous flow. For a smaller vein, a temporary arteriovenous fistula (AVF) can be added between the superficial femoral artery and the saphenous or common femoral vein using a 4- to 5-mm polytetrafluoroethylene (PTFE) graft or a large tributary of the saphenous vein. This fistula must be taken down at 6 weeks to 3 months to enjoy the full benefit of the saphenous bypass. Endovascular occlusion of the fistula with coils or a plug should be considered [8]. The Palma procedure, however, should not be performed with veins 4 mm or smaller. Saphenous vein graft in morbidly obese patients is also not recommended because of the high chance of external compression of the vein.

Overall patency of Palma grafts in 9 series, including 412 operations, ranged between 70 and 83% at 3–5 years [7, 9–11]. Results were better in patients who had no or minimal infrainguinal venous disease and in those with MTS without previous deep vein thrombosis. In the Mayo Clinic experience, primary patency of 70% and secondary patency of 78% at 5 years were noted in 25 Palma vein grafts [7]. Endoscopic vein harvest was linked with decreased primary but not secondary patency rates.

Crossover Femoral Venous Prosthetic Bypass

When the saphenous vein is small or not available, a crossover femoral venous prosthetic bypass with an 8- or 10-mm externally supported expanded PTFE (ePTFE) graft is a good alternative. Similar to the autologous femoral suprapubic bypass, the femoral veins are exposed bilaterally, the ePTFE graft is positioned in the subcutaneous suprapubic tunnel, and an end-to-side anastomosis is performed to the common femoral veins at each side. A distal AVF on the affected side is routinely added to the procedure using a 4- to 5-mm tapered or a 6-mm externally supported PTFE graft for the fistula between the PTFE crossover graft and the superficial femoral artery.

Variable patency rates of ePTFE grafts in this location have been reported and range between 0 and 100%, with data from one large series quoting a 100% (19 of 19) patency rate at long-term follow-up [12]. Gruss and Hiemer observed 77% patency at 5 years in 27 PTFE Palma grafts [13]. The authors recommend use of saphenous crossover grafts over prosthetic bypass grafts based on observed patency.

Saphenous Vein Transposition to the Distal Femoral or Popliteal Vein (May–Husni Procedure)

The May–Husni procedure is helpful in relieving unilateral deep venous outflow obstruction involving the femoral vein. A vertical incision at the level of the distal thigh and the great saphenous vein and distal femoral vein/proximal popliteal vein is exposed. A thigh tourniquet is used to provide a bloodless field after administration of heparin. The distal femoral vein/popliteal vein is then opened longitudinally and old recanalized thrombus excised. An end-to-side anastomosis between the great saphenous vein and the distal femoral vein/popliteal vein using a running 6-0 monofilament suture is then performed (Fig. 38.3).

AbuRahma and colleagues reported their results of their review of 19 patients who underwent the procedure. At a mean follow-up of 66 months, a 56% cumulative 8-year patency was noted [10]. A University of Michigan study of 17 patients with a median follow-up of 103 months noted a primary patency of 56%, primary assisted patency of 69%, and a secondary patency of 75%. An 82% success rate for near or complete resolution of venous claudication and a 67% success rate for venous ulcer healing were also observed [14].

Iliocaval and Femorocaval Bypass

Good risk operative candidates with bilateral iliac obstructions or with iliocaval obstruction should be considered for a femorocaval (Fig. 38.4) or iliocaval (Fig. 38.5) bypass. An ePTFE graft with external support is the preferred conduit for in-line reconstruction of ilioca-

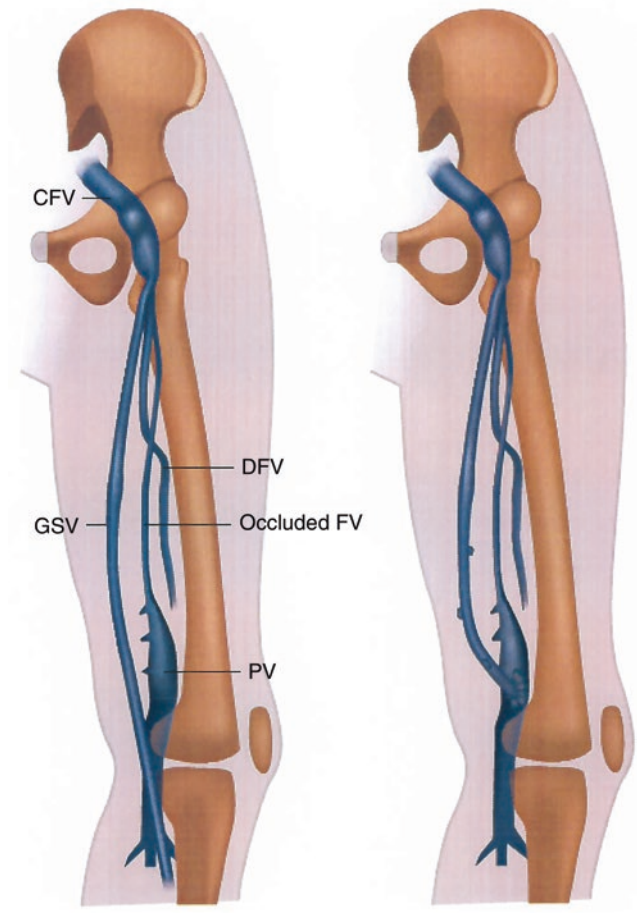

Fig. 38.3 May–Husni procedure. *CFV* common femoral vein, *GSV* great saphenous vein, *FV* femoral vein, *DFV* deep femoral vein, *PV* popliteal vein (Reproduced with permission from the Mayo Foundation)

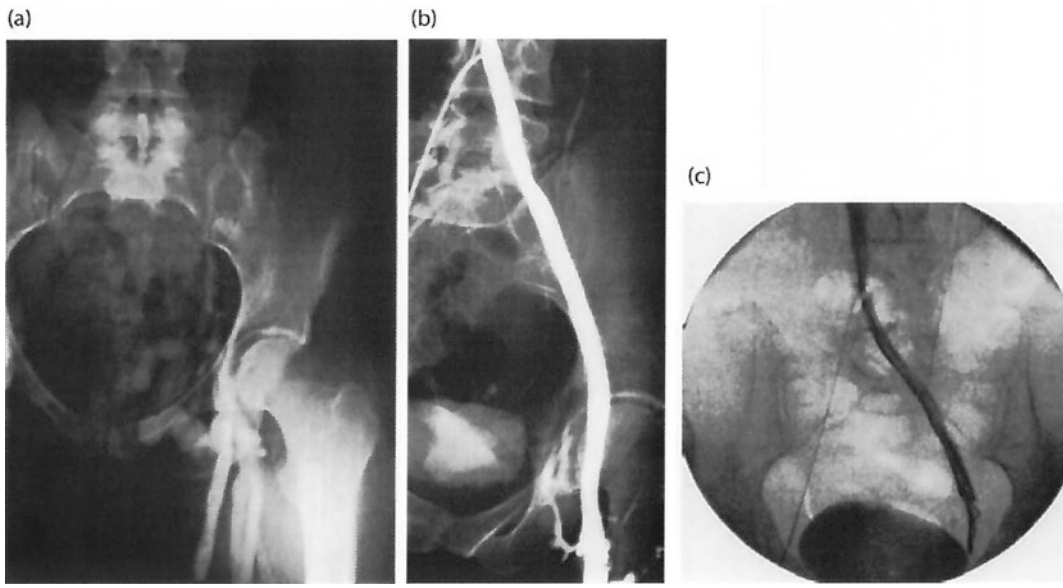

Fig. 38.4 (**a**) Ascending venogram of a 36-year-old woman confirms left iliac vein thrombosis. (**b**) Venogram 1.6 years after implantation confirms widely patent left femorocaval expanded polytetrafluoroethylene graft. (**c**) Venogram at 11.7 years after graft placement. The patient has excellent clinical result (Reproduced with permission from the Mayo Foundation)

val or caval occlusions. A diameter of 12–14 mm is used for iliocaval bypasses and at least 10 mm for femorocaval bypass. The upper portion of the infrarenal IVC at and immediately distal to the renal veins is best approached transperitoneally through a midline incision, reflecting the ascending colon medially and mobilizing the duodenum using the Kocher maneuver. The lower portion of the IVC just above the iliac bifurcation is well approachable through a right flank incision retroperitoneally. If the occlusion is limited to the right common iliac vein, the same incision is used to expose the external iliac vein for the distal anastomosis. The graft is tunneled under the ureter. If a femorocaval graft is placed, a separate 8-cm-long vertical groin incision is made on the affected side, and the graft is tunneled under the inguinal ligament. To all grafts originating from the femoral vein and to most long iliocaval grafts, an AVF is added at the groin. The use of autologous vein for femoroiliac or femorocaval reconstruction is also an option. Because of a relatively small size, saphenous vein in this location can only rarely be used. If short segment of the common femoral or iliac vein must be reconstructed, a better size match is a spiral saphenous vein graft, prepared using the contralateral saphenous vein. The excised vein is opened longitudinally, the valves are excised, and the graft is wrapped around a 28- or 32-mm argyle chest tube. The edges are approximated with running 6-0 polypropylene sutures or with stainless steel nonpenetrating vascular clips. The internal or external jugular veins are other conduits that can be considered for venous reconstruction. The femoral vein is also an alternative for reconstruction of abdominal veins, although morbidity of removing this vein in many of these patients with underlying thrombophilia or PTS is high and other options are recommended. Cryopreserved saphenous or femoral vein has also been reported for venous reconstruction, but long-term patency of these grafts for venous replacement in our experience has been poor.

Reported primary and secondary patency rates at 2 years for femorocaval or iliocaval PTFE bypass grafts for benign disease were 37 and 54%, respectively. In one series, published by Sottiurai, long-term patency of 77% (10 of 13) was reported [12]. The Mayo Clinic has observed

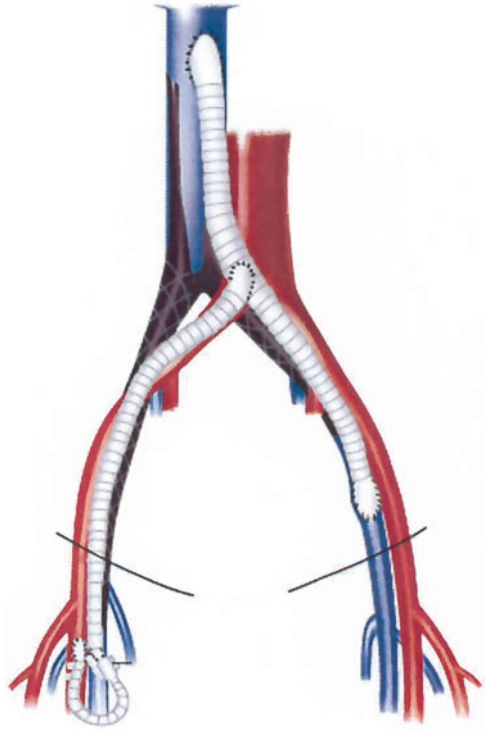

Fig. 38.5 Complex venous reconstruction. A 61-year-old male with previous deep vein thrombosis and inferior vena cava (IVC) filter presented with severe bilateral swelling and venous claudication. He had a partially occluded IVC and bilateral iliac and right femoral obstruction, with occluded bilateral venous stents. Proximal and distal anastomosis of the left external iliac vein (EIV) to the IVC bypass with 14-mm ringed polytetrafluoroethylene (PTFE). An interposition PTFE graft to the right femoral vein from the IVC to the left EIV graft was performed (Reproduced with permission from the Mayo Foundation)

an 86% 5-year patency in short femoroiliac or iliocaval grafts and a 57% patency of long femorocaval bypasses [7].

Cavoatrial Bypass

Patients with symptomatic short membranous occlusion of the IVC or longer congenital or acquired narrowing (caval coarctation) without or with hepatic venous outflow obstruction (Budd–Chiari syndrome) can be treated by cavoatrial bypass when attempts at percutaneous angioplasty or stenting have failed or if transcardiac membranotomy is not feasible. An anterolateral right thoracotomy gives access to the suprahepatic IVC or right atrium, and the pericardium is opened anterior to the phrenic nerve. For short, localized membranous occlusions, a short PTFE interposition graft can be performed through this exposure. If the occlusion extends distal to the hepatic veins, then the abdomen is entered through the same thoracotomy. Transecting the diaphragm circumferentially, mobilization of the liver forward and medially is carried out by division of the triangular and the right coronary ligament. The adrenal gland and the kidney are left in their bed and dissection is moved more medially. Excellent exposure of the suprarenal IVC can be achieved through this approach. If the distal anastomosis has to be made more caudally, a separate right subcostal or midline incision can be performed as previously described. For a cavoatrial bypass, an end-to-side anastomosis to the IVC is performed, and the graft is routed under the liver parallel to the IVC. The graft is then anastomosed end to side to the suprarenal IVC or the lower portion of the right atrium. Partially occluding clamps can be used for vascular control while performing the anastomoses, and cardiopulmonary bypass is not required. Traumatic or iatrogenic occlusions can also be managed by this technique. The use of a 16- to 20-mm externally supported PTFE graft is recommended.

The reported clinical success rate with cavoatrial grafts is about 77%, with a perioperative mortality of 3% and 2-, 5-, and 10-year patency rates of 86, 78, and 57%, respectively. Three cavoatrial grafts placed for nonmalignant disease have been 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 [7]. Kieffer's group reported on long-term patency in five of six grafts placed for membranous occlusion of the vena cava [15]. Victor and coworkers reported patent grafts at 21 months to 6 years after the operation in 5 patients [16].

Special Considerations

Endophlebectomy

Partial recanalization of the thrombus frequently results in multiple residual lumens in the post-thrombotic femoral vein. Excision of such organized and fibrotic thrombus will enlarge the lumen, although the resulting exposed collagen in the media of the vein wall is more thrombogenic than the intact venous wall. Nevertheless, careful endophlebectomy will improve inflow to a great extent; attention, however, must be paid to avoid injury to the thin residual venous wall. This procedure has also been performed combined with deep venous valve transplantation in patients with PTS. In patients who have localized high-grade stenosis of the common femoral vein, this operation alone is sufficient to improve venous outflow. The defect is closed with a patch using a segment of the saphenous vein or bovine pericardium. The endophlebectomized segment can also be used to improve inflow for iliocaval stenting or for a cross-femoral or femorocaval bypass. In a series of ten patients who underwent endophlebectomy alone, early results showed 77% patency of the operated segments at 8 months [17].

Adjunctive Procedures

With the exception of caval reconstructions or short iliocaval grafts, prosthetic bypasses used for venous outflow obstruction of the legs need an adjunctive temporary AVF to maintain patency. The best technique is a 4- to 5-mm PTFE graft (Fig. 38.5) that is about 2-cm long and is placed between the superficial femoral artery and the lower portion of the PTFE venous graft. The authors use a tapered 4 × 7-mm PTFE graft to obtain a segment suitable for AVF. Short straight graft or a small loop fistula with a 6-mm PTFE can be created. Both anastomoses are performed with 6-0 polypropylene sutures. A small Silastic sheet is wrapped around the bypass to prevent development of surrounding scar tissue. A 2-0 polypropylene suture is then tied to this Silastic sheath and positioned under the skin incision for easy identification at time of open closure. A longer PTFE straight or loop graft used for the fistula can also be closed later percutaneously, using an Amplatzer vascular plug (St Jude Medical, St. Paul, MN) [8]. Patients who have saphenous Palma grafts undergo takedown of the fistula at 3 months, with endovascular or open procedure. Patients who have PTFE grafts will keep the AVF longer, if possible. The AVF increases flow through the graft, decreases platelet and fibrin deposition, and contributes to improved patency. It also provides time for pannus formation over the anastomoses during the initial period when the graft surface is most thrombogenic. Potential side effects include high cardiac output, functional outflow obstruction resulting in high distal venous pressures, and accelerated intimal hyperplasia.

Anticoagulation

Due to relatively slower venous velocities, grafts placed in the venous system have a higher rate of thrombosis than arterial grafts. Infrainguinal venous obstruction and valvular incompetence further decrease inflow to the graft and are major contributing factors to failure. Thrombophilia is prevalent among patients undergoing venous reconstructions, and many patients have absent circulating anticoagulants, such as protein factor C, protein factor S, and antithrombin III, or have factor V Leiden mutation. The thrombogenic surface of any prosthetic graft also increases the risk of graft failure. For these reasons, perioperative anticoagulation is indicated in patients undergoing reconstructive venous surgery for deep venous obstruction. The patient is fully heparinized during reconstruction, and protamine is avoided at the completion of the procedure. Heparin at a dose of 500 units/h is started in the operating room through a 20-gauge pediatric central line that is placed through the saphenous vein of the affected limb and advanced to the distal anastomosis of the prosthetic graft. Complete postoperative systemic heparinization is achieved by 48 h, and full-dose low-molecular-weight heparin is continued subcutaneously for another 3–5 days, given simultaneously with warfarin. The incidence of postoperative bleeding has been between 5 and 10%, mainly as a result of anticoagulation. Warfarin is continued indefinitely in most patients

with prosthetic grafts and in all with a known underlying coagulation abnormality.

Follow-Up and Reintervention

Duplex scan on the first postoperative day or contrast CT/MR venography is performed to confirm graft patency. Stenosis or thrombosis is corrected immediately after recognition. If thrombosis occurred in a graft without fistula, thrombectomy is done with addition of a fistula. Graft stenosis discovered during surveillance is treated first with angioplasty or venous stenting. Graft thrombosis is treated with thrombolysis, angioplasty, and stenting. Surgical revision is usually limited to patch angioplasty of the stenotic portion of the graft, although occasionally aneurysmal dilation of the saphenous crossover graft may also need surgical correction.

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Hybrid Reconstruction for Post-thrombotic Iliofemoral Venous Obstruction

39

Anthony J. Comerota and Zakaria Assi

Clinical Pearls

1. Hybrid iliofemoral reconstruction can be performed in a staged fashion with venogram first to obtain access and wire crossing followed by open endovenectomy of the femoral vein.
2. Percutaneous popliteal vein access ensures wire crossing and allows intraoperative venography with IVUS and immediate postoperative local administration of low-dose anticoagulation.
3. There is no "thrombus" in chronically occluded veins after deep vein thrombosis, and the lumen is obliterated by fibrotic tissue that resembles neointimal hyperplasia.

Introduction

Iliofemoral deep venous thrombosis (IFDVT), which sometimes presents as phlegmasia cerulea dolens (PCD), is associated with significant acute morbidity and severe post-thrombotic syndrome (PTS). Compartment pressures are often significantly elevated to a level consistent with an acute compartment syndrome [1] and may remain elevated if iliofemoral recanalization does not occur. Strategies of thrombus removal have been shown to reduce compartment pressures and reduce post-thrombotic morbidity [2, 3] and improve quality of life [4]. However, most patients today continue to be treated with anticoagulation, thereby leaving occlusive thrombus in situ. Most patients with IFDVT treated with anticoagulation alone fail to recanalize, resulting in chronic post-thrombotic obstruction of the iliofemoral venous system. Long-term follow-up of these patients has demonstrated that 95% have chronic venous insufficiency, 70% fail to recanalize, and 30% develop venous claudication or venous ulceration within 5 years [5, 6].

Labropoulos et al. [7] studied patients with post-thrombotic venous disease, measuring venous pressures at rest and after post-occlusive reactive hyperemia. They demonstrated that patients with iliofemoral post-thrombotic disease had the highest resting and hyperemic venous pressures. These high venous pressures translate into post-thrombotic morbidity as reported by Kahn et al. [8] demonstrating that severe PTS

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was much more likely in patients with IFDVT with a calculated odds ratio of 2.23.

The principles for successful treatment of post-thrombotic iliofemoral venous obstruction are the same as those that vascular surgeons have recognized as important for arterial reconstruction. Successful venous reconstruction requires good outflow, good inflow, and an adequate conduit. An underlying prothrombotic condition also must be properly addressed. Chronic post-thrombotic iliofemoral obstruction can be treated with percutaneous stenting if the common femoral vein (CFV) is patent. However, if the CFV is chronically obstructed, the success of venous stenting is markedly compromised, as inflow to the stent is inadequate to maintain patency. Because of this observation, we have adopted a treatment strategy which includes disobliteration of the CFV with open endovenectomy. Following the endovenectomy, the iliac venous system is recanalized with balloon venoplasty and stenting [9, 10].

Patient Selection

Patients selected for this procedure are those with severe, incapacitating PTS who have been treated for IFDVT with anticoagulation alone or failed attempts at thrombus removal. The majority of patients have had recurrent episodes of DVT and most are on indefinite anticoagulation. The overwhelming majority have C4–C6 disease. Occasionally, a patient can have debilitating venous claudication with minimal associated edema or pigmentation.

Preoperative Evaluation

Following a complete history and physical examination, a venous clinical severity score (VCSS) and a Villalta score are documented. The patients are also classified according to the clinical classification of CEAP. Completion of the validated venous insufficiency epidemiologic and economic study-quality of life/symptom (VEINS-QOL)/SYM questionnaire is completed.

The VCSS identifies 9 clinical characteristics of chronic venous disease that are graded from 0 to 3 (absent, mild, moderate, severe) with specific criteria to avoid overlap or arbitrary scoring [11]. The Villalta scale consists of six clinician-rated physical signs and five patient-rated venous symptoms of which each is rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) [12]. Points are summed to produce a total score (range 0–33). Subjects are classified as having no PTS if the score is 0–4, mild if the score is 5–9, moderate if the score is 10–14, and severe if the score is ≥15. Patients with venous ulceration are given 15 points. The Villalta scale is a validated, reliable method of identifying patients with PTS [12]. The CEAP clinical classification is based on a 7-point clinical assessment of venous disease [13]. The anatomical distribution of venous obstruction includes the CFV and iliac venous segments in all patients. The VEINS-QOL/SYM questionnaire is a tool designed to assess quality of life (QOL) and symptoms of chronic venous insufficiency [14, 15] and is modeled after the SF-36.

All patients undergo ascending phlebography, most commonly from an ultrasound-guided popliteal vein puncture (Fig. 39.1). Bilateral ascending phlebography is now part of the routine preoperative evaluation. This is important in those who require the contralateral iliofemoral venous system to serve as the outflow channel. These studies are discussed with the patient and a plan of treatment is proposed and scheduled. Three days prior to the procedure, the patient is started on combined platelet inhibition using aspirin 81 mg/day and clopidogrel 75 mg/day. Chlorhexidine showers twice daily are implemented and vitamin K antagonists discontinued.

The day prior to the hybrid procedure, the iliofemoral segment is recanalized from a popliteal approach, and a 5 French catheter is advanced from the popliteal vein into the patent vena cava (Fig. 39.2). This procedure can take 2 h or more. This ensures there will be access to and through the occluded iliac vein segments on the next day, which is the day of operation. If it is not possible to pass the guidewire through the ipsilateral occlusion preoperatively, a cross-pubic, femoral

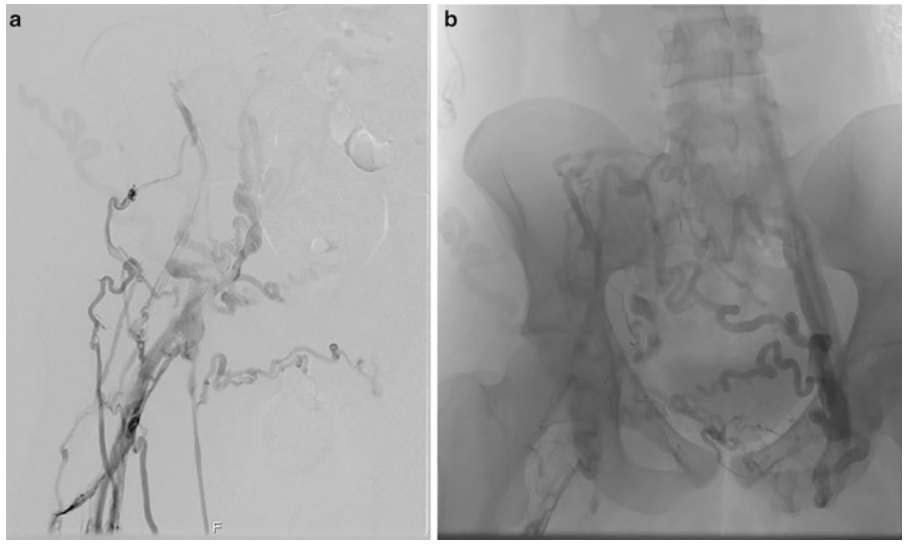

Fig. 39.1 Ascending phlebogram in prone position the day prior to the operative procedure. The sheath and catheter were accessed through the left popliteal vein. Note occlusion of the left common femoral vein and iliac veins (**a**) with cross pelvic collaterals filling the right iliac venous system (**b**)

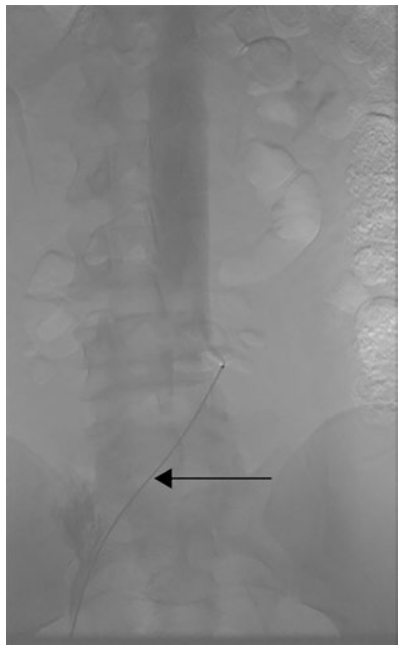

Fig. 39.2 A preoperative guidewire and catheter were advanced from the left popliteal vein into the distal IVC (*arrow*). This facilitates efficient guidewire and catheter passage to deliver balloon catheters and stents during the operative procedure

to contralateral external iliac vein bypass or a Palma procedure is planned.

On the operative day, exposure of the entire CFV, proximal femoral vein and profunda femoris vein, saphenofemoral junction, and distal external iliac vein is obtained via a longitudinal inguinal incision (Fig. 39.3). Control of all branches is crucial to a bloodless procedure. Small tributaries are ligated. Patients are fully anticoagulated with 100 IU/kg bolus of unfractionated heparin (UFH), which is supplemented hourly during the procedure. A limited venotomy is initially performed in order to establish that there is no back-bleeding from any tributary. If bleeding from the limited venotomy is observed, the entire section of CFV is reexamined so that the patent back-bleeding side branch can be controlled. The venotomy extends the entire length of the CFV, extending from the distal external iliac vein to the proximal femoral vein. Dense fibrous tissue and weblike synechiae are removed from within the lumen with sharp and blunt dissection; often the entire lumen is obliterated. The majority of patients require sharp excision of

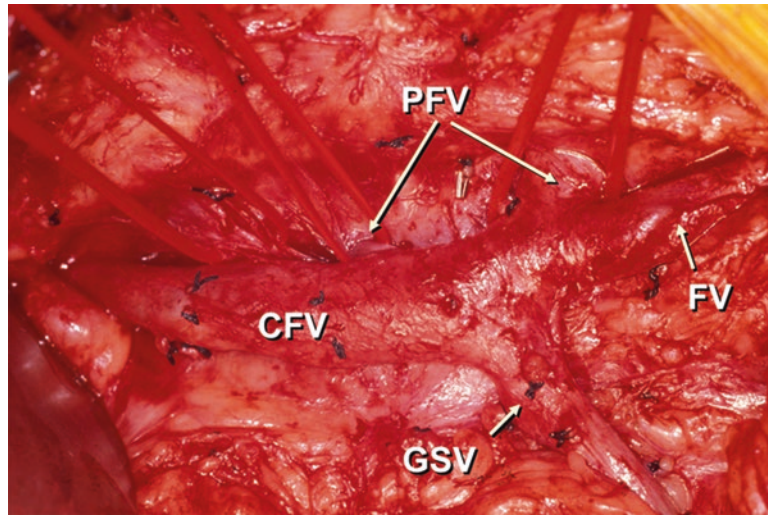

Fig. 39.3 Operative exposure showing the common femoral vein (CFV), profunda femoris veins (PFV), femoral vein (FV), and great saphenous vein (GSV) at the saphenofemoral junction

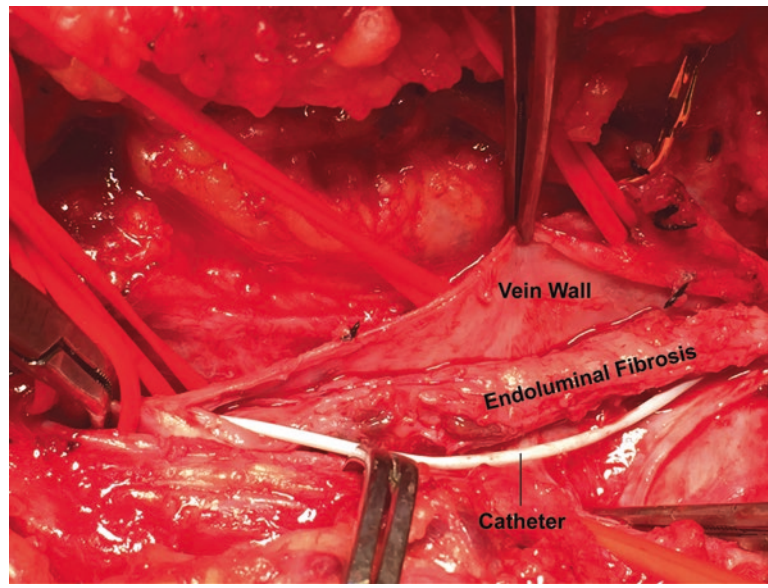

Fig. 39.4 Intraoperative image of the long venotomy with dissection of the endoluminal fibrosis away from the vein wall. This image shows the catheter which was advanced from the popliteal vein to the patent IVC. This catheter will be used for efficient and rapid passage of a guidewire into the IVC

their fibrous occlusion. Occasionally, small segments of fibrous disease can be teased away from the vein wall with an endarterectomy spatula; however, this is the exception rather than the rule. This procedure is unlike an arterial endarterectomy, where atherosclerotic plaque peels away from the vessel wall quite easily.

Care is taken to extend the endovenectomy over the orifice of the profunda femoris vein; there is always a large posterior branch of the CFV above the profunda, which is likely another important branch of the profunda system. Figure 39.4 shows the catheter traversing the CFV and the dissection of the intraluminal fibrosis away from the vein wall. After the endovenectomy of the entire CFV is completed (Fig. 39.5), patch closure of the venotomy is performed using bovine pericardium, leaving the distal centimeter open to introduce a 10 French sheath through which the endoluminal stenting of the iliac venous segment is performed.

The catheter in the CFV is transected and an Amplatz Super Stiff (Boston Scientific, Natick, MA) guidewire advanced through the catheter

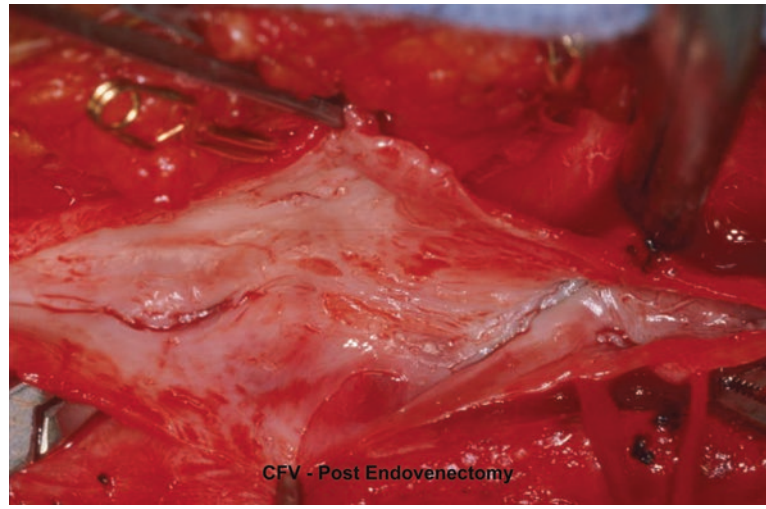

Fig. 39.5 Intraoperative image after endovenectomy is completed

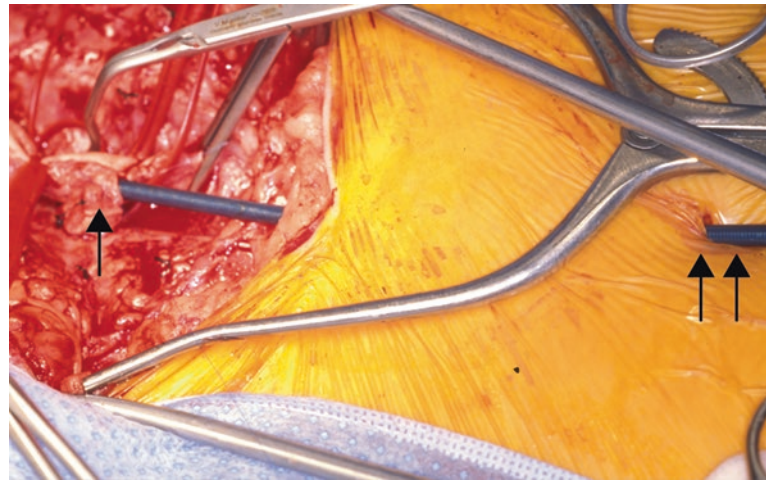

Fig. 39.6 Photograph showing a 10 F sheath entering the upper thigh through a separate puncture wound (*double arrow*) and subsequently entering the distal endovenectomized CFV (*single arrow*). This permits easy access for balloon catheters and stents without angulation. A tourniquet is placed around the CFV just above the entry of the sheath into the CFV

into the vena cava. The catheter is then removed and the guidewire used for ipsilateral angioplasty and stenting. A separate stab incision is made below the inguinal wound through which the 10 French sheath is passed traversing the subcutaneous tissue and enters the venotomy over the guidewire (Fig. 39.6) with no angulation.

The iliac venous system and, if necessary, vena cava are sequentially recanalized with balloon dilation and stenting. In general Wallstents (Boston Scientific, Marlborough, MA) are currently preferred because of their resistance to compression. 14–16 mm stents are used for the common iliac veins and 12–14 mm stents for the external iliac veins. Stenting generally progresses from the cephalad CFV or distal external iliac vein superiorly (Fig. 39.7). The stents are post-dilated to their target diameter. A vena cavogram is obtained to facilitate accurate stent delivery into the common iliac vein and IVC (Fig. 39.8). Following recanalization and venographic confirmation of unobstructed venous drainage from the CFV into the IVC (Fig. 39.9), an intravascular ultrasound is performed to further examine stent position and degree of compression (Figs. 39.10 and 39.11). Occasionally, stents have to be reinforced with additional stents to increase the radial force. The sheath is removed and closure of the patch venoplasty is completed.

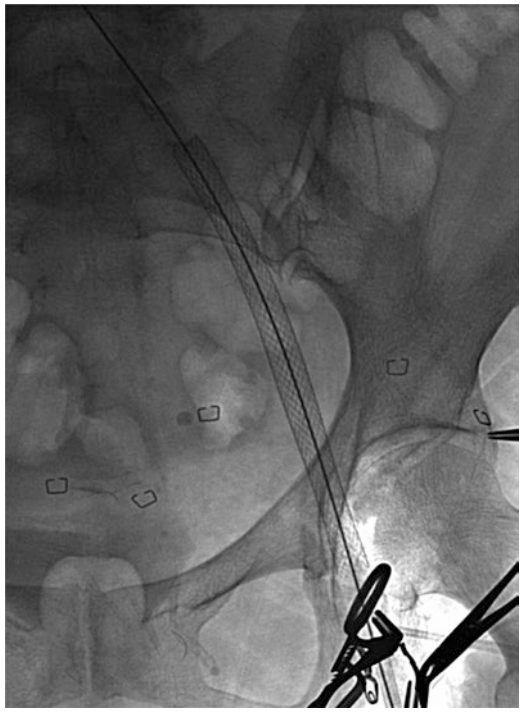

Fig. 39.7 Intraoperative plain film demonstrating partially stented iliofemoral segment. The stents are constructed from the CFV to IVC

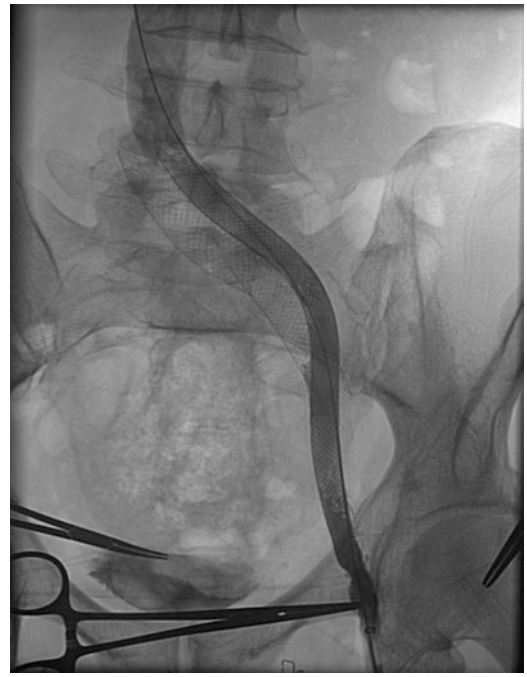

Fig. 39.9 Intraoperative completion phlebogram showing unobstructed venous drainage from the operated CFV to the IVC

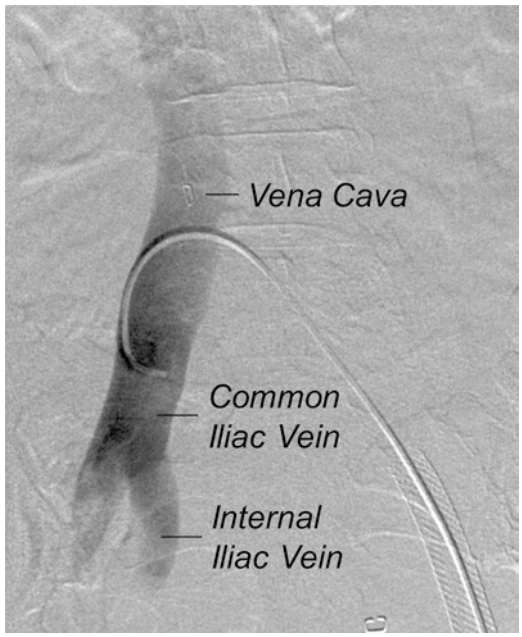

Fig. 39.8 Intraoperative venogram of the vena cava to guide precise placement of the left common iliac vein stent

An arterial venous fistula (AVF) is then constructed from the superficial femoral artery to the distal CFV. A 3.5 mm arterial punch is used to remove a circular piece of arterial and venous wall. The AVF is limited to 3.5–4 mm in diameter. When an autogenous AVF is performed, a piece of bovine pericardium is wrapped circumferentially around the AVF and sutured in place to prohibit enlargement (Fig. 39.12). If a prosthetic is required to construct the AVF, a 4 mm PTFE graft is used.

A 7 French Silastic closed suction drain is brought through the stab incision used for the 10 French sheath and maintained on suction postoperatively until drainage volume is less than 20 mL/12 h. The incision is closed with several layers of running absorbable suture, obliterating dead space with the goal of ensuring lymphostatic and hemostatic closure of the subcutaneous tissue. Heparin is not reversed.

Initially postoperative systemic anticoagulation was used, which was accompanied by an unac-

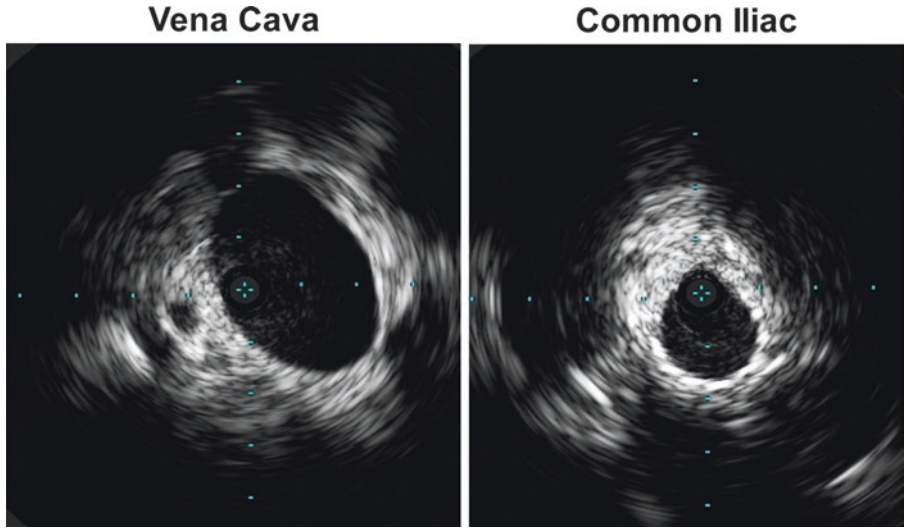

Fig. 39.10 Completion intravascular ultrasound (IVUS) showing normal vena cava and normal common iliac vein

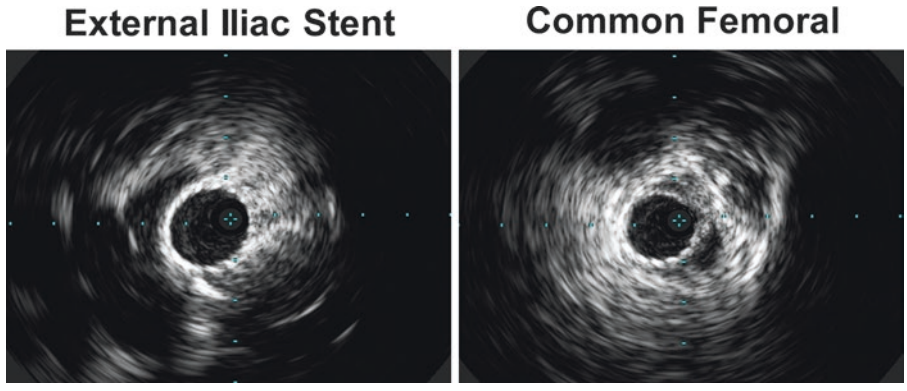

Fig. 39.11 Intraoperative completion IVUS showing a normal external iliac stent and normal common femoral stent

ceptable number of wound hematomas. Presently, a sheath in the ipsilateral popliteal vein, placed preoperatively, is used for regional anticoagulation. This allows us to use 700–800 IU/h of UFH, delivering a high concentration of heparin into the target vein but minimizing the overall systemic dose of heparin, which has been associated with a major drop in wound hematomas. The patients are converted to warfarin with a target INR of 2.5–3.5. The patient's leg is wrapped from the base of the toes to the thigh, and the patient is encouraged to ambulate, using a IV pole with wheels carrying the UFH infusion. Most patients are anticoagulated indefinitely. Clopidogrel is continued for 8 weeks, as we believe the stents are endothelialized by that time.

Technical Evolution and Procedure Outcomes

We have performed CFV endovenectomy with endoluminal recanalization for the past 8 years. During this time, the procedure has evolved to one in which we believe success can be anticipated

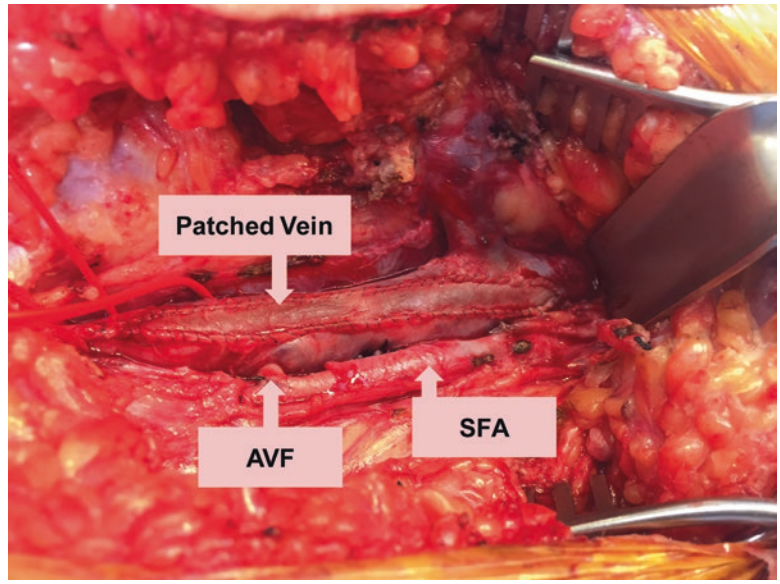

Fig. 39.12 Intraoperative photograph showing completed operation. The long venotomy was closed with a bovine pericardial patch. The distal stent is landed in the cephalad portion of the endovenectomized and patched CFV. A small AV fistula is constructed from the SFA to the distal CFV

and complications and failures minimized. The initial procedure consisted of preoperative venography, common femoral vein endovenectomy, patch venoplasty, and intraoperative passage of a guidewire into the patent IVC followed by venoplasty and stenting, with postoperative systemic anticoagulation. Iliac vein rupture (occurring once) was treated with a stent graft.

The "contemporary" procedure begins with a full preoperative evaluation including bilateral venography; a plan of reconstruction is then discussed with the patient and scheduled as mentioned; dual platelet inhibition is begun 3 days preoperatively, the day before the procedure with a guidewire/catheter advancement into the IVC via sheath in the ipsilateral popliteal vein. The following day, the patient receives open operation, a complete CFV endovenectomy, patch venoplasty, intraoperative balloon venoplasty, stenting of the IVC (if necessary) and iliac veins, landing the stent into the endovenectomized CFV above the saphenofemoral junction, completion IVUS, construction of a small (4 mm) distal CFV-AVF wrapping autogenous AVFs so they don't dilate, low-dose regional anticoagulation with UFH via the popliteal vein sheath, conversion to oral anticoagulation with warfarin to a target of 2.5–3.5, and early ambulation and indefinite oral anticoagulation. Ruptured iliac veins are now treated with a second bare-metal stent relining the first and prolonged balloon inflation (n = 1). When comparing the initial and our present techniques (Table 39.1), we found that 17 patients (53%) treated with the early technique had major complications. These complications included iliofemoral thromboses, major wound bleeds, and two wound infections. One iliac vein rupture treated with a stent graft is thrombosed.

2 of 14 (14%) patients treated with the "contemporary" technique had procedural complications, 1 seroma and 1 wound infection. One iliac vein rupture treated with a second stent relining the first remains patent. It appears that this evolved technique insures that unobstructed venous drainage is restored from at least the profunda femoris vein to the IVC. The increased velocity produced by the routine AVF reduces thrombosis, and the lower heparin dose permitted by regional infusion reduces bleeding complications.

Results

The procedural results (30 days) are summarized in Table 39.1. We have long-term results on the first ten patients who underwent CFV endovenectomy with endoluminal recanalization. The remaining 21 patients are being presently studied with their long-term outcomes being evaluated.

Table 39.1 Comparison of the technical evolution and procedural outcomes of CFV endovenectomy with iliocaval recanalization

	Procedure	
Variable	Initial ($N = 17$)	Present ($N = 14$)
Preoperative venogram: bilateral	No	Yes
Preoperative guidewire/ catheter	No	Yes
Preoperative combined platelet inhibition	Yes	Yes
Rx rupture vein	Stent graft	Second bare-metal stent to reline
Completion IVUS	No	Yes
Patch closure	Yes	Yes
Arteriovenous fistula	Selective	Routine
Postoperative heparin	Systemic	Regional
Complications	82% (9/17) 5—acute thrombosis 4—major bleed 3—wound infection 2— CFV stenoses requiring intervention	14% (2/14) 1—seroma 1—wound infection

The first ten patients demonstrated an improved VCSS score from 17 to 9.8 ($p = 0.02$). The Villalta scores improved from 13.6 preoperatively to 6 postoperatively ($p = 0.002$). Overall QOL and symptoms improved as assessed by the VEINS-QOL/SYM ($p = 0.01$ and 0.02). Preoperative CEAP scores in the study patients ranged from C4 (pigmentation changes, venous eczema, lipodermatosclerosis) to C5 (healed venous ulceration) and C6 (active venous ulceration). Two patients with venous ulcers healed and therefore moved from C6 to C5. Patients with pigmentation seemed to improve; however, their pigmentation has not yet resolved.

Ultrasound evaluation and follow-up demonstrated one segmental occlusion of the CFV, a segmental occlusion of the external iliac vein, and thrombosis of the stent graft used in the patient who was treated for a ruptured external iliac vein. The remaining patients continued to have patent veins.

Histologic Characterization of Post-thrombotic Tissue

The intraluminal contents of 18 chronically occluded post-thrombotic CFVs were obtained from our first 16 patients undergoing endovenectomy and intraluminal recanalization of their occluded iliocaval venous segments. The specimens were studied to determine the nature of the tissue causing chronic iliofemoral venous obstruction and whether the tissue evolved over time [16].

The initial phase of this study described the morphologic composition of the intraluminal tissue, specifically to identify tissue type and the presence of recanalization and neovascular channels. The von Kossa stain, Masson trichrome stain, and hematoxylin and eosin (H&E) stains were used to examine histologic morphology including the relative density of collagen, presence of inflammatory cells, neovascularization and recanalization channels, and location of neovessels and their relationship to recanalization channels. The second phase of this study was to assess if there was an evolutionary difference of the tissues within the specimens over time by comparing young specimens (<1 year) to mature specimens (> 10 years). The endothelial cells within neochannels were evaluated using antibodies to specific biomarkers for functional characterization. The biomarkers used were vascular endothelial cell growth factor receptor-2 (VEGFR-2), angiopoieten-1 receptor (TIA-2), platelet endothelial cell adhesion molecule-1 (CD-31), and von Willebrand factor (vWF).

The gross specimens are illustrated in Fig. 39.13. Grossly, all looked similar and appeared to be completely fibrous with no evidence of thrombus. The tissue was composed predominately of collagen. When collagen subtyping was completed, collagen type I composed 80–90% of the specimens and collagen type 3 in 10–20% of the specimens. VEGFR-2, a biomarker for neovascularization and angiogenesis, was more prominent in young specimens indicating more angiogenic activity in younger patients. There was a more prominent reaction with the stabilized TIE-2 antibody in the channels of mature specimens than in the

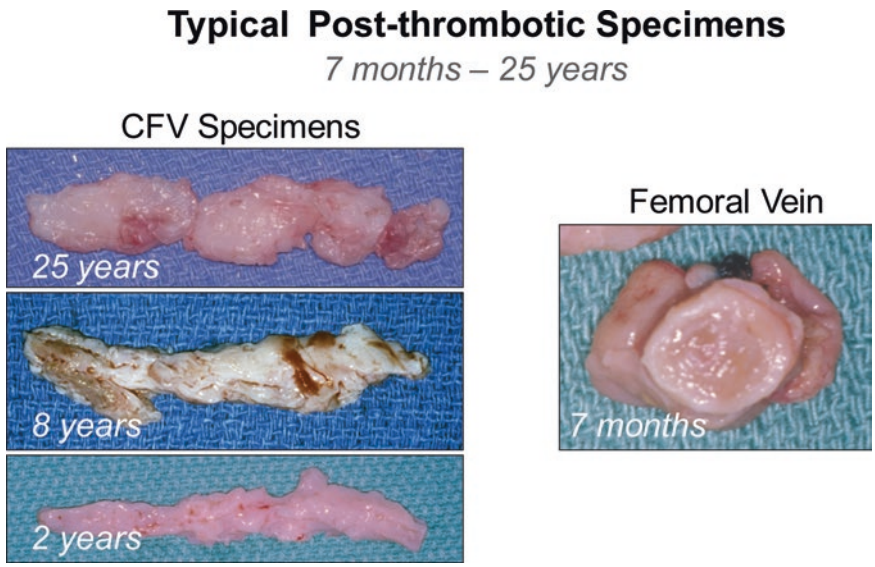

Fig. 39.13 Photograph of four operative specimens ranging from 7 months to 25 years after DVT. All specimens reveal collagen with no evidence of thrombus

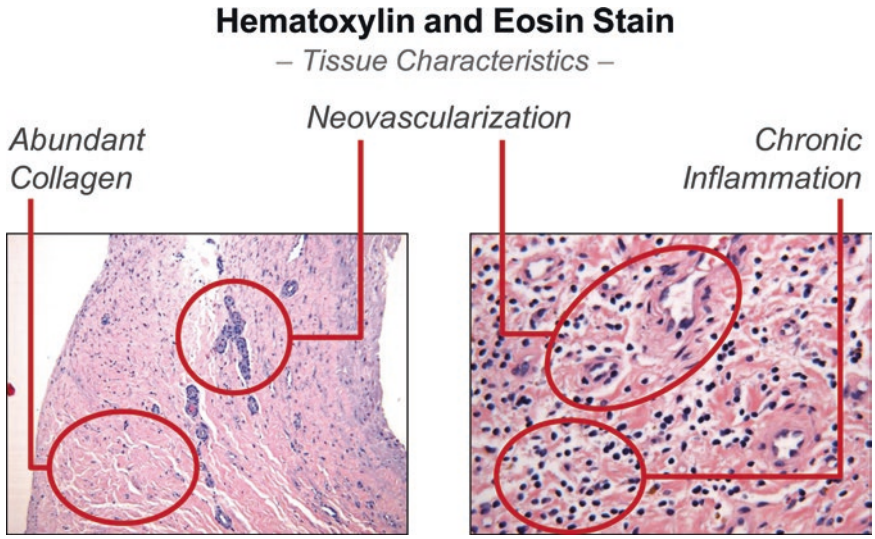

Fig. 39.14 Hematoxylin and eosin stain of typical post-thrombotic tissue removed from the CFV. Abundant collagen, neovascularization, and chronic inflammation are routinely observed. There is no evidence of thrombus

young specimens. CD-31, a transmembrane glycoprotein regulating vascular integrity and cell survival and modulating integrin function, was similarly expressed in the neovascular channels of young and mature intraluminal tissue. As might be expected, there was a greater concentration of vWF in mature specimens compared to young specimens. Figure 39.14 demonstrates the abundant collagen and the neovascularization occurring predominately in loose collagen as well as chronic inflammatory cells.

Summary

Common femoral vein endovenectomy is important in restoring an outflow channel to the lower extremity for patients with post-thrombotic iliofemoral obstruction involving the CFV. The hemodynamic goal is to provide unobstructed venous drainage from the orifice of the profunda femoris vein to the vena cava. In patients in whom ipsilateral venous recanalization cannot be successfully completed, a cross-pubic venous bypass is performed. This decision is made preoperatively, allowing appropriate planning and conduct of the procedure. The procedure has evolved over the course of the past 8 years, with its current iteration being associated with improved success and fewer operative complications. It remains a procedure in evolution.

The tissue occluding post-thrombotic veins is predominately type I collagen. The tissue appears to evolve over time as illustrated by biomarker evaluation using VEGFR-2, tie-1, CD-31, and vWF. There was no evidence of thrombus in any of the specimens; therefore, the term "chronic thrombus" should be eliminated as it may lead to misconceptions on the part of clinicians caring for these patients.

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Chronic Obstruction of the Inferior Vena Cava

40

Jordan R. Stern and Andrew J. Meltzer

Clinical Pearls

1. IVC occlusion is very rare with incidence estimated at 1.7 cases per 100,000 of hospitalized patients.
2. Cancer is diagnosed in up to 37% of patients with IVC occlusion.
3. Chronically thrombosed IVC filters can be displaced and excluded in situ using balloon angioplasty and stenting to recreate a flow channel in the cava.

Introduction

Venous thromboembolism (VTE) represents a significant public health issue in the United States, with over 900,000 cases and 300,000 deaths estimated annually [1]. A minority of deep vein thrombosis cases affect the central veins, including the iliofemoral system and the inferior vena cava. Chronic obstruction of the inferior vena cava can occur due to a variety of causes, including primary thrombotic disease, complications from inferior vena cava (IVC) filter placement, and direct or indirect effects of malignancy. Patients can present with a range of symptoms, and a large proportion may be asymptomatic if collateralization is robust. For symptomatic patients, medical therapy including systemic anticoagulation, compressive therapy, and local wound care may not be sufficient. Endovascular and open surgical techniques can lead to significant clinical improvement with durable, long-term relief. In this chapter, we aim to summarize the technique and results for both approaches.

Epidemiology and Etiology

In the United States, IVC thrombosis is a rare entity, occurring in approximately 0.07% of hospitalized patients and 1.7 cases per 100,000 in the general population. The incidence increases with age, perhaps at least in part due to the correlation with underlying malignancies. IVC thrombosis is most common in African-Americans, followed by Caucasian patients. There is a very low incidence of IVC thrombosis (and, indeed, DVT in general) among patients of Asian descent [2].

Congenital abnormalities of the inferior vena cava represent a very small population of those with chronic IVC occlusion, with a prevalence of 0.3–0.6% in the general population [3]. These

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patients have some failure of embryogenesis, manifested by a range of phenotypes ranging from various intravascular membranes and webs to venous aneurysms and complete absence of the vena cava [4]. Further exacerbating the problem, there appears to be an independent correlation with inherited hypercoagulable states [5, 6]. Congenital lesions are generally divided into three types, based on anatomic location. Intrarenal pathology includes congenitally absent, left-sided, and duplicated IVC. Retroaortic left renal vein and circumaortic renal venous rings comprise the renal abnormalities, and suprarenal pathology includes absent IVC with azygous or hemiazygous continuation. Aneurysms, membranes, and webs can occur in any segment [3]. These abnormalities generally lead to thrombosis and subsequent caval occlusion due to narrow flow channels which predispose to venous hypertension, stasis, and thrombus formation [7].

The most common acquired cause of inferior vena cava occlusion is deep vein thrombosis (DVT). Most patients have isolated, primary thrombosis of the IVC, with only 22% demonstrating additional thrombotic foci [2]. The converse is also true, and caval thrombosis is only present in about 1–2% of all patients with DVT [2, 8]. A large proportion of these patients have an underlying malignancy: when an IVC thrombus is diagnosed, cancer is present in approximately 37% [2]. Primary suprahepatic IVC thrombosis may lead to organized, fibrous membranes and subsequent development of hepatic venous outflow obstruction and liver failure (Budd-Chiari syndrome). This variant is often termed obliterative hepatocavopathy and can have devastating clinical consequences [9]. Iatrogenic thrombosis can occur secondary to instrumentation and endothelial damage and presence of indwelling catheters [10] but is most frequently associated with placement of IVC filters (Fig. 40.1). IVC filters can lead to caval thrombosis in 4–30% of cases [11]. Less common causes include direct extension of tumor thrombus (most commonly secondary to renal cell carci-

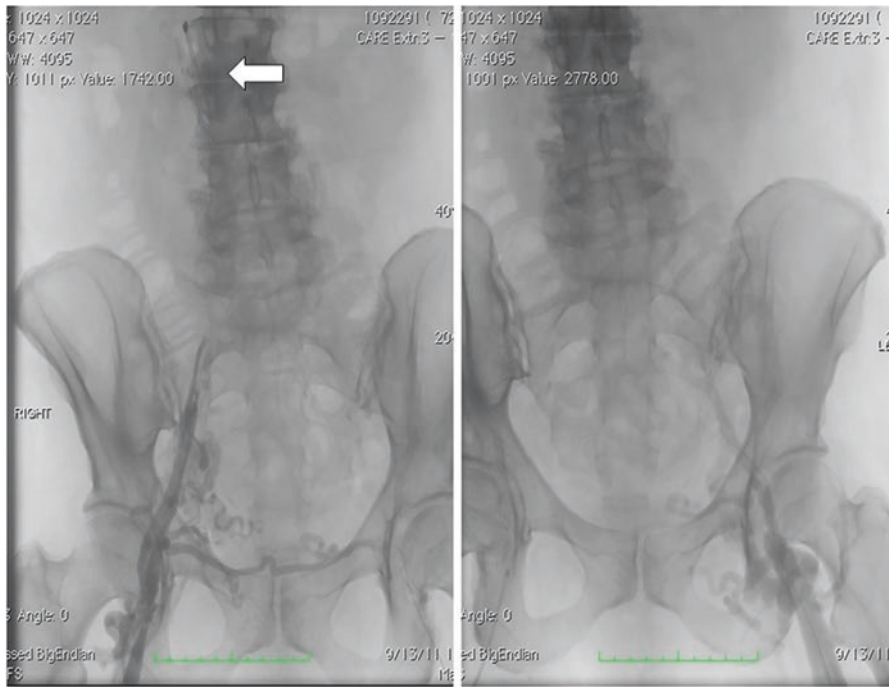

Fig. 40.1 Chronic total occlusion of the inferior vena cava secondary to thrombosed IVC filter. Digital subtraction venography demonstrates no flow into the IVC from either iliac vein, with multiple collateral vessels seen bilaterally. IVC filter is indicated by the *white arrow*

noma) [12], trauma [13], radiation exposure, and retroperitoneal fibrosis [14].

Clinical Features

Depending on chronicity and degree of collateralization, as well as anatomic location of the obstruction, thrombosis of the IVC can present with a range of clinical signs and symptoms. Patients with acute thrombosis may present with severe pain and lower extremity edema or even life- and limb-threatening sequelae such as phlegmasia cerulea dolens [3]. Neurologic symptoms such as sciatic pain and cauda equina syndrome have also been described [15].

Those with chronic obstructive pathologies tend to present more innocuously, and some are completely asymptomatic [16]. Many of these patients develop extensive collateral networks through the iliac, hemiazygous, and azygous venous networks [17] and may only become symptomatic if thrombus propagates caudally into the iliac or femoral veins [18]. Chronic lower extremity symptoms are generally classified by the revised CEAP grading system [19] and may range from mild-limb swelling to venous claudication and ulcer formation. Symptom severity may also be affected by concomitant lower extremity venous reflux and venous hypertension, which is more likely to lead to venous ulceration and pain than deep venous obstruction alone [20].

Clinical history should be focused on severity and chronicity of symptoms and the degree to which the patient's lifestyle has been affected. Often times, patients have already attempted noninvasive therapies such as compression stockings and local wound care, as well as lower extremity venous procedures such as vein stripping or ablation, prior to presentation. Bilateral symptoms may be a clue suggestive of occlusion of the vena cava, rather than pathology limited to the iliofemoral veins. A history of hepatic insufficiency, even if seemingly unrelated, should arouse suspicion for suprahepatic caval involvement and Budd-Chiari syndrome [21]. The patient should be interviewed regarding personal and family history of DVT or hypercoagulability, as well as malignancy.

Physical examination should evaluate for signs of chronic venous disease, including swelling, lymphedema, varicose veins, lipodermatosclerosis, and ulcerations. Superficial varicosities may be noted on the proximal thigh or abdominal wall, suggestive of long-term central venous occlusion. Distal pulses should be assessed to rule out any associated peripheral arterial disease. Finally, lymphadenopathy or masses suggestive of malignancy may be appreciated during a thorough exam.

Noninvasive Diagnostic Testing

The majority of patients being evaluated for lower extremity venous disease will first be assessed with duplex ultrasonography. Testing is noninvasive and safe and provides both anatomic and physiologic information. The presence of DVT can be accurately and reliably assessed, as well as valvular incompetence leading to reflux [22]. Duplex ultrasound has been shown to be as accurate as descending phlebography in detecting reflux and is more easily tolerated by the patient [23]. However, the utility of duplex in the iliocaval system is somewhat limited due to user variability, patient body habitus, and presence of overlying bowel gas. When central occlusion is suspected, cross-sectional imaging is of critical importance. CT venography is accurate in identifying congenital anomalies such as caval interruption with azygous or hemiazygous continuation, duplicated or left-sided IVC, and intracaval membranous webs. Renal tumors, leiomyosarcomas, and pheochromocytomas, all of which can lead to direct or indirect caval obstruction, are also easily identified. Perhaps most importantly, the extent of obstruction can be assessed, specifically involvement of the renal and hepatic veins [24]. Due to the flow dynamics in the IVC, there may be artifact related to contrast timing and mixing of non-opacified blood, leading to false-positive results or "pseudothrom-

bus" [25, 26]. Magnetic resonance venography may obviate some of these issues, does not use ionizing radiation, and is the most reliable modality for evaluating tumor thrombus [24]. However, MRI is time-consuming and costly, and many patients have ferromagnetic implants which preclude them from undergoing the scan. Following some combination of ultrasound and cross-sectional imaging, the majority of patients will proceed to contrast venography in the angiography suite for further diagnostics and potential treatment.

Medical Management

For those patients with acute thrombosis of the IVC, systemic anticoagulation should be initiated in the form of unfractionated heparin, low molecular weight heparin, or fondaparinux [27]. Thrombolytic therapy may also be of benefit, specifically in reducing the incidence of post-thrombotic syndrome; PTS may occur in upward of 50% of patients with iliocaval thrombosis [28, 29]. The role of anticoagulant therapy in chronic IVC obstruction is less clear, although most patients are maintained on systemic anticoagulation to prevent thrombus propagation and mitigate the risk of pulmonary embolism [3]. Duration of therapy is dependent on the underlying etiology; for those patients with inherited thrombophilia, lifelong anticoagulation may be necessary. There are no guidelines with regard to the various congenital IVC lesions and duration of anticoagulation therapy; thus the decision is tailored to the individual circumstance. However, if the underlying pathology is not corrected, then the thrombotic risk is not abated and presumably these patients should be anticoagulated for life as well. In contrast, if the thrombosis is related to an identifiable cause and that cause is treated, then in the absence of additional indications, anticoagulation may be reasonably stopped after 3 months' duration [27]. As an example, tumor thrombus from a renal cell carcinoma extending into the IVC may be adequately treated by removal of the tumor and thrombectomy, and a short course of anticoagulation may be sufficient. Additional medical therapies are focused on symptomatic relief of the lower extremities: compression stockings or wraps, local wound care for venous ulcerations, and correction of any venous reflux pathology.

Surgical Indications

The decision to intervene on a patient with chronic IVC occlusion is made based on weighing individual patient risks and potential benefits. For patients with primary IVC thrombosis, surgery is reserved for those with debilitating or lifestyle-limiting symptoms who have failed medical therapy. Patients who have not improved with a course of compressive wraps and systemic anticoagulation should be considered for intervention. However, with more recent data suggesting good outcomes from less invasive endovascular techniques, the threshold for intervention has been somewhat lowered. In general, patients with CEAP scores of C_3–C_6 warrant intervention. It is important to note that patients with long-standing venous disease and symptoms of post-thrombotic syndrome may not improve clinically, due to ongoing infrainguinal pathology [30]. Patients with complications such as pulmonary embolism, venous ulcerations or gangrene, or renal or hepatic insufficiency should be intervened upon sooner rather than later. For patients with tumors causing IVC occlusion, either by means of tumor thrombus extension or direct caval compression, the indications for surgery should be primarily geared toward the desired oncological outcome. Our general treatment algorithm is outlined in Fig. 40.2.

Open and Hybrid Surgical Treatment

For those patients deemed appropriate for intervention, open surgical reconstruction has been the traditional treatment of choice. Although this has now largely been relegated to a secondary option, there is still a role for open surgery when endovascular intervention has failed. There is also a role for open bypass in patients with trau-

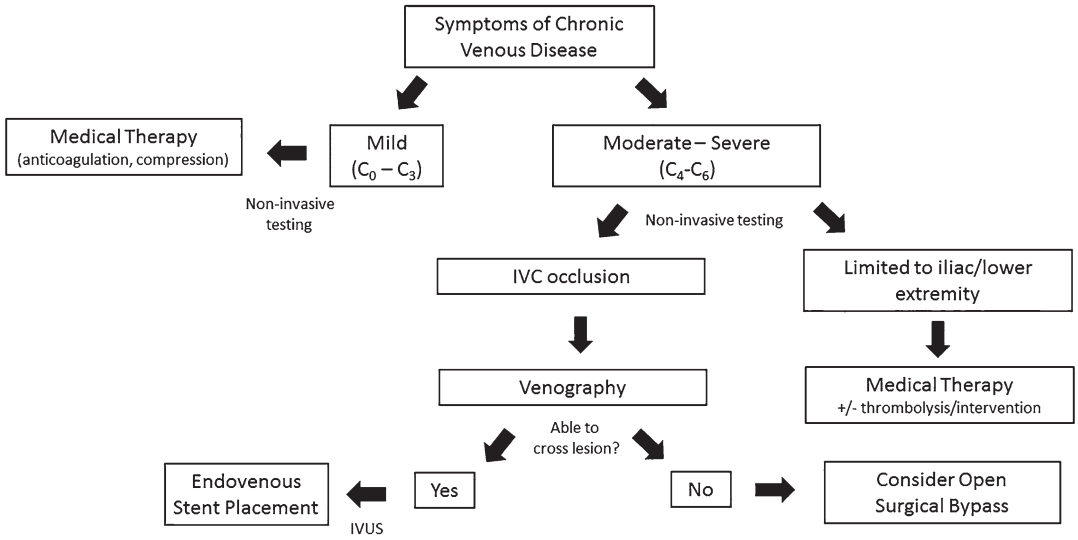

Fig. 40.2 Treatment algorithm for chronic central venous occlusion. Treatment for mild disease is primarily medical, with interventions reserved for moderate to severe symptoms. Choice of intervention is dependent on anatomic location and other considerations

matic IVC injuries not amenable to primary repair and for tumor resections which require resection of a portion of the IVC for oncologic clearance [31].

Surgical bypass should be performed using autologous tissue whenever possible, preferably with reversed greater saphenous vein. When no vein is available, the best choice for prosthetic conduit has been ePTFE [30], as outcomes for cryopreserved vein have been mediocre at short-term follow-up [32]. The best results for venous bypass in the central veins are with the Palma procedure or femoral-femoral crossover bypass (Fig. 40.3) [33]. Patency rates in the 70–80% range have been reported at 5-year follow-up with use of a high-quality venous conduit [34–36]. Although this is the patency standard to which central venous bypass should be compared, it is not appropriate for IVC obstruction because the crossover bypass relies on a contralateral iliac system with normal drainage for outflow.

For IVC obstruction, options include bypass from the iliac or femoral vein to the infra- or suprahepatic vena cava or resection and replacement with an interposition graft. The Mayo Clinic group has reported their experience with both

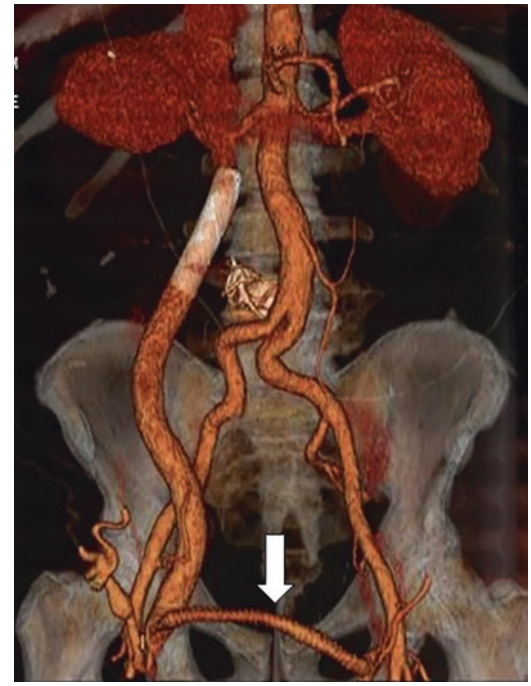

Fig. 40.3 Palma procedure. Crossover femoral-femoral venous bypass can be used with unilateral chronic occlusions of the iliac veins. CT venogram with 3D reconstruction demonstrates the left-to-right PTFE bypass (*white arrow*), which subsequently drains into the vena cava. The left iliac vein is occluded and thus does not appear on the reconstructed images

scenarios [36]. They noted that early occlusion is common, occurring in 17% of cases. However, with re-intervention, patency at discharge was 96%. At 5-year follow-up, primary and secondary patency of iliocaval bypasses was 75% and 86%, respectively. For femorocaval bypass, the results were much worse, with 44% and 57% patency, respectively. This underscores the importance of a robust inflow to prevent graft thrombosis. In order to augment inflow, many have advocated the use of adjunctive arteriovenous fistulae (AVFs), especially when femoral vein is used as inflow or a less than ideal conduit is used [30]. AVFs do increase flow in experimental models [37, 38], but no substantial clinical data exists and the use is left to surgeon preference. In general, AVF should be used in prosthetic grafts utilizing the femoral vein as inflow, as well as iliocaval grafts longer than 10 cm [39]. Other factors adversely affecting patency have also been well defined in this group; use of prosthetic grafts, smoking, and male gender have all been associated with poorer outcomes [36]. Use of adjunctive AVF could also be considered in these cases, although there is no data to support this other than anecdotal evidence.

For patients in need of IVC replacement during tumor resection, the results have been positive. In one study of patients undergoing ePTFE interposition grafts, 27/29 grafts remained patent at an average of 2.8-year follow-up, and one of the failures was due to tumor recurrence at 6 years [40]. These patients have high perioperative morbidity and mortality, in line with the expected outcomes from the tumor resection itself. No adjunctive arteriovenous fistulae were constructed and are generally not needed when the inflow is from the infrahepatic vena cava.

Endovascular Therapy: Technique

In recent years, the use of endovenous stents for central venous occlusive disease has increased significantly with good results and minimal morbidity [41] and should be considered first-line therapy for most patients. Despite the chronicity of occlusion, technical success is achievable in the majority of cases.

Percutaneous access is gained through the femoral, greater saphenous or popliteal vein based on individual clinical situation. Bilateral access may be of some benefit in certain scenarios. The lower extremity may be edematous, and ultrasound guidance is recommended. Preoperative diagnostics including duplex ultrasound and cross-sectional imaging such as CT venography have usually been performed prior to entering the angiography suite and can help guide access and therapy decisions. Contrast venography is then performed to further characterize the lesion, although venography has a sensitivity of only around 50% and intraluminal lesions are easily missed [42]. Chronic, obstructive lesions are characterized by the presence of multiple, robust collateral vessels, although these may only be present in approximately one third of cases [41]. Multiple projections may be needed to identify the native, obstructed vein among many collaterals. Because of these limitations, intravascular ultrasound (IVUS) has become the gold standard for evaluating venous pathology and should be used whenever feasible as an adjunct to traditional subtraction venography. IVUS can reliably detect intravascular webs and membranes, accurately measure diameter, and distinguish between intraluminal obstruction and extrinsic compression [41, 42]. IVUS also limits contrast usage and radiation exposure to both the operator and the patient.

Once the lesion has been appropriately characterized, it is crossed using a wire-catheter combination of the surgeon's preference. Often this is possible with a 0.035 in. stiff or floppy glide wire and angled glide catheter (Terumo Medical, Somerset, NJ). If the lesion is not easily navigable in this manner, a looped wire technique may also be employed (Fig. 40.4) [43]. It is imperative to use either IVUS or contrast injection to confirm appropriate reentry into the IVC after crossing. Sequential balloon pre-dilatation is then performed to allow for stent deployment. Large, self-expanding Wallstents (Boston Scientific, Marlborough, MA) work well and are sized based on IVUS diameter measurements.

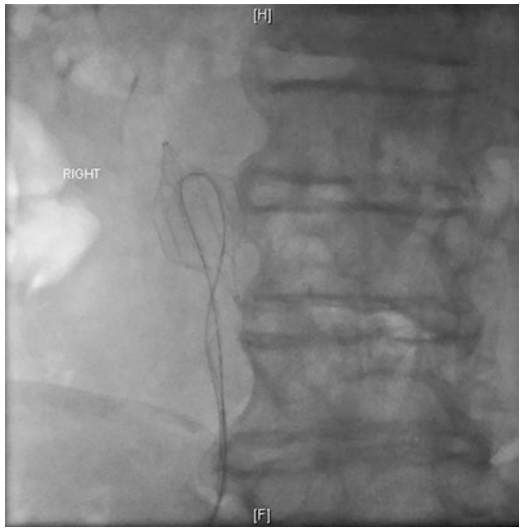

Fig. 40.4 Looped wire technique for crossing venous chronic total occlusions. For difficult to cross lesions, a wire may be looped and pushed through the occlusion

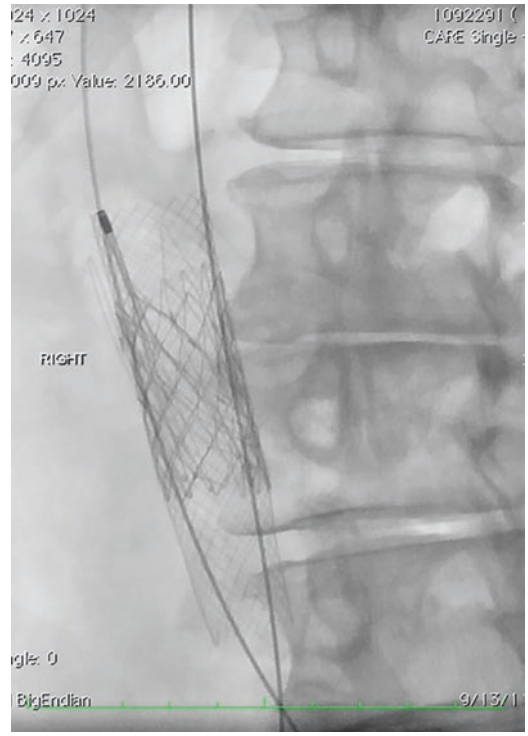

Fig. 40.5 IVC filter displacement. A Palmaz stent (Cordis, Miami Lakes, FL) may be used to crush and displace the filter due to its high radial force, resulting in an improved flow lumen. Adjunctive Wallstents (Boston Scientific, Marlborough, MA) can be used, as shown here

Wallstents can foreshorten significantly on post-dilatation, so they should be deployed with generous overlap to avoid gaps [16]. Stents can be deployed across the renal or hepatic veins with no clinical sequelae [16]. Completion IVUS should be used to ensure all sites of disease have been appropriately covered and there is no residual stenosis which may serve as a nidus for recurrence.

An additional note should be made regarding treatment of patients with IVC occlusion secondary to vena cava filter thrombosis. Both Neglen et al. [44] and Meltzer et al. [43] have described successful techniques to cross and treat these occlusions. The latter study utilized balloon-mounted Palmaz stents (Cordis, Miami Lakes, FL) to displace the filter and improve the size of the flow channel in the recanalized vena cava, with good technical results (Fig. 40.5).

Endovascular Therapy: Results

Early case reports described technical feasibility and outcomes of percutaneous transluminal angioplasty alone, with patients achieving satisfactory symptomatic relief in the short term [45]. However, long-term studies demonstrated a lack of durability, with most patients requiring re-intervention [46]. This is thought to be secondary to the extensive recoil seen in chronically occluded and scarred veins [47]. Results with endovenous stenting have been much more favorable. Early reports again demonstrated the technical ability to cross these chronic lesions and successfully deploy large diameter stents [48]. Longer-term studies then confirmed the durability advantage of stenting. Hartung et al. [49] reported on 89 patients with chronic, disabling, nonmalignant central venous obstructions, of whom 8 had involvement of the IVC. At a mean follow-up of 38 months, their primary, assisted primary, and secondary patency rates were 83%, 89%, and 93%, respectively. The largest data set comes from the River Oaks Hospital/University of Mississippi group, having treated nearly 1000 patients [50]. They demonstrated primary,

assisted primary, and secondary cumulative patency rates of 79%, 100%, and 100% in non-thrombotic disease and 57%, 80%, and 86% in thrombotic disease, respectively, at 72 months. In terms of clinical improvement, they showed a significant increase in quality of life (QOL) scores and specific decreases in both pain and swelling. They also noted that 58% of patients with venous ulcers had healed completely. Complications were low, with no mortality and a thrombotic event rate of 1.5% at 30 days and 3% during the follow-up period.

Conclusions and Recommendations

Chronic obstruction of the inferior vena cava can present with a range of clinical symptomatology, from mild swelling to severe venous ulceration and gangrene. For patients with severe symptoms, intervention is warranted. Endovenous stenting has shown excellent results in the short and long term in terms of both patency and clinical improvement and should be first-line therapy in the majority of cases. This includes patients with chronically occluded vena cava secondary to IVC filter thrombosis. Surgical therapy should be considered if attempts at endovascular recanalization have failed or if the patient is already undergoing open surgery for tumor resection. Although no specific guidelines exist, the majority of patients should be maintained on systemic anticoagulation postoperatively and continue compressive therapy and local wound care as indicated.

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Venous Reconstruction in Oncologic Surgery

41

M. Libby Weaver, Michael J. Osgood, and Ying Wei Lum

Clinical Pearls

1. Renal cell carcinoma is the most common cancer that involves the IVC, and up to 10% will have an IVC thrombus on presentation.
2. Management of large intra-abdominal veins includes primary repair, patch angioplasty, or bypass interposition grafting.
3. The prognosis depends on the type of cancer, but several series demonstrated a patency of 70% or more for reconstruction of the large major abdominal veins.

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Introduction

The role of vascular surgeons in the management of patients with various malignancies prone to vascular invasion is becoming increasingly important as improvement in surgical planning and techniques allows for acceptable outcomes with aggressive surgical approaches aimed at curative intent by complete resection of the tumor burden. Venous resection and reconstruction of the inferior vena cava (IVC), portal vein, superior mesenteric vein (SMV), iliac veins, and femoral veins may all be necessary in the treatment of such malignancies inclined toward vascular extension. These include renal, hepatic, pancreatic, colorectal, and soft tissue tumors, as well as primary venous leiomyosarcomas. Evidence now suggests many tumors previously deemed unresectable due to vascular invasion have comparable results when operative management with proper resection and reconstruction techniques is employed. This has even resulted in changes in staging definitions for certain malignancies, such as pancreatic adenocarcinoma. The purpose of this chapter is to explore the role of vascular surgeons in venous reconstruction during surgical management of malignancies.

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Inferior Vena Cava Reconstruction

Several malignancies have a propensity for invasion of the IVC. Most commonly renal cell carcinoma can present with extension of tumor thrombus into the renal veins and IVC. Other malignancies that are also known to invade the IVC include adrenal, hepatic, and retroperitoneal sarcomas and ovarian, endometrial, and colorectal cancers. Additionally, primary venous leiomyosarcomas are rare but known to most commonly affect the cava. Each of these is known to be amenable to IVC resection and reconstruction when necessary with acceptable results [1–9].

Tumors Involving the IVC

Leiomyosarcomas are primary tumors of the vasculature. These are rare soft tissue sarcomas arising from smooth muscle cells of the media of vessel walls anywhere in the vascular system but most commonly in the IVC [10, 11]. Although rare, they are the most common primary malignancy arising from blood vessels [10]. The majority of patients are women in their sixth decade of life [5, 12]. Tumors may demonstrate extraluminal or intraluminal growth patterns or a combination of each. They most commonly arise from segment II of the IVC which is bordered inferiorly by the renal veins and superiorly by the main hepatic veins [11].

Secondary tumors involving the IVC are most commonly renal in origin. IVC thrombus is believed to occur in 10% of those presenting with a diagnosis of renal cell carcinoma on average, with various series ranging from an incidence of 4–25% [13–17]. These thrombi may remain intravascular or may directly invade the caval wall.

Clinical Presentation and Preoperative Evaluation and Management

Patients presenting with primary leiomyosarcoma may present with abdominal pain or with vague constitutional symptoms [5]. Lower extremity edema may also occur, although many patients develop an extensive collateral system with occlusion of the IVC and may not have edema. Computed tomography (CT) with delayed venous phases appears to be the most useful diagnostic modality in determining the local extent of tumor involvement and evaluating for distant metastases. Magnetic resonance imaging (MRI) is reserved for those with equivocal CT findings or are unable to tolerate intravenous contrast.

Patients with renal cell carcinoma may be symptomatic or may have incidentally detected tumors. Patients with IVC thrombus associated with renal cell carcinoma are more likely to be symptomatic than those without thrombus [18, 19]. Common symptoms include lower extremity edema, hematuria, abdominal pain, and flank pain [5, 19, 20]. The extent and composition of an IVC thrombus dictate the necessity for IVC resection and reconstruction. Preoperative imaging is necessary to accurately define thrombi characteristics. Historically MRI was considered the imaging modality of choice, but with the advancements in the quality of CT, the two modalities have demonstrated equivalent accuracy with regard to characterizing IVC thrombi [1, 19, 21]. Several classification systems, including the Neves, Novick, and Hinman systems, describe the level of tumor thrombus [22]. The Neves system is generally the most commonly used of these. It describes four levels of thrombus extension (Fig. 41.1). Properly identifying the level of tumor thrombus is important for surgical planning, particularly in 1% of all patients presenting with

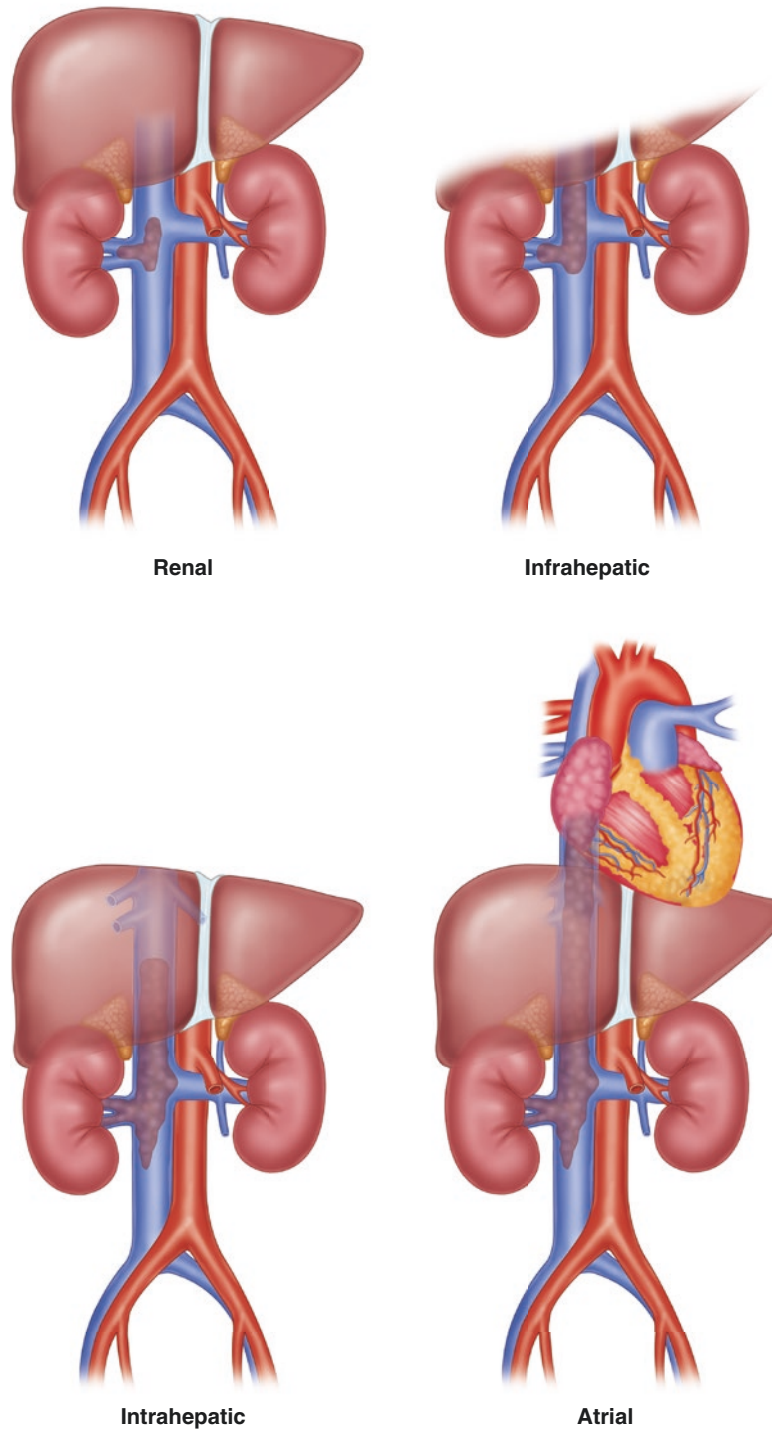

Fig. 41.1 The Neves and Zincke classification indicating cephalad extent of inferior vena cava tumor thrombus. Level I tumor thrombus is located and confined to <2 cm above renal vein. Level II thrombus extends >2 cm above the renal vein but still infrahepatic. Level III tumor thrombus is retrohepatic but below diaphragm, and Level IV tumor thrombus is atrial and above the diaphragm

renal cell carcinoma who are found to have thrombus extension into the right atrium of the heart (level IV), necessitating the use of cardiopulmonary bypass [23]. It is essential to recognize these thrombi may evolve at a rapid pace. As such, intraoperative transesophageal echocardiography should be performed to evaluate for atrial extension of thrombus in such cases [1]. Previously, strategies including renal angioembolization and the use of targeted agents such as sunitinib, bevacizumab, temsirolimus, and sorafenib were attempted to allow for regression and downgrade of the thrombus level prior to operative intervention, but these have not proven effective and in some cases have even demonstrated progression of tumor thrombus [1, 19, 24, 25].

Determining the consistency of a tumor thrombus is of importance for two major reasons. First, thrombi may be characterized as tumor thrombi or bland thrombi. Tumor thrombus refers to a thrombus that is composed of tumor components and is a direct extension of the primary tumor invading local vasculature. Bland thrombus is associated with tumor thrombus but consists of nonmalignant thrombotic elements that result from flow changes within the IVC due to the concomitant presence of a tumor thrombus. Approximately, 15–20% of patients presenting with grade II–IV thrombus will have an associated bland thrombus. The presence of bland tumor thrombus suggests the necessity for more complex surgical intervention [26]. At least half of those patients with bland thrombus require IVC interruption in the form of resection with reconstruction or ligation [27]. Those patients with bland thrombus in particular should be considered for preoperative anticoagulation with low-molecular-weight heparin (LMWH) [19]. Fewer than 6% of all patients presenting with IVC thrombus will experience pulmonary embolism (PE). However, the high mortality rate of up to 75% associated with PE advocates for anticoagulation prior to thrombus extraction [28]. There is level I evidence demonstrating an association of fewer episodes of venous thromboembolic events, as well as improved survival, with the use of LMWH as compared to treatment with warfarin in patients with malignancies [19]. The use of IVC filters preoperatively is not recommended as filters may be thrombogenic and can increase the rate of embolic events [1, 16, 28].

A second important reason to determine thrombus consistency prior to operative intervention in renal cell carcinoma is that friability of the thrombus may be a predictor of prognosis [29]. Weiss et al. demonstrated that in all patients with renal cell carcinoma, overall survival is less (29 months) in those with a friable thrombus, as compared to those with a solid thrombus (89 months). In those with non-metastatic disease, overall survival was 40 months in those with friable thrombi, versus 135 months in those with solid thrombi [30]. This is especially important in that it suggests those with non-metastatic disease and friable tumor thrombus have a worse prognosis than those with metastatic disease and solid thrombus. Other studies, however, do not demonstrate a correlation between thrombus consistency and survival [31].

Surgical Approach to IVC Resection and Reconstruction

The aim of surgical management of all tumors involving the IVC is complete resection of the tumor. In over half of those patients presenting with renal cell carcinoma and associated IVC tumor thrombus, the thrombus likely invades the caval wall if it is adherent to it [10]. The optimal surgical approach is dictated by the level of tumor thrombus. Midline abdominal, subcostal, or chevron incisions generally offer adequate exposure for resection and reconstruction of level I–II tumor thrombus. In cases involving level III tumor thrombus, a thoracoabdominal incision through the eighth or ninth interspace may be preferable as it allows superior exposure of the suprahepatic IVC. Cases involving level IV tumor thrombus may be approached through a midline laparotomy which can be extended to a median sternotomy to facilitate cardiopulmonary bypass. Alternatively, a thoracoabdominal incision through the sixth or seventh interspace allows sufficient exposure for cardiopulmonary bypass in the case of IV tumor thrombi. Intra-abdominal exploration is performed upon entry into the peritoneum to assess for involvement of regional lymph nodes or metastatic disease. Intraoperative ultrasonography may be a useful adjunct to assess the tumor, particularly in cases with higher-level thrombi [32]. Put simply,

the operation then consists of three basic steps: renal artery ligation, thrombectomy, and nephrectomy. Ligation of the renal artery allows for retraction of the tumor thrombus and decreases bleeding from venous collaterals that have formed due to obstruction of the IVC by the thrombus [33]. Vascular isolation with thrombectomy can be performed prior to kidney mobilization to decrease the likelihood of pulmonary embolism. One study showed zero occasions of intraoperative embolism as compared to the average of 1–4% when employing this strategy [34]. Vessel loops or umbilical tapes are applied to achieve vascular control proximal and distal to the tumor. When tumor involvement is limited to the infrahepatic portion of the IVC, it is sufficient to obtain control of the renal veins, suprarenal IVC, and infrarenal IVC. When there is more extensive involvement of the IVC, additional control of the suprahepatic IVC and porta hepatis are required in order to facilitate the Pringle maneuver and achieve total hepatic vascular isolation. This necessitates mobilization of the hepatic suspensory ligaments. Obtaining control of large lumbar veins is also imperative as these may contribute to extensive back-bleeding upon creation of the IVC venotomy. Valsalva maneuvers with flushing of the inferior vena cava upon completion of the IVC reconstruction can be helpful. Systemic anticoagulation is administered in the form of intravenous heparin (100 U/kg) prior to cross-clamping of vasculature with dosing targeted to maintain an activated clotting time >250 s until venous flow is restored [2, 35].

The anesthesiology team plays an integral role in IVC resection and reconstruction. Clamping of the IVC causes a profound decrease in venous return that some patients may not be able to tolerate. Patients should be adequately resuscitated prior to IVC clamping and may require additional intravenous fluids or blood products to ensure adequate preload. Temporary occlusion of the IVC with a test clamp should be performed to assess each patient's ability to tolerate this extreme cardiovascular change. If measures such as intravenous fluid administration, inotropic support, and Trendelenburg positioning are not adequate to facilitate successful IVC clamping, the patient will require extracorporeal support with veno-venous or cardiopulmonary bypass or temporary aortic cross-clamping. Aortic cross-clamping is not a maneuver to be utilized during extensive reconstruction as end-organ ischemia may result when clamp time exceeds 30 min [2, 36].

When IVC reconstruction is undertaken, there are several approaches that may be utilized based on the extent of resection and repair required, including primary repair, patch angioplasty, and interposition grafting [35] (Fig. 41.2). Primary repair is an acceptable choice when partial resection of the caval wall is sufficient for tumor removal, and the subsequent repair results in less than 50% narrowing of the IVC [1, 18, 19, 35, 37]. When resection is more extensive and primary repair would result in narrowing of the IVC by greater than 50%, patch angioplasty with bovine pericardium, PTFE, or Dacron patches is indicated [35]. Finally, if there is circumferential involvement of the IVC necessitating segmental vessel resection, reconstruction with interposition grafting is performed. Conduits described for interposition reconstruction include prosthetic grafts, such as polytetrafluoroethylene (PTFE) or polyester (Dacron), or may be autogenous, such as the superficial femoral vein [15, 35, 38, 39]. Ring-reinforced PTFE is most commonly used as the external support provided by the rings prevents collapse in the low-pressure venous system and thus has superior patency and low thrombogenic potential [15, 39]. Notably, cryopreserved graft conduits have demonstrated poor outcomes with regard to graft patency in IVC reconstruction and are therefore not a recommended choice of conduit here [40]. In our experience, we use cryopreserved conduits only in cases where there is likely contamination from concomitant bowel or biliary surgery as well.

Renal vein reimplantation is sometimes necessary in patients undergoing reconstruction by interposition grafting. Ligation of the left renal vein without reimplantation is generally tolerated due to the venous collateral system of adrenal, ovarian, and lumbar veins, which empty into the hemiazygos system, whereas collateral flow is less well developed for the right renal vein.

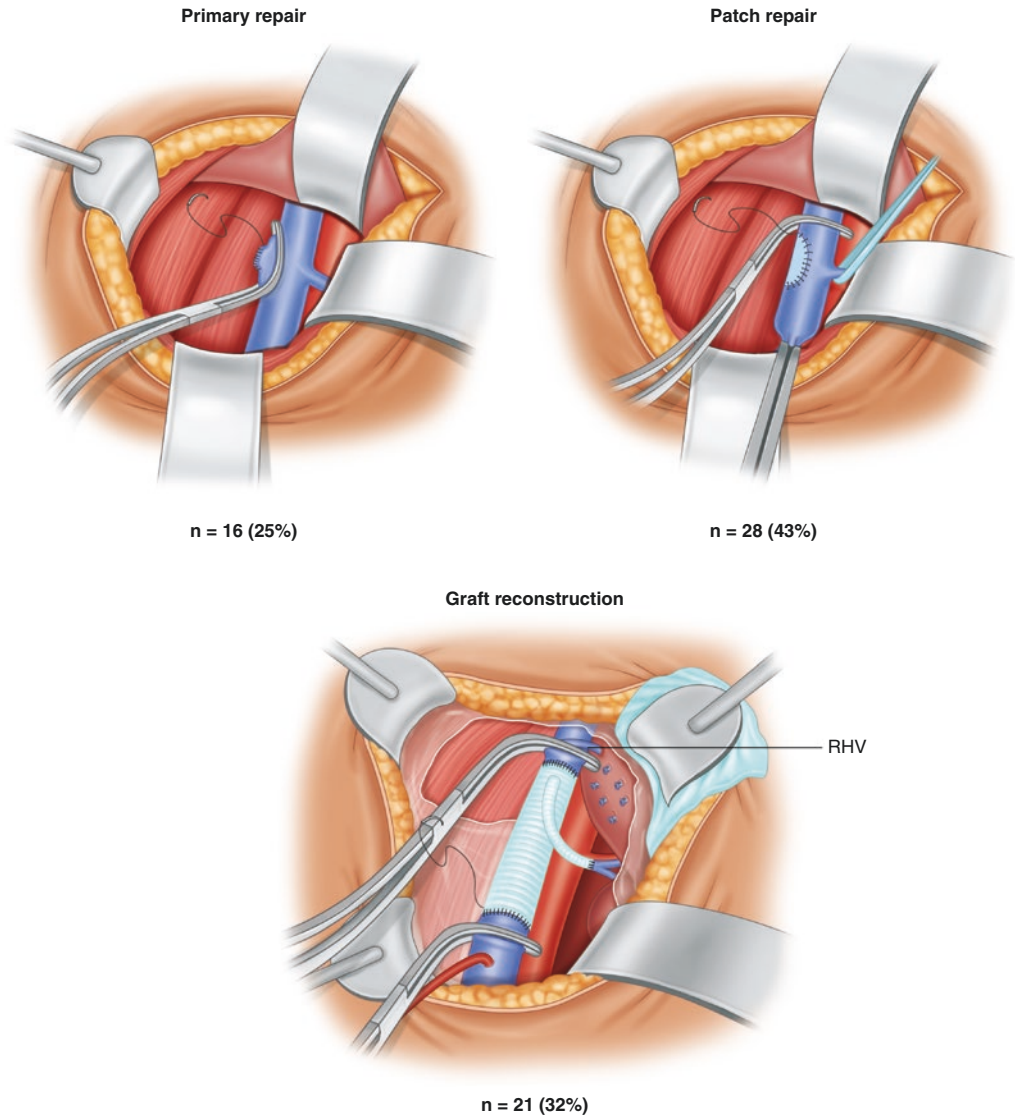

Fig. 41.2 Depiction of inferior vena cava (IVC) reconstruction methods and distribution. Over the 15-year study period, 16 patients underwent primary IVC repair, 28 patients underwent patch IVC repair, and 21 patients underwent IVC graft reconstruction

Sufficient collateral flow can be determined intraoperatively by measuring left renal vein stump pressure. A measurement of less than 40 mm Hg is considered acceptable for simple ligation of the vein [36].

IVC ligation without reconstruction is another option in patients presenting with complete chronic occlusion of the IVC. Patients presenting with chronic IVC occlusion develop an extensive venous collateral system. Proponents of this approach argue that careful dissection makes it possible to ligate the IVC entirely and preserve this collateral system with low postoperative morbidity [12, 41]. However, it is extremely difficult to preserve these collateral vessels, and they are typically interrupted during the extensive dissection involved with tumor removal, and several institutions, including our own, report significant postoperative morbidity with severe lower extremity edema when reconstruction is not performed; we therefore routinely perform IVC reconstruction following resection [2, 42].

Adjunctive Extracorporeal Bypass Techniques

Veno-venous bypass (VVB) is rarely necessary during IVC resection and reconstruction. The decision to use VVB is dependent on whether the patient is able to tolerate IVC clamping. If VVB is necessary, the infrarenal IVC may be cannulated directly with a 24-French angled cannula, or the femoral vein may be percutaneously cannulated with insertion of a straight cannula placed just below the IVC clamp site. The cannula is then connected to the bypass circuit, which consists of a Biomedicus perfusion pump. Venous return is accomplished by connecting it to a cordis placed into the right internal jugular (IJ) vein. VVB is then initiated and performed in a normothermic fashion with flow rates maintained at a mean arterial perfusion pressure of 60–80 mmHg. At cessation of bypass, the inflow cannula is removed with venous repair as appropriate and the outflow tubing is disconnected from the IJ cordis cannulae.

Occasionally, when the IVC tumor thrombus extends above the hepatic veins and into the right atrium, cardiopulmonary bypass (CPB) or deep hypothermic circulatory arrest (DHCA) may be necessary [43].

The use of adjunctive bypass support, including VVB, CPD, and DHCA, involves greater surgical complexity and therefore is associated with an increased rate of perioperative morbidity. While utilization of bypass support is associated with an overall increased risk of perioperative complications, its use does not have an effect on long-term outcomes or survival [2].

Perioperative and Long-Term Outcomes

Following IVC reconstruction, patients are at risk for thromboembolic events and acute kidney injury or renal failure. Kidney injury occurs approximately 10% of the time and can be decreased or avoided using renal vein reimplantation strategies as described above [2]. In addition, some institutes advocate for administration of sodium bicarbonate and furosemide upon restoration of normal blood flow intraoperatively to provide added protection to the remaining kidney [44]. Preoperative anticoagulation strategies to avoid thromboembolic events were discussed previously. Thromboembolic events are also a notable complication in the postoperative period. Patients with larger tumor sizes, renal vein reimplantation, and increased administration of blood products intraoperatively are at increased risk of deep venous thrombosis (DVT), graft thrombosis, or pulmonary embolism. Reconstruction with prosthetic graft material, level of IVC thrombus, and history of venous thromboembolism (VTE) are not associated with postoperative VTE. Reports vary for incidence of DVT in the postoperative period and range from 0 to 22%, while graft thrombosis when using PTFE is 7%. Postoperative anticoagulation regimens vary greatly among institutions. At our institution 22% of patients were found to experience DVT or PE postoperatively, but only half of these were symptomatic, and there were no mortalities. We do not advocate for routine postoperative anticoagulation following IVC reconstruction [35]. Others recommend indefinite anticoagulation beginning 48 h postoperatively for those patients with incomplete tumor resection or metastatic disease, as well as those who are to receive systemic adjuvant therapy or who presented with a PE [28].

The overall survival of patients undergoing IVC resection and reconstruction differs depending on the primary malignancy resected. Median survival ranges from 14 to 37 months among all malignancies invading the IVC [45]. In renal cell carcinoma, there is much debate regarding tumor thrombus level as a predictor of overall survival. Some studies indicate tumor thrombus level is an independent factor predictive of survival [17, 34, 39, 46–48]. Others show no correlation between thrombus level and overall survival [13, 18, 23, 30, 33, 49–53]. It does appear, however, that thrombus involving the IVC at any level is associated with lower overall survival than that which involves only the renal vein [23, 33, 50].

Graft patency after reconstruction with prosthetic interposition grafts is excellent with 80–100% patency rates at 9 months to 5 years reported in several small series [54–57]. Large, multi-institutional series similarly demonstrate excellent patency rates of 95 and 92% at 1 and 5 years, respectively [58]. Graft thrombosis is associated with tumor recurrence and graft infection [54].

Portal Vein and Superior Mesenteric Vein Reconstruction in Pancreatic Adenocarcinoma

Portal vein (PV) and superior mesenteric vein (SMV) reconstruction due to tumor involvement may be necessary in pancreatic malignancies. Tumor invasion involving the superior mesenteric-portal vein confluence often occurs in patients with pancreatic adenocarcinoma due to the anatomical relationship of these structures posterior to the head of the pancreas, where most of these tumors arise. Most patients undergoing pancreatectomy with simultaneous PV/SMV reconstruction are those in which pathology demonstrates pancreatic ductal adenocarcinoma [59]. Between 75 and 90% of patients with pancreatic adenocarcinoma are at an advanced stage upon presentation such that surgical resection is not possible or indicated [60, 61]. Surgical resection, however, is the only curative treatment option for this disease process. Therefore, aggressive surgical management is becoming increasingly accepted as the standard of care, even in those tumors manifesting with venous infiltration.

Clinical Presentation and Preoperative Evaluation and Management

Patients with pancreatic adenocarcinoma classically present with painless jaundice due to the peri-ampullary location of most tumors. Patients may also present simply with abdominal or back pain which leads to an incidental finding of a pancreatic mass detected on CT imaging. Like most malignancies, options for surgical intervention are dependent upon tumor staging. The American Joint Committee on Cancer and the National Comprehensive Cancer Network each provide staging systems for pancreatic adenocarcinoma. The former is a standard TNM staging system while the latter defines stages based on surgical resectability. Pertinent to the topic at hand is the NCCN classification of "borderline resectable" tumors. This category includes those tumors in which there is involvement of the PV and/or SMV [62]. Tumors involving the superior mesenteric artery or celiac artery are generally deemed unresectable. It is suggested that due to the poor prognosis of the disease in general, along with confusion surrounding what qualifies as a resectable lesion by nonsurgical medical professionals, only 1/3 of those with disease that is potentially resectable are referred for surgical evaluation [63].

To best evaluate involvement of vasculature during preoperative evaluation, a CT imaging study is obtained following administration of intravenous contrast and imaged in three phases or "triple phase." The venous phase of this study allows for adequate visualization of any involvements of the SMV or PV which is necessary for optimal surgical planning. Only 77–79% of patients with preoperative imaging consistent with venous invasion ultimately have true vascular invasion as determined by histopathology results [64, 65].

When a lesion is classified as "borderline resectable" preoperatively, thus necessitating venous resection and reconstruction, preoperative treatment with chemoradiation therapy results in a much higher rate of R0 resection (5% in the surgery-first group as compared to 71% in the neoadjuvant group) and demonstrates benefit for overall survival [66]. Thus, the NCCN recommends neoadjuvant therapy as part of the preoperative management plan for those patients presenting with borderline resectable pancreatic malignancies.

Surgical Approach to Portal Vein and Superior Mesenteric Vein Resection

Reconstruction of the PV and SMV is most commonly performed in conjunction with pancreaticoduodenectomy. However, up to 29% of patients undergoing PV/SMV reconstruction may require total, subtotal, or distal pancreatectomy [67].

PV/SMV resection and reconstruction are generally performed following complete dissection and excision of the pancreatectomy specimen. This minimizes portal vein clamp time, which is associated with a higher rate of thrombosis and results in venous engorgement of the intestines due to disruption of the portal venous flow. Vascular control is obtained using vessel loops after circumferential dissection of the PV and SMV is performed. Extensive involvement of the SMV and PV may require vascular control of the splenic and left gastric veins as well. Upon optimal dissection and mobilization of the pancreatectomy specimen, vascular clamps are applied to each of these veins to allow for interruption of venous flow. The involved venous structures are resected sufficiently for complete tumor removal while maintaining maximal preservation of uninvolved portions of the venous wall such that the complexity of vascular reconstruction is limited. Involvement of the PV/SMV most commonly occurs on the right anterolateral wall of the vessels. Thus, exposure is often best attained with retraction of the specimen to the patient's right.

Methods of Portal Vein and Superior Mesenteric Vein Reconstruction

Several methods of venous reconstruction may be employed depending on the extent of reconstruction required, including primary end-to-end anastomosis, lateral venorrhaphy, patch angioplasty, and interposition grafting [59] (Fig. 41.3). The patient's physiologic state at the time of reconstruction may play a role in the choice of reconstruction methods as well. For example, patients who have experienced a large amount of blood loss may be unable to tolerate the additional procedural time required for procurement of autologous vein. Systemic heparinization is frequently used during reconstruction but not necessarily indicated based on some published reports [59].

Primary lateral venorrhaphy is an adequate option for repair if <30% of the lumen of the involved vein is compromised. When >30% of the venous circumference is compromised, primary end-to-end anastomosis should be considered. Generally, the length of involved vein segment must be less than 2 cm for successful performance of this technique. Extensive mobilization, including that of the right colon, mesenteric root, or liver by division of the suspensory ligaments, may be required to allow for a tension-free anastomosis. In our institution's series of 173 patients undergoing pancreaticoduodenectomy with concomitant portal vein reconstruction, 83% of the reconstructions were amenable to primary repair [59].

When there is compromise of 30–50% of the venous circumference and when the segment of involved vein exceeds 2 cm, vein patch angioplasty is the preferred method of reconstruction. In this circumstance, an elliptical venectomy can be performed to remove the portion of vein involved with tumor, followed by overlying patch reconstruction. Various patch materials may be utilized, including autologous vein, bovine pericardium, or synthetic graft materials (Dacron and PTFE) [59, 68–70].

When both the length and circumference of tumor involvement exceed that which is considered adequate for successful repair with the above-described techniques, interposition grafting is recommended [59, 71]. Various conduits may be utilized for interposition grafting with good results, including autologous vein grafts, cryopreserved homografts, and synthetic grafts. Options for autologous graft include the femoral vein, internal jugular vein, left renal vein, and splenic vein. Both Dacron and PTFE have also been used for successful PV and SMV reconstruction [59, 68, 69]. The left renal vein and splenic vein offer adequate options available for harvest within the already established surgical

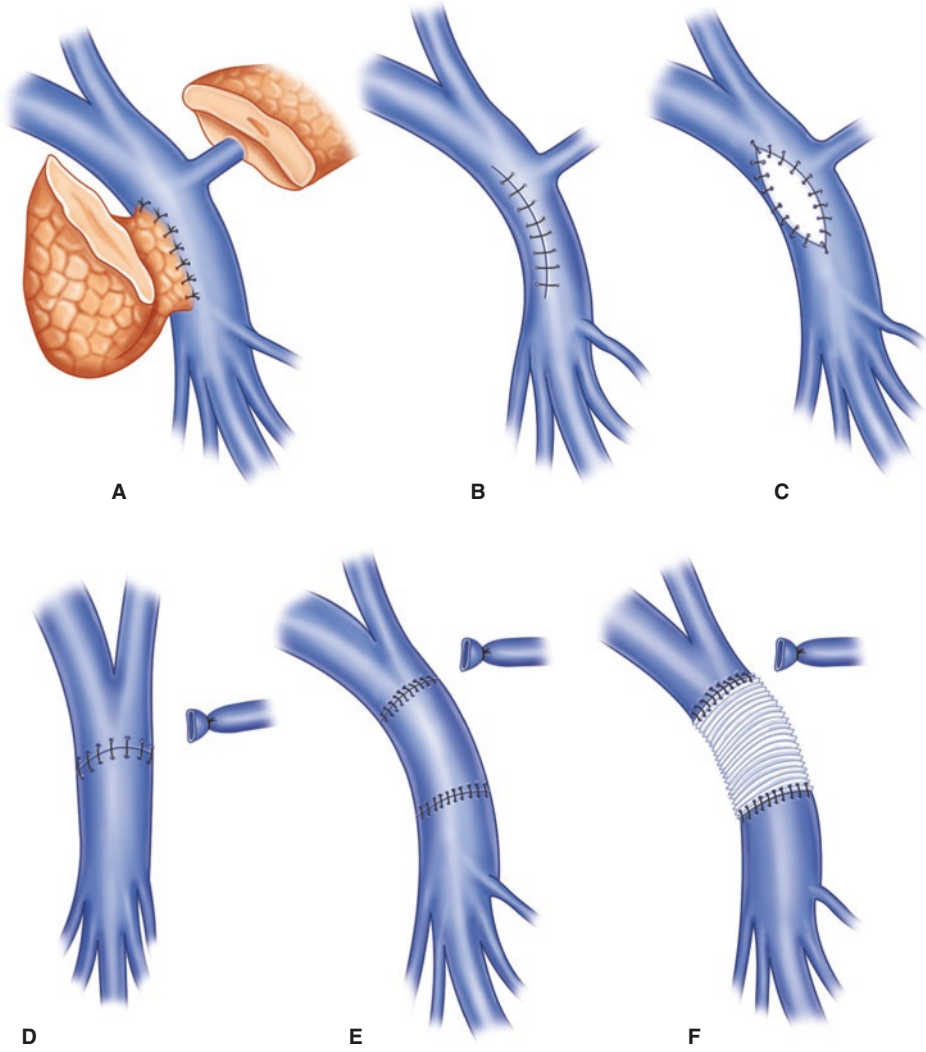

Fig. 41.3 Illustrations showing involvement of the portal vein with tumor originating in the head of the pancreas (**A**) and techniques for portal vein reconstruction (PVR): primary repair by lateral venorrhaphy (**B**), patch repair (**C**), primary repair by portal vein mobilization and end-to-end anastomosis (**D**), vein interposition (**E**), and prosthetic graft interposition (**F**)

field, whereas other abovementioned conduits require creation of a second surgical site. Although the greater saphenous vein may be an excellent option for patch angioplasty, size mismatch makes it a less desirable candidate for interposition grafting [72]. Recently, reconstruction using jejunal vein flap for those resections not amenable to primary repair or patch angioplasty has also been described with successful short-term and long-term results [73].

With extensive venous reconstruction, concurrent splenic vein ligation may be required. Splenic vein reimplantation may be performed, but studies suggest there is no difference in postoperative complications or hypersplenism with splenic vein ligation as compared to preservation [74]. At our institution we perform reimplantation of the splenic vein, except when interposition grafting is performed below the level of the splenic vein [59].

Minimally Invasive Techniques for PV and SMV Resection and Reconstruction

Pancreaticoduodenectomy and the above-described techniques for venous reconstruction can be applied using laparoscopic techniques with equivalent morbidity and mortality as compared to open techniques. Laparoscopic approaches in this setting are difficult due to the retroperitoneal location of the involved vasculature, but a study comparing the two demonstrated no difference in mean operative time, rate of complications, 30-day mortality, graft patency, or overall survival. The laparoscopic group was shown to have nearly 50% less blood loss and a higher rate of R0 resection than the open group. However, vascular clamp time was nearly twice as long in the laparoscopic group. These results demonstrate equal efficacy with the performance of laparoscopic pancreaticoduodenectomy with venous resection by those surgeons comfortable with this approach as compared to open surgical resection and venous reconstruction [75]. Recently, techniques involving vein patch angioplasty using parietal peritoneal patch reconstruction have demonstrated acceptable results [76].

Long-Term Outcomes

Controversy continues to exist regarding the resectability of pancreatic adenocarcinoma involving the portal and superior mesenteric veins. In those patients undergoing standard operative resection without vascular involvement, the 5-year survival rate is an estimated 28% [60]. There are several single institution studies from centers performing a high volume of pancreaticoduodenectomies that demonstrate equivalent overall survival for those patients undergoing straightforward pancreaticoduodenectomy as compared to those in which pancreaticoduodenectomy with venous reconstruction is performed [62–64, 71, 77]. Several systematic reviews and meta-analyses also conclude there is no survival difference, and thus advocate for aggressive surgical resection of those tumors involving venous structures [78–81]. However, there is also evidence from several series suggesting overall survival is worse in patients undergoing venous reconstruction in conjunction with pancreaticoduodenectomy [66, 82, 83]. Castleberry et al. analyzed NSQIP data for over 3000 patients and found a significant difference in both perioperative morbidity and mortality, but this data is notably limited to 30 days postoperatively and was de-identified such that it is not clear if outcomes differ when looking at low-volume as compared to high-volume centers [84]. Another series demonstrated no difference in overall survival when venous reconstruction was performed if the involved segment of superior mesenteric and/or portal vein involved was less than 3 cm. When tumor invasion was greater than 3 cm, however, overall survival was worse in those undergoing venous reconstruction.

The depth and histopathological extent of vascular invasion may affect outcome as well. As mentioned previously, many tumors with perceived vascular invasion based on preoperative imaging do not ultimately demonstrate invasion on histopathology when resected. Some studies show patients without true vascular invasion who undergo venous resection have better outcomes than those who have true vascular invasion [64, 65]. The depth of invasion also correlates with poorer outcomes [65]. One series even demonstrated better outcomes in those undergoing vascular resection without true vascular invasion as compared to those undergoing pancreaticoduodenectomy only without evidence of vascular invasion, suggesting venous resection may provide benefit in all patients, although this difference did not reach statistical significance [64]. Still, other series demonstrate there is no difference in overall survival of patients undergoing pancreaticoduodenectomy with venous reconstruction with or without true vascular invasion [66].

Reported graft patency widely varies among institutions with patency rates ranging from 76 to 100% [62, 63, 68–70, 72, 75, 85]. Autogenous grafts trend toward higher patency rates than

PTFE [62, 63, 70, 72, 79]. As mentioned previously, the left renal vein is an excellent choice of conduit that does not require establishment of a second operative field for harvest. The size and properties of the renal vein are similar to that of the PV, allowing for a suitable match. Preoperative imaging should be reviewed to verify the presence of patent gonadal and adrenal veins providing collateral outflow. Although patients may exhibit a transient elevation in creatinine levels postoperatively, these levels quickly resolve to baseline, and patients do not experience long-term kidney dysfunction [69]. Postoperative anticoagulation is not necessary as a prophylactic measure as studies demonstrate no difference in patency between those patients receiving systemic anticoagulation and those who do not [85, 86].

It is not clear whether there are better outcomes when vascular surgeons perform the reconstruction as compared to surgical oncologists. Some studies show no difference, while others demonstrate superior patency rates when vascular surgeons perform the resection and reconstruction as compared to those demonstrated in other series with surgical oncologists performing the repair [62, 63, 84].

Iliac and Femoral Vein Reconstruction

Malignancies involving the pelvis and lower extremities may invade and necessitate resection and reconstruction of venous structures, particularly the iliac and femoral veins. Iliac venous reconstruction may be required for adequate resection of large primary colorectal cancers or lateral wall recurrences of primary rectal cancers for which pelvic exenteration is warranted [87–90]. Additionally, gynecologic malignancies, sarcomas, and neurofibromas have all been known to invade both iliac and femoral veins [40, 91–100]. The basic principles for management of venous involvement for any of these malignancies involve complete resection of the tumor burden. Like other malignancies discussed previously in this chapter, reconstruction strategies vary depending upon the location and extent of venous resection required.

Clinical Presentation and Preoperative Evaluation

Patients with primary colorectal cancer that present with venous involvement generally have local recurrence of previously resected disease, although some do present with advanced primary tumors. Primary tumors may be detected during preventive screening colonoscopy, or upon development of obstructive symptoms or gastrointestinal bleeding, whereas recurrences may be detected during surveillance colonoscopy or imaging. Some patients with lateral pelvic wall recurrence may even present with lower extremity neurologic deficits due to involvement of the lumbar nerve plexus. Pelvic recurrence after primary rectal cancer resection occurs in 7–33% of patients [90]. Lateral side wall recurrence is difficult to resect due to the proximity of tumor to the bony pelvis. Recurrence here can often involve the iliac vessels. When treated nonoperatively with chemotherapy and radiation, the prognosis is poor, with a 4% survival rate at 4 years [90].

Soft tissue sarcomas most commonly present in the extremities but are also seen regularly in the retroperitoneum. Most patients present with a painless mass. The slow growth pattern exhibited by most sarcomas can enable them to grow quite large prior to detection, particularly in the retroperitoneal space. These tumors rarely metastasize via lymphatics. Rather, they possess a propensity for hematogenous spread [101]. In the retroperitoneum they may involve iliac vessels, while femoral, popliteal, or tibial vessel involvement may be present in sarcomas of the lower extremities [95, 97, 100].

Optimal preoperative evaluation of vascular involvement is less well established for pelvic and lower extremity tumors than for tumors previously described in this chapter. However, CT, MRI, and US may all be useful adjuncts for preoperative planning.

Surgical Approach to Iliac and Femoral Vein Resection and Reconstruction

As with other tumors involving venous structures, some surgeons advocate for ligation of veins without reconstruction [91, 92]. This can lead to venous hypertension and postoperative edema of the lower extremities, particularly if extensive collateral veins were ligated during dissection and resection of the tumor. If venous ligation is performed, there should be close monitoring in the postoperative period to assess for compartment syndrome.

As such, it is usually our preference to reconstruct the iliac veins if they are involved. As with other venous reconstructions, synthetic or autogenous grafts may be utilized for reconstruction. Femoral vein or saphenous vein grafts are most commonly used when reconstruction is performed with an autogenous conduit [90, 100, 102]. This should be considered particularly if concomitant bowel resections need to be performed and there is concern for contamination. It is in our experience that saphenous vein conduits can be spatulated to accommodate the size dimensions of an external iliac vein. Adjunctive arteriovenous fistulas have been reportedly done in the past to help assist with patency.

Long-Term Outcomes

In colorectal cancer, there is some debate whether tumors involving vasculature, those requiring pelvic exenteration, should be offered surgical management. As mentioned previously, patients offered with chemotherapy and radiation have poor prognoses. Evidence demonstrates acceptable outcomes with median survival of 34 months in one series [87]. Another series demonstrated only 28% mortality at 30 months follow-up in those patients undergoing iliac vessel resection and reconstruction due to colorectal tumor involvement [90]. R0 resection occurs in 38–53% of those undergoing resection of colorectal tumors involving vasculature [87, 90].

Similarly, patients undergoing iliac or femoral vessel reconstruction for sarcomas have comparable outcomes, both with regard to long-term function and survivability, to those not involving vasculature [40, 95, 98–100]. This is important because historically limb-preserving resection of extremity sarcomas was associated with poor outcomes due to inadequate surgical margins [97]. Limb-salvage rates in those undergoing iliac or femoral vein resection for sarcoma are now 84–93%, allowing for improved function and quality of life in patients undergoing tumor excision [40, 95, 100].

In both groups, graft patency is an important factor in postoperative morbidity. Autologous conduits offer the advantage of lower infection rates which may be of particular importance in reconstruction during resection for colorectal cancer due to the clean-contaminated nature of the operation, although some series have demonstrated acceptable results with the use of PTFE [88, 90]. One series comparing the use of synthetic grafts to autogenous grafts in sarcoma resection showed no significant difference in graft occlusion [96] while another demonstrated significantly greater graft occlusion when synthetic conduits were used in both iliac and femoral veins [97]. Patency rates widely differ depending on the series and range from 33 to 96% with a range of 1–5 years follow-up [40, 57, 87, 100, 103, 104]. The use of preventive anticoagulation in these patients to prevent graft thrombosis is not well established. However, one series did demonstrate double the graft thrombosis rate in patients not receiving systemic anticoagulation postoperatively, suggesting standard systemic anticoagulation postoperatively may be beneficial in maintaining graft patency [95].

Postoperative edema, particularly in those in whom venous ligation without reconstruction is performed, also contributes to morbidity. Some series demonstrate no reduction in edema postoperatively with venous reconstruction as compared to ligation [104], but most advocate for reconstruction with less edema and better functionality long term [40, 99, 105].

Wound dehiscence, particularly in those patients undergoing saphenous vein graft harvest, may have a significant impact on postoperative morbidity. There is some suggestion that myocutaneous flap transfer may decrease the rate of

infection postoperatively. However, one series in which myocutaneous flap transfer was performed in all patients resulted in a 50% rate of wound dehiscence [96], while another in which no patients underwent myocutaneous flap transfer demonstrated a 36% rate of wound dehiscence [100]. Still, other series are inconclusive as to whether or not there is benefit in performing flap transfer [99].

Summary and Conclusions

The role of vascular surgeons in the operative management of malignancies including renal cell carcinoma, sarcomas, pancreatic adenocarcinomas, and colorectal cancer just to name a few continues to evolve. With complete tumor resection as the only curative option for many of these malignancies, aggressive surgical approaches are increasingly accepted, particularly as evidence indicates comparable results to those undergoing less extensive resections and proven superior results to those undergoing medical management only in the case of some. Improved vascular reconstruction techniques also allow for improved function and quality of life, particularly in the case of extremity sarcomas where limb-sparing surgery is now possible with excellent outcomes. Further studies are needed to establish optimal reconstruction approaches and consistent perioperative management. Surgical innovation will continue to lead to better overall survival outcomes, and vascular surgeons are imperative in persisting to push the boundaries of surgical possibilities for tumor resection with the refinement of current reconstruction techniques and development of new operative approaches.

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Superior Vena Cava Syndrome

42

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Clinical Pearls

1. The epidemiology of SVC syndrome has shifted from infectious to oncologic with rise in iatrogenic causes related to central venous instrumentation.
2. Endovascular therapy is the primary modality of treatment in patients who have severe symptoms.
3. Open surgical reconstruction involves a median sternotomy and is reserved for patients who fail endovascular therapy or as part of oncological resection.

Introduction

Superior vena cava (SVC) syndrome is a clinical condition that develops when the blood flow from the SVC into the right atrium becomes obstructed (Fig. 42.1). This syndrome can be due to an intrinsic obstruction or an extrinsic compression of the SVC or the major veins draining into it [1]. William Hunter was the first to describe this pathophysiological entity back in 1757 [2]. Since then and with the expansion in utilization of antimicrobial therapy, SVC syndrome's primary cause evolved from an infectious (tuberculosis or syphilitic) to malignant etiology [3]. Currently, up to 90% of the cases of SVC syndrome are attributed to a malignant process with adenocarcinoma of the lung as the most common cause; however, with the rise in the number of central intravenous catheterization and pacemaker placement and their associated stenosis of the brachiocephalic veins and SVC (Fig. 42.2), this percentage may be overestimated [4]. SVC syndrome has a wide range of etiologies, presentations, clinical evaluation, and imaging techniques. The treatments are also diverse depending on urgency and palliative or definitive therapy goals [5]. Surgical reconstruction was the treatment of choice until endovascular repair of SVC was introduced in 1986. Currently, endovascular recanalization has become the first line of treatment in the management in most patients with SVC syndrome [6].

Anatomy

The SVC carries approximately one-third of the cardiac venous return, constituting one of the great veins of the human body. It measures approximately 7 cm in length and is formed by the confluence of the right and left brachiocephalic veins. The azygos venous arch drains into the SVC posteriorly, just before it enters into the right atrium. Surrounding structures include the right phrenic nerve, the vagus nerve, and the pulmonary artery, as well as the pleura, the ascending aorta, the azygos arch, and the sternocostal

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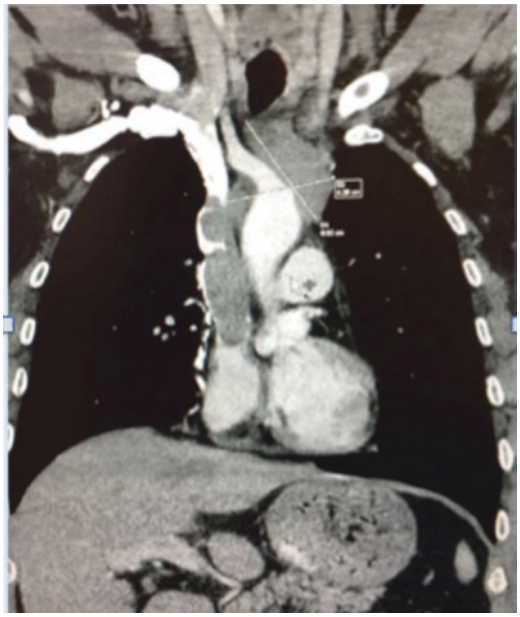

Fig. 42.1 SVCS due to an occluding tumor thrombus in the superior vena cava (SVC)

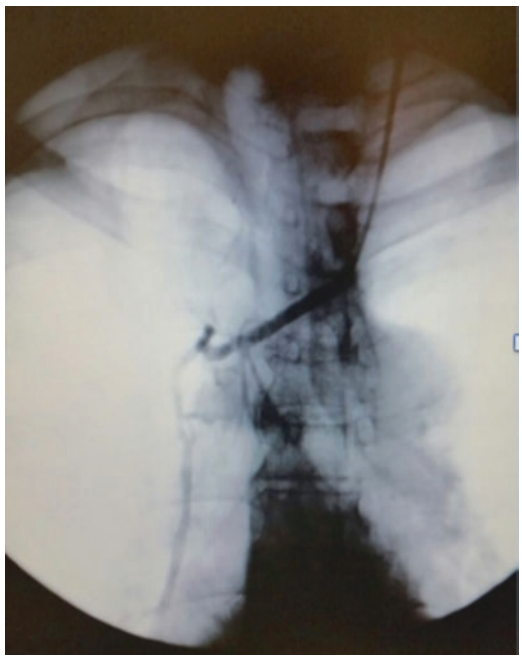

Fig. 42.2 SVCS due to bilateral obstruction of the brachiocephalic veins shown by venography through the internal jugular vein

junction. Half of the SVC is suspended with the pericardium: anteriorly it is free of any attachments, while posteriorly it lies in close relation to the left atrium, the right pulmonary artery, and the posterior and lateral pericardium [7]. Within the anterior-superior and middle mediastina, this great vein is bound by several anatomical structures that may play a role in the pathophysiology of the SVC syndrome. The wall of the SVC is fairly thin and easily compressible by any external masses, such as tumors, enlarged lymph nodes, or aortic aneurysms [5].

Etiology

After the decrease in the incidence of tuberculous and syphilitic mediastinitis in the 1900s with the advent of antibiotic use, malignant tumors became the predominant cause of SVC syndrome (78–93% of cases). Non-small cell and small cell carcinoma, lymphoma, and thymoma are among the leading malignant causes of SVC syndrome [5]. Benign causes are responsible for approximately 40% of all SVC syndrome cases [8], of which indwelling catheters and pacemakers are responsible for up to 71%. Central intravenous catheterization and the use of cardiac pacemakers have significantly increased over the past 20 years. Up to 33% of patients who undergo these common procedures develop upper extremity and central venous thrombosis. Subsequently, SVC syndrome is reported in around 1–3% of patients with indwelling catheters and up to 3.3% of those with cardiac pacemakers. Some studies have suggested that this may be due to catheters placed in suboptimal positions or their short length size [9]. It is also thought that such procedures cause intimal injury predisposing to thrombosis [6]. Other benign causes include mediastinal fibrosis, granulomatous diseases, histoplasmosis, mediastinal radiation, venous thrombosis, hypercoagulable states, Bechet's syndrome, tuberculosis lymphangitis, retrosternal goiter, and very rarely surgical iatrogenic injuries with oversewing of the junction of the right and left brachiocephalic veins [8, 10].

Presentation and Classification

When the flow through the SVC is reduced by more than 60%, blood preferentially is redirected into smaller venous collaterals leading to several hemo-

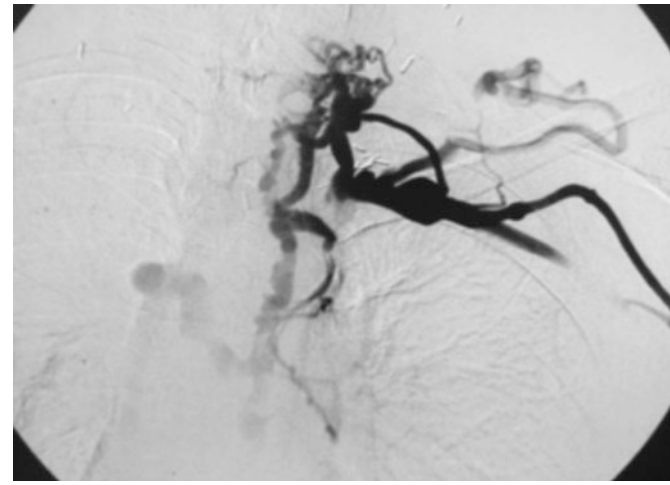

Fig. 42.3 SVC obstruction with collateral circulation

dynamic changes [11] (Fig. 42.3). Most patients with SVC syndrome are between 50 and 70 years of age with a male predominance [6]. The majority of patients with SVC syndrome remain asymptomatic throughout their lifetime; however, some of them present with features of edema in the head and neck region (60–100%), upper extremity edema (14–75%), distended neck/chest veins (27–86%), or facial plethora. The resultant interstitial edema and venous hypertension can also cause respiratory symptoms, such as cough (38–70%), dyspnea (23–74%), hoarseness, or stridor. Neurologic sequelae may be evident in up to 10% of cases, including syncope, cerebral edema, headaches, confusion, cerebrovascular accidents, and herniation [12].

Several scores have been devised to classify the degree of SVC syndrome [11]:

1. Kishi score (clinical gravity score)
   (a) Neurological signs
   (b) Thoracic/pharyngeal-laryngeal signs
   (c) Facial signs
   (d) Vessel dilation
2. Stanford and Doty
   (a) Type I: high-grade SVC stenosis but still normal direction of blood flow through the SVC and azygos vein. There is increased collateral circulation through the hemiazygos and accessory hemiazygos veins in type I.
   (b) Type II: greater than 90% stenosis or occlusion of the SVC but a 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.
3. Qanadli (anatomic)
   (a) Type I: stenosis <90% of the SVC
   (b) Type II: 90–99% stenosis of the SVC
   (c) Type III: occlusion of the SVC
   (d) Type IV: occlusion of the SVC and one or several of its tributaries
4. Bigsby's classification
   (a) Low risk
   (b) High risk

Diagnosis and Imaging

Taking a detailed clinical history and proper physical examination will most often lead to the diagnosis of SVC syndrome. The next step in the investigation consists of radiographic imaging. A chest x-ray is ordered initially, and around 84% of the chest x-rays show some sort of abnormal findings (widened superior mediastinum or pleural effusions) [5]. However, normal findings do not preclude the diagnosis of SVC syndrome. Venous duplex scanning has been found to be a helpful noninvasive tool in screening for SVC obstruction. An internal thoracic vein flow reversal is diagnostic of SVC syndrome [13]. It can also pro-

vide information about resolution of disease and return of normal flow pattern after treatment [14]. The duplex scanning may reveal bilateral jugular and subclavian vein thrombosis or engorged neck veins with abnormal venous flow pattern and loss of flow variation with respiration.

More accurate imaging techniques are computed tomography angiography and contrast-enhanced venography that confer higher sensitivity and specificity (>90%) [5]. They have been widely used in the diagnosis of SVC syndrome and in depicting the degree of central venous obstruction (Fig. 42.4). CT has the added benefit of identifying different benign and malignant structural causes. It can also delineate the small collateral pathways and venous shunts. On the other hand, venography is the gold standard in mapping out the venous circulation in preparation for endovascular or surgical repair. Stanford and Doty classified SVC syndrome into four types according to degree of stenosis and direction of flow through the azygous system [8, 15]. These patterns can identify those at risk for major life-threatening consequences and the need for immediate intervention [15].

Magnetic resonance venography (MRV) is another modality that has gained popularity in the diagnosis of central venous obstruction. Abnormal anatomical variations and compressing structures can easily be identified with this noninvasive modality. It can also outline the central venous circulation and associated collateral pathways [5].

Contrast-induced renal complications may limit the use of some of these diagnostic radiographic techniques. Some relative contraindications to venography include active cellulitis and iodinated contrast allergy. Patients who have aneurysm clips or specific non-MR compatible pacemakers should not undergo MRV.

Tissue diagnosis remains one of the most important factors, especially in malignant SVC syndrome. Specific treatment options rely on the histopathology of the obstructing mass discovered on imaging. Biopsy of lymph nodes, fluid cytology, and more invasive procedures such as bronchoscopy, mediastinoscopy, or thoracoscopy may be needed to identify the type of tumor involved and determine the staging of the disease [5]. It should be kept in mind that invasive diagnostic techniques come with higher morbidity and complication rates in patients with SVC obstruction as compared to those without it [16].

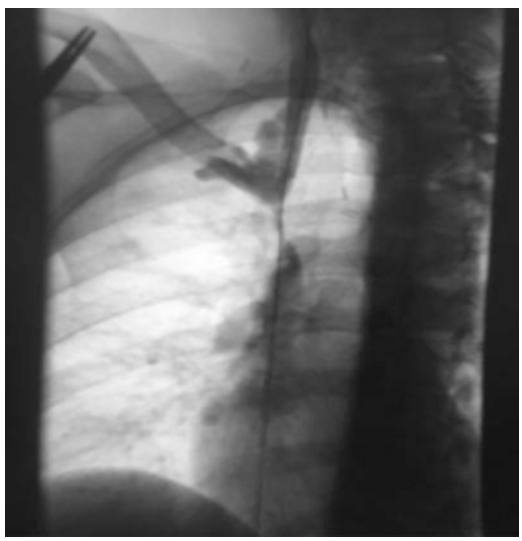

Fig. 42.4 SVCS in a patient post thyroidectomy and breast cancer with multiple central line placement showing a very tight stricture of the right brachiocephalic vein

Management

There are no established guidelines for the treatment of SVC syndrome. The clinical management should be tailored to each patient and the associated radiographic/pathologic findings. The management will depend on the acuity of the presentation, the severity of the symptoms, the etiology and degree of stenosis, and finally the life expectancy. The decision to intervene or proceed to palliation should be promptly reached. The approach to treatment can thus be divided into medical, surgical, or endovascular.

Medical Management

Medical care may be initially aimed at symptomatic relief of patients presenting with signs of SVC obstruction. Conservative management can include lifestyle changes such as assuming an orthostatic position, not wearing tight neck col-

lars, and decreasing daily maneuvers that may increase upper body hydrostatic pressure. The use of diuretics to decrease the resultant edema, supplemental oxygen, and fluid restrictions has been suggested [10, 17]. Steroid use has been advocated especially in patients who present with airway edema or those who will undergo radiotherapy to prevent radiation-induced edema [5, 6]. However, there is no solid evidence attributing a direct effect of steroids on SVC syndrome. Antibiotics are the first-line therapy for patients who present with SVC syndrome caused by infectious processes. For SVC syndrome caused by an indwelling catheter, it is recommended to remove the catheter and start on systemic anticoagulation therapy for a minimum of 3 months. Anticoagulation may prevent the propagation of the venous thrombus and worsening of the obstruction [18]. However, the decision of removing the catheter must not be done hastily. The catheter may be the only venous access remaining or may serve as an essential route for endovascular therapy.

In malignant cases, patients may also benefit from radiation, chemotherapy, or a combination of both. Histopathology aids in targeted therapy and for long-term symptom relief. Several studies showed evidence of early improvement ranging from 3 to less than 30 days post radiation [5, 19]. This may well be due to the decrease in tumor size and burden. However, radiotherapy was not able to ensure patency of the central veins involved. There has been a dose-dependent relationship between radiation dose in gray (Gy) and response to treatment [20]. Certain protocols for the definitive radiation therapy of malignant SVC syndrome should be followed when clinically necessary.

Endovascular Intervention

Except for certain malignancies that respond rapidly to chemotherapy, endovascular therapy has become the first-line treatment of choice in both benign and malignant SVC syndrome [6, 8]. Its use has risen especially paralleling the increasing number of central venous catheters in cancer patients and indwelling cardiac pacemakers.

The endovascular management is typically offered when the symptoms are severe and have not responded to conservative medical therapy. The approach will depend on the obstructive pathology, the presence or absence of intraluminal thrombus, the length of the pathology, and if it is new or recurrent.

In the presence of recent intraluminal thrombus, which can be determined by history and CT scan, an attempt at lytic therapy to dissolve the thrombus will be considered. A multiside hole infusion catheter is navigated to the level of the thrombus, and alteplase is injected at a rate of 1 mg per hour. This may be coupled with pharmaco-mechanical therapy to expedite the process especially when the pathology is bilateral brachiocephalic obstruction. In the presence of total occlusion, a key factor in the success of the therapy is the ability to cross the stenosis or occlusion. For occlusive pathology in the brachiocephalic veins, the ipsilateral brachial vein is typically punctured under ultrasound guidance. A size 5 or 6 French sheath (10 cm) is typically introduced to obtain access. Then a catheter with a longer sheath or guiding catheter is advanced to the level of the occlusion [21]. A hydrophilic wire is navigated through the stenosis or occlusion and then exchanged with a stiff wire to allow for additional intervention (Fig. 42.5).

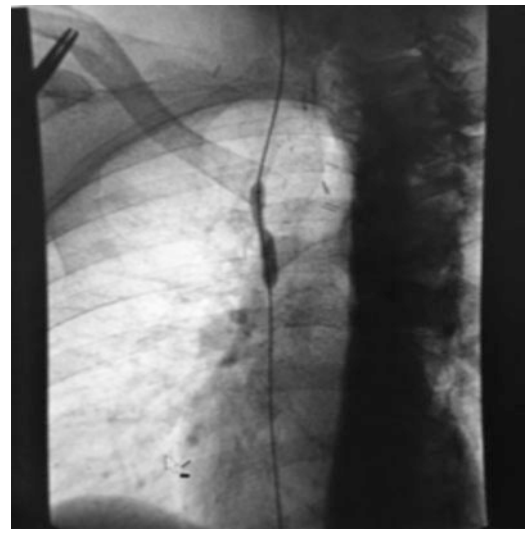

Fig. 42.5 Hydrophilic wire navigated through the stenosis with balloon angioplasty

When the occlusion is in the SVC, the approach may be started from a basilic vein access. An approach from the right internal jugular may be more desired as it provides the shortest and most direct route [22]. This may be coupled with a femoral approach as well in an attempt to recanalize an occluded SVC in tenacious cases. Once the occlusion is crossed, it is important to document with a venogram that the wire is indeed intraluminal and did not perforate the SVC or the brachiocephalic vein landing in an extraluminal position. The area of stenosis or occlusion may be gently predilated to create a working channel that allows for progressive dilatation. Most often balloon angioplasty alone is not sufficient as it is followed by prompt recoil and vein wall collapse (Fig. 42.6). As such a stent is typically needed to maintain the patency of the recanalized vein. A balloon expandable stent delivered through a long sheath can provide the most accurate deployment and may be more resistant to external compression (Fig. 42.7). Self-expanding stent with post-stent balloon dilatation may also be used depending on the location and if there is a significant difference in the size between the proximal and distal part of the stenotic area. If the occlusion is due to an in-stent restenosis, balloon angioplasty alone may be sufficient. A drug-coated balloon may offer some theoretical advantages to prevent recurrent in-stent restenosis (Fig. 42.8). A stent graft appeared to be a safe and effective method for treating patients with malignant SVC syndrome. When compared to uncovered stents, endovascular placement of ePTFE-covered stents appeared to be superior in terms of stent patency [23]. In such situations, concern is often expressed regarding the placement of a covered stent across the confluence of the brachiocephalic veins and whether a unilateral recanalization is adequate. A recent study revealed that unilateral covered stent placement appears to be a safe and effective method for treating malignant SVC syndrome, despite the location of SVC occlusion [24].

Antiplatelet therapy and anticoagulation are typically maintained as long as possible post intervention as most patients are hypercoagulable for a variety of reasons. Follow-up imaging is recommended when recurrence is suspected. All outcomes reporting in the literature have relied on case studies of limited numbers. It is estimated that 80–95% of patients with malignant SVC syndrome achieve symptomatic relief post endovascular stenting. Recurrence in these cases "ranges between 0 and 40% during the period of follow-up (3 days to 8 months)" [22]. Re-intervention was required in the majority of these cases.

A mortality rate of 2% was reported in studies evaluating stenting in malignant SVC syndrome, typically due to hemorrhage, cardiac events, respiratory failure, and PE. Overall complication rate was approximately 4% and includes stent

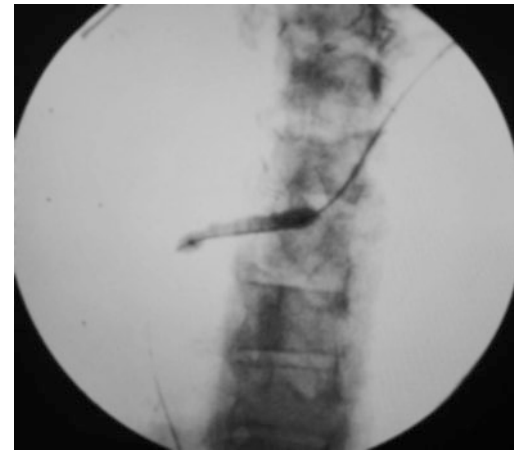

Fig. 42.6 Wire crossed balloon angioplasty and stenting needed to treat

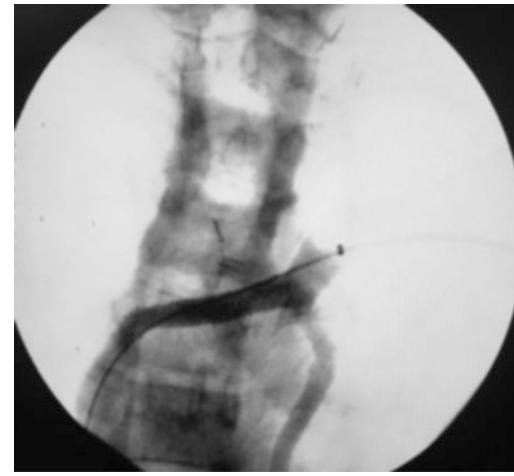

Fig. 42.7 Stented brachiocephalic vein

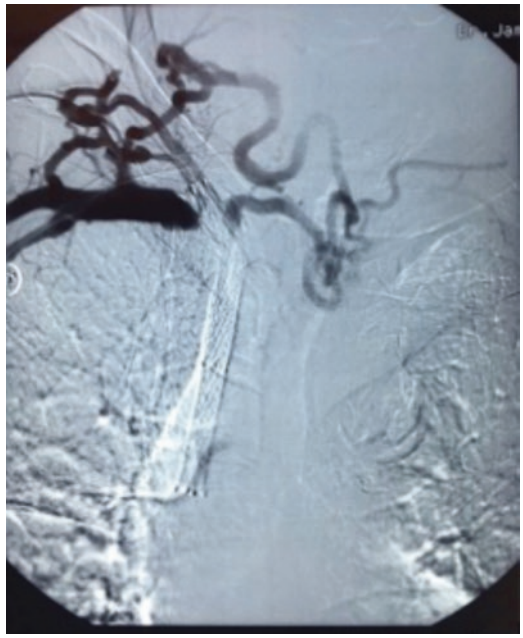

Fig. 42.8 Recurrent superior vena cava (SVC) occlusion with an occluded covered stent in the SVC

migration, bleeding, infection, SVC rupture, pericardial tamponade, and heart failure [6]. Endovascular repair has been associated with less morbidity and faster recovery period as compared to open surgical approach [6, 25]. In a retrospective comparative study done by Rizvi et al., endovascular stenting had better periprocedural morbidity (4%) as compared to open surgical repair (19%) without any significant difference in early mortality [8].

Surgical Reconstruction

With the advances in endovascular treatment of SVC syndrome, surgical reconstruction became restricted to patients who fail or are not candidates of endovascular stenting [26] such as SVC which are directly infiltrated by thymomas or in N0-N1 non-small cell lung cancer. Until recently, open surgical reconstruction was widely adopted as a better option for treatment for benign SVC syndrome in contrary to malignant disease.

Open surgical reconstruction for benign SVC syndrome is typically carried by a venous bypass procedure with various rerouting or reimplantation of the opposite innominate vein depending on the obstructing anatomy (Fig. 42.9). Several types of repairs have been suggested with various types of grafts used. These grafts include autologous vein such as spiral saphenous vein, straight graft, bifurcated graft, straight graft + reimplantation of opposite innominate vein, femoral vein, iliocaval allograft, and expanded polytetrafluoroethylene (ePTFE) [27].

The main challenge is to identify the best graft material to replace or bypass the SVC. The major size discrepancy precludes the use of the saphenous vein unless it is fashioned as a spiral vein. The autologous spiral saphenous vein graft (SSVG) is created by slitting the saphenous vein longitudinally and then resuturing in spiral fashion over a 24–32 French chest tube. Another possible vein with less size mismatch is the femoral vein. However, its harvesting may be associated with the unwanted long-term leg swelling and venous hypertension in a young patient with benign disease. SSVG is preferred especially in young patients with benign SVC syndrome. This type of graft has low thrombogenic tendency but may not achieve the same lengths femoral vein grafts provide. Doty first implanted an SSVG after Chiu et al. described it in animal models achieving patency rates up to 88% [15, 28].

The SVC reconstruction or bypass procedure will typically require access to the mediastinum and the right atrium. The exposure is obtained using a median sternotomy under general anesthesia. The simplest method is to drain into the right atrial appendage which is accessed through the pericardial sac. A C-clamp is applied to the atrial appendage to which the vein graft is connected in an end-to-side configuration. The other end of the graft is anastomosed to the major upper body draining vein. This vein could be the internal jugular or innominate vein, and the anastomosis is performed typically using an end-to-end configuration or end-to-side fashion less frequently. Other forms of direct reconstruction can be used if repairing an iatrogenic injury or following resection of an invading tumor along with a small segment of the SVC. The defect is then repaired using autologous, prosthetic, or bovine pericardial patches.

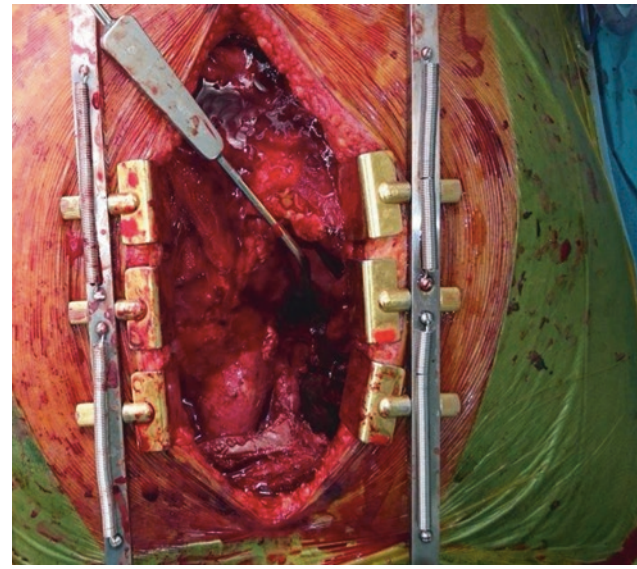

Fig. 42.9 Open surgical repair of the confluence of the left and right brachiocephalic veins

This mediastinal direct surgical reconstruction carries a wide range of complications. These include mediastinal hematoma, deep venous thrombosis, pulmonary emboli, prolonged mechanical ventilation, and pericardial effusion [8]. Reported long-term complications of this procedure are recurrent stenosis and thrombosis [29].

SVC grafting in benign disease can be justified by its long-term secondary patency rates. Endovascular procedures may be used as a salvage of the SVC grafts [26]. Currently however, endovascular procedures are being used as a first-line therapy and reserving the more morbid open reconstruction to failed endovascular therapy. This approach is very justifiable in view of its minimal invasiveness compared to the open reconstruction especially when no bridges are burned. The risks and benefits are to be expressed to the patient and the selected procedure individualized based on the age and anatomy.

Extra-Anatomic Bypass

When endovascular treatment fails and there are contraindications for direct surgical reconstruction, extra-anatomic bypass of the SVC in SVC syndrome may be used as a last resort. When faced with such circumstances, peripheral venous bypass grafts can be used for venous decompression of the brachiocephalic trunk. The major upper body draining vein is typically anastomosed to a graft emptying into the common femoral vein. The upper body draining vein typically used is the internal jugular vein. The external jugular vein may also be used as dictated by the anatomical findings and obstructive pattern. The limitation of such procedures are identifying a vein graft long enough to reach the groin and the possibility of kinking or external compression of such low-pressure graft. To address the length issue, both greater saphenous veins are harvested, anastomosed in an end-to-end fashion, and then tunneled subcutaneously forming a conduit between the internal or external jugular veins and the femoral vein.

A modification to this method has been reported in the literature, whereby this venous conduit is embedded in a prosthetic graft to avoid kinking of the bypass. Panneton et al., for example, used a modified saphenojugular bypass which connects the right internal jugular vein to the femoral vein using a spliced saphenous vein tunneled inside a PTFE graft [30]. Vincze et al. reported palliative decompression therapy of SVC syndrome caused by bronchial carcinoma using a saphenojugular bypass [31].

When the saphenous veins are not available, a PTFE graft or other grafts have been used such as aortic allograft [32], cryopreserved femoral veins, and homograft [27].

Anticoagulation postoperatively and up to 3 months is generally advised in patients with saphenous or femoral vein grafts. Lifelong anticoagulation with heparin, warfarin or new oral anticoagulants is needed for hypercoagulable states and for patients with ePTFE grafts.

Conclusion

SVC syndrome is a challenging condition most commonly due to a malignant pathology with a gradual rise in benign causes. The management is individualized based on the etiology and anatomical factors. In malignant SVC syndrome, chemoradiation is typically used to address the primary malignancy and endovascular therapy to achieve recanalization. In benign SVC syndrome, endovascular therapy is attempted as first-line therapy although open reconstruction may provide a longer-lasting result.

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Management of Chronic Thromboembolic Pulmonary Hypertension

43

Stuart W. Jamieson

Clinical Pearls

1. Pulmonary hypertension due to thromboembolic disease is commonly missed in the diagnosis of shortness of breath. "You have to think of the diagnosis to make the diagnosis."
2. The work up includes an echocardiogram and a V/Q scan in all patients with unexplained dyspnea and pulmonary hypertension.
3. Pulmonary endarterectomy should be bilateral and using periods of complete circulatory arrest to assure good visibility. The results in an experienced center are good, with complete resolution of symptoms, and a mortality of 2%.

Introduction

In approximately 5% of patients who survive acute pulmonary embolic episodes, the clot does not resolve completely, with the result that the thrombus becomes fibrotic and incorporated into the pulmonary artery wall. The progressive occlusion of the pulmonary vasculature results in pulmonary hypertension and eventual right heart failure [1, 2].

The reasons for the failure of emboli to dissolve are incompletely understood and may be from a combination of factors, including repetitive thrombi or embolization of already partially fibrotic material. The volume of acute embolic material may simply overwhelm the lytic mechanisms, or a total occlusion of a major arterial branch may prevent lytic enzymes from reaching, and thus dissolving, the embolus completely. The lytic mechanisms themselves may be abnormal, and some patients may have a hypercoagulable state with a propensity for thrombus formation. It should be noted that many patients (up to 50%) with chronic pulmonary hypertension from thromboembolic disease do not have a history of DVT or pulmonary embolus.

Regardless of the predisposing factors to residual thrombus within the vessels, the final genesis of the resultant pulmonary vascular hypertension in some patients may be complex. The increased pressure and flow because of redirected pulmonary blood flow in the previously normal pulmonary vascular bed can create a vasculopathy in the small precapillary blood vessels, similar to that seen in Eisenmenger's syndrome [3, 4]. These changes are not operable or revers-

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ible. With the current success and attendant low mortality with the pulmonary endarterectomy operation, we thus advise earlier operation, before these changes can occur [5].

The prognosis for all patients with pulmonary hypertension is poor. For patients with chronic pulmonary hypertension due to thromboembolic disease, survival is proportional to the degree of hypertension. If the mean pulmonary pressure at presentation is over 50 mmHg, the 2-year survival rate is 20%, and the 5-year survival is 10%. Surgical therapy offers a vastly improved prognosis, both in survival and in quality of life.

Twenty-five years ago, only the University of California, San Diego, was performing the pulmonary endarterectomy (PEA) operation. It was thought that the condition of thromboembolic pulmonary hypertension was exceedingly rare and that operative treatment was unjustified, ineffective, and dangerous. However, it has now become recognized that this form of pulmonary hypertension is common, and that operation to relieve the condition is safe and effective, and vastly superior to medical management, which is only palliative and limited to the treatment of right heart failure. Surgical treatment is curative and, with current techniques, has a low mortality and morbidity [6].

Symptoms

Patients may be asymptomatic until signs of dyspnea, exercise intolerance, or right heart failure develop. Because of the large area of the pulmonary vascular bed, generally more than 60% of the vasculature must be occluded before pulmonary hypertension occurs at rest. With exercise and the attendant increase in cardiac output, however, even with lesser degrees of occlusion, the pulmonary artery pressures will increase, and the increase in pulmonary blood flow may be associated with a widening of the alveolar-arterial oxygen tension gradient, with subsequent hypoxemia.

The principal symptom in patients is therefore progressive exercise intolerance. It is not until the relatively late stages of the disease when signs of right heart failure become obvious that the diagnosis can easily be made. In the late stages, the patient will have cor pulmonale and right heart failure, with hepatomegaly, ascites, and severe peripheral edema.

Studies

Chest X-ray, electrocardiogram, and pulmonary function tests are of little value in differentiating thromboembolic pulmonary hypertension from other forms of pulmonary hypertension, though they often give the initial clues that pulmonary hypertension exists.

The most useful screening studies are two-dimensional surface echocardiography with Doppler imaging and radionuclide ventilation-perfusion scanning.

The echocardiogram typically demonstrates right atrial, right ventricular, and pulmonary artery enlargement, with right ventricular hypertrophy. The interventricular septum may be flattened and often will exhibit paradoxical motion, with encroachment of the right ventricular septum into the left ventricle. Varying degrees of tricuspid regurgitation are usually seen. Continuous wave Doppler of the tricuspid regurgitant jet is helpful in estimating the pulmonary artery systolic pressure (PAP = (tricuspid envelope)^2 × 4 + CVP). Because exercise typically increases the degree of pulmonary hypertension, echocardiography should be repeated with exercise whenever the disease is suspected, but the resting echocardiogram demonstrates only subtle abnormalities.

A perfusion scan should be performed. The major differential diagnosis is from that of primary pulmonary hypertension, where the scan is usually normal, or has a patchy and mottled appearance, in contrast to the multiple punched-out lobar or segmental defects of chronic thromboembolic disease.

Computerized tomography scanning is increasingly being used in the diagnosis. This is capable of confirming occlusion of at least the main and lobar pulmonary arteries but may miss smaller degrees of occlusion. Occlusion local-

ized to the main pulmonary vessels is an unusual finding and may point to a pulmonary artery tumor. A mosaic pattern of lung attenuation at CT is a sign of variable region perfusion and will suggest chronic pulmonary thromboembolism.

The pulmonary angiogram remains the gold standard for the diagnosis. Together with right heart catheterization, it evaluates the severity of pulmonary hypertension, assesses the surgical accessibility and operative risk, and excludes other diagnoses. Measurement of the pulmonary vascular resistance (Mean PA pressure—mean LA pressure)/(cardiac output = PVR in Wood Units, Wood Units × 80 = resistance as dynes/s/cm^{-5}) is a useful tool. A PVR above 1000 dynes/s/cm^{-5} is a relative risk factor, particularly if associated with only moderate pulmonary vascular occlusion seen on angiogram, though this should not preclude operation.

Both MRI and CT are additive to the angiogram and need not be performed if the angiogram is negative or clearly diagnostic.

In general, the lower lobes of the lung are more involved with occlusion than the upper lobes, and the right lung is more affected than the left. This is probably because of the larger blood flow to the right side. Although the term "surgically accessible" thromboembolic disease is often used, pulmonary hypertension as a result of emboli is almost always operable. The possibility of restoration of completely normal flow to the pulmonary vascular bed, however, may depend on the pattern of thrombotic occlusion and the presence of a secondary vasculopathy.

In addition to pulmonary angiography, patients over 45 undergo coronary arteriography and other cardiac investigation as necessary. If significant disease is found, additional cardiac surgery is performed at the time of pulmonary endarterectomy. Most patients who undergo operation are within New York Heart Association class III or class IV (III: Marked limitation in activity due to symptoms, comfortable only at rest, IV: Severe limitations. Mostly bedbound patients).

A typical patient will have a severely elevated pulmonary vascular resistance at rest, the absence of significant comorbid disease unrelated to right heart failure, and the appearances of chronic thrombi on angiogram that seem in balance with the measured pulmonary vascular resistance.

With the growth of our surgical experience, surgical treatment is offered to patients with more distal thromboembolic disease that is contributing to, but probably not entirely responsible for, the patient's symptoms (Type III disease—see below) and, at the other end of the spectrum, those with advanced right-sided cardiac failure with ascites and hepatic and renal dysfunction that are presumed reversible. There is no upper limit of pulmonary vascular resistance, pulmonary artery pressure, or right ventricular hypertrophy or failure that will exclude a patient from operation at our institution.

If not previously implanted, an inferior vena cava filter is routinely placed prior to the operation, usually at the time of cardiac catheterization.

Operation

Pulmonary embolization rarely results in tissue necrosis because the bronchial circulation maintains viability of the lung parenchyma. Surgical endarterectomy thus allows the lung tissue to regain function in gas exchange.

There are several guiding principles for the operation [6]. It must be bilateral, since for pulmonary hypertension to be a major factor, both pulmonary arteries must be substantially involved (a patient with a pneumonectomy is rarely pulmonary hypertensive). The only practical approach to both pulmonary arteries is through a median sternotomy incision.

Cardiopulmonary bypass is used to ensure cardiovascular stability when the operation is carried out and to cool the patient to allow circulatory arrest. Excellent visibility is required, in a bloodless field, to define an adequate endarterectomy plane and to then follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually seen in these cases (because of the augmented bronchial circulation after pul-

monary artery occlusion), periods of circulatory arrest are necessary to ensure perfect visibility. The circulatory arrest periods are limited to 20 min, with restoration of flow between each arrest. With experience the endarterectomy usually can be performed with a single period of circulatory arrest on each side.

A true endarterectomy in the plane of the media must be accomplished, to remove the fibrotic scar tissue that has incorporated into the vessel wall. Removal of visible red or brown thrombus is largely incidental to this operation. Indeed, in most patients, no free thrombus is present, and on initial direct examination the pulmonary vascular bed may appear normal.

Typically the right heart is enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation (Fig. 43.1). There is usually severe right ventricular hypertrophy, and with critical degrees of obstruction, the patient may become unstable with manipulation of the heart.

Full bypass is instituted with high ascending aortic cannulation and two caval cannulae. In unstable patients, bypass is begun with one caval cannula, with the other added after bypass is initiated. These cannulae are inserted into the superior and inferior vena cava sufficiently to later open the right atrium if necessary. A temporary pulmonary artery vent is placed in the midline of the main pulmonary artery one-centimeter distal to the pulmonary valve.

The blood is cooled with the pump oxygenator, maintaining a 10°C gradient between arterial blood and bladder or rectal temperature. Surface cooling with both a head jacket and a cooling blanket is begun. With cooling the tympanic membrane measurements fall fastest, but circulatory arrest is not initiated until temperatures of the rectum or bladder are within a degree or two of the head temperatures.

During perfusion the venous saturations increase; saturations of 80% at 25°C and 90% at 20°C are typical. Hemodilution is used to decrease the blood viscosity during hypothermia and to optimize capillary blood flow; the hematocrit is maintained in the range of 18–25 during profound hypothermia.

Cooling generally takes 45 min to an hour, varying according to the body mass of the patient. When ventricular fibrillation occurs, a further

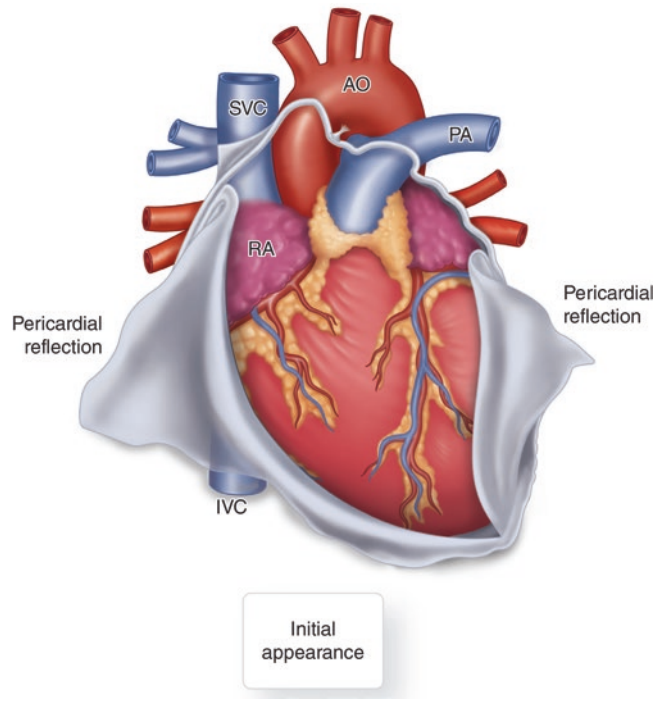

Fig. 43.1 The initial appearance of the heart with the reflected pericardium

vent is placed in the left ventricle through the right upper pulmonary vein. It is most convenient for the surgeon to be placed initially on the patient's left side. During the cooling period, some preliminary dissection can be carried out. The aorta is freed from the right pulmonary artery. The superior vena cava is mobilized all the way to the innominate vein and also dissected free of the right pulmonary artery. All dissection of the pulmonary arteries takes place intrapericardially, and neither pleural cavity is entered. The distal right pulmonary artery is exposed (between the aorta and superior vena cava) by reflecting the pericardial covering upward, so that the takeoff of upper and middle lobes can be seen (Fig. 43.2).

An incision is then made in the right pulmonary artery from the lateral border of the ascending aorta, out toward the reflected superior vena cava, and entering the lower lobe branch of the pulmonary artery just after the takeoff of the middle lobe (Fig. 43.3). It is important that the incision stays in the center of the vessel and continues into the lower, rather than the middle lobe. The distal limit of the incision is dictated by the accessibility required to repair this subsequently. Any loose thrombus, if present, is now removed. In most cases no thrombus is present, and initially the pulmonary vascular bed may appear normal even in severe embolic pulmonary hypertension.

When the patient's temperature reaches 20°C, the aorta is cross clamped and a single dose of cold cardioplegic solution (1 l) administered. Additional myocardial protection is obtained by the use of a cooling jacket. The entire procedure

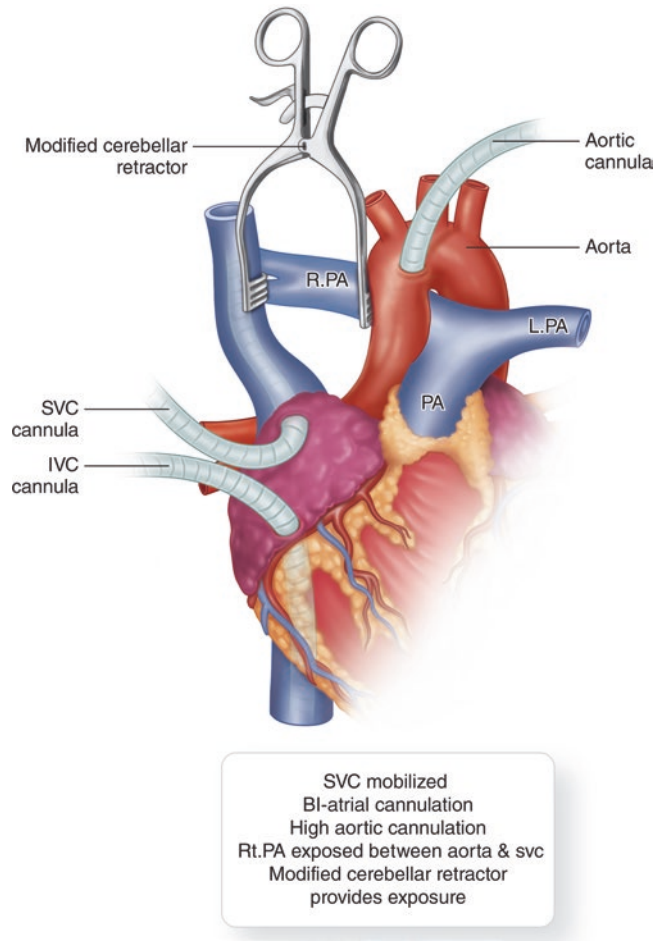

Fig. 43.2 Bypass is established with high aortic cannulation and superior and inferior vena cava cannulae The superior vena cava is mobilized, and the right pulmonary artery is exposed between the superior vena cava and aorta using a modified cerebellar retractor

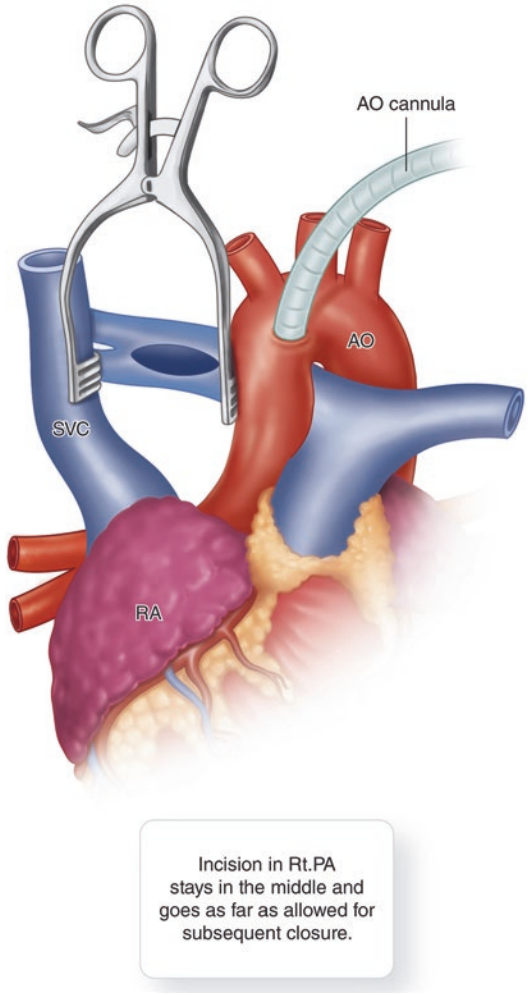

Fig. 43.3 The incision in the right pulmonary artery should stay in the center of the vessel, going past the upper lobe and into the lower lobe if visibility is adequate

can now carried out with a single aortic cross clamp period with no further administration of cardioplegic solution.

A modified cerebellar retractor is placed between the aorta and superior vena cava, and this lifts the superior vena cava off the pulmonary artery and affords excellent exposure for the incision in this vessel. The approach medial to the superior vena cava, together with tilting the patient to the right, allows visualization of all distal vessels of the right pulmonary vascular bed.

Circulatory arrest is initiated, and the patient exsanguinated. Then, a microtome knife is used to develop the endarterectomy plane posteriorly, since any inadvertent egress at this site could be readily repaired or simply left alone (Fig. 43.4). The plane is not initiated at the initial incision site, unlike the situation in a carotid or femoral endarterectomy, since the residual thin pulmonary artery will not hold hemostatic sutures for repair. Dissection in the correct plane is critical because if the plane is too deep, the pulmonary artery may perforate, with fatal results, and if the dissection plane is not deep enough, inadequate amounts of the chronically thromboembolic material will be removed. The plane is in the media of the vessel.

When the proper plane is entered, the layer will strip easily. The ideal layer is marked with a pearly white layer, which strips easily. There should be no residual yellow plaque. If the dissection is too deep, a reddish or pinkish color indicates the adventitia has been reached. A more superficial plane should immediately be sought.

A full-thickness layer is left in the region of the initial incision, to ease subsequent repair (Fig. 43.5). The vessel is progressively endarterectomized with an eversion technique. As the fibrotic occluding layer becomes free, it is progressively grasped more distally until each subsegmental branch becomes free, and the entire cast is liberated. Although many of these vessels cannot be seen initially, progressive dissection and traction allow a complete endarterectomy of the entire pulmonary vascular bed. Absolute visualization in a completely bloodless field provided by circulatory arrest is essential. A perforation at subsegmental level will become inaccessible later. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction. It is possible to remove occluding material as far distally as the diaphragmatic level.

The dissection is carried out with a dissector with a rounded tip, the body of which is attached to the cell-saver suction. The use of this dissector ("Jamieson dissector," Fehling Corporation) is essential for a complete endarterectomy. At the completion of the dissection, the lumen of the pulmonary artery is carefully inspected, and any residual debris removed.

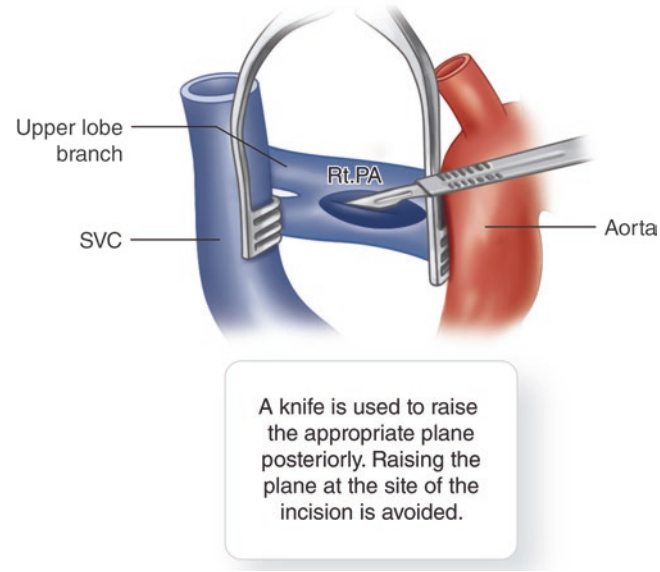

Fig. 43.4 A knife is used to raise the appropriate plane posteriorly. Raising the plane at the site of the incision is avoided

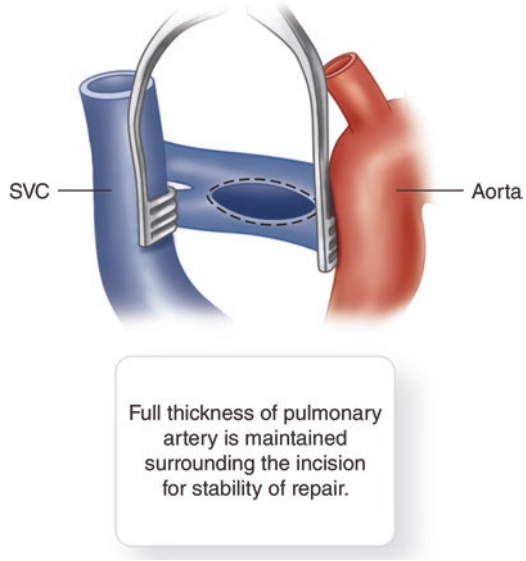

Fig. 43.5 The area surrounding the incision is not endarterectomized, to provide full thickness of the vessel for subsequent repair

Circulatory arrest periods are limited to 20 min, followed by, if necessary, a reperfusion period. Reperfusion is carried out at 18°C for 10 min. After this time the venous oxygen saturations return to above 90%. However, with experience the entire endarterectomy on one side can usually be performed within a 20 min circulatory arrest period, and the reperfusion period can be used to repair the arteriotomy on the right side before proceeding to the left.

After repairing the right arteriotomy, the surgeon moves to the patient's right side. The pericardial attachment is mobilized off the left pulmonary artery with electrocautery, again with care taken to avoid phrenic nerve injury. An arteriotomy is made from the central main pulmonary artery below the vent hole proceeding laterally to the distal end of the raised pericardial reflection, avoiding entry into the left pleural space (Fig. 43.6). The left-sided dissection is similar to that done on the right. As on the right, the endarterectomy plane is initiated posteriorly, and distal dissection is facilitated by circumferential development of the plane distal to the arteriotomy. The duration of circulatory arrest intervals during performance of the left-sided dissection is subject to same restrictions as on the right.

There are four broad types of pulmonary occlusive disease related to thrombus that can be appreciated, and we use the following classification:

Type I: (Approximately 10% of cases). Major vessel clot is present and readily visible upon opening the pulmonary arteries. As mentioned above, all central thrombotic material has to be completely removed prior to the endarterectomy.

Type II: (Approximately 60% of cases). No major vessel thrombus can be appreciated. In

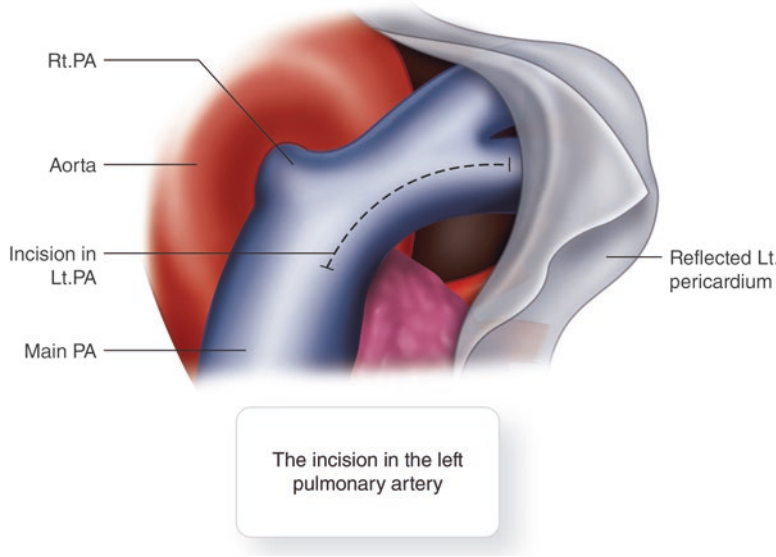

Fig. 43.6 The *dotted line* shows the site of the incision of the left pulmonary artery

these cases only thickened intima can be seen, occasionally with webs, and the endarterectomy plane is raised in the main, lobar, or segmental vessels.

Type III: (Approximately 30% of cases). This presents the most challenging surgical situation. Here the disease is very distal and confined to the segmental and subsegmental branches. Initially, no occluded vessels can be seen. The endarterectomy plane has to be carefully and painstakingly raised in each segmental and subsegmental branch. Type III disease is most often associated with presumed repetitive thrombi from indwelling catheters, such as pacemaker wires, ventriculo-atrial shunts, or "burnt-out" disease, where all major vessel thrombus has been resolved, but distal vessel disease remains, often in association with secondary vasculopathy.

Type IV: Disease here does not represent primary thromboembolic pulmonary hypertension and is inoperable. In this entity there is intrinsic small vessel disease, though secondary thrombus may occur as a result of stasis. Here small vessel disease either occurs as a result of a high flow state similar to Eisenmenger's syndrome or possible sympathetic "cross talk" from an affected contralateral side (IVa) or with primary pulmonary hypertension (IVb).

After repair of the left arteriotomy, the pulmonary artery vent is replaced, cardiopulmonary bypass is reinstituted and warming commenced. During rewarming a 10°C temperature gradient is maintained between the blood and body temperature. The rewarming period generally takes about 90 min but varies according to the body mass of the patient.

If other cardiac procedures are required, such as closure of a patent foramen ovale, coronary artery, or valve surgery, these are performed during the rewarming period. Although tricuspid valve regurgitation is invariable in these patients, and is often severe, tricuspid valve repair is not performed unless there is structural disease of the tricuspid valve. Right ventricular remodeling occurs within a few days, with return of tricuspid competence.

Bypass is discontinued when the patient has rewarmed. The systemic vascular resistance is generally initially low, a result of hypothermic circulatory arrest, and alpha-adrenergic drugs may be necessary to keep the systemic blood pressure within a low normal range. The cardiac output is generally high. Temporary atrial and ventricular epicardia pacing wires are placed.

Postoperative Management

Postoperative management is similar to that of regular open-heart surgery except that diuresis is maintained with the goal of reaching the patient's preoperative weight within 24 h.

Postoperative venous thrombosis prophylaxis with intermittent pneumatic compression devices is used, and the use of subcutaneous heparin is begun on the evening of surgery. Anticoagulation with warfarin is begun as soon as the pacing wires, and mediastinal drainage tubes are removed, with a target international normalized ratio (INR) of 2.5–3 times the control value.

Complications

Complications of the procedure, apart from the usual complications sometimes seen after heart surgery, include residual pulmonary hypertension and reperfusion lung injury.

The decrease in pulmonary vascular resistance usually results in an immediate and sustained restoration of pulmonary artery pressures to normal levels, with a marked increase in cardiac output. However, there are some patients in whom some degree of residual pulmonary hypertension is permanent. Generally, this is seen in patients where the preoperative PVR and the degree of angiographic occlusion are discordant, with the presence of damage to previously unaffected small vessels, as described above.

Residual pulmonary hypertension may result in right heart failure with hemodynamic instability, and sometimes also hypoxia, while reperfusion injury of the lung results in hypoxia. If these conditions are life-threatening, and considered reversible given adequate support and time, extracorporeal membrane oxygenation (ECMO) support may be initiated. Veno-arterial support is used for a hemodynamic problem; removal of venous blood unloads the right ventricle and pulmonary artery, and the circuit provides gas exchange and increased cardiac output as blood is returned to the arterial side. If the issue is only the lack of oxygenation, then veno-venous ECMO is used.

Although an increased PVR preoperatively poses an increased risk, this statement should come with the caveat that it is postoperative PVR that signifies risk rather than preoperative PVR. Thus, every effort should be made to remove all obstructing material, even if this increases circulatory arrest time.

A specific complication that occurs in many patients to some degree is localized pulmonary edema or the "reperfusion response." Reperfusion injury is defined as a radiological opacity seen in the lungs within 72 h of pulmonary endarterectomy. This loose definition may thus encompass many causes, such as fluid overload, and infection. Early measures should be taken to minimize the development of pulmonary edema with diuresis, maintenance of the hematocrit, and the early use of PEEP.

True reperfusion injury that directly adversely impacts the clinical course of the patient occurs in about 10% of patients. In this condition a capillary leak occurs in (and is limited to) the endarterectomized areas of the lung. The cause of the leak can be multifactorial. In its most dramatic form, it occurs within a few hours after operation and is associated with profound desaturation. Edema-like fluid, sometimes with a bloody tinge, is suctioned from the endotracheal tube.

Once the capillary leak has been established, treatment is supportive, since reperfusion pulmonary edema will eventually resolve if satisfactory hemodynamics and oxygenation can be maintained. Careful management of ventilation and fluid balance is required; the hematocrit is kept high (32–36), and the patient is diuresed aggressively, even if this requires ultrafiltration. The patient's ventilatory status may be dramatically position sensitive. The FiO_2 is kept as low as is compatible with an oxygen saturation of 90%. A careful titration of positive end-expiratory pressure is carried out, with a progressive transition from volume limited to pressure limited, inverse ratio ventilation, and the acceptance of moderate hypercapnia. Infrequently, inhaled nitric oxide at 20–40 parts per million can improve gas exchange.

Frank blood from the endotracheal tube, which fortunately is very rarely seen, generally

signifies a mechanical violation of the blood airway barrier that has occurred at surgery, usually unrecognized at the time. It is also occasionally seen when a patient preoperatively has a necrotic cavity of the lung (this is rare because of the bronchial arterial supply, as discussed above) which is revascularized by endarterectomy of the feeding vessels, previously blocked. Airway bleeding should be managed, if possible, by identification of the affected area by bronchoscopy, and balloon occlusion of the affected lobe until coagulation can be normalized.

The University of California, San Diego (UCSD) has the world's largest experience in this operation, now exceeding 3700 patients. The mortality rate is in the range of 2%, with the vast majority of patients returned to normal activity [7].

Conclusion

It is increasingly apparent that pulmonary hypertension due to chronic pulmonary embolism is a condition which is under-recognized. Thromboembolic pulmonary hypertension carries a poor prognosis. Medical therapy is ineffective in prolonging life, and only transiently improves symptomatology.

Pulmonary endarterectomy is technically demanding and requires careful dissection of the pulmonary artery planes and the use of circulatory arrest. There is a distinct learning curve for the procedure. The postoperative management is more complex than in the usual heart surgery case. However, surgical therapy is curative, with excellent short and long term results achieved in an experienced center.

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