Chapter 1

The hemodynamics and diagnosis of venous disease

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The venous system is, in many respects, more complex than the arterial system and a thorough understanding of venous anatomy, pathophysiology, and available diagnostic tests is required in the management of acute and chronic venous disorders. The venous system develops through several stages, which may be associated with a number of development anomalies. A thorough knowledge of lower extremity venous anatomy, anatomic variants, and the recently updated nomenclature is required of all venous practitioners. Effective venous return from the lower extremities requires the interaction of the heart, a pressure gradient, the peripheral muscle pumps of the leg, and competent venous valves. In the absence of pathology, this system functions to reduce venous pressure from approximately 100 mm Hg to a mean of 22 mm Hg within a few steps. The severe manifestations of chronic venous insufficiency result from ambulatory venous hypertension, or a failure to reduce venous pressure with exercise. Although the precise mechanism remains unclear, venous hypertension is thought to induce the associated skin changes through a number of inflammatory mechanisms. Several diagnostic tests are available for the evaluation of acute and chronic venous disease. Although venous duplex ultrasonography has become the standard for detection of acute deep venous thrombosis, adjuvant modalities such as contrast, computed tomographic, and magnetic resonance venography have an increasing role. Duplex ultrasonography is also the most useful test for detecting and localizing chronic venous obstruction and valvular incompetence. However, it provides relatively little quantitative hemodynamic information and is often combined with measurements of hemodynamic severity determined by a number of plethysmographic methods. Finally, critical assessment of venous treatment modalities requires an understanding of the objective clinical outcome and quality of life instruments available.

INTRODUCTION

The venous system is in many respects far more complicated than the arterial system, depending on a series of valved conduits and peripheral muscle pumps to return blood against the forces of gravity. In the acute situation, stasis within these conduits is at least a permissive factor in the formation of deep venous thrombosis. Chronically, a diverse array of clinical manifestations may result from either venous obstruction or valvular incompetence. Regardless of the underlying etiology, ambulatory venous hypertension is the final pathway leading to the more severe manifestations of chronic venous insufficiency. A thorough understanding of venous anatomy and physiology, the corresponding pathophysiology, and the limitations of available diagnostic tests is required for the appropriate management of both acute and chronic venous disease. Furthermore, an understanding of the natural history of venous disease and relevant outcome measures is critical in evaluating various treatment options.

DEVELOPMENT, ANATOMY AND TERMINOLOGY OF THE LOWER EXTREMITY VENOUS SYSTEM

Development of the venous system

During development, the vascular system undergoes differentiation through multiple stages, first described by Woolard in 1922.1 Primitive vascular channels in the limb first appear in the third week of gestation. Only a capillary network is present during stage 1, the undifferentiated stage. Large plexiform structures subsequently appear during stage 2, the retiform stage. Stage 3, present by the third week of gestation, includes the development of large channels, arteries, and veins and is termed the maturation stage.
Vascular endothelial growth factor (VEGF), secreted by keratinocytes, induces the penetration of capillary vessels into the avascular epidermis.² The venous system in the trunk first appears as bilateral, symmetrical vessels.³ The left sided structures subsequently regress and the right-sided vessels develop as the superior and inferior vena cavae (Fig 1).⁴ These patterns of development can result in differences among individuals. A double inferior vena cava (2% to 3%) usually occurs distal to the renal veins and results from bilateral persistence of the supracardinal veins. A left inferior vena cava (<0.5%) results from caudal regression of the right supracardinal vein with persistence of the left supracardinal vein. Renal vein anomalies include the persistent (circumaortic) renal collar (1% to 9%) and the posterior (retroaortic) left renal vein (1% to 2%).⁵

Persistence of embryonic veins after birth is associated with venous malformations of the lower extremities and pelvis. A large lateral embryonic vein (marginal vein) is seen in patients with the Klippel-Trenaunay syndrome.⁶ A persistent sciotic vein can also be observed in venous malformations of the leg and may lead to chronic venous insufficiency.⁷ Other developmental anomalies of the venous system include valvular agenesis, congenital venous aneurysms, and primary valvular insufficiency.⁸

The anatomy of the leg and pelvic veins

The nomenclature of the lower extremity veins has been recently updated, clarifying many definitions and eliminating most eponyms (Tables I and II).⁹ The venous system of the lower extremities includes the deep veins, which lie beneath the muscular fascia and drain the lower extremity muscles; the superficial veins, which are above the deep fascia and drain the cutaneous microcirculation; and the perforating veins that penetrate the muscular fascia and connect the superficial and deep veins. Communicating veins connect veins within the same compartment.⁹ The superficial, deep, and most perforating veins contain bicuspid valves that assure unidirectional flow in the normal venous system.

Superficial veins. The principle veins of the medial superficial system are the great saphenous vein and the anterior and posterior accessory great saphenous veins. Duplex scanning has resulted in recognition of a saphenous subcompartment and saphenous fascia.⁹,¹⁰ The saphenous fascia covers the saphenous subcompartment and separates the great saphenous vein from other veins in the superficial compartment (Fig 2). The term great saphenous vein (GSV) is preferred over the previously used terms of greater or long saphenous vein (Fig 3).³,¹¹ This avoids confusion when an abbreviation is used (ie, LSV, the acronym of long saphenous vein [old terminology]). The saphenofemoral junction, formed by the GSV, the superficial circumflex iliac, superficial epigastric, and the external pudendal veins, is now properly called the confluence of superficial inguinal veins.¹¹

The lesser or short saphenous vein should now be called the small saphenous vein (SSV). The SSV is the most important posterior superficial vein of the leg. It originates from the lateral side of the foot and drains into the popliteal vein, most commonly joining it just proximal to the knee crease. The intersaphenous vein (previously termed the vein of Giacomini) connects the small and great saphenous veins.¹¹

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Deep veins. The most important terminology change of the leg veins is that the superficial femoral vein (a deep vein) is now called the femoral vein (Fig 4).⁹,¹² It connects the popliteal vein to the common femoral vein. Paired femoral or popliteal veins are not unusual. The deep veins of the calf (anterior, posterior tibial, and peroneal veins)
The lower and middle group veins are frequently associated with pelvic reflux and the pelvic congestion syndrome. Valvular incompetence of the ovarian veins can be associated with stenosis or occlusion of the left common iliac vein. Such compression may be associated with pelvic congestion, varicosities, and chronic skin changes including ulceration. The main pelvic veins include the external, internal, and common iliac veins, which drain into the inferior vena cava. The overlying right common iliac artery can compress the left common iliac vein. Such compression may be associated with stenosis or occlusion of the left common iliac vein, a frequent cause of “spontaneous” left iliofemoral venous thrombosis (May-Thurner syndrome). Compression of the left renal vein between the superior mesenteric artery and the aorta can cause left flank pain and hematuria (nut-cracker syndrome). Large gonadal veins drain into the IVC on the right and the left renal vein on the left side. Valvular incompetence of the ovarian veins can be associated with pelvic reflux and the pelvic congestion syndrome.

Perforating veins. By definition, the perforating veins pass through the deep fascia separating the superficial and deep compartments. Direct perforators connect superficial to deep axial veins while indirect perforators join other veins in the muscles to drain blood from the superficial venous system. While unidirectional flow in these veins assures superficial to deep flow in the calf and thigh, perforating vein valvular incompetence may contribute to venous congestion, varicosities, and chronic skin changes including ulceration.

The most important perforating veins of the lower extremity are the medial calf perforators. There are two main groups of medial calf perforators, the posterior tibial and the more proximal paratibial perforating veins. The posterior tibial perforating veins (Cockett perforators) connect the posterior accessory GSV with the posterior tibial veins and form three groups (lower, middle, and upper). (Fig 5) The lower and middle group veins are frequently located either within a fascial duplication or the deep posterior compartment. Paratibial perforators connect the main GSV trunk with the posterior tibial veins. Other perforators of the leg are classified according to their topology: anterior, lateral, medial and lateral gastrocnemius, intergемellar, and Achilles perforating veins. Perforators around the knee include the infra- and suprapatellar, medial, lateral, and popliteal fossa perforating veins. The perforators of the femoral canal connect the GSV to the femoral vein in the distal thigh.

### PHYSIOLOGY AND HEMODYNAMICS OF THE VENOUS CIRCULATION

The primary function of the venous circulation is to return blood to the heart. The enormous capacity of the venous reservoir facilitates cardiovascular homeostasis through volume shifts.

Effective venous return requires the interaction of a central pump, a pressure gradient, a peripheral venous pump, and competent venous valves. An appreciation of the relationship between volume and pressure in the venous system is essential to understanding normal and abnormal function. The physiological effects of gravity and hydrostatic pressure oppose return venous flow in the upright position. However, a system of valves, an efficient peripheral pump mechanism, and a small dynamic pressure gradient overcome the forces of gravity.

### Venous capacitance and the relationship of pressure to volume

The shape of the venous wall varies greatly depending upon pressure, volume, and flow. When empty or flaccid, vein walls are coapted and pressure is low. Large shifts in flow (or volume) are accommodated with minimal change...
in pressure over the normal range of 5 to 25 mm Hg, reflecting the large capacitance of the venous system. However, as the veins fill, distention is accompanied by an escalating increase in pressure per unit volume (Fig 6). Substantial, acute volume shifts can be accommodated by expansion or contraction of the large, variably sized venous reservoir. In the healthy individual, an acute 10% decrease in blood volume can be accommodated without significant physiological consequence. Large increases in total body fluid volume are also rapidly accommodated by a healthy venous system.

Regulation of venous physiology
Regulation of venous tone is an important aspect of volume accommodation and works in concert with arterial tone to control the distribution of cardiac output. Sympathetic mediated adjustments of smooth muscle tone are most pronounced in the splanchnic and cutaneous distributions.

Circulatory homeostasis upon assumption of upright posture is largely achieved by immediate changes in heart rate followed by adjustments in arterial resistance. Reflex mediated control of the resistance (precapillary) vessels is thus a major determinant of the distribution of the circulation. Depending upon activity and posture, 60% to 80% of the resting blood volume (70 ml/kg in men; 65 ml/kg in women) resides in the venous system. Twenty-five to fifty percent of this volume resides in the smaller postcapillary venules and their collecting systems. Approximately 25% (18 ml/kg) resides in the splanchnic network.

A diurnal increase in late day capacitance is normal after standing and sitting.

Cutaneous blood flow is approximately 3 ml/min/100 gm of tissue in cool weather. Skin blood flow increases with reduced adrenergic impulses leading to both arterial and venous dilation; maximal flow may increase by over 10-fold to 30 ml/100g/min or 2 to 3 L/minute. Venous pressure measurements are unreliable at the extremes of ambient temperature (0° to 55° C). A cold extremity never achieves a full hydrostatic pressure head and requires prolonged filling to reach even a reduced hydrostatic pressure. A warm extremity achieves full hydrostatic pressure almost immediately, making assessment of post exercise pressures difficult. Thus, physiologic venous testing should be conducted in the morning and examinations performed in rooms maintained at a comfortable temperature range.

Determinants of venous pressure
Blood moves through both arteries and veins because of dynamic pressure derived from the pumping action of the heart. In a closed circulatory system, venous return must equal cardiac output. The majority of dynamic pressure is dissipated in the arterial circulation. The remaining energy is released in the venous system. Under normal circumstances, the pressure is 12 to 18 mm Hg at the venous end of the capillary and falls steadily toward atrial pressures of 4 to 7 mm Hg. When supine, gravitational pressures are neutralized and blood flows along this dynamic pressure gradient. Respiratory motion also strongly
influences venous return in the supine position but has little effect when the extremity is dependent.

Hydrostatic pressure derives from the weight of the blood column below the right atrium. The density of blood and the acceleration of gravity determines hydrostatic pressure. Hydrostatic and gravitational pressures are expressed as a constant multiplier (0.77 mm Hg/cm) of the vertical distance in cm below the atrium (Fig 7). The pressure is highest in the upright (sitting or standing) but motionless individual. However, measured pressures also reflect external factors such as muscle contraction. Other external factors also alter flow through the collapsible venous conduits. During inspiration, diaphragmatic contraction increases intra-abdominal and lower extremity venous pressure. Ascites and obesity produce similar increases in pressure even when supine.

Pressures in the dependent upper extremity reflect the vertical distance between the atrium and the first rib. Upper extremity veins that are held above the atria in an upright subject will collapse, as will extracranial veins of the head and neck. Pressures in venous structures above the atrium, therefore, do not fall below zero. Edema and reflux are uncommon in the upper extremity, even when venous valves are congenitally absent. Isolated central vein thrombosis often produces only a transient, proximal edema. Under unusual circumstances (ie, when combined with the increased flow of a functional arteriovenous fistula), upper extremity venous obstruction may, however, produce typical lipodermatosclerotic skin changes.

**Lower extremity venous return**

Venous return from the dependent lower extremity is achieved by the ejection of blood by the lower extremity muscle pumps, assisted by competent venous valves. The valves function to divide the hydrostatic column of blood into segments and prevent retrograde venous flow. It is unclear whether the femoral and popliteal valves or the distal valves have the greatest functional importance. The greater number of valves in the infrapopliteal segment suggests their greater functional importance, but hydrostatic pressure can be significantly altered by the correction of femoral or popliteal vein incompetence. Perforating vein valves prevent deep to superficial flow, a concept consistent with the pressure/flow relationships of the calf pump. The perforating veins of the foot are an exception; bidirectional flow is considered normal.
The muscular pumps of the lower limb include those of the foot, calf, and thigh. Among these, the calf muscle pump is the most important as it is the most efficient, has the largest capacitance and generates the highest pressures (200 mm of mercury during muscular contraction). The normal limb has a calf volume ranging from 1500 to 3000 cc, a venous volume of 100 to 150 cc, and ejects over 40% to 60% of the venous volume with a single contraction.

During contraction, the gastrocnemius and soleus muscles drive blood into the large capacity popliteal and femoral veins. The valves prevent retrograde flow (reflux) during subsequent relaxation, generating negative pressure and drawing blood from the superficial to the deep system through competent perforating veins. As a consequence, venous pressure is incrementally lowered until arterial inflow equals venous outflow. When exercise ceases, the veins slowly fill from the capillary bed, causing a slow return to the resting venous pressure.

Although the thigh veins are surrounded by muscle, the contribution of thigh muscle contraction to venous return is minimal compared with the calf muscle pump. The plantar venous plexus is compressed during ambulation and this pumping action is thought to prime the calf pump.

Although the interaction between the various leg pumps is not fully understood, all work with competent valve function to return venous blood from the distal to proximal extremity.

Pressure and volume: Relationship to extremity muscle contraction

With walking, lower extremity venous pressure is reduced from approximately 100 mm Hg (depending on height) to a mean of 22 mm Hg within 7 to 12 steps.

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Fig 5. Relationship of the posterior tibial perforators to the deep and superficial posterior compartments (SPC) of the calf (PTVs, posterior tibial veins). From Mozes G, Gloviczki P. New discoveries in anatomy and new terminology of leg veins: clinical implications. Vasc and Endovasc Surg 2004;38:367-74.

Fig 6. Pressure/volume relationships in the distensible venous lumen are reflected in this diagram. Considerable volume is introduced before pressure rises; pressures begin to rise as the vein becomes elliptical and increase further as a circular configuration is reached. Katz AI, Chen Y, Moreno AH. Flow through a collapsible tube; Experimental analysis and mathematical model. Biophysical J 1969;9:1261-79.

Fig 7. Relative venous hydrostatic (HP) and dynamic (DP) pressures at various heights (Ht) and distances from the right atrium (RA) in the upright individual. Dynamic pressure derive from the activity of the cardiac pump while hydrostatic pressures are related to position and gravity. The figure has been standing motionless with the dependent veins filling by gravity. Upper extremity pressures vary with the position of the arm.
Similar pressure changes are observed with standing ankle plantar flexion or heel raising, transferring weight to the forefoot (the tip-toe maneuver). Ambulatory venous pressure (AVP) can be determined using a 21-gauge needle to measure the response to 10 tip-toe maneuvers, usually at a rate of 1 per second, in a dorsal foot vein. When resuming a static standing position, hydrostatic pressure is restored after a mean of 31 seconds (Fig 8). The incidence of ulceration has a linear relationship to increases in AVP above 30 mm Hg. An increased AVP is also associated with a 90% venous refill time of $\frac{1}{2}$ seconds.

In contrast to the AVP, volume changes can be measured non-invasively using plethysmography. Rapid reflux (ie, venous filling of greater than 7 ml/sec) and calf pump dysfunction are associated with a high incidence of ulceration. Various authors have described the volume changes associated with elastic compression, surgical intervention, CEAP clinical class, avarulvala, diminished joint function, and late day deterioration of venous function. The interrelationship between pressure and volume is summarized schematically in Fig 8.

PATHOPHYSIOLOGY OF CHRONIC VENOUS INSUFFICIENCY

Chronic venous insufficiency defines those manifestations of venous disease resulting from ambulatory venous hypertension, defined as a failure to reduce venous pressure with exercise. Under normal circumstances, the venous valves and the muscular pumps of the lower extremity limit the accumulation of blood in the lower extremity veins. Failure of the lower extremity muscle pumps due to outflow obstruction, musculo-fascial weakness, loss of joint motion, or valvular failure is associated with peripheral venous insufficiency. However, an efficient peripheral pump may compensate for some degree of reflux and obstruction and prevent symptoms of chronic venous insufficiency (CVI).

Determinants of ambulatory venous pressure include venous reflux and obstruction as well as calf muscle pump function. Valvular incompetence is associated with a rapid recovery time after muscular contraction. If the deep vein valves are incompetent, blood simply oscillates within the deep veins and there is no reduction in pressure. Deep
The cause of primary valvular incompetence in the superficial veins remains unknown. Many structural and biochemical abnormalities of the vein wall have been reported. Varicose veins demonstrate increased collagen with a decrease in smooth muscle and elastin content.\textsuperscript{31,32} Most recent evidence suggests that such changes in the vein wall precede the development of reflux.\textsuperscript{33-35} Valvular incompetence is thus a secondary phenomenon resulting from dilatation of a weakened vein wall with enlargement of the valve ring preventing the coaptation of the leaflets.\textsuperscript{36} Studies suggest the strength of the valves is far greater than the strength of the venous wall.\textsuperscript{35}

The perforating veins may become primarily incompetent, similar to the superficial veins, or may develop reflux secondary to deep venous obstruction. When related to the varicos process, the perforating veins may become dilated, allowing blood refluxing down the saphenous system to enter the deep veins. These re-entry perforators may disappear when the saphenous system is removed. In the case of secondary incompetence, the perforating veins allow blood to escape from the calf when normal venous outflow is obstructed. High pressures within the calf are then directly transmitted to the superficial veins, causing enlargement of the dermal capillary bed and extravasation of intravascular contents into the interstitial space.

Although reflux is the only hemodynamic abnormality in primary venous disease, secondary venous disease most commonly involves a combination of reflux and obstruction.\textsuperscript{37} The incidence of primary incompetence versus post-thrombotic damage as a cause of chronic venous insufficiency is not clearly defined, but has been estimated to be approximately 80\% post-thrombotic vs 20\% primary valvular incompetence. Although the venous lumen is most often recanalized after an episode of deep venous thrombosis,\textsuperscript{38-40} lysis is rarely complete. Residual thrombus is replaced by fibrous tissue that may cause complete obstruction or cribriform synchia formed by endothelialized strands of residual thrombus. Valve leaflets may be entrapped, collaterals develop, and the fibrotic process, which may extend to the outer part of the vein wall, may act as a functional obstruction. The calf perforating veins may become important collaterals when the popliteal vein is obstructed. A combination of popliteal vein obstruction and iliofemoral damage causes severe symptoms, often resulting in venous claudication and/or ulceration. Other causes of deep vein obstruction include venous agenesis associated with the Klippel-Trenaunay syndrome, trauma, surgical mishap, and tumors.

Although less common than secondary deep venous incompetence, duplex ultrasonography has demonstrated primary deep venous reflux to be more common than originally thought. A powerful calf pump may compensate for primary deep venous reflux. However, patients will often still develop chronic venous insufficiency after many years.

**Pathophysiology of venous skin changes**

Although venous hypertension underlies the manifestations of chronic venous insufficiency, the pathophysiological relationship between venous hypertension and ulceration remains unclear. Early hypotheses that venous stasis caused ulceration have been challenged by many studies. The oxygen content of venous blood draining ulcers is high; the passage of dye through the lower extremity arterial and venous systems in ulcer patients is rapid; and PET scanning shows that although oxygen uptake is reduced, blood flow through the ulcer bed is rapid.\textsuperscript{41,42}

Later theories have suggested that arteriovenous fistulae open in response to high venous pressures. However, studies using macroaggregates and PET scanning have failed to confirm the presence of such fistulae.\textsuperscript{25} Persistently elevated pressures on the venous side of the capillary bed cause transudation and exudation of fluid and macromolecules. Pappenheimer and Soto Rivera initially described the "stretched pore phenomenon" to explain the high protein content of interstitial fluid associated with elevated venous pressure. Landis\textsuperscript{44} also demonstrated that the interstitial protein content increases as the capillary pressure rises. Fibrin cuffs and venous halos have been demonstrated in lipodermatosclerotic skin and have been postulated to cause ulceration by acting as a diffusion block.\textsuperscript{45,46} There are, however, theoretical reasons why fibrin itself cannot act as a diffusion block while other proteins have not been assessed.\textsuperscript{47}

It seems unlikely that ulceration results from local tissue ischemia and several recent theories have focused on inflammatory mechanisms including white cell trapping in the lower extremities.\textsuperscript{48,49} Other theories include release of free radicals, mast cell activation, mechanical damage, and the fibrin cuff acting as a trap to growth factors.

**DIAGNOSIS OF ACUTE AND CHRONIC VENOUS DISEASE**

Growing knowledge of the pathophysiology and natural history of venous disease, along with information regarding the efficacy and limitations of different treatment modalities, provides the basis for contemporary management of patients with venous disease. This approach requires thorough investigation addressing specific questions in individual patients. Modern technology has made it possible to answer most clinically relevant questions regarding venous disease with noninvasive laboratory testing.

In cases of acute deep venous thrombosis (DVT), the location of the thrombus, its age and recent dynamics (propagation, organization, recanalization) may be as important as identifying the presence of thrombus. Duplex
ultrasound is the standard test addressing these diagnostic needs.

The CEAP classification provides the framework for investigating patients with chronic venous disease. The details of the CEAP classification are discussed in the primary chronic venous disease section of this supplement. Diagnosis of the disease and definition of clinical class (“C” of CEAP) are based on clinical examination. Noninvasive testing identifies pathophysiologic changes (reflux or obstruction) in individual venous segments and, in some cases, defines the underlying etiology (“EAP” of CEAP).

Other than clinical class, CEAP does not estimate the severity of disease. It is not designed to measure changes in patient condition. Venous severity scores (clinical, segmental, and disability) address clinical severity by grading the variables used in CEAP. Thus, the combination of clinical examination and noninvasive testing is sufficient for classifying (CEAP) and estimating the severity of chronic venous disease.

Acute venous thrombosis

The clinical symptoms of deep vein thrombosis are very nonspecific. The classic findings of pain, swelling, and tenderness are equally as common in limbs with and without objectively confirmed thrombosis. The diagnosis of DVT therefore requires confirmatory testing.

First described in 1923 by Berberich and Hirsch, ascending venography remained the gold standard diagnostic test for DVT for over 60 years. Unfortunately, venography is invasive, not easily repeatable, may be impossible to perform or interpret in 9% to 14% of patients, and may be associated with interobserver disagreements in 4% to 10% of studies. Real-time venous ultrasonography has overcome many of these limitations and has largely replaced venography for the diagnosis of acute DVT. Alternative venous imaging modalities have concomitantly advanced at a rapid rate, particularly the development of computed tomography (CT) and magnetic resonance imaging (MRI). These modalities are being increasingly utilized in concert with ultrasonography for the diagnosis of DVT and with venography for a variety of venous interventions.

Contrast venography. Despite its limitations as a diagnostic test, rapid technological advances in endovascular devices and thrombolytic drugs have led to a resurgence of contrast venography as a guide to therapeutic interventions. Previous publications vital to the methods of ascending and descending venography include those by Rabinov and Paulin and Kistner, respectively. Although a detailed description of venography is beyond the scope of this discussion, several points warrant attention:

1. Cannulation and contrast injection (nonselective, selective, or super-selective) closer to the veins of interest will provide better visualization.
2. Preferential filling of the deep veins during ascending venography of the lower limb may be achieved by applying tourniquet compression above the cannulated vein.
3. A tilt table, valsalva’s maneuver, and manual compression of the thigh and calf will further improve filling of the deep veins.
4. In performing retrograde cannulation (ipsilateral or contralateral) of the lower limb veins (iliac, femoral, and popliteal) with guidewires and catheters, the supine position facilitates valve crossing.
5. When using a power injector for contrast injection of larger veins, venous trauma can be avoided by using multi-side hole catheters and decreasing injection pressure to approximately one-half that of arterial injections (200 to 400 pounds/inch).
6. Descending contrast venography is best performed during a valsalva’s maneuver and with manual injection of 10 to 20 ml boluses.

Duplex ultrasonography.

Duplex diagnosis of acute venous thrombosis. The lower extremity venous ultrasound examination should be performed with the head elevated in 10 to 20 degrees reverse Trendelenburg position. The examination may include the lower abdominal and pelvic veins as well as the infrainguinal veins. (Fig 9, B) As the inferior vena cava and iliac veins may be partially obscured with limited compressibility, examination of these segments is largely based on Doppler insonation. The infrainguinal veins are more easily visualized and should be examined in both the transverse and longitudinal views. Posterior imaging allows optimal examination of the popliteal vein, and the lesser saphenous and the gastrocnemial veins. Inability to compress the infrainguinal veins in cross-section is the primary basis for diagnosis of lower extremity DVT. However, the presence of thrombus, the overall characteristics of the thrombus, absence of spontaneous venous flow, absence of respiratory phasicity, and absent or incomplete color filling, may be adjuncts in assessing the presence of thrombus. Additionally, venous distension and fixed valves should be noted.

All incidental findings should be included in the final reports as they may aid in determining the etiology of any lower extremity symptoms. Stenotic vein segments have reduced velocities proximal to the stenosis and increased velocities just distal to the stenosis. This may be seen in the May Thurner syndrome, in which the overlying right common iliac artery compresses the left common iliac vein. Other extrinsic changes may be present and cause edema in the absence of thrombosis. Other incidental findings include Baker’s cyst, hematomas, lymph nodes, atherosclerotic disease, musculoskeletal injuries, aneurysms, and vascular anomalies including duplications and aberrant anatomy.

The appropriate use of unilateral examinations in patients with unilateral symptoms has been a source of controversy. Uncertainty exists regarding the frequency and importance of identifying thrombi in the asymptomatic limb. However, the Intrasocietal Commission for the Accreditation of Vascular Laboratories (ICAVL) has ac-
knowledged the need for limited unilateral scans and has published revised guidelines. The upper extremity examination begins at the thoracic inlet and is performed with the patient supine and head turned to the contralateral side. Both the internal jugular and subclavian vein should be insonated (Fig 9, A). Overlying bone and muscle may prevent continuous imaging. Respiratory response should be documented in areas difficult to image.

**Pitfalls in venous duplex imaging.** The sensitivity and specificity of venous ultrasound for symptomatic proximal DVT exceeds 90% and approaches 100% in some series.\(^6^8\)\(^-\)\(^7^1\) However, visualization of the calf veins may be limited. All three pairs of calf veins are adequately seen in only 60% to 90% of studies.\(^7^2\),\(^7^3\) If the study is adequate, however, the accuracy of modern calf vein imaging approaches that of the proximal infrainguinal veins.

Other pitfalls in venous duplex imaging include the misidentification of veins (ie, mistaking the great saphenous vein for the femoral vein; the cephalic vein for the axillary vein; or the basilic vein for the brachial vein. The veins of the calf are also frequently misidentified). Experience and proper attention to venous anatomy can help prevent these problems. Anatomic landmarks aid in proper identification of the extremity veins and should always be used. Technical limitations, often beyond the sonographer’s control, include suboptimal image quality related to obesity and soft tissue edema. Attention to proper transducer selection, optimal instrument settings, and appropriate imaging planes can help clearly delineate veins. Areas of inadequate visualization should be included in the ultrasound report as this limits the diagnostic utility of the examination.

Venous compression is not possible at some sites, including the iliac vein, the adductor segment of the femoral vein, the calf veins, and the subclavian vein. Although limited compressibility can lead to false positive diagnoses, this can be largely avoided with the use of color flow Doppler to demonstrate patency.

Venous duplications may be another source of diagnostic errors as a thrombus in the duplicated segment can be easily overlooked. Duplications should be suspected when a vein is smaller than its normal caliber or when the location is atypical. Common areas of duplication include the brachial, femoral, and popliteal veins.

Color flow scanning is a valuable tool, but may also contribute to diagnostic inaccuracy. Color artifacts may obscure small to moderate size thrombi if the color Doppler gain is set too high. False-positive studies may similarly be generated if the gains are improper, the Doppler angle is incorrect, or the wrong velocity range has been selected. Finally, examination in a cool room may lead to false positive studies. Lack of venous distension, due to systemic illness or hypovolemia, may result in false-negative studies.

**Special issues in venous duplex–free-floating thrombi and recurrent thrombosis.** Free-floating thrombi associated with an acute thrombus indicate a recently formed coagulum that is not completely adherent to the vein wall. Duplex definitions of a free floating thrombus have varied,

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**Fig 9.** A, Zones of reference for upper extremity venous scanning: midline = 1.0, acromion = 3.0, elbow = 5.0, wrist = 8.0, fingertips = 9.0. B, Zones of reference for lower extremity venous scanning: femoral vessels at the inguinal ligament = 1.0, midpatella to popliteal crease = 5.0, midmedial malleolus to midlateral malleolus = 8.0, tips of the toes = 9.0.
Table III. Thrombus characteristics: Relative value in thrombus aging

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Four asterisks indicate an excellent diagnostic level; three asterisks, good; two asterisks, fair; and one asterisk, poor (nondiagnostic). Each asterisk indicates the relative value to be given to each criterion in interpretation of thrombus age; many criteria are only valuable when present, and the overall decision represents a weighted average.

From Practical Noninvasive Vascular Diagnosis, 2nd edition, Richard F. Kempczinski, MD and James S. T. Yao, MD, PhD, p. 482, 1987, with permission from Elsevier.

but can be identified by color imaging when flow is observed completely surrounding a central filling defect. It has also been suggested that movement of the unattached segment within the flow stream be included in the definition. There is a higher incidence of pulmonary embolism at the time of presentation in patients with free-floating thrombus. The risk associated with a free floating thrombus remains controversial, but pulmonary embolism (PE) has been reported in 36% to 60% of patients despite anticoagulation and placement of an inferior vena cava filter has been suggested by some.

The acute symptoms of DVT usually resolve as venous outflow is restored through recanalization or the development of collaterals. Fifty-six percent of patients followed with sequential scans will have complete resolution of their thrombus. However, recurrent symptoms of pain and edema are also common and may result from either the post-thrombotic syndrome or recurrent DVT. Differentiating between the two is important as recurrent DVT carries the risk of pulmonary embolism and more severe post-thrombotic manifestations. The risk of recurrent DVT has been reported to be 17% at 2 years, 25% at 5 years, and 30% at 8 years and is significantly higher in patients with malignancy or hypercoagulable states when compared with those whose original episode was associated with surgery or recent trauma.

Unfortunately, differentiating acute from chronic thrombus may be challenging for most diagnostic modalities. Although thrombus echogenicity and heterogeneity tend to increase with thrombus age, significant variation may occur and this has not proven consistently useful. Other characteristics that may aid in differentiating include the observations that acutely thrombosed segments are often dilated while chronically thrombosed segments have reduced diameters; a free floating tail tends to suggest an acute thrombus; and the presence of venous collaterals and multiple flow channels within the lumen suggest chronic thrombosis (Table III).
syndrome. Magnetic resonance imaging is also the primary modality for identifying the venous drainage of venous malformations and other soft tissues.88

**Image guided venous interventions.** Depending on the clinical scenario, CT and/or MRI may be indicated prior to venography and venous intervention to “road map” the venous anatomy and associated pathology. These noninvasive imaging tests are useful when contemplating endoluminal intervention for DVT. In some circumstances, duplex ultrasound may not be sufficient to completely assess the extent of thrombus. Examples of this below the inguinal ligament include the presence of external orthopedic hardware, large wounds, morbid obesity, and marked interstitial edema. Above the inguinal ligament, veins and associated DVT are better imaged with CT and/or MRI in the presence of obesity, bowel gas, or a need to assess surrounding structures.

Not only does road mapping with CT or MRI provide detailed information regarding the extent and location of thrombus, these modalities can further guide the approach to treatment. This includes defining potential puncture sites, the direction of puncture, the need for a temporary caval filter, what devices and drug may be needed, and overall feasibility. Other benefits of utilizing CT or MRI prior to venous intervention include reduced contrast and cost.89

**Inferior vena cava (IVC) filter placement.** Placement of IVC filters has increased with the development of removable filters and more aggressive prophylactic indications such as multitrauma90 and bariatric91 surgery. Methods of image guidance have concurrently expanded to include use of bony landmarks with fluoroscopy,92 transabdominal ultrasound,93 intravascular ultrasound,94 and selective and nonselective venography.95

Selective venography involves cannulating specific branch veins, such as the contralateral common iliac and renal veins, to assess for venous anomalies and allow more precise filter placement. Recent evidence suggests that selective venography identifies more venous anomalies and variations, frequently leading to a change in standard infrarenal filter placement.95 In a cohort of 80 patients, of whom 44% had selective venography, aberrant venous findings were significantly more common in the selective group (49%) vs the nonselective group (9%). More importantly, selective venography led to changes in IVC filter placement 31% of the time compared with 4% using nonselective venography.

Aberrant venous findings that may affect filter placement include duplicated IVC, intracaval thrombus, accessory renal veins, caval tortuosity, micro or mega cava, and caval compression. CT and combined nonselective/selective venography can reliably identify these types of anomalies. However, if imaging modalities other than venography are used, comprehensive review of an abdominal CT for venous variations and abnormalities is warranted prior to filter placement. In a large review of 1822 abdominal CTS, 5.6% of patients had a major venous anomaly.96 Fortunately, many patients, such as trauma victims, will have had a recent abdominal CT prior to filter placement.

**Iliac vein compression (May-Thurner) syndrome.** Compression of the left common iliac vein between the right common iliac artery and the fifth lumbar vertebrae can lead to symptoms including left lower extremity edema, pain, varicosities, skin changes, and deep venous thrombosis. Also known as the May-Thurner syndrome, diffuse iliac vein thrombosis involving the left lower extremity causes extensive swelling that is often refractory to conventional anticoagulation therapy. Although duplex ultrasound can reliably establish a diagnosis of iliac vein thrombosis, MRI and/or CT provide a more comprehensive evaluation for causes of compression. Aside from MRI/CT providing an accurate measurement of the degree of left common iliac vein compression, other causes of compression such as pelvic masses, bone spurs, iliac artery aneurysms, retroperitoneal fibrosis, and inflammatory processes can be identified. Among these modalities, MRI frequently provides more comprehensive multiplanar views and a high degree of resolution.97,98

Knowledge of the underlying cause of iliac vein compression syndrome can help guide endoluminal therapy. Anticoagulation therapy alone may be indicated if intervention appears futile. Alternatively, MRI can assist in planning the approach to lysis and management of the underlying compressive lesion. For example, an initial contralateral approach that avoids thrombus may be less desirable than ultrasound guided antegrade access of the ipsilateral common femoral vein. An antegrade approach to occlusive vascular lesions is frequently more successful. Finally, if venography discloses only subtle findings of compression after restoring patency, MRI may provide further guidance as to need for percutaneous venoplasty and stenting.

**Venous malformations.** MRI has become a mainstay in the diagnostic evaluation of venous malformations. While problems are complex and management can range from observation to microcoil embolization to radical surgical resection, MRI provides the most comprehensive view of the anatomic distribution of a venous malformation. In comparison, CT can often underestimate the extent of soft tissue and boney involvement. MRI can also assist in defining high-flow malformations. Increased arteriovenous shunting can be visualized on magnetic resonance arteriography and magnetic resonance venography can further delineate communications with the superficial and deep venous systems.

**Chronic venous disease**

It is well known that venous obstruction, valvular incompetence, or both are present in the limbs of patients suffering from CVI. The physical findings of CVI are characteristic and the diagnosis is often easily established by visual inspection of the limb. Yet, physical findings provide little clue to the presence, location, extent, or severity of venous valvular incompetence or venous obstruction. More detailed evaluation of the venous system may be necessary in establishing an etiology for nonspecific complaints such
as pain or swelling; selecting appropriate patients for surgical or percutaneous procedures; assessing hemodynamic improvement after such procedures; and establishing the natural history of chronic venous disease.

Descending venography and ambulatory venous pressure have historically been the gold standards for the anatomic localization and hemodynamic quantification of reflux, respectively. Although descending phlebography may still have a role in situations such as venous reconstruction, it is an invasive test with recognized limitations. Ambulatory venous pressure measurements are physiologic and do correlate with the incidence of ulceration, but the test is also invasive and requires reflux at multiple sites, may be insensitive to isolated segmental reflux, and cannot precisely localize valvular incompetence.

Several noninvasive alternatives are now available for the evaluation of chronic venous disease. Continuous-wave (CW) Doppler examinations provide segmental physiologic information but have little accuracy in identifying specific incompetent or obstructed venous segments and differentiating major axial veins from duplicated or collateral veins. Duplex ultrasonography is the most clinically useful test for detecting, localizing, and evaluating chronic venous obstruction and venous valvular incompetence. Global hemodynamic tests, including photoplethysmography (PPG) and air plethysmography (APG), use measurements of venous volume to reflect reflux. Unfortunately, as with their invasive counterparts, most of the noninvasive tests display the fundamental dichotomy of providing either anatomic or hemodynamic information. These tests are often complimentary, and it may be necessary to combine the ability of duplex scanning to localize both anatomic obstruction and reflux with measurements of hemodynamic severity determined by plethysmography.

Unfortunately, the assessment of chronic venous disease is hampered by the relatively poor and inconsistent relationship between objective findings and the clinical manifestations of chronic venous insufficiency. Possible explanations include an inadequate understanding of the events occurring at the microvascular level, the confusing overlap of different clinical stages with similar hemodynamic dysfunction, and the fact that the physiologic consequences of venous incompetence may depend on the location of the incompetent valve or valves rather than the actual number of incompetent valves present.

**Continuous-wave (CW) Doppler.** Continuous wave (CW) Doppler evaluation is often used as an adjuvant to clinical examination. Lower frequencies (5MHz) are usually best for studying deep veins. The relatively low velocity of blood flow in superficial veins is often more clearly detected when higher frequencies (10MHz) are used. In the majority of cases the audible signal is all that is required. At each venous location, the presence of a “spontaneous” (unaugmented) Doppler signal is documented. Augmentation maneuvers are most useful in small veins with low flow velocities and are performed by compressing the limb above or below the site of the Doppler probe.

Venous valvular incompetence is detected by demonstrating flow reversal in a venous segment. Occurrence of a signal during a valsala’s maneuver is sufficient to diagnose valvular incompetence in the common femoral vein. At other more distal sites, limb compression is better for demonstrating segmental reflux. The upright position is ideal for evaluating the presence of valvular incompetence as it more closely approximates the physiologic conditions in which reflux is important. Bidirectional flow detected along the medial calf when the calf is manually compressed above the site of the Doppler probe can be used to identify incompetent perforating veins.

**Duplex ultrasonography.** Duplex scanning overcomes many of the limitations of CW Doppler examinations. The B-mode image allows veins to be visualized directly and ensures accurate placement of the pulsed-Doppler sample volume. These features permit individual interrogation of paired veins, allow nonaxial veins to be examined, and avoids confusing a major axial vein with a collateral vein. Spectral analysis of the Doppler signal is used to confirm the presence or absence of flow, to indicate the direction of flow, and to record venous flow patterns. The addition of a color-coded flow map simplifies the examination. Color flow imaging immediately distinguishes arteries from veins, permits visualization of flow over long vessel segments, and allows simultaneous visualization of flow in multiple vessels. Color also makes it unnecessary to interrogate the limb every centimeter or so as with the CW Doppler. Absence of flow in an occluded segment is immediately apparent and disturbance of flow by encroachment of thrombus within the venous lumen readily detected. The direction of flow is clearly depicted by the color flow image. Color immediately identifies the presence of reflux by inversion of the color pattern (convention has blood flow toward the heart in blue and toward the periphery in red).

**Venous obstruction.** As in the examination for acute DVT, the entire venous system from the iliac to the ankle is studied. Once a vein is identified, patency is ascertained by evaluating compressibility and assessing the Doppler signal. A totally thrombosed vein will be noncompressible and devoid of Doppler signals. A partially thrombosed vein will be incompletely compressible and Doppler signals will be obtained from part of the lumen. Chronically occluded veins are often shrunken and have thick walls that may be more echogenic owing to fibrosis. Calcification may occasionally be present. The residual thrombus may also be more echogenic.

**Venous valvular incompetence.** Patient positioning is similar to that described for the CW Doppler examination. In the standing position, the patient holds on to a support and is instructed to shift his or her weight to the opposite leg. After the vein-of-interest has been located on the B-mode image and its identity confirmed by the characteristic audible Doppler signal, velocity spectrum or color-flow map, the position of the probe is adjusted to provide a long-axis view. An inverted spectrum or color flow map indicates retrograde flow. Reflux may be assessed at the
groin by having the patient perform a valsalva’s maneuver. A period of reversed flow lasting longer than 1.5 seconds is considered abnormal in the common femoral vein. Further down the leg, manual compression either above or below the knee may be used to evaluate valvular incompetence.

Many investigators prefer the distal cuff deflation method proposed by Van Bemmelen. This method is considered a more reliable and consistent way of identifying and quantifying valvar incompetence. The velocity spectrum is recorded continuously during cuff inflation and for at least 4 seconds after deflation. Retrograde flow persisting longer than 0.5 seconds is considered to be indicative of valvular incompetence.

Perforator incompetence is indicated by outward flow during manual compression or calf contraction. Color flow duplex imaging is helpful in confirming bidirectional flow, which is indicated by the color change that occurs when compression is applied and released.

Attempts have been made to quantify the magnitude of reflux and to correlate this with clinical manifestations of chronic venous insufficiency. Mean flow rates, scoring systems based on the number of incompetent valve sites, and the mean or total duration of reflux flow have been used by different investigators as a measure of clinical severity. Average scores and mean reflux times correlate with disease severity but provide little predictive value for ulcer healing or clinical success after treatment.

Accuracy of duplex ultrasonography. Duplex scanning is highly accurate for the detection of venous obstruction, with sensitivities and specificities of greater than 90% for the proximal veins. However, the correlation between descending phlebography and duplex scanning for identifying and quantifying reflux in individual veins is relatively poor. The majority of errors relate to disease below the knee when a competent valve is present in the upper part of the leg.

Clinical applications of duplex ultrasonography. The primary role of duplex scanning is to identify the location of incompetent valves or obstructed veins. Incompetence of the popliteal vein and deep veins of the calf may be a factor of great importance producing the signs and symptoms associated with chronic venous insufficiency. Incompetence of the distal superficial veins appears to be more strongly associated with ulcer development than incompetence limited to the proximal superficial veins. Incompetent perforator veins occur in two-thirds of limbs with class 4, 5, and 6 disease. They occur less commonly in limbs with class 0 to 3 disease. Chronic thrombotic obstruction of a major axial vein may have major physiologic implications. The presence of chronic obstruction and valvular incompetence can result in venous claudication or limbs with the most severe cutaneous manifestations of chronic venous insufficiency.

The extent of duplex evaluation varies depending on the patient’s clinical manifestations and planned treatment approach. Conservative nonoperative therapy (elastic support, compression, Unna’s boots) may require only the need to exclude concomitant arterial disease. On the other hand, surgical considerations require a thorough knowledge of the location and extent of venous valvar disease.Venous wall abnormalities, valvular incompetence, and presence of perforator incompetence must be examined. Anatomic variability must be properly identified, particularly in the popliteal fossa where the saphenopopliteal junction may reside either proximal or distal to popliteal skin crease. Duplex scanning is helpful in determining the cause of recurrent varicose veins. Multiple sites of reflux are common. When patients present with symptoms suggestive of venous claudication, the limb should be surveyed for major axial vein obstruction.

Future considerations. The use of ultrasound contrast agents may improve the accuracy of duplex scanning in the detection of chronic venous obstruction and venous valvular incompetence. Ultrasound contrast agents have been postulated to improve direct visualization of the venous valves by enhancing the return of ultrasonic echoes. This echo enhancement may allow the examiner to more clearly evaluate recanalized venous segments and thus help distinguish chronic from acute DVT. This enhancement can occur with or without color flow. Small pilot studies looking at the safety and efficacy of these new agents in the evaluation of patients with chronic venous insufficiency are currently in progress (personal communication; Phillip J. Bendick, PhD, RVT, Royal Oaks, Minn).

Indirect noninvasive tests for chronic venous disease (plethysmography). Despite their value in the anatomic localization of disease, imaging modalities such as ultrasound and venography cannot assess the global severity of reflux or obstruction in a limb. A “segmental” approach to the pathophysiology of CVD makes it difficult to assess the impact of disease in an individual segment on overall function of the lower extremity venous system. It is difficult to understand the dynamics of physiologic changes occurring in different segments at different times. Assessment of physiologic outcomes of treatment and changes in CVD severity over time and after surgery is especially challenging.

These limitations dictate the need for a method of assessing global venous in the lower extremity. Venous pressure measurements can serve as a surrogate for this purpose, but are invasive and unpractical. Plethysmography is the only existing practical noninvasive modality for global physiologic evaluation of extremity veins. As such, it provides valuable information on the impact of reflux and obstruction on overall venous function, and can provide a measure of calf muscle pump function. The use of plethysmography as a complementary modality to duplex ultrasound is reasonable for quantification of reflux or obstruction, for monitoring of dynamics of venous disease over time, and for evaluation of treatment outcomes. Finally, when venous obstruction is suspected, but not identified by duplex scan, plethysmography can help to overcome low sensitivity of the ultrasound for detection of venous obstruction.
Technique principles. The indirect noninvasive tests most often used in the evaluation of patients with chronic venous disease are APG and strain-gauge plethysmography (SGP). Both of these techniques assess venous function by measuring changes in the size of the extremity in response to exercise, postural changes, and application and release of a venous tourniquet. The tests assume that arterial blood supply to the extremity and transcapillary fluid exchange do not change significantly in response to provocative maneuvers. Changes in extremity volume are therefore attributed to filling and emptying of the veins.

The two methods calculate volume changes differently. APG measures pressure changes in a leg cuff calibrated to reflect volume changes. SGP calculates volume changes from changes in leg circumference. This technique assumes the extremity has a cylindrical shape with a uniform distribution of volume changes. Therefore, the two methods give quantitatively different, but qualitatively identical information.113

Both methods require considerable patient cooperation. Inconsistency in performing exercise, maintaining position, and distributing weight between the legs contributes significantly to variability of results. External mechanical, thermal, and chemical (pharmacological) stimuli will cause significant changes in the size of the venous lumen and venous capacitance. All of these factors, along with changes in central venous hemodynamics and arterial supply, should be considered when results are analyzed.

Photoplethysmography (PPG) and light reflection rheography calculate changes in tissue blood density by measuring the intensity of reflected light. Because of the inability of the light to penetrate deeply through the skin, difficulties in calibration, and poor specificity, these techniques have little current application in venous disease.114

Venous obstruction. Physiological roles of the lower extremity venous system include adjustment to changes in circulating blood volume and central hemodynamics by accumulation and release of additional volumes of blood. To serve this need, veins maintain significant reserve capacitance under normal conditions. Venous obstruction can measurably decrease this reserve as well as the rate of emptying of distal veins through increased resistance to outflow. The identification and assessment of venous obstruction by plethysmography is based on an estimation of these two parameters: venous capacitance and venous resistance.

Venous occlusion plethysmography measures increases in calf volume in response to venous occlusion by a tourniquet and the rate of calf volume decrease after rapid tourniquet release. While venous pressure rises to equal the pressure of the tourniquet, blood accumulates in the veins of the extremity. Veins easily increase their diameter and volume under low pressure, but become inextensible after pressure exceeds 50 to 80 mm Hg. This reflects the maximal calf size and venous capacity.

Rapid release of the tourniquet creates a pressure gradient, allowing venous resistance to be determined by measuring the rate at which calf volume decreases. Unless collaterals have normalized venous outflow in extremities with venous obstruction, this resistance can be threefold or higher than normal.115

Venous valvular incompetence. Leg elevation or exercise can be used to decrease lower extremity venous volume. When the extremity is positioned upright, venous refilling occurs from relatively slow arterial inflow, or, in the presence of valvular incompetence, by rapid reflux from the proximal segments. Measuring the rate of venous refilling, usually indexed to 90% of total volume, provides an overall estimate of valvular competence, or severity of reflux in extremities with no venous obstruction.

Calf muscle pump function. Evaluation of muscle pump function in patients with chronic venous disease is important because its impairment contributes significantly to disease severity.16 Improvement of the muscle pump by physical therapy28 or elastic compression26 has been shown to have beneficial effects.

The decrease in calf volume after a single calf muscle contraction and the volume remaining after repeated contractions, both indexed to venous volume, can be useful measures of calf muscle pump function. Such plethysmographic findings correlate well with measurements of ambulatory venous pressure100 and since they are noninvasive, are the only practical option for evaluation of the calf muscle pump in routine clinical practice.

Reliability/repeatability. Several investigators have demonstrated the reliability and repeatability of plethysmography.116 Reproducibility does, however, differ significantly between reports and should be defined by systematic investigation. Unfortunately, the relationship of clinical findings to the results of indirect noninvasive venous testing remains to be defined. Although the potential to predict ulceration was demonstrated in early work117 later analysis has revealed that deterioration of venous hemodynamics (as measured by plethysmography) parallels clinical severity only before skin changes have developed100 or during ulcer healing.16

MEASURING OUTCOMES IN CHRONIC VENOUS DISEASE

The scientific future of studies of chronic venous disease and its management depends on using proper outcome assessment methods, and this should be a major priority of all those engaged in the study of venous disease. However, measuring outcomes in CVD is complex and more difficult than most other vascular diseases. It should be based on before-and-after treatment comparisons using standardized objective criteria which, taken together, accurately characterize patient status. Comparative parameters might include disease classification, venous hemodynamics, clinical severity score, patient disability, quality of life, and cost-effectiveness. Each will be discussed in terms of recent progress and unresolved problems and the complexities of assessing outcomes in CVD will be illustrated by comparison with peripheral arterial occlusive disease (PAD).
Table IV. Venous clinical severity score

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Absent = 0</th>
<th>Mild = 1</th>
<th>Moderate = 2</th>
<th>Severe = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional, not restricting activity or requiring analgesics</td>
<td>Daily, moderate activity limitation, occasional analgesics</td>
<td>Daily, severe limiting activities or requiring regular use of analgesics</td>
</tr>
<tr>
<td>Varicose veins*</td>
<td>None</td>
<td>Few, scattered: isolated branch VVs</td>
<td>Multiple: single segmental GS or LS distribution involving calf only</td>
<td>Extensive: multisegmental GS and LS distribution, involving calf and thigh</td>
</tr>
<tr>
<td>Venous edema†</td>
<td>None</td>
<td>Evening ankle edema only</td>
<td>Afternoon edema, above ankle</td>
<td>Morning edema above ankle and requiring activity change, elevation</td>
</tr>
<tr>
<td>Skin pigmentation‡</td>
<td>None or focal, low intensity, (tan)</td>
<td>Diffuse, but limited tin area and old (brown)</td>
<td>Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)</td>
<td>Wider distribution (above lower 1/3) and recent pigmentation</td>
</tr>
<tr>
<td>Inflammation</td>
<td>None</td>
<td>Mild cellulitis, limited to marginal area around ulcer</td>
<td>Moderate cellulitis, involves most of gaiter area (lower 1/3)</td>
<td>Severe cellulitis (lower 1/3 or above) and significant venous eczema</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal, circum-malleolar (&lt;5 cm)</td>
<td>Medial or lateral, less than lower third of leg</td>
<td>Entire lower third of leg or more</td>
</tr>
<tr>
<td>No of active ulcers</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Active ulceration, duration</td>
<td>None</td>
<td>&lt;3 mos</td>
<td>&gt;3 mos, &lt;1 y</td>
<td>Not healed &gt;1 year</td>
</tr>
<tr>
<td>Active ulcer, size§</td>
<td>&lt;2 cm diameter</td>
<td>2-6 cm diameter</td>
<td>&gt;6 cm diameter</td>
<td>Full compliance: stockings + elevation</td>
</tr>
<tr>
<td>Compressive therapy§</td>
<td>None</td>
<td>Intermittent use of stockings</td>
<td>Wears elastic stockings most days</td>
<td></td>
</tr>
</tbody>
</table>

Qualifying comments:

*To assure differentiation between C1 and C2 venous pathology, “varicose” veins must be >4 mm diameter to qualify. GS, LS refers to greater (long) and lesser (short) saphenous varicosities.

†Presumes venous origin by characteristics, eg, Brawny (not pitting or spongy) edema, with significant effect of standing/limb elevation and/or other clinical evidence of venous etiology, ie, varicose veins, h/o DVT. Edema must be regular finding, eg, daily occurrence. Occasional or mild edema does not qualify.

‡Focal pigmentation over VVs does not qualify.

§Largest dimension/diameter of largest ulcer.


Disease classification

As discussed in the Primary Chronic Venous Disease section of this document, the CEAP classification system has been recently revised and improved. Its clinical classification has progressive levels of signs (swelling, pigment and fibrotic changes in the skin and subcutaneous tissues, and healed or active ulceration - C3, 4, 5, 6) that do reflect severity of disease. Most of the C components are, however, relatively static and not sensitive to change following treatment and others, in the EAP part of the scheme, use alphabetical designations and, thus, are not quantifiable. Complicating matters further, pain can be present at all levels; varicose veins can be present with or without pain and with or without swelling, skin changes or ulceration. A patient with a venous ulcer, even though healed, cannot move beyond C5 regardless of the degree of improvement produced by any form of treatment. Therefore, while CEAP is quite valuable in comparing patient mix and establishing a starting point before treatment, it cannot serve the broader purposes of venous outcomes assessment.

In contrast, PAD has a chronic ischemia classification scheme with discrete categories that are based on symptoms and signs that reflect progressively more severe ischemia (claudication, ischemic rest pain, ischemic ulceration, or gangrene). These levels of severity can change with treatment and they constitute accepted reporting standards in both the Fontaine and Rutherford classifications.

Venous hemodynamics

The abnormalities in venous physiology associated with chronic venous disease, and their quantification by diagnostic tests, are also considerably more complex than for PAD. In PAD one is dealing only with obstruction and arterial physiologic testing performed in the supine position enables objective confirmation of the assigned classification level. Claiming an improved outcome as a result of treatment requires improvement of at least one clinical category accompanied by a significant change in a designated physiologic test. With CVD one must gauge the effects of obstruction and/or reflux in a vascular bed uniquely designed to return venous blood to the heart against gravity with the aid of a peripheral muscle pump and in phase with respiratory mechanics. Furthermore, CVD does not have a single noninvasive test, such as the ankle-brachial index (ABI), which correlates with disease severity to serve as an objective index of change following operative interventions.
Table V. Venous segmental disease score (Based on venous segmental involvement with reflux or obstruction*)

<table>
<thead>
<tr>
<th>Reflux</th>
<th>Obstruction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 Lesser saphenous</td>
<td>† Greater saphenous (only if thrombosed or previously excised in association with superficial femoral-popliteal occlusion)</td>
</tr>
<tr>
<td>1 Greater saphenous</td>
<td>†</td>
</tr>
<tr>
<td>1/2 Perforators, thigh</td>
<td>†</td>
</tr>
<tr>
<td>1 Perforators, calf</td>
<td>†</td>
</tr>
<tr>
<td>2 Calf veins, multiple (PT alone =1)</td>
<td>1 Calf veins, multiple</td>
</tr>
<tr>
<td>2 Popliteal vein</td>
<td>2 Popliteal vein</td>
</tr>
<tr>
<td>1 Superficial femoral vein</td>
<td>1 Superficial femoral vein</td>
</tr>
<tr>
<td>1 Profunda femoris vein</td>
<td>1 Profunda femoris vein</td>
</tr>
<tr>
<td>1 Common femoral vein</td>
<td>2 Common femoral</td>
</tr>
<tr>
<td>†</td>
<td>1 Iliac vein</td>
</tr>
<tr>
<td>1/2 Perforators, thigh</td>
<td>1 IVC</td>
</tr>
<tr>
<td>10 Maximum reflux score†</td>
<td>10 Maximum obstruction score‡</td>
</tr>
</tbody>
</table>

*As determined by appropriate venous imaging (phlebography or Duplex scan). Although some segments may not be routinely studied in some labs (eg, profunda femoris and tribial veins, points cannot be awarded on the basis of presumption, without interrogating the segments for obstruction or reflux.
† Normally there are no valves above the common femoral vein so no reflux points are assigned to them. In addition, perforator interruption and saphenous ligation/excision (with the single exception noted) do not count in the obstruction score, but as a reduction of the reflux score.
‡Not all of the 11 segments can be involved in reflux or obstruction. 10 is the maximum score which can be assigned, and this might be achieved by complete reflux at all segmental levels.
§The excision, ligation or traumatic obstruction of deep venous segments counts towards obstruction points just as much as their thrombosis.

Qualifying comments:
1. Reflux means that all the valves in that segment are incompetent. Obstruction means there is total occlusion at some point in the segment or >50% narrowing of at least half of the segment.
2. Most segments are assigned one point but some segments have been weighted more or less to fit with their perceived significance, eg, increasing points for common femoral or popliteal obstruction and for popliteal and multiple calf vein reflux and decreasing points for lesser saphenous or thigh perforator reflux.
3. Points can be assigned for both obstruction and reflux in the same segment. This will be uncommon but can occur in some post thrombotic states, potentially giving secondary venous insufficiency higher severity scores than primary disease.


Historically, the venous equivalent of the ankle arterial pressure was the AVP. As discussed above, the AVP has been supplanted by a number of noninvasive physiologic tests, primarily plethysmographic studies, which indirectly measure venous return, venous filling, venous ejection, venous outflow, etc. in relation to changes in leg position and calf muscle activity. The duplex scan has added an additional perspective and has almost completely replaced descending venography in evaluating reflux. However, we do not have a noninvasive surrogate for ambulatory venous pressure.

The potential of these noninvasive tests in the objective assessment of chronic venous disease, and thus in assessing venous outcomes, is great. Reporting subjective improvement or freedom from recurrence of some sign or symptom after at a certain interval has well recognized limitations. Bolstering clinical assessment by objective improvement in universally accepted venous tests could have a tremendous impact on venous outcomes assessment. However, this approach requires that the normal range for each venous test parameter be standardized, to allow separation of “normal” from “abnormal”. In addition, what constitutes a significant change in each of these parameters also needs to be established, to provide an objective basis for claiming improvement in response to an intervention. Finally, test protocols must be standardized and variability established for this approach to have universal application. This is not an easy task because the range of values appears to widen as one progresses from C1 to C6. Standardization of venous tests will likely require multicenter studies of patients with a wide range of CVD carried out against a background of CEAP classification and disease severity scoring. This difficult but necessary task is a current focus of the Venous Outcomes subcommittee of the American Venous Forum.

Disease severity scoring

Some measure of disease severity is needed to properly compare the outcomes of the various approaches with the treatment of CVD. No matter how appropriate the endpoints and criteria, valid comparisons will not result if the severity of the underlying venous disease in the treatment groups is unknown or unequal. Comparing the outcomes of two or more treatments in a clinical trial, or the same treatment in two or more reports from the literature, cannot be done with confidence unless the relative severity of disease in each treatment group is known and quantified by attributes that are capable of change in response to treatment. The former requirement (assessing case mix) can be met to a great extent by CEAP, but the latter cannot. To complement CEAP, and compensate for the as yet unmet need for standardized venous testing, the committee on Venous Outcomes Assessment of the American Venous Forum developed a venous severity scoring system.51
Two severity scores were proposed for use. The Venous Clinical Severity Score, based on the best usable elements of the CEAP system, grades 9 clinical characteristics of chronic venous disease from 0 to 3 (absent, mild, moderate, severe) using specific criteria to avoid overlap or arbitrary scoring. It adds 0 to 3 points for differences in background conservative therapy (compression and elevation) to produce a 30 point-maximum flat scale. (Table IV) The Venous Clinical Severity Score has been increasingly used in assessing venous outcomes and validation studies have been reported.118,119 Interobserver variability in grading some elements has been noted in reports of internal and external consistency and reproducibility.118 It has been correlated with disease severity in other reports120 and has been increasingly used in reports assessing the treatment of CVD (increasing citations). In a survey of French angiologists, Perrin121 concluded that the Clinical Severity Score did not serve the lower end of the CVD spectrum (C1 to 3) as well. The Venous Segmental Disease Score (Table V) has been used in fewer studies than the Venous Clinical Severity Score. Though based on expert opinion, these two scoring schemes are admittedly arbitrary. They both could benefit from further validation and, based on broader clinical experience, further modifications may be appropriate.

Disability

The original CEAP system contained a disability-scoring scheme gauged to an 8-hour working day. In recognition of the fact that many people with chronic venous disease either did not work at a formal 8-hour day job (eg, a housewife), or simply could not hold an 8-hour a day job, the scheme was modified to eliminate reference to work and an 8-hour day, substituting instead the patient’s prior normal activities.

Quality of life

Patient based assessments of the outcomes of treatment are generally accepted as being of significant value and a needed adjunct to physician based assessments. General/generic quality of life (QOL) instruments have been developed and validated (eg, The Medical Outcomes Study Short Form [SF 36], EuroQol, the Nottingham Health Profile and the Sickness Impact Profile). The SF 36, or the shorter SF 12, are simpler and more widely used than the others but are preferably combined with a venous disease specific QOL. However, although there has been a proliferation of such instruments (n = 7) in the last decade, none of the four most used venous specific QOLs instruments have gained general acceptance, possibly because none is entirely satisfactory for application to a wide spectrum of chronic venous disease. The CIVIQ122 is short (only 20 questions) and has good internal consistency and stability, but the four dimensions it emphasizes do not sufficiently cover the severe end of the spectrum of CVD and it includes some vague and non-specific end points (heavy legs, paresthesia, burning sensations, nocturnal cramps). Two other venous QOLs have been well validated and more widely used, but primarily in evaluating patients with either varicose veins - the Aberdeen questionnaire123 or venous ulceration - The Charing Cross Venous Ulcer Questionnaire.124 Finally the VEINES QOL,125 which was developed on 1531 CVD patients from Belgium, France, Italy, and Canada, has generated at least 15 articles evaluating CVD, CEAP classes, the post-thrombotic syndrome, venous thromboembolism, varicose veins, and other aspects of venous disease. However, it has not been used outside of studies authored by those who developed it.

The question remains whether to use one of the two venous QOL designed for assessing outcomes of treatment of varicocities or venous ulceration to test the suitability of VEINES with studies outside of those designed by the VEINES investigators, or combine the best features of the existing venous QOLs into one with more universal application to the broad spectrum of CVD. This is clearly an area needing definitive action.

Cost effectiveness and cost effectiveness ratios

A number of new methods of treating venous disease have been introduced in the last decade (radio-frequency and laser ablation of the great saphenous vein, powered phlebectomy, etc.) Many feature new technology and require expensive instrumentation. Even if objective outcomes can be shown to be better than traditional methods, it remains to be shown, by proper cost comparisons, if they are worth the degree of improvement achieved. Accepted methods for doing this are available and are being widely used in other medical and surgical disciplines. There is no good scientific reason why they are not being applied in the evaluation of new therapies for chronic venous disease. This represents a final aspect of venous outcomes assessment that deserves attention.

Summary

CEAP has been revised and can serve as the basis for initial evaluation of patients with CVD and comparing patient mix among treatment groups. Evaluation of venous hemodynamics by noninvasive tests before and after treatment can provide an objective basis for claiming improvement, but the appropriate test(s), their normal range, and the degree of change which can be accepted as significant have not yet been standardized for universal reporting practices. Venous severity scoring (both the “clinical” and the “anatomic” score) has been increasingly used, but may eventually require modification on the basis of reported experiences. The disability score has been modified to refer to the patient’s former activities rather than to an 8-hour working day. Disease specific QOL instruments are available for patient based evaluation of varicose veins and venous ulcers, and there is an additional instrument (VEINES) that its developers have applied to a wider spectrum of venous disease, but there is currently no universally accepted instrument for assessing the full spectrum of patients with CVD. Finally, new technologies that have been developed for treating chronic venous disease, and particularly varicose veins, should be subjected to proper
cost comparisons with the traditional methods they are being touted to have supplanted.

REFERENCES


