Venous Disease: The Missing Link in Cardiovascular Medicine

Hooman Madyoon, MD, FACP, FACC, Norman E. Lepor, MD, FACC, FAHA, FSCAI
Westside Medical Associates of Los Angeles and Geffen School of Medicine-UCLA Cedars-Sinai Heart Institute, Los Angeles, CA

Until recently, medical literature and the practice of vascular medicine focused on the cosmetic aspects of venous disease and the advanced stages of venous insufficiency such as painful varicose veins and venous ulcers. The systemic effects of venous insufficiency resulting from a reduction of venous return and increased transit time of blood from the lower extremities that can mimic heart failure are only recently being recognized. This article reviews the diagnosis and treatment options for the patients with venous insufficiency, and increases awareness about the systemic effects of venous disease and its role in the practice of cardiovascular medicine.

[Rev Cardiovasc Med. *2013;14(1):7-19 doi: 10.3909/ricm0683]*

KEY WORDS

Chronic venous insufficiency • Venous reflux disease • Deep vein thrombosis • Venous duplex ultrasound • Ablation

The venous circulation as an integral part of the cardiovascular system has been largely ignored compared with the heart and the arterial system. A greater appreciation of the role of chronic venous disease (CVD), in particular chronic venous insufficiency (CVI), has occurred with the advent of more effective and less invasive percutaneous treatments that attracted the attention of interventional cardiologists and other physicians involved in the practice of clinical medicine.

More than 25 million people have venous reflux disease, the underlying cause of CVI, and more than 2 million adults have more advanced CVD with skin changes or venous ulcers.[1] Direct medical costs attributed to CVD are estimated to be as high as $1 billion. It also has a huge negative impact on quality of life.[2] Venous ulcers, or stasis ulcers, account for 80% of lower extremity ulcerations.[3] Of the estimated 25 million people with symptomatic superficial venous reflux disease, fewer than 2 million seek treatment

annually, leaving nearly 23 million untreated. Many of you reading this review will be able to evaluate your own lower extremities and visually identify features consistent with venous insufficiency. It is estimated that more than 70% of women and 40% of men will have varicose veins by the time they reach their 60s.

Venous reflux disease is two times more prevalent than coronary heart disease and five times more prevalent than peripheral arterial disease (PAD). Compared with the importance given to the diagnosis and treatment of coronary artery disease, PAD, heart failure, and stroke, it is understandable that CVD has been ignored in the practice of cardiovascular medicine.

A functional and healthy cardiovascular system requires the proper functioning of its three important components: the heart, the arteries, and the veins. Unlike the arterial system, which has the heart as its powerful pump, the venous system relies on a low-pressure, high-capacitance space that has a less sophisticated "calf-muscle pump." This pumping action is primarily dependent on the calf muscles as its main generator, pushing the blood back to the heart. The proper function of the venous valves, ensuring one-way flow, is necessary to propel blood from the extremities to the heart.[4] Without the proper function of the venous valves, transmission of blood against gravity becomes difficult, if not impossible. The disruption of competency of the venous valves is responsible for the failure of this system, resulting in venous hypertension and stasis, which are responsible for most of the signs and symptoms of venous disease, and primarily venous insufficiency.

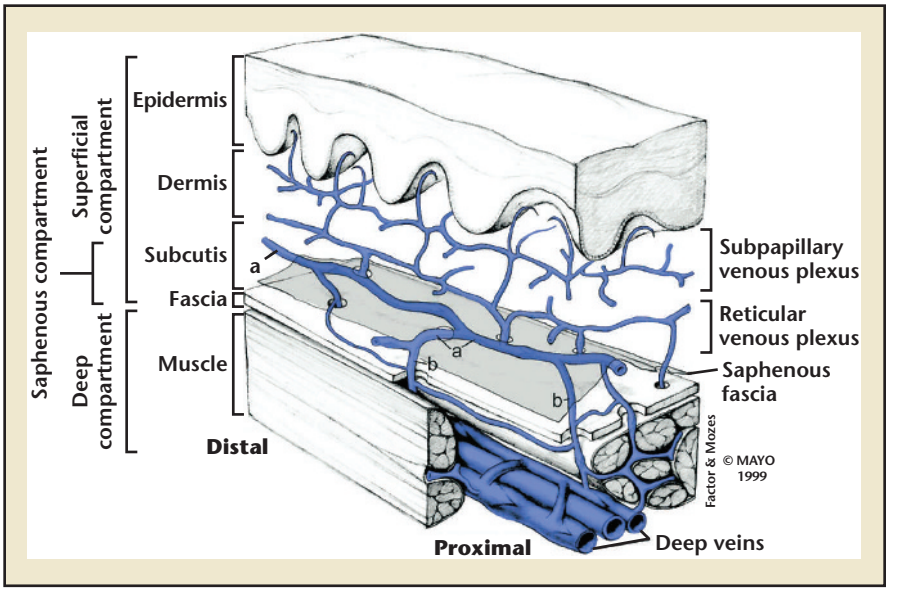


Figure 1. Relationship between the fascia and veins of the lower extremity. The fascia covers the muscle and separates the deep from the superficial compartments. Superficial veins **(a)** drain the subpapillary and reticular venous plexuses and are connected to deep veins through perforating veins **(b)**. The saphenous fascia invests the saphenous vein. The saphenous compartment is a subcompartment of the superficial compartment. From Mozes G, Gloviczki P. New discoveries in anatomy and new terminology of leg veins: clinical implications. *Vasc Endovascular Surg.* 2004;38: 367-374.[13] Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

These factors can be exacerbated by muscle pump dysfunction in the lower extremity and obstruction of blood flow in the deep venous system.[5] Venous hypertension up to 80 mm Hg at the ankle can occur as a result of a pressure of a column of blood extending vertically from that vein to the level of the heart. During exercise, the venous pressure falls to approximately 20 to 30 mm Hg with an intact muscle-vein pump and venous valves. Nonambulatory and ambulatory venous hypertension, as a result of the malfunction of the pump-valve system, is the cornerstone for the development of venous insufficiency and most of its severe manifestations (eg, edema, varicose veins, and venous ulcers culminating in amputation).

Venous reflux disease is two times more prevalent than coronary heart disease and five times more prevalent than peripheral arterial disease.

Knowledge of venous anatomy is crucial for understanding venous disease states. The veins of the lower extremity are divided into the superficial and deep venous system. It comprises an interconnecting network of veins, which serve as the primary collecting system, and several truncal superficial veins, which function as a conduit to return blood to the deep venous system. Unlike the arterial system, the anatomy of the lower extremity venous system is highly variable (Figure 1).

The principal superficial veins of the lower extremity are the short saphenous vein, which runs from the ankle typically to join the popliteal vein at the saphenopopliteal junction (SPJ), and the great saphenous vein (GSV), which runs from the ankle to join the common femoral vein at the saphenofemoral junction (SFJ). The deep venous system is located below the muscular fascia and serves as collecting veins and the outflow from the extremity to the inferior vena cava (Figure 2). The deep veins of the lower extremity follow the course of the major arteries and the intramuscular veins. Paired calf veins, corresponding to the axial arteries, merge to form a single large

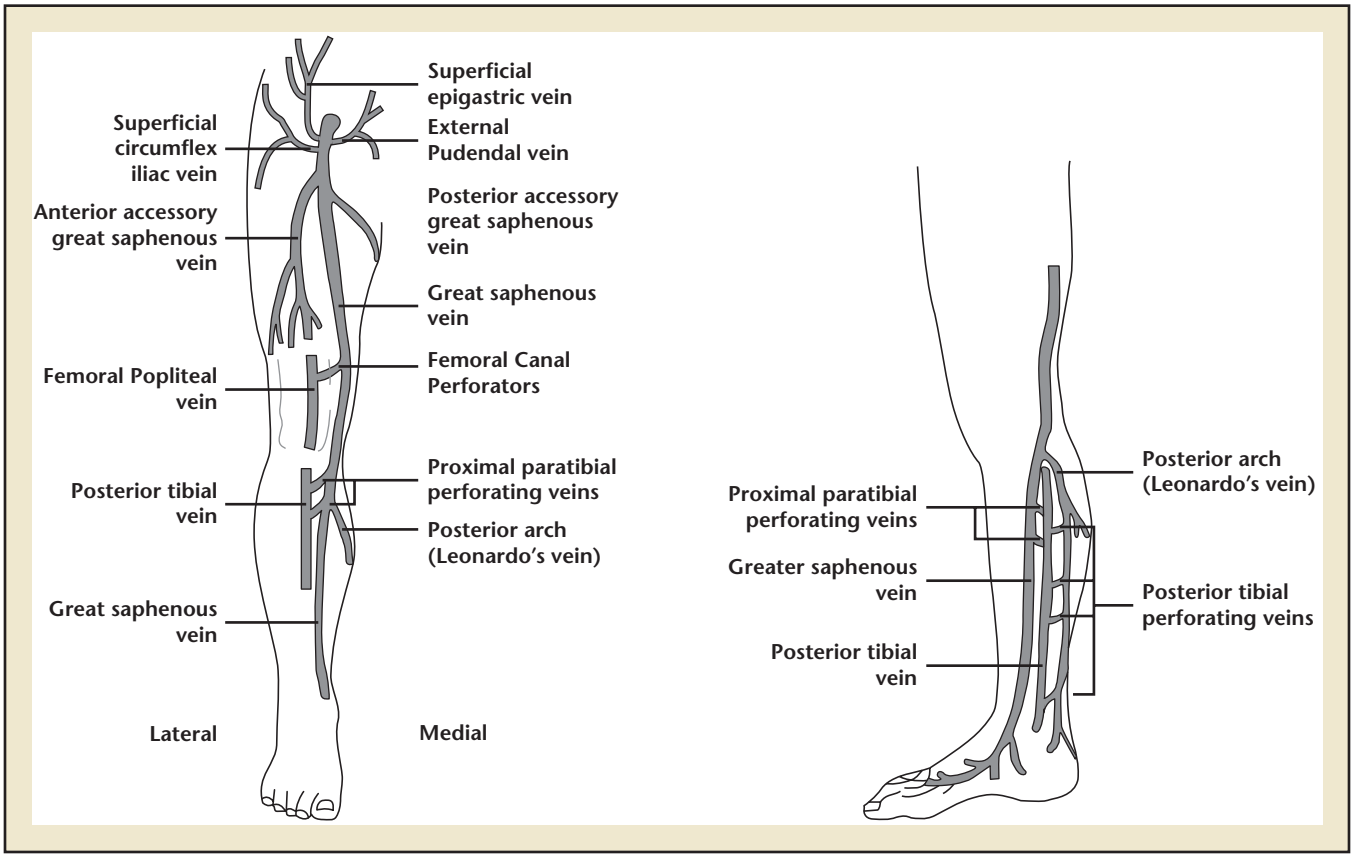


Figure 2. Anatomy of the lower extremity venous system. Reprinted with permission from Hallett JW Jr et al.[14]

popliteal vein. The popliteal vein, after passing through the adductor canal, is known as the femoral vein. The femoral vein is joined by the profunda femoris vein in the upper thigh to form the major outflow of the leg, the common femoral vein, and eventually the external iliac vein. In addition to these connections, the superficial veins are connected to the deep venous system by a number of perforating veins in the leg as conduits for blood flow, normally from the superficial system to the deep veins. These perforating veins also have valves to maintain flow from the superficial veins to the deep system. Perforator vein valve dysfunction can also lead to reversal of this flow pattern, and can be the source of reflux.

Manifestations of venous reflux disease become apparent when the venous valves that are critical to maintaining one-way flow from the superficial veins to the deep veins and then from the deep veins to the heart become incompetent. Because the veins are a low pressure system, the increased weight of the column of blood resulting from this reflux can cause reversal of the flow in both the superficial and deep venous system. Varicosities usually start at points where superficial veins communicate with deep veins, particularly at the SFJ and SPJ and the perforating veins. Primary varicose veins result from venous dilatation without previous thrombosis. Secondary varicose veins are caused by valvular damage after deep vein thrombosis (DVT).

In order to expertly diagnose and treat CVD, knowledge, understanding, and experience in treating the entire spectrum of disorders from venous insufficiency to venous thrombosis are required. The spectrum of venous disease extends from venous insufficiency to obstructive venous disease. Obstruction of the deep veins may occur because of an intrinsic venous process, such as previous DVT with inadequate recanalization or venous stenosis, or because of extrinsic compression, as in May-Thurner syndrome (compression of the left common iliac vein as it traverses between the right common iliac artery and the lumbosacral region).

In order to expertly diagnose and treat CVD, knowledge, understanding, and experience in treating the entire spectrum of disorders from venous insufficiency to venous thrombosis are required.

Other than the patients who present with symptomatic (painful or unduly varicose) visible surface vein problems or those who present with acute DVT, the majority of patients with venous insufficiency

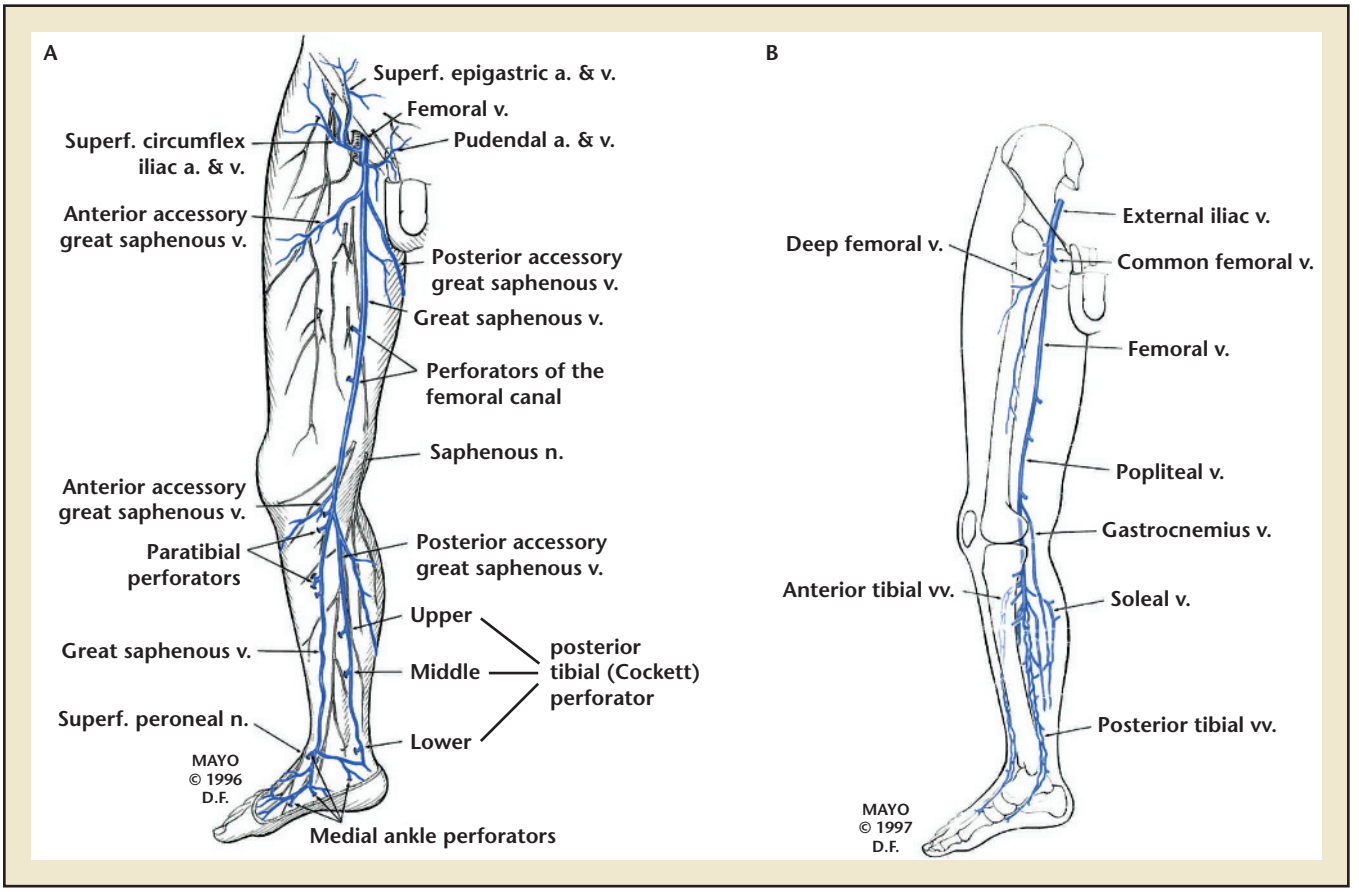


Figure 3. **(A)** Superficial and perforating veins of the leg. **(B)** Deep veins of the leg. From Mozes G, Gloviczki P. New discoveries in anatomy and new terminology of leg veins: clinical implications. *Vasc Endovascular Surg.* 2004;38: 367-374.[13] Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

present with leg edema. The separation of these patients into three categories, those with DVT, CVI, or a combination of the two, is important at the outset of the evaluation of these patients.

Pathophysiology and Natural History of Venous Insufficiency

The venous system is composed of deep veins, superficial veins, and perforating veins (Figure 3). The deep veins are surrounded by leg muscle and fascia that maintain their structural integrity and prevent pressure-induced dilation and stretching. Incompetence and resultant reflux disease in the deep system cause fewer symptoms than reflux in the superficial venous system, where the pressure outside the vein is lower and allows exudation of fluid, toxic metabolites, and other damaging proteins into the surrounding subcutaneous tissue. The normal flow of blood is from the superficial venous system to the deep, governed by the unidirectional flow created by competent venous valves. At the SFJ, usually located about 4 cm below the inguinal ligament, the saphenofemoral valve (SFV) prevents the reversed downward flow of blood from the deep femoral vein and the column of blood above it up to the right atrium and back down the leg. The importance of the SFV and the implications of its failure resulting in venous insufficiency and venous hypertension are clear. The GSV drains the medial aspect of the foot and the entire leg and pours that blood into the deep femoral vein at the SFJ. The small saphenous vein (SSV) drains the back of the leg and pours the blood into the popliteal vein at the knee level at the SPJ near the popliteal fossa. The third superficial venous drainage system is called the lateral venous complex and it drains the blood flow from the lateral aspect of the thigh via accessory veins into the SFJ.

Manifestations of Venous Insufficiency

Superficial venous reflux is a chronic and progressive disease. Among the manifestations of this disease are spider veins (telangiectasias), reticular veins, varicose veins, edema, hyperpigmentation, and ulcers (Figure 4). There is no definitive stepwise progression from spider veins to ulcers. Spider veins are small red, blue, or purple superficial veins that commonly appear as thin wiggly lines on the

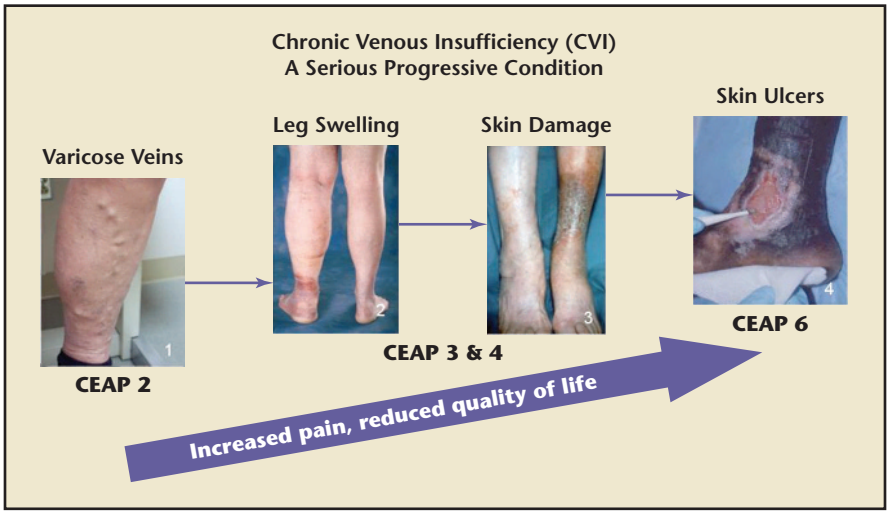


Figure 4. Progression of chronic venous insufficiency. CEAP, class, etiology, anatomy, and pathophysiology.

thighs, legs, and ankles. Spider veins are much more common in the general population than are varicose veins. Reticular veins are larger than spider veins but smaller than varicose veins, approximately 1 to 3 mm in diameter. They are usually flat and less tortuous than bulging varicose veins and appear as dilated blue and green veins beneath the skin surface. Reticular veins are most often noted in the outer thighs, backs of the thighs, and knees. These veins can exist independently but can also be the underlying problem that gives rise to surface spider veins. Because spider veins can result from refluxing reticular veins, they are also known as feeder veins. All of these complications are related to the increasing venous hypertension that leads to enlargement of veins, accumulation of fluid, and macromolecules in the extravascular space due to increases in capillary permeability, extravasation of erythrocytes, and reduced tissue perfusion. Other complications of CVI include restless legs syndrome, lipodermatosclerosis (thickening of the skin around the ankle due to submucosal fat necrosis) and venous eczema, otherwise known as stasis dermatitis. Obstruction of the deep venous system can lead to symptoms similar to those of superficial disease, but can also cause venous claudication or pain with ambulation that may be difficult to distinguish clinically from arterial insufficiency and is often mistakenly attributed to an arterial process.

Differentiation among spider veins, reticular veins, and varicose veins is related to size and location, with a varix being at least 3 mm in diameter. Valvular dysfunction does not need to be present in either the GSV or SSV for large varicosities to develop; it can happen because of local incompetence alone. Secondary varicose veins are those developing as collateral pathways, typically after stenosis or occlusion of the deep veins, a common sequel of extensive DVT.

Varicose veins are classified using the CEAP (class, etiology, anatomy, and pathophysiology) system. By convention, most practitioners use the CEAP clinical classification obtained at the time of a thorough physical examination to identify the baseline state of clinical disease severity (Table 1). The venous clinical severity score is much simpler and seems to be better suited to follow both the natural course of CVI and its response to therapy (Table 2).

Diagnosis

Proper evaluation of venous disease begins with a full history to identify predisposing factors, such as the amount of standing during the work day, number of pregnancies, and family history of venous insufficiency, followed by an examination of the patient in the upright position with proper lighting, which typically takes longer than when performed during a routine physical examination.

The complete evaluation of patients with leg edema should include specific examination of the

TABLE 1

CEAP Clinical Classification of Varicose Veins

Classification	Description/Definition
0	No venous disease
1	Telangiectasias
2	Varicose veins
3	Edema
4	Lipodermatosclerosis or hyperpigmentation
5	Healed ulcer
6	Active ulcer

CEAP, class, etiology, anatomy, and pathophysiology.

TABLE 2

Venous Clinical Severity Score

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe activity limitation or requiring regular use of analgesics
Varicose veins[a]	None	Few, scattered: branch VVs	Multiple: GS VVs confined to calf or thigh	Extensive: thigh and calf or GS and LS distribution
Venous edema[b]	None	Evening ankle edema only	Afternoon edema, above ankle	Morning edema above ankle and requiring activity change, elevation
Skin pigmentation[c]	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower one-third) or recent pigmentation (purple)	Wider distribution (above lower one-third) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of greater gaiter area (lower one-third)	Severe cellulitis (lower one-third and above) or significant venous eczema
Induration	None	Focal, circumalleolar (< 5 cm)	Medical or lateral, < lower third of leg	Entire lower third of leg or more
Active ulcers (n)	0	1	2	> 2
Active ulceration (duration)	None	< 3 mo	> 3 mo, < 1 y	Not healed > 1 y
Active ulceration (size)[d]	None	< 2-cm diameter	2- to 6-cm diameter	> 6-cm diameter
Compressive therapy[e]	Not used or not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance: stockings + elevation

[a]Varicose veins must be > 4 mm diameter to qualify so that differentiation is ensured between C1 and C2 venous pathology.
[b]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, history of deep vein thrombosis). Edema must be regular finding (eg, daily occurrence). Occasional or mild edema does not qualify.
[c]Focal pigmentation over varicose veins does not qualify.
[d]Largest dimension/diameter of largest ulcer.
[e]Sliding scale to adjust for background differences in use of compressive therapy.
GS, greater saphenous; LS, lesser saphenous; VV, varicose vein.
Reprinted with permission from Rutherford RB et al.[15]

superficial veins, GSV, and SSV in the upright position when the superficial veins are maximally distended by hydrostatic pressure. A failure to properly evaluate these patients is one of the most common pitfalls in the diagnostic work-up of patients with venous disease and can lead to both under- and overtreatment.

Duplex Ultrasound, Computed Tomography, and Magnetic Resonance Venography

Venous duplex ultrasound is the key imaging modality used to identify venous thrombosis and venous insufficiency in the superficial and deep venous systems. Venous duplex imaging combines B-mode imaging with pulsed Doppler assessment and color Doppler assessments of venous flow. The equipment required to perform the ultrasound examination should include gray scale imaging, pulsed-wave Doppler, and a linear 7.5- to 10-MHz transducer along with color Doppler.

This equipment provides information about the anatomic extent of disease involving the deep and superficial systems and perforator veins. A standard venous duplex examination is performed to exclude venous obstruction and DVT; this is followed by a similar examination of the GSV and SSV. Many inpatient and outpatient vascular laboratories fall short of the full venous examination with a limited report that there is "no DVT" and "no deep venous reflux," neglecting any comment on the examination of the superficial venous system, not realizing that the most common cause of CVI is superficial venous reflux disease. It is incumbent on the ordering physician to use a laboratory that provides a comprehensive venous evaluation including the superficial and deep veins for insufficiency and thrombosis. Unfortunately, most duplex ultrasound-based algorithms for the diagnosis of DVT, and some vascular laboratories, still do not include an initial ultrasound evaluation of the calf veins as part of their routine evaluation for DVT, even in symptomatic patients. This is largely the result of outdated perceptions of the inaccuracy of ultrasound evaluation of DVT isolated to the calf veins.

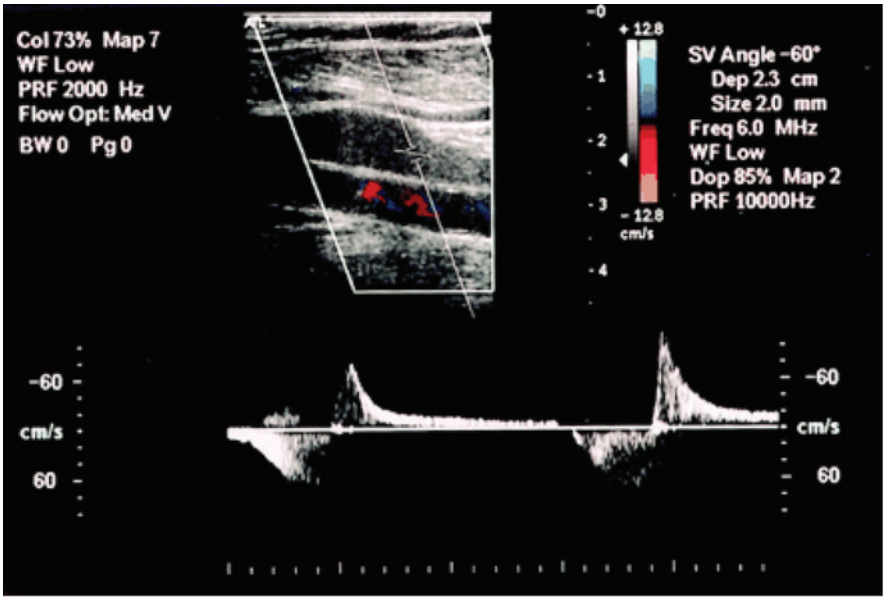
Duplex ultrasound examination of the venous system starts with an assessment of the deep venous system to rule out DVT using direct venous compression. A thrombosed vein filled with thrombus cannot be compressed. Identifying nonocclusive DVT and differentiating acute from chronic thrombus is also an important aspect of this examination. Compression ultrasound is typically performed on the proximal deep veins, specifically the common femoral, femoral, and popliteal veins, whereas a combination of duplex ultrasound and color Doppler imaging is more often used to interrogate the calf and iliac veins.

Assessing the direction of blood flow with color flow and continuous-wave Doppler during provocative measures such as limb compression or Valsalva maneuver to augment reversed blood flow direction toward the feet is a critical part of the examination. Areas of deep venous system incompetence are examined at this time, both at the SFJ and different areas along the femoral vein. Following the examination of the deep system, the superficial veins are assessed for reflux and thrombus in the large branches (GSV and SSV), junctional tributaries, and perforator branches. The evaluation for reflux in the superficial system is performed by obtaining continuous Doppler wave samples at the SFJ and at multiple sites along the GSV and SSV where the sources of reflux can be identified. The Valsalva maneuver is helpful to augment flow at the SFJ to assist in reflux detection, but below that level, leg compression augmentation should be used to provoke reflux. Reflux is defined as the reversal of venous flow toward the feet that lasts longer than 0.5 seconds after an augmentation maneuver (Figure 5).

Assessing the direction of blood flow with color flow and continuous-wave Doppler during provocative measures such as limb compression or Valsalva maneuver to augment reversed blood flow direction toward the feet is a critical part of the examination.

The most important principle in the diagnosis and treatment of venous insufficiency and its superficial manifestations is to identify the source of reflux and treat it effectively. This is sometimes difficult to do with ultrasound. In addition to conventional imaging with ultrasound, at our institution, Westside Medical Imaging (Beverly Hills, CA), we have employed a novel approach involving computed tomography (CT)

Figure 5. Doppler sampling gate in popliteal vein with abnormal reflux. Calf compression results in antegrade flow (spectral curve below baseline); when compression is released the spectral curve shows reflux (retrograde flow above baseline) for 2 seconds, until the next compression. Reprinted with permission from Mantoni M et al.[16]



and magnetic resonance (MR) venography to complement the conventional examination. This algorithm has allowed for the identification not only of perforators or tributaries not found by ultrasound examinations, but of nonocclusive thrombus that can be missed on ultrasound, and congenital and iatrogenic causes of venous hypertension, such as arteriovenous fistulas. Using the venogram as an anatomical guide, we then apply the ultrasound to determine if there is reflux in the hidden perforators or accessory veins identified by CT or MR venography. If reflux is detected, then the refluxing veins are treated leading to an optimal patient outcome. Using this multidisciplinary imaging approach, we have been successful in treating some patients who initially were nonresponders or partial responders to therapy for the main sources of reflux (GSV or SSV) by treating important secondary less appreciated sources of reflux. Our experience has shown the importance of a dedicated multidisciplinary venous imaging laboratory to improve diagnostic accuracy, enhance patient selection, and improve safety of the therapeutic procedures.

Treatment Options and Strategies

The effective treatment of CVI and its visible manifestations (including varicose veins, reticular veins, spider angiomas, swollen legs, skin pigmentations, and ulcers) starts with identifying the source of venous hypertension and reflux disease. Venous hypertension can be either systemic or local in origin. Heart failure, obesity, and pulmonary hypertension secondary to sleep apnea and/or chronic obstructive pulmonary disease are common and treatable causes of systemic venous hypertension. Other causes of venous reflux are primary venous valvular failure or secondary valvular failure due to thrombophlebitis and/or venous thrombosis.

Heart failure, obesity, and pulmonary hypertension secondary to sleep apnea and/or chronic obstructive pulmonary disease are common and treatable causes of systemic venous hypertension.

Conservative treatments of venous insufficiency and varicose veins with techniques including weight loss, regular exercise, use of compression stockings, and leg elevation are important initial approaches to treating the patient with CVI. They lead to a reduction of lower extremity venous hypertension and improvements in edema and ulcers. Compression stockings are typically ordered to provide 20- to 30-mm Hg compression leading to a reduction of venous capacitance. However, compliance with wearing compression stockings is similar to that of continuous positive airway pressure masks in sleep apnea, as they can be difficult to apply in older and obese patients. Adherence rates with compression stockings are low, at 30% to 60% overall.[6,7]

Regardless of the etiology, venous reflux should preferably be treated first and foremost, before surface manifestations of CVI, such as varicose veins and spider angiomas.

Regardless of the etiology, venous reflux should preferably be treated first and foremost, before surface manifestations of CVI, such as varicose veins and spider angiomas. Therefore, a comprehensive treatment plan that addresses both the underlying cause of the problem as well as its superficial manifestations should be outlined for every patient. A failure to take this approach will result in patient confusion and an inappropriate (and thereby ineffective) approach to the management of the patient's expectations. Complete resolution of the cosmetic concerns of the patients and elimination of the disease process is usually hard to achieve; therefore, a good principle for the venous interventionists is, "promise less and deliver more."

A variety of interventions are available to treat CVI (Table 3). Catheter-based therapies or endovascular ablation (EVA) of the refluxing vein with endovenous laser ablation (ELA) or radiofrequency ablation (RFA) energy has, for the most, replaced formerly popular surgical therapies such as vein stripping and venous ligation as a new generation of phlebologists are trained.

Surgical Approach

In the past, surgical stripping usually meant the removal of the entire saphenous vein from the ankle to the groin; however, this was associated with an increased risk of saphenous nerve injury. Most surgeons now limit the removal of the GSV only from the groin to the calf. Surgical treatment of the SSV is most often performed by ligation of the vein. Surgical vein stripping may be preferred to EVA in specific circumstances, including a very superficial location of the GSV to avoid thermal injury to the skin or EVA failures. In our experience, we have found that even in these superficial veins, adequate tumescent infiltration can usually push the vein down and allow safe performance of RFA.

TABLE 3

Review of Potential Therapies

Therapy	Indication	Complications	Results	Failure	Recurrence
Stockings/lifestyle changes/ medications	Relief of pressure, pain, and swelling	Stockings: skin damage; medications: allergic reactions and specific adverse effects	Temporary	40%-60%; nonadherence for stockings	100% noncurative
Sclerotherapy	Spider veins and small varicose veins	Hyperpigmentation, matting, cellulitis, small ulcers, phlebitis	60%-70% cosmetic improvement		> 70% lifetime
Thermocoagulation/ laser	Spider veins and small varicose veins	Hyperpigmentation, skin damage, hypopigmentation	60%-70% cosmetic improvement		> 70% lifetime
Endovenous ablation					
Radiofrequency ablation	Ablation of GSV or SSV (axial reflux)	Paresthesia, phlebitis, thermal skin injury, DVT	70%-90% durable GSV occlusion		10%-30% recanalization
Endovenous laser therapy	Ablation of GSV or SSV (axial reflux)	Bruising, erythema, hyperpigmentation, paresthesia, phlebitis, skin slough, DVT	70%-90% durable GSV occlusion		10%-30% recanalization
Stripping and excision	Removal of GSV or SSV (axial reflux and excision of branch varicose veins)	Wound infection, saphenous nerve neurapraxia, hematoma, phlebitis, DVT	80% intermediate term		10%-20% neovascularization
Microphlebectomy	Removal of branch varicose veins alone or after endovenous ablation	Wound infection, paresthesia, hematoma, phlebitis	> 90% intermediate term		> 60% lifetime recurrence of varicose veins

DVT, deep vein thrombosis; GSV, great saphenous vein; SSV, small saphenous vein.
Reprinted with permission from Hamdan A.[17]

Endovascular Ablation

Despite the differences between ELA and RFA, these two techniques are very comparable, at least with regard to their effectiveness and side-effect profiles. These techniques rely on injury to the wall of the vein to induce fibrosis and thrombosis of the treated vein. With RFA, a generator uses RF energy to heat a catheter tip element that is then brought into direct contact with the vein wall tissue. Target temperature is approximately 120°F. This can cause denaturation of the proteins in the wall of the veins and their subsequent closure. After 6 weeks, new

collagen (scar) has formed on the vessel wall, leading to lumen obliteration. RF catheters are usually 7F with a 4F shaft. The presence of thrombus is a contraindication to use of RFA or ELA. Complications of RFA include perforation, thrombosis, pulmonary emboli, phlebitis, skin discoloration, infection, and adjacent nerve injury. These complications are rare and occur in fewer than 2% of patients.

We have a robust clinical experience with both RFA and ELA. We have found them to be equally effective but have seen more patient satisfaction and less pain and bruising with RFA. We employ ELA when the veins are smaller and tortuous. For primary navigation, we use a 0.018-inch or nitinol 0.014-inch guide wire to reach the SFJ from the entry site around or below the knee. In these cases, the lower profile of the ELA catheter is helpful and makes it easier to push the catheter over the wire, past the tortuous and narrowed vein segments.

We have a robust clinical experience with both RFA and ELA. We have found them to be equally effective but have seen more patient satisfaction and less pain and bruising with RFA.

The mechanism of vein wall injury after ELA is controversial. It has been postulated to be mediated both by direct effect and indirectly via laser-induced steam generated by the heating of small amounts of blood within the vein.[8] Treatments for the skin surface disease include microphlebectomy, sclerotherapy, and surface laser therapy.

Selection of Therapy

There is a body of clinical trial data that provides some guidance on the selection of therapy. The REACTIV (Randomised Clinical Trial, Observational Study and Assessment of Cost-Effectiveness of the Treatment of Varicose Veins)[9] trial randomized 246 patients to compression therapy versus surgical vein stripping. Trial results showed a significant enhancement in quality of life with surgery as the primary endpoint and a reduction of cost. Most comparisons of surgical vein stripping with percutaneous ablation procedures show similar rates of venous reflux elimination and quality of life enhancements with greater patient satisfaction. In addition, there seem to be similar rates of success and complication when comparing ELA and RFA procedures (Table 4).

Swollen Leg Syndrome

Swollen leg syndrome (SLS) is a very common problem that is poorly understood and ineffectively treated. Other than the more commonly appreciated underlying causes such as right heart failure and chronic kidney disease, the most common cause, CVI, is rarely understood, or properly evaluated and treated. The most common examination ordered for patients with SLS is the standard venous duplex ultrasound, which only addresses DVT and deep venous reflux, and fails to evaluate superficial venous reflux, which happens to be the most common cause of peripheral vascular edema.

The diagnostic process and development of a treatment plan can be systematically approached by first ordering the proper evaluation after a full patient history and physical examination. The appropriate diagnostic examination involves an assessment for both deep and superficial venous reflux disease. If the cause of venous reflux is not identified with duplex imaging, a CT venogram should be performed to rule out occlusive disease in the iliac veins and inferior vena cava as the cause of venous hypertension and edema, as well as other vascular anomalies such as arteriovenous fistulae. Lymphedema, another cause of SLS, is usually easy to differentiate from venous edema based on its nonpitting nature at the ankle or foot and the classic "squaring" pattern that develops in the foot and toes.

Systemic and Cardiovascular Effects of CVI

Impaired fibrinolysis has been determined in several studies in numerous patients with varicosities.[10] The precise mechanism for the defect in fibrinolysis in the majority of patients appears to be an increase in the plasminogen activator inhibitor-1.[11] Increased plasma fibrinogen levels have been frequently observed in patients with CVI. In patients with lipodermatosclerosis, immunohistochemical studies have shown that capillaries of the papillary plexus in the skin are surrounded by an infiltrate of inflammatory cells (macrophages and T-lymphocytes), as well as the fibrin cuff.[12]

The precise mechanism for the defect in fibrinolysis in the majority of patients appears to be an increase in the plasminogen activator inhibitor-1.

Our experience with treating more than 300 patients with symptomatic CVI indicates that there may be an important cardiovascular and hemodynamic effect of CVI and its treatment for cardiovascular disease that is not yet

TABLE 4

Comparison of Therapies

Comparison	Types/Number of Trials	Main Outcomes	Limitations	Potential Future Studies or Procedures
Surgery vs conservative management	5 RCTs	At 2-y surgery improved quality-adjusted life-years and symptoms	Majority of trials included patients with ulcers	Inclusion of venoactive drugs; stockings easier to apply
Surgery vs endovenous laser therapy	4 RCTs	Early benefit to endovenous laser therapy in pain and bruising but no change at 26 mo in cosmetic results or pain Endovenous laser therapy: earlier return to work and decreased duration of postoperative disability	Two trials had for-profit funding; short follow-up; blinded outcomes	Unlikely to repeat trials given lack of patient interest in surgery
Surgery vs RF ablation	4 RCTs, 3 observational studies	RF ablation: faster return to work, less pain, better short-term quality of life No difference in varicose vein recurrence or freedom from reflux	Short follow-up; no description of bias protection	Unlikely to repeat trials given lack of patient interest in surgery
RF ablation vs endovenous laser therapy	4 RCTs	Less bruising and tenderness with RF ablation Durability of GSV occlusion better in endovenous laser therapy (1 trial)	Small trials; industry funding	Additional trials unlikely because of multiple laser suppliers and wavelengths
Foam sclerotherapy vs endovenous ablation	Limited	Durability of GSV occlusion; neurologic or retinal complications with foam; pain; return to work	Multiple companies; standardization of foam particles and techniques	Steam ablation also a candidate to replace other thermal techniques

GSV, great saphenous vein; RCT, randomized controlled trial; RF, radiofrequency.

fully understood and appreciated. This stems from the observation that effective treatment of CVI often leads to a reduced need for diuretics and vasodilators, weight loss, and a decrease in peripheral edema. It is not uncommon to see patients on high doses of loop diuretics for the treatment of edema and develop renal insufficiency secondary to intravascular volume depletion. CVI-induced

edema is resistant to the effects of loop diuretics because they do not impact the primary pathophysiology. With effective treatment of CVI in patients with heart failure, we have observed the need for less diuretic and vasodilator therapy, as well as profound improvements in their assessments of quality of life. We hypothesize that the decrease in effective circulating volume in patients with CVI may lead to neurohormonal activation resembling what occurs in patients with heart failure. We have initiated a prospective observational study to examine the effects of the treatment of CVI on the markers of neurohormonal activation such as renin, angiotensin, aldosterone, catecholamines, and brain natriuretic peptide, as well as inflammatory markers.

Venous Disease: The Missing Link

CVI could be the missing link in our understanding of some edema-related cardiovascular syndromes. Activation of the renin-angiotensin-aldosterone axis can lead to a host of maladaptive effects, including salt and water retention. Endothelial cell dysfunction, platelet activation, smooth muscle cell proliferation, superoxide generation, endothelin secretion, monocyte activation, increased levels of cytokines and reduced fibrinolysis, and glomerular and renal interstitial fibrosis are all sequelae of this undesired neurohormonal activation and can lead to or worsen important clinical syndromes of hypertension, heart failure, and atherosclerosis. The proof of concept will be in the demonstration that CVI is associated with elevated markers of neurohumoral activation and that effective treatment can modify that effect. ■

CVI could be the missing link in our understanding of some edema-related cardiovascular syndromes.

References

1. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53(suppl):2S-48S.
2. Guex JJ, Myon E, Didier L, et al. Chronic venous disease: health status of a population and care impact on this health status through quality of life questionnaires. *Int Angiol*. 2005;24:258-264.
3. O'Meara S, Al-Kurdi D, Ovington LG. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev*. 2008;(1):CD003557.
4. Laughlin MH. Skeletal muscle blood flow capacity: role of muscle pump in exercise hyperemia. *Am J Physiol*. 1987;253(5 Pt 2):H993-H1004.
5. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med*. 2004;164:17-26.
6. Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease. *Ann Vasc Surg*. 2007;21:790-795.
7. Jull AB, Mitchell N, Arroll J, et al. Factors influencing concordance with compression stockings after venous leg ulcer healing. *J Wound Care*. 2004;13:90-92.
8. Proebstle TM, Sandhofer M, Kargl A, et al. Thermal damage of the inner vein wall during endovenous laser treatment: key role of energy absorption by intravascular blood. *Dermatol Surg*. 2002;28:596-600.
9. Michaels JA, Campbell WB, Brazier JE, et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of

MAIN POINTS

- More than 25 million people have venous reflux disease, the underlying cause of chronic venous insufficiency, and more than 2 million adults have more advanced chronic venous disease (CVD), although it has been relatively ignored in the practice of cardiovascular medicine.
- In order to expertly diagnose and treat CVD, knowledge, understanding, and experience in treating the entire spectrum of disorders from venous insufficiency to venous thrombosis are required.
- The complete evaluation of patients with leg edema should include specific examination of the superficial veins, great saphenous vein, and small saphenous vein, in the upright position when the superficial veins are maximally distended by hydrostatic pressure.
- Venous duplex ultrasound is the key imaging modality used to identify venous thrombosis and venous insufficiency in the superficial and deep venous systems. Assessing the direction of blood flow with color flow and continuous-wave Doppler during provocative measures such as limb compression or Valsalva maneuver to augment reversed blood flow direction toward the feet is also a critical part of the examination.
- Conservative treatments of venous insufficiency and varicose veins are usually ineffective and do not address the root cause of the disease. Treating the source of venous reflux with radiofrequency ablation and endovenous laser ablation is very effective and efficient and results in much better systemic and cosmetic outcomes over time.

varicose veins (REACTIV trial). *Health Technol Assess*. 2006;10:1-196, iii-iv.
10. Wolfe JHN, Morland M, Browse NL. The fibrinolytic activity of varicose veins. *Br J Surg*. 1979;66: 185-187.
11. Boisseau MR, Taccoen A, Garreau C, et al. Fibrinolysis and hemorheology in chronic venous insufficiency: a double blind study of troxerutin efficiency. *J Cardiovasc Surg (Torino)*. 1995;36:369-374.
12. Wilkinson LS, Bunker C, Edwards JC, et al. Leukocytes: their role in the etiopathogenesis of skin damage in venous disease. *J Vasc Surg*. 1993;17:669-675.
13. Mozes G, Gloviczki P. New discoveries in anatomy and new terminology of leg veins: clinical implications. *Vasc Endovascular Surg*. 2004;38:367-374.
14. Hallett JW Jr, Mills JL, Earnshaw J, et al, eds. *Comprehensive Vascular and Endovascular Surgery*. 1st ed. Edinburgh, Scotland: Mosby; 2004.
15. Rutherford RB, Padberg FT Jr, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31:1307-1312.
16. Mantoni M, Larsen L, Lund O, et al. Evaluation of chronic venous disease in the lower limbs. *Br J Radiol*. 2002:75:578-583.
17. Hamdan A. Management of varicose veins and venous insufficiency. *JAMA*. 2012 26;308:2612-2621.