Chronic Venous Insufficiency

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KEYWORDS

• Chronic venous insufficiency (CVI) • Valvular incompetence • Plethysmography
• Superficial venous reflux • Radiofrequency ablation • Sclerotherapy • Phlebectomy
• Deep vein reflux

KEY POINTS

- Varicose veins are a common manifestation of chronic venous disease and affect approximately 25% of adults in the western hemisphere.
- The historical standard treatment has been surgery, with high ligation and stripping, combined with phlebectomies.
- In the past decade, alternative treatments such as endovenous ablation with laser, radiofrequency ablation, and ultrasonography-guided foam sclerotherapy have gained popularity.
- Performed as office-based procedures using tumescent local anesthesia, the new minimally invasive techniques have been shown in numerous studies to obliterate diseased veins, eliminate reflux, and improve symptoms safely and effectively.

INTRODUCTION

Chronic venous disease is a prevalent source of morbidity in western Europe and the United States. Varicose veins are a common manifestation of chronic venous insufficiency and affect approximately 25% of adults in the western hemisphere. The prevalence varies greatly by geographic area. The reported incidence of chronic venous insufficiency varies from less than 1% to 40% in women and from less than 1% to 17% in men. Estimates for varicose veins are higher; less than 1% to 73% in women and 2% to 56% in men.[1] These reported ranges reflect differences in the population distribution of risk factors, accuracy in the application of diagnostic criteria, and the quality and availability of medical diagnostic and treatment resources. Various risk factors are responsible for these incidences. These risk factors include older age, pregnancy (especially multiple), family history of venous disease, female gender, obesity, and occupations that involve long times standing resulting in significant orthostasis.[2] Venous insufficiency is most often associated with great saphenous vein (GSV) reflux, but can also be present in the small saphenous vein (SSV) or perforator veins.

The historical treatment has been surgery, with high ligation and stripping, combined with phlebectomies. Such treatment efficiently reduces symptoms, improves quality of life (QOL), and reduces the rate of reoperation compared with high ligation and phlebectomies only. However, the operation may occasionally be associated with significant postoperative morbidity, including bleeding, groin infection, thrombophlebitis, and saphenous nerve damage. Major complications are rare based on the current available data. Conventional surgery is often performed in hospital

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Intervent Cardiol Clin 3 (2014) 593–605
http://dx.doi.org/10.1016/j.iccl.2014.07.001
2211-7458/14/$ – see front matter

using general or regional anesthesia, which increases costs.

In the past decade, alternative treatments such as endovenous laser ablation (EVLA), radiofrequency ablation (RFA), and ultrasonography-guided foam sclerotherapy have gained popularity. Performed as office-based procedures using tumescent local anesthesia, the new minimally invasive techniques have been shown in numerous studies to obliterate the affected vein, eliminate reflux, and improve symptoms safely and effectively.[3]

PREDISPOSING FACTORS

Age and Gender

The prevalence of varicose veins in women is approximately twice that in men.[4] Advanced age has also been determined to be a risk factor in long-term studies.[5] Varicose veins have an estimated prevalence between 5% and 30% in the adult population, with a female to male predominance of 3 to 1, although a more recent study supports a higher male prevalence.[6] The Edinburgh Vein Study screened 1566 subjects for venous reflux and found chronic venous insufficiency (CVI) in 9.4% of men and 6.6% of women. After age adjustment, the prevalence increased with age (21.2% in men >50 years old, and 12.0% in women >50 years old).[7]

The Tampere study investigated a large cohort of 3284 men and 3590 women with varicose veins and showed a prevalence of 18% and 42%, respectively. The overall prevalence of varicose veins at ages 40, 50, and 60 years was 22%, 35%, and 41%, respectively.[8]

Pregnancy

Multiparity has been shown to be a major predisposing factor for development of varicose veins and part of its increase in prevalence has been attributed to female gender. In the Tampere study, the prevalence of varicose veins in women with 0, 1, 2, 3, and 4 or more pregnancies was 32%, 38%, 43%, 48%, and 59%, respectively.[8] The exact mechanism of pregnancy-induced venous insufficiency is not fully understood. It has been attributed to both hydrostatic and hormonal effects. Pressure of the gravid uterus on the pelvic vasculature is associated with lower extremity venous hypertension, venous distention, and valve rupture. High serum estradiol levels have been shown by Ciardullo and colleagues[9] to increase venous distensibility and varicose vein formation in menopausal women. The saphenous veins have been shown to contain estrogen and progesterone receptors that may enable the estradiol-rich hormonal state of pregnancy to exert a similar effect.[9]

Hereditary

A positive family history of varicose veins is associated with a significantly increased risk of development of varicose veins. One study conducted in Japan showed that 42% of women with varicose veins reported a positive family history compared with 14% without the disease.[10] Various genetic predispositions have been linked to development of varicose veins. Downregulation of the desmuslin gene affecting the smooth muscle cells in the saphenous vein wall, thrombomodulin mutation (−1208/−1209 TT deletion) caused by varicose vein formation via deep vein thrombosis, expression of structural genes regulating the extracellular matrix (ECM), cytoskeletal proteins, and myofibroblasts have all been shown to be associated with increased risk.

Certain mutations have been linked to a variety of syndromes, including Klippel-Trénaunay syndrome (translocation involving chromosome 8q22.3 and 14q13 [cutaneous capillary malformations, t tissues]), lymphedema distichiasis syndrome (FOXC2 mutation [extra eyelashes from meibomian glands, varicose veins, congenital heart defects, vertebral anomalies, extradural cysts, ptosis, and cleft palate]), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; heterozygous mutation, -1279G > T), Chuvash polycythemia (autosomal recessive disorder caused by homozygous mutation of the von Hippel-Lindau gene [598 > T] on chromosome 3p25), and other genes have been associated with poor wound healing causing venous ulceration (F13A1 gene: factor XIII deficiency, HFE gene mutation, FGFR-2 [SNP 2451AG] mRNA instability, MMP-12 [SNP 82AA]; functional change predisposing to ulcer).[11]

Lifestyle

Sedentary work and prolonged standing at work are independent risk factors for development of venous insufficiency.[12] In the Tampere study, the prevalence of varicose veins in standing versus sitting workers was 36% and 27%, respectively. The Edinburg Vein Study has also shown predisposition of varicose veins in patients having prolonged standing time at their work places.

Body Habitus

Epidemiologic studies have shown that varicose veins are more common in female patients with increased body mass index (BMI) (especially >30 kg/m^2). It has been assumed that subcutaneous deposition of adipose and fibrous

tissue disrupts the cutaneous venous network, impairs drainage, and promotes stasis. The Edinburgh Vein Study supported the findings that increased BMI in women is a risk factor. Callam,[2] in his epidemiologic review series, reached similar conclusions.

PATHOGENESIS OF CVI

Several theories have been proposed for the causal basis of CVI. There are 2 universally accepted theories: (1) primary valvular incompetence and (2) primary, congenital vein wall weakness.

Primary valvular incompetence is the oldest theory and was postulated by Sir William Harvey in 1628. It states that varicose veins develop as a sequela of central valvular incompetence related to paucity or atrophy of its valves. It causes venous hypertension in the vein segment below, which in turn damages adjacent peripheral valves and propagates varicose transformation in a central-to-peripheral direction. This theory conflicts with the fact that valves are strong structures capable of withstanding pressures of 200 mm Hg without leakage or degenerative changes in leaflets and that varicose veins can occur below or between competent valves.[13]

The primary vein wall weakness theory states that varicose veins develop from a defect in vein wall integrity rather than from a problem within the valves. The components of a normal vein wall include collagen matrix that provides strength, elastic fibers that provide compliance, and 3 smooth muscle layers (circular media surrounded by longitudinal intimal and adventitial layers) that control vascular tone. Histologic studies show that, compared with normal veins, varicose veins show proliferation of the collagen matrix with disruption and distortion of the muscle fiber layers. In the most diseased areas, the muscle layer is completely disrupted, leaving only elastic tissue and collagen as the sole components of the vein wall. This histologic alteration in turn causes loss of contractility, sagging of the muscular grid, and vessel dilatation in response to venous hypertension. The characteristic serpiginous appearance of varicose veins reflects segments of dilatation interspersed between segments of normal vein.[14]

Various factors influence the development of CVI:

Venous Stasis

This concept suggests that stagnant accumulation of blood in tortuous, nonfunctioning, dilated skin veins results in subsequent tissue anoxia and cell death leading to skin changes and ulceration. Arteriovenous fistulae in limbs with varicosities have also been attributed to low oxygen content and CVI skin changes.[15]

Venous Hypertension

This concept has been attributed to muscle pump dysfunction and venous ulceration. It has been hypothesized that venous hydrostatic pressure is equal in the deep and superficial venous systems both at rest and in the erect position. During calf muscle contraction, the pressure in the deep veins increases more than in the superficial veins. However, valve closure prevents the pressure from being transmitted to the superficial veins. In contrast, pump dysfunction or valvular incompetence causes venous pressure to be transmitted to the superficial veins leading to CVI symptoms and ulceration.[16–19]

Fibrin Cuff

Pericapillary fibrin cuff has been associated with restriction of oxygen diffusion across the vessel wall leading to edema and dermatosclerotic skin changes. Pericapillary fibrin cuffs may act as a barrier, a marker for endothelial cell damage, or as part of an overall mechanism of macromolecular leakage and trapping.[20]

Water Hammer Effect

This theory is the most widespread pathogenesis of CVI. It contends that reflux is mainly transmitted to the superficial veins through perforators. Studies by Raju and Fredericks have shown that this effect explains and correlates with most venous ulceration cases. At rest 20% to 25% of patients might have normal ambulatory venous pressure; nonetheless Valsalva-induced venous hypertension transmits pressure, resulting in skin changes and ulceration.[18,21]

Leukocyte Trapping

The concept of leukocyte trapping was described very early and explains most of the CVI symptoms. Because of stasis and venous pressure changes, margination of the white cells occurs resulting in capillary plugging with further tissue hypoxia and damage. These white cells also activate free radicals and cytokine (interleukin-1, tumor necrosis factor) release, resulting in tissue damage and apoptosis.[22] Unifying concepts of leukocyte trapping and venous hypertension have also been proposed.[16]

CLINICAL MANIFESTATIONS

CVI manifests at different stages. At first it may present as telangiectasia or reticular veins and advance to more complicated stages such as skin fibrosis and venous ulceration. The main

clinical features of CVI are leg pain, leg edema, varicose veins, and cutaneous changes. Various pathogenic mechanisms produce different clinical manifestations (incompetent valves as varicose veins, venous obstruction as leg edema, and pump dysfunction as either symptom).

Varicose veins are dilated superficial veins that become progressively more tortuous and large. They are prone to develop bouts of superficial thrombophlebitis.

Edema begins in the perimalleolar region but ascends. Leg edema with dependent accumulation of fluid. The leg pain or discomfort is described as heaviness or aching after prolonged standing and is relieved by elevation of the leg. Edema produces pain by increasing intracompartmental and subcutaneous volume and pressure. Tenderness along varicose veins is in the result of venous distention. Obstruction of the deep venous system may lead to venous claudication, or intense leg cramping with ambulation.

Cutaneous changes include skin hyperpigmentation with hemosiderin deposition and eczematous dermatitis. Fibrosis also develops in the dermis and subcutaneous tissue (lipodermatosclerosis). There is an increased risk of cellulitis, leg ulceration, and delayed wound healing. Longstanding CVI may also lead to the development of lymphedema, representing a combined disease process.[23]

Several tools have been described to assess the severity of CVI and also monitor the effects of therapy. The CEAP (clinical, etiology, anatomic, pathophysiology) classification was the initial module developed by an international consensus conference to provide a basis for uniformity in reporting, diagnosing, and treating CVI. The CEAP classification takes into account all the diagnostic variables of CVI. In 2004, the CEAP revised consensus refined the class definitions and improved reproducibility of physician observations (**Box 1**, **Table 1**).[24–26] Because of limitations of the CEAP clinical classification in delineating categories, a venous severity score was developed to complement the CEAP classification. The venous clinical severity score consists of 10 attributes (pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, number of ulcers, duration of ulcers, size of ulcers, and compressive therapy) with 4 grades (absent, mild, moderate, severe). The venous anatomic segmental score assigns a numerical value to segments of the venous system in the lower extremity that account for both reflux and obstruction (**Table 2**).[27,28] The venous disability score comes from the ability to perform normal activities of daily living with or without compressive stockings. The venous severity score has been mainly shown to be useful in evaluating the response to treatment.[29] The REVAS classification identifies patients with recurrent varices after surgery. In conjugation with the CEAP classification, it adds valuable information in evaluating patients with chronic venous disease after surgery.[30]

Box 1
Advanced CEAP classification

Superficial Veins

1. Telangiectasias/reticular veins
2. GSV above knee
3. GSV below knee
4. Lesser saphenous vein
5. Nonsaphenous veins

Deep veins

6. Inferior vena cava
7. Common iliac vein
8. Internal iliac vein
9. External iliac vein
10. Pelvic: gonadal, broad ligament veins, other
11. Common femoral vein
12. Deep femoral vein
13. Femoral vein
14. Popliteal vein
15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
16. Muscular: gastrocnemial, soleal veins, other

Perforating veins

17. Thigh
18. Calf

This classification is the same as the basic classification with the addition that any of 18 named venous segments can be used as locators for venous disorders.

From Eklof B, Rutherford R, Bergan J, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248.

CVI: QOL AND ECONOMIC IMPACT

The impact of venous insufficiency on QOL was investigated by the Venous Insufficiency Epidemiologic and Economical Study (VEINES), an international survey. In VEINES, 65.2% of subjects with varicose veins had additional venous disease processes (edema, skin changes, ulceration),

Table 1
CEAP classification for chronic venous disorders

Clinical classification	
C0	No visible or palpable signs of venous disease
C1	Telangiectasias, reticular veins, malleolar flares
C2	Varicose veins
C3	Edema without skin changes
C4	Skin changes attribute to venous disease (eg, pigmentation, venous eczema, lipodermatosclerosis)
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Skin changes as defined earlier with healed ulceration
C6	Skin changes as defined earlier with active ulceration
S	Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction
A	Asymptomatic
Causal classification	
Ec	Congenital
Ep	Primary
Es	Secondary (postthrombotic)
En	No venous cause identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

Therapy may alter the clinical category of chronic venous disease. Limbs should therefore be reclassified after any form of medical or surgical treatment.

Adapted from Eklof B, Rutherford R, Bergan J, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248.

and both physical and mental QOL scores concomitant with the severity of their venous disease.[31] In the most severe cases, those in which venous ulceration was present, the QOL rating was worse than with chronic lung disease, back pain, or arthritis.[32] The VEINES study has 2 components: a QOL assessment (VEINES-QOL), which estimates disease effect, and a symptoms questionnaire, which measures symptoms prevalence (VEINES-Sym). Other assessment programs used in clinical practice to assess the impact of CVI on QOL are the Aberdeen Varicose Vein Questionnaire (AVVQ), Charing Cross Venous Ulcer Questionnaire (CXVUQ), and Specific Quality of Life and Outcomes Response–Venous (SQOR-V) questionnaire.[33,34]

DIAGNOSIS OF CVI

Multiple modalities have shown benefit in diagnosing the cause of CVI. Physical examination is the most important one. A thorough physical examination is usually enough to diagnose CVI. It also provides guidance during therapy.

PHYSICAL EXAMINATION

Physical examination involves inspection of the skin for signs of CVI. Skin changes such as hyperpigmentation, stasis dermatitis, atrophic blanche (white scarring at the site of previous ulcerations with a paucity of capillaries), or lipodermatosclerosis are frequently seen. Varicose veins follow the path of superficial vein insufficiency.[23] Tenderness

Table 2
Revised venous clinical severity score

	Severity Score			
Attribute	**None: 0**	**Mild: 1**	**Moderate: 2**	**Severe: 3**
Pain or other discomfort (ie, aching, heaviness, fatigue, soreness, burning) Presumes venous origin	—	Occasional pain or other discomfort (not restricting regular daily activities)	Daily pain or other discomfort (interfering with but not preventing regular daily activities)	Daily pain or discomfort (limits most regular daily activities)
Varicose veins Varicose veins must be ≥3 mm in diameter to qualify in the standing position	—	Few: scattered (ie, isolated branch varicosities or clusters) Also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema Presumes venous origin	—	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation caused by other chronic diseases (ie, vasculitis purpura)	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (ie, erythema, cellulitis, venous eczema, dermatitis)	—	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (ie, chronic edema with fibrosis, hypodermitis). Includes white atrophy and lipodermatosclerosis	—	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Active ulcer number	0	1	2	3
Active ulcer duration (longest active)	N/A	<3 mo	>3 mo but <1 y	Not healed for >1 y
Active ulcer size (largest active)	N/A	Diameter<2 cm	Diameter 2–6 cm	Diameter>6 cm
Use of compression therapy	Not used	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings

Abbreviation: N/A, not applicable.

From Vasquez MA, Rabe E, McLafferty RB, et al, American Venous Forum Ad Hoc Outcomes Working Group. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52(5):1387–96.

is almost always observed along the varicose veins. Skin edema is usually pitting, unless chronic edema makes the skin brawny and difficult to examine. Venous ulcerations are most common along the medial supramalleolar area at the site of a major perforator vein of high hydrostatic pressure. The classic tourniquet or Trendelenburg test may be performed at the bedside to help distinguish between deep and superficial reflux. The test is performed with the patient lying down to empty the lower extremity veins. The upright posture is then resumed after applying a tourniquet or using manual compression at various levels. In the presence of superficial disease the varicose veins remain collapsed if compression is distal to the point of reflux. With deep (or combined) venous insufficiency, the varicose veins appear despite the use of the tourniquet or manual compression. Although useful to help determine the distribution of venous insufficiency, this test does not help to determine the extent or severity of disease or to provide information about the cause.[35]

DUPLEX IMAGING

Doppler is an important tool in diagnosing CVI and monitoring therapy. The goal of Duplex imaging is to identify any obstruction or reflux in the deep veins, look for any presence of deep vein thrombosis, diagnose reflux in the superficial veins (great saphenous vein, perforator vein, and small saphenous vein), and localize branch varicose veins and perforator veins. Low-frequency transducers (2–3 MHz) are usually used to evaluate the iliac veins and inferior vena cava. High-frequency transducers (5–10 MHz) are used to evaluate lower extremity veins. Reflux thresholds for deep veins are greater than 1000 milliseconds, superficial veins greater than 500 milliseconds, and for perforators greater than 350 milliseconds.[36,37] The most common site for reflux is the confluence of the GSV and common femoral vein, contributing to 65% of all cases, in a review of 2036 patients.[38] However, duplex has a weak correlation with the severity of the disease. Physical examination and duplex scan can guide most therapy. Venous compressibility complimented with flow characteristics are key element in excluding thrombosis. The use of a cuff inflation-deflation method with rapid cuff deflation in the standing position is preferred to induce reflux.[39]

PLETHYSMOGRAPHY

Photoplethysmography (PPG) may be used to establish a diagnosis of CVI.[38] Relative changes in blood volume in the dermis of the limb can be determined by measuring the backscatter of light emitted from a diode with a photosensor. The venous refill time is the time required for the PPG tracing to return to 90% of the baseline after cessation of calf contraction. A venous refill time less than 18 to 20 seconds, depending on the patient's position during the study, indicates CVI. A venous refill time greater than 20 seconds suggests normal venous filling. The use of a tourniquet or low-pressure cuff allows superficial disease to be distinguished from deep venous disease. Refill time depends on several factors, including the volume of reflux and the vessel diameter. This technique has been used to assess emptying of the venous system during calf muscle contraction and venous outflow. PPG may provide an assessment of the overall physiologic function of the venous system, but it is most useful in determining the absence or presence of disease.[40,41]

Air plethysmography (APG) has the ability to measure each potential component of the pathophysiologic mechanisms of CVI: reflux, obstruction, and muscle pump dysfunction. Venous outflow is assessed during rapid cuff deflation on an elevated limb that has a proximal venous occlusion cuff applied. The outflow fraction at 1 second (or venous outflow at 1 second expressed as a percentage of the total venous volume) is the primary parameter used to evaluate the adequacy of outflow. A normal venous filling index is less than 2 mL/s, whereas higher levels (>4–7 mL/s) have been found to correlate with the severity of CVI. Complications of CVI, such as ulceration, have been shown to correlate with the severity of reflux assessed with the venous filling index and ejection capacity.[42,43]

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE VENOGRAPHY

It is used in identifying more rare and complex causes of CVI. Computed tomography is an important tool in recognizing thromboembolic disease in the proximal veins, whereas magnetic resonance venography plays a major role in determining the age of thrombus. CVI syndromes such as May-Thurner syndrome, nutcracker syndrome, pelvic congestion syndrome, venous malformations, and atrioventricular malformations can be diagnosed effectively via these advanced imaging techniques.[44,45]

CVI TREATMENT

Initial Treatment: Behavioral Measures and Compression Garments

Conservative measures have been proposed to reduce symptoms caused by CVI and prevent

secondary complications and progression of disease. Behavioral measures such as elevating the legs to minimize edema and reducing intra-abdominal pressure should be advocated. The use of compressive stockings is the mainstay of conservative management. The Bisgaard regimen has been proposed for the healing of venous ulcers. This regimen has 4 components: patient education, foot elevation, elastic compression garments, and evaluation subsequently with CEAP classification. Non-elastic ambulatory bellow-knee compression aggressively counters the impact of reflux from venous pump failure. Compression therapy is used for venous leg ulcers and can decrease blood vessel diameter and pressure, preventing blood from flowing backwards.[46,47] Compression is also used to decrease release of inflammatory cytokines, reduce capillary leak, prevent swelling, and delay clotting by decreasing activation of thrombin and increasing that of plasmin. Compression is applied using elastic bandages or boots specifically designed for the purpose. It is not clear whether non-elastic systems are better than multilayer elastic ones. Patients should wear as much compression as it is comfortable. The type of dressing applied beneath the compression does not seem to matter, and hydrocolloid has not been shown to be superior to simple low-adherent dressings. The use of graded elastic compressive stockings (with 20–50 mm Hg of tension) is well established in the treatment of CVI. Treatment with 30 to 40 mm Hg compression stockings results in significant improvement in pain, swelling, skin pigmentation, activity, and overall well-being as long as a compliance of 70% to 80% is achieved.[48] In patients with venous ulcers, graded compression stockings and other compressive bandage modalities are effective in both healing and preventing recurrences of ulcers. With a structured regimen of compression therapy, 93% of patients with venous ulcers can achieve complete healing at a mean of 5.3 months. Compression stockings have been shown to reduce residual volume fraction, an indicator of improvement in the calf muscle pump function, and to reduce reflux in vein segments.[49]

Failure of Conservative Therapy

Symptomatic patients who fail conservative therapy should be followed closely. These patients should have venous duplex studies and/or air plethysmography if conservative therapy fails or if there is any progression of symptoms in CEAP class. Further treatment is based on the results of noninvasive studies and specific treatment is based on severity of disease, with CEAP clinical classes 4 to 6 often requiring invasive treatment. Referral to a vascular specialist should be made for patients with CEAP classes 4 to 6 (and probably for CEAP class 3 with extensive edema). These patients with uncorrected advanced CVI are at risk for ulceration, recurrent ulceration, and nonhealing venous ulcers with progression to infection and lymphedema.

NONINVASIVE STUDY: VENOUS REFLUX DISEASE

Superficial Venous Reflux

Various therapies have been used for superficial venous reflux.

Cool-touch laser

The first procedure to replace ligation and stripping of the GSV was radiofrequency-mediated thermal ablation. Long-term experience with cool-touch endovenous laser ablation showed that tissue water within the vein wall has a specific target chromophore of 1320-nm laser and the presence or absence of red blood cells within the vessels is unimportant. Water is the main component in the walls of a vein. They are composed mainly of water and collagen. The chromophore for the 1.32-μm or 1320-nm wavelength laser is water. This wavelength penetrates as deep as 500 μm in tissue. This provides a safety margin by reducing the risks of penetration of laser energy beyond the vein wall. For even greater control of energy distribution, the 1320-nm CTEV is coupled with an automatic pullback device that can retract the fiber at a rate of 0.5, 1, or 2 mm/s.[50] Endovenous laser treatments at 810, 940, and 980 nm are designed to produce endothelial and vein wall shrinkage by nonspecific heating of the vessel.[51] This nonspecific heating is accomplished by creating a superheated coagulum at the fiber tip or by the heating of hemoglobin within red blood cells to create steam bubbles at extremely high temperatures. Without the presence of blood in the vein, such as an experimental situation in which the vein is filled with saline, laser-induced vessel wall injury is confined to the site of direct laser impact. By contrast, blood-filled veins show extensive thermal damage even in remote areas from the laser fiber, including the vein wall opposite to the laser impact. In the absence of blood, the situation is even worse; the areas of vein wall injury or burning result in intense postoperative pain and early recanalization of the treated vein. More importantly, superheating of hemoglobin leads to high temperatures (often higher than 1200°C), which results in vein perforations, hematoma, and postoperative pain.[52]

RFA therapy

Few studies have shown the superiority of RFA compared with EVLA in terms of pain, bruising, and postprocedure recovery, with GSV occlusion rates being comparable. The LARA study was a randomized control trial conducted to determine whether RFA of the GSV is associated with less pain and bruising than EVLA in 87 leg interventions.[53] In the bilateral group, RFA resulted in significantly less pain than EVLA on days 2 to 11 after surgery. RFA also resulted in significantly less bruising than EVLA on days 3 to 9. There were no significant differences in mean postoperative pain, bruising, and activity scores in the unilateral group. Both RFA and EVLA resulted in occlusion rates of 95% at 10 days after surgery.[54] The RECOVERY study randomized 87 veins in 69 patients to Closure FAST or 980-nm EVLA treatment of the GSV. It was a multicenter, prospective, randomized, single-blinded trial, performed at 5 American sites and 1 European site. All scores referable to pain, ecchymosis, and tenderness were statistically lower in the Closure FAST group at 48 hours, 1 week, and 2 weeks. Minor complications were more prevalent in the EVLA group ($P = .0210$); there were no major complications. Venous clinical severity scores and QOL measures were statistically lower in the Closure FAST group at 48 hours, 1 week, and 2 weeks. Radiofrequency thermal ablation was significantly superior to EVLA as measured by a comprehensive array of postprocedural recovery and QOL parameters.[55] The EVOLVeS trial studied the clinical outcomes of rates of recurrent varicosities, neovascularization, ultrasonography changes of the GSV, and QOL changes in patients undergoing RFA, ligation, or vein stripping. 2-year clinical results of radiofrequency obliteration are at least equal to those after high ligation and stripping of the GSV.[56]

Venous sclerotherapy

This treatment modality is used for obliterating telangiectasias, varicose veins, and venous segments with reflux. Sclerotherapy may be used as a primary treatment or in conjunction with surgical procedures in the correction of CVI. Sclerotherapy is indicated for a variety of conditions including spider veins (<1 mm), venous lakes, varicose veins of 1 to 4 mm in diameter, bleeding varicosities, and small cavernous hemangiomas (vascular malformation). The terminal interruption of reflux source technique involves blocking off the veins that drain the ulcer bed using Sotradecol or Polidocanol foam, administered under ultrasonography guidance.[57]

Patients with CVI need to be evaluated for surgical treatment if they have a nonhealing ulcer refractory to conservative and minimally invasive therapy resulting in delayed healing, recurrent varicose veins, CVI with disabling symptoms, persistent discomfort refractory to other therapy, noncompliant patients with conservative therapy, and to complement therapy with conservative measures.

Ligation and venous phlebectomy

Surgical ligation of the GSV has been shown to improve symptoms in patient with CEAP classes from 2 to 6. GSV removal with high ligation of the saphenofemoral junction has long been considered the standard treatment for patients with significant venous reflux, nonhealing ulcers, and symptomatic patients with concomitant deep venous reflux.[58] Transilluminated power phlebectomy (or TriVex) is a new surgical technique that uses tumescent dissection, transillumination, and powered phlebectomy. A prospective randomized controlled trial of 141 patients comparing conventional versus powered phlebectomy has shown a trend toward reduced operating time in extensive varicosities, and significantly fewer incisions. There was no difference in nerve injury, bruising, and cosmetic score during follow-up.[59] The ESCHAR study evaluated around 500 patients with venous ulcer and reflux of superficial and deep venous systems and randomized them to either conventional saphenous vein surgery with compression or to compression alone. The study showed a significant reduction in ulcer recurrence at 12 months in favor of surgery with compression compared with compression alone (12% vs 28%).[60] A follow-up study to observe the improvement in perforating vein incompetence included 261 patients from the ESCHAR trial. Surgical correction of superficial reflux was shown to abolish incompetence in some calf perforators but also helped wound healing and reflux symptoms by preventing development of new perforator incompetence.[61]

DEEP VENOUS REFLUX

Valve Reconstruction Surgery/Valvuloplasty

CVI has been shown to be partially attributable to venous valve injury and incompetence. Venous valve reconstruction of the deep vein valves has been performed in selected patients with advanced CVI who have recurrent ulceration with severe and disabling symptoms.[62] Open valve surgery was initially performed to repair the femoral vein valve but subsequently transcommissural valvuloplasty was developed for venous repair. Venous valvuloplasty has been shown to provide 59% competency and 63% ulcer-free recurrence at 30 months. Complications from valvuloplasty

include bleeding (because patients need to remain anticoagulated), DVT, pulmonary embolism, ulcer recurrence, and wound infections.[63] This procedure is reserved for selected patients refractory to other therapies. Valve replacements and transposition procedures have been attempted successfully when native valves have postthrombotic valve destruction (not amenable to valvuloplasty). Valve transposition has been performed with the axillary vein valve, profunda femoris valve, or cryopreserved valve allografts. Cryopreserved vein valve allografts have also been shown to have early thrombosis, poor patency and competency, as well as high patient morbidity, precluding their use as a primary intervention.[64]

PERFORATOR REFLUX

Subfascial Endoscopic Perforator Surgery

Perforator vein incompetence has been proposed as a cause for CVI. Some surgical options have been proposed for the treatment of incompetent perforators, including subfascial endoscopic perforator surgery (SEPS). This procedure involves ligation of the incompetent perforator veins by gaining access from a remote site on the leg that is away from the area with lipodermatosclerosis or ulcers. The North American Study Group performed a study with 146 patients showing cumulative ulcer healing at 1 year of 88% (median time to healing was 54 days). Concomitant ablation of superficial reflux and lack of deep venous obstruction predicted ulcer healing ($P<.05$). Clinical score improved from 8.93 to 3.98 at the last follow-up ($P<.0001$). Cumulative ulcer recurrence at 1 year was 16% and at 2 years was 28% (standard error, <10%). Postthrombotic limbs had a higher 2-year cumulative recurrence rate (46%) than did those limbs with primary valvular incompetence (20%; $P<.05$).[65] The interruption of perforators with ablation of superficial reflux is effective in decreasing the symptoms of CVI and rapidly healing ulcers. SEPS in conjunction with vein ablation showed better ulcer healing and improvement in clinical severity score.[66]

NONINVASIVE STUDY: CHRONIC VENOUS FLOW OBSTRUCTION

Endovascular therapy in the treatment of CVI has become increasingly important to restore outflow of the venous system and provide relief of obstruction. Approximately 10% to 30% of patients with severe CVI can be diagnosed with a significant abnormality in venous outflow involving iliac vein segments that contributes to persistent symptoms. Before endovascular therapy, iliac vein stenosis and obstruction causing CVI was treated with surgical procedures such as cross-femoral venous bypass or iliac vein reconstructions with prosthetic materials. Because of the success of venous stenting, surgical venous bypass is infrequently performed. In a large single-center series of 429 patients with CVI and outflow obstruction, iliac vein stenting resulted in significant clinical improvement: 50% of patients were completely relieved of pain and 33% experienced complete resolution of edema. Furthermore, 55% of patients with venous ulcers experienced complete healing of their ulcers. Patency of iliac vein stents is good, with a primary patency of 75% at 3 years. Close follow-up is mandatory to ensure that stent patency is maintained. Also mandatory is to intervene early in patients with recurrent symptoms that may indicate in-stent restenosis, which occurs in approximately23% of patients.[67,68]

NONINVASIVE STUDY: MUSCLE PUMP DYSFUNCTION

Abnormalities in the calf and foot muscle pumps play a significant role in the pathophysiology of CVI. Graded exercise programs have been used in an effort to rehabilitate the muscle pump and improve CVI symptoms. In a small controlled study, 31 patients with CEAP class 4 to 6 CVI were randomized to structured calf muscle exercise or routine daily activities. Venous hemodynamics were assessed with duplex ultrasonography, air plethysmography, and muscle strength assessed with a dynamometer. After 6 months, patients receiving a calf muscle exercise regimen had normalized their calf muscle pump function parameters but experienced no change in the amount of reflux or severity scores. Padberg and colleagues[69] concluded that structured exercise to reestablish calf muscle pump function in CVI may prove beneficial as a supplemental therapy to medical and surgical treatment in advanced disease.

REFERENCES

1. Beebe-Dimmer JL, Pfeifer JR, Engle JS, et al. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol 2005;15(3):175–84.
2. Callam MJ. Epidemiology of varicose veins. Br J Surg 1994;81:167–73.
3. Dwerryhouse S, Davies B, Harradine K, et al. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. J Vasc Surg 1999; 29:589–92.

4. Brand FN, Dannnenberg AL, Abbott RD, et al. The epidemiology of varicose veins: the Framingham study. Am J Prev Med 1988;4:96–101.
5. Sisto T, Reunanen A, Laurikka J, et al. Prevalence and risk factors of varicose veins in the lower extremities: Mini-Finland Health Survey. Eur J Surg 1995;161:405–14.
6. Evans CJ, Fowkes FG, Ruckley CV, et al. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health 1999;53:149–53.
7. Ruckley CV, Evans CJ, Allan PL, et al. Chronic venous insufficiency: clinical and duplex correlations. The Edinburgh Vein Study of venous disorders in the general population. J Vasc Surg 2002; 36(3):520–5.
8. Laurikka JO, Sisto T, Tarkka MR, et al. Risk indicators for varicose veins in forty- to sixty-year-olds in the Tampere varicose vein study. World J Surg 2002;26:648–51.
9. Ciardullo AV, Panico S, Bellati C, et al. High endogenous estradiol is associated with increased venous distensibility and clinical evidence of varicose veins in menopausal women. J Vasc Surg 2000;32:544–9.
10. Hirai M, Naiki K, Nakayama R. Prevalence and risk factors of varicose veins in Japanese women. Angiology 1990;41:228–32.
11. Anwa MA, Georgiadis KA, Shalhoub J, et al. A review of familial, genetic, and congenital aspects of primary varicose vein disease. Circ Cardiovasc Genet 2012;5:460–6. http://dx.doi.org/10.1161/CIRCGENETICS.112.963439.
12. Hobson J. Venous insufficiency at work. Angiology 1997;48:577–82.
13. Rose SS, Ahmed A. Some thoughts on the aetiology of varicose veins. J Cardiovasc Surg (Torino) 1986;27:534–43.
14. Lim CS, Davies AH. Pathogenesis of primary varicose veins. Br J Surg 2009;96:1231–42. http://dx.doi.org/10.1002/bjs.6798.
15. Gourdin FW, Smith JG Jr. Etiology of venous ulceration. South Med J 1993;86(10):1142–6.
16. Mustoe T. Understanding chronic wounds: a unifying hypothesis on their pathogenesis and implications for therapy. Am J Surg 2004;187(5A): 65S–70S.
17. Recek C. Calf pump activity influencing venous hemodynamics in the lower extremity. Int J Angiol 2013;22(1):23–30.
18. Recek C. Impact of the calf perforators on the venous hemodynamics in primary varicose veins. J Cardiovasc Surg (Torino) 2006;47(6):629–35.
19. Stanley AC, Lounsbury KM, Corrow K, et al. Pressure elevation slows the fibroblast response to wound healing. J Vasc Surg 2005;42(3):546–51.
20. Van de Scheur M, Falanga V. Pericapillary fibrin cuffs in venous disease. A reappraisal. Dermatol Surg 1997;23(10):955–9.
21. Raju S, Fredericks R. Evaluation of methods for detecting venous reflux. Perspectives in venous insufficiency. Arch Surg 1990;125(11):1463–7.
22. Hahn TL, Unthank JL, Lalka SG. Increased hind limb leukocyte concentration in a chronic rodent model of venous hypertension. J Surg Res 1999; 81(1):38–41.
23. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation 2005;111:2398–409. http://dx.doi.org/10.1161/01.CIR.0000164199.72440.08.
24. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. J Vasc Surg 1995;21:635–45.
25. Eklof B, Rutherford R, Bergan J, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40: 1248.
26. Carpentier PH, Cornu-Thenard A, Uhl JF, et al, Societe Francaise de Medecine Vasculaire, European Working Group on the Clinical Characterization of Venous Disorders. Appraisal of the information content of the C classes of CEAP clinical classification of chronic venous disorders: a multicenter evaluation of 872 patients. J Vasc Surg 2003;37:827–33.
27. Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307–12.
28. Vasquez MA, Rabe E, McLafferty RB, et al, American Venous Forum Ad Hoc Outcomes Working Group. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52(5):1387–96.
29. Kakkos SK, Rivera MA, Matsagas MI, et al. Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003;38:224–8.
30. Perrin MR, Labropoulos N, Leon LR Jr. Presentation of the patient with recurrent varices after surgery (REVAS). J Vasc Surg 2006;43(2):327–34.
31. Abenhaim L, Kurz X. The VEINES study (VEnous INsufficiency Epidemiologic and economic Study): an international cohort study on chronic venous disorders of the leg. Angiology 1997;48:59–66.
32. Kurz X, Lamping DL, Kahn SR, et al. Do varicose veins affect quality of life? Results of an international population-based study. J Vasc Surg 2001; 34:641–8.
33. Lamping DL, Schroter S, Kurz X, et al. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. J Vasc Surg 2003;37(2):410–9.

34. Kahn SR, Lamping DL, Ducruet T, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. J Clin Epidemiol 2006;59(10): 1049–56.
35. Bradbury A. Clinical assessment of patients with venous disease. In: Gloviczki P, Yao JS, editors. Handbook of venous disorders. 2nd edition. New York: Arnold; 2001. p. 71–83.
36. Van Bemmelen PS, Bedford G, Beach K, et al. Quantitative segmental evaluation of venous valvular reflux with duplex ultrasound scanning. J Vasc Surg 1989;10(4):425–31.
37. Malgor RD, Labropoulos N. Diagnosis of venous disease with duplex ultrasound. Phlebology 2013; 28(Suppl 1):158–61.
38. García-Gimeno M, Rodríguez-Camarero S, Tagarro-Villalba S, et al. Duplex mapping of 2036 primary varicose veins. J Vasc Surg 2009;49(3): 681–9.
39. Markel A, Meissner MH, Manzo RA, et al. A comparison of the cuff deflation method with Valsalva's maneuver and limb compression in detecting venous valvular reflux. Arch Surg 1994;129: 701–5.
40. Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. Circulation 2000;102:e126–63.
41. Abramowitz HB, Queral LA, Finn WR, et al. The use of photoplethsmography in the assessment of venous insufficiency: a comparison to venous pressure measurements. Surgery 1979;86:434–41.
42. Owens LV, Farber MA, Young ML. The value of air plethysmography in predicting clinical outcome after surgical treatment of chronic venous insufficiency. J Vasc Surg 2000;32:961–8.
43. Gillespie DL, Cordts PR, Hartono C, et al. The role of air plethysmography in monitoring results of venous surgery. J Vasc Surg 1992;16:674–8.
44. Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg 2007;46(Suppl S):4S–24S.
45. Davies MG, Lumsde AB, editors. Chronic venous insufficiency, vol. 1. 2011.
46. Van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. BMJ 2010;341: 1092–6.
47. Motykie GD, Caprini JA, Arcelus JI, et al. Evaluation of therapeutic compression stockings in the treatment of chronic venous insufficiency. Dermatol Surg 1999;25:116–20.
48. Mayberry JC, Moneta GL, Taylor LM, et al. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. Surgery 1991;109: 575–81.
49. Begbuna V, Delis KT, Nicolaides AN, et al. Effect of elastic compression stockings on venous hemodynamics during walking. J Vasc Surg 2003; 37:420–5.
50. Goldman MP, Mauricio M, Rao J. Intravascular 1320-nm laser closure of the great saphenous vein: a 6- to 12-month follow-up study. Dermatol Surg 2004;30(11):1380–5.
51. Weiss RA. Comparison of endovenous radiofrequency versus 810 nm diode laser occlusion of large veins in an animal model. Dermatol Surg 2002;28(1):56–61.
52. 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(7):596–600.
53. Goode SD, Chowdhury A, Crockett M, et al. Laser and radiofrequency ablation study (LARA study): a randomized study comparing radiofrequency ablation and endovenous laser ablation (810 nm). Eur J Vasc Endovasc Surg 2010;40(2):246–53.
54. Nordon IM, Hinchliffe RJ, Brar R, et al. A prospective double blind randomized controlled trial of radiofrequency versus laser treatment of the great saphenous vein in patients with varicose veins. Ann Surg 2011;254(6):876–81.
55. Lurie F, Creton D, Eklof B, et al. Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow-up. Eur J Vasc Endovasc Surg 2005;29:67–73.
56. Almeida JI, Kaufman J, Göckeritz O, et al. Radiofrequency endovenous closure FAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol 2009;20(6):752–9.
57. Bush R. New technique to heal venous ulcers: terminal interruption of the reflux source (TIRS). Perspect Vasc Surg Endovasc Ther 2010;22(3):194–9.
58. Sarin S, Scurr JH, Coleridge Smith PD. Stripping of the long saphenous vein in the treatment of primary varicose veins. Br J Surg 1994;81:1455–8.
59. Aremu MA, Mahendran B, Butcher W, et al. Prospective randomized controlled trial: conventional versus powered phlebectomy. J Vasc Surg 2004; 39(1):88–94.
60. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004; 363(9424):1854–9.
61. Gohel MS, Barwell JR, Wakely C, et al. The influence of superficial venous surgery and compression on incompetent calf perforators in chronic venous leg ulceration. Eur J Vasc Endovasc Surg 2005;29(1):78–82.
62. Kistner RL. Surgical repair of the incompetent femoral vein valve. Arch Surg 1975;110:1336–42.

63. Raju S, Berry MA, Neglen P. Transcommissural valvuloplasty: technique and results. J Vasc Surg 2000;32:969–76.
64. Neglen P, Raju S. Venous reflux repair with cryopreserved vein valves. J Vasc Surg 2003;38:1139–40.
65. Gloviczki P, Bergan JJ, Rhodes JM, et al. Mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American subfascial endoscopic perforator surgery registry. The North American Study Group. J Vasc Surg 1999;29:489–502.
66. Bianchi C, Ballard JL, Abou-Zamzam AM, et al. Subfascial endoscopic perforator vein surgery combined with saphenous vein ablation: results and critical analysis. J Vasc Surg 2003; 38:67–71.
67. Danza R, Navarro T, Baldizan J. Reconstructive surgery in chronic venous obstruction of the lower limbs. J Cardiovasc Surg 1991;32:98–103.
68. Neglen P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg 2002;35:694–700.
69. Padberg FT, Johnston MV, Sisto SA. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. J Vasc Surg 2004;39:79–87.