Chronic Venous Insufficiency and Varicose Veins

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A 52-year-old receptionist presents with an ulcer on her ankle that has persisted for a year. The use of narcotic analgesics once or twice a day and elevation of the leg reduce the pain. She does not have a history of diabetes and does not smoke. Physical examination reveals an ulcer, approximately 5 cm in diameter, above the medial malleolus. The ulcer has a clean bed of granulation and is surrounded by hyperpigmented skin. Pedal pulses are easily palpable. How should she be evaluated and treated?

THE CLINICAL PROBLEM

Chronic venous insufficiency is associated with a wide clinical spectrum ranging from cosmetic problems to severe symptoms, including ulceration.1-6 The incidence of this condition increases with age and is higher among women than among men. Chronic venous insufficiency worsens with pregnancy.

The venous system of the lower limbs consists of an interconnected network of superficial veins, perforator veins, and deep veins. The severity of symptoms tends to increase according to the number of systems affected.6

Varices are caused by systemic weakness in the vein wall; thus, their recurrence is common.7 Varicose changes may involve the great and small saphenous veins (“truncal varices”), their tributaries (“branch varicosities”), or both. Valve reflux in the saphenous veins is often associated with varices, and this may worsen the dilatation of branch varicosities.

Most cases of chronic deep venous disease have a nonthrombotic (primary or idiopathic) or post-thrombotic (secondary) cause. Either type can involve reflux, obstruction, or a combination of the two, which is most common.8,9 Patients with isolated reflux in the perforator veins or segmental deep reflux (single valve) are generally asymptomatic;8,10; reflux at multiple valve sites is required for symptom expression. Axial reflux with no competent femoropopliteal valves is a highly symptomatic, severe form.

Obstruction in the iliac vein plays a major role in chronic venous insufficiency, more so than obstructive lesions at the levels of the crural and femoral veins and the inferior vena cava.8,9,11-13 Iliac-vein lesions, which are often occult, are the basis of symptoms in patients with post-thrombotic disease, even when venous obstruction is more obvious elsewhere. Nonthrombotic obstructions occur in the iliac vein where it is crossed by the iliac or hypogastric artery, and they are thought to be caused by the trauma of arterial pulsations.9 Such lesions are present in about 60% of the asymptomatic general population14,15 but are found in more than 90%
of symptomatic patients.\textsuperscript{9} In many cases, correction of these lesions may result in resolution of symptoms.\textsuperscript{8}

Tissue damage in chronic venous insufficiency results from perivascular inflammation caused by a variety of cytokine mechanisms\textsuperscript{16} that weaken the usual dermal barrier against pathogens and allergens.\textsuperscript{17} Lymphatic dysfunction, detected by means of nucleotide lymphangiography, is present in up to one third of cases of chronic venous insufficiency and may resolve with correction of the venous abnormalities.\textsuperscript{18}

**Classification**

Chronic venous insufficiency is classified with the use of the CEAP (clinical, etiologic, anatomical, and pathophysiological) system; (see the Table in the Supplementary Appendix, available with the full text of this article at NEJM.org).\textsuperscript{21} Tests (as described below) are necessary for the proper use of this system. An adjunctive scoring system allows for a standardized clinical evaluation and assessment of clinical severity (Table 2).\textsuperscript{22} Common clinical patterns are shown in Table 3.

**Imaging**

Duplex ultrasonography is used routinely in the evaluation of suspected venous disease; when performed by an experienced technologist, it can detect acute or chronic thrombosis, post-thrombotic changes, patterns of obstructive flow, and reflux. Duplex ultrasonography performed with the standard technique is unreliable for assessment of the iliac and caval veins. Reflux in perforator veins that are smaller than 4 mm in diameter is not considered to be clinically significant.

Venography is recommended in patients with post-thrombotic disease, especially if intervention is planned, since it provides greater detail than duplex ultrasonography. Ascending venography with injection of contrast material into the foot is commonly used. However, visualization of the pelvic veins is often unsatisfactory with this technique, and transfemoral injection of contrast material may be required for sufficient opacification. The iliac veins should be assessed in patients with post-thrombotic disease, since these veins are commonly involved,\textsuperscript{23} and should also be considered in patients with nonthrombotic disease, if the clinical presentation is more severe than would be expected from the abnormalities detected in other veins of the lower limb.\textsuperscript{9} Although transfemoral venography can detect extensive iliac-vein lesions, it is unreliable for the detection of focal obstructions with a post-thrombotic or nonthrombotic cause.\textsuperscript{24} High-resolution magnetic resonance venography or computed tomography appears to be sensitive for focal iliac-vein lesions,\textsuperscript{15} but experience with these techniques is limited and their role in practice is uncertain. Intravascular ultrasonography allows definitive identification of focal lesions and can be used to guide correction of the obstruction with the use of a stent (Fig. 1 in the Supplementary Appendix)\textsuperscript{25-27}; however, this
technique may not be available and currently is not widely used for the evaluation of venous disease.

**TREATMENT OPTIONS**

Many patients with chronic venous insufficiency are anxious about “circulation problems” and fear the loss of limb or life because of arterial disease. Patients should be reassured regarding the distinction between these entities. Initial treatment should be conservative, starting with compression, as noted below. If compression is not feasible or is ineffective, specific corrective procedures, especially those that are minimally invasive, can be considered. In complex venous disease, comprehensive correction is neither feasible nor necessary; partial correction of multifocal disease often relieves symptoms.\(^9\,28,29\)

**COMPRESSION STOCKINGS**

Compression stockings are clinically effective, but they may not be usable for a wide variety of rea-

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**Table 1. Differential Diagnosis of Chronic Venous Insufficiency (CVI).**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Alternative Diagnoses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>Arterial claudication (peripheral arterial disease)</td>
<td>Arterial pressures in the ankle diminished during treadmill exercise testing in peripheral arterial disease†</td>
</tr>
<tr>
<td>Nocturnal pain</td>
<td>Ischemic pain at rest (peripheral arterial disease)</td>
<td>Arterial pressures in the ankle at rest show severe reduction in peripheral arterial disease†</td>
</tr>
<tr>
<td>Orthostatic pain</td>
<td>Sciatica, radiculopathy, spinal stenosis</td>
<td>Physical examination and MRI of spine can help differentiate these alternative diagnoses from CVI</td>
</tr>
<tr>
<td>Swelling</td>
<td>Congestive failure, renal disease, hypothyroidism, lymphedema</td>
<td>The first three disorders should be ruled out by appropriate clinical evaluation and laboratory tests; lymphedema cannot be differentiated clinically from CVI; isotope lymphangiography shows abnormalities in primary lymphedema but also in up to a third of cases of CVI due to secondary lymphatic damage; secondary lymphedema may resolve if underlying CVI is identified and corrected</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Acanthosis nigricans, hemosiderosis</td>
<td>Hyperpigmentation patterns are more diffuse or involve other areas in the body in nonvenous conditions; venous testing reveals advanced disease in cases of hyperpigmentation due to CVI</td>
</tr>
<tr>
<td>Stasis dermatitis</td>
<td>Psoriasis, periarteritis nodosa, allergic dermatitis, other causes of dermatitis</td>
<td>Skin biopsy can be definitive</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Ischemic ulcer (peripheral arterial disease), skin ulceration associated with rheumatic disease</td>
<td>Ischemic ulcers are deeper than ulcers due to CVI and often have gangrenous edges or a gangrenous base; pedal pulses are absent or weak, and arterial pressures in the ankle on Doppler ultrasonography are severely reduced in ischemic ulcers; systemic findings and serologic tests suggest rheumatic disease; palpable pedal pulses rule out most ischemic ulcers except those due to microangiopathy (diabetes) or arteriolitis (rheumatic disease)</td>
</tr>
<tr>
<td></td>
<td>Marjolin’s ulcer, ulcerating skin cancer, Kaposi’s sarcoma, pyoderma gangrenosum</td>
<td>Skin biopsy can differentiate these alternative diagnoses from CVI; venous studies reveal advanced disease in CVI</td>
</tr>
</tbody>
</table>

\(^*\) MRI denotes magnetic resonance imaging.  
† Since venous disease is quite common, it may coexist with other pathologic conditions. The arterial pressure of the ankle as measured by Doppler ultrasonography is reduced in combined arterial–venous disease; the arterial component is typically corrected first in such combined disease.
sons, including application difficulty (because of frailty or arthritis), physical constraints (e.g., limb obesity, contact dermatitis, or tender, fragile, or weepy skin), and coexisting arterial insufficiency. In a large community clinic, nearly 50% of patients were not able to use stockings for these reasons. Many patients who can wear stockings abandon them after initial use for a variety of stated reasons, such as tightness and warmth. Reported rates of noncompliance have ranged from 30 to 65%, even under clinical supervision in venous-ulcer clinics.

Stockings variably improve venous dynamics during orthostasis and may be removed during recumbency. Elastic stockings with graduated compression, which is preferred over nongraduated compression, are available in a wide range of compressive pressures (15 to 60 mm Hg) and lengths, with a choice of latex or synthetic material, allowing a switch in case of allergy. The below-the-knee portion of the stocking, where orthostatic venous pressure is highest, is the key functional element; the other features affect only comfort and fit. Stockings in the lower pressure range (class 1, 20 to 30 mm Hg) are sufficient to control edema, but higher pressures (class 2, >30 to 40 mm Hg; or class 3, >40 mm Hg) are recommended to control venous dermatitis or ulcers. Stockings commonly used for prophylaxis against deep venous thrombosis (e.g., T.E.D. stockings, Kendall) provide only 10 to 18 mm Hg of pressure at the ankle.

A Cochrane meta-analysis of 22 trials showed that compression stockings were more effective than no compression in healing venous ulcers, and higher compression pressures were more effective than lower ones; multilayer compression bandaging was superior to single-layer bandaging. The rate of efficacy of compression stockings for ulcer healing ranged from 23% to 84% (average, 50%) at 3 months to 1 year.

Once an ulcer heals, lifelong maintenance of compression is recommended to reduce the risk of recurrence. In a review involving 466 patients followed after initial healing of ulcers, the recurrence rate at 3 to 5 years was significantly higher among patients who were noncompliant with stockings than among those who were compliant (ranging from 32% to 64% vs. 19% to 34%, respectively, in different series). Noncompliance with prescribed stockings is the major cause of compression failure. In the Effect of Surgery and Compression on Healing and Recurrence study (Current Controlled Trials number, ISRCTN07549334), a randomized trial involving 500 limbs, initial ulcer healing was similar in patients treated with saphenectomy and compression therapy (93%) and in those treated with compression alone (89%), but ulcer recurrence at 4 years was significantly less common in the saphenectomy group (in 24% vs. 52% of patients). These findings suggest that correction of saphenous reflux may be necessary for durable relief of symptoms. This trial did not include a group of patients who underwent saphenectomy alone, without compression. Reports on case series.
have described rapid healing of ulcers after specific correction of reflux or obstruction (without compression) and with reductions in or discontinuation of the use of compression stockings afterward.

**Drug Therapy**

Pentoxifylline (Trental, Sanofi-Aventis), a drug that targets inflammatory cytokine release, leukocyte activation, and platelet aggregation at the microcirculatory level, is occasionally used for chronic venous insufficiency, but the reported efficacy is variable, and the benefit, when present, is generally small. In a meta-analysis of five trials involving a total of 445 patients, the combination of compression and pentoxifylline (1200 mg per day in most studies) modestly improved ulcer healing as compared with compression and placebo (relative risk, 1.3; 95% confidence interval, 1.1 to 1.5). The most common side effect of this medication is mild gastrointestinal discomfort.

Long-term application of topical agents and antibiotics should be discouraged because they may induce erythema from local allergic reactions due to compromise of the dermal barrier.

**Corrective Procedures**

**Ablation of Angiomas and Varicosities**

Spider angiomas and branch varicosities may warrant ablation because of symptoms or cosmetic concerns. Injections of a sclerosant and laser ablations are effective in more than 90% of patients. Multiple sessions are typically required for disseminated lesions. Complications include anaphylaxis in reaction to the chemical sclerosant, hypopigmentation or hyperpigmentation of the treated area, and local skin necrosis; the incidence of each of these complications is less than 5%. Extensive varices can be treated in a single session, while the patient is under general anesthesia, by surgical removal through minute incisions (“stab phlebectomy”) that generally do not result in permanent scars. Associated reflux of the saphenous veins is also treated concurrently to reduce the risk of recurrence and help relieve symptoms.

**Ablation of the Saphenous Veins**

Routine “stripping” of the saphenous veins has been replaced by percutaneous ablation performed in an outpatient setting with the use of radiofrequency or laser-energy sources; stripping is reserved for patients in whom these endovenous techniques are not successful. Foam sclerotherapy, an office-based procedure involving injection of a sclerosant foam (to increase the time and area of contact of the foam with the vein wall) into the saphenous veins is increasingly performed. In a meta-analysis of 64 studies involving 12,320 legs, the success rates for ablation (as measured by means of duplex ultrasonography) were 78% with the use of surgical stripping, 77% with the use of foam sclerotherapy, 84% with the use of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score 0</th>
<th>Score 1 (mild)</th>
<th>Score 2 (moderate)</th>
<th>Score 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>Occasional; no use of analgesics</td>
<td>Daily; occasional use of non-narcotic analgesics</td>
<td>Constant use of narcotic analgesics</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>None</td>
<td>Few, scattered</td>
<td>Multiple</td>
<td>Extensive</td>
</tr>
<tr>
<td>Edema</td>
<td>None</td>
<td>Evening, ankle only</td>
<td>Afternoon, above ankle</td>
<td>Morning above ankle</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>None</td>
<td>Limited</td>
<td>Diffuse over lower third of leg</td>
<td>Wide distribution</td>
</tr>
<tr>
<td>Inflammation and cellulitis</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Induration</td>
<td>None</td>
<td>Focal</td>
<td>Less than lower third of leg</td>
<td>Entire lower third of leg or more</td>
</tr>
<tr>
<td>Active ulcers — no.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Duration of active ulceration — mo</td>
<td>None</td>
<td>&lt;3</td>
<td>3–12</td>
<td>Not healed at &gt;12</td>
</tr>
<tr>
<td>Diameter of active ulcer — cm</td>
<td>None</td>
<td>&lt;2</td>
<td>2–6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>Use of stockings</td>
<td>None</td>
<td>Occasional</td>
<td>Most days</td>
<td>Constant</td>
</tr>
</tbody>
</table>

* An aggregate score for the limb is calculated by adding the individual component scores. The range of the total score is 0 to 30.
radiofrequency, and 94% with the use of laser treatment at a mean follow-up of 32 months. Major complications of these techniques include deep venous thrombosis, which occurs in less than 3% of patients. Local bruising, tenderness, and paresthesias occur in 7 to 15% of patients. Foam embolization to the retina or brain has occurred in 2 to 6% of patients after foam sclerotherapy; clinical symptoms are usually transient, but rare cases of stroke have been reported.

**Interruption of the Perforator Veins**

The current preferred technique for correction of reflux in the perforator vein is endoscopic resection (subfascial endoscopic perforator surgery, or SEPS). In a meta-analysis of 20 studies involving 1140 legs, SEPS resulted in ulcer healing in 88% of patients, with a recurrence rate of 13% at an average follow-up of 21 months; wound infections occurred in 6% of patients, hematoma in 8%, neuralgia in 7%, and deep venous thrombosis in 1%. SEPS is less effective in post-thrombotic disease than in primary disease, with a reported rate of ulcer recurrence of 56% at 5 years. Moreover, the role of interruption of the perforator vein is controversial because of doubts about the pathologic significance of reflux involving this vein and because its specific efficacy is uncertain, since ablation of the saphenous vein was also performed in most reported series.

**Treatment of Iliac-Vein Obstruction**

Percutaneous treatment of stenoses and chronic total occlusions of the iliac and caval veins with the use of stents (Fig. 2) on an outpatient basis is becoming increasingly common, although...
indications for stent placement and refinement of this procedure are still evolving. In a selected case series involving 982 legs with advanced clinical manifestations of chronic venous disease diagnosed by means of intravascular ultrasonography, stents were used for the treatment of iliac-vein obstructions\(^2,48\); the cumulative rates of stent patency at 5 years were 86% in cases of post-thrombotic disease and 100% in nonthrombotic cases. A reduction in pain of more than 3 points on a visual-analogue scale (with 0 indicating no pain and 10 indicating severe pain) was reported by 79% of the patients, with complete pain relief reported by 64%. A reduction in swelling (defined as an improvement of at least one grade in the clinical severity score) occurred in 58% of the patients, with complete resolution in 34%; stasis ulcers completely healed in 58%. Symptom relief was similar even if uncorrected reflux was present after stent placement. Complications included deep venous thrombosis (occurring in 1.5% of patients within 30 days after the procedure) and transient postoperative back pain (in 25% of the patients).

**Deep-Valve Reconstruction**

Deep venous valves with reflux due to either a non-thrombotic or post-thrombotic cause can be reconstructed by means of open surgery, but this procedure may not be available outside of specialized centers. It is generally performed only when other, simpler therapeutic options have been unsuccessful. In one case series involving reconstruction of 582 valve segments in 347 legs with venous ulcers,\(^49\) ulcer healing was reported in 93% of cases at 90 days; complications included deep venous thrombosis in 4% and wound complications in 7%. Cumulative rates of venous ulcer healing 5 to 10 years after deep-valve reconstruction have ranged from 53% to 73% in selected series of patients.\(^29,50-53\)

**Areas of Uncertainty**

The pathophysiology of chronic venous insufficiency, including the relative roles of obstruction and reflux, is not well understood. There have been few randomized comparative trials; available data are limited by the previous lack of both disease classification and measures of clinical severity. In addition, quantitative methods are lacking to measure reflux or obstruction at individual valve stations and vein segments in order to selectively target the correction of these abnormalities. Rapid technological advances have resulted in new ablation catheters, perforator-vein interruption devices, and ultrasound-guided sclerotherapy, but their roles in clinical practice remain uncertain.

**Guidelines**

The CEAP classification and the adjunctive clinical-severity scoring system jointly developed by the American Venous Forum and the Society for Vascular Surgery have been widely endorsed. The current review is in concordance with these systems. Currently there are no guidelines published by vascular societies in the United States for the treatment of chronic venous disease.

**Conclusions and Recommendations**

The patient described in the vignette has clinical manifestations of advanced chronic venous disease. Duplex ultrasonographic examination and additional tests when indicated can clarify whether the pathologic process is entirely confined to the superficial system (i.e., complex varicose disease with reflux of the saphenous vein) or reflects multisystem disease; results of these tests are used to classify disease according to the CEAP classification and to guide therapy. We would rec-
omitted intensive compression (four-layer bandaging) to heal the ulcer; in addition, pentoxifylline (1200 mg per day) could be considered. High-pressure (30 to 45 mm Hg) stockings should be prescribed for long-term use. Ablation of the saphenous vein also should be considered in order to minimize the risk of ulcer recurrence; if this procedure is not performed initially, we would recommend it as the next step (possibly with SEPS in cases of primary disease), if compression does not heal the ulcer in 3 to 4 months or if the persist. Ulcer healing is likely with these approaches, but the patient should understand that further intervention in the deep veins may be required in refractory cases.

Dr. Raju and Neglén report filing a patent application related to the use of intravascular ultrasonography in the diagnosis of venous disease but receiving no royalties. No other potential conflict of interest relevant to this article was reported.

**REFERENCES**


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