CLINICAL PRACTICE

Chronic Venous Insufficiency and Varicose Veins

Seshadri Raju, M.D., and Peter Neglén, M.D., Ph.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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[4,10]; 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 population[14,15] but are found in more than 90%

From the University of Mississippi Medical Center (S.R.) and River Oaks Hospital (S.R., P.N.), Jackson. Address reprint requests to Dr. Raju at 1020 River Oaks Dr., No. 420, Flowood, MS 39232, or at rajumd@earthlink.net.

N Engl J Med 2009;360:2319-27.

An audio version of this article is available at NEJM.org

of symptomatic patients.[9] In many cases, correction of these lesions may result in resolution of symptoms.[9]

Tissue damage in chronic venous insufficiency results from perivascular inflammation caused by a variety of cytokine mechanisms[16] that weaken the usual dermal barrier against pathogens and allergens.[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.[18]

STRATEGIES AND EVIDENCE

EVALUATION

Clinical features of chronic venous disease include limb pain, swelling, and stasis skin changes or frank ulceration. Itching, restless legs, and nocturnal leg cramps are common symptoms. The differential diagnosis of chronic venous insufficiency is shown in Table 1. Venous leg pain is characteristically worse when the leg is dependent and is relieved by elevation of the leg, use of support stockings, and walking — all measures that lower venous pressures. Many patients even sleep with their legs elevated. Patients may not report such habitual pain-relieving practices without direct questioning. Leg pain is absent in an estimated 20% of patients with other clinical features of chronic venous insufficiency, whereas it is the only clinical feature of chronic venous insufficiency in about 10% of patients.

Pain should be assessed with the use of a visual-analogue scale[19] and by asking about the type and frequency of analgesic use. Spider angiomas and varices, when symptomatic, are locally painful. A report of pain beyond the area of the varices (often the calf or the shin) suggests reflux in the saphenous vein, deep venous disease, or both.

Prominent swelling is not a common feature of superficial venous disease, although episodic ankle edema is common. Edema extending beyond the ankle suggests deep venous disease. Leg swelling varies markedly with the time of day and orthostasis.[20] Measurements of the circumference of the calf are not informative unless they are always performed at the same time of the day for serial follow-up assessments.

Venous ulcers have characteristic features (Table 1 and Fig. 1).

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).[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).[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,[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.[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.[24] High-resolution magnetic resonance venography or computed tomography appears to be sensitive for focal iliac-vein lesions,[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)[25-27]; however, this

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

Feature	Alternative Diagnoses	Comments
Leg		
Claudication	Arterial claudication (peripheral arterial disease)	Arterial pressures in the ankle diminished during treadmill exercise testing in peripheral arterial disease†
Nocturnal pain	Ischemic pain at rest (peripheral arterial disease)	Arterial pressures in the ankle at rest show severe reduction in peripheral arterial disease†
Orthostatic pain	Sciatica, radiculopathy, spinal stenosis	Physical examination and MRI of spine can help differentiate these alternative diagnoses from CVI
Swelling	Congestive failure, renal disease, hypothyroidism, lymphedema	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
Skin		
Hyperpigmentation	Acanthosis nigricans, hemosiderosis	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
Stasis dermatitis	Psoriasis, periarteritis nodosa, allergic dermatitis, other causes of dermatitis	Skin biopsy can be definitive
Ulcer	Ischemic ulcer (peripheral arterial disease), skin ulceration associated with rheumatic disease	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)
	Marjolin's ulcer, ulcerating skin cancer, Kaposi's sarcoma, pyoderma gangrenosum	Skin biopsy can differentiate these alternative diagnoses from CVI; venous studies reveal advanced disease in CVI

* 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.

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-

Figure 1. Classic Appearance of a Venous Stasis Ulcer.
A venous stasis ulcer is usually located above the medial malleolus and has an indolent appearance, with granulation tissue at its base that does not appear to be ischemic. Scarring of variable extent usually surrounds chronic and recurrent ulcers. Hyperpigmentation, lipodermatosclerosis (induration involving skin and subcutaneous fat), and stasis dermatitis are variably present in the lower third of the leg (the "gaiter" area). Pedal pulses are usually palpable. If they are not palpable because of induration or swelling, ankle pressures measured by means of Doppler ultrasonography will be normal in the absence of associated ischemic 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.[30] Many patients who can wear stockings abandon them after initial use for a variety of stated reasons, such as tightness and warmth.[31] Reported rates of noncompliance have ranged from 30 to 65%, even under clinical supervision in venous-ulcer clinics.[32-34]

Stockings variably improve venous dynamics during orthostasis[35,36] 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[37] 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,[38] 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.[31,39] In the Effect of Surgery and Compression on Healing and Recurrence study[40] (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[2-4]

Table 2. Venous Clinical Severity Score.*

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

* An aggregate score for the limb is calculated by adding the individual component scores. The range of the total score is 0 to 30.

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,[41] 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,[42] 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.[17]

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.[43] 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 3. Common Clinical Patterns in Chronic Venous Insufficiency.*

Clinical Pattern	Symptoms and Presentation	Treatment and Recommendations†
Varices		
Uncomplicated	Cosmetic or health concerns, or both	Reassurance and cosmetic treatment
With local symptoms	Pain is confined to the varices and is not diffuse	Local ablation of varices; saphenous-vein ablation is required when reflux is present, to reduce chances of recurrence
With local complications	Superficial thrombophlebitis, internal rupture with hematoma or external rupture through a "pinpoint" ulcer that is painless and can cause considerable blood loss when patient is in upright position	Antiinflammatory regimen and local treatment for thrombophlebitis; repeated episodes may require thrombophilia and neoplastic workup and ablation of varices or saphenous veins; ablation is advisable in cases of ruptured varices; patients should be advised to lie down and elevate the leg to control bleeding, if it recurs
Complex varicose disease	Diffuse limb pain, swelling, skin changes or ulcer	Truncal reflux is present; saphenous-vein ablation may be curative
Venous hypertension syndrome	Severe orthostatic venous pain; patients are often young or middle-aged women; other features of CVI are minimal or absent	Main pathologic process is axial deep venous reflux, often combined with obstruction; deep-vein tests (duplex ultrasonography, venography, IVUS) and correction (of obstruction or reflux) recommended
Venous leg swelling	Other features of CVI may be absent or variable; patients are often elderly sedentary women; swelling is often bilateral	Main pathologic process is iliac-vein obstruction; prolonged sitting with decreased calf-muscle pump action from immobility aggravates swelling; empirical diuretic use is often ineffective; iliac-vein stenting may be required for relief
Complex multisystem venous disease	Clinical features of advanced CVI (i.e., pain, swelling, stasis dermatitis) or ulceration present in varying combinations	Multiple venous system disease is often present; comprehensive testing necessary to identify all pathologic components; partial correction of disease often relieves symptoms; simpler techniques (e.g., saphenous-vein ablation, SEPS) should be performed first, before resorting to more complex procedures

* CVI denotes chronic venous insufficiency, IVUS intravascular ultrasonography, and SEPS subfascial endoscopic perforator surgery.
† Compression therapy is recommended in all symptomatic patients except when it is not appropriate or not tolerated or when it is ineffective. Specific correction of the disease (e.g., saphenous-vein ablation) may reduce recurrence in the long term.

radiofrequency, and 94% with the use of laser treatment at a mean follow-up of 32 months.[44] 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.[43]

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).[45] In a meta-analysis of 20 studies involving 1140 legs,[46] 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.[45] Moreover, the role of interruption of the perforator vein is controversial because of doubts about the pathologic significance of reflux involving this vein[47] 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,[13,25,26] 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 nonthrombotic 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.

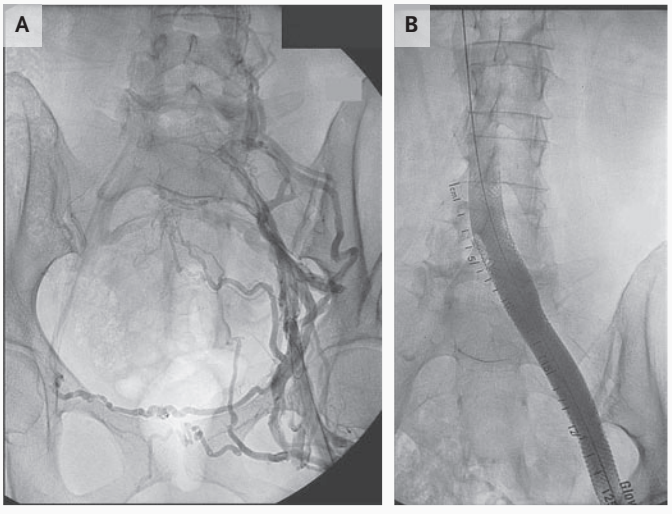

Figure 2. Recanalization of an Occluded Iliac Vein with Stent Placement.
Panel A shows collateral veins around the occluded iliac vein. In Panel B, the collateral vessels disappear with stent placement.

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-

ommend 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 pain persists. 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.

Drs. 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

1. Meissner MH, Gloviczki P, Bergan J, et al. Primary chronic venous disorders. J Vasc Surg 2007;46:Suppl:54S-67S.
2. Neglén P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. J Vasc Surg 2007;46:979-90.
3. Neglén P, Hollis KC, Raju S. Combined saphenous ablation and iliac stent placement for complex severe chronic venous disease. J Vasc Surg 2006;44:828-33.
4. Raju S, Fredericks R. Valve reconstruction procedures for nonobstructive venous insufficiency: rationale, techniques, and results in 107 procedures with two- to eight-year follow-up. J Vasc Surg 1988;7:301-10.
5. Raju S, Owen S Jr, Neglén P. The clinical impact of iliac venous stents in the management of chronic venous insufficiency. J Vasc Surg 2002;35:8-15.
6. Neglén P, Raju S. A rational approach to detection of significant reflux with duplex Doppler scanning and air plethysmography. J Vasc Surg 1993;17:590-5.
7. Clarke H, Smith SR, Vasdekis SN, Hobbs JT, Nicolaides AN. Role of venous elasticity in the development of varicose veins. Br J Surg 1989;76:577-80.
8. Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. J Vasc Surg 1995;21:307-12.
9. Raju S, Neglén P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. J Vasc Surg 2006;44:136-43.
10. Delis KT, Ibegbuna V, Nicolaides AN, Lauro A, Hafez H. Prevalence and distribution of incompetent perforating veins in chronic venous insufficiency. J Vasc Surg 1998;28:815-25.
11. Neglén P, Thrasher TL, Raju S. Venous outflow obstruction: an underestimated contributor to chronic venous disease. J Vasc Surg 2003;38:879-85.
12. Labropoulos N, Volteas N, Leon M, et al. The role of venous outflow obstruction in patients with chronic venous dysfunction. Arch Surg 1997;132:46-51.
13. Raju S, Hollis K, Neglén P. Obstructive lesions of the inferior vena cava: clinical features and endovenous treatment. J Vasc Surg 2006;44:820-7.
14. Cockett FB, Thomas ML, Negus D. Iliac vein compression — its relation to iliofemoral thrombosis and the post-thrombotic syndrome. Br Med J 1967;2:14-9.
15. Kibbe MR, Ujiki M, Goodwin AL, Eskandari M, Yao J, Matsumura J. Iliac vein compression in an asymptomatic patient population. J Vasc Surg 2004;39:937-43.
16. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. N Engl J Med 2006;355:488-98.
17. Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: medical management and beyond. Ann Vasc Surg 2007;21:652-62.
18. Raju S, Owen S Jr, Neglén P. Reversal of abnormal lymphoscintigraphy after placement of venous stents for correction of associated venous obstruction. J Vasc Surg 2001;34:779-84.
19. Scott J, Huskisson EC. Graphic representation of pain. Pain 1976;2:175-84.
20. Katz ML, Comerota AJ, Kerr RP, Caputo GC. Variability of venous-hemodynamics with daily activity. J Vasc Surg 1994;19:361-5.
21. Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248-52.
22. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307-12.
23. Raju S, Fredericks R. Venous obstruction: an analysis of one hundred thirty-seven cases with hemodynamic, venographic, and clinical correlations. J Vasc Surg 1991;14:305-13.
24. Negus D, Fletcher EW, Cockett FB, Thomas ML. Compression and band formation at the mouth of the left common iliac vein. Br J Surg 1968;55:369-74.
25. Hartung O, Benmiloud F, Barthelemy P, Dubuc M, Boufi M, Alimi YS. Late results of surgical venous thrombectomy with iliocaval stenting. J Vasc Surg 2008;47:381-7.
26. Hurst DR, Forauer AR, Bloom JR, Greenfield LJ, Wakefield TW, Williams DM. Diagnosis and endovascular treatment of iliocaval compression syndrome. J Vasc Surg 2001;34:106-13.
27. Neglén P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. J Vasc Surg 2002;35:694-700.
28. Kalra M, Gloviczki P. Surgical treatment of venous ulcers: role of subfascial endoscopic perforator vein ligation. Surg Clin North Am 2003;83:671-705.
29. Raju S, Fredericks RK, Neglén PN, Bass JD. Durability of venous valve reconstruction techniques for "primary" and postthrombotic reflux. J Vasc Surg 1996;23:357-66.
30. Franks PJ, Oldroyd MI, Dickson D, Sharp EJ, Moffatt CJ. Risk factors for leg ulcer recurrence: a randomized trial of two types of compression stocking. Age Ageing 1995;24:490-4.
31. Raju S, Hollis K, Neglén P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. Ann Vasc Surg 2007;21:790-5.
32. Jull AB, Mitchell N, Arroll J, et al. Factors influencing concordance with compression stockings after venous leg ulcer healing. J Wound Care 2004;13:90-2.
33. Kiev J, Noyes LD, Rice JC, Kerstein MD. Patient compliance with fitted compression hosiery monitored by photoplethysmography. Arch Phys Med Rehabil 1990;71:376-9.
34. Erickson CA, Lanza DJ, Karp DL, et al. Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. J Vasc Surg 1995;22:629-36.
35. Mayberry JC, Moneta GL, DeFrang RD, Porter JM. The influence of elastic compression stockings on deep venous hemodynamics. J Vasc Surg 1991;13:91-9.
36. Ibegbuna V, Delis KT, Nicolaides AN, Aina O. Effect of elastic compression stockings on venous hemodynamics during walking. J Vasc Surg 2003;37:420-5.
37. Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression bandages and stockings for venous leg ulcers. Cochrane Database Syst Rev 2000;2:CD000265.
38. Nelson EA, Bell-Syer SE, Cullum NA. Compression for preventing recurrence of

venous ulcers. Cochrane Database Syst Rev 2000;4:CD002303.
39. Mayberry JC, Moneta GL, Taylor LM Jr, Porter JM. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. Surgery 1991;109:575-81.
40. 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;363:1854-9.
41. Pascarella L, Schönbein GW, Bergan JJ. Microcirculation and venous ulcers: a review. Ann Vasc Surg 2005;19:921-7.
42. Jull A, Waters J, Arroll B. Pentoxifylline for treatment of venous leg ulcers: a systematic review. Lancet 2002;359:1550-4.
43. Morrison N, Cavezzi A, Bergan J, Partsch H. Regarding "Stroke after varicose vein foam injection sclerotherapy." J Vasc Surg 2006;44:224-5.
44. van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. J Vasc Surg 2009;49:230-9.
45. Kalra M, Gloviczki P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency — is it justified? Vasc Endovascular Surg 2002;36:41-50.
46. Tenbrook JA Jr, Iafrati MD, O'Donnell TF Jr, et al. Systematic review of outcomes after surgical management of venous disease incorporating subfascial endoscopic perforator surgery. J Vasc Surg 2004;39:583-9.
47. O'Donnell TF Jr. The present status of surgery of the superficial venous system in the management of venous ulcer and the evidence for the role of perforator interruption. J Vasc Surg 2008;48:1044-52.
48. Raju S. Endovenous treatment of patients with iliac-caval venous obstruction. J Cardiovasc Surg (Torino) 2008;49:27-33.
49. Raju S, Hardy JD. Technical options in venous valve reconstruction. Am J Surg 1997;173:301-7.
50. Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. J Vasc Surg 1994;19:391-403.
51. Perrin M. Reconstructive surgery for deep venous reflux: a report on 144 cases. Cardiovasc Surg 2000;8:246-55.
52. Raju S, Fountain T, Neglén P, Devidas M. Axial transformation of the profunda femoris vein. J Vasc Surg 1998;27:651-9.
53. Raju S, Neglén P, Doolittle J, Meydrech EF. Axillary vein transfer in trabeculated postthrombotic veins. J Vasc Surg 1999;29:1050-62.