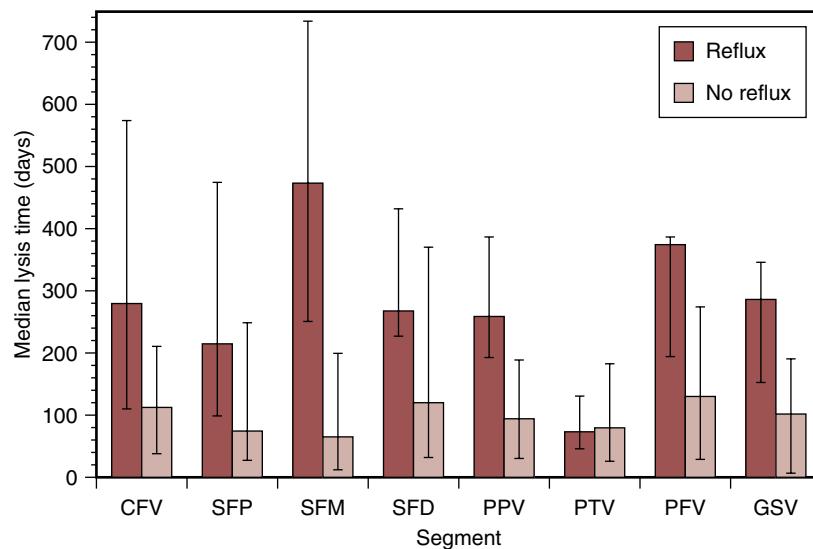


of thrombosed segments, development of reflux, and development of early and late onset of venous edema (as a measure of PTS). Eight segments in the deep venous system (common iliac vein to the posterior tibial veins) were investigated using duplex ultrasound. Three patient groups were identified, including those with early recanalization, early thrombus extension, and late thrombus extension. In the early recanalization group, 53% of limbs experienced complete recanalization by 90 days, with 28% of early complete recanalized limbs occurring within 30 days.<sup>28</sup> Within the group with early DVT extension, 14% of patients had extension of DVT within 7 days. Within the group with late DVT extension, 19% of patients had extension of the DVT within 30 to 180 days. All patients were treated with anticoagulation. Valvular insufficiency occurred in 62% of patients; it developed much later than recanalization and in segments not previously occluded, indicating that the mechanism by which valvular insufficiency occurs must involve more than a physical effect of the thrombus on the valve. In 38% of patients, valvular insufficiency was not present, and four of the five patients had complete recanalization by 30 days, suggesting that early DVT recanalization may be a protective factor for venous valve function. Assessing edema early (7 to 30 days) may serve as a marker of subsequent PTS. Patients with edema were more likely to have residual occlusion than valvular insufficiency. The late development of edema at 90, 180, and 270 days was more closely correlated with valvular insufficiency.<sup>28</sup>

A key factor leading to valvular insufficiency following DVT appears to be the rate of clot resolution; preservation of valve function is greatest with early recanalization. In an interesting study evaluating the natural history of DVT, 127 patients with acute DVT (55% male, average age of 52 years) were assessed at days 1 and 7, at 1-month and at 3-month intervals for the first year, and yearly thereafter. Duplex ultrasound was used to evaluate eight

venous segments from the common femoral vein to the posterior tibial veins. Thrombus resolution of a vein segment was defined as complete recanalization. Median follow-up was 23 to 25 months for all veins except the posterior tibial vein, which was 12 months. Nearly 90% of patients had anticoagulation treatment. The important findings of the study were that the median time to resolution for venous segments developing reflux (214 to 474 days) was 2.3 to 7.3 times longer than for corresponding venous segments not developing reflux (65 to 130 days), for all except the posterior tibial vein (Fig. 156.2). The differences between the two groups reached statistical significance in the mid femoral vein, popliteal vein, and profunda femoris vein segments ( $P = 0.002$ ,  $0.006$ , and  $0.04$ , respectively), and a clear trend toward significance was present in all other segments except the posterior tibial vein.<sup>29</sup> When the cumulative percent resolution during the first 9 months was analyzed, a significantly greater proportion of proximal femoral vein segments not developing reflux had resolved by 3 months (56% vs. 13%;  $P = 0.012$ ). A similar pattern was present in the distal femoral veins at 6 months (54% vs. 0%;  $P = 0.04$ ) and in the great saphenous vein at 9 months (100% vs. 33%;  $P = 0.02$ ). The median time at which reflux appeared was less than the median time to resolution for all segments (development of reflux coincided with or preceded complete clot resolution in the venous segments); however, it was only significant for the mid femoral ( $P = 0.008$ ) and distal femoral vein ( $P = 0.04$ ) segments. This indicated that the onset of reflux appeared prior to complete recanalization, and that valves are subject to early reflux even if a small amount of recanalizing thrombus is present. If resolved, however, valve function was sometimes restored. Finally, there was a small group of patients in whom vein segments with early clot resolution developed reflux, and patients in whom vein segments with late resolution (>9 months) did not develop reflux. The authors concluded that early recanalization is important in preserving valve integrity, but



**Figure 156.2** Median time from thrombosis to recanalization for all segments (lysis time), grouped according to reflux status at last visit. Error bars show interquartile range (25th to 75th percentile). CFV, common femoral vein; GSV, great saphenous vein; PFV, profunda femoris vein; PPV, popliteal vein; PTV, posterior tibial vein; SFD, superficial femoral vein distal; SFM, superficial femoral vein middle; SFP, superficial femoral vein proximal. (From Meissner MH, Manzo RA, Bergelin RO, et al. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg*. 1993;18:596–605.)

other factors (re-thrombosis and recanalization, thrombus burden, biochemical factors, incompetence of axial venous channels, residual proximal stenosis, the presence of incompetent perforators and collaterals, differences in fibrinolytic activity in the endothelium) also contribute to valvular insufficiency.<sup>29</sup> Additional information addressing outcomes following lysis of DVT can be found in Chapters 146, Acute Deep Venous Thrombosis: Epidemiology and Natural History and 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment.

Other studies have investigated changes in the deep venous system following DVT and development of PTS. In a study of 447 limbs in 429 patients with venous outflow obstruction, the presence of both reflux and obstruction produced more severe signs and symptoms of CVD compared with obstruction alone (CEAP class 4 to 6, 53% vs. 24%, respectively;  $P < 0.001$ ). Importantly, venous leg ulcers in limbs with both obstruction and reflux were seen in 24%, compared with 3% in those with obstruction alone ( $P < 0.001$ ).<sup>30</sup> These studies indicate that reflux in the presence of obstruction leads to significantly higher rates of severe PTS with skin changes and venous ulcer risk.

In a study of first-time DVT in 120 limbs of 105 patients (59 men, 46 women; mean age of 54 years), patients were stratified into two groups, those with DVT isolated to one venous segment and those with DVT in multiple levels. The majority of patients were treated with anticoagulation. Duplex ultrasound and clinical examination was performed at the initial visit, within the first 6 months, at 1 year, and yearly thereafter. Groups with single level and multilevel involvement were comparable in age and sex. Venous claudication was exclusively found in the multilevel group (8.8%) and was present only when iliac veins were involved. More advanced PTS (skin damage and ulceration) was found in the multilevel group compared with the single level group (26 of 41;  $P < 0.001$ ). Skin damage developed in 35 limbs (29%) at a mean follow-up of 3.4 years. The prevalence of skin damage (usually occurring  $>3$  years after DVT) was more common in the multilevel group. Venous pathology (reflux, obstruction, or a combination of the two) was more common in the multilevel group compared with the single level group ( $P < 0.0001$ ). Limbs with both reflux and obstruction were more likely to develop skin damage in both groups. The authors concluded that multisegment venous disease with iliac involvement can lead to venous claudication, and that patients with reflux and obstruction developed increased risk of skin damage than those with reflux or obstruction alone.<sup>15</sup>

In addition to the importance of multilevel and iliac vein involvement, other specific locations had poorer outcomes. It has been shown that poor popliteal vein function correlated with worse clinical manifestations. Patients with popliteal vein abnormalities were found to be greater than 3.5 times more likely to develop PTS when compared with those without popliteal vein involvement. A high peak reflux velocity in the popliteal vein was a strong predictor for CVD, and multisegmental occlusion involving the popliteal vein increased the risk for developing PTS. Thrombosis in multiple calf veins produced more frequent and significant PTS than thrombosis in a single calf vein, and calf vein involvement in the presence of proximal DVT increased the likelihood of PTS.<sup>15</sup>

The rate of progression of CVD is greater with secondary venous disease (DVT) than with primary venous disease (varicose veins and venous insufficiency). An elegant study evaluated 46 limbs in 41 patients with a first episode of DVT. Patients were assessed clinically and by duplex ultrasound at the initial visit, at 3, 6, and 12 months and yearly thereafter for up to 5 years. Outcomes in this group were compared with those in 41 patients with primary disease (50 limbs), age- and sex-matched with disease duration of 5 to 10 years. There was also a control group (15 subjects, 30 limbs), with no evidence of CVD, also matched for sex and age. In the DVT group, at 5 years follow-up, complete obstruction occurred in 9.3%; partial recanalization occurred in 50.9%, and complete recanalization occurred in 39.8%. At the 5-year follow-up, the prevalence of skin damage was 4 times higher in the DVT group compared with patients with primary CVD (23.9% vs. 6%,  $P = 0.019$ ) and versus control (0%,  $P < 0.01$ ). In patients with DVT the incidence of skin damage at 1 year was 4%, and significantly increased at 5 years to 24% ( $P = 0.014$ ). Importantly, in patients with DVT, the combination of proximal and distal obstruction and the combination of reflux with obstruction were more common in limbs with skin damage (CEAP clinical classes 4 to 6;  $P = 0.012$  and  $P = 0.013$ , respectively), indicating that proximal obstruction and the combination of reflux and obstruction are a significant risk factor for the development of PTS.<sup>31</sup>

Other investigators have demonstrated that skin damage is significantly increased in patients following a first episode of DVT. In a study of 355 consecutive patients, skin damage occurred with a cumulative incidence of 22.8% after 2 years and 28% after 5 years.<sup>8</sup> In another longitudinal study (68 patients with a first diagnosis of lower extremity DVT, 50% male, 73 limbs), a 20.5% prevalence of skin damage was observed at a mean follow-up of 55 months. No active ulcers were present, but 2.7% of the study group had a healed ulcer.<sup>32</sup>

In this study, male patients were significantly more likely to have advanced signs of hyperpigmentation or ulceration compared to female patients (32.4% vs. 8.3%, respectively;  $P = 0.01$ ). However, enrollment was not large enough for a multiple variable analysis, and further studies are necessary to determine if gender is a risk factor for advanced disease. There is some evidence that women may have differences in the fibrinolytic system, with higher plasminogen levels, lower plasminogen activator inhibitor levels, and increased fibrinolytic activity compared with men both at baseline and after venous occlusion.<sup>32</sup>

Recanalization following acute DVT was also significantly inversely related to baseline levels of activated coagulation prothrombin fragments (conversion of prothrombin to thrombin) and to fibrinolytic inhibition as measured by tPA antigen (primarily reflects PAI-1 levels). At presentation there is marked elevation of prothrombin fragments and D-dimer, which is determined by total thrombus load, and these decrease rapidly with initiation of anticoagulation therapy. However, D-dimer remains elevated long after the initial DVT.<sup>33,34</sup>

The pathophysiology of PTS is complex, but evidence suggests that venous hypertension is central to developing this debilitating disease. In PTS, ambulatory venous hypertension can result from outflow obstruction and/or valvular insufficiency.

In this situation, ambulation does not reduce the venous pressure, and a state of ambulatory venous hypertension persists. Sustained venous hypertension can cause structural and biochemical abnormalities of the vein wall, with persistent chronic inflammation, resulting in pathologic effects in the skin and subcutaneous tissues.<sup>4,5</sup>

After an acute DVT there is venous obstruction and a sterile inflammatory response, with subsequent recanalization of the thrombosed veins, which occurs through a combination of fibrinolysis, thrombus organization, and neovascularization. Vein wall damage and valvular damage along with incomplete recanalization, leads to venous outflow obstruction and persistent venous hypertension, which may interfere with calf muscle pump function and cause further damage to venous valves. Collateral venous outflow through the profunda femoris and pelvic venous system also develops. There are several clinical tools to quantify the severity of PTS, and include the Villalta scale, Ginsberg measure, and Brandjes scale. The Villalta scale is a clinical measure of five subjective patient-derived venous symptoms (pain, cramps, heaviness, paresthesia, and pruritus) and six objective clinician-derived venous signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression), as well as the presence or absence of ulcer, in the DVT affected leg. The scoring of each component is 0–3 (none, mild, moderate, severe) with a total score of 0–33. The rating of the total score translates into the following: 0 to 4 indicates no PTS, 5 to 9 indicates mild PTS, 10 to 14 indicates moderate PTS, and a score of ≥15 or the presence of a venous ulcer as severe PTS. The Villalta score is the most widely used outcome tool in studies determining the severity of PTS, and correlates well with quality of life. The Ginsberg measure defines PTS by the presence of daily leg pain and swelling that persists for at least 1 month, is typical in character (worse with standing or walking and relieved by rest or leg elevation), and occurs at least 6 months after acute DVT. The Ginsberg measure identifies more severe forms of PTS, and may miss milder forms of PTS, and is not quantitative. The Brandjes scale is similar to the Villalta scale, and assesses a number of subjective and objective criteria, including leg circumference.<sup>4</sup>

The relationship between the extent of thrombus on initial presentation and the ultimate clinical outcomes has been addressed, although some controversy remains.<sup>4,32</sup> In one study, PTS developed more frequently in patients who had persistent venous obstruction within the first 6 months after an episode of acute proximal DVT (relative risk 1.6; 95% CI 0–2.4).<sup>35</sup> This would suggest that proximal DVT may be more important in terms of developing PTS. In a multicenter study of 387 patients with an acute DVT, patients were evaluated for the frequency, time course, and predictors of PTS (197 men and 190 women, mean age 56 years). Patient follow-up was at 1, 4, 8, 12, and 24 months. Assessment of PTS using the Villalta scale, evaluation of anticoagulation regimens, and use of elastic compression stockings were all performed. At all study intervals, approximately 30% of patients had mild, 10% had moderate, and 3% had severe PTS. A more severe postthrombotic category at the 1-month visit strongly predicted higher mean postthrombotic scores throughout 24 months of follow-up.

These findings suggest that the pathophysiologic progenitor of PTS occurs in the first few weeks after DVT. Important predictors of PTS included venous thrombosis of the common femoral or iliac vein (2.23 increase in Villalta score vs. calf;  $P < 0.001$ ), a higher body mass index (0.14 increase in score per  $1 \text{ kg/m}^2$ ;  $P < 0.001$ ), previous ipsilateral DVT (1.78 increase in score;  $P = 0.001$ ), older age (0.30 increase in score per 10-year age increase;  $P = 0.011$ ), and female sex (0.79 increase in score;  $P = 0.020$ ). The authors concluded that patients with extensive DVT, specifically if the iliac and common femoral veins were involved, and those with more severe postthrombotic manifestations at 1 month after DVT, had much poorer long-term outcomes.<sup>36</sup> Patients with more extensive thrombosis involving the iliac and common femoral veins, may experience worse outcomes due to a greater likelihood of residual thrombosis. Thus early thrombus lysis may help prevent PTS, although definitive data is lacking (see Ch. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment). Interestingly, older age and higher BMI are associated with higher postthrombotic scores, which may relate to age- or weight-related impaired fibrinolysis or vein wall changes.<sup>16</sup> In a large review, at least eight studies demonstrated the relationship between the extent of proximal DVT and the risk of developing PTS, confirming that iliofemoral DVT carries significant weight in the determination of progression to PTS.<sup>4</sup> Importantly, the iliofemoral location of DVT also appears to be a strong predictor of venous claudication, and other studies have found that the risk of PTS associated with proximal venous thrombosis ranges from 40% to 600%.<sup>7</sup>

In conclusion, PTS can result in a very debilitating disease with significant socioeconomic impact. Symptoms of PTS can be from mild to severe, the latter accounting for about 8%–10%. Significant risk factors for PTS are iliofemoral DVT, recurrent ipsilateral DVT, reflux and obstruction, and multi-venous segments involved, with these risks increasing the likelihood for PTS progression. Most DVT undergo recanalization, and about 50% have full recanalization, which may offer better outcomes and decrease PTS. The pathophysiology is complex and further understanding in DVT molecular pathways and inflammatory cascade will undoubtedly produce novel treatment strategies with equal or better effectiveness and improved bleeding safety profiles.

## CLINICAL SUMMARY POINTS OF NATURAL HISTORY, EPIDEMIOLOGY, AND PATHOPHYSIOLOGY

1. DVT affects up to 3 individuals per 1000 annually in the general population.
2. Nearly 20% of calf vein DVT extend into the femoral–popliteal and iliac veins.
3. The greatest changes following a DVT occur during the first 3 months, with an approximate 50% reduction in thrombus burden during this time.
4. Approximately 50% of patients will show complete recanalization within 6 to 9 months of the initial DVT.

5. Median lysis times for venous segments developing reflux are 2.3 to 7.3 times longer than for corresponding venous segments not developing reflux.
6. The incidence of recurrent venous thromboembolism is approximately 17%, 24%, and 30% at 2 years, 5 years, and 8 years, respectively.
7. PTS will develop in 20% to 50% of patients within 1 to 2 years of a symptomatic DVT.
8. About 25% of limbs following DVT will have advanced skin changes at 5 years, with more aggressive progression of skin changes occurring in postthrombotic limbs compared with those with primary venous disease.
9. Ipsilateral recurrent DVT is a strong predictor of progression of CVD (RR, 4.4; 95% CI, 1.4 to 13.3,  $P = 0.0049$ ).
10. The most important risk factor for developing PTS is a recurrent ipsilateral DVT, which increases the risk of PTS by as much as sixfold.
11. Limbs with the PTS have more than three times the odds of having combined reflux and obstruction compared with limbs without PTS (odds ratio [OR] 3.5, 95% CI, 1.4 to 8.6), and limbs with both obstruction and reflux have higher rates and severity of PTS.
12. Ulceration may develop as a consequence of PTS, with a cumulative incidence of approximately 4% at 20 years.
13. Limbs with multisegment venous disease with iliac involvement are more likely to develop PTS, venous claudication, skin changes, venous ulceration, and venous pathology (combined obstruction and reflux) compared with limbs with only single venous segment involvement.
14. Patients with popliteal vein obstruction and/or reflux were found to be greater than 3.5 times more likely to develop PTS, and patients with multisectional occlusion involving the popliteal vein are also at increased risk for developing PTS.
15. The pathophysiology of PTS is a complex set of events involving inflammation, thrombosis, resolution of thrombus, and vein wall damage, which result in outflow obstruction, valvular insufficiency, and calf muscle pump dysfunction, which leads to venous hypertension and subsequent signs and symptoms of PTS.
16. Greater postthrombotic symptom severity 1 month following an acute DVT strongly predicts higher mean post-thrombotic scores throughout 24 months of follow-up. In other words, higher Villalta scores at 1 month predict worse PTS at later time points.

## SELECTED KEY REFERENCES

- Kahn SR, Comerota AJ, Cushman M, et al. American Heart Association Council on Peripheral Vascular Disease, Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014;130:1636–1661.  
*Comprehensive review of the risk factors associated with the development of PTS following a DVT, with diagnostic and treatment recommendations.*
- Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med*. 2008;149:698–707.  
*Large study clearly defining that early onset of PTS at 1 month is predictive of progression of PTS up to 2 years, and that iliofemoral DVT is strongly associated with development of PTS.*
- Killewich LA, Bedford GR, Beach KW, Strandness Jr DE. Spontaneous lysis of deep venous thrombi: rate and outcome. *J Vasc Surg*. 1989;9:89–97.  
*Study identifying the natural history of DVT resolution, the time course for recanalization, and the development of valvular insufficiency and PTS.*
- Meissner MH, Manzo RA, Bergelin RO, Markel A, Strandness Jr DE. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg*. 1993;18:596–605.  
*Establishes the effect of early lysis on the development of valvular insufficiency, and assesses the association between time of lysis and the development of reflux in patients following DVT.*
- Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125:1–7.  
*Large study of patients followed for 8 years assessing the rate of recurrent DVT, the development of PTS, and independent risk factors that predicted PTS.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com)

## REFERENCES

1. Labropoulos N, Gasparis AP, Tassiopoulos AK. Prospective evaluation of the clinical deterioration in post-thrombotic limbs. *J Vasc Surg.* 2009;50:826–830.
2. Nicolaides AN, Kakkar VV, Field ES, Renney JT. The origin of deep vein thrombosis: a venographic study. *Br J Radiol.* 1971;44:653–663.
3. Kearon C. Natural history of venous thromboembolism. *Circulation.* 2003;107(23 suppl 1):I22–I30.
4. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation.* 2014;130:1636–1661.
5. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med.* 2004;164:17–26.
6. Lester PA, Diaz JA, Shuster KA, Henke PK, Wakefield TW, Myers DD. Inflammation and thrombosis: new insights. *Front Biosci (Schol Ed).* 2012;4:620–638.
7. Galanaud JP, Monreal M, Kahn SR. Predictors of the post-thrombotic syndrome and their effect on the therapeutic management of deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2016;4:531–534.
8. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med.* 1996;125:1–7.
9. Aschwanden M, Jeanneret C, Koller MT, Thalhammer C, Bucher HC, Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. *J Vasc Surg.* 2008;47:1015–1021.
10. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med.* 2004;164:17–26.
11. Labropoulos N, Gasparis AP, Tassiopoulos AK. Prospective evaluation of the clinical deterioration in post-thrombotic limbs. *J Vasc Surg.* 2009;50:826–830.
12. Roumen-Klappe EM, den Heijer M, Janssen MCH, et al. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. *Thromb Haemost.* 2005;94:825–830.
13. Labropoulos N, Leon M, Nicolaides AN, et al. Venous reflux in patients with previous deep venous thrombosis: correlation with ulceration and other symptoms. *J Vasc Surg.* 1994;20:20–26.
14. Johnson BF, Manzo RA, Bergelin RO, Strandness Jr DE. 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;21:307–312.
15. Labropoulos N, Waggoner T, Sammis W, et al. The effect of venous thrombus location and extent on the development of post-thrombotic signs and symptoms. *J Vasc Surg.* 2008;48:407–412.
16. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med.* 2008;149:698–707.
17. Rice JB, Desai U, Cummings AK, et al. Burden of venous leg ulcers in the United States. *J Med Econ.* 2014;17:347–356.
18. ten Cate-Hoek AJ, Henke PK, Wakefield TW. The post thrombotic syndrome: Ignore it and it will come back to bite you. *Blood Rev.* 2016;30:131–137.
19. Wakefield TW, Myers DD, Henke PK. Mechanisms of venous thrombosis and resolution. *Arterioscler Thromb Vasc Biol.* 2008;28:387–391.
20. DeRoo EP, Wroblekski SK, Shea EM, et al. The role of galectin-3 and galectin-3-binding protein in venous thrombosis. *Blood.* 2015;125:1813–1821.
21. Myers Jr DD, Wroblekski SK, Longo C, et al. Resolution of venous thrombosis using a novel oral small-molecule inhibitor of P-selectin (PSI-697) without anticoagulation. *Thromb Haemost.* 2007;97:400–407.
22. Myers Jr D, Lester P, Adili R, et al. A new way to treat proximal deep venous thrombosis using E-selectin inhibition. *J Vasc Surg Venous Lymphat Disord.* 2020;8:268–278.
23. Devata S, Angelini DE, Blackburn S, et al. Use of GMI-1271, an E-selectin antagonist, in healthy subjects and in 2 patients with calf vein thrombosis. *Res Pract Thromb Haemost.* 2020;4:193–204.
24. Killewich LA, Martin M, Beach KW, Strandness DE. An objective assessment of the physiological changes in the postthrombotic syndrome. *Arch Surg.* 1985;120:424–426.
25. Roumen-Klappe EM, den Heijer M, Janssen MCH, et al. The post-thrombotic syndrome: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. *Thromb Haemost.* 2005;94:825–830.
26. Johnson BF, Manzo RA, Bergelin RO, Strandness Jr DE. 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;21:307–312.
27. Labropoulos N, Leon M, Nicolaides AN, et al. Venous reflux in patients with previous deep venous thrombosis: correlation with ulceration and other symptoms. *J Vasc Surg.* 1994;20:20–26.
28. Killewich LA, Bedford GR, Beach KW, Strandness Jr DE. Spontaneous lysis of deep venous thrombi: rate and outcome. *J Vasc Surg.* 1989;9:89–97.
29. Meissner MH, Manzo RA, Bergelin RO, Markel A, Strandness Jr DE. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg.* 1993;18:596–605.
30. Neglen P, Thrasher TL, Raju S. Venous outflow obstruction: an underestimated contributor to chronic venous disease. *J Vasc Surg.* 2003;38:879–885.
31. Labropoulos N, Gasparis AP, Pefanis D, et al. Secondary chronic venous disease progresses faster than primary. *J Vasc Surg.* 2009;49:704–710.
32. Meissner MH, Caps MT, Zierler BK, et al. Determinants of chronic venous disease after acute deep venous thrombosis. *J Vasc Surg.* 1998;28:826–833.
33. Meissner MH, Zierler BK, Bergelin RO, et al. Coagulation, fibrinolysis, and recanalization after acute deep venous thrombosis. *J Vasc Surg.* 2002;35:278–285.
34. Meissner MH, Zierler BK, Bergelin RO, et al. Markers of plasma coagulation and fibrinolysis after acute deep venous thrombosis. *J Vasc Surg.* 2000;32:870–880.
35. Prandoni P, Frulla M, Sartor D, et al. Vein abnormalities and the post-thrombotic syndrome. *J Thromb Haemost.* 2005;3:401–402.
36. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med.* 2008;149:698–707.

# Treatment of Chronic Venous Disorders

JOVAN N. MARKOVIC and CYNTHIA K. SHORTELL

## NONOPERATIVE TREATMENT OF CVD 2071

### Lifestyle Modification 2071

*Exercise* 2071

*Leg Elevation* 2071

*Weight Loss* 2072

### Compression Therapy 2072

*Gradient Elastic Stockings* 2072

GRADIENT COMPRESSION STOCKINGS IN C<sub>1</sub>–C<sub>2</sub>  
DISEASE 2073

SURGERY VERSUS COMPRESSION IN C<sub>2</sub>–C<sub>3</sub>  
DISEASE 2073

GRADIENT COMPRESSION STOCKINGS IN C<sub>4</sub>–C<sub>6</sub>  
DISEASE 2073

GRADIENT COMPRESSION STOCKINGS AND PREVENTION  
OF POST-THROMBOTIC SYNDROME IN ACUTE DEEP VEIN  
THROMBOSIS 2074

*CircAid Garment* 2075

*Unna Boot* 2076

*Layered Elastic and Nonelastic Compression  
Bandages* 2076

*Intermittent Pneumatic Compression* 2078

ADAPTIVE PRESSURE MULTI-CHAMBER SYSTEM 2078

SURGERY VERSUS COMPRESSION IN C<sub>6</sub> DISEASE 2079

## Pharmacologic Therapies 2081

*Diuretics* 2081

*Zinc* 2081

*Fibrinolytic Agents* 2081

*Pentoxifylline* 2081

*Phlebotropic Agents* 2082

*Prostaglandins* 2082

*Other Medications* 2083

## CONCLUSION 2083

Chronic venous disease (CVD) of the lower extremity is one of the most common chronic diseases in western Europe and the United States.<sup>1–5</sup> The manifestations of CVD vary and include telangiectasias, enlarged reticular veins, varicose veins, lipodermatosclerosis, lower extremity pain and swelling, and venous ulcers. Its prevalence reported in studies from different countries ranges from 2% to 56% in men and 1% to 60% in women.<sup>4,6–12</sup> In the Edinburgh Vein Study from the UK, varicose veins were present in 40% of men and 16% of women, ankle edema was found in 7% of men and 16% of women, and ulcers were seen in 1% of men and women.<sup>6</sup> In the same study, the incidence of superficial vein reflux was noted to be 9.4% in men and 6.6% in women, and to increase with age.<sup>6</sup> A follow-up examination of patients from Edinburgh Vein Study 13 years later ( $13 \pm 0.4$  years [mean  $\pm$  SD]), which included CVD reclassification to ascertain progression of development of venous pathophysiology and/or increase in severity of symptoms, found progression in 57.8% of cases (annual equivalent increase of 4.3%) and increase in symptoms in 31.9% of cases.<sup>13</sup> The study also demonstrated that superficial venous reflux was

a predictor for increased likelihood of progression, especially with co-existing deep venous reflux (Odds Ratio [OR], 2.57; 95% Confidence Interval [CI], 1.55–4.25) and when located in the small saphenous vein (OR, 4.73; 95% CI, 1.37–16.39), emphasizing the value of early treatment.<sup>13</sup>

In the United States it is estimated that approximately 25% and 15% of women and men, respectively, have CVD symptom(s) and approximately 1% to 4% of the adult population is affected by more advanced stages of the disease including chronic, nonhealing venous ulcers (Class C6; Clinical Severity, Etiology or Cause, Anatomy, Pathophysiology [CEAP] classification).<sup>14–20</sup> When disease progresses to the advanced stages and venous ulceration develops, it not only significantly reduces patients' quality of life (QoL) but also imposes a significant economic burden on society related to increased direct healthcare costs and decreased productivity.<sup>21,22</sup> The estimated annual healthcare cost in the USA alone for the management of venous ulcers is between \$1.9 and \$3 billion with the greatest burden on the Medicare system.<sup>23,24</sup> These costs do not include decreases in mobility and work capacity, patients'

out-of-pocket expenses, and treatment of adverse psychologic effects related to venous ulcers. It should also be emphasized that CVD is increasing in prevalence as a result of increasing life expectancy in general and aging of the “baby boomer” generation; subsequently its impact on healthcare will likely become even more significant.<sup>24–27</sup> A recent review from 2019 showed that CVD represents a growing economic burden and that estimated global market for varicose veins treatment alone in 2021 will increase approximately 35% when compared to 2016, with respective values of US \$396 million and \$290.59 million.<sup>28</sup> Market analysis performed by The Millennium Research Group projected that total cost for treatment of varicose veins will reach approximately \$8 trillion by the year 2021.<sup>29</sup>

Whereas the invasive treatment of CVD includes surgical (high ligation of the saphenofemoral junction, saphenous vein stripping, stab phlebectomies), endovascular procedures (saphenous vein thermal and non-thermal techniques) and/or percutaneous stenting for iliac outflow venous obstruction, the initial treatment of CVD has traditionally been nonoperative, with the main goals of symptom control and QoL improvement. In addition, conservative measures are currently mandated by most third-party payers in the United States before approval of therapeutic surgical interventions. In this setting, the success of conservative management has long been considered to be a contraindication to more definitive surgical treatments. However, a QoL analysis from Lurie and Kistner questions the validity of this approach.<sup>30</sup> In this study, the authors compared the outcomes of surgical therapy in patients with favorable and unfavorable responses to initial conservative management using the Specific QoL and Outcomes Response—Venous questionnaire. Patients who improved with conservative therapy and who elected to proceed with surgical correction were 15 times more likely to improve with surgery at 1 month and 21 times at 12 months of follow-up, compared with those who did not improve with conservative therapy.<sup>30</sup> The authors concluded that conservative therapy should be used as a benchmark to predict success after surgical therapy, rather than as a contraindication to definitive intervention.

## NONOPERATIVE TREATMENT OF CVD

The nonoperative approach to patients with CVD includes lifestyle modification, compression, and pharmacologic therapies.

### Lifestyle Modification

The most common initial recommendations for lifestyle modification in patients with CVD are moderate exercise, leg elevation, and weight loss.<sup>31</sup>

### Exercise

In a review of literature, Brown<sup>31</sup> concluded that although vigorous exercise may increase the likelihood of venous ulcerations, increased mobility and moderate physical activity may be beneficial for ulcer healing and may be an adjunct to compression therapies. In 2019 Lurie’s group<sup>32</sup> analyzed the immediate effect of physical activity (30 lifts to tiptoes at a frequency

of one time per second) on venous hemodynamics using ultrasound in 61 patients with primary GSV incompetence. Data from this study showed statistically significant changes in reflux duration and reflux volume with respective rates of 4.85 seconds (interquartile range [IQR], 3.71–6.00 seconds) and 17.05 mL (IQR, 10.32–25.34 mL) before exercise and 2.86 seconds (IQR, 2.14–3.33 seconds) and 10.07 mL (IQR, 6.08–16.48 mL) after exercise. They also demonstrated that a decrease in the volume of reflux rate was inversely related to both the diameter of GSV and the Venous Clinical Severity Score (VCSS) of a patient ( $r = -0.56$ , and  $r = -0.41$ , respectively,  $P < 0.0001$ ). Findings from this study suggest that reduction of the volume of retrograde flow is due to the shortening of reflux time (and not the flow rate), implying that the GSV reflux is affected by exercise-induced changes in the volume of the lower extremity venous reservoir.<sup>32</sup>

Overall, patients with CVD should be encouraged to engage in regular moderate physical activity.<sup>31</sup> In a study by Roaldsen et al.,<sup>33</sup> it was observed that walking speed, endurance, and self-perceived exertion were significantly lower in 34 women aged 60 to 85 years with current or previous ulcers compared with age-matched controls. It was also noted that ankle plantar flexion and dorsiflexion were significantly reduced in patients with active ulcers, mostly because of pain. Patients with low levels of physical activity displayed stronger fear avoidance beliefs and more pain than those with higher levels of physical activity. These findings and observations from other studies emphasize the need for physical therapists to be highly involved in the care of patients with advanced C4–C6 disease, highlighting the importance of adequate pain control and a supervised exercise program tailored to improve ankle mobility and overall functional ability.<sup>31,33</sup>

### Leg Elevation

Leg elevation has been shown to aid venous drainage, to increase venous return to the heart, and to reduce ankle edema.<sup>31</sup> Patients with significant CVD are advised to elevate their legs 30 cm above the heart several times during the day.<sup>31</sup> In addition, Abu-Own et al.<sup>34</sup> have shown enhancement of cutaneous microcirculation after leg elevation using Doppler fluxometry in patients with lipodermatosclerosis, with a median 45% Doppler flux increase.

Transcutaneous tissue oxygen saturation levels have been used as an indicator of skin perfusion. These have been found to be reduced in patients with venous ulcers. Several authors have reported higher transcutaneous tissue oxygen saturation levels with compression strategies, standing position, and ambulation compared with leg elevation with or without compression.<sup>35</sup> However, it is unclear how the transcutaneous tissue oxygen saturation levels correlate with ulcer healing. A retrospective Australian study of 122 patients with previous venous ulcers observed for 12 to 40 months found that significantly lower rates of recurrence were associated with compression therapy and longer leg elevation times (33 min/day).<sup>36</sup> Recurrence was observed with a 14-min/day period of leg elevation. The authors of the study recognized limitations due to the retrospective design of their analysis and possible response

bias, as all the measures of physical activity, psychosocial scales, and self-care activities were obtained from self-report questionnaires.<sup>36</sup>

Leg elevation seems to be beneficial in symptom control in all patients with CVD. There is a trend supporting some advantage in ulcer healing, despite the evidence of levels of evidence 1 and 2 studies.<sup>31</sup> In addition, the utility of leg elevation is limited by the practical difficulty of prolonged leg elevation for many patients.

### Weight Loss

Numerous epidemiologic and clinical studies have identified obesity as an important factor for the development of CVD, disease progression, and correlation of symptoms.<sup>37–43</sup> Three landmark epidemiologic studies (the Edinburgh Vein Study, the Bonn Vein Study, and the San Diego Study) showed that, in addition to age, obesity was an independent risk factors for the development and progression of CVD.<sup>38,40,41,43,44</sup> Data from the Bonn Vein Study showed that patients with a BMI ( $\text{kg}/\text{m}^2$ ) of 25–29.9, 30–40, and  $>40$  had odds ratio for the risk of disease progression of 2.26, 2.86, and 3.47, respectively, when compared to patients with a normal BMI.<sup>38</sup> More recently, in 2020 Deol et al.<sup>37</sup> showed an inverse relationship between progressive increase in BMI and CVD-related treatment outcomes efficacy as measured using the revised VCSS and Chronic Venous Insufficiency Quality of Life Questionnaire 20-item (CIVIQ-20). This study showed progressively worse outcomes in patients with a BMI  $>35 \text{ kg}/\text{m}^2$  and poor outcomes in patients with a BMI  $\geq 46 \text{ kg}/\text{m}^2$ . Based on this data authors of the study consider BMI  $\geq 46 \text{ kg}/\text{m}^2$  to be a relative contraindication for treatment and recommend weight loss counseling for these patients.

Although pathophysiologic mechanism(s) pertinent to the role of obesity in the progression and severity of CVDs remains to be elucidated, sufficient evidence is available of its effects on disease severity and treatment outcomes to warrant recognition of obesity as significant comorbidity and to incorporate weight loss in the treatment of CVD.

## Compression Therapy

Both Hippocrates (460–370 BCE) and Aurelius Celsus (25 BCE–AD14) utilized compression in their treatment of venous disease.<sup>45,46</sup> Although compression therapy is one of the oldest treatment modalities for patients with CVD it was only recently that quantitative parameters of compression were established. The “dose” of compression is the pressure amount applied by a compression device to the skin (referred as “interface pressure”).<sup>47</sup> It is worth emphasizing that at the time of writing this chapter only graduated compression stockings are standardized using the interface pressure parameter. In addition, standardization of compression stockings usage required consensus among practitioners pertinent to determination of a specific anatomic point for the measurement of interface pressure in the lower extremity.

By consensus, the so called “B1 point” was defined to be the most feasible to determine clinically, as it is located

approximately 80 mm above the ankle and is anatomically delineated as the most distal part of the medial gastrocnemius muscle (point on the skin overlying the anatomic location where a tendon inserts into the gastrocnemius muscle).<sup>48</sup> “The B1 point” is used as the reference point for the label on all graduated compression stockings and it represents the pressure measured *ex vivo* at this point only. It is important to note that the aforementioned method utilized for labeling of compression stockings also implies the fact that the pressure applied outside of the point B1 is unknown and may significantly differ from the label on the stocking.<sup>49,50</sup>

Compression therapy is an essential component of the care of patients with CVD (C2–C6). The rationale for gradient external compression is to oppose the main pathologic factor underlying CVD, venous hypertension, and compression therapy has been found to have a number of additional benefits.<sup>51</sup> Given a normal standing resting venous pressure of 60 to 80 mm Hg, major hemodynamic effects can be expected, with an interface compression of 35 to 40 mm Hg. External compression of more than 60 mm Hg has been found to occlude lower extremity veins in standing individuals. Therefore 60 mm Hg has been considered the safe upper limit for externally applied sustained compression, as shown by dermal blood flow investigations, even in patients with an ankle–brachial index above 0.5 and absolute ankle pressure higher than 60 mm Hg.<sup>21,51,52</sup>

Compression therapy has also been shown to improve venous pump function. Enhanced venous flow velocities have been noted with low-grade interface pressure of 15 to 25 mm Hg with prevention of thromboembolic events in supine patients.<sup>51</sup> The biomolecular mechanisms by which compression therapy functions are unclear. Animal and clinical studies have documented that compression therapy improves cutaneous microcirculation.<sup>53</sup> Video capillary microscopy showed an increase in capillary density with decreased capillary diameter and pericapillary halo in 20 patients with varicose veins and lipodermatosclerosis treated with compression therapy.<sup>53</sup> Several authors have also noted enhancement of lymphatic drainage and cutaneous oxygenation, as demonstrated by increased transcutaneous tissue oxygen saturation levels.<sup>35,53–55</sup> Decreased serum levels of tumor necrosis factor- $\alpha$  and vascular endothelial growth factor have been observed in patients with healing ulcers treated with four-layer graduated compression.<sup>56</sup> The improved cutaneous microcirculatory environment has been thought to promote venous ulcer healing as has been suggested by several studies.<sup>57–59</sup>

A number of compression garments are available. These include gradient elastic stockings and the CircAid garment, paste gauze boots (Unna boot), layered elastic and nonelastic compression bandages, and intermittent pneumatic compression (IPC).

### Gradient Elastic Stockings

Gradient elastic stockings were first developed in the 1950s; they are currently manufactured by numerous companies and are available in various strengths and lengths. The compression applied by the stocking is calculated on the basis of the mechanical properties of the fabric used by each manufacturer.

The pressure applied to the ankle by the stocking is expressed as a range and is a function of *in vitro* measurements based on leg circumferences.

Gradient compression stockings are currently available in 4 strengths: 10 to 15 mm Hg (class 1; over-the-counter); 20 to 30 mm Hg (class 2; prescription); 30 to 40 mm Hg (class 3; prescription); and 40 to 50 mm Hg (class 3 – high compression; prescription). They are also available in different lengths, including knee-high, thigh-high, and panty hose. They are fitted on the basis of measurements of circumference, usually at thigh, midcalf, and ankle levels, and may be individually customized in patients with atypical leg morphology, such as may be seen in the obese or patients with advanced CVD. Compression garments should be replaced every 6 to 9 months, as the elasticity is lost after this time.<sup>57</sup>

#### Gradient compression stockings in C1–C2 disease

A number of studies have reported the efficacy of gradient elastic stockings in early and advanced stages of CVD. In a prospective randomized multicenter trial conducted in France of 125 women with CEAP classification of C1-3SEpAs1-5, it was noted that regular wearing of compression stockings (10–15 mm Hg) during a 15-day period was associated with significant symptom control when a high level of compliance in wearing the hose was achieved.<sup>60</sup> In a review of 11 prospective randomized trials, 12 nonrandomized studies, and two guidelines, no agreement was found regarding the appropriate class of compression for the management of early CVD stages.<sup>61</sup> Compression improved symptoms in patients with uncomplicated symptomatic varicose veins when high compliance was reached.<sup>61</sup> However, the use of compression stockings was not shown to prevent disease progression or recurrence of varicose veins after treatment. The same review highlighted that the majority of the published literature was often contradictory and had methodologic flaws, and that the results of several studies were confounded by a high number of noncompliant patients.<sup>61</sup>

It can be concluded that wearing of light compression stockings with a pressure below 20 mm Hg may be beneficial in the following indications: symptom control in C1s (grade 1B level of evidence); varicose veins in pregnancy (grade 1B level of evidence); prevention of leg edema related to prolonged sitting and standing (grade 1B level of evidence); and prevention of venous thromboembolism in non-ambulatory patients or after surgery (grade 1A level of evidence).<sup>21</sup> The recommendation for use of class 2 compression stockings in uncomplicated symptomatic varicose veins is also weak (grade 2B level of evidence) and only for symptom relief. Class 2 stockings have also been found to be poorly associated with the prevention of varicose veins after surgery and the treatment of venous ulcers (grade 2B level of evidence).<sup>21</sup>

#### Surgery versus compression in C2–C3 disease

In the “Randomised clinical trial, observational study, and assessment of cost-effectiveness of treatment of varicose veins” (REACTIV trial),<sup>62</sup> out of 1009 patients, 357 patients were placed in 3 groups based on clinical severity and then

randomized to treatment groups as follows: 34 patients with minor varicose veins and no superficial venous reflux (group 1) were randomized to conservative management versus sclerotherapy; 77 patients with moderate varicose veins and superficial venous reflux (group 2), were randomized to sclerotherapy versus surgery; and 246 patients with severe varicose veins and superficial venous reflux (group 3) were randomized to conservative treatment versus surgery. The remaining 652 patients were used to form the observational part of the trial.<sup>62</sup> Conservative treatment included lifestyle modification, leg elevation, and compression stockings; the surgery arm included high ligation of the saphenofemoral junction, saphenous vein stripping, and phlebectomies. The study demonstrated a significant benefit in QoL, symptom relief, and patient satisfaction in the surgical treatment at two-year follow-up in groups 2 and 3. In group 1, sclerotherapy produced an incremental benefit over conservative therapy. Surgery was found to be more cost-effective than conservative management in patients with C2 disease. Injection sclerotherapy also appeared to be cost-effective for patients with superficial venous reflux but was found to produce less benefit compared with surgery.<sup>62</sup>

Sell et al. analyzed 153 patients with class C2–C3 venous disease randomized to receive either conservative treatment with compression stockings ( $n = 77$ ) or surgical stripping of the GSV ( $n = 76$ ).<sup>63</sup> At 2-year follow-up data from this study demonstrated that VCSS without compression stockings (VCSS-S) decreased from 4.6 to 3.5 in the compression group ( $P < 0.01$ ) and from 4.8 to 0.6 in the surgery group ( $P < 0.001$ ). Data also showed that Venous Segmental Disease Score (VSDS) decreased from 7.7 to 7.0 in the compression group and from 8.2 to 0.9 in the surgery group ( $P < 0.0001$ ). Health-related quality of life (HR-QoL) measured with a disease-specific Aberdeen Varicose Vein Questionnaire (AVVQ) did not change in the compression group, but improved significantly in the surgery group at both 1 and 2-year follow-up.<sup>63</sup>

The current guidelines from the Society for Vascular Surgery and the American Venous Forum recommend against conservative therapy alone for patients with C2 and C3 disease when there is a compelling indication for saphenous stripping or ablation.<sup>21</sup> These guidelines also highlight the lack of scientific evidence to support the initial period of conservative therapy mandated by many health insurers in patients who are suitable candidates for surgical therapy.<sup>21</sup>

#### Gradient compression stockings in C4–C6 disease

Class 3 gradient elastic stockings are the standard of care in advanced disease (C4–C6). The authors of a cohort study from Oregon Health Sciences University reported a 15-year experience in 113 patients with C4–C6 disease who were treated with initial bed rest, ulcer debridement, dressing changes, and class 3 compression stockings.<sup>64</sup> Ulcer healing required an average of 5.3 months, occurring in 97% of compliant patients, with a 16% recurrence rate. The 2012 update of a Cochrane review from Nelson et al.<sup>65</sup> specifically assessed the effects of compression therapy in preventing ulcer recurrence. Four trials (979 patients) were identified. In one trial ( $n = 153$ ), recurrence rates were significantly reduced in the compression group

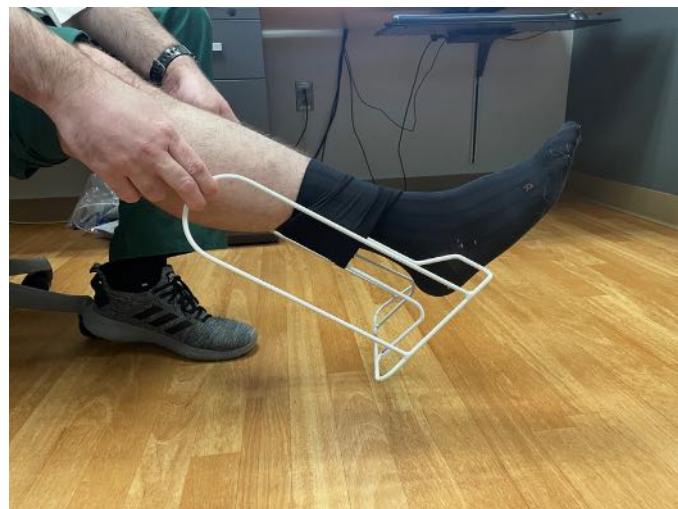
at a 6-month follow-up. No difference was noted between high compression (Class 3 and Class 4) and moderate compression (Class 2) in ulcer recurrence in the other three trials. Moderate compression stockings were associated with higher compliance to therapy.<sup>65</sup>

Patient compliance with compression therapy is both critical to the successful treatment of chronic venous insufficiency (C3–C6), particularly in patients with C4–C6 disease, and at the same time one of the biggest challenges for patients, particularly those with advanced age, obesity, and arthritis. Patients must be educated about the importance of compression therapy with ongoing reinforcement of this concept. Aids have been developed to allow application of stockings in patients who are challenged; stocking donners (Fig. 157.1) have been designed and are currently available on the market, although many insurers do not cover these adjuncts.

### Gradient compression stockings and prevention of post-thrombotic syndrome in acute deep vein thrombosis

Data from Centers for Disease Control and Prevention estimates that as many as 600,000 people (1–2 per 1000) are affected by deep vein thrombosis (DVT) and pulmonary embolism (PE) annually, with estimates of 60,000 to 100,000 patients dying from these diseases in the United States.<sup>66</sup> Approximately 33% of the population with DVT/PE will develop a recurrence within 10 years, and 20% to 50% of those patients will experience long-term complications such as post-thrombotic syndrome PTS.<sup>66</sup>

The pathogenesis of PTS is complex and includes a post-thrombotic inflammatory reaction involving the venous wall and valves with subsequent remodeling, development of venous hypertension, varicose veins, skin changes, and ultimately



**Figure 157.1** A stocking donner. Metallic frame and plastic sleeve designed to facilitate the application of graduated compression stockings. (From Moneta GL, Partsch H. Chronic venous disorders: non-operative treatment. In: Cronenwett JL, Johnston KW, eds. *Rutherford's Vascular Surgery*. 7th ed. Philadelphia: Saunders Elsevier; 2010.)

venous ulcers.<sup>67</sup> Gradient compression stockings can potentially reduce the risk of PTS by counteracting this basic pathogenetic mechanism.

Numerous clinical studies evaluated the efficacy of compression stockings in the management of PTS.<sup>68</sup> In two prospective randomized trials,<sup>69,70</sup> a statistically significant 50% PTS absolute risk reduction was found in patients with a first episode of proximal DVT (iliac, femoral, and/or popliteal vein) who wore a class 3 compression stocking for 2 years. Data from a relatively recent, multicenter (12 hospitals), randomized, single-blind study of optimal duration of compression therapy in DVT treatment (Individualized Versus Standard Duration of Elastic Compression Therapy for Prevention of Post-thrombotic Syndrome – IDEAL DVT trial)<sup>71</sup> that included 865 patients randomized to individualized duration compression stockings ( $n = 437$ ) and to standard 24 months duration ( $n = 428$ ) showed that PTS occurred in 125 of 432 patients (29%) who were in the individualized duration group and in 118 of 424 (28%) patients treated with standard duration of therapy (OR, 1.06; 95% CI: 0.78–1.44). Per trial protocol, patients with two consecutive Villalta scores of 4 or less assigned to individualized treatment stopped compression therapy after 6 months. The overall mortality rate was 6% (24 patients) with respective rates of 4% (17 patients) and 2% (7 patients) in the individualized treatment group and in the standard duration group. There were no treatment related deaths. In summary, data from IDEAL DVT trial demonstrated that individualized duration of elastic compression stocking was non-inferior to standard duration of 24 months.<sup>71</sup>

Data from another randomized, multicenter clinical study (One Versus Two Years of Elastic Compression Stockings for Prevention of Post-thrombotic Syndrome – OCTAVIA trial)<sup>72</sup> that evaluated the impact of compression therapy duration on its efficacy in 519 patients with proximal DVT showed that discontinuing compression therapy after 12 months in compliant patients was non-inferior to continuing therapy for 24 months. Nineteen percent (51 of 256) and 13.0% (34 of 262) of patients developed PTS in 12 months' and 24 months' duration of compression therapy group, respectively.<sup>72</sup>

However, data from a multicenter, randomized study (Compression Stockings to Prevent the Post-Thrombotic Syndrome after Symptomatic Proximal Deep Vein Thrombosis – The SOX trial)<sup>73</sup> that included 806 patients with proximal DVT treated either with elastic compression (30–40 mm Hg) stockings ( $n = 410$ ) or placebo elastic compression ( $n = 396$ ) contradicted previous studies and found no benefit of elastic compression stockings in the treatment of PTS. Data showed the cumulative incidence of PTS of 14.2% in elastic compression group versus 12.7% in placebo group and no statistical significance among groups ( $P = 0.58$ ).<sup>73</sup>

Although data from the SOX trial showed no benefit of elastic compression, some authors argued that the aforementioned results of the trial might have been due to several study limitations pertinent to selection bias, study endpoints, primarily related to timing of application of elastic compression stockings, the application itself, and definition and evaluation of compliance, as well as inadequate adherence to the treatment.<sup>68,74,75</sup>

Data from a 2019 meta-analysis showed that treatment with compression stockings is still likely to result in some degree of benefit.<sup>76</sup> In this study Avila et al. showed that the probability of observing large and small treatment benefits with compression therapy ranged between 47% (OR < 0.50) and 95% (OR < 1.00) for any PTS and between 16% and 82% for severe PTS.<sup>76</sup> However, another recent Cochrane review, also published in 2019,<sup>77</sup> based on the assessment of four clinical trials with 116 patients, showed that high-certainty evidence to support the use of compression therapy in prevention of PTS is currently lacking. The authors suggested that any conclusions drawn from current body of published evidence should be interpreted with care and that further research with long-term follow-up is needed to assess the efficacy of compression in the treatment of PTS.<sup>77</sup> These findings were consistent with data from a systematic review and meta-analysis published by Skervin et al. in 2016.<sup>78</sup> Data from their study that included 1177 patients failed to demonstrate benefit of compression stockings in preventing PTS due to sampling variability and statistical heterogeneity among trials.<sup>78</sup>

Similarly Jayaraj and Meissner showed that the use of graduated compression stockings does not reduce the incidence of PTS.<sup>79</sup> They evaluated 69 consecutive patients with duplex ultrasonography-confirmed DVT who were randomized to treatment with graduated compression stockings or no compression stockings. Both Villalta–Prandoni Score and VCSS were used as instruments for the assessment of PTS at 3, 6, 12, 18, and 24 months following DVT diagnosis. Kaplan–Meier analysis from this study showed the graduated compression stockings group had a lower incidence of PTS compared to the control group when 1 month was used as the cut-off time

for the first diagnosis of PTS.<sup>79</sup> However, when 6 months and 1 year were used as the cut-off time there was no difference in the PTS incidence. Interestingly, they also noted a significant difference in the PTS incidence at 2 years when detected by Villalta–Prandoni Score and by VCSS with respective rates of approximately 75% and 30%.<sup>79</sup> These findings emphasize the need for standardization of reporting methodology, primarily related to the selection of measuring instruments and definition of cut-off time intervals, for more accurate evaluation of compression stockings' role in the PTS treatment.

In summary, the evidence that gradient compression therapy prevents PTS after a first DVT episode is currently inconclusive and the subject is a matter of debate among practitioners. Compression stockings may be beneficial in symptom control in patients with severe DVT.

### CircAid Garment

The CircAid (Fig. 157.2) is a nonelastic compression appliance with multiple, stiff, pliable, adjustable Velcro bands. The system is as effective as compression stockings in reducing edema and promoting venous pump function, and may be recommended in patients who are unable or unwilling to wear class 3 stockings.<sup>80</sup> In a small prospective randomized trial, including 24 extremities with advanced CVD (C6) from Blecken et al., the CircAid system was found to have a significantly faster ( $P = 0.0173$ ) ulcer healing rate at 12 weeks' follow-up compared with a four-layer elastic bandage (hazard ratio: 0.56; 95% CI: 0.33–0.96).<sup>81</sup>

The CircAid system allows adjustment for limb size changes, ease and speed of application with improvement of comfort, and tolerance compared with compression stockings and



**Figure 157.2** The CircAid is a nonelastic adjustable compression appliance with multiple, stiff, pliable, adjustable Velcro bands. (From Moneta GL, Partsch H. Chronic venous disorders: non-operative treatment. In: Cronenwett JL, Johnston KW, eds. *Rutherford's Vascular Surgery*, 7th ed. Philadelphia: Saunders Elsevier; 2010.)

bandaging. In a review of nonelastic compressions, Bergan et al.<sup>82</sup> suggested that the CircAid legging device provides a counter force to perforating vein outflow (mimicking the action of the Unna boot). The authors also concluded that this action could result in improvement of cutaneous and subcutaneous microcirculation in a manner characteristic to results of perforating vein surgery, a surgical treatment modality that was associated with accelerated leg ulcer healing.<sup>83</sup>

### Unna Boot

The Unna boot was first developed by the German dermatologist Paul Gerson Unna at the end of the 19th century.<sup>84,85</sup> It consists of a multilayered compression dressing made of an inner layer of gauze bandage impregnated with calamine, zinc oxide, glycerin, sorbitol, gelatin, and magnesium aluminum oxide, and an outer layer of an elastic wrap exerting graded compression.

The bandage stiffens with drying, with improvement of venous return during ambulation and reduction of edema. The pressure exerted varies from 50 to 60 mm Hg. The dressing is changed weekly or sooner, depending on the amount of drainage.<sup>86</sup>

In a 15-year retrospective survey of 998 patients with venous ulcers, the Unna boot achieved a 91% healing rate for first-time ulcers and overall 73.3% healing rate in compliant patients. All patients were treated 12 times in 32 weeks.<sup>87</sup> The overall wound healing rate was superior with the Unna boot compared with polyurethane dressings in a multi-institutional randomized study.<sup>87</sup>

### Layered Elastic and Nonelastic Compression Bandages

Compression bandages are single-layer or multilayer dressings commonly used in patients with advanced CVD (Fig. 157.3).

Pressure, layers, components, elastic properties, and stiffness are all factors to be considered when such a dressing is applied. The pressure is a function of the outer bandage, and a sustained pressure of 60 to 70 mm Hg is the upper limit, especially over bony prominences.<sup>21,58,59</sup> The choice of dressings varies from wet to dry, hydrocolloids or impermeable (occlusive; Table 157.1) dressings.<sup>88</sup> Indications for each dressing type vary by the characteristics of the ulcer, the degree of skin inflammation, and the presence of infection (see Table 157.1).<sup>88</sup>

Bandages can be elastic, such as the Ace, SurePress, and Perfecta, or nonelastic, such as the Putter, Comprilan, and Coban bandages. The main disadvantage of nonelastic bandages is the loss of pressure over time after application as the limb loses volume in response to compression. Training in application of the bandage is also important, because incorrect overlapping may cause additional ulcers. Elastic bandages are easier to apply. They may exert a higher resting pressure that is maintained over time. Disadvantages are possible discomfort due to higher resting pressure and the possibility of skin ulcer, especially over bony prominences if adequate skin padding is not applied.

In a systematic review from O'Meara et al., 48 randomized, controlled trials with 4321 venous ulcer patients were identified.<sup>89</sup> Several bandage systems were compared, with ulcer healing rate as the primary outcome. The results were consistent with an overall increased effectiveness of multicomponent systems containing an elastic bandage versus those with inelastic constituents.<sup>89</sup>

O'Meara et al. also compared the effectiveness of four-layer and short stretch single-layer bandages in a meta-analysis published in 2009.<sup>90</sup> Four eligible trials with a total of 887 patients were identified. It was noted that four-layer bandages were associated with shorter healing time and larger ulcers; chronic ulceration and previous ulcerations were found to be independent predictors for delayed ulcer healing.<sup>90</sup>



**Figure 157.3** Compression bandages can be single layer (A), nonelastic (B), or multilayer (C and D). (From Enoch S, Grey JE, Harding KG. ABC of wound healing. Non-surgical and drug treatments. *BMJ*. 2006;332:900–903.)

**TABLE 157.1** Different Types of Dressings and their Uses

Type of Dressing	Trade Names	Features	Indications
Hydrocolloids	Comfeel Plus, DuoDERM E, Algoplaque HP, Askina Biofilm, Suprasorb H, Hydrocoll standard	Thick adhesive 1 application/2–7 days without secondary dressing	Mildly exuding ulcer
	Comfeel Plus transparent, Comfeel Plus Brûlures, Comfeel Oval, DuoDERM extra thin, DuoDERM extra thin oval, Algoplaque film, Hydrocoll thin	Thin adhesive 1 application/2–7 days without secondary dressing	
Foam dressings Granulation and epidermization stages, exudative ulcers	Allevyn adhesive, Biatain adhesive, Cellosorb adhesive, CombiDERM, Mepilex Border, PermaFoam comfort, Suprasorb P adhesive, Tielle	Thick adhesive 1 application/2–7 days without secondary dressing	Heavily exuding ulcer, granulating ulcer, altered peripheral wound skin (nonadhesive form)
	Allevyn Lite, Cellosorb Lite, Mepilex Border em	Thin adhesive 1 application/2–7 days without secondary dressing	
	Allevyn nonadhesive, Biatain nonadhesive, Cellosorb, CombiDERM N, Mepilex Transfer, Suprasorb P nonadhesive, Tielle S	Nonadhesive 1 application/2–7 days with a secondary dressing	
	Allevyn Gentle, Biatain Contact, Mepilex, Mepilex em	Microadherent 1 application/2–7 days with a secondary dressing	
	Biatain Ibu, Biatain Ibu contact		Painful ulcer
Alginates	Algosteril, Melgisorb, SeaSorb Soft, Sorbalgon Plus, Urgosorb	1 application/1 to 2 days with a secondary dressing	Infected ulcer, hemorrhagic ulcer, heavily exuding ulcer (debridement stage)
Hydrogels	DuoDERM hydrogel, Hydrosorb gel or plaque, Hypergel, IntraSite gel conformable, Normigel, Purilon Gel, Urgo Hydrogel	1 application/2 days with a secondary dressing	Necrotic ulcer, dry ulcer
Hydrofibers	Aquacel	1 application/1–2 days with a secondary dressing	Infected ulcer, heavily exuding ulcer (debridement stage)
Impregnated or coated meshes (interface dressings or low-adherence dressings)	Adaptic (paraffin), Urgotul (lipidocolloid), Physiotulle (petroleum and hydrocolloid), Mepitel (silicone)	1 application/1–7 days with a secondary dressing	Mildly exuding ulcer, altered peripheral wound skin
Hyaluronic acid-based dressing	Hyalgan (alginate hydrogel film), Hyalofill, Hyalogram (alginate hydrogel and alginate), Jaloskin (alginate hydrogel film), Ialuset cream or impregnated gauze, Effidia	1 application/1–7 days with a secondary dressing	Mildly exuding ulcer
Charcoal dressings	Carbonet Actisorb Plus (containing silver) CarboFLEX (containing hydrofiber)	1 application/1–7 days with a secondary dressing	Foul-smelling ulcer
Silver dressings	Acticoat, Actisorb Silver, Urgotul S/Ag	1 application/1–3 days with a secondary dressing	Infected ulcer, foul-smelling ulcer
	Biatain Ag nonadhesive, adhesive (foam plus silver)	1 application/1–7 days	Infected ulcer, foul-smelling ulcer
	Cellosorb Ag nonadhesive (foam plus silver)		
	Aquacel Ag (hydrofiber plus silver) Ialuset Plus (hyaluronic acid plus silver)	1 application/day with a secondary dressing	Exuding ulcers
Protease-modulating dressings	Promogran (collagen-based dressing) Cellostart (foam dressing)	1 application/2–7 days with a secondary dressing	Hard-to-heal ulcer
Paraffin or petroleum gauzes	Grassolind neutral, Jelonet, Vaseline, Tulle gras Solvay	1 application/2 days with a secondary dressing	

Modified from Senet P. Local treatment of venous leg ulcers. *Phlebology*. 2010;17:7.

A systematic review of compression treatment for venous ulcers identified 24 randomized trials.<sup>91</sup> The results confirmed that compression therapy is the treatment of choice in patients with advanced CVD, and that high compression is associated with an overall significant increase in the odds of healing at 3 months. No difference was found between high compression single-layer versus multilayer systems and the Unna boot. In the same meta-analysis, two small trials showed superiority of compression stockings (84% healed at 3 months) versus short stretch bandages (52% healed at 3 months).<sup>91</sup>

Two systematic reviews from Partsch et al.<sup>92</sup> and Coleridge-Smith<sup>93</sup> found that the use of class 3 compression stockings promotes ulcer healing and reduces ulcer recurrence (grade 1A evidence).

A 2018 publication by Milic et al. compared the efficacy of 2 strengths of knee-high compression stockings (class 2 and class 3) in the prevention of venous ulcer recurrence.<sup>94</sup> Data from this open, prospective, randomized, single-center trial that included 308 patients (170 men, 138 women; mean age: 59 years) showed a statistically significant difference ( $P < 0.001$ ) in ulcer recurrence rates in patients treated with class 2 compression and class 3 compression with respective rates of 60.0 % and 28.9% at 5-year follow-up. Data also showed statistically significant difference ( $P < 0.001$ ) in absolute ulcer-free time (46 vs. 40 months, class 3 and class 2, respectively) and ulcer-free time rates (77% vs. 67%, class 3 and class 2, respectively) at 5-year follow-up. Rates of non-compliance after 5 years were 10.23% for the compression class 3 group and 6.25% for the compression class 2 group ( $P = 0.188$ ). Although data from this study suggested that class 3 compression stockings resulted in lower recurrence rates compared with class 2 compression stockings, further studies are needed for more accurate assessment and confirmation of these results.<sup>94</sup>

### Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) is a mechanical compression method in which external pressure is applied by the intermittent inflation of pneumatic boots (Fig. 157.4). Some devices include a single inflation chamber at a single pressure, while others include 2 to 3 chambers with different pressures at the ankle, calf, and thigh. These devices can be used to treat venous leg ulcers and lymphedema.<sup>95</sup> A Cochrane review authored by Nelson et al. identified seven randomized trials, including 367 patients treated with IPC.<sup>96</sup> In one trial (80 patients), IPC was found to be more beneficial than compression stockings in ulcer healing (62% vs. 28%;  $P = 0.002$ ). In four trials, IPC plus compression stocking therapy was compared with compression stocking therapy alone. Of these four trials, only one (45 patients) showed increased ulcer healing (relative risk [RR] for healing, 11.4%; 95% CI 1.6–82) in the IPC plus compression stocking group. The remaining three trials noted no evidence of benefit of IPC over compression stockings in ulcer healing. In one trial (104 patients), a higher rate of healed ulcers was associated with devices in which the inflation was rapid compared with those with slow inflation (86% vs. 61%; log rank  $P = 0.003$ ). Based



**Figure 157.4** Intermittent compression device. (From Enoch S, Grey JE, Harding KG. ABC of wound healing. Non-surgical and drug treatments. *BMJ*. 2006; 332:900–903.)

on these studies, IPC may be effective in controlling edema, particularly in patients with a lymphedema component, but there is no strong evidence to support its use in the treatment of venous ulcers.<sup>96</sup>

### Adaptive pressure multi-chamber system

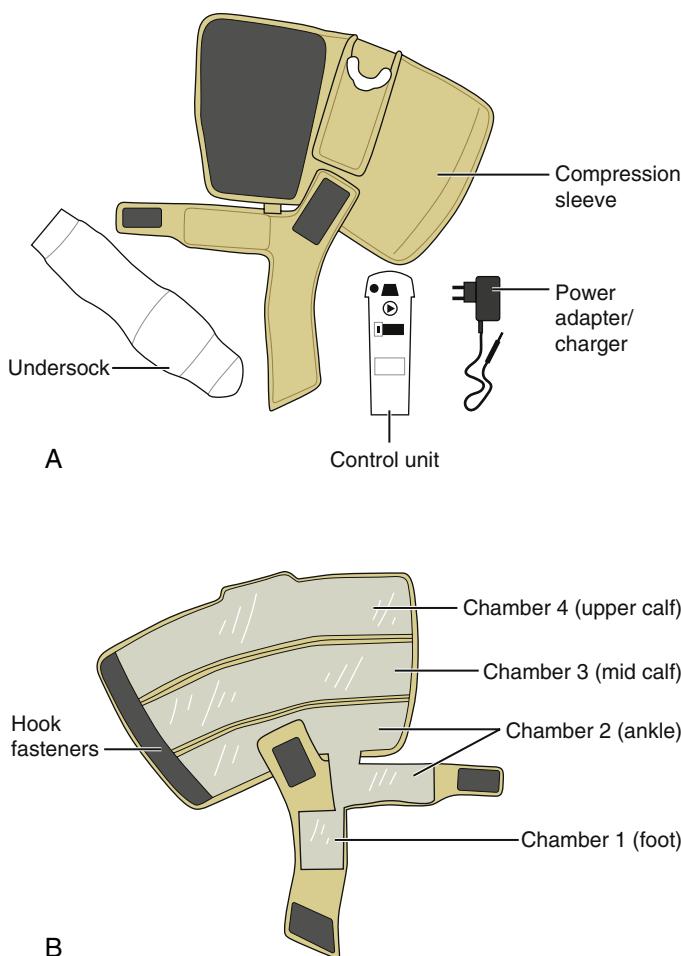
Recently, multicomponent pneumatic compression devices have become available to treat patients with C6 disease and poor compliance to compression stockings and/or bandages.

The ACTitouch device (ACT; Fig. 157.5) provides adaptive, intermittent, and sustained pneumatic compression. The device consists of a foot, and ankle and calf cuffs, linked together to form one complete functional unit. The inflation of the cuffs is controlled by a small, lightweight, low voltage microprocessor that monitors and continuously adjusts the degree of inflation of each cuff to the targeted pressure. The device can function in IPC and/or sustained pressure mode. When operated in sustained mode, a graded compression of 40 mm Hg is applied at the ankle, 30 mm Hg at midcalf, and 20 mm Hg at the knee. The IPC mode provided intermittent compression of 50 mm Hg at the foot and ankle, 45 mm Hg at the midcalf, and 40 mm Hg at the knee.

In a prospective randomized study, 90 patients with C6 disease were divided in two groups: ACT ( $n = 38$ ) and a four-layer bandage system ( $n = 52$ ).<sup>97</sup> Patients were instructed to wear the device for most of the day with 2 hours of IPC mode. At 12 weeks, ulcer healing rate and time to ulcer healing were similar between the treatments.<sup>97</sup>

In the ACT group, treatment performance was significantly higher in terms of exudate management, skin protection, removal ease, bathing, and sleep comfort. Quality of life was measured using the EQ-5D-3L health questionnaire<sup>98</sup> completed at baseline and at the end of the study. The QoL score was found to be 0.1025 higher in patients wearing the ACT device ( $P < 0.0375$ ). The ACT system may be considered in patients with C6 disease who failed graduated compression stockings and other means of compression therapy (Unna Boot, bandages, CircAid).<sup>97</sup>

A two-arm, randomized, multicenter study that included 89 C3 to C6 patients (136 limbs) with a history of low compliance

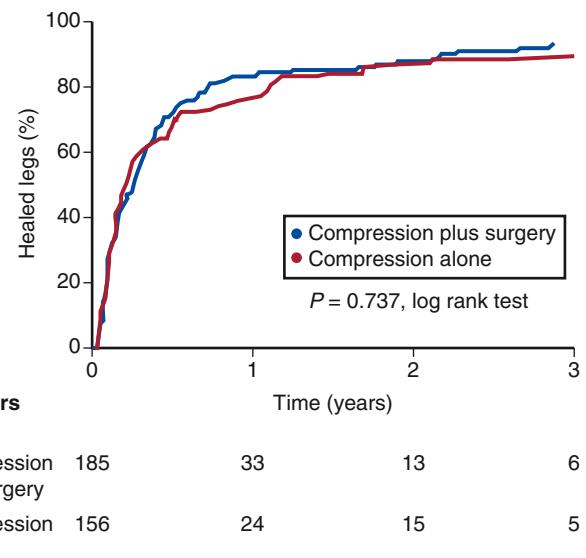


**Figure 157.5** ACTitouch device: (A) outer side views and (B) underside views. (From Harding KG, Vanscheidt W, Partsch H, et al. Adaptive compression therapy for venous leg ulcers: a clinically effective, patient-centered approach. *Int Wound*. 2016; 13(3):317–325.)

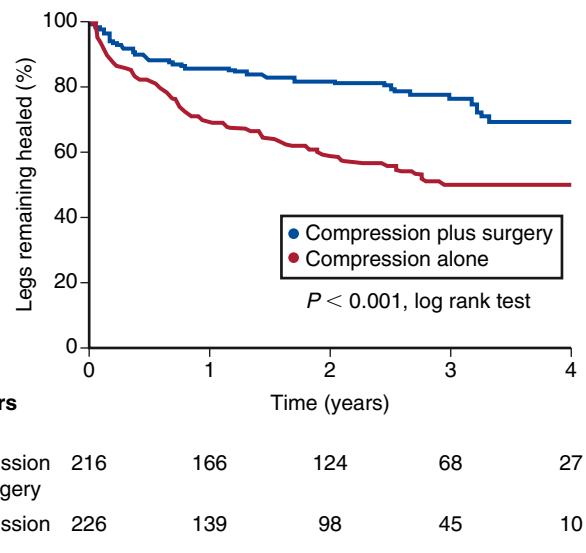
with compression stockings compared the ACTitouch device ( $n = 66$  limbs) with 30 to 40 mm Hg graduated compression stockings ( $n = 70$  limbs).<sup>99</sup> There was no statistically significant difference ( $P = 0.97$ ) in compliance with compression therapy between the groups (100% vs. 88% in ACTitouch and compression stockings groups, respectively, at 15 days and 87% vs. 85% at 1-month follow-up). Despite short follow-up times, based on data from this study authors implied that the ACTitouch device is comparable to compression stockings in the patient's acceptance and compliance of therapy.<sup>99</sup>

#### Surgery versus compression in C6 disease

In the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study, 500 patients with leg ulcers were randomized to compression alone and compression plus surgery (high ligation and stripping of the saphenous vein).<sup>100,101</sup> Compression consisted of multilayered bandaging every week until healing, then class 2 knee-high stockings. Whereas 24-week healing rates were similar in the two groups (65% vs. 65%; hazard, 0.84 [95% CI, 0.77–1.24];  $P = 0.85$ ), at 24 months the recurrence rate was significantly lower in the compression–surgery group (12% vs. 28%; hazard,  $-2.76$  [95% CI,

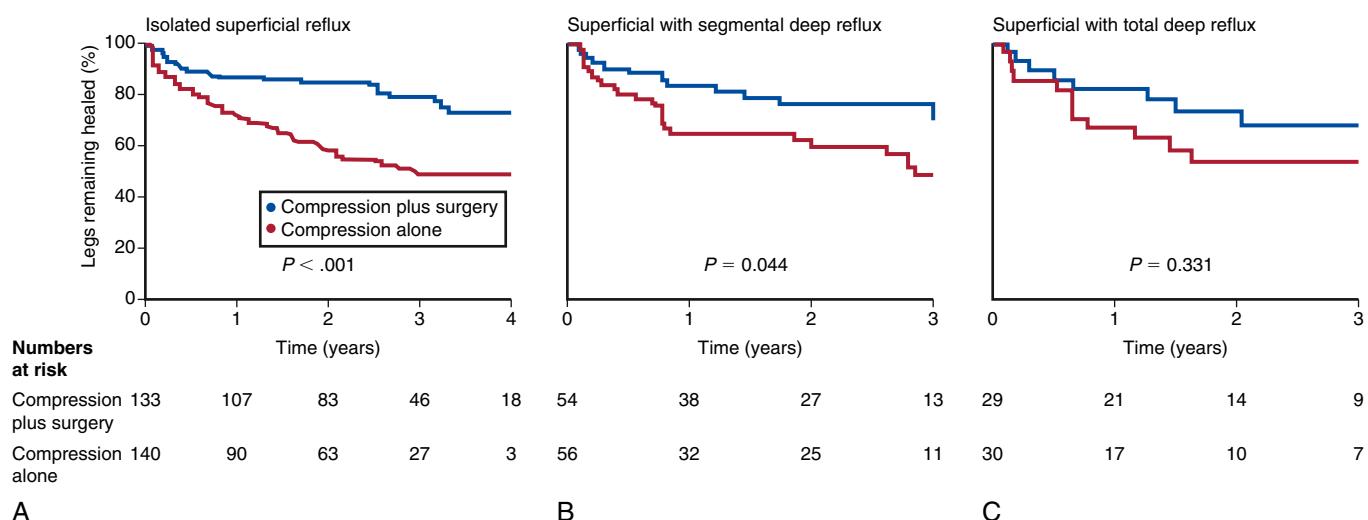


**Figure 157.6** Ulcer healing rates were not statistically significantly different between the groups at 3 years (compression, 89%; surgery–compression, 93%;  $P = 0.73$ ). (From Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration [ESCHAR study]: randomized controlled trial. *Lancet*. 2004;363:1854–1859.)



**Figure 157.7** The rates of ulcer recurrence at 4 years were 56% for the compression-alone group and 31% for the compression–surgery group. (From Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration [ESCHAR study]: randomized controlled trial. *Lancet*. 2004;363:1854–1859.)

$-1.78$  to  $-4.27$ ;  $P < 0.0001$ ). In a second report published in 2007, long-term results of the ESCHAR trial were analyzed.<sup>102</sup> Overall ulcer healing rates were not statistically significantly different between the groups at 3 years (Fig. 157.6). The rates of ulcer recurrence at 4 years were 56% for the compression-alone group and 31% for the compression–surgery group (Fig. 157.7).<sup>102</sup> The benefit of the combined compression–surgery approach was noted mostly in the subgroup of patients with superficial or segmental deep vein reflux (Fig. 157.8).<sup>100,102</sup>



**Figure 157.8** Ulcer recurrence rates were significantly reduced in the subgroup of patients with superficial (A and C) or segmental deep vein reflux (B). (From Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. *Lancet.* 2004;363:1854–1859.)

A systematic review and meta-analysis published in 2014 by the Mayo Group that included data from seven randomized trials, two non-randomized studies and one retrospective cohort study compared surgical intervention (open or endovascular) with compression with respect to ulcer healing, ulcer recurrence, and time to ulcer healing.<sup>103</sup> Seven studies evaluated ulcer healing in 1143 lower extremities treated either with open surgery ( $n = 572$ ) or compression therapy ( $n = 571$ ).<sup>101,102,104–109</sup> The pooled risk ratio (RR) was 1.06 (95% CI, 1.00–1.13;  $I^2 = 9.9$ ), indicating that ulcer healing outcomes were just marginally superior in the surgery group. A subgroup analysis that evaluated outcomes of randomized trials only, showed no difference in ulcer healing outcomes (pooled RR of 1.04; 95% CI, 0.98–1.09;  $I^2 = 0.0$ ).<sup>103</sup> Ulcer recurrence outcome was evaluated in 887 patients from three studies.<sup>102,105,109</sup> Data showed a pooled RR of 0.54 (95% CI, 0.34–0.85;  $I^2 = 26.6$ ), demonstrating statistically significant reduction of ulcer recurrence with surgical intervention. A subgroup analysis following exclusion of nonrandomized trials showed no statistically significant ulcer recurrence reduction defined by pooled RR of 0.67 (95% CI, 0.41–1.10;  $I^2 = 0.0$ ).<sup>103</sup> Time to ulcer healing was not significantly different among 150 and 158 limbs treated with surgery and compression, respectively demonstrated by the pooled difference in means from three randomized trials, which was –0.41 months (95% CI: –0.89 to 0.07;  $I^2 = 10$ ).<sup>104–106</sup> Additionally, in the Mayo Group review<sup>103</sup> ulcer healing outcomes following treatment with endovenous ablation or compression therapy were evaluated based on data from 93 and 94 limbs, respectively (total 187 limbs) that were extrapolated from two randomized trials and one cohort study.<sup>110–112</sup> They found no statistically significant difference among compared treatment modalities as determined by the pooled RR of 1.29 (95% CI: 0.76–2.19;  $I^2 = 51.7$ ).<sup>103</sup> Ulcer recurrence rate and time to ulcer healing were reported in one retrospective study.<sup>112</sup> Recurrence rates

at 12 months were 26.2% and 57.5% in patients undergoing endovenous ablation and compression treatment, respectively. These data suggest that endovenous ablation is beneficial in reducing venous ulcer recurrence when compared to compression therapy alone. Endovenous ablation also resulted in faster healing of ulcers when compared to compression with respective median times of 7.9 weeks (IQR, 8.1 weeks) and 22.0 weeks (IQR, 44.7 weeks).<sup>112</sup> In summary, the Mayo Group review and meta-analysis showed that surgical treatment improves venous ulcer healing but didn't definitely demonstrate superiority of endovascular treatment modalities.<sup>103</sup> However the quality of this evidence was low because it included a significant amount of data from observational studies.

In a prospective, randomized, multicenter trial with long-term follow-up (mean 97 months; range 72–172 months) that included 198 lower extremities in 170 patients van Gent et al. confirmed the benefit of surgical intervention.<sup>113</sup> Their intention-to-treat analysis demonstrated statistically higher ( $P = 0.007$ ) ulcer-free incidence rates in limbs treated with combined superficial and perforating vein surgery when compared with compression therapy, with respective rates of 58.9% and 39.6%. In addition, ulcer recurrence was documented in 48.9% in limbs treated with surgery whereas the rate in the compression group was approximately twofold higher (94.3%).<sup>113</sup> Not surprisingly, the number of incompetent perforating veins was identified as a statistically significant ( $P < 0.001$ ) predictor for ulcer nonhealing. Interestingly, despite described differences in objective outcomes, there was no statistically significant difference ( $P = 0.635$ ) in QoL between the two groups as documented by mean AVVQ of 22.0 (SD = 9.5, range 7.0–39.6) for the conservative treatment group and mean AVVQ of 23.6 (SD = 12.4, range 2.6–45.0) for the surgically treated group.<sup>113</sup>

The ESCHAR trial<sup>100,102</sup> and other studies provide strong evidence that compression therapy, in conjunction with appropriate surgical intervention (high ligation and stripping,

endovenous ablation of saphenous veins by thermal and chemical methods), is a vital part of the ongoing care and treatment of patients with venous ulcers. The clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)<sup>22</sup> also support this approach.

## Pharmacologic Therapies

Pharmacologic therapy in venous disease is directed toward symptom control in patients with mild to moderate CVD and the treatment of venous ulcers. Pharmacologic targets have been identified on the basis of advances in the understanding of the pathogenesis of the molecular mechanisms of CVD, and a substantial number of agents have been developed and studied.<sup>21,114</sup> A cost analysis of severe CVD in 19,750 German patients showed that 11% had consumed medications designed to treat venous disease in the preceding 12 months; 80% of the purchasers were women, and the majority were older than 50 years.<sup>115</sup> Indications for the medications were varicose veins (58%), leg pain (30%), and various degrees of lower extremity venous disease (30%). A Cochrane database review<sup>116</sup> published in 2005 included 44 prospective randomized trials involving 4413 patients, in which the efficacy of several medications was assessed. Outcomes included edema, venous ulcers, lipodermatosclerosis, subjective symptoms, global assessment measures, and adverse reactions. Among the different medications, phlebotropic drugs, of which the micronized purified flavonoid fraction (MPFF) is the most prominent, showed some degree of benefit (RR, 0.72; 95% CI: 0.65–0.81). The authors concluded, “There is not enough evidence to globally support the efficacy of phlebotonics for chronic venous insufficiency. There is a suggestion of some efficacy of phlebotonics on edema but this is of uncertain clinical relevance. Due to the limitations of current evidence, there is a need for further randomized, controlled clinical trials with greater attention paid to methodologic quality.”<sup>116</sup>

### Diuretics

The role of diuretics in CVD treatment is still controversial as only anecdotal evidence from historical practices and small-scale obsolete research suggests their benefits. It seems they may have some benefit in reducing edema in patients with chronic congestive heart failure.

### Zinc

Zinc ( $Zn^{2+}$ ) is a trace element and a cofactor of more than 100 enzymatic processes involved in DNA replication, protein synthesis, and cell division. Zinc also plays a key role in the humoral and cell-mediated immunity responses and wound-healing.<sup>117</sup> More importantly for the purpose of this chapter,  $Zn^{2+}$  plays an important role in the physiology of the venous wall, since the outermost venous layer (the adventitia) consists of fibroblasts that are embedded in an extracellular matrix (ECM) of proteins such as collagen and elastin.<sup>118–120</sup> The ECM is modulated by multi-domain,  $Zn^{2+}$ -dependent matrix metalloproteinase (MMPs) secreted by fibroblasts, vascular smooth

muscle (VSM), and leukocytes as inactive pro-MMPs.<sup>118,121</sup> Studies demonstrated that MMPs may promote cell proliferation, migration, and differentiation and could play a role in cell apoptosis, immune response, tissue healing, and angiogenesis which all combined have a significant function in the pathogenesis of CVD.<sup>122–126</sup> Despite initial enthusiasm regarding MMPs’ implications in the pathogenesis of CVD (and vascular diseases in general) and for the development of potential novel therapeutic modalities that would target these endopeptidases, the exact molecular mechanism how  $Zn^{2+}$ -dependent MMPs affects venous system in CVD patients remains to be elucidated, and therefore therapeutic applications remain theoretical.

Consistent with the aforementioned basic science considerations, it is also clear from the clinical literature that there is insufficient evidence to determine if topical  $Zn^{2+}$ -based wound products are effective in venous ulcer(s) healing despite the fact that numerous wound care products contain topical  $Zn^{2+}$ .<sup>127,128</sup> Similarly, despite reports of low  $Zn^{2+}$  levels in patients with venous ulcers and a few reports of a beneficial effect of oral  $Zn^{2+}$  supplementation in the healing of venous ulcers, a Cochrane review from Wilkinson<sup>129</sup> including 6 small trials found no evidence of benefit in oral  $Zn^{2+}$  supplementation on the number of ulcers healed.

### Fibrinolytic Agents

In 1982, Burnand et al.<sup>130</sup> observed the presence of fibrin cuffs surrounding the dermal capillaries of 26 lower extremities with lipodermatosclerosis. This finding was confirmed by Falanga et al.<sup>131</sup> in 1987, along with reduced transcutaneous tissue oxygen saturation levels in the skin around the ulcer. They postulated that, in the setting of venous hypertension, increased intraluminal pressure favors diffusion of fibrinogen through the capillary endothelium from the intravascular space to the interstitial compartment. After fibrinogen is polymerized within the pericapillary space, fibrin cuffs served as the restricting barrier for oxygen diffusion, which ultimately led to tissue hypoxia.<sup>130,132</sup> Despite these observations, trials involving medications with fibrinolytic activity, such as stanozolol and sulodexide glycosaminoglycan, failed to prove beneficial in ulcer healing.<sup>114</sup> Additionally, this is supported by data from a study of 25 patients (10 with lipodermatosclerosis) that showed that molecules 4 times bigger than oxygen (such as Xenon-133 isotope) were capable to diffuse through the tissue affected by lipodermatosclerosis showing no support to the proposition that the delivery of oxygen is affected by fibrinous cuffs.<sup>133</sup>

### Pentoxifylline

Pentoxifylline was initially developed to treat PAD and has been used off label in patients with venous ulcers.<sup>134–136</sup> It is a competitive nonselective adenylate cyclase inhibitor with several activities, including increase of intracellular cyclic adenosine monophosphate, activation of protein kinase A, inhibition of tumor necrosis factor, and promotion of leukotriene synthesis.<sup>137–140</sup> The pharmacologic effects of pentoxifylline are related to red blood cell deformability and inhibition of platelet aggregation and thrombus formation.<sup>141</sup> Pentoxifylline also has an anti-inflammatory effect that is probably related to

the selective depression of tumor necrosis factor expression and significant inhibitory effect on cytokine-mediated neutrophil activation, leukocyte adhesion to endothelium, and oxidative stress.<sup>142</sup> A prospective randomized trial published in 2007 compared the effectiveness of pentoxifylline, knitted viscose or hydrocolloid dressings, and single-layer or four-layer bandaging for venous ulceration.<sup>143</sup> The study enrolled 245 patients with venous ulcers. The main outcome was time to complete ulcer healing. The dose of pentoxifylline administered was 1200 mg by mouth daily. Initial results showed that pentoxifylline was associated with a statistically nonsignificant improvement in ulcer healing (62% vs. 53%;  $P = 0.21$ ). Further analysis with a Cox regression model resulted in a clinically significant improvement in ulcer healing with pentoxifylline (RR for healing, 1.4; 95% CI: 1.0–2.0).<sup>143</sup>

A Cochrane review, from 2012, included 12 trials and 864 patients.<sup>144</sup> In 11 trials that compared pentoxifylline (400 mg PO 3 times a day [TID], with an exception of one arm of a three-armed study that administered 800 mg TID)<sup>145</sup> with placebo or no treatment, a significant improvement or ulcer healing was noted (RR, 1.70; 95% CI: 1.30–2.24) in pentoxifylline groups. Pentoxifylline plus compression was found to be more effective than compression alone (RR, 1.56; 95% CI: 1.14–2.13). Pentoxifylline alone was more effective than placebo or no treatment (RR, 2.25; 95% CI: 1.49–3.39). Seventy-two percent of patients complained mostly of gastrointestinal adverse reactions. The authors concluded that there is evidence that pentoxifylline may be an effective adjunct to compression therapy in advanced CVD. This study also suggested that in the absence of compression, pentoxifylline alone was safe and effective for treating venous ulcers. The authors emphasized the statistical heterogeneity of evaluated trial results likely due to amount of “hard-to-heal” patients included, which could have resulted in an overall sample bias.<sup>144</sup>

### *Phlebotropic Agents*

Phlebotropic agents are medications with multiple pharmacologic microcirculatory activities that show a unique tropism for veins. The most important phlebotropics are found in the family of the  $\gamma$ -benzopyrone family (flavonoids).<sup>146</sup>

The “venoactive drugs,” especially flavonoids such as micronized purified flavonoid fraction (MPFF – Diosmin, Daflon, Hidrosmin), have been extensively used in Europe for a significant amount of time and their safety and efficacy have been studied in the reviews of numerous studies and guidelines.<sup>147–155</sup> However it was not until relatively recently when standardized formulation of MPFF became available in the U.S. (Vasculera, a micronized, highly purified 600 mg of Diosmin glycoside in combination with 30 mg alkaline granules Alka4-complex).<sup>156</sup> Despite this most of the physicians still have limited knowledge of MPFF pertinent to mechanism of action and potential for utilization as adjunct therapy for the management of patients with CVD.

Histopathology studies have shown that MPFF results in reduction of leukocyte adhesion and migration as well as in inhibition of the production of inflammatory molecules that

cause damage to the endothelium and subsequently increase capillary permeability.<sup>157</sup> The use of these agents has also been evaluated in numerous studies including systemic reviews and meta-analyses.<sup>151,156,158–167</sup> The meta-analysis included 10 prospective randomized trials published between 1975 and 2009, with a total of 1010 patients.<sup>158</sup> The primary outcome was effective treatment of venous edema by ankle diameter reduction. The result was a significant reduction in ankle diameter with MPFF ( $0.80 \pm 0.53$ ), compared with ruscus extract ( $0.58 \pm 0.47$ ), hydroxyethylrtoside ( $0.58 \pm 0.31$ ), diosmin ( $0.20 \pm 0.42$ ), and placebo ( $0.11 \pm 0.42$ ).<sup>158</sup> This confirmed 1A level of evidence assigned to MPFF in the management of symptoms and edema.

Another meta-analysis published by Coleridge Smith in 2005<sup>166</sup> included five prospective randomized trials and 723 patients with venous ulcers. MPFF and conventional treatment (local wound care and compression) were compared with conventional treatment plus placebo in two studies ( $n = 309$ ) and conventional treatment alone in three studies ( $n = 414$ ). Primary outcome was ulcer healing at 6 months. At 6 months, ulcer healing was 32% higher in the MPFF group (RR, 32%; 95% CI: 3%–70%). MPFF at a dose of 500 mg twice per day was found to be more beneficial in the group of patients, with ulcers between 5 and 10 cm<sup>2</sup> and in ulcers with a 6- to 12-month duration.<sup>166</sup>

In a systematic review from 2016, Bush et al. confirmed findings from previous studies that the use of MPFF medical therapy alone or adjunctive to compression therapy had beneficial outcomes without serious side effects for the reduction in symptoms of CVD patients.<sup>156</sup> In the most recent publication from 2020, Nicolaides reiterated conclusions from the 2019 European Venous Forum symposium that were based on data from numerous controlled clinical trials and multiple meta-analyses showing that MPFF provides therapeutic benefits at each stage of CVD by reducing CVD-specific symptoms, inflammation and by facilitating the healing of ulcers.<sup>164</sup>

### *Prostaglandins*

Prostaglandin-E<sub>1</sub> (PG-E<sub>1</sub>) is known to attenuate white blood cell activation and platelet aggregation.<sup>168</sup> In a prospective randomized trial involving 87 patients with venous ulcers, PG-E<sub>1</sub> was administered by intravenous infusion for 20 days in addition to topical therapy. The primary endpoint was ulcer healing at 120 days. The results showed that healing time in PG-E<sub>1</sub> group was less than 100 days, with more than 75% of patients healing at 75 days. This was statistically significant compared with the placebo (84.2% patients healing at 120 days).<sup>168</sup>

Horse chestnut is an herbal medication with moderate anti-inflammatory activity through the release of PG-F.<sup>169</sup> A Cochrane review of seven placebo-controlled randomized trials showed a statistical improvement in leg pain in six trials, which was equivalent to compression therapy in patients with uncomplicated symptomatic varicose veins.<sup>170</sup> In a small prospective triple-blind randomized placebo-controlled trial of 54 patients with venous leg ulcers, oral therapy with horse

chestnut did not show evidence of improvement in venous ulcer healing.<sup>171</sup>

Utilizing modern advancements pertinent to sequencing of the human genome that have opened up access to previously inaccessible areas of investigation of vascular disorders, Markovic and Shortell evaluated the gene expression and metabolic pathways of the entire human genome including the relative expression levels of more than 47,000 transcripts and variants and approximately 38,500 well-characterized genes in 20 patients (10 CVD patients; 10 non-CVD patients).<sup>172</sup> Microarray Hybridization and Gene Set Enrichment Analysis comparison, among the aforementioned groups, showed that hydroxyl-prostaglandin dehydrogenase-15 (HPGD-15) gene with genetic locus on chromosome number 4 (Ch4q34-35) was the highest ranked up-regulated gene in CVD patients with statically significant ( $P < 0.05$ ) relative expression fold change of  $1.77 \pm 0.035$  (mean  $\pm$  SD).<sup>172</sup> This gene is an important regulator in development of the cardiovascular system, inflammation homeostasis as well as in PG synthesis pathways.<sup>161,162,173-176</sup> The HPGD-15 gene-regulated enzymes significantly reduce the biological activity of PGs and reduce inflammatory reaction *in vivo* by catalyzing the conversion of the 15-hydroxy group of PGs into keto-group.<sup>177</sup>

Overexpression of HPGD-15 gene in CVD patients in our study showed that, under the influence of the increased amounts of inflammatory mediators (including PGs), the expression of the HPGD is induced as venous intrinsic anti-inflammatory mechanism, because, as mentioned above, the HPGD gene (and its product enzyme PG dehydrogenase) reduces PG activity and consequently reduces the inflammatory reaction.<sup>172</sup> These findings may be beneficial for development of pharmaceutical agents that would target genetically identified metabolic pathways that underline CVD pathogenesis.

### Other Medications

Aspirin and ifetroban (oral thromboxane A<sub>2</sub> receptor antagonist) have failed to demonstrate benefit in either uncomplicated or complicated CVD.<sup>54</sup> A Cochrane review published in 2016 suggested that currently available studies that reported on the safety and efficacy of aspirin in the management of venous ulcers are characterized by small number of patients, potential selection bias and low quality evidence.<sup>178</sup> Similarly in 2019 the authors of a phase II pilot randomized controlled clinical trial (Aspirin for Venous Ulcers Randomized Trial – AVURT trial) showed no evidence that aspirin was effective in healing of C6 patients when compared to placebo (hazard ratio 0.58; 95% CI: 0.18–1.85;  $P=0.357$ ).<sup>179</sup> Based on data the authors suggested that progressing to phase III study to further evaluate aspirin in CVD patients is not feasible without substantial amendment of study design.<sup>180</sup>

Calcium dobesilate is a drug that has been shown to reduce capillary permeability. Whereas some benefit has been shown in reducing ankle edema, no advantage has been proved in the care of patients with venous ulcers.<sup>54</sup>

## CONCLUSION

High-grade compression therapy is the mainstay of treatment for patients with advanced CVD (C4–C6). The ESCHAR trial showed that there is a subgroup of patients who may benefit from elimination of venous reflux, in addition to compression therapy to prevent ulcer recurrence. In patients with uncomplicated C1–C2 CVD, compression therapy may be beneficial in symptom control, but it is not associated with disease regression.

The evidence to support the use of gradient compression therapy in prevention of PTS is inconclusive and is the subject of debate among practitioners. This emphasizes the need for standardization of reporting standards and the necessity for well-designed studies for more accurate assessment of the efficacy of compression therapy in PTS treatment.

MPFF is currently the most effective medication in C1–C2 CVD, and there is level 1A evidence that its use is advantageous, mainly in symptom control. MPFF may be a useful adjunct in the care of patients with C6 disease. Lastly, fundamental advancements in our knowledge of the human genome and understanding of the genetic basis of CVD represent an opportunity to develop new diagnostic, prognostic, preventive and nonsurgical therapeutic modalities in the management of CVD in the future.

## SELECTED KEY REFERENCES

- Allaert FA. Meta-analysis of the impact of the principal venoactive drugs agents on malleolar venous edema. *Int Angiol.* 2012;31:310–315.
- In this meta-analysis of 10 prospective randomized trials, the micronized purified flavonoid fraction was found to be effective in the management of symptoms and edema, compared with other venoactive drugs (ruscus extract, hydroxyethylrutoside, diosmin).
- Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. *Lancet.* 2004;363:1854–1859.
- In this prospective randomized trial, compression alone was compared with compression plus surgery (high ligation and stripping of the saphenous vein) in patients with C6 disease. At 24 months, the recurrence rate was significantly lower in the compression–surgery group.
- Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomized controlled trial. *BMJ.* 2007;335:83.
- The long-term results of the ESCHAR trial are analyzed in this report. Lower ulcer recurrence rate was noted in the compression–surgery group compared with compression therapy only at a 4-year follow-up. The benefit of the combined compression–surgery approach was noted mostly in the subgroup of patients with superficial or segmental deep vein reflux.
- Michaels JA, Campbell WB, Brazier JE, et al. Randomized clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol Assess.* 2006;10:1–196. iii–iv.
- In this prospective randomized trial, surgery (high ligation of the saphenofemoral junction, great saphenous vein stripping, and phlebectomies) was found to be more cost-effective than conservative therapy (lifestyle modification, leg elevation, and compression stockings) in patients with C2 disease. Injection sclerotherapy also appeared to be cost-effective for patients with superficial venous reflux but was found to produce less benefit compared with surgery.

Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. *Cochrane Database Syst Rev*. 2012;8:CD002303.

*This 2012 update of a Cochrane review emphasizes the importance of compression therapy in preventing ulcer recurrence. No difference was noted between high compression and moderate compression in ulcer recurrence in three trials. Moderate compression stockings were associated with higher compliance to therapy.*

Nelson EA, Prescott RJ, Harper DR, et al. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers. *J Vasc Surg*. 2007;45:134–141.

*In this prospective randomized trial, pentoxifylline was associated with a statistically nonsignificant improvement in ulcer healing. However, Cox regression analysis modeling resulted in a clinically significant improvement in ulcer healing with pentoxifylline.*

O'Donnell Jr TF, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (R) and the American Venous Forum. *J Vasc Surg*. 2014;60(2 suppl):S3–S9S.

*Evidence-based clinical practice guidelines for the care of patients with venous ulcers are discussed in this report.*

O'Meara S, Tierney J, Cullum N, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomized controlled trials with data from individual patients. *BMJ*. 2009;338:b1344.

*In this meta-analysis comparing the effectiveness of four-layer and short stretch single-layer compression bandages, it was noted that four-layer bandages were associated with shorter healing time in larger ulcers. Chronic ulceration and previous ulcerations were found to be independent predictors for delayed ulcer healing.*

Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev*. 2012;11:CD003230.

*This is the 2012 update of a Cochrane database review first published in 2002. Efficacy and Safety of Horse Chestnut Seed (HCSE) versus placebo are reviewed. Leg pain was assessed in seven placebo-controlled trials. In six trials, a significant reduction of leg pain was observed with HCSE. Leg volume was also noted to be significantly decreased (95% CI 13.49 to 50.72) in the HCSE cohort in six trials. The authors conclude that HCSE is an efficacious and safe short-term treatment for CVI.*

Smith PC. Daflon 500 mg and venous leg ulcer: new results from a meta-analysis. *Angiology*. 2005;56(suppl 1):S33–S39.

*The micronized purified flavonoid fraction at a dose of 500 mg twice per day was noted to increase ulcer healing, particularly in patients with long-standing large (5 and 10 cm<sup>2</sup>) venous ulcers.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. Bush RL, Gloviczki P. A survey of current practice of vascular surgeons in venous disease management. *J Vasc Surg Venous Lymphat Disord.* 2013;1(1):90–95.
2. Meissner MH, Eklof B, Smith PC, et al. Secondary chronic venous disorders. *J Vasc Surg.* 2007;46(Suppl):68s–83s.
3. Meissner MH, Gloviczki P, Bergan J, et al. Primary chronic venous disorders. *J Vasc Surg.* 2007;46(Suppl):54s–67s.
4. Tran NT, Meissner MH. The epidemiology, pathophysiology, and natural history of chronic venous disease. *Semin Vasc Surg.* 2002;15(1):5–12.
5. Pannier F, Rabe E. Progression in venous pathology. *Phlebology.* 2015;30(1 Suppl):95–97.
6. Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. *Phlebology.* 2008;23(3):103–111.
7. Seidel AC, Miranda Jr F, Juliano Y, Novo NF, dos Santos JH, de Souza DF. Prevalence of varicose veins and venous anatomy in patients without truncal saphenous reflux. *Eur J Vasc Endovasc Surg.* 2004;28(4):387–390.
8. Fan CM. Epidemiology and pathophysiology of varicose veins. *Techniques Vasc Interv Radiol.* 2003;6(3):108–110.
9. Evans CJ, Fowkes FG, Hajivassiliou CA, et al. Epidemiology of varicose veins. A review. *Int Angiol.* 1994;13(3):263–270.
10. Callam MJ. Epidemiology of varicose veins. *Br J Surg.* 1994;81(2):167–173.
11. Beaglehole R. Epidemiology of varicose veins. *World J Surg.* 1986;10(6):898–902.
12. Widmer LK. [Epidemiology of varicose veins. Consequences for the practice]. *Ther Umsch.* 1969;26(4):185–186.
13. Lee AJ, Robertson LA, Boghossian SM, et al. Progression of varicose veins and chronic venous insufficiency in the general population in the Edinburgh Vein Study. *J Vasc Surg Venous Lymphat Disord.* 2015;3(1):18–26.
14. Criqui MH, Jamosmos M, Fronek A, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol.* 2003;158(5):448–456.
15. Eklof B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg.* 2004;40(6):1248–1252.
16. Gloviczki ML, Kalsi H, Gloviczki P, et al. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification codes for estimating the prevalence of venous ulcer. *J Vasc Surg Venous Lymphat Disord.* 2014;2(4):362–367.
17. Lawrence PFGG. Epidemiology of chronic venous Insufficiency. In: Ballard J, Bergan JJ, eds. *Chronic Venous Insufficiency.* London: Springer; 2000.
18. Lurie F, Passman M, Meisner M, et al. CEAP classification system and reporting standard, revision 2020. *J Vasc Surg Venous Lymphat Disord.* 2020;8(3):342–352.
19. Nelzen O, Bergqvist D, Lindhagen A. The prevalence of chronic lower-limb ulceration has been underestimated: results of a validated population questionnaire. *Br J Surg.* 1996;83(2):255–258.
20. Nelzen O, Bergqvist D, Lindhagen A, Hallböök T. Chronic leg ulcers: an underestimated problem in primary health care among elderly patients. *J Epidemiol Community Health.* 1991;45(3):184–187.
21. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(5 Suppl):2s–48s.
22. O'Donnell Jr TF, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (R) and the American Venous Forum. *J Vasc Surg.* 2014;60(2 Suppl):3s–59s.
23. Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol.* 2001;44(3):401–421; quiz 422–424.
24. Markovic JNSC. Varicose vein surgery. In: Ashley S, Cance W, Jurkovich G, et al., eds. *American College of Surgeons: Principles and Practice.* 6th ed. USA: Decker Intellectual Properties Publishing; 2014.
25. Lafuma A, Fagnani F, Peltier-Pujol F, Rauss A. [Venous disease in France: an unrecognized public health problem]. *J Mal Vasc.* 1994;19(3):185–189.
26. Olin JW, Beusterien KM, Childs MB, et al. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. *Vasc Med.* 1999;4(1):1–7.
27. Hankin CS, Knispel J, Lopes M, et al. Clinical and cost efficacy of advanced wound care matrices for venous ulcers. *J Manag Care Pharm.* 2012;18(5):375–384.
28. Davies AH. The seriousness of chronic venous disease: a review of real-world evidence. *Adv Ther.* 2019;36(Suppl 1):5–12.
29. Millennium Research Group—DRG. *Varicose Vein Treatment Devices. US 2015 Market Analysis.* Global Information IncA; 2015.
30. Lurie F, Kistner RL. Trends in patient reported outcomes of conservative and surgical treatment of primary chronic venous disease contradict current practices. *Ann Surg.* 2011;254(2):363–367.
31. Brown A. Life-style advice and self-care strategies for venous leg ulcer patients: what is the evidence? *J Wound Care.* 2012;21(7):342–344, 346, 348–350.
32. Tauraginskii RA, Simakov S, Borsuk D, et al. The immediate effect of physical activity on ultrasound-derived venous reflux parameters. *J Vasc Surg Venous Lymphat Disord.* 2020;8(4):640–645.
33. Roaldsen KS, Rollman O, Torebjork E, et al. Functional ability in female leg ulcer patients—a challenge for physiotherapy. *Physiother Res Int.* 2006;11(4):191–203.
34. Abu-Owain A, Scull JH, Coleridge Smith PD. Effect of leg elevation on the skin microcirculation in chronic venous insufficiency. *J Vasc Surg.* 1994;20(5):705–710.
35. Sindrup JH, Kastrup J, Kristensen JK. Diurnal variations in lower leg subcutaneous blood flow rate in patients with chronic venous leg ulcers. *Br J Dermatol.* 1991;125(5):436–442.
36. Finlayson K, Edwards H, Courtney M. Factors associated with recurrence of venous leg ulcers: a survey and retrospective chart review. *Int J Nursing Studies.* 2009;46(8):1071–1078.
37. Deol ZK, Lakhanpal S, Franzon G, Pappas PJ. Effect of obesity on chronic venous insufficiency treatment outcomes. *J Vasc Surg Venous Lymphat Disord.* 2020;8(4):617–628.e1.
38. Wrona M, Jöckel KH, Pannier F, et al. Association of venous disorders with leg symptoms: results from the Bonn Vein Study 1. *Eur J Vasc Endovasc Surg.* 2015;50(3):360–367.
39. Wittens C, Davies AH, Bækgård N, et al. Editor's Choice – Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2015;49(6):678–737.
40. 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):520–525.
41. Bradbury A, Evans CJ, Allan P, et al. The relationship between lower limb symptoms and superficial and deep venous reflux on duplex ultrasonography: The Edinburgh Vein Study. *J Vasc Surg.* 2000;32(5):921–931.
42. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The Epidemiology of Varicose Veins: The Framingham Study. *Am J Preventive Med.* 1988;4(2):96–101.
43. Maurins U, Hoffmann BH, Lösch C, et al. Distribution and prevalence of reflux in the superficial and deep venous system in the general population – results from the Bonn Vein Study, Germany. *J Vasc Surg.* 2008;48(3):680–687.
44. Criqui MH, Jamosmos M, Fronek A, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol.* 2003;158(5):448–456.
45. Adams EF. Hippocrates. In: Adams EF, ed. *The Genuine Works of Hippocrates.* Vol. 2. New York: Wm Wood & Co; 1886.
46. Anning ST. Historical aspects. In: Dodd H, Cockett FB, eds. *The Pathology and Surgery of Veins of the Lower Limb.* Edinburgh: Livingstone; 1956:6–28.
47. Lurie F, Bittar S, Kasper G. Optimal compression therapy and wound care for venous ulcers. *Surg Clin North Am.* 2018;98(2):349–360.

48. Uhl J-F, Benigni J-P, Cornu-Thénard A. Where should stiffness be measured in vivo? *Veins Lymphatics*. 2013;2.
49. Ma H, Blebea J, Malgor RD, Taubman KE. Variability in leg compression provided by gradient commercial stockings. *J Vasc Surg Venous Lymphat Disord*. 2015;3(4):431–437.
50. Lurie F, Kistner R. Variability of interface pressure produced by ready-to-wear compression stockings. *Phlebology*. 2014;29(2):105–108.
51. Partsch B, Partsch H. Calf compression pressure required to achieve venous closure from supine to standing positions. *J Vasc Surg*. 2005;42(4):734–738.
52. Mosti G, Iabichella ML, Partsch H. Compression therapy in mixed ulcers increases venous output and arterial perfusion. *J Vasc Surg*. 2012;55(1):122–128.
53. Wipke-Tevis DD, Stotts NA, Williams DA, et al. Tissue oxygenation, perfusion, and position in patients with venous leg ulcers. *Nursing Res*. 2001;50(1):24–32.
54. Klyszc T, Galler S, Steins A, et al. Einfluss einer Kompressionstherapie auf die Mikrozirkulation der Haut bei Patienten mit chronischer Veneninsuffizienz (CVI). *Der Hautarzt*. 1997;48(11):806–811.
55. Adams J. Tissue oxygenation, perfusion, and position in patients with venous leg ulcers. *Nurs Older People*. 2001;13(2):8.
56. Murphy MA, Joyce WP, Condon C, Bouchier-Hayes D. A reduction in serum cytokine levels parallels healing of venous ulcers in patients undergoing compression therapy. *Eur J Vasc Endovasc Surg*. 2002;23(4):349–352.
57. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2005;111(18):2398–2409.
58. Iabichella ML, Melillo E, Mosti G. A review of microvascular measurements in wound healing. *Int J Low Extrem Wounds*. 2006;5(3):181–199.
59. Pascarella L, Schmid Schonbein GW. Causes of telangiectasias, reticular veins, and varicose veins. *Semin Vasc Surg*. 2005;18(1):2–4.
60. Benigni JP, Sadoun S, Allaert FA, Vin F. Efficacy of Class 1 elastic compression stockings in the early stages of chronic venous disease. A comparative study. *Int Angiol*. 2003;22(4):383–392.
61. Palfreyman SJ, Michaels JA. A systematic review of compression hosiery for uncomplicated varicose veins. *Phlebology*. 2009;24(Suppl 1):13–33.
62. Michaels JA, Campbell WB, Brazier JE, et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol Assess*. 2006;10(13):1–196. iii–iv.
63. Sell H, Vikatmaa P, Alback A, et al. Compression therapy versus surgery in the treatment of patients with varicose veins: A RCT. *Eur J Vasc Endovasc Surg*. 2014;47(6):670–677.
64. Mayberry JC, Moneta GL, Taylor Jr LM, Porter JM. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. *Surgery*. 1991;109(5):575–581.
65. Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. *Cochrane Database Syst Rev*. 2012;(8):CD002303.
66. Beckman MG, Hooper WC, Critchley SE, Ortell TL. Venous thromboembolism: a public health concern. *Am J Prevent Med*. 2010;38(4 Suppl):S495–501.
67. Chi YW, Raffetto JD. Venous leg ulceration pathophysiology and evidence based treatment. *Vasc Med*. 2015;20(2):168–181.
68. Labropoulos N. Elastic compression therapy to prevent post-thrombotic syndrome. *Lancet Haematol*. 2018;5(11):e494–e495.
69. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349(9054):759–762.
70. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med*. 2004;141(4):249–256.
71. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol*. 2018;5(1):e25–e33.
72. Mol GC, van de Ree MA, Klok FA, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. *BMJ*. 2016;353:i2691.
73. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383(9920):880–888.
74. ten Cate-Hoek AJ. Elastic compression stockings—is there any benefit? *Lancet*. 2014;383(9920):851–853.
75. Labropoulos N, Gasparis AP, Caprini JA, Partsch H. Compression stockings to prevent post-thrombotic syndrome. *Lancet*. 2014;384(9938):129–130.
76. Avila ML, Montoya M, Lumia C, et al. Compression stockings to prevent post-thrombotic syndrome in adults, a Bayesian meta-analysis. *Thrombosis Res*. 2019;182:20–26.
77. Azirar S, Appelen D, Prins MH, et al. Compression therapy for treating post-thrombotic syndrome. *Cochrane Database Syst Rev*. 2019;9:CD004177.
78. Skervin AL, Thapar A, Franchini AJ, et al. Systematic review and meta-analysis of utility of graduated compression stockings in prevention of post-thrombotic syndrome. *Eur J Vasc Endovasc Surg*. 2016;51(6):838–845.
79. Jayaraj A, Meissner M. Impact of graduated compression stockings on the prevention of post-thrombotic syndrome - results of a randomized controlled trial. *Phlebology*. 2015;30(8):541–548.
80. Lund E. Exploring the use of CircAid legging in the management of lymphoedema. *Int J Palliative Nurs*. 2000;6(8):383–391.
81. Blecken SR, Villavicencio JL, Kao TC. Comparison of elastic versus nonelastic compression in bilateral venous ulcers: a randomized trial. *J Vasc Surg*. 2005;42(6):1150–1155.
82. Bergan JJ, Sparks SR. Non-elastic compression: an alternative in management of chronic venous insufficiency. *J Wound Ostomy Continence Nursing*. 2000;27(2):83–89.
83. Sparks SR, Ballard JL, Bergan JJ, Killeen JD. Early benefits of subfascial endoscopic perforator surgery (SEPS) in healing venous ulcers. *Ann Vasc Surg*. 1997;11(4):367–373.
84. Janbon C, Laborde JC, Quere I. [History of the treatment of varices]. *J Mal Vasc*. 1994;19(3):210–215.
85. Vernick SH, Shapiro D, Shaw FD. Legging orthosis for venous and lymphatic insufficiency. *Arch Phys Med Rehabil*. 1987;68(7):459–461.
86. Lippmann HI, Fishman LM, Farrar RH, et al. Edema control in the management of disabling chronic venous insufficiency. *Arch Phys Med Rehabil*. 1994;75(4):436–441.
87. Rubin JR, Alexander J, Plecha EJ, Marman C. Unna's boot vs polyurethane foam dressings for the treatment of venous ulceration. A randomized prospective study. *Arch Surg*. 1990;125(4):489–490.
88. Senet P. Local treatment of venous leg ulcers. *Phlebology*. 2010;17(2):87–94.
89. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database Syst Rev*. 2012;11:CD000265.
90. O'Meara S, Tierney J, Cullum N, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients. *BMJ*. 2009;338:b1344.
91. Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. *BMJ*. 1997;315(7108):576–580.
92. Partsch H, Flour M, Smith PC. Indications for compression therapy in venous and lymphatic disease consensus based on experimental data and scientific evidence. Under the auspices of the IUP. *Int Angiol*. 2008;27(3):193–219.
93. Coleridge-Smith PD. Leg ulcer treatment. *J Vasc Surg*. 2009;49(3):804–808.
94. Milic DJ, Zivic SS, Bogdanovic DC, et al. A randomized trial of class 2 and class 3 elastic compression in the prevention of recurrence of venous ulceration. *J Vasc Surg Venous Lymphat Disord*. 2018;6(6):717–723.

95. Feldman JL, Stout NL, Wanchai A, Stewart BR, et al. Intermittent pneumatic compression therapy: a systematic review. *Lymphology*. 2012;45(1):13–25.
96. Nelson EA, Mani R, Thomas K, Vowden K. Intermittent pneumatic compression for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2011;(2):CD001899.
97. Harding KG, Vanscheidt W, Partsch H, et al. Adaptive compression therapy for venous leg ulcers: a clinically effective, patient-centred approach. *Int Wound J*. 2016;13(3):317–325.
98. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208.
99. Lurie F, Schwartz M. Patient-centered outcomes of a dual action pneumatic compression device in comparison to compression stockings for patients with chronic venous disease. *J Vasc Surg Venous Lymphat Disord*. 2017;5(5):699–706.e1.
100. 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):1854–1859.
101. Gohel MS, Barwell JR, Earnshaw JJ, et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study)—haemodynamic and anatomical changes. *Br J Surg*. 2005;92(3):291–297.
102. Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. *BMJ*. 2007;335(7610):83.
103. Mauck KF, Asi N, Undavalli C, et al. Systematic review and meta-analysis of surgical interventions versus conservative therapy for venous ulcers. *J Vasc Surg*. 2014;60(2 Suppl):60S–70S.e1–2.
104. Warburg FE, Danielsen L, Madsen SM, et al. Vein surgery with or without skin grafting versus conservative treatment for leg ulcers. A randomized prospective study. *Acta Dermato-Venereol*. 1994;74(4):307–309.
105. van Gent WB, Hop WC, van Praag MC, et al. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg*. 2006;44(3):563–571.
106. Guest M, Smith JJ, Tripuraneni G, et al. Randomized clinical trial of varicose vein surgery with compression versus compression alone for the treatment of venous ulceration. *Phlebology*. 2003;18(3):130–136.
107. Zamboni P, Cisino C, Marchetti F, et al. Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. *Eur J Vasc Endovasc Surg*. 2003;25(4):313–318.
108. Vranic H, Hadzimehmedagic A, Kacila M, et al. Combined compressive-surgical treatment of chronic venous ulcer of the leg. *HealthMED*. 2010;4:890–895.
109. Barwell JR, Taylor M, Deacon J, et al. Surgical correction of isolated superficial venous reflux reduces long-term recurrence rate in chronic venous leg ulcers. *Eur J Vasc Endovasc Surg*. 2000;20(4):363–368.
110. Viarengo LM, Poterio-Filho J, Poterio GM, et al. Endovenous laser treatment for varicose veins in patients with active ulcers: measurement of intravenous and perivenous temperatures during the procedure. *Dermatol Surg*. 2007;33(10):1234–1242; discussion 1241–1242.
111. O'Hare JL, Earnshaw JJ. Randomised clinical trial of foam sclerotherapy for patients with a venous leg ulcer. *Eur J Vasc Endovasc Surg*. 2010;39(4):495–499.
112. Alden PB, Lips EM, Zimmerman KP, et al. Chronic venous ulcer: minimally invasive treatment of superficial axial and perforator vein reflux speeds healing and reduces recurrence. *Ann Vasc Surg*. 2013;27(1):75–83.
113. van Gent WB, Catarinella FS, Lam YL, et al. Conservative versus surgical treatment of venous leg ulcers: 10-year follow up of a randomized, multicenter trial. *Phlebology*. 2015;30(1 Suppl):35–41.
114. Gohel MS, Davies AH. Pharmacological agents in the treatment of venous disease: an update of the available evidence. *Curr Vasc Pharmacol*. 2009;7(3):303–308.
115. Uber A. The socioeconomic profile of patients treated by phlebotropic drugs in Germany. *Angiology*. 1997;48(7):595–607.
116. Martinez MJ, Bonfill X, Moreno RM, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev*. 2005;3:CD003229.
117. Cheatle TR, Sarin S, Coleridge Smith PD, Scurr JH. The pathogenesis of skin damage in venous disease: a review. *Eur J Vasc Surg*. 1991;5(2):115–123.
118. Chen Y, Peng W, Raffetto JD, Khalil RA. Matrix metalloproteinases in remodeling of lower extremity veins and chronic venous disease. *Prog Mol Biol Transl Sci*. 2017;147:267–299.
119. MacColl E, Khalil RA. Matrix metalloproteinases as regulators of vein structure and function: implications in chronic venous disease. *J Pharmacol Exp Ther*. 2015;355(3):410–428.
120. Birdina J, Pilmane M, Ligers A. The morphofunctional changes in the wall of varicose veins. *Ann Vasc Surg*. 2017;42:274–284.
121. Raffetto JD, Khalil RA. Matrix metalloproteinases in venous tissue remodeling and varicose vein formation. *Curr Vasc Pharmacol*. 2008;6(3):158–172.
122. Kucukguven A, Khalil RA. Matrix metalloproteinases as potential targets in the venous dilation associated with varicose veins. *Curr Drug Targets*. 2013;14(3):287–324.
123. Rusak A, Karuga-Kuzniewska E, Wiatrak B, et al. Venous insufficiency: Differences in the content of trace elements. A preliminary report. *Adv Clin Experimental Med*. 2018;27(5):695–701.
124. Shadrina AS, Smetanina MA, Sevost'yanova KS, et al. Polymorphism of Matrix Metalloproteinases Genes MMP1, MMP2, MMP3, and MMP7 and the Risk of Varicose Veins of Lower Extremities. *Bull Experimental Biol Med*. 2017;163(5):650–654.
125. Slonkova V, Slonkova Jr V, Vasku A, Vasku V. Genetic predisposition for chronic venous insufficiency in several genes for matrix metalloproteinases (MMP-2, MMP-9, MMP-12) and their inhibitor TIMP-2. *J Eur Acad Dermatol Venereol*. 2017;31(10):1746–1752.
126. Wang X, Khalil RA. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. *Adv Pharmacol*. 2018;81:241–330.
127. O'Connor S, Murphy S. Chronic venous leg ulcers: is topical zinc the answer? A review of the literature. *Adv Skin Wound Care*. 2014;27(1):35–44; quiz 45–46.
128. Williams C. Examining the range of medicated and paste-impregnated bandages. *Br J Nursing*. 1999;8(15):1019–1020.
129. Wilkinson EA. Oral zinc for arterial and venous leg ulcers. *Cochrane Database Syst Rev*. 2014;(9):CD001273.
130. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *Br Med J*. 1982;285(6348):1071–1072.
131. Falanga V, Moosa HH, Nemeth AJ, et al. Dermal pericapillary fibrin in venous disease and venous ulceration. *Arch Dermatol*. 1987;123(5):620–623.
132. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet*. 1982;2(8292):243–245.
133. Cheatle TR, McMullin GM, Farrah J, et al. Skin damage in chronic venous insufficiency: does an oxygen diffusion barrier really exist? *J Royal Soc Med*. 1990;83(8):493–494.
134. Bedenis R, Stewart M, Cleanthis M, et al. Cilostazol for intermittent claudication. *Cochrane Database Syst Rev*. 2014;10:CD003748.
135. Salhiyyah K, Forster R, Senanayake E, et al. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev*. 2015;9:CD005262.
136. Tulsyn N, Ouriel K, Kashyap VS. Emerging drugs in peripheral arterial disease. *Expert Opin Emerging Drugs*. 2006;11(1):75–90.
137. Stefanovich V. Concerning specificity of the influence of pentoxifylline on various cyclic AMP phosphodiesterases. *Res Comm Chemical Pathol Pharmacol*. 1974;8(4):673–680.
138. Bohm L, Roos WP, Serafin AM. Inhibition of DNA repair by Pentoxifylline and related methylxanthine derivatives. *Toxicology*. 2003;193(1–2):153–160.
139. Marcinkiewicz J, Grabowska A, Lauterbach R, Bobek M. Differential effects of pentoxifylline, a non-specific phosphodiesterase inhibitor, on the production of IL-10, IL-12 p40 and p35 subunits by murine peritoneal macrophages. *Immunopharmacology*. 2000;49(3):335–343.
140. Zargari O. Pentoxifylline: a drug with wide spectrum applications in dermatology. *Dermatol Online J*. 2008;14(11):2.

141. Graninger W, Wenisch C. Pentoxifylline in severe inflammatory response syndrome. *J Cardiovasc Pharmacol.* 1995;25(Suppl 2):S134–S138.
142. Sullivan GW, Carper HT, Novick Jr WJ, Mandell GL. Inhibition of the inflammatory action of interleukin-1 and tumor necrosis factor (alpha) on neutrophil function by pentoxifylline. *Infect Immun.* 1988;56(7):1722–1729.
143. Nelson EA, Prescott RJ, Harper DR, et al. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers. *J Vasc Surg.* 2007;45(1):134–141.
144. Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2012;12:CD001733.
145. Falanga V, Fujitani RM, Diaz C, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. *Wound Repair Regen.* 1999;7(4):208–213.
146. Ramelet AA. Pharmacologic aspects of a phlebotropic drug in CVI-associated edema. *Angiology.* 2000;51(1):19–23.
147. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest.* 2016;149(2):315–352.
148. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6 Suppl):454s–545s.
149. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. *Int Angiol.* 2018;37(3):181–254.
150. Nicolaides A, Kakkos S, Eklof B, et al. Management of chronic venous disorders of the lower limbs - guidelines according to scientific evidence. *Int Angiol.* 2014;33(2):87–208.
151. Nicolaides AN, Allegra C, Bergan J, et al. Management of chronic venous disorders of the lower limbs: guidelines according to scientific evidence. *Int Angiol.* 2008;27(1):1–59.
152. das Gracas CdSM, Cyrino FZ, de Carvalho JJ, et al. Protective Effects of Micronized Purified Flavonoid Fraction (MPFF) on a Novel Experimental Model of Chronic Venous Hypertension. *Eur J Vasc Endovasc Surg.* 2018;55(5):694–702.
153. Kirienko A, Radak D. Clinical acceptability study of once-daily versus twice-daily micronized purified flavonoid fraction in patients with symptomatic chronic venous disease: a randomized controlled trial. *Int Angiol.* 2016;35(4):399–405.
154. Kirienko A, Radak D, Maggioli A. Clinical efficacy of once-daily micronized purified flavonoid fraction 1000 mg tablet in patients with symptomatic chronic venous disease. *Curr Med Res Opin.* 2019;35(3):553–557.
155. Maggioli A, Carpenter P. Efficacy of MPFF 1000 mg oral suspension on CVD C0s-C1-related symptoms and quality of life. *Int Angiol.* 2019;38(2):83–89.
156. Bush R, Comerota A, Meissner M, et al. Recommendations for the medical management of chronic venous disease: The role of Micronized Purified Flavonoid Fraction (MPFF). *Phlebology.* 2017;32(1\_suppl):3–19.
157. Wollina U, Abdel-Naser MB, Mani R. A review of the microcirculation in skin in patients with chronic venous insufficiency: the problem and the evidence available for therapeutic options. *Int J Low Extrem Wounds.* 2006;5(3):169–180.
158. Allaert FA. Meta-analysis of the impact of the principal venoactive drugs agents on malleolar venous edema. *Int Angiol.* 2012;31(4):310–315.
159. Carpenter P, van Bellen B, Karetova D, et al. Clinical efficacy and safety of a new 1000-mg suspension versus twice-daily 500-mg tablets of MPFF in patients with symptomatic chronic venous disorders: a randomized controlled trial. *Int Angiol.* 2017;36(5):402–409.
160. Coleridge-Smith P, Lok C, Ramelet AA. Venous leg ulcer: a meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. *Eur J Vasc Endovasc Surg.* 2005;30(2):198–208.
161. Gomez I, Benyahia C, Louedec L, et al. Decreased PGE(2) content reduces MMP-1 activity and consequently increases collagen density in human varicose vein. *PLoS One.* 2014;9(2):e88021.
162. Gomez I, Ozan G, Deschildre C, et al. Reverse regulatory pathway (H2S / PGE2 / MMP) in human aortic aneurysm and saphenous vein varicosity. *PLoS One.* 2016;11(6):e0158421.
163. Kakkos SK, Nicolaides AN. Efficacy of micronized purified flavonoid fraction (Daflon(R)) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. *Int Angiol.* 2018;37(2):143–154.
164. Nicolaides AN. The benefits of Micronized Purified Flavonoid Fraction (MPFF) throughout the progression of chronic venous disease. *Adv Ther.* 2020;37(Suppl 1):1–5.
165. Scallon C, Bell-Syer SE, Aziz Z. Flavonoids for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2013;(5):CD006477.
166. Coleridge Smith P. Daflon 500 mg and venous leg ulcer: new results from a meta-analysis. *Angiology.* 2005;56(Suppl 1):S33–S39.
167. Ulloa JH. Micronized Purified Flavonoid Fraction (MPFF) for patients suffering from chronic venous disease: a review of new evidence. *Adv Ther.* 2019;36(Suppl 1):20–25.
168. Milio G, Mina C, Cospite V, et al. Efficacy of the treatment with prostaglandin E-1 in venous ulcers of the lower limbs. *J Vasc Surg.* 2005;42(2):304–308.
169. Tiffany N, Boon H, Ulbricht C, et al. Horse chestnut: a multidisciplinary clinical review. *J Herbal Pharmacother.* 2002;2(1):71–85.
170. Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev.* 2012;11:CD003230.
171. Leach MJ, Pincombe J, Foster G. Clinical efficacy of horsechestnut seed extract in the treatment of venous ulceration. *J Wound Care.* 2006;15(4):159–167.
172. Markovic JN, Shortell CK. Genomics of varicose veins and chronic venous insufficiency. *Semin Vasc Surg.* 2013;26(1):2–13.
173. Nandy A, Jenatschke S, Hartung B, et al. Genomic structure and transcriptional regulation of the human NAD+-dependent 15-hydroxyprostaglandin dehydrogenase gene. *J Mol Endocrinol.* 2003;31(1):105.
174. Coggins KG, Latour A, Nguyen MS, et al. Metabolism of PGE2 by prostaglandin dehydrogenase is essential for remodeling the ductus arteriosus. *Nature Med.* 2002;8(2):91–92.
175. Nandy A, Jenatschke S, Hartung B, et al. Genomic structure and transcriptional regulation of the human NAD+-dependent 15-hydroxyprostaglandin dehydrogenase gene. *J Mole Endocrinol.* 2003;31(1):105–121.
176. Pichaud F, Delage-Mourroux R, Pidoux E, et al. Chromosomal localization of the type-I 15-PGDH gene to 4q34-q35. *Human Genet.* 1997;99(2):279–281.
177. Xu W, Ahmad A, Dagenais S, et al. Chromosome 4q deletion syndrome: narrowing the cardiovascular critical region to 4q32.2-q34.3. *Am J Med Genet A.* 2012;158A(3):635–640.
178. de Oliveira Carvalho PE, Magolbo NG, De Aquino RF, Weller CD. Oral aspirin for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2016;2:CD009432.
179. Helen T, Liz C, Laura C, et al. Aspirin versus placebo for the treatment of venous leg ulcers-a phase II, pilot, randomised trial (AVURT). *Trials.* 2019;20(1):459.
180. Tilbrook H, Clark L, Cook L, et al. AVURT: aspirin versus placebo for the treatment of venous leg ulcers - a Phase II pilot randomised controlled trial. *Health Technol Assess.* 2018;22(55):1–138.

# Chronic Venous Insufficiency: Treatment of Perforator Vein Incompetence

FEDOR LURIE, ALESSANDRA PUGGIONI, and  
TODD E. RUSSELL

<b>PATHOPHYSIOLOGY</b>	2086
Normal Perforating Veins	2086
Hemodynamic Impact of Perforating Vein Incompetence	2086
Clinical Correlations of Perforating Vein Incompetence	2087
<b>ANATOMY</b>	2087
<b>DIAGNOSTIC EVALUATION</b>	2088
Clinical Investigation (CEAP Level 1)	2088
Noninvasive Vascular Investigation (CEAP Level 2)	2089
<b>INDICATIONS FOR INTERRUPTION</b>	2089
<b>OPERATIVE PLANNING OPTIONS</b>	2090

<b>OPEN SURGERY</b>	2091
Subfascial Endoscopic Perforator Surgery	2091
Results and Complications	2091
<b>PERCUTANEOUS ABLATION OF PERFORATING VEINS</b>	2094
Techniques	2095
<i>Laser Ablation</i>	2095
<i>Radiofrequency Ablation</i>	2095
<i>Sclerotherapy</i>	2095
New Treatment Modalities	2095
Results and Complications	2096
Postoperative Management	2096
<b>CHAPTER ALGORITHM</b>	2097

Perforating veins (PVs) were not described until drawings by Justus Christian Von Loder were published in 1794.<sup>1</sup> From that time, for more than a century, their role in venous disease remained unappreciated despite the illuminating work of M. Verneuil and subsequent analysis by John Gay.<sup>2</sup> In 1917, John Homans suggested that incompetent perforating veins (IPVs) played a key role in the genesis of venous ulcers.<sup>3</sup> Subsequently, Beecher and Warren formulated the concept of transmission of ambulatory pressure through IPVs into the superficial system, which was supported by the investigations of Cockett and Dodd and provided a physiologic basis for the surgical interruption of IPVs.<sup>4–6</sup> In 1938, Linton described a surgical approach to IPVs in the distal portion of the calf that became the standard in treating venous ulcers for several decades.<sup>7</sup> Multiple modifications of Linton's original technique were proposed to decrease wound complications and to avoid incisions too close to the ulcer. This led to a minimally invasive approach pioneered by DePalma and Edwards and culminated in the use of endoscopy, first described by Hauer.<sup>8</sup> Adding a tourniquet

and gas insufflation, Gloviczki et al. and Conrad transformed subfascial endoscopic perforating vein surgery (SEPS) into a reliable procedure that was disseminated around the world and replaced the open surgical approach.<sup>9,10</sup>

The development of endovascular treatment options for reflux in superficial veins has established a new standard for patients with chronic venous insufficiency (CVI), in whom the invasiveness and risk for wound complications associated with SEPS exceed those of the treatment of saphenous veins. As a result, new modalities, such as ultrasound-guided percutaneous ablation of perforating veins (PAPS) with sclerosing solutions or thermal energy, have become the preferable option.<sup>11</sup>

Renewed interest in outcomes following treatment of IPVs and their role in venous pathophysiology uncovered a lack of reliable information related to their impact on the natural history and severity of CVI. Despite a growing body of evidence substantiating decision-making in the management of patients with CVI, the indications for eliminating PV reflux remain imprecise.

In this chapter we describe the role of IPVs in the pathogenesis and natural history of chronic venous disease (CVD) and its progression to CVI, diagnostic techniques for identification of PVs, and criteria for assessing their incompetence. We discuss indications and techniques for the interruption of IPVs as well as the outcomes of these treatment modalities. We have made every attempt to stay within the framework of evidence-based medicine. However, because some or perhaps many aspects of the topic have not been subjected to proper scientific investigation, we refer to our individual and group experience when appropriate. We identify such statements because they introduce substantial bias.

## PATOPHYSIOLOGY

The role of PVs in normal physiology and in the pathogenesis of CVD are discussed in Chapter 156 (Chronic Venous Disorders: Post-Phlebitic Syndrome, Natural History, Pathophysiology, and Etiology). In this chapter, we review only the relevant aspects of PVs to better understand the rationale for the treatment of IPVs.

### Normal Perforating Veins

The venous system of the lower extremity is rich in interconnections between the individual vessels. Because of the numerous collateral circulatory routes established, disruption of venous flow as well as compression of the veins by contracting muscles during locomotion or external pressure is prevented during changes in position of the body and of the extremity itself. By crossing the proper fascia of the extremity, PVs provide a connection between the superficial and deep venous systems in the calf and thigh. There are approximately 60 PVs in a lower extremity,<sup>12</sup> and most if not all of them have valves directing flow from the superficial to the deep veins.

Our understanding of PV anatomy and normal physiology is based mainly on studies conducted during the 1960s and 1970s and on inferences from clinical observations of pathologic conditions. Although some anatomic studies demonstrated that all PVs have valves,<sup>13</sup> others showed that some PVs are avalvular.<sup>12,14</sup> The latter, however, are found in only a minority of extremities and not more frequently than two veins per extremity.<sup>12</sup> These anatomic data are consistent with findings from duplex scans of asymptomatic legs, only 3.6% of which have bidirectional flow in PVs.<sup>15</sup> Whether PVs provide collateral ways for blood flow to bypass areas of obstruction of the superficial veins, such as compression from outside during sitting, or their presence facilitates outflow from superficial veins when pressure in the deep veins drops during walking, or both, it is clear that flow in healthy PVs is directed from the superficial into the deep system. Although the hemodynamic role of PVs in normal circulation has not been addressed by experimental or direct observational studies, it is unlikely that the current theory could be meaningfully challenged.

The role and significance of IPVs are much less obvious. In the absence of functioning valves, blood flow in a PV is governed mainly by the pressure gradient in adjoined segments

of the superficial and deep systems. Active contraction of the venous wall and compression by surrounding muscles cannot compensate for the absence of the valve, especially in enlarged PVs with significantly degenerated walls. Therefore, knowledge of the hemodynamic function of the deep and superficial systems is critical for understanding the role of IPVs, and this role may differ according to the status of each of the two systems.

### Hemodynamic Impact of Perforating Vein Incompetence

IPVs can be found in 40% to 60% of extremities with primary CVD and even more frequently in legs with postthrombotic disease.<sup>16–18</sup> Isolated incompetence of a PV is extremely rare,<sup>19,20</sup> and in most cases IPVs coexist with insufficiency of the superficial veins, deep veins, or both. Although the prevalence of IPVs is slightly higher in legs with both deep and superficial reflux than in limbs with only superficial reflux,<sup>17</sup> the presence of axial superficial reflux appears to be the major factor associated with a higher prevalence of IPVs.<sup>18</sup> More than 60% of extremities with axial reflux in the great saphenous vein (GSV) have incompetent PVs, as opposed to 38% of extremities with only segmental superficial reflux.<sup>16</sup> An association between axial superficial reflux and PV incompetence has been shown during the progression to CVI. About a third of patients with symptomatic varicose veins develop new refluxing segments in 1 year.<sup>21,22</sup> In half of these cases, the new IPVs also develop during the same time.<sup>21,23</sup>

The observation that correction of superficial reflux leads to resolution of perforator incompetence in most limbs supports the concept that superficial reflux causes an “overload” of PVs, resulting in dilation and incompetence.<sup>24</sup> However, treatment of saphenous reflux by either stripping or ablation results in obstruction of the superficial veins to which PVs are connected, or in a significant increase in resistance to outward flow in PVs. Therefore, elimination of PV reflux after such treatment does not necessarily mean that the competence of the PV valves will be regained. Rather, it simply means that the blood cannot flow through PVs into (obstructed) superficial veins, even if the PVs themselves remain open. The presence of these incompetent perforators without demonstrated reflux may be a reason that “isolated” IPVs are found in previously treated extremities and cause new symptoms and worsening hemodynamics.<sup>19,25</sup> In addition, surgical treatment of superficial veins often fails to reverse PV incompetence and new IPVs develop in limbs previously treated surgically.<sup>23,26</sup>

The presence of deep reflux further complicates the situation. An IPV may cause reversal of flow in an adjoining segment of deep vein, which is sometimes mistakenly interpreted as deep venous insufficiency but really reflects flow from the segment of deep vein between competent valves through an incompetent perforator into a connected superficial vein. In these cases, correction of superficial insufficiency with or without IPV interruption leads to disappearance of reversed flow in the deep vein segment.<sup>27</sup> When deep reflux is caused by true valvular incompetence, reflux may persist after the treatment of superficial veins.<sup>28</sup> Thus, interpretation of IPV function based on data from clinical studies is not always possible.

Direct measurement of blood flow in IPVs and venous pressure in superficial veins has demonstrated that even when incompetent, a PV can function in a way similar to competent PVs. During standing, there is no blood flow through the IPV, and during walking, the net flow through the IPV is from superficial veins to deep veins despite the bidirectional nature of flow during muscle contractions.<sup>29</sup>

Occlusion of an IPV does not influence venous pressure in superficial veins, whereas occlusion of an incompetent GSV normalizes ambulatory hypertension.<sup>29</sup> In light of these findings, the concept of transmission of the higher blood pressure from deep into superficial veins via IPVs during ambulation becomes questionable. Indirectly, this was confirmed by the demonstration of independent pressure changes in superficial and deep veins during ambulation.<sup>30</sup>

## Clinical Correlations of Perforating Vein Incompetence

The presence of IPVs is just one of many factors that determine the progression to advanced stages or affect the functional status and quality of life of CVD patients. The specific role of IPVs in the natural history and pathogenesis of CVD is less clear. The concept that IPVs can cause symptoms such as swelling and skin changes led to the development of more aggressive approaches to treatment and remains the latter's justification.<sup>5</sup> IPVs alone can cause symptoms, affect hemodynamics, and increase the severity of disease.<sup>19,25</sup> Even more convincing is the fact that successful treatment of an "isolated" IPV is associated with the relief of symptoms and improvement of severity scores.<sup>19</sup>

In addition to their role in symptom development and disease progression, IPVs can be a source of recurrent varices after treatment. This concept is supported by consistent findings of a high prevalence of IPVs in extremities with recurrent varices.<sup>31–34</sup> Whether this association is important only in the presence of deep reflux or also plays a role in extremities with a competent deep system remains to be investigated.<sup>33,35</sup>

The relationship between IPVs and skin ulcers in the leg was historically the first to be demonstrated and was consistently confirmed in multiple small case series in which it was shown that surgical interruption of IPVs promotes healing and prevents the recurrence of venous ulcers.<sup>36</sup> This effect is especially prominent in primary CVD and less so in limbs with postthrombotic disease.<sup>37</sup> Even treating IPVs alone can promote healing of ulcers in the majority of limbs with primary CVD.<sup>19</sup> Large randomized controlled trials, however, have failed to confirm this effect of IPV treatment. The Dutch Ulcer Trial, for example, showed ulcer healing rates of 83% in the surgical group and 73% in the group treated by compression. Ulcer recurrence was almost the same in the two groups: 22% in the surgical group and 23% in the compression group.<sup>38</sup> The results of this and other trials<sup>23,39,40</sup> should be interpreted cautiously because their designs are far from ideal to answer the question of the role of IPVs in ulceration.

In a systematic review of the literature, O'Donnell showed that there is no level 1 evidence that treatment of IPVs alone

affects ulcer healing or recurrence; level 1 evidence is available only for ligation of the GSV alone for decreasing recurrence of venous ulcers.<sup>41</sup> He concluded that there is a need for randomized controlled trials to prove the role of IPV treatment for classes C5 and C6 disease in the Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) classification system.

Given the uncertainty of the physiologic role of IPVs and the lack of high-level evidence of efficacy of IPV interruptions, decision-making in the treatment of IPVs can be a challenging task. The relatively low risk of IPV interruption procedures may be the reason that they have been used in the past for the following indications: (1) normalization of venous hemodynamics; (2) prevention of the progression of CVD to more advanced stages; (3) resolution of symptoms and thereby a decrease in disease severity; (4) prevention of recurrent varicose veins; (5) promotion of ulcer healing; and (6) prevention of recurrent venous ulcers. Clear identification of one or more of these six points as a treatment goal in a patient or as an outcome to be measured in a study may facilitate our progress toward better understanding of the role that IPVs play in limbs with CVD.

## ANATOMY

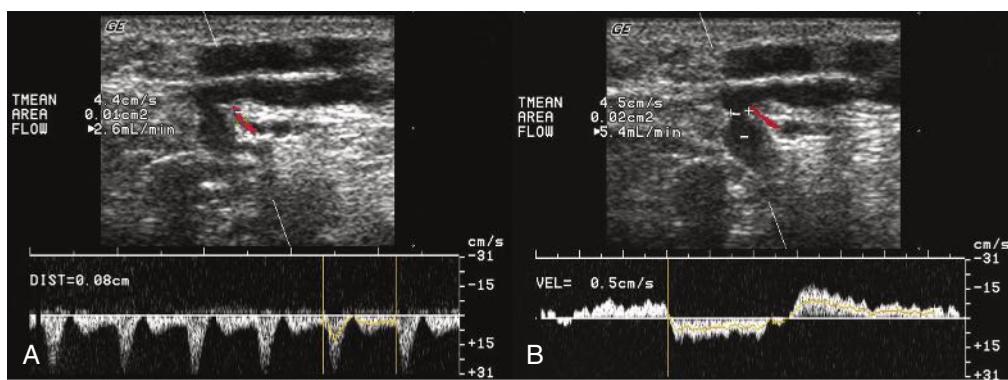
As their name suggests, PVs perforate the deep fascia of the leg, which separates the superficial and deep compartments; they can be classified as direct or indirect. Direct perforators connect the superficial to the deep venous systems, whereas indirect perforators join the venous sinuses of the calf muscles. Furthermore, PVs connect to each other via communicating veins above and underneath the deep muscle fascia. The majority of PVs are accompanied by perforating arteries (Fig. 158.1) and nerves that provide blood supply and innervation to the skin.<sup>12,42</sup> Within the fascial orifice the artery is usually located proximal to the vein, but the topography of the subfascial and suprafascial segments of perforator arteries varies significantly. These arteries can be clearly identified by duplex ultrasound, and their position should be taken into account, especially if sclerotherapy is being considered as a treatment option.<sup>43</sup>

The International Interdisciplinary Consensus Committee on Venous Anatomical Terminology recommends classifying PVs into six groups according to the segment of the lower extremity in which they are found<sup>44</sup>:

- Perforators of the foot (*venae perforantes pedis*)
- Perforators of the ankle (*venae perforantes tarsalis*)
- Perforators of the leg (*venae perforantes cruris*)
- Perforators of the knee (*venae perforantes genus*)
- Perforators of the thigh (*venae perforantes femoris*)
- Perforators of the gluteal muscles (*venae perforantes glutealis*).

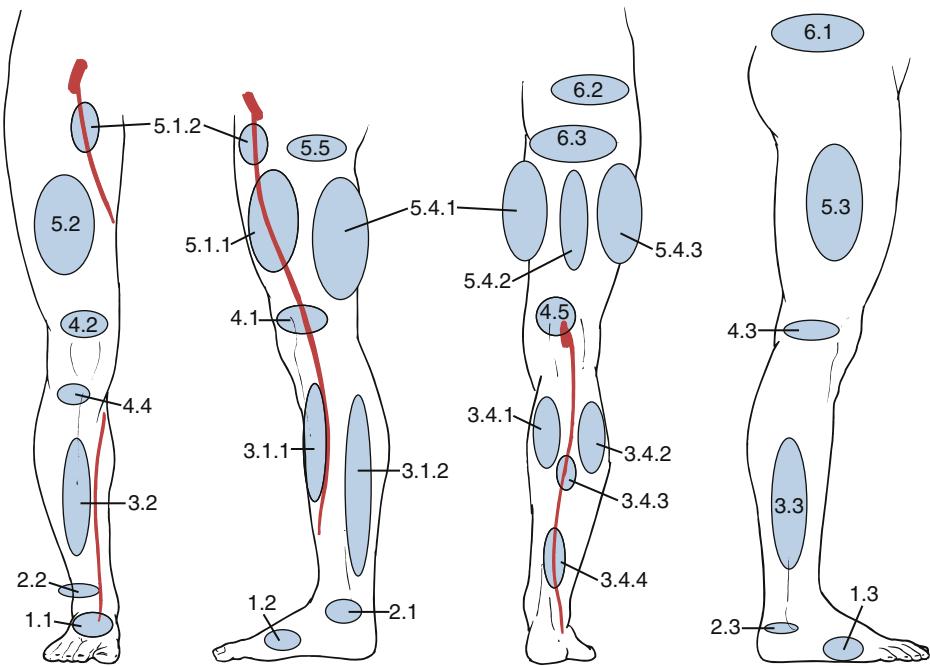
Each group includes several subgroups (Fig. 158.2). One of the aims of this classification is to allow topographic description of PVs to avoid the use of personal names, which are often historically inaccurate.

Many PVs are small vessels and have little clinical significance. The most important perforators from a clinical standpoint are the direct medial calf perforators, which cross the



**Figure 158.1** (A) A small perforating artery is located next to the perforating vein at the fascial level. Pulsed-wave Doppler confirms arterial flow. (B) Doppler signal from the incompetent perforating vein indicates bidirectional flow.

**Figure 158.2** Schematic representation of the topography of the main groups of perforating veins (PVs). Foot PVs: 1.1, dorsal foot PV; 1.2, medial foot PV; 1.3, lateral foot PV. Ankle PVs: 2.1, medial ankle PV; 2.2, anterior ankle PV; 2.3, lateral ankle PV. Leg PVs: 3.1.1, paratibial PV; 3.1.2, posterior tibial PV; 3.2, anterior leg PV; 3.3, lateral leg PV; 3.4.1, medial gastrocnemius PV; 3.4.2, lateral gastrocnemius PV; 3.4.3, intergemellar PV; 3.4.4, para-achillean PV. Knee PVs: 4.1, medial knee PV; 4.2, suprapatellar PV; 4.3, lateral knee PV; 4.4, infrapatellar PV; 4.5, popliteal fossa PV. Thigh PVs: 5.1.1, PV of the femoral canal; 5.1.2, inguinal PV; 5.2, anterior thigh PV; 5.3, lateral thigh PV; 5.4.1, posteromedial thigh PV; 5.4.2, sciatic PV; 5.4.3, posterolateral thigh PV; 5.5, pudendal PV. Gluteal PVs: 6.1, superior gluteal PV; 6.2, midgluteal PV; 6.3, lower gluteal PV. (Redrawn from Caggiati A, Bergan JJ, Głowiczki P, et al. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg*. 2002;36:416–422.)



superficial posterior compartment. The posterior tibial PVs originate from the posterior accessory saphenous vein of the calf (posterior arch vein in the old terminology). The most distal posterior tibial perforators are located behind the medial malleolus, whereas the middle and upper posterior tibial perforators are located more proximally in the calf (at 7–9 cm and 10–12 cm from the medial malleolus, respectively) and about 1 inch medial to the tibia; these PVs connect the posterior arch vein to the posterior tibial veins (Cockett perforators). More proximal direct PVs are the paratibial direct perforators or “24-cm perforators,” which are located closer to the tibia and 18 to 22 cm from the medial malleolus, as evident in anatomic cadaveric studies (Fig. 158.3). Another group of medial calf perforators, found just below the knee, is known as Boyd’s perforators. They connect the GSV and its tributaries to the tibial or popliteal veins. Also of probable clinical importance are the posterolateral or peroneal perforators, which connect tributaries of the short saphenous vein to the peroneal veins. Among these, the most important are Bassi’s perforator, located at 5 to 7 cm from the lateral aspect of the ankle, and the “12-cm

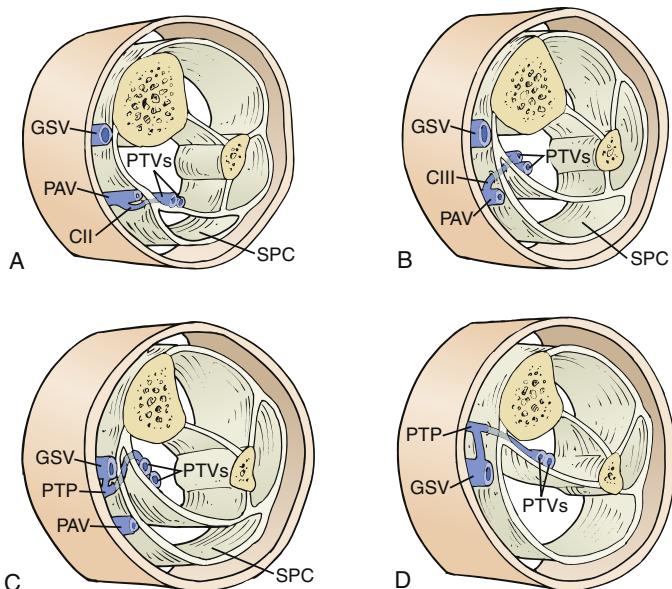
perforator,” located at 12 to 14 cm. Thigh perforators are less developed than calf PVs. The main instances are the Dodd perforators and the Hunterian perforators, which are located in the medial aspect of the thigh and connect the GSV to the popliteal or femoral veins. Other PVs connect the superficial system to the profunda femoris vein.

Some perforating veins can connect the GSV or other superficial veins with transosseous veins that provide drainage from distal tibia.<sup>45</sup> A few case reports and a case series of 32 patients suggest that incompetence of these veins can be associated with atypical venous symptoms.<sup>46</sup> The incidence and clinical importance of these venous connections is unclear, and the suggestion to call them “bone perforators” has limited support.

## DIAGNOSTIC EVALUATION

### Clinical Investigation (CEAP Level 1)

Large IPVs can be identified by palpation of the fascial defect, especially when varicose veins are located in the same area. By



**Figure 158.3** Compartments and medial veins of the leg. Cross sections are shown at the level of Cockett II (posterior tibial perforator) (A), Cockett III (B), “24 cm” (C), more proximal paratibial (D) perforating veins. CII, Cockett II; CIII, Cockett III; GSV, great saphenous vein; PAV, posterior arch vein; PTP, paratibial perforator; PTVs, posterior tibial veins; SPC, superficial posterior compartment. (From Gloviczki P, Bergan J, eds. *Atlas of Endoscopic Perforator Vein Surgery*, London: Springer-Verlag; 1998.)

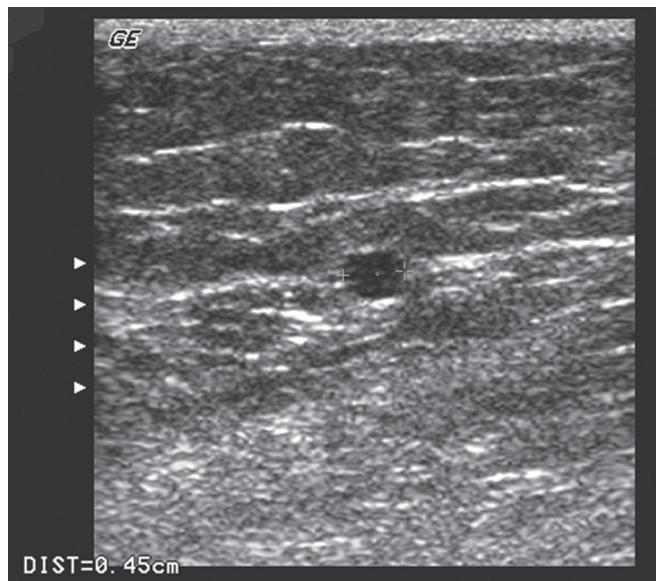
applying gentle pressure against this defect, an investigator can feel retrograde flow when a patient performs the Valsalva maneuver or coughs. Handheld continuous-wave Doppler ultrasonography can be the next diagnostic step, but its sensitivity is insufficient and its specificity is not different from that of physical examination, which is close to zero.<sup>47</sup>

The best test to identify IPVs is duplex ultrasound. This test should be performed in all patients with CVD. The invasive nature of venography, its questionable diagnostic properties for identification of IPVs,<sup>47</sup> and its inability to map the exact location of IPVs make its use in CVD limited to selected cases requiring venous reconstruction.

## Noninvasive Vascular Investigation (CEAP Level 2)

The size of PVs and their hemodynamic properties are to a great extent affected by the position of the body. It is recommended that duplex scanning be performed while the patient is standing or sitting; however, the 30-degree head-up supine position gives similar results.<sup>48</sup> All surfaces of the extremity should be carefully scanned. The location of IPVs varies, and indirect IPVs can be found at a distance from major axial veins.

Because most PVs are rather short veins, induction of reversed flow in them is a great challenge. To initiate a reversed flow of appropriate duration, the connected superficial vein should be almost empty and the adjoined deep vein should contain a sufficient volume of blood. In many cases this is difficult to achieve, especially when the test is performed on a standing patient. To solve this problem, two sets of criteria for PV incompetence were suggested: a shorter-time cut point of



**Figure 158.4** Measurement of perforating vein diameter is performed in a B-mode transverse section of the PV at the level of the fascial orifice.

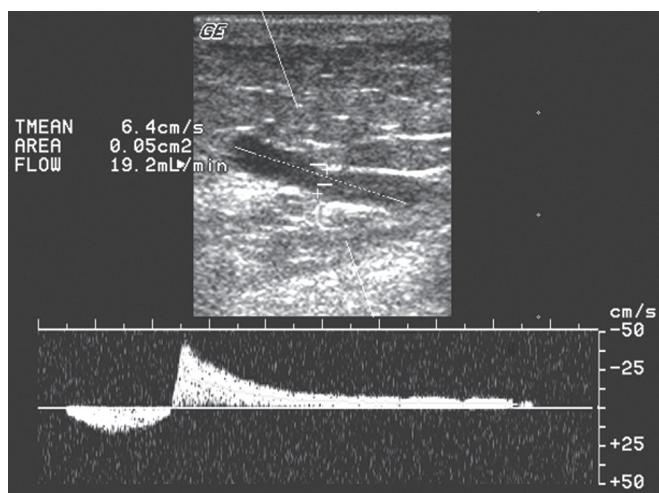
0.35 seconds to define the reflux<sup>21</sup> and the use of PV diameter instead of reflux time.<sup>49</sup> Diameter should be measured on a B-mode transverse section at the site where the vein penetrates the fascia (Fig. 158.4). Reflux time should be measured on a longitudinal section using a pulsed-wave mode combined with simultaneous B-mode (duplex) or with the addition of a color Doppler mode (triplex). The site for measurement of reflux time should be the same as that for measurement of diameter – at the level of the fascial orifice (Fig. 158.5).

In our experience, using both approaches simultaneously has proved beneficial. Small PVs less than 2 mm in diameter have questionable clinical significance, even when reversed flow through them exceeds the cut point for reflux. They also present a technical challenge for treatment and often undergo spontaneous thrombosis and resolution after ablation of the connected segment of superficial vein. PVs larger than 4 mm in diameter are almost certainly pathologic and may be identified as incompetent even when the reversed flow through them is shorter than the cut point for reflux. Finally, PVs 2 to 4 mm in diameter should be considered incompetent only when they meet the appropriate hemodynamic criteria.

When treatment of an IPV is being considered, duplex scanning should be repeated in the exact position as the patient will be in during the treatment. This can be supine, prone, or on the side, depending on the selected access point. Shifting of anatomic structures can markedly affect the topographic relationship between subfascial and suprafascial segments of the IPV and superficial veins, which, in turn, will change the position of a desirable access point.

## INDICATIONS FOR INTERRUPTION

Precise definition of the indications for interruption of IPVs is necessary in clinical practice because it provides a basis for assessment of treatment outcomes. It is even more important



**Figure 158.5** Measurement of flow velocity in a perforating vein (PV) is performed in duplex mode in a longitudinal section of the PV at the level of the fascial orifice.

when research studies are planned and executed. Although definitive studies to identify when IPV interruption should be considered are yet to be conducted, one or more of the following reasons can serve as the indication for treatment of IPVs:

1. Promotion of ulcer healing in extremities with CEAP clinical class C6
2. Prevention of ulcer recurrence in extremities with clinical classes C5 and C6
3. Prevention of progression to more advanced stages in C4b extremities.

The presence of an IPV alone does not justify interruption. The decision to intervene should be based on clinical judgment and assessment of the role of a specific IPV in the overall hemodynamic picture of the extremity. The benefits of interruption and the risks of leaving this PV untreated should also be considered.

Key suggestions and recommendations from the AVF/SVS guidelines<sup>50</sup> for the treatment of CVD include the following:

- We suggest treatment of pathologic PVs that includes those with outward flow of 500 ms duration and a diameter of 3.5 mm located adjacent to healed or open venous ulcers (class C5–C6, grade 2B).
- We suggest treatment of pathologic perforators in patients with advanced C4 disease, especially in those with pending ulceration (class C4, grade 2C).
- We recommend against selective treatment of incompetent PVs in patients with simple varicose veins (class C2, grade 1B).
- We suggest preferential use of ultrasonographically guided percutaneous techniques (thermal ablation or sclerotherapy) for perforator ablation over subfascial endoscopic perforator surgery (SEPS) or open surgical phlebectomy or perforator ligation (grade 2C).

The most recent AVF/SVS guidelines provide more specific indications for treating limbs with C4b–C6 disease.<sup>51</sup>

These guidelines include the following statements:

- In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition

to pathologic PVs (outward flow of less than 500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins in addition to standard compressive therapy to aid in ulcer healing and prevent recurrence (grade 2; level of evidence, C).

- In a patient with skin changes suggestive of an impending venous ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic PVs (outward flow of >500 ms duration and a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer (grade 2; level of evidence, C). Treatment of the incompetent PVs can be performed simultaneously with correction of axial reflux or can be staged with reevaluation of perforator veins for persistent incompetence after correction of axial reflux (grade 2; level of evidence, C).
- In a patient with isolated pathologic perforator veins (outward flow >500 ms duration and a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed regardless of the status of the deep veins, we suggest ablation of the pathologic PVs in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence (grade 2; level of evidence, C).

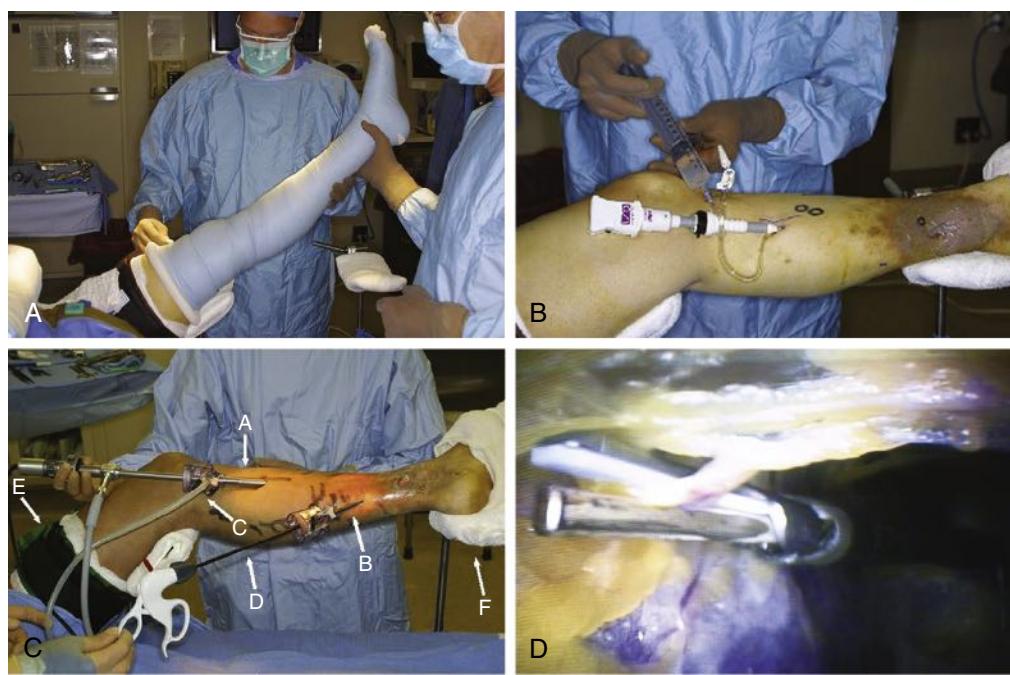
## OPERATIVE PLANNING OPTIONS

The timing and technique of IPV interruption are important. Although procedures can be staged, performing simultaneous saphenous vein ablation and perforator ablation has two major advantages. First, all invasive procedures are performed in one session, which is highly desirable for the patient and reduces the cost of treatment. Second, it has been suggested that any remaining incompetent tributaries and IPVs connected to the saphenous veins can increase the chance of recanalization after thermal and chemical ablation.

Thus, treating IPVs at the time of saphenous vein ablation possibly improves the results of the saphenous vein ablation with reported 17% improvement in healing at 36 months.<sup>52</sup>

On the other hand, elimination of saphenous reflux has a profound effect on the global venous hemodynamics of the leg. Segments not specifically targeted during surgery, such as PVs and deep veins, may partially reverse their incompetence when the total venous “overload” of the leg is reduced. In as many as 58% of IPVs, incompetence will reverse during the 2 years after stripping.<sup>53</sup> Even when IPVs persist after stripping of the GSV, their impact on the clinical status of the extremity is questionable. The ESCHAR (Effect of Surgery and Compression on Healing and Recurrence) study showed that presence of IPVs after stripping does not affect the healing time and rate of ulcers.<sup>54</sup>

When simultaneous treatment of IPVs and incompetent saphenous veins is planned, selection of the IPV interruption technique is very much dependent on the method of treating the saphenous vein. The less invasive options for saphenous



**Figure 158.6** (A) Endoscopic division of a perforator is performed in a bloodless field. A pneumatic tourniquet is placed on the thigh, and the extremity is exsanguinated with an Esmark bandage. A tourniquet inflated to 300 mm Hg is used to create a bloodless field. (B) Balloon dissection is used to widen the subfascial space. (C) Subfascial endoscopic perforator vein surgery is performed via two ports: a 10-mm camera port (*A*) and a 5- or 10-mm distal port (*B*) inserted under video control. Carbon dioxide is insufflated through the camera port into the subfascial space to a pressure of 30 mm Hg to improve visualization and access to the perforators (*C*). A harmonic scalpel (*D*) is inserted through the distal port. The leg is positioned on a holder (*F*), and the tourniquet is kept inflated (*E*). (D) The subfascial space is widely explored from the medial border of the tibia to the posterior midline and down to the level of the ankle. Division of the perforator is performed with endoscopic scissors after placement of vascular clips or with a harmonic scalpel placed through the second port. (A–D, Reproduced with permission of the Mayo Foundation.)

ablation limit the use of open surgical interruption because it may increase immediate postoperative morbidity and negate the advantages of minimally invasive procedures. When IPV interruption is performed alone, selecting a minimally invasive option still has the advantage of minimizing immediate postoperative morbidity, thereby allowing early ambulation and reducing impact on quality of life.

## OPEN SURGERY

The original open perforator interruption described by Linton in 1938 – in which an extensive longitudinal medial calf incision was used to expose perforator veins – has been abandoned to be replaced by less invasive methods. Interruption of PVs through small stab wounds plus avulsion by a vein hook is now preferred among the open surgical methods because this procedure is significantly less invasive and does not require hospitalization. With this technique, duplex scanning is used for preoperative mapping and the IPVs are marked on the skin, which allows performance of a more precise procedure. Ligation of incompetent perforators can also be done by making a short incision directly over the marked sites and ligating them at the fascia with absorbable sutures. Alternatively, the position of the vein hook can be controlled with the use of intraoperative transcutaneous ultrasound to ensure that a targeted IPV is actually interrupted. Selection of an open perforator

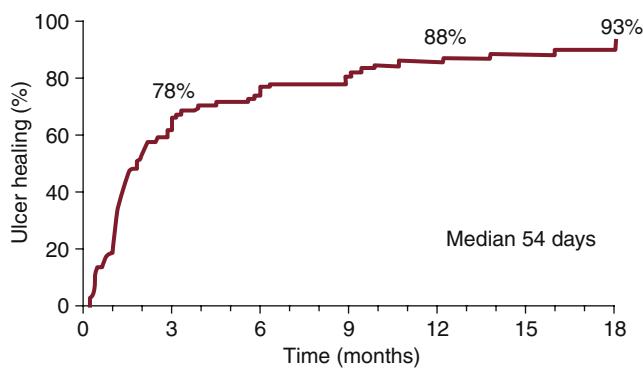
interruption technique does not guarantee 100% success; 5% of perforators are usually missed and 32% recur within 3 years, half of them being incompetent.<sup>55,56</sup>

## Subfascial Endoscopic Perforator Surgery

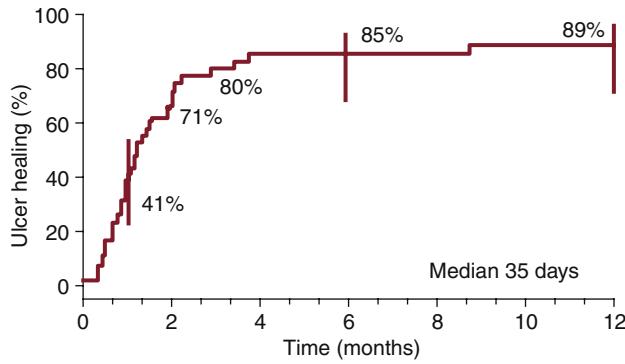
SEPS uses endoscopic instrumentation to achieve interruption of incompetent perforators through small incisions placed remotely from areas of lipodermatosclerosis or ulceration. First described by Hauer in the 1980s,<sup>8</sup> SEPS became a more accepted surgical treatment of CVI because of its less invasive nature and safety profile compared with the Linton procedure. SEPS can be performed through one or two endoscopic ports after exsanguination of the limb with leg elevation and the Esmark bandage, followed by application of a thigh tourniquet inflated to 300 mm Hg (Fig. 158.6). Carbon dioxide is insufflated to enlarge and optimally visualize the subfascial space, with pressure maintained at around 30 mm Hg. On completion of the procedure, the ports and instrumentation are removed, the tourniquet is deflated, and the carbon dioxide is manually expressed from the subfascial space.<sup>57</sup>

## Results and Complications

Open and endoscopic perforator surgery are performed less routinely due to invasive nature and high complication rates.



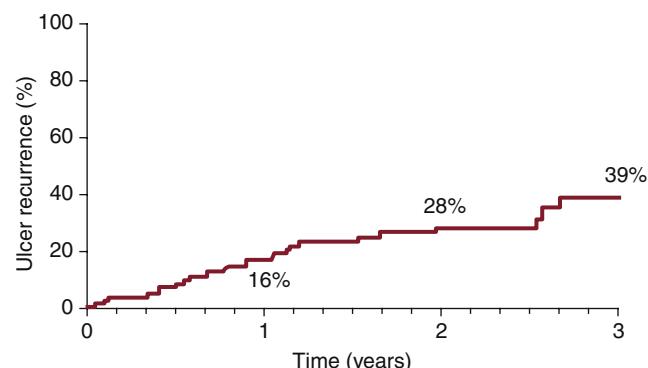
A



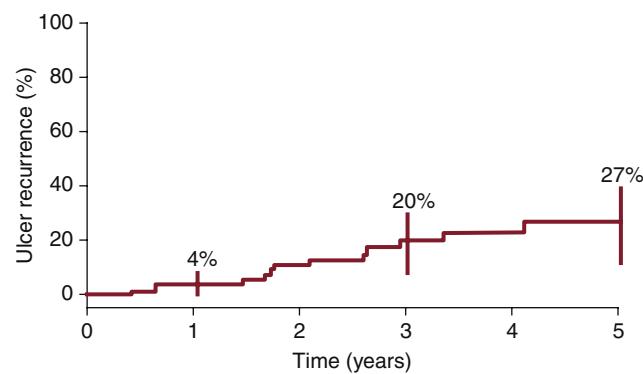
B

**Figure 158.7** (A) Cumulative ulcer healing in 101 patients after subfascial endoscopic perforator vein surgery. The 90-day, 1-year, and 1.5-year healing rates are indicated. The standard error is less than 10% at all time points. (B) Cumulative ulcer healing in 42 patients after subfascial endoscopic perforator vein surgery. The 90-day and 1-year healing rates are indicated. The standard error is less than 10% at all time points. (A, From Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM. North American Study Group: mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American Subfascial Endoscopic Perforator Surgery [NASEPS] registry. *J Vasc Surg*. 1999;29:489–499. B, From Kalra M, Gloviczki P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency—is it justified? *Vasc Endovasc Surg*. 2002;36:41–50.)

Retrospective data from the North American SEPS registry on 146 patients demonstrated an 88% ulcer healing rate at 1 year, with a median ulcer healing time of 54 days and a complication rate of 6% (Fig. 158.7).<sup>37</sup> Complications encountered were deep venous thrombosis (DVT) (<1%), superficial thrombophlebitis (3%), and saphenous neuralgia (7%).<sup>37</sup> Other complications of SEPS include wound infection, paresthesias, and subfascial space hematoma.<sup>57</sup> The ulcer recurrence rate was 28% at 2 years (Fig. 158.8), significantly better than most published series on nonoperative management. Several other studies have demonstrated a benefit of SEPS in early ulcer healing and decreased recurrence rates (Table 158.1). Nonetheless, other studies did not prove the clinical efficacy of PV reflux ablation, even in patients with ulcerated limbs.<sup>58</sup> In a meta-analysis, Tenbrook and coworkers analyzed pooled data of surgical treatment in 1140 limbs with advanced CVD from 20 mostly nonrandomized studies.<sup>59</sup> Ulcers healed in 88% of the limbs treated by SEPS, with or without superficial venous ablation. The recurrence



A



B

**Figure 158.8** (A) Cumulative ulcer recurrence in 106 patients after subfascial endoscopic perforator vein surgery (SEPS). The 1-year, 2-year, and 3-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points. (B) Cumulative ulcer recurrence in 72 patients after SEPS. The 1-year, 3-year, and 5-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points. (A, From Gloviczki P, Bergan JJ, Rhodes JM, et al. North American Study Group: mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American Subfascial Endoscopic Perforator Surgery [NASEPS] registry. *J Vasc Surg*. 1999;29:489–499. B, From Kalra M, Gloviczki P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency—is it justified? *Vasc Endovasc Surg*. 2002;36:41–50.)

rate was 13% at a mean follow-up period of 21 months, although almost invariably those studies lacked a comparison group. Risk factors for nonhealing and recurrent ulcers included new or recurrent IPVs, postthrombotic syndrome, and ulcers larger than 2 cm in diameter. Surgical complications included wound infection (6%), hematoma (9%), neuralgia (7%), and DVT (1%). The Dutch SEPS trial, a randomized, prospective, multicenter study designed to compare SEPS with conservative treatment of venous ulcers, has been performed and published (Table 158.2). Of 200 legs with ulcers included in the study, 94 were treated surgically and 102 were treated conservatively. Healing rates were 83% in the surgical group and 73% in the conservative group (difference not significant; median time to healing, 27 months). Recurrence rates were the same in both treatment groups (22% with

**TABLE 158.1** Results of Subfascial Endoscopic Perforating Vein Surgery in Main Published Series

Series	Number of Limbs	Number of Limbs With History of Ulcer	Number of Limbs With Active Ulcer	Saphenous Vein Ablation (%)	Ulcer Healing (%)	Number of Limbs With Ulcer Recurrence	Mean Follow-Up (Months)
Jugenheimer, 1992 <sup>a</sup>	103	NR	17	NR	94	0	27
Pierik, 1995 <sup>b</sup>	40	40	16	10	100	1	46
Bergan, 1996 <sup>c</sup>	31	25	15	100	93	0	NR
Gloviczbek, 1999 <sup>d</sup>	146	122	101	60	84	26	24
Lee, 2001 <sup>e</sup>	36	19	NR	92	89	2	14
Baron, 2001 <sup>f</sup>	45	45	37	40	89	0	10
Iafrati, 2002 <sup>g</sup>	51	51	29	55	74	7	38
Ciostek, 2002 <sup>h</sup>	146	74	36	90	86	11	56
Kalra, 2002 <sup>i</sup>	103	76	42	72	90	21	39
Bianchi, 2003 <sup>j</sup>	74	74	58	77	91	4	44
Roka, 2006 <sup>k</sup>	92	41	21	97	95	2	44
Ting, 2006 <sup>l</sup>	53	15	34	100	100	3	31

NR, not reported.

<sup>a</sup>Jugenheimer M, Junginger T. Endoscopic subfascial sectioning of incompetent perforating veins in treatment of primary varicosis. *World J Surg*. 1992;16:971–975.<sup>b</sup>Pierik EG, Wittens CH, van Urk H. Subfascial endoscopic ligation in the treatment of incompetent perforating veins. *Eur J Vasc Endovasc Surg*. 1995;9:38–41.<sup>c</sup>Bergan JJ, Murray J, Greason. Subfascial endoscopic perforator vein surgery: a preliminary report. *Ann Vasc Surg*. 1996;10:211–219.<sup>d</sup>Gloviczbek 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.<sup>e</sup>Lee DW, Chan AC, Lam YH, et al. Early clinical outcomes after subfascial endoscopic perforator surgery (SEPS) and saphenous vein surgery in chronic venous insufficiency. *Surg Endosc*. 2001;15:737–740.<sup>f</sup>Baron HC, Saber AA, Wayne M. Endoscopic subfascial surgery for incompetent perforator veins in patients with active venous ulceration. *Surg Endosc*. 2001;15:38–40.<sup>g</sup>Iafrati MD, Pare GJ, O'Donnell TF, Estes J. Is the nihilistic approach to surgical reduction of superficial and perforator vein incompetence for venous ulcer justified? *J Vasc Surg*. 2002;36:1167–1174.<sup>h</sup>Ciostek P, Myrcha P, Noszczyk W. Ten years experience with subfascial endoscopic perforator vein surgery. *Ann Vasc Surg*. 2002;16:480–487.<sup>i</sup>Kalra M, Gloviczbek P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency—is it justified? *Vasc Endovasc Surg*. 2002;36:41–50.<sup>j</sup>Bianchi C, Ballard JL, Abou-Zamzam AM, Teruya TH. Subfascial endoscopic perforator vein surgery combined with saphenous vein ablation: results and critical analysis. *J Vasc Surg*. 2003;38:67–71.<sup>k</sup>Roka F, Binder M, Bohler-Sommeregger K. Mid-term recurrence rate of incompetent perforating veins after combined superficial vein surgery and subfascial endoscopic perforating vein surgery. *J Vasc Surg*. 2006;44:359–363.<sup>l</sup>Ting AC, Cheng SW, Ho P, Wu LL, Cheung GC. Clinical outcomes and changes in venous hemodynamics after subfascial endoscopic perforating vein surgery. *Surg Endosc*. 2003;17:1314–1318.**TABLE 158.2**

Results of Surgical Treatment of Perforator Vein Incompetence Versus Conservative Treatment Alone in a Randomized, Prospective, Multicenter Study (the Dutch SEPS Trial)

Number of Limbs Treated	Number of Limbs with Active Ulcer (%)	Number Treated Conservatively (%)		Number Treated Surgically (%)		Mean Follow-Up (Months)	
		Number of Ulcers Healed (%)	Number of Ulcers That Recurred (%)	Number of Ulcers Healed (%)	Number of Ulcers That Recurred (%)		
200	196 (100)	102 (52)	94 (48)	74 (73)	23 (23)	78 (83)	21 (22)

SEPS, subfascial endoscopic perforating vein surgery.

surgical treatment vs. 23% with conservative treatment). During follow-up at a mean of 29 months in the surgical group and 26 months in the conservative group, the ulcer-free rate was 72% in the surgical group and 53% in the conservative group ( $P = 0.11$ ). Patients with recurrent ulceration or medially located ulcers in the surgical group had a longer

ulcer-free period than those treated in the conservative group ( $P = 0.02$ ). The trial did not recognize an overall benefit of surgical treatment over compression alone except in selected cases of medial or recurrent ulceration (or both) and in patients who underwent the SEPS procedure in expert venous centers.<sup>38</sup> The same group later published a 10-year follow-up

study including 41% of patients available from the previous study. At a mean of 97 months the ulcer-free rate was higher in the SEPS group (58.9%) than in the conservative group (39.6%;  $P = 0.007$ ) and overall recurrence rates were 48.9% in the surgical group and 94.3% in the conservative group.<sup>60</sup> In a recent Cochrane review, including articles prior to 2014, it has been concluded that SEPS in combination with compression may improve healing of venous ulcers, but the authors were unable to draw conclusions as to the effect of SEPS on ulcer recurrence and its effect when combined with other surgical techniques.<sup>61</sup> Until recently, SEPS was considered the main minimally invasive alternative to open surgery for the treatment of PV incompetence. Compared with the classic open procedures, the incidence of complications lower with SEPS. However, the occurrence of other complications, such as DVT, superficial thrombophlebitis, and neuralgia, as well as the complex learning curve and significant cost, stimulated interest in percutaneous, less invasive methods. Furthermore, the procedure is limited by an inability to reliably access all incompetent perforator sources and to discriminate between competent and incompetent perforators at the time of treatment. It has been reported that in up to 55% of patients one (29%) or more (26%) perforators can be missed during SEPS, and that while an incomplete SEPS procedure does not affect healing, it can significantly affect recurrence rates.<sup>62</sup>

## PERCUTANEOUS ABLATION OF PERFORATING VEINS

The introduction of percutaneous endovenous therapies for superficial venous reflux (thermal and chemical ablation) has established a new standard of office-based procedures that obviate the need for general anesthesia and hospital stay. Thermal and chemical ablation of saphenous veins gained popularity rapidly, thanks to a significant reduction in patient discomfort, fewer complications, and earlier return to work.<sup>63</sup> PAPS combines the precision of a surgical approach with the minimal invasiveness of an injection. PAPS requires a higher level of technical skill than GSV ablation does but offers patients a truly minimally invasive procedure. After PAPS, either as the sole treatment or in conjunction with saphenous ablation, patients can ambulate immediately and experience minimal post-operative pain. PAPS has almost no negative impact on quality of life.<sup>64,65</sup>

The AVF/SVS clinical practice guidelines recommend PAPS over open surgical techniques. "For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin (grade 1; level of evidence, C)."<sup>50</sup>

The two most important technical aspects of PAPS are ultrasound-guided intraluminal access and verification of the initial anatomic success of the treatment. Selection of the



**Figure 158.9** Closure RFS (radiofrequency stylet).

access point depends on the technique and instrumentation that will be used. For example, if treatment is planned with the rigid Closure RFS (radiofrequency stylet, Fig. 158.9), an access point should be lined up with the continuation of the subfascial portion of the perforator. More flexible laser fibers allow selection of the entry point to access either the epifascial segment of the IPV or the adjoining superficial vein. A larger and straighter segment of the superficial vein can be selected to provide easier access and a more stable needle position. A guide wire can then be advanced into the perforator and a microintroducer positioned over the wire to secure the precise position for placement of the laser fiber. Alternatively, the fiber can be placed directly through a 21-gauge needle for the 400-μm fiber or through a 16-gauge needle for the 600-μm fiber. If sclerotherapy is planned as the treatment technique, the access selected should be at a safe distance from the perforating artery. If it is not clearly identifiable by duplex scan, the superficial vein connected to the perforator and located a distance of 1 to 2 cm from the fascial orifice should be selected for the access.

For all techniques, successful access and the position of the catheter or needle should be confirmed sonographically. Aspiration of blood is not sufficient because the needle may be in a neighboring vein not connected to the IPV. In the case of thermal ablation, the subfascial position of the catheter should also be verified. The advantage of using the radiofrequency stylet is the ability to measure impedance, which can confirm the intravascular position of the catheter. Sonographic verification, however, is still necessary.

Assessment of initial anatomic success is also based on duplex ultrasound. In addition to verification of the absence of blood flow in the PV, assessment of changes in diameter and echogenicity of the vein wall and lumen is necessary. An increase in echogenicity and thickening of the venous wall, increased echogenicity of the lumen, and absence of spontaneous or induced flow immediately after treatment are signs of successful ablation. An increase in diameter and a decrease in echogenicity with an absence of flow indicate thrombosis in the IPV, which is less desirable because of the risk of propagation in deep veins and the high rate of recanalization. Assessment

of success after foam sclerotherapy is most challenging and should be postponed for 24 hours or more because the PV cannot be clearly visualized; flow can be induced by compression of the extremity distal to the PV immediately after successful treatment. As an indirect sign of successful PAPS, we found it helpful to use the dilation and increased flow velocity in the perforating artery accompanying the treated IPV immediately after treatment.<sup>43</sup>

## Techniques

### Laser Ablation

Several different fibers and kits have been used for endovenous laser ablation of IPVs. The use of lasers with wavelengths of 810-, 940-, and 1320-nm and 980-nm diode lasers has been reported.<sup>64,65</sup>

The patient is placed in the reverse Trendelenburg position and the skin is prepared with sterile technique. Incompetent perforators are visualized and marked on the skin; it is important to document the exact location by measuring its distance from the medial malleolus and tibia for localization during follow-up studies.

The target perforator and its connecting branches are visualized by ultrasound to identify the best location for access. If the perforator and a significant branch can be treated during the same session, the success is better in our experience. Once an access site is selected local anesthetic is injected. Ultrasound-guided access is performed using low negative pressure on the needle with a slip tip syringe. A guide wire and a micro sheath is placed. For certain applications an 18-gauge angio-catheter can be used instead. After access is gained the laser fiber is advanced into the perforator with care to avoid advancement below the fascia. Tumescent anesthesia is injected generously around the vein to ensure adequate anesthesia for patient comfort and an effective heat sink. After tumescent is verified to be adequate the micro sheath is withdrawn to expose the tip of the laser fiber. Two or three segments of each perforator should be treated, starting at the level of the fascia and moving more superficially. Each segment should receive between 60 and 100 Joules. Treatment time may vary from under a minute to a few minutes depending on the treatment length and responses. Color flow duplex is used on completion to verify closure. We routinely apply a light compression wrap upon completion, although the benefit after perforator treatment may be less than after saphenous vein ablation.

### Radiofrequency Ablation

The Closure RFS made by Medtronic/Covidien (Mansfield, MA) is a rigid device that has two electrodes on the shaft and a removable needle trocar. The vein is punctured either directly with the stylet or with a needle, followed by access over a 0.035-inch guide wire (see Fig. 158.9). Ideally, extrinsic compression should be maintained during treatment (approximately 80 to 90 mm Hg of pressure). After intravascular access has been confirmed by return of blood into the device, tumescent anesthetic is infiltrated around the vein. The vein should

be treated in a subfascial segment to ensure the best results, but this should be at least 0.5 cm away from the deep veins. Impedance is maintained between 150 and 350 Ω at a mean temperature of 85°C and a power level of less than 3.5 W. The Closure RFS should be angulated against all four quadrants of the vein wall for 1 minute each, thus requiring 4 minutes of treatment per segment. More segments within the same perforator, ideally two or more, may require treatment to obtain satisfactory closure.

### Sclerotherapy

Sclerotherapy can be performed to treat IPVs with a diameter of 4 to 7 mm at the level of the fascia. Smaller veins are seldom incompetent, and larger veins require larger volumes of sclerosant, which can potentially increase the rate of complications. Most commonly used are sodium tetradecyl sulfate (Sotradecol), sodium morrhuate, and polidocanol (Aethoxysklerol) in a liquid form or an off-label foam using the Tessari method. Larger veins require higher concentrations. In general, the patient is placed in the supine position, the skin is prepared by sterile technique, and the IPV is punctured under duplex guidance. Alternatively, a varicosity approximately 5 cm away from the perforator can be selected as the target for injection.<sup>66</sup>

Venous blood is withdrawn first, just enough to confirm correct needle positioning, and 1 to 2 mL of sclerosing agent is injected. The needle is withdrawn and compression is applied for a few minutes. When foam is injected, pressure is held at the junction of the IPV and the deep vein for about 2 minutes with an ultrasound probe to prevent excessive escape of foam into the deep system. The vein is reimaged to ascertain the absence of residual flow in the treated perforator. Identification of the accompanying perforating arteries should be attempted to avoid possible skin necrosis, but when this is not possible, it is preferable to inject the perforator in a location well above the fascial opening, where the artery and vein are not so close to each other. Patients with known allergic reactions to sclerotherapy agents, those who are pregnant or lactating, and those with a known or suspected prothrombotic state should not be treated by this technique. The presence of severe arterial occlusive disease or active vasculitis is also a contraindication, because inadvertent intraarterial injection can potentially aggravate preexisting chronic ischemia.

## New Treatment Modalities

Similar to thermal ablation techniques that were initially designed for saphenous veins but were adapted to treat IPVs, new technologies are either already being used or likely to be used for this purpose outside their primary indications. Mechanicochemical ablation (MOCA) has ablation rates similar to those of thermal ablation but does not require tumescent anesthesia.<sup>67-69</sup>

Although the use of other new nontumescent nonthermal ablation modalities for the treatment of IPVs has not yet been

established, it is only a matter of time before technologies such as cyanoacrylate embolization<sup>70</sup> will be applied for treatment of IPVs. Initial enthusiasm regarding cyanoacrylate adhesive embolization (CAPE) of perforating veins<sup>71</sup> was followed by more realistic reports of CAPE outcomes.<sup>72,73</sup> The techniques of CAPE vary, but key aspects include ensuring that a proper volume of cyanoacrylate (0.06–0.12 mL) is delivered to the target perforating vein, and keeping a safe distance between ablated perforator and its junction with a deep vein.<sup>72,73</sup> Reported ablation rate of CAPE is 76% at 6 months,<sup>72</sup> and outcomes are improved when CAPE is combined with sclerotherapy of adjoining varicose veins.<sup>73</sup>

## Results and Complications

Early success rates with greater than 90% absence of flow within the treated perforator at 6 months have been reported with radiofrequency ablation.<sup>74,75</sup> Unlike GSV closure, skin burns are very rare with the Closure RFS, even when the probe is at a depth of less than 1 cm from the skin.

The early occlusion rate of IPVs treated by laser is reported to be between 85% and 100%.<sup>72,73</sup> Side effects included ecchymosis, induration, and pain (40% to 50%), paresthesias (16%), hyperpigmentation (8%), and phlebitis (4%).<sup>76,77</sup> A 6-month duplex follow-up from a series of 27 perforators treated by laser demonstrated an ablation success rate of greater than 90%.<sup>77</sup> Although detailed documentation of perforator location before treatment is necessary for follow-up comparison, no reliable method exists to determine whether a suspected perforator recurrence is a newly formed perforator or indeed a recanalized perforator.

The early results of duplex-guided sclerotherapy for perforators reported by Guex showed a 90% occlusion rate after three or fewer sessions.<sup>18</sup> IPV obliteration rates vary between 54% and 98% of cases.<sup>18,78</sup> Skin complications consisting of superficial skin necrosis may occur in about 1.5% of cases,<sup>18</sup> and DVT in 3%.<sup>78</sup> Concomitant use of anticoagulants has been associated with decreased rates of successful IPV occlusion, which in turn is predictive of reduced rates of ulcer healing, as expected.<sup>78</sup> In our experience recanalization of a successfully treated IPV occurred in 23% of cases at a mean follow-up of 17 months. Venous clinical severity scores decreased on average

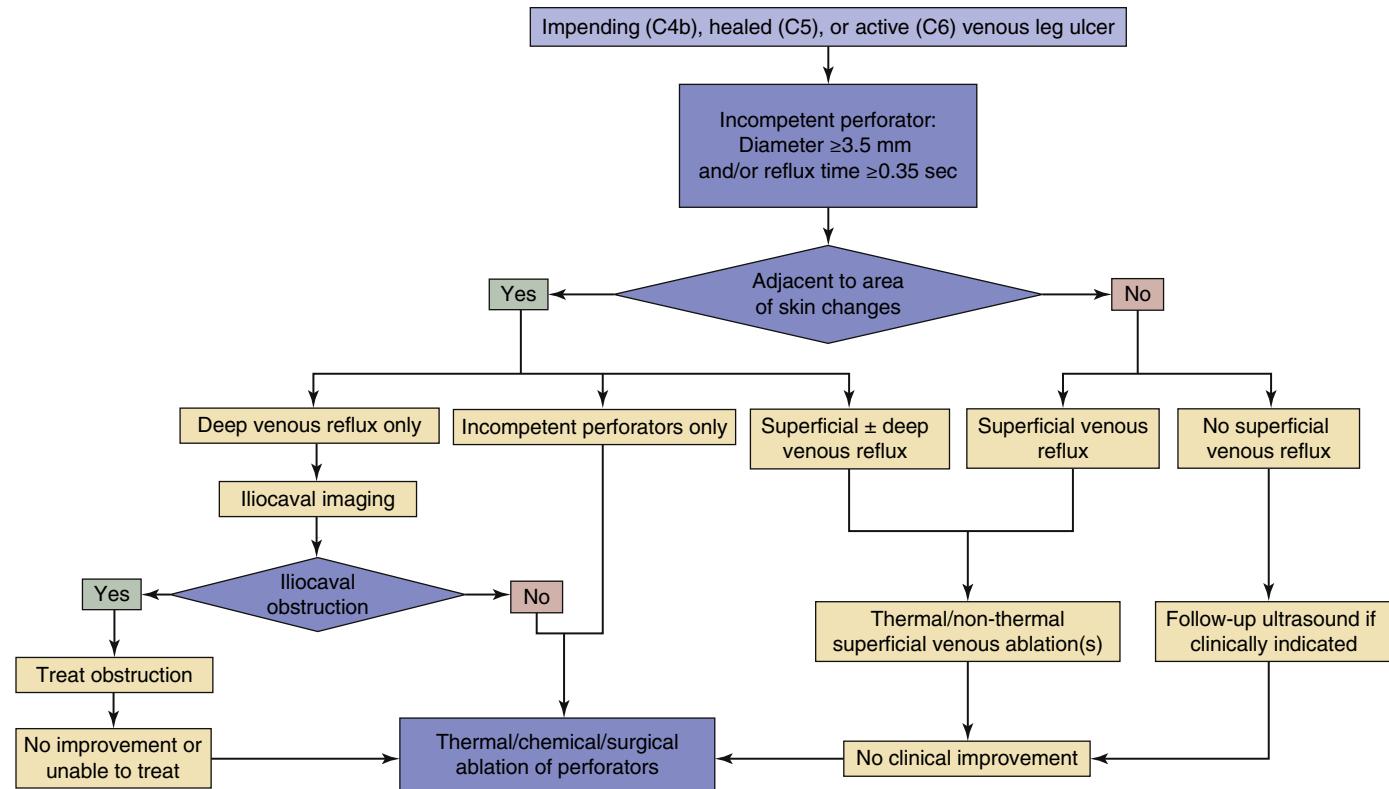
from 11.95 before treatment to 6.5 after treatment ( $P < 0.05$ ). Likewise, venous disability scores dropped from 1.86 before treatment to 0.81 after treatment ( $P < 0.05$ ). Perforator recurrence was more common in limbs with ulcerations. Except for the rare occurrence of skin necrosis, cosmetic results were excellent, often with partial reversal of preexisting skin changes and relief of symptoms. Although complications of sclerotherapy are rare, some clinical scenarios should be mentioned. Multiple needle punctures can lead to vasospasm or a hematoma (or both), which may make the procedure technically challenging or technically unsuccessful. Pain during sclerotherapy injection may be due to intraarterial puncture, in which case the injection should be stopped immediately. Should such pain occur, injection of procaine around the injected artery, local cooling, systemic heparinization, and infusion with low-molecular-weight dextran is recommended. Extravasation in subcutaneous tissues is usually painless unless the sclerosant solution had been mixed with normal saline, which may result in skin necrosis. Post-sclerotherapy calf DVT can be successfully treated by full-dose ASA.<sup>78</sup> Another possible serious complication, although rare, is anaphylactic shock. When any sclerotherapy injection is performed, all the necessary equipment to manage this event must be readily available (oxygen, epinephrine, and steroids) because it could be a life-threatening situation.<sup>79,80</sup>

No comparative studies of different PAPS modalities are currently available, but published data suggest that predictors of success differ. A large size of the perforator is more likely to be a risk for failure of sclerotherapy, and a pulsatile flow pattern may cause failure of laser ablation.<sup>65</sup>

## Postoperative Management

Immediately after treatment, deep veins should be imaged to rule out DVT, and a compression dressing should be worn continuously for 24 hours, followed by during the day only for the next 3–5 days. The first follow-up visit should be scheduled within 1 week after the procedure. Duplex scans should be repeated at this time to ensure the absence of DVT and to assess the early anatomic outcome of treatment. The follow-up schedule should be based on other treatment modalities used at the time of treatment of the IPV, but long-term clinical and duplex follow-up is desirable.

## CHAPTER ALGORITHM



## SELECTED KEY REFERENCES

Elias S, Peden E. Ultrasound-guided percutaneous ablation for the treatment of perforating vein incompetence. *Vascular*. 2007;15:281–289.

*Most recent literature review of PAPS.*

Gloviczki P, Bergan J, eds. *Atlas of Endoscopic Perforator Vein Surgery*. London: Springer-Verlag; 1998.

*Most comprehensive text on perforating vein surgery.*

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;29:78–82.

*Retrospective analysis of the data related to the role of IPV in ulcer healing and recurrence from the ESCHAR randomized controlled trial.*

Labropoulos N, Tassiopoulos AK, Bhatti AF, Leon L. Development of reflux in the perforator veins in limbs with primary venous disease. *J Vasc Surg*. 2006;43:558–562.

*First duplex ultrasound study of the natural history of CVD focused on PV.*

Sarin S, Shields DA, Farrah J, Scull JH, Coleridge-Smith PD. Does venous function deteriorate in patients waiting for varicose vein surgery? *J R Soc Med*. 1993;86:21–23.

*First study of the natural history of primary CVD with clinical and duplex ultrasound examinations.*

van Gent WB, Hop WC, van Praag MC, et al. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg*. 2006;44:563–571.

*The largest randomized controlled study to date with post hoc analysis of data related to IPV.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

- Caggiati A, Mendoza E. The discovery of perforating veins. *Ann Vasc Surg.* 2004;18:502–503.
- Gay J. *On Varicose Disease of the Lower Extremities and Its Allied Disorders, Skin Discoloration, Induration, and Ulcer.* John Churchill; 1868.
- Homans J. The etiology and treatment of varicose ulcer of the leg. *Surg Gynecol Obstet.* 1917;300:311.
- Eastcott HHG. The pathology and surgery of the veins of the lower limb. Harold Dodd and Frank B. Cockett. 2nd ed. 250 × 190 mm. Pp. 323. Illustrated. 1976. Edinburgh: Churchill Livingstone. £15.50. *Br J Surg.* 1977;64:380.
- Cockett F. The role of the ankle perforating veins in the post-thrombotic syndrome and in primary hereditary varicose veins. In: May R, ed. *Perforating Veins.* Munchen: Urban & Schwarzenberg; 1981:106–108.
- Dodd H. The diagnosis and ligation of incompetent ankle perforating veins. *Ann R Coll Surg Engl.* 1964;34:186–196.
- Linton RR. A new surgical technic for the treatment of postphlebitic varicose ulcers of the lower leg. *N Engl J Med.* 1938;219:367–373.
- Hauer G. Endoscopic subfascial discussion of perforating veins—preliminary report. *Vasa.* 1985;14:59–61.
- Gloviczk P, Cambria RA, Rhee RY, et al. Surgical technique and preliminary results of endoscopic subfascial division of perforating veins. *J Vasc Surg.* 1996;23:517–523.
- Conrad P. Endoscopic exploration of the subfascial space of the lower leg with perforator vein interruption using laparoscopic equipment: a preliminary report. *Phlebology.* 1994;9:154–157.
- Dillavou ED, Harlander-Locke M, Labropoulos N, et al. Current state of the treatment of perforating veins. *J Vasc Surg Venous Lymphat Disord.* 2016;4:131–135.
- Thomson H. The surgical anatomy of the superficial and perforating veins of the lower limb. *Ann R Coll Surg Engl.* 1979;61:198–205.
- Pirner F. On the valves of the perforating veins. In: May R, ed. *Perforating Veins.* Munchen: Urban & Schwarzenberg; 1981:46–48.
- Cotton LT. Varicose veins. Gross anatomy and development. *Br J Surg.* 1961;48:589–598.
- Labropoulos N, Delis KT, Nicolaides AN. Venous reflux in symptom-free vascular surgeons. *J Vasc Surg.* 1995;22:150–154.
- Cooper DG, Hillman-Cooper CS, Barker SG, et al. Primary varicose veins: the sapheno-femoral junction, distribution of varicosities and patterns of incompetence. *Eur J Vasc Endovasc Surg.* 2003;25:53–59.
- Sakurai T, Matsushita M, Nishikimi N, et al. Hemodynamic assessment of femoropopliteal venous reflux in patients with primary varicose veins. *J Vasc Surg.* 1997;26:260–264.
- Guex JJ. Ultrasound guided sclerotherapy (USGS) for perforating veins (PV). *Hawaii Med J.* 2000;59:261–262.
- Masuda EM, Kessler DM, Lurie F, et al. The effect of ultrasound-guided sclerotherapy of incompetent perforator veins on venous clinical severity and disability scores. *J Vasc Surg.* 2006;43:551–556.
- Almgren B, Eriksson I. Valvular incompetence in superficial, deep and perforator veins of limbs with varicose veins. *Acta Chir Scand.* 1990;156:69–74.
- Labropoulos N, Tassiopoulos AK, Bhatti AF, et al. Development of reflux in the perforator veins in limbs with primary venous disease. *J Vasc Surg.* 2006;43:558–562.
- Sarin S, Shields DA, Farrah J, et al. Does venous function deteriorate in patients waiting for varicose vein surgery? *J R Soc Med.* 1993;86:21–23.
- 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;29:78–82.
- Stuart WP, Lee AJ, Allan PL, et al. Most incompetent calf perforating veins are found in association with superficial venous reflux. *J Vasc Surg.* 2001;34:774–778.
- Mendes RR, Marston WA, Farber MA, et al. Treatment of superficial and perforator venous incompetence without deep venous insufficiency: is routine perforator ligation necessary? *J Vasc Surg.* 2003;38:891–895.
- Gohel MS, Barwell JR, Earnshaw JJ, et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study)—haemodynamic and anatomical changes. *Br J Surg.* 2005;92:291–297.
- Puggioni A, Lurie F, Kistner RL, et al. How often is deep venous reflux eliminated after saphenous vein ablation? *J Vasc Surg.* 2003;38:517–521.
- Stuart WP, Adam DJ, Allan PL, et al. Saphenous surgery does not correct perforator incompetence in the presence of deep venous reflux. *J Vasc Surg.* 1998;28:834–838.
- Bjordal RI. Circulation patterns in incompetent perforating veins in the calf and in the saphenous system in primary varicose veins. *Acta Chir Scand.* 1972;138:251–261.
- Neglen P, Raju S. Ambulatory venous pressure revisited. *J Vasc Surg.* 2000;31:1206–1213.
- Jiang P, van Rij AM, Christie R, et al. Recurrent varicose veins: patterns of reflux and clinical severity. *Cardiovasc Surg.* 1999;7:332–339.
- Labropoulos N, Touloukakis E, Giannoukas AD, et al. Recurrent varicose veins: investigation of the pattern and extent of reflux with color flow duplex scanning. *Surgery.* 1996;119:406–409.
- May R. The clinical importance of incompetent perforating veins in primary varicosis. In: May R, ed. *Perforating Veins.* Munchen: Urban & Schwarzenberg; 2016:118–122.
- Rutherford EE, Kianifard B, Cook SJ, et al. Incompetent perforating veins are associated with recurrent varicose veins. *Eur J Vasc Endovasc Surg.* 2001;21:458–460.
- Allegro C, Antignani PL, Carlizza A. Recurrent varicose veins following surgical treatment: our experience with five years follow-up. *Eur J Vasc Endovasc Surg.* 2007;33:751–756.
- Iafrati MD, Pare GJ, O'Donnell TF, et al. Is the nihilistic approach to surgical reduction of superficial and perforator vein incompetence for venous ulcer justified? *J Vasc Surg.* 2002;36:1167–1174.
- Gloviczk 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.
- van Gent WB, Hop WC, van Praag MC, et al. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg.* 2006;44:563–571.
- Bacon JL, Dinneen AJ, Marsh P, et al. Five-year results of incompetent perforator vein closure using TRAns-Luminal Occlusion of Perforator. *Phlebology.* 2009;24:74–78.
- Harlander-Locke M, Lawrence P, Jimenez JC, et al. Combined treatment with compression therapy and ablation of incompetent superficial and perforating veins reduces ulcer recurrence in patients with CEAP 5 venous disease. *J Vasc Surg.* 2012;55:446–450.
- 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;48:1044–1052.
- Schafer K. The course, structure and passage through the fascia of the perforating veins. In: *Perforating Veins.* Mnnchen. Baltimore: Urban & Schwarzenberg; 1981:37–45.
- Lurie F, Kessler D, Puggioni A. Blood flow in perforating arteries can change after ablation of incompetent perforating veins—preliminary ultrasound observations. *Praktika Flebologie.* 2005;14:55–56.
- Caggiati A, Bergan JJ, Gloviczk P, et al. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg.* 2002;36:416–422.
- Schobinger R, Weinstein CE. Varix involving the tibia. *J Bone Joint Surg Am.* 1962;44-A:371–376.
- Ramelet AA, Crebassa V, D Alotto C, et al. Anomalous intraosseous venous drainage: Bone perforators? *Phlebology.* 2017;32(4):241–248.
- O'Donnell Jr TF, Burnand KG, Clemenson G, et al. Doppler examination vs clinical and phlebographic detection of the location of incompetent perforating veins: a prospective study. *Arch Surg.* 1977;112:31–35.

48. Masuda EM, Kistner RL, Eklof B. Prospective study of duplex scanning for venous reflux: comparison of Valsalva and pneumatic cuff techniques in the reverse Trendelenburg and standing positions. *J Vasc Surg.* 1994;20:711–720.
49. Sandri JL, Barros FS, Pontes S, et al. Diameter-reflux relationship in perforating veins of patients with varicose veins. *J Vasc Surg.* 1999;30:867–874.
50. Głowiczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53:2S–48S.
51. O'Donnell Jr TF, Passman MA. Clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)—Management of venous leg ulcers. Introduction. *J Vasc Surg.* 2014;60:1S–2S.
52. Lawrence PF, Hager ES, Harlander-Locke MP, et al. Treatment of superficial and perforator reflux and deep venous stenosis improves healing of chronic venous leg ulcers. *J Vasc Surg Venous Lymphat Disord.* 2020;8(4):601–609.
53. Blomgren L, Johansson G, Dahlberg-Akerman A, et al. Changes in superficial and perforating vein reflux after varicose vein surgery. *J Vasc Surg.* 2005;42:315–320.
54. 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;363:1854–1859.
55. Kianifard B, Holdstock J, Allen C, et al. Randomized clinical trial of the effect of adding subfascial endoscopic perforator surgery to standard great saphenous vein stripping. *Br J Surg.* 2007;94:1075–1080.
56. van Rij AM, Hill G, Gray C, Christie R, et al. A prospective study of the fate of venous leg perforators after varicose vein surgery. *J Vasc Surg.* 2005;42:1156–1162.
57. Głowiczki P, Bergan JJ, Menawat SS, et al. Safety, feasibility, and early efficacy of subfascial endoscopic perforator surgery: a preliminary report from the North American registry. *J Vasc Surg.* 1997;25:94–105.
58. Luebke T, Brunkwall J. Meta-analysis of subfascial endoscopic perforator vein surgery (SEPS) for chronic venous insufficiency. *Phlebology.* 2009;24:8–16.
59. Tenbrook Jr JA, Iafrati MD, O'Donnell Jr TF, et al. Systematic review of outcomes after surgical management of venous disease incorporating subfascial endoscopic perforator surgery. *J Vasc Surg.* 2004;39:583–589.
60. van Gent WB, Catarinella FS, Lam YL, et al. Conservative versus surgical treatment of venous leg ulcers: 10-year follow up of a randomized, multicenter trial. *Phlebology.* 2015;30(1 Suppl):35–41.
61. Lin ZC, Loveland PM, Johnston RV, et al. Subfascial endoscopic perforator surgery (SEPS) for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2019;3(3):CD012164.
62. van Gent W, Wittens C. Influence of perforating vein surgery in patients with venous ulceration. *Phlebology.* 2015;30(2):127–132.
63. 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.
64. Elias S, Peden E. Ultrasound-guided percutaneous ablation for the treatment of perforating vein incompetence. *Vascular.* 2007;15:281–289.
65. Proebstle TM, Herdemann S. Early results and feasibility of incompetent perforator vein ablation by endovenous laser treatment. *Dermatol Surg.* 2007;33:162–168.
66. Hager E, Washington C, Steinmetz A. Factors that influence perforator vein closure rates using radiofrequency ablation, laser ablation, or foam sclerotherapy. *J Vasc Surg Venous Lymphat Disord.* 2016;4(1):51–56.
67. Elias S, Raines JK. Mechanocellular tumescence endovenous ablation: final results of the initial clinical trial. *Phlebology.* 2012;27:67–72.
68. Bishawi M, Bernstein R, Boter M, et al. Mechanocellular ablation in patients with chronic venous disease: a prospective multicenter report. *Phlebology.* 2014;29:397–400.
69. Tadros RO, Faries PL, Reynolds K, et al. A novel technique for closure of the perforator vein using the ClariVein Occlusion Catheter. *Ital J Vasc Endovasc Surg.* 2016;23(1):68–75.
70. Proebstle TM, Alm J, Dimitri S, et al. Twelve-month follow-up of the European Multicenter Study on Cyanoacrylate Embolization of Incompetent Great Saphenous Veins. *J Vasc Surg Venous Lymphat Disord.* 2014;2:105–106.
71. Yang GK, Mordhorst A, Gagnon J. Ultrasound-guided cyanoacrylate injection for the treatment of incompetent perforator veins. *J Vasc Surg.* 2018;68(3):e78.
72. Toonder IM, Lam YL, Lawson J, et al. Cyanoacrylate adhesive perforator embolization (CAPE) of incompetent perforating veins of the leg, a feasibility study. *Phlebology.* 2014;29(1 suppl):49–54.
73. Prasad Bp K, Joy B, Toms A, Sleeba T. Treatment of incompetent perforators in recurrent venous insufficiency with adhesive embolization and sclerotherapy. *Phlebology.* 2018;33(4):242–250.
74. Lawrence PF, Alktaifi A, Rigberg D, et al. Endovenous ablation of incompetent perforating veins is effective treatment for recalcitrant venous ulcers. *J Vasc Surg.* 2011;54:737–742.
75. Hingorani AP, Ascher E, Marks N, et al. Predictive factors of success following radio-frequency stylet (RFS) ablation of incompetent perforating veins (IPV). *J Vasc Surg.* 2009;50:844–848.
76. Corcos L, Pontello D, DE Anna D, et al. Endovenous 808-nm diode laser occlusion of perforating veins and varicose collaterals: a prospective study of 482 limbs. *Dermatol Surg.* 2011;37:1486–1498.
77. Black CM, Hatch D, Brown D. An endovenous approach to symptomatic perforator ablation. *J Vasc Interv Radiol.* 2007;18:S23.
78. Kiguchi M, Hager E, Winger D, Hirsch S. Factors that influence perforator thrombosis and predict healing with perforator sclerotherapy for venous ulceration without axial reflux. *J Vasc Surg.* 2014;59(5):1368–1376.
79. Brzoza Z, Kasperska-Zajac A, Rogala E, Rogala B. Anaphylactoid reaction after the use of sodium tetradecyl sulfate: a case report. *Angiology.* 2007;58:644–646.
80. Yiannakopoulou E. Safety concerns for sclerotherapy of telangiectases, reticular and varicose veins. *Pharmacology.* 2016;98:62–69.

# Chronic Venous Insufficiency: Deep Vein Valve Reconstruction

MICHAEL C. DALSING, OSCAR MALETI, and  
GREGORY G. WESTIN

INTRODUCTION	2098
PATHOGENESIS	2099
Relevant Anatomy	2099
Etiology/Pathology	2099
Hemodynamics/Pathophysiology	2100
DIAGNOSTIC EVALUATION	2100
History and Physical Examination	2100
Noninvasive Evaluation	2101
Invasive Evaluation	2101
Overall Diagnostic Classification	2101
TREATMENT SELECTION	2102
Natural History/Patient Risk Assessment	2102
Surgical Options/Operative Planning	2103
SURGICAL TREATMENT	2103
Perioperative Management	2103
Techniques	2103
Overall Exposure	2103
Internal Valvuloplasty	2104
External Valvuloplasty	2104
External Banding	2105
Valve Transposition	2105
Valve Transplantation	2106
Substitute Venous Valves	2106
Postoperative Management	2107
Results	2108
Complications and Initial Results	2108
Late Results	2108
INTERNAL VALVULOPLASTY	2108
EXTERNAL VALVULOPLASTY	2109
EXTERNAL BANDING	2109
VALVE TRANSPOSITION	2109
VALVE TRANSPLANTATION	2110
SUBSTITUTE VENOUS VALVE	2110
MULTILEVEL VALVE RECONSTRUCTION	2110
REOPERATIVE SURGERY	2111
Follow-up	2111
Long-term Surveillance	2111
SUMMARY	2111

## INTRODUCTION

Using modern classification methods for lower extremity venous disease and considering the entire disease spectrum within given populations, roughly 15% of patients will have edema, 7% skin hyperpigmentation, 1.4% healed and 0.7% active venous ulcers.<sup>1,2</sup> Due to the technical challenges and increased risks of a venous valve repair in relation to less invasive treatments, essentially all other venous pathology is treated before deep venous reflux is addressed. Even then deep venous reflux is only treated at select centers and in those patients with truly disabling symptoms. Venous ulceration is the most distressing,

disabling and costly for the patient and society; therefore, patients with venous ulcers are the most likely to be evaluated for venous valve repair.<sup>3,4</sup> The patient population that might benefit most from valve repair are those patients who have ulcer recurrence despite conservative therapy, which in compliant patients is ~40% and in poorly compliant nearly 100%.<sup>5,6</sup> Following failure of conservative therapy, superficial and perforator insufficiency is generally eliminated by percutaneous ablation with ulcer recurrence in 30%–50% of cases.<sup>7</sup> Correcting iliac venous obstruction without addressing deep venous insufficiency can result in long-term ulcer healing in 60%–80% of cases.<sup>8,9</sup> If the estimate of venous ulcer prevalence per year in

the US population of 500,000 is correct<sup>3</sup> and we assume the best outcome for each prior intervention (60% conservative treatment, 70% superficial ablation and 60% stenting success) that would still leave 24,000 patients per year who may benefit from deep vein valve repair to heal their ulcer. An even more conservative calculation arrived at nearly 5000 candidates in need of venous valve repair to aid ulcer healing. This would require at least 20 surgeons adept at deep vein valve reconstruction performing 250 operations yearly to meet the demand.<sup>10</sup> In addition, if other symptoms are causing major disability, valve reconstruction might be a reasonable consideration.

## PATHOGENESIS

### Relevant Anatomy

The common femoral, profunda femoris, and femoral veins are covered by skin, soft tissue, and fascia in the groin and by the sartorius muscle more distally. Just proximal to the knee, the femoral vein occupies the adductor (Hunter's) canal, which places it deep to the sartorius and flanked by the vastus medialis and adductor longus muscles. Distal to the adductor canal, the femoral vein becomes the popliteal vein and lies between the heads of the gastrocnemius muscle distally, but is covered only by skin, soft tissue, and fascia directly behind the knee. The anterior tibial veins lie in the anterior calf compartment, deep to the anterior tibialis muscle. The posterior tibial and peroneal veins lie in the deep posterior compartment and are covered by the soleus and gastrocnemius muscles, which form the superficial posterior compartment. Illustrations that can aid in visualizing the anatomy are available in the literature and should be referenced.<sup>10,11</sup> Each deep vein involved with a venous disorder is named in a complete CEAP classification, as reviewed in the most recent update to that system.<sup>12</sup>

Venous valves are thin but very strong connective tissue structures with minimal muscular media covered by endothelium and generally bicuspid in design. Valves are universally present in the paired tibial and peroneal veins, with 3 to 12 valves evenly distributed in each vein.<sup>13</sup> The majority of popliteal veins (>90%) have one to three valves, with a slight trend to be located more caudal in the leg.<sup>13</sup> The femoral veins have one to five valves.<sup>13,14</sup> In about 90% of patients, the most constant valve location is in the proximal femoral vein 1 to 2 cm distal to its confluence with the profunda femoris vein.<sup>13–15</sup> In 88% of patients, the profunda femoris vein has one to four valves.<sup>13</sup> The common femoral vein, often thought to have no valves, actually has one or even two valves within a few centimeters of the inguinal ligament in 30%–50% of patients.<sup>13–15</sup> Rarely does the external iliac vein have a valve (~25%), and the common iliac vein lacks a valve in most cases.<sup>16</sup>

### Etiology/Pathology

The proper nomenclature for the etiology of deep venous insufficiency is found in the CEAP (Clinical/Etiologic/Anatomic/Pathologic) classification, which was recently updated by an American Venous Forum task force.<sup>12,17</sup> The most important

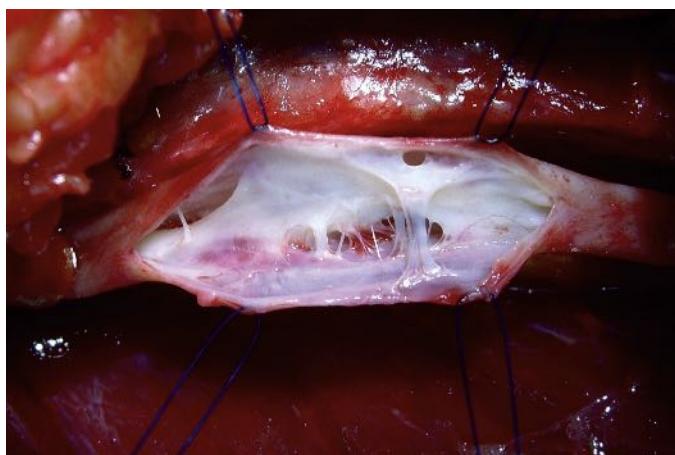


**Figure 159.1** Floppy and asymmetrical venous valve leaflets seen after vein opened in the method of Kistner to reveal the valve cusps.

factor for venous valve repair is the state of the valve leaflets; namely, whether they are architecturally preserved allowing primary repair by reefing techniques or whether they are absent or so damaged that they are beyond repair. Congenital absence of lower extremity venous valves, venous aplasia, or dysplasia as a cause of axial venous reflux is rare<sup>18</sup> but can be seen in cases such as Klippel–Trenaunay syndrome or arterial venous malformations.

Much more common than congenital venous insufficiency is primary venous insufficiency. This can occur in patients with retained valve architecture but floppy, redundant, elongated valve cusps (Fig. 159.1) and/or from defects in the vein wall that cause the valve ring to dilate. Either cause results in mal-approximation of valve cusps and reflux in the involved veins. Primary venous insufficiency is a degenerative condition which progresses over time and generally involves the deep veins late in the process.<sup>19</sup> One explanation for deep venous insufficiency occurring after superficial insufficiency is called the “overload” theory: superficial venous incompetence results in recirculation of blood, increasing the volume of blood in the deep venous system and distending them until their valves no longer function properly. This explains why deep venous reflux may resolve after superficial vein ablation.<sup>20,21</sup> In some patients thought to have primary venous insufficiency, asymmetrical insertion or development of cusps may be only identifiable at the time of operation and thus represent an occult congenital defect.<sup>21</sup>

Secondary venous insufficiency is defined as having an apparent pathology that caused valve damage. The pathology is often acute deep venous thrombosis (DVT), and may be the cause of 40% to 70% of the deep venous valvular incompetence.<sup>22–25</sup> The resulting inflammation and scarring with re-canulation can cause foreshortening and fibrosis of the valve



**Figure 159.2** Valve destruction resulting from deep vein thrombosis with scarring within the vein, bridges of scar wall to wall (synechia), but overall patent vein due to recanalization.

leaflets, small perforations, or valve adhesion and luminal narrowing (Fig. 159.2).<sup>22</sup> The valves are so damaged that direct repair is not possible. Other potential intravenous and extravenuous etiologies such as traumatic arteriovenous fistula or primary intravenous sarcoma may also cause secondary venous insufficiency.<sup>12</sup> Options to repair axial reflux in these cases must involve construction of a competent valve: one can recruit a competent valve from another local system, transplant one from a distant site, or make a substitute valve.

The line between primary and secondary presentations can be blurred in some patients. In these cases both pathologies can be observed, either in diagnostic studies or during open surgical inspection.<sup>22,26</sup> Several theories have been proposed to explain a relatively normal valve within otherwise damaged vein.<sup>22,27–29</sup> Secondary etiologies other than DVT that can result in venous insufficiency with retained valve architecture include traumatic arteriovenous fistula or systemic issues such as prolonged congestive heart failure.<sup>12</sup> Regardless of the reason for the observed changes, the critical issue is whether valve leaflets remain sufficiently intact to allow for direct repair that will render the valve competent.

## Hemodynamics/Pathophysiology

The primary hemodynamic consequence of venous valve incompetence is reflux across the valve, particularly when standing. In general, the lower leg muscles push the blood toward the heart with each step, counteracting gravity to recirculate the blood. With enough incompetent valves present, this system of blood return becomes ineffective, resulting in sustained venous hypertension. This is most prominent at the microcirculatory level and is reflected in the signs/symptoms recognized as chronic venous insufficiency. In one series evaluating only venous ulcers, 73% had deep venous reflux with or without reflux in the superficial/perforator veins; the femoral/popliteal vein was the most commonly affected, and primary disease predominated.<sup>25</sup> To realize the goal of controlling lower limb ambulatory venous hypertension,

correction of deep axial reflux proximal to the calf is required. Because two deep venous pathways exist for blood in the thigh, an isolated femoral vein or profunda femoris vein valve reconstruction could result in clinical failure when prominent reflux remains in the other pathway. If one of the two is competent, providing a functional valve in the other can result in overall clinical success.<sup>30,31</sup> In some cases of complete femoral vein occlusion, there is tremendous dilation of the profunda femoris vein, such that only correction of reflux in it will lead to an improvement in venous hemodynamics.<sup>32</sup> An alternative method of correcting significant axial reflux when both femoral systems are incompetent is to position a competent valve in the popliteal vein (sometimes called the gatekeeper position), to allow more normal venous pressures in the calf vein during exercise.<sup>33–35</sup> At least one investigator has performed multiple tibial vein valve repairs to accomplish the same goal.<sup>36</sup>

## DIAGNOSTIC EVALUATION

### History and Physical Examination

Patients with chronic venous disease due to deep venous incompetence can present with any of the CEAP clinical classifications, from C0 to C6, with or without associated symptoms.<sup>12</sup> Physical examination and evaluation of venous reflux, including using a simple handheld Doppler unit, is considered the first step in a complete venous patient evaluation (level of investigation I in the CEAP system).<sup>12,17</sup> In those patients with an ulcer, an arterial pulse examination and measurement of ankle–brachial index are critical to rule out the presence of arterial occlusive disease (grade 1, level of evidence B).<sup>3</sup> A careful history should take note of previous episodes of DVT, known hypercoagulable conditions, and any limitations in physical and occupational activity resulting from venous insufficiency. As importantly, the physical examination can eliminate other causes of the patient's symptoms, such as ischemic ulcers, diabetic ulcers, dermatologic disorders, and even skin or soft tissue cancer; a more complete list is provided in SVS/AVF guidelines.<sup>3</sup>

Each patient should ultimately be stratified according to the CEAP classification to clearly define the venous disease present, which will allow the formation of a focused and appropriate management strategy.<sup>3</sup> Candidates for deep venous valvular reconstruction typically have class C4b to C6 disease, or disabling signs and symptoms such as severe edema (C3). The Venous Clinical Severity Score provides a quantification of disease severity and is a useful evaluation tool to determine a patient's response to treatment.<sup>37</sup> Quality-of-life instruments provide an estimation of the impact of venous disease on the patient's life and the effect that therapy has on the patient's overall well-being.<sup>38</sup> Performance of these evaluations is considered a best practice; Societal guidelines give quality-of-life measures a grade 1 recommendation for all classes of venous disease and is considered critical to determining treatment success.<sup>3,39</sup>

## Noninvasive Evaluation

A complete venous duplex evaluation (see Ch. 25, Vascular Laboratory: Venous Duplex Scanning) comprises the next major step in the evaluation of the patient with suspected deep venous disease (level of investigation II in the CEAP).<sup>12,17,19</sup> Duplex evaluation is essential prior to any interventional procedure (grade 1/level of evidence A/B).<sup>3,39</sup> It clarifies the extent and anatomic location of all venous disease, provides an indication of the etiology (congenital, primary, or secondary), and aids in determining the pathophysiologic mechanism (reflux, obstruction, or both) of the disease present. The imaging is often so clear in primary deep venous incompetence that venous valve cusps can be seen moving in the venous stream. Insufficiency within any segment of the deep venous system is defined as a prolonged reflux time through the valve after a provocative test. The recommended cutoff value for abnormal reversed flow (reflux) is 1 second in the femoropopliteal veins and 500 milliseconds for the deep femoral and tibial veins.<sup>3,39</sup> Venous obstruction is seen as thickened, scarred, and constricted veins or valves with absent or poor flow and absent or diminished augmentation after distal or proximal compression. Respiratory variation can be lost because of local disease or proximal obstruction.

Plethysmography (see Ch. 24, Vascular Laboratory: Venous Physiologic Assessment) can provide a method to quantify the impact of deep venous insufficiency prior to and after deep venous valvular reconstruction with some insight into treatment success. Plethysmography is used for specific indications in patients with advanced disease or as a research tool (grade 2, level of evidence B) and can be part of an investigation level II evaluation.<sup>3,12,17,39</sup> Air plethysmography provides a quantitative estimate of venous insufficiency in the form of venous filling index (abnormal >2 mL/s), while the residual volume fraction (abnormal >35%) has a linear correlation with ambulatory venous pressure measurements. The ejection fraction correlates with the efficiency of the calf muscle pump; a value of less than 60% is considered abnormal. The ability of the calf muscle to function well is a critical factor in the ultimate outcome of deep venous reconstruction.<sup>40</sup> Some early work suggests that it might be useful in evaluating the influence of iliac vein occlusive disease.<sup>41</sup>

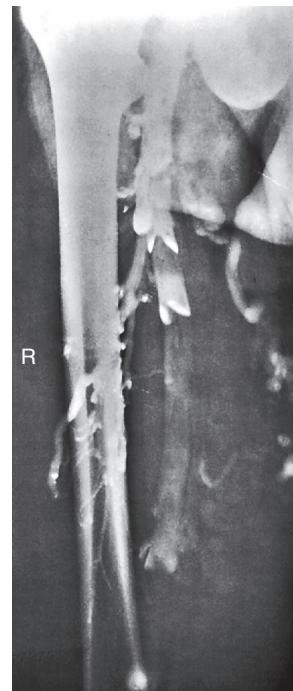
## Invasive Evaluation

For patients being readied for deep vein valve surgery, venography aids in precise operative planning if no other less invasive modality can provide the same detail. Ascending venography (see Ch. 28, Venography) defines deep vein anatomy and eliminates or confirms obvious obstruction, thereby providing a means of selecting the most disease-free area for surgery; for example, when valve transplantation is contemplated.<sup>22,42</sup> Ambulatory venous pressure with or without thigh tourniquet and venous reflux time can be measured, if desired, but is rarely used in current practice.<sup>22,42,43</sup> The importance of significant iliac vein occlusive disease is determined best by the use of intravenous ultrasonography.<sup>44</sup>

Descending venography (see Ch. 28, Venography) is used to determine valve leaflet integrity, anatomic location, and the extent/degree of reflux within the femoral, profunda femoris, popliteal, and tibial veins (Fig. 159.3).<sup>45</sup> It has challenges in accurately determining the presence of valvular incompetence in all cases and as such direct operative inspection remains the “gold standard”.<sup>22</sup> However, the combination of venous duplex examination and descending venography provides the best available preoperative determination of valve architecture to date. Magnetic resonance imaging and computed tomography are generally used to evaluate occlusive venous disease rather than to provide evidence in the evaluation for valve repair. Each may be useful in detecting extrinsic compression, especially at the iliocaval level. These types of studies constitute those included in investigation level III of the CEAP classification and are generally reserved for those with more advanced/complicated venous disorders.<sup>17</sup>

## Overall Diagnostic Classification

Evaluation of the patient with suspected venous disease should follow a standard protocol in clinical practice (CEAP). The patient's examination (including handheld lower extremity venous Doppler investigation) and history confirms the presence of disease, the clinical classification (C of CEAP), and the potential etiology (E of CEAP). The addition of venous duplex imaging (with or without plethysmography) confirms the clinical impression; identifies the location of disease and the types of veins involved (superficial, perforator and/or deep, the A of CEAP); and indicates whether the underlying pathophysiology is due to reflux, obstruction, or both (P of



**Figure 159.3** Descending venogram demonstrating the presence of valves with architecturally preserved cusps available for *in situ* repair.

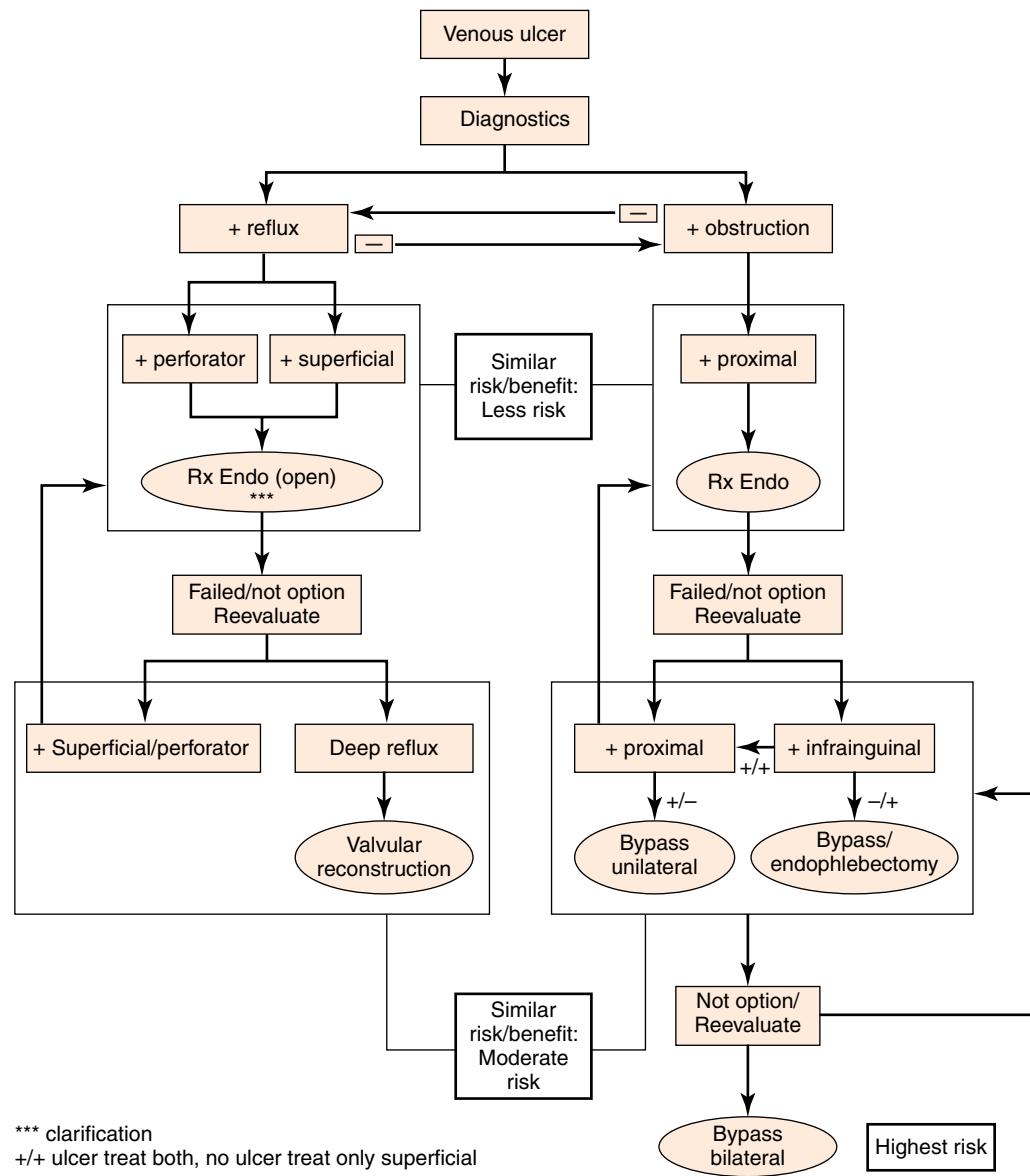
CEAP). The investigation often stops at this point if superficial/perforator disease is the predominant pathology, and this disease is treated. If the patient has recurrent problems, a more in-depth investigation for proximal (iliofemoral) venous occlusive disease is undertaken with invasive imaging (venography with intravascular ultrasonography). Investigation has advanced to diagnostic level of investigation III with these studies. If occlusive disease is present and the symptoms are sufficiently severe, angioplasty and stenting of the affected outflow vein(s) is undertaken. If unsuccessful in relieving disabling patient symptoms and deep vein axial reflux is the major pathologic condition demonstrated by duplex imaging and descending venography, valvular reconstruction is advisable. As an example and in terms of a basic CEAP classification, the patient requiring an internal valvuloplasty to treat a symptomatic venous ulcer would be a C<sub>6</sub>-S:E<sub>p</sub>;A<sub>d</sub>;P<sub>r</sub> (Level 3; 4/1/2020) with a descending venogram performed on 4/1/2020.<sup>19</sup>

## TREATMENT SELECTION

### Natural History/Patient Risk Assessment

Patients being considered for deep venous valvular repair have generally failed all other interventional therapy to resolve their symptoms. Societal guidelines suggest that in select patients with clinical class C4b, C5, and C6 disease; valve repair (internal valvuloplasty, external valvuloplasty, external banding), valve transposition or transplantation, and/or autogenous valve substitutes can aid in venous leg ulcer healing and prevent recurrence when added to standard compression therapy (grade 2, level of evidence C).<sup>3</sup> An algorithm for the surgical care of patients with venous ulcers, which can be extrapolated to all those who might benefit from deep venous valve repair, is found in a pertinent societal guideline (Fig. 159.4).<sup>3</sup>

Patient risk assessment must follow the tenets of any open operative intervention. Hemodynamic instability from the



**Figure 159.4** Proposed algorithm for operative and endovascular treatment of patients with venous leg ulcer based on involved anatomic venous system and presence of venous reflux or obstruction. The risk-to-benefit ratio is weighed for those procedures with more risk (lower, moderate, higher) considered later in the treatment when the benefit is similar.

operation is minimal, but because the operative intervention is time-consuming and technically challenging, general anesthesia is typically required. An acceptable cardiac and pulmonary status is required. Systemic infection should be treated before intervention. Other potential causes of venous hypertension such as obesity, heart failure, or external compression from tumors, for example, require treatment regardless of the underlying venous effects. The presence of systemic diseases that may impact healing, such as collagen vascular disease, diabetes, chronic renal insufficiency, or lower extremity arterial occlusive disease, is a relative contraindication to venous intervention unless these conditions are corrected or medically optimized first.

## Surgical Options/Operative Planning

The treatment options to correct deep venous valvular insufficiency are determined by the availability of structurally intact venous valves, as documented by imaging or, in some cases, by direct surgical exploration. Selection of the operative technique when the valve cusps are preserved is determined by the degree of cusp prolapse and the surgeon's preference/skills. In the case of valve prolapse secondary to limited vein wall dilation and often seen to normalize during vasospasm, decreasing the vein diameter may re-establish a competent valve. In such cases, external banding of the vein at the valve site may provide a workable solution to prevent reflux. With more extensive wall dilation and cusp prolapse, external valvuloplasty may more dependably decrease the wall diameter and allow some reefing of the valve cusps. Extensive valve leaflet prolapse and wall dilation is best treated with internal valvuloplasty that allows direct cusp leaflet shortening in addition to wall diameter reduction. Experience determines which method to use in each patient and, when in doubt, internal valvuloplasty provides the ultimate repair.

When there is no identifiable valve structure within an incompetent system, options are still available. If a parallel axial venous system has a competent valve, then a transposition procedure is possible. When this is not feasible, valve transplantation of a competent valve from a distant location remains an option. Alternatively, a valve can be made from autogenous pieces of vein sewn into the correct configuration. The delicate and technically demanding procedure of shaving the vein wall to fashion a valve is gaining support in the literature. Although most attempts at constructing a valve using synthetic components have failed, there remain a few options.

Multiple valve repairs in the same incompetent axial system (e.g., two or more in the femoral vein) may decrease the rate of recurrent reflux and thus symptoms. However, many surgeons have reported success when only one valve per incompetent system is repaired.

In the situation of architecturally intact incompetent valve(s) confirmed by preoperative imaging, most experienced surgeons choose the proximal femoral or profunda femoris vein for valvuloplasty when isolated disease exists or, when both systems are incompetent, repair both the proximal femoral and profunda femoris valves. This decision is based on the ease of exposure,

proximity of the valves, familiarity with the approach, and size of the veins available for repair. When both the femoral and profunda femoris systems are incompetent, some have chosen to repair the popliteal vein valve, which is considered the "gatekeeper" to the lower leg venous system.<sup>33,46</sup> However, mid- or distal femoral vein valves can be repaired if they are surgically accessible and architecturally intact, and repair will accomplish the task of preventing distal reflux. As one proceeds more peripherally in the venous system, vein diameters and valve leaflets become smaller and thus more difficult to repair. Nevertheless, even tibial vein valves have been successfully repaired.<sup>47</sup>

If a transposition operation is planned, appropriate imaging must have identified the presence of a competent valve (or one that can be repaired) in at least one axial venous system (femoral/profunda/great saphenous) to allow transposition of the incompetent system below the valve. Valve transplantation requires having identified an architecturally preserved competent valve in the axillary or brachial vein. The optimal place for implantation into the lower extremity is into the least damaged vein segment available, which will prevent axial reflux into the calf area. If transposition or transplantation is not an option, an autogenous alternative should be considered.

Selecting the optimal operative technique and location is based on the knowledge provided by preoperative imaging, expected long-term success, operative difficulty and risk/benefit ratio.<sup>3</sup>

## SURGICAL TREATMENT

### Perioperative Management

Prophylactic antibiotics are given prior to surgical incision and on a scheduled basis during the procedure (e.g., first-generation cephalosporin).<sup>48–50</sup> Intraoperative heparin is commonly given when venous occlusion is required; a typical intravenous dose is 2000 to 10,000 units, which is not generally reversed.<sup>47–52</sup> General anesthesia is commonly used since the procedure is invasive and can be time-consuming.

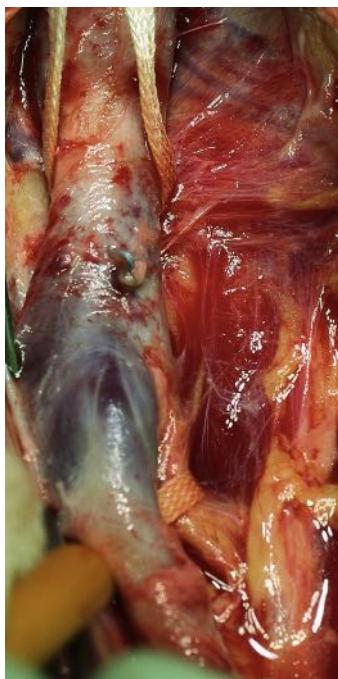
### Techniques

#### Overall Exposure

If reconstruction of the proximal femoral veins (femoral or profunda femoris) is the goal, a groin incision is made in the direction of the vessels to expose the first and second femoral valves. Further dissection through the fascia that lies beneath the sartorius muscle will expose the profunda femoris vein, if necessary. After exposure of the targeted valve and enough vein proximal and distally to see the valve well, the strip test should be performed to evaluate for valve competence. This test entails first milking blood antegrade past the valve while inflow is occluded; with subsequent application of retrograde pressure against the valve, reflux is demonstrated by filling of the vein distal to the valve. Lack of caudal vein filling signifies a competent valve. This incision may also provide exposure for valve transposition, transplantation, or neovalve reconstruction when these are the planned procedure.<sup>10</sup>

After identification of the valve station to be repaired, careful adventitial dissection to identify the valve attachment site is very useful (Fig. 159.5).<sup>47</sup> This dissection facilitates proper placement of the venotomy, when required, so as not to damage the valve leaflets, and verifies that the valve is present and available for repair. A lack of valve attachment lines may signify destruction of the valve, suggesting the need for techniques other than *in situ* repair.<sup>47</sup>

In other situations, a more distal femoral, popliteal, or even tibial vein may be the desired location for valve repair



**Figure 159.5** The white line clearly visible in this operative photo shows the cusp insertion site prior to opening the vein.

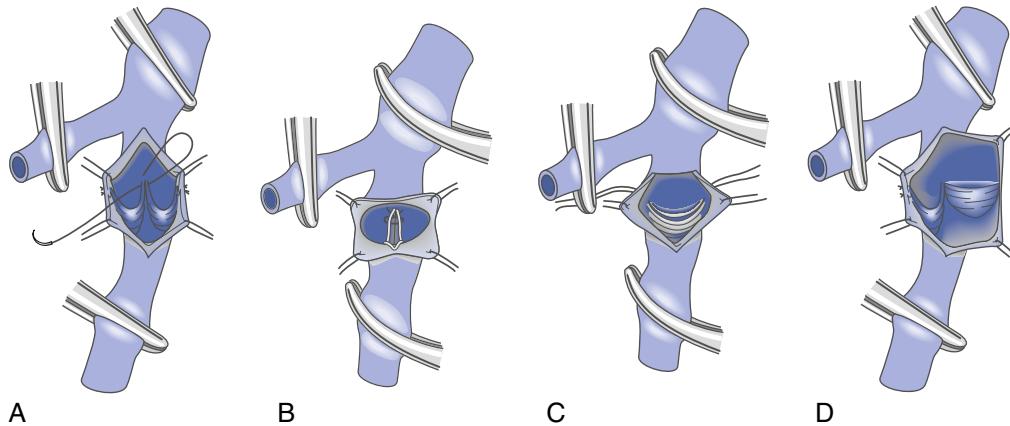
or transplantation. In these situations, the medial exposure is much like that used for exposure of the like-named artery.<sup>11</sup> The popliteal vein can also be exposed through an S-shaped incision in the popliteal fossa, with the transverse portion made in the knee crease to decrease the chance of scar contraction.<sup>11</sup>

### Internal Valvuloplasty

The open method of direct valve cusp tightening (reefing) has been the mainstay for correction of primary deep venous valvular reflux. This technique involves venotomy and suturing of the elongated valve leaflets under direct visualization. The redundant valve cusps are plicated to the vein wall with interrupted 6- or 7-0 polypropylene suture to allow proper alignment of the cusps. In 1968, Kistner was the first to report success using a longitudinal venotomy extending through the valve commissure (Figs. 159.6A and 159.7).<sup>53</sup> Raju later described a supracommissural approach in which a transverse venotomy was performed at least 2.5 cm above the valve, staying away from the delicate valve itself (Figs. 159.6B and 159.8).<sup>54</sup> Sottiurai described a combination approach in which a supravalvular transverse venotomy with distal extension into the valve sinus (a T-shaped venotomy) was used (Fig. 159.6C).<sup>55</sup> The “trap door” approach of Tripathi and Ktenidis involved two transverse incisions on the vein connected by a single vertical incision (Fig. 159.6D).<sup>56</sup> Regardless of the approach, suturing of the valve leaflets remains essentially the same. It is estimated that plication of approximately 20% of the length of the valve leaflet can restore valve competency in the majority of cases.<sup>57</sup> A recent atlas of venous surgery provides a detailed intraoperative pictorial-based description of the Kistner technique.<sup>10</sup>

### External Valvuloplasty

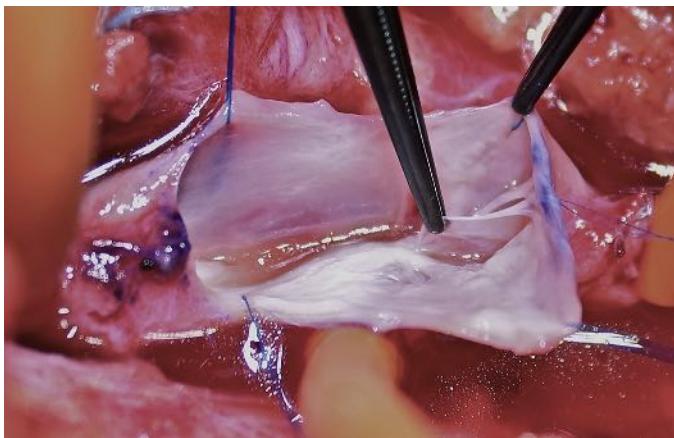
The technique of external valvuloplasty was pioneered by Kistner and reported in 1990.<sup>58</sup> This approach offers the advantage of valve repair without venotomy. It is performed by



**Figure 159.6** Internal valvuloplasty can be accomplished by a variety of techniques used to visualize the incompetent valve leaflets. (A) Artist's representation of the method first proposed by Kistner, in which he opens the vein through the anterior commissure. (B) Representation of the method of Raju, who uses a supravalvular transverse venotomy to view the valve from above without incising through the valve commissural angle. (C) Representation of the method of Sottiurai, who performs a supracommissural incision with extension toward a cusp sinus to improve visualization. (D) Representation of the technique used by Tripathi, who uses a “trap door” incision to provide optimal visualization of the valve cusps for repair. The method of reefing the valve to re-establish a competent valve is essentially the same in each instance.

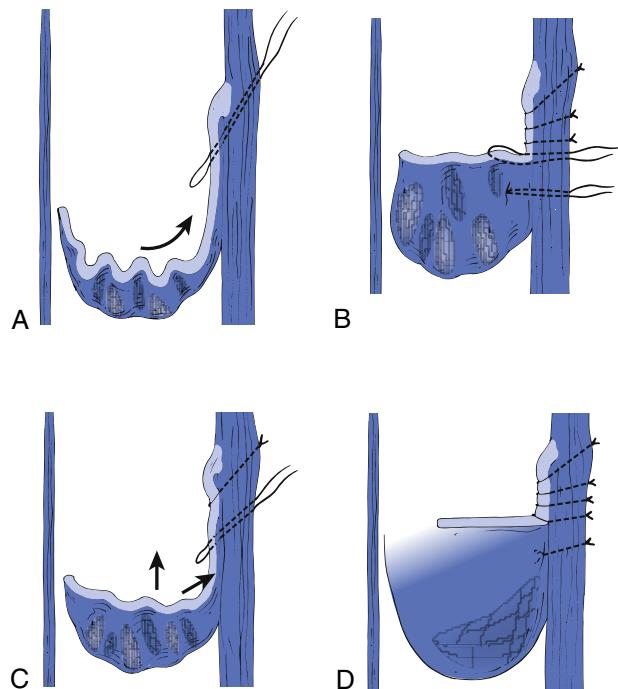


**Figure 159.7** This operative photograph shows the vein opened by the technique of Kistner to visualize the valve cusps to be repaired. Note sutures already placed on posterior wall to tighten (reef) the valve leaflets into the proper tension for optimal apposition when the vein is closed.



**Figure 159.8** This operative photograph demonstrates the vein opened via the technique of Raju, with valves seen below the vein incision.

placing interrupted sutures transmurally through the valve attachment lines, which on tying, leaves a decreased commissural angle, competent valve, and reduced vein diameter. Others have used a running suture to accomplish the same effect.<sup>47</sup> Both anterior and/or posterior plication can result in clinical success, and the same is true when performed with or without angioscopy.<sup>47,59,60</sup> Raju and colleagues believe that identifying the valve cusp attachment lines externally with the use of adventitial dissection is critical to technical success. Figure 159.9 illustrates the technique of transcommissural valvuloplasty.<sup>48</sup> A continuous suture can also be used to accomplish the repair.<sup>49,61</sup> Limited anterior plication, a modification of this method, involves anterior vein dissection and placement of a running mattress suture at the anterior commissure, which runs from a point 3 to 4 mm cranial to the angle of the valve cusp insertion lines up to the angle of the valve cusp insertion and incorporates 3 mm of the vein wall.<sup>62</sup> It has been used most commonly in conjunction with saphenous vein stripping and is limited to the proximal femoral vein valve.



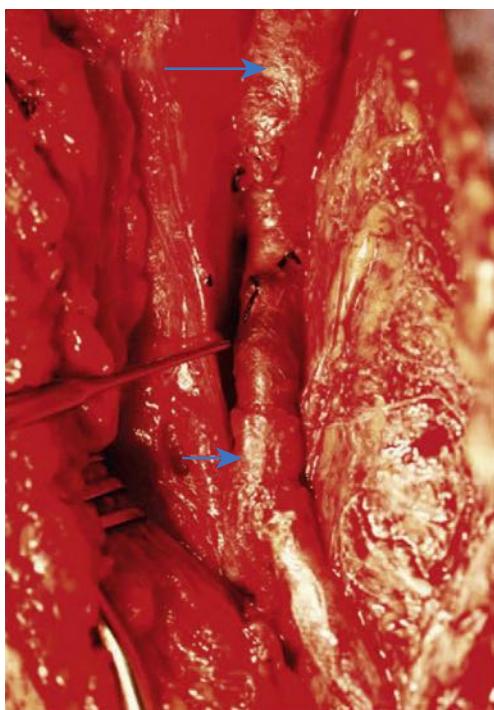
**Figure 159.9** The initial through-and-through oblique transluminal suture placed at the commissural apex catches sagging leaflets and resuspends them. (A–D) Transluminal sutures, with each successive suture biting deeper and less oblique than the suture above to pull up the valve, tighten the cusp edges, deepen the sinus, and appose the valve attachment lines. Each suture is tied before the next is placed. One or two of the most caudally placed sutures may pass through the body of the leaflet rather than through the edge, with no subsequent ill effects. (Redrawn from Raju S, Berry MA, Neglén P. Transcommissural valvuloplasty: technique and results. *J Vasc Surg*. 2000;32:969–976.)

### External Banding

An external sleeve made of synthetic (e.g., polyester, polytetrafluoroethylene) or xenograft (e.g., bovine pericardium) is wrapped around the circumference of the vein at the site of the valve and tightened to reduce the vein diameter until valve competence is restored. The sleeve is anchored to the adventitia by sutures to avoid migration.<sup>50</sup> One investigator used a spiral device screwed around the outside of the vein to decrease the diameter until endoscopic confirmation of valve competence.<sup>63</sup> External banding after valvuloplasty to prevent dilation over time remains controversial.<sup>48,64</sup> A quite unusual variation places a constricting polyester-urethane wrap around a valve free area of the popliteal vein to reduce the circumference by one-third; in one series of over a thousand patients, this procedure did not apparently cause distal hypertension while reducing reflux time and resulting in clinical improvement. However, this last technique was reported only in this series and the investigators treated superficial and perforator disease at the same time, so the effect of the deep banding per se is hard to determine.<sup>65</sup>

### Valve Transposition

If a single groin axial venous valve is spared from reflux, a transposition procedure can be performed by placing the incompetent venous system distal to the competent valve. Most commonly, the femoral system is incompetent and the profunda femoris

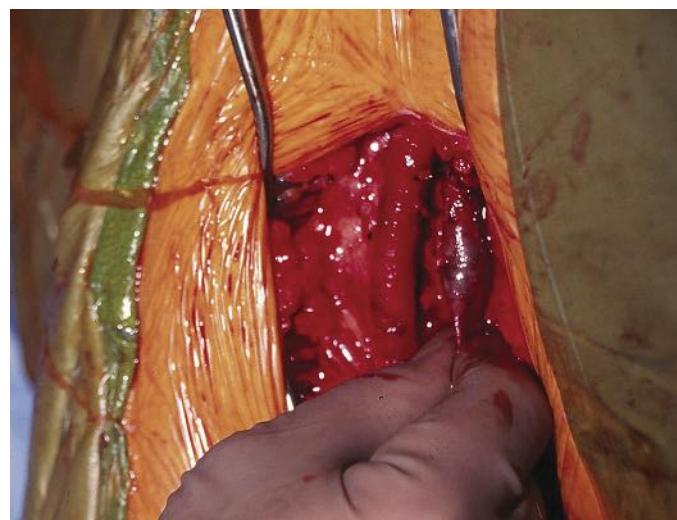


**Figure 159.10** Note the competent valve (forceps point to the area) beyond which the incompetent venous system has been placed in this operative picture of valve transposition. The long arrow points to common femoral vein. The forceps points to a deep femoral vein valve that is competent. The short arrow points to a femoral vein that has been transposed to below the competent profunda femoris vein valve.

valve remains competent. The incompetent femoral vein can be transected and replanted distal to a competent profunda femoris valve (Fig. 159.10) or competent valve in the great saphenous vein. When the profunda femoris valves are incompetent, the profunda femoris vein can be placed distal to a competent valve in either the femoral vein or the great saphenous vein. Alternatively, the size discrepancy of the great saphenous and femoral veins can be mitigated by performing a distal end great saphenous vein to side of femoral vein anastomosis, with ligation of the proximal femoral vein below the profunda femoral vein orifice.<sup>66</sup>

### Valve Transplantation

Valve transplantation was first described clinically by Taheri and colleagues.<sup>67</sup> A 2- to 3-cm segment of upper extremity vein containing a competent valve (or one that can be made competent) is first removed. Other investigators have utilized great or small saphenous veins as the valve donor.<sup>68</sup> The incompetent femoral vein system is approached just distal to its junction with the profunda femoris vein, and the axillary vein segment is sutured in place after removal of an appropriate length of femoral vein. The proximal anastomosis is often accomplished first to confirm valve competency and to allow distention and lengthening of the vein to facilitate the distal anastomosis (Fig. 159.11). In trabeculated post-thrombotic veins, Raju and coworkers have described excision of intraluminal synechiae to create a single lumen suitable for implantation.<sup>69</sup> Interrupted sutures are preferred to avoid suture line stenosis.<sup>57</sup> Valve competence is determined by the intraoperative strip test. Because



**Figure 159.11** This intraoperative picture shows a valve transplant with the proximal anastomosis complete. Any fluid or blood was pushed forward from the distal vein past the valve, and the valve is competent, allowing vein elongation and therefore proper positioning of the distal anastomosis. A similar maneuver is performed when a “strip test” is used to confirm valve competence. During a “strip test” the vein distal to the valve is occluded (in this case by the surgeon’s fingers but may be by a vascular clamp or forceps) and the blood is pushed or milked from the vein distal to the valve-containing vein segment. As blood refills the vein from proximal to distal, if the valve is competent, blood cannot reflux further and, therefore, will not be present in the vein distal to the valve.

approximately 40% of axillary vein valves are incompetent at the time of explantation, bench repair may be required.<sup>47,57</sup> Should bench repair be necessary, external or internal valvuloplasty has achieved success.<sup>47,70</sup> However, more proximal or distal valves in the upper extremity that are *de novo* competent should be sought before resorting to this added surgical intervention. Transplantation to a more distal site such as the popliteal vein is a viable option as well (Fig. 159.12).

### Substitute Venous Valves

Valve substitutes could address difficulties in treating patients with deep venous valvular insufficiency that have no autogenous valves available. Various attempts using synthetics, xenografts, and allografts have been studied experimentally and, in some cases, reached clinical trials but without success. Some designs for percutaneous valve reconstruction have been tested experimentally and even clinically without apparent long-term success. Details can be found in Chapter 60 of Rutherford’s 8th edition and reviews.<sup>3,71</sup> There is currently an on-going study using a synthetic valve placed operatively into the femoral vein with some acceptable early results.<sup>72</sup> An invagination of the vein into itself to create a valve has been tested experimentally but not clinically.<sup>73,74</sup>

The use of autogenous tissue to reconstruct a valve has been relatively successful in small series.<sup>47</sup> The procedure involves using a piece of autogenous vein wall as a donor from which semilunar cusps are fashioned after trimming the adventitia and part of the media. This reduced mass vein tissue is sutured into the recipient vein with the nonendothelial surface directed toward the lumen.<sup>47</sup>

Another attempt to use autogenous vein as a valve substitute has been reported by Plagnol and associates.<sup>75</sup> In this approach,

a stump of the great saphenous vein is invaginated into the femoral vein to fashion a bicuspid valve, after which the vein wall is closed. Others have mentioned using this technique in situations where no other option is available.<sup>76</sup>

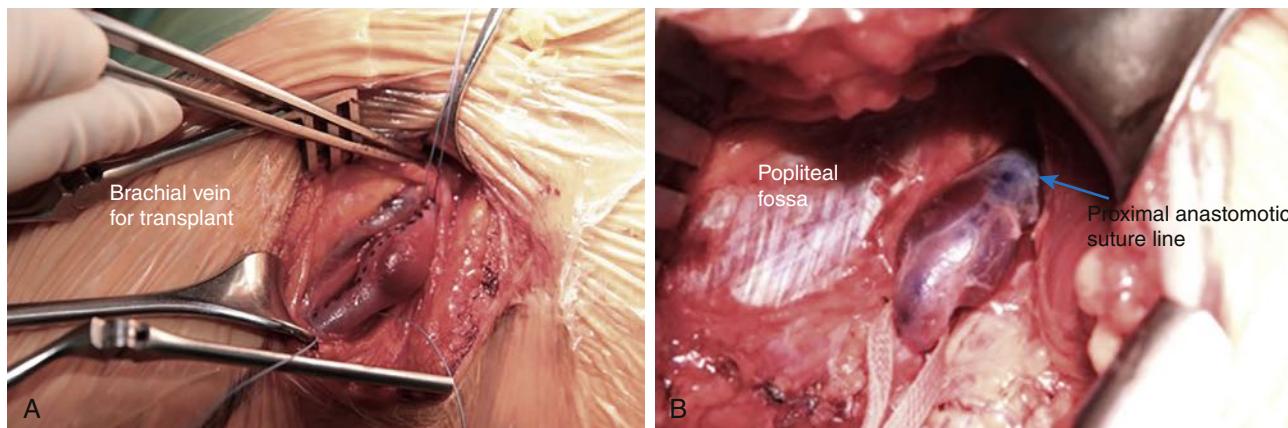
Maleti and colleagues reported a technique for constructing a bicuspid or monocuspisid venous valve by dissecting the intimal-medial wall of the thickened post-phlebitic vein with an ophthalmic knife to delicately divide the vein wall into the one or two sheets needed to fashion the cusp(s) (Fig. 159.13).<sup>77,78</sup> The patients received anticoagulation for 6 months. The most recent improvement to this technique has been to place two sutures on the cusp or cusps to hold the valve in the semi-open position and thereby prevent valve collapse (Fig. 159.14) and improve competence.<sup>79</sup> Some excellent intraoperative images and illustrations can be found in a review article by Maleti and Perrin.<sup>80</sup> This interesting work has been verified by at least one other investigator.<sup>81</sup> A percutaneous method of constructing this type of valve is under clinical investigation.<sup>82</sup>

A hybrid approach invented by Opie involves invaginating a cuboidal piece of the vein wall, still attached at its caudal

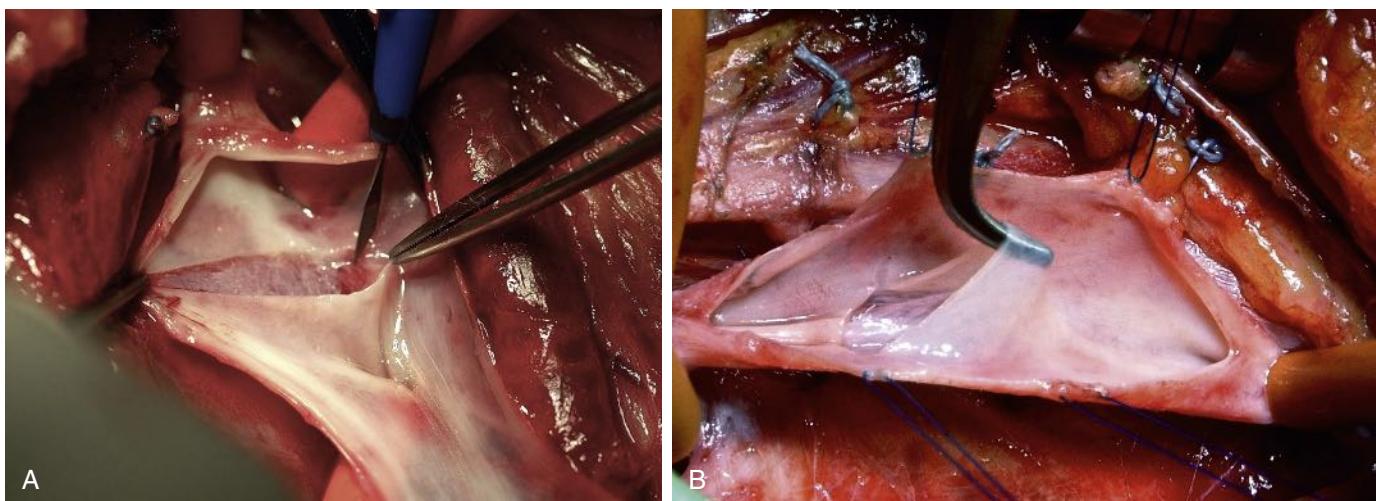
edge, into the vein lumen, with two sutures attached to the cephalad edge to prevent reflux of the flap into the distal vein, thereby forming a monocuspisid valve. The opening in the vein wall is repaired with a flexible expanded polytetrafluoroethylene patch.<sup>83</sup> It is difficult to explain how the valve can prevent all reflux, being open on both sides, but clinical improvement is reported. Investigators from Russia have successfully used this technique.<sup>84</sup>

### Postoperative Management

Pneumatic compression devices should be applied postoperatively to decrease swelling and the risk of DVT.<sup>48,51,52,85,86</sup> This may also increase flow through the valve repair when the patient is sedentary. Because therapeutic or low-dose heparin is often administered for some time postoperatively, closed drainage of wounds is used by some surgeons and removed when minimal drainage is noted. Long-term prophylactic or therapeutic oral anticoagulation (generally warfarin in early studies and direct oral anticoagulants recently) is recommended for 3 to 6 months in operations



**Figure 159.12** The first intraoperative photo (A) shows a brachial vein with intact valve exposed for removal and eventual transplantation to the popliteal vein location (B).



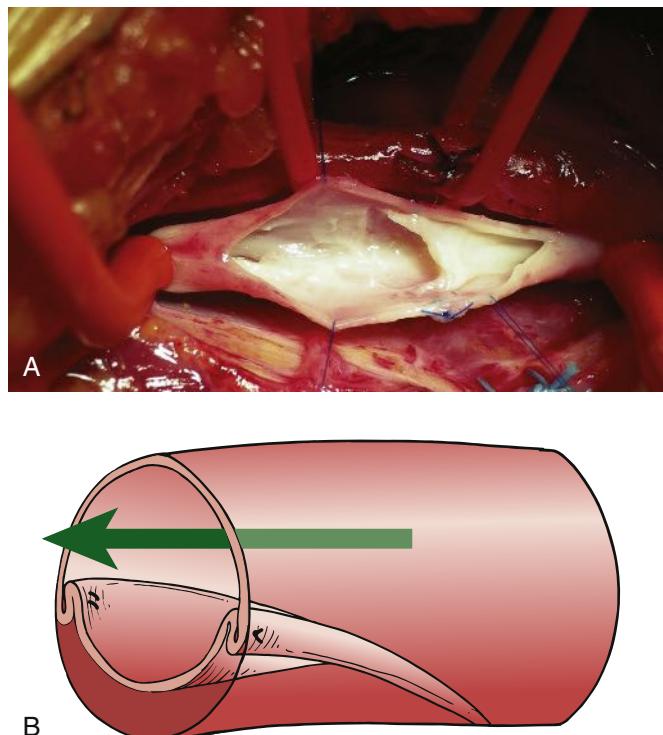
**Figure 159.13** This is a neovalve construction being performed by Dr. Maleti with the first photo (A) demonstrating the use of an ophthalmic knife to construct the valve and (B) a bicuspid valve in another patient with the second leaflet yet to be constructed.

requiring open venotomy.<sup>21,47–49,52,61,64,85–90</sup> Although many surgeons encourage the use of compressive support after venous valve reconstruction, compliance continues to be problematic.<sup>22,91</sup>

## Results

### Complications and Initial Results

Valve repair series report essentially no mortality and low associated systemic morbidity (<1%).<sup>47–49,64,85,88,92,93</sup> Local issues are



**Figure 159.14** (A) This intraoperative photograph shows a monocuspid valve made from the inner wall of a post-thrombotic vein with a fine ophthalmic knife. Two sutures (blue color) are placed near the outer edges to keep the valve from collapsing while at rest. (B) Artist's depiction of how the monocuspid valve does not completely collapse against the nonluminal wall during antegrade venous flow. The arrow demonstrates the direction of normal venous blood flow toward the heart during exercise.

**Figure 159.15** Cumulative clinical success rates for all limbs of patients who underwent a venous valve reconstruction for advanced venous disease. Numbers in parentheses represent total limbs at risk for each time interval. (Redrawn from Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. *J Vasc Surg*. 1994;19:394.)

more common but manageable. Hematoma and seroma formation are seen in up to 15% of cases, with some expected variation depending on anticoagulation intensity.<sup>48,51,57,64,85,86,91,94</sup> Wound infections have been seen in 1% to 7% of cases.<sup>47,48,57,64,85,91</sup>

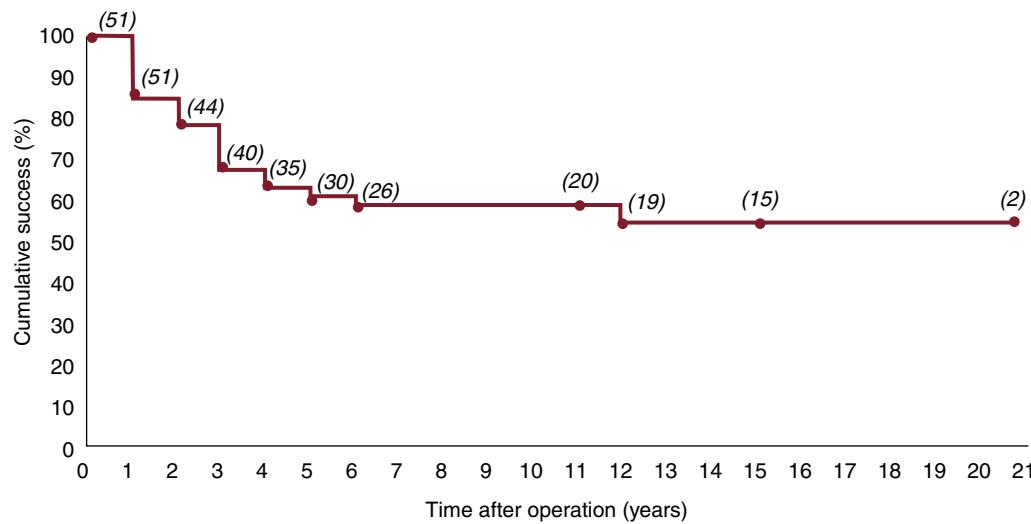
Although of great concern, most investigators report a clinical DVT rate of well less than 10% and often not involving the repair site.<sup>47,48,50,51,57,85,86,91,94</sup> An extensive review including most types of valve repair did note a difference based on etiology, with primary venous insufficiency having a DVT rate of 6.7% versus a 25.4% rate in post-thrombotic repairs, providing an indication of when anticoagulation is most warranted.<sup>64</sup> If a significant DVT does occur, catheter-directed thrombolysis may help: in one series, it resulted in complete thrombus resolution in 60% of cases (three of five) and salvage of the involved valve repair in 50% of cases (one of two).<sup>48</sup> Pulmonary embolism can occur but is rare. One series with an aggressive surveillance plan found 1 in 129 patients.<sup>48</sup>

Patency and valve competency of all types of repairs within the perioperative period (30 days) are reported as excellent by most investigators. A few series report a less than 1% incidence of early failure.<sup>47,48</sup> Valve leaflet trauma is rare but occurs and most often during venotomy.<sup>64</sup> Intraoperative repair with 8-0 sutures resulted in a successful 2-year competency rate of 57.1% (four of seven) in one series.<sup>64</sup>

### Late Results

#### Internal valvuloplasty

Kistner and colleagues have monitored their patients who required internal valvuloplasty for decades with published lifetable results of clinical success (Fig. 159.15). Table 159.1 is a compilation of series reporting success with internal valvuloplasty. It confirms excellent clinical results in patients who would otherwise have experienced unrelenting symptoms because of chronic deep venous insufficiency. Valves are competent in 60% to 70% of patients at 5 years in most series.<sup>21,30,35,51,53,56,64,86,89,91,93,95–97</sup> In general, a patent and competent valve translates into clinical improvement, whereas recurrent reflux is associated with clinical failure. A similar comment can be made regarding all types of venous valvular reconstruction.



**TABLE 159.1** Results of Internal Valvuloplasty

Series	Year	Main Site	Number of Limbs	Months of Follow-Up (Average)	Number Competent <sup>a</sup>	Number Symptom Recurrence/Unchanged <sup>b</sup>	Hemodynamic Improvement <sup>c</sup>
Kistner <sup>93</sup>	1975	FV	15	36–84 (60)	5/14	2/15	
Ferris and Kistner <sup>95</sup>	1982	FV	32	12–156 (72)	16/22	6/32	7/8
Raju <sup>54</sup>	1983	FV	15	3–40	15/15 <sup>d</sup> 4/5 <sup>e</sup>	0/15	10/15
Ericksson and Almgren <sup>30</sup>	1986	FV	19	84 (44)	13/19	5/19	12/19
Cheatle and Perrin <sup>51</sup>	1994	FV	52	3–54	46/52 <sup>f</sup> 23/27 <sup>g</sup>	7/51	40/42 <sup>f</sup> 24/25 <sup>g</sup>
Masuda and Kistner <sup>91</sup>	1994	FV	32	48–256 (127)	24/31	9/32	
Raju et al. <sup>35</sup>	1996	FV	81	12–144	30/71	16/68	
Lurie et al. <sup>96</sup>	1997	FV	49	36–108 (74)		18/49	
Perrin <sup>97</sup>	1997		75	24–96 (58)		6/33	54/74
Perrin et al. <sup>89</sup>	1999	FV	33	24–96 (51)	22/33	6/33	16/27
Perrin <sup>86</sup>	2000	FV	85	12–96 (58)	51/83	10/35	43/68
Tripathi and Ktenidis <sup>h,56</sup>	2001	FV	25	1–12 (6)	35/41	4/25	
Tripathi et al. <sup>h,64</sup>	2004		90	24	115/144	61/90	
Maleti, et. al. <sup>21</sup>	2017	FV	13	40	13	1	12

<sup>a</sup>Determined by phlebography, duplex ultrasonography, or both.<sup>b</sup>Includes C3–6 (majority C5/6).<sup>c</sup>Determined by plethysmography or intravenous pressure (preoperative vs. postoperative findings).<sup>d</sup>Determined by ultrasonography.<sup>e</sup>Determined by phlebography.<sup>f</sup>Immediately after surgery.<sup>g</sup>Twelve months after surgery.<sup>h</sup>More than one valve repair per limb.

FV, femoral vein.

## External valvuloplasty

External valvuloplasty may be a less durable repair than open valvuloplasty.<sup>35</sup> Much of the current work involving isolated deep venous reflux surgery by various techniques of external valvuloplasty has involved the repair of multiple valves in the same axial system, which makes it difficult to compare with other types of repair per valve repair. As an example, transcommissural repair of 179 valves in 141 limbs resulted in a valve competence rate of 63% and clinical improvement in ~70% with statistical improvement in venous hemodynamics at 3 years.<sup>48</sup> One report using standard external valvuloplasty (19 repairs in 12 limbs) reported a competency rate of 31.6% and ulcer free rate of 50% at 2 years.<sup>64</sup> Another series reported 3- and 5-year competency rates of 64% and 52%, respectively, but many patients had multi-station or multi-level repairs.<sup>61</sup>

Superficial saphenous ablation with or without proximal femoral vein external valvuloplasty has been evaluated in four randomized controlled trials.<sup>62,88,92,98</sup> A Cochrane review did analyze the results from these four studies but could not

conclude whether the addition of the deep vein valve repair was beneficial or not due to small study size, differences in assessment, and overall low quality by the criteria used.<sup>99</sup>

## External banding

The prosthetic sleeve method of valve repair has achieved acceptable results in selected patients with less advanced disease.<sup>35,50</sup> In one series involving repair of femoral (60) or popliteal (53) valves in 42 limbs, long-term ulcer healing rates were directly associated with the number of valves repaired; one, 51%; two, 65%; and three, 86%.<sup>50</sup> Another group treating only the proximal femoral vein valve with known functional profunda femoris vein valves reported a 78% valve competency rate and symptom relief at 50 months.<sup>100</sup>

## Valve transposition

Good clinical results have been observed in 40% to 50% of patients at 5 years of follow-up.<sup>31,91,95,97,101,102</sup> A review specifically addressing those with venous ulcers as the indication for surgery finds similar results.<sup>3</sup> The method of placing the

**TABLE 159.2** Results of Valve Transplantation

Series	Year	Main Site	Number of Limbs	Months of Follow-Up (Average)	Number Competent <sup>a</sup>	Number Symptom Recurrence/ Unchanged <sup>b</sup>	Hemodynamic Improvement
Taheri et al. <sup>67</sup>	1982	FV	6	12	4/4	4/4	5/5
Raju <sup>54</sup>	1983	FV	21	3–40	2/14	10/21	10/13
Taheri et al. <sup>103</sup>	1986	POP	46	8–36	22/24	5/46	12/14
O'Donnell et al. <sup>33</sup>	1987	POP	10	>24	0/10	0/10	1/10
Nash <sup>46</sup>	1988	POP	25	12–18	20/25	2/25	21/25
Rai and Lerner <sup>104</sup>	1991	POP	12	6–24 (16)	6/6	0/12	11/12
Bry et al. <sup>34</sup>	1995	POP	15	15–132 (64)		3/14	
Perrin <sup>97</sup>	1997	FV	30	12–120 (58)	6/20	8/20	
Sotturai <sup>105</sup>	1997		31	8–156 (74)	14/31	17/31	
Tripathi et al. <sup>64</sup>	2004 <sup>d</sup>		38	24	29/61	17/38	

<sup>a</sup>Determined by phlebography, duplex ultrasonography, or both.

<sup>b</sup>Includes C3–6 (majority C5/6).

<sup>c</sup>Determined by plethysmography or intravenous pressure (preoperative vs. postoperative findings).

<sup>d</sup>More than one valve repair per limb.

FV, femoral vein; POP, popliteal vein.

femoral system below a competent great saphenous valve with ligation to offset the size discrepancy has resulted in 55% of the patients being free of ulcers at 10 years.<sup>66</sup>

### Valve transplantation

**Table 159.2** provides a synopsis of the results that one can anticipate when valve transplantation is required to treat chronic deep venous valvular incompetence.<sup>33,34,46,54,67,97,103–105</sup> Clinical improvement is seen in about 50% of patients, even at 8 years of follow-up.<sup>23,57,102</sup> The use of great or small saphenous vein valve transplants provide similar results at 3 and 7 years.<sup>68</sup>

### Substitute venous valve

The Plagnol type of valve has acceptable clinical results reported with 19 of 20 reconstructions being patent and competent at a mean of 10 months.<sup>75</sup> Others have used the technique in situations where no other good option exists.<sup>76</sup> Invagination of an adventitial surface into the venous lumen, while being of some concern, does not appear an issue clinically.

The Maleti neovalve initial design demonstrated early thrombosis below the valve in 2 patients, and there was one late occlusion shortly after starting oral contraceptives.<sup>78</sup> At a mean follow-up of 2 years, 95% of treated segments remained primarily patent and competent with significantly improved duplex and air plethysmography findings. Ulcer healing occurred in 16 cases (88.9%) at a median of 12 weeks with no recurrences.<sup>78</sup> Long-term results at a median follow-up of 54 months, reported valve competency at 68% (13 of 19) with one episode of DVT and ulcer healing rate of 84% with two recurrences.<sup>79</sup> The modification noted in the techniques section was instituted to improve these results; in 21 operations with a median of 5 months of surveillance, all valves were competent, with 95% ulcer healing

rate and two recurrences (9.5%).<sup>79</sup> Technical details can be found in a 2015 review by Maleti and colleagues.<sup>76</sup>

Opie reported no incompetent valves in 14 operations at 4 years and excellent clinical improvement.<sup>83</sup> Another series reported on 26 patients (mean follow-up 29.5 months) with cumulative clinical success of 76.5%, ulcer free at 4 years 83.4%, and valve competency of 70.6%.<sup>84</sup>

Substitute valve techniques can be used in situations where planned options were found intraoperatively to not be possible.<sup>76</sup>

### Multilevel valve reconstruction

There is increasing evidence that multilevel valve reconstruction (more than one valve repair in the same axial system) improves maintenance of valve competence in at least one of the repaired valves and, consequently, improves clinical outcome. Raju and his group have been advocates of this approach for many years.<sup>36,48</sup> At 2 years, Tripathi and colleagues found that patients with primary reflux disease undergoing single-level valvuloplasty could expect a 59.4% valve competence rate and 54.7% ulcer healing rate, which was significantly lower ( $P < 0.05$ ) than results achieved with multilevel repair, which demonstrated rates of 79.7% and 72.9%, respectively.<sup>64</sup> A similar trend was noted in those requiring valve transplantation; valve competence and ulcer healing rates were 38.9% and 46.1%, respectively, for single-level repairs, versus 55.8% and 57% for multilevel repairs.<sup>64</sup> Rosales and colleagues have accumulated data on external valvuloplasty that suggest improved clinical results, especially in CEAP class 4 patients, with the use of a multi-level (different locations in the same axial system) and multi-station (more than one valve in the same location) technique, but statistical significance was not obtained, and clear determination of valve competence was not provided.<sup>61</sup> Lane and associates

found that as the number of external banding repairs per axial system increased, so did long-term ulcer healing.<sup>50</sup>

### Reoperative surgery

Reoperative surgery can be difficult, but is sometimes required.<sup>47</sup> The best approach appears to be to use a new incision remote from the original operative site. One choice might be the mid-femoral vein at the adductor canal, as it is easily accessible and generally is not the first choice for valve reconstruction. As a note, Raju and Hardy<sup>47</sup> have tended to refrain from popliteal valvuloplasty because of an often thick adventitial coat making adventitial dissection and visualization of the valve commissures difficult.

## Follow-up

### Long-term Surveillance

A typical method of clinical follow-up includes physical examination at 6 weeks, 3 to 9 months, and then annually, but with considerable variability in the exact timing of visits.<sup>48–51,62,64,86,89,93</sup> During each visit, venous duplex ultrasonography is performed to determine valve site patency and valve competence. Noninvasive testing has generally replaced descending venography, which was often used in earlier series.<sup>52,91</sup> Most surgeons include some type of hemodynamic assessment. Some use a visual analogue pain score or assessment for swelling.<sup>48,88</sup> Reclassification by the CEAP criteria, venous severity scoring, and use of quality-of-life assessment tools are encouraged to provide quantifiable parameters of clinical success.<sup>21,48–51,64,85,86,89,100</sup>

## SUMMARY

A wide experience has accumulated in the field of deep venous valvular reconstruction. Most of these procedures are performed to alleviate disabling symptoms (C4b–C6) that otherwise could not be treated. Deep venous valvular treatment requires careful diagnostic workup to allow optimal selection from among the various surgical options available. The technical approaches have varied widely, with some extensively reproduced by multiple surgeons and others isolated to reports in small series. The commonalities among the reports are a sustained clinical success ranging from 40% to 80% at >5 years. Maintenance of a patent vein with a competent valve is essential for sustained ulcer healing and symptom relief. To advance this field of vascular surgery, we need a better understanding of venous pathophysiology, improved diagnostic accuracy, and comparative studies of venous interventions with patient-reported outcomes.

## SELECTED KEY REFERENCES

- Dalsing MC, Kistner RL. Deep venous incompetence and valve repair. In: Almeida JI, ed. *Atlas of Endovascular Venous Surgery*. Philadelphia, PA: Elsevier, Inc; 2019:517–545.
- A well-illustrated atlas specifically designed to provide operative details with some practical information from the father of venous valve repair, Dr. Robert Kistner.*
- Kistner RL. Surgical repair of a venous valve. *Straub Clin Proc*. 1968;24:41–43.
- Those who have the courage to be the first should be recognized for the effort, and this is one of those articles.*
- Lugli M, Guerzoni S, Garofalo M, et al. Neovalve construction in deep venous incompetence. *J Vasc Surg*. 2009;49:156–163.
- It is selected as a recent innovative and cutting-edge approach to venous valve repair as a treatment of the post-thrombotic insufficient venous system.*
- Maleti O, Lugli M, Tripathi RK. Deep venous reconstructive surgery. *Semin Vasc Surg*. 2015;28(1):39–45.
- An excellent and more recent review on the general field of venous valve reconstruction with some practical comments on appropriate use.*
- 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.
- This group was the first to report on the repair of venous valves to prevent deep venous reflux, and this study still stands as the longest follow-up of such patients.*
- Raju S, Fredericks RK, Neglén PN, Bass JD. Durability of venous valve reconstruction techniques for “primary” and postthrombotic reflux. *J Vasc Surg*. 1996;23:357–367.
- This report compares various methods of valve repair in terms of valve competence and clinical result. It is from one of the few centers that have enough to make such a comparison with statistical validity.*
- Raju S, Hardy JD. Technical options in venous valve reconstruction. *Am J Surg*. 1997;173:301–307.
- This article provides excellent technical points on the various types of venous valve repair from a group with possibly the largest experience in the world. They have the experience to teach us all something.*
- Sotturai VS. Results of deep-vein reconstruction. *Vasc Surg*. 1997;31:276–278.
- A large experience from a surgeon who invented one approach to open valvuloplasty.*
- Taheri SA, Elias SM, Yacobucci GN, Heffner R, Lazar L. Indications and results of vein valve transplant. *J Cardiovasc Surg*. 1986;27:163–168.
- A landmark article on a new approach to treatment of the post-thrombotic insufficient lower leg venous system.*
- Tripathi R, Sieunarine K, Abbas M, Durrani N. Deep venous valve reconstruction for non-healing leg ulcers: techniques and results. *Aust N Z J Surg*. 2004;74:34–39.
- A large study of various methods of valve repair highlighting the use of multiple valve repairs in the same axial system to decrease clinical recurrence.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. Criqui MH, Jamosmos M, Fronek A, et al. Chronic venous disease in an ethnically diverse population: the San Diego Population Study. *Am J Epidemiol.* 2003;158:448–456.
2. Rabe E, Guex JJ, Puskas A, et al. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. *Int Angiol.* 2012;31:105–115.
3. O'Donnell Jr TF, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. *J Vasc Surg.* 2014;60(2 Suppl):S5–S9S.
4. Lal BK. Venous ulcers of the lower extremity: Definition, epidemiology, and economic and social burdens. *Semin Vasc Surg.* 2015;28(1):3–5.
5. Mayberry JC, et al. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. *Surgery.* 1991;109:575–581.
6. Erickson CA, et al. Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. *J Vasc Surg.* 1995;22:629–636.
7. Montminy ML, Jayaraj A, Raju S. A systematic review of the efficacy and limitations of venous intervention in stasis ulceration. *J Vasc Surg Venous Lymphat Disord.* 2018;6:376–389.
8. Raju S, Owen Jr S, Neglen P. The clinical impact of iliac venous stents in the management of chronic venous insufficiency. *J Vasc Surg.* 2002;35(1):8–15.
9. Williams ZF, Dillavou ED. A systematic review of venous stents for iliac and venacaval occlusive disease. *J Vasc Surg Venous Lymphat Disord.* 2020; 8:145–153.
10. Dalsing MC, Kistner RL. Deep Venous Incompetence and Valve Repair. In: Almeida JI, ed. *Atlas of Endovascular Venous Surgery.* Philadelphia PA: Elsevier, Inc; 2019:517–745.
11. Valentine RJ, et al. Vessels of the leg. In: Valentine RJ, Wind GG, eds. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:467–522.
12. Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord.* 2020;8:342–352.
13. Sun J, et al. Anatomic and histologic studies on the valves of the venous system in lower extremities. *Vasc Surg.* 1990;24:85–90.
14. Powell T, et al. The valves of the external iliac, femoral, and upper third of the popliteal veins. *Surg Gynecol Obstet.* 1951;92:453–455.
15. Basmajian JV. The distribution of valves in the femoral, external iliac, and common iliac veins and their relationship to varicose veins. *Surg Gynecol Obstet.* 1952;95:537–542.
16. Lepage PA, Villavicencio JL, Gomez ER, et al. The valvular anatomy of the iliac venous system and its clinical implications. *J Vasc Surg.* 1991;14:678–683.
17. Eklof B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg.* 2004;40(6):1248–1252.
18. Plate G, et al. Physiologic and therapeutic aspects in congenital vein valve aplasia of the lower limb. *Ann Surg.* 1983;198(2):229–233.
19. Kistner RL, Eklof B. Classification and etiology of chronic venous disease. In: Gloviczki P, ed. *Handbook of Venous and Lymphatic Disorders.* Fourth Edition ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2017:39–49.
20. Marston WA, Brabham VW, Mendes R, et al. The importance of deep venous reflux velocity as a determinant of outcome in patients with combined superficial and deep venous reflux treated with endovenous saphenous ablation. *J Vasc Surg.* 2008;48(2):400–405; discussion 405–406.
21. Maleti O, Lugli M, Perrin M. After superficial ablation for superficial reflux associated with primary deep axial reflux, can variable outcomes be caused by deep venous valve anomalies? *Eur J Vasc Endovasc Surg.* 2017;53:229–236.
22. Raju S, Fredericks RK, Hudson CA, et al. Venous valve station changes in “primary” and postthrombotic reflux: an analysis of 149 cases. *Ann Vasc Surg.* 2000;14(3):193–199.
23. O'Donnell TF. Chronic venous insufficiency: an overview of epidemiology, classification, and anatomic considerations. *Semin Vasc Surg.* 1988;1:60–65.
24. Kistner RL, et al. Deep venous valve reconstruction. *Cardiovasc Surg.* 1995;3:129–140.
25. Danielson G, et al. Reflux from thigh to calf, the major pathology in chronic venous ulcer disease: surgery indicated in the majority of patients. *Vasc Endovasc Surg.* 2004;38:209–219.
26. Budd TW, et al. Histopathology of veins and venous valves of patients with venous insufficiency syndrome: ultrastructure. *J Med.* 1990;21:181–199.
27. Killewich LA, Bedford GR, Beach KW, Strandness DE. Spontaneous lysis of deep venous thrombi: rate and outcome. *J Vasc Surg.* 1989;9(1):0089–0097.
28. Masuda E, et al. The natural history of calf vein thrombosis: lysis of thrombi and development of reflux. *J Vasc Surg.* 1998;28:67–73.
29. McLafferty RB, et al. Late clinical and hemodynamic sequelae of isolated calf vein thrombosis. *J Vasc Surg.* 1998;27:50–56.
30. Eriksson I, Almgren B. Influence of the profunda femoris vein on venous hemodynamics of the limb. Experience from thirty-one deep vein valve reconstructions. *J Vasc Surg.* 1986;4(4):390–395.
31. Queral LA, Whitehouse WMJ, Flinn WR, et al. Surgical correction of chronic deep venous insufficiency by valvular transposition. *Surgery.* 1980;87(6):688–695.
32. Raju S, et al. Axial transformation of the profunda femoris vein. *J Vasc Surg.* 1998;27:651–659.
33. O'Donnell Jr TF, Mackey WC, Shepard AD, Callow AD. Clinical, hemodynamic, and anatomic follow-up of direct venous reconstruction. *Arch Surg.* 1987;122(4):474–482.
34. Bry JD, Muto PA, O'Donnell TF, Isaacson LA. The clinical and hemodynamic results after axillary-to-popliteal vein valve transplantation. *J Vasc Surg.* 1995;21(1):110–119.
35. Raju S, Fredericks RK, Neglen P, Bass JD. Durability of venous valve reconstruction techniques for “primary” and postthrombotic reflux. *J Vasc Surg.* 1996;23:357–367.
36. Raju S. Multiple-valve reconstruction for venous insufficiency: indications, optimal technique, and results. In: Veith FJ, ed. *Current Critical Problems in Vascular Surgery.* 4th ed. St. Louis, MO: Quality Medical Publishing; 1992:122–125.
37. Vasquez MA, Rabe E, McLafferty RB, et al. 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):1387–1396.
38. Vasquez MA, Harris L. Outcomes assessment for chronic venous disease. In: *Handbook of Venous and Lymphatic Disorders.* 4th ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2017:771–781.
39. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(5 Suppl):S2–S48S.
40. Araki CT, Back TL, Pagberg FT, et al. The significance of calf muscle function in venous ulceration. *J Vasc Surg.* 1994;20:872–879.
41. Nicolaides AN, Maleti O, Lugli M, Guerzoni S. Noninvasive measurement of lower limb outflow resistance and implications for stenting. *Vasc Invest Ther.* 2019;2:88–94.
42. Raju S. New approaches to the diagnosis and treatment of venous obstruction. *J Vasc Surg.* 1986;4:42–54.
43. Nicolaides MS, Hussein MK, Szendro G, et al. The relation of venous ulceration with ambulatory venous pressure measurements. *J Vasc Surg.* 1993;17:414–419.
44. Neglen P, Raju S. Proximal lower extremity chronic venous outflow obstruction: recognition and treatment. *Semin Vasc Surg.* 2002;15:57–64.
45. Kistner RL, Ferris EB, Randhawa G, Kamida C. A method of performing descending venography. *J Vasc Surg.* 1986;4:464–468.
46. Nash T, et al. Long-term results of vein valve transplants placed in the popliteal vein for intractable post-phlebitic venous ulcers and pre-ulcer skin changes. *J Cardiovasc Surg.* 1988;29:712–716.

47. Raju S, Hardy JD. Technical options in venous valve reconstruction. *Am J Surg.* 1997;173(4):301–307.
48. Raju S, Berry MA, Neglen P. Transcommissural valvuloplasty: technique and results. *J Vasc Surg.* 2000;32(5):969–976.
49. Us M, Basaran M, Sanioglu S, et al. The use of external banding increases the durability of transcommissural external deep venous valve repair. *Eur J Vasc Endovasc Surg.* 2007;33(4):494–501.
50. Lane JL, et al. Intermediate to long-term results of repairing incompetent multiple deep venous valves using external valvular stenting. *Aust N Z J Surg.* 2003;73:267–274.
51. Cheatle TR, Perrin M. Venous valve repair: early results in fifty-two cases. *J Vasc Surg.* 1994;19:404–413.
52. Nishibe T, Kudo F, Flores J, et al. Femoral vein valve repair with angioscopy-assisted anterior valve sinus plication. Early results. *J Cardiovasc Surg (Torino).* 2001;42(4):529–535.
53. Kistner RL. Surgical repair of a venous valve. *Straub Clin Proc.* 1968;24:41–43.
54. Raju S. Venous insufficiency of the lower limb and stasis ulceration. Changing concepts and management. *Ann Surg.* 1983;197(6):688–697.
55. Sottiurai VS. Technique in direct venous valvuloplasty. *J Vasc Surg.* 1988;8(5):646–648.
56. Tripathi R, Ktenidis KD. Trapdoor internal valvuloplasty—a new technique for primary deep vein valvular incompetence. *Eur J Vasc Endovasc Surg.* 2001;22(1):86–89.
57. Raju S, Fredericks RK. Valve reconstruction procedures for non-obstructive venous insufficiency: Rationale, techniques, and results in 107 procedures with two- to eight-year follow-up. *J Vasc Surg.* 1988;7(2):301–310.
58. Kistner RL. Surgical technique of external venous valve repair. *Straub Clin Proc.* 1990;55:15–16.
59. Nishibe T, Kudo F, Miyazaki K, et al. Intermediate-term results of angioscopy-assisted anterior valve sinus plication for primary deep venous insufficiency. *J Cardiovasc Surg (Torino).* 2007;48(1):21–25.
60. Gloviczki P, Merrell SW, Bower TC. Femoral vein valve repair under direct vision without venotomy: a modified technique with use of angioscopy. *J Vasc Surg.* 1991;14(5):645–648.
61. Rosales A, et al. External venous valve plasty (EVVP) in patients with primary chronic venous insufficiency (PCVI). *Eur J Endovasc Surg.* 2006;32:570–576.
62. Belcaro G. Femoral vein valve repair with limited anterior plication (LAP). *J Cardiovasc Surg.* 1993;34(5):395–398.
63. Makhatriov G, Askerkhanov G, Kazakmurzaev MA, Ismailov I. Endoscopically directed external support of femoral vein valves. *J Vasc Surg.* 2009;49(3):676–680; discussion 680.
64. Tripathi R, et al. Deep venous valve reconstruction for non-healing leg ulcers: techniques and results. *Aust N Z J Surg.* 2004;74:34–39.
65. Ma T, Fu W, Ma J. Popliteal vein external banding at the valve-free segment to treat severe chronic venous insufficiency. *J Vasc Surg.* 2016;64(2):438–445. e1.
66. Cardon JM, Cardon A, Joyeux A, et al. Use of ipsilateral greater saphenous vein as a valved transplant in management of post-thrombotic deep venous insufficiency: long-term results. *Ann Vasc Surg.* 1999;13(3):284–289.
67. Taheri SA, Lazar L, Elias SM, Marchand P. Vein valve transplant. *Surgery.* 1982;91(1):28–33.
68. Rosales A, Jorgensen JJ, Slagsvold CE, et al. Venous valve reconstruction in patients with secondary chronic venous insufficiency. *Eur J Vasc Endovascular Surg.* 2008;36:466–472.
69. Raju S, Neglén P, Doolittle J, Meydreich EF. Axillary vein transfer in trabeculated postthrombotic veins. *J Vasc Surg.* 1999;29(6):1050–1062.
70. Sottiurai VS. Supravalvular incision for valve repair in primary valvular insufficiency. In: Bergan JJ, Kistner RL, eds. *Atlas of Venous Surgery.* Philadelphia, PA: WB Saunders; 1992:137–138.
71. Meissner MH, Eklof B, Smith PC, et al. Secondary chronic venous disorders. *J Vasc Surg.* 2007;46(Suppl S):68S–83S.
72. Glickman MH, Ulloa JH. Results of first-in-human implantation of a prosthetic venous valve. *J Vasc Surg.* 2020;71(1).
73. Dalsing MC, Lalka SG, Unthank JL, et al. Venous valvular insufficiency: influence of a single venous valve (native and experimental). *J Vasc Surg.* 1991;14(5):576–587.
74. Rosenbloom MS, Schuler JJ, Bishara RA, et al. Early experimental experience with a surgically created, totally autogenous venous valve: a preliminary report. *J Vasc Surg.* 1988;7(5):642–646.
75. Plagnol P, Ciostek P, Grimaud JP, Prokopowicz SC. Autogenous valve reconstruction technique for post-thrombotic reflux. *Ann Vasc Surg.* 1999;13(3):339–342.
76. Maleti O, Lugli M, Tripathi RK. Deep venous reconstructive surgery. *Semin Vasc Surg.* 2015;28(1):39–46.
77. Maleti O. Venous valvular reconstruction in post-thrombotic syndrome. A new technique. *J Mal Vasc.* 2002;27(4):218–221.
78. Maleti O, Lugli M. Neovalve construction in postthrombotic syndrome. *J Vasc Surg.* 2006;43(4):794–799.
79. Lugli M, Guerzoni S, Garofalo M, et al. Neovalve construction in deep venous incompetence. *J Vasc Surg.* 2009;49(1):156–162. , 162.e1–2; discussion 162.
80. Maleti O, Perrin M. Reconstructive surgery for deep vein reflux in the lower limbs: techniques, results and indications. *Eur J Vasc Surg.* 2011;41:837–848.
81. Corcos L, Peruzzi G, Procacci T, et al. A new autologous venous valve by intimal flap. One case report. *Minerva Cardioangiolog.* 2003;51(4):395–404.
82. Vasudevan T, Hill AA, Gagnon J, et al. Twelve-month results of a clinical feasibility study for endovenous valve formation to treat deep vein reflux. *J Vasc Surg Venous Lymphat Disord.* 2020;8(2):314–315.
83. Opie JC, Izdebski T, Payne DN, Opie SR. Monocusp - novel common femoral vein monocusp surgery uncorrectable chronic venous insufficiency with aplastic/dysplastic valves. *Phlebology.* 2008;23(4):158–171.
84. Ignatyev IM, Akhmetzyanov RV. Long-term results of the monocusp valve formation in the common femoral vein in patients with avascular deep veins of the lower extremities. *Int Angiol.* 2017;36(2):116–121.
85. Jamieson WG, Chinnick B. Clinical results of deep venous valvular repair for chronic venous insufficiency. *Can J Surg.* 1997;40(4):294–299.
86. Perrin M. Reconstructive surgery for deep venous reflux: a report on 144 cases. *Cardiovasc Surg.* 2000;8(4):246–255.
87. Camilli S, et al. External banding valvuloplasty of the superficial femoral vein in the treatment of primary deep valvular incompetence. *Int Angiol.* 1994;13:218–222.
88. Belcaro G, Nicolaides AN, Ricci A, et al. External femoral vein valvuloplasty with limited anterior plication (LAP): a 10-year randomized, follow-up study. *Angiology.* 1999;50(7):531–536.
89. Perrin M, Hiltbrand B, Bayon JM. Results of valvuloplasty in patients presenting deep venous insufficiency and recurring ulceration. *Ann Vasc Surg.* 1999;13(5):524–532.
90. Poller L, McKernan A, Thomson JM, et al. Fixed minidose warfarin: a new approach to prophylaxis against venous thrombosis after major surgery. *Br Med J (Clin Res Ed).* 1987;295(6609):1309–1312.
91. Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. *J Vasc Surg.* 1994;19(3):391–403.
92. Wang SM, Hu ZJ, Li SQ, et al. Effect of external valvuloplasty of the deep vein in the treatment of chronic venous insufficiency of the lower extremity. *J Vasc Surg.* 2006;44(6):1296–1300.
93. Kistner RL. Surgical repair of the incompetent femoral vein valve. *Arch Surg.* 1975;110(11):1336–1342.
94. Welch HJ, McLaughlin RL, O'Donnell TFJ. Femoral vein valvuloplasty: intraoperative angioscopic evaluation and hemodynamic improvement. *J Vasc Surg.* 1992;16(5):694–700.
95. Ferris EB, Kistner RL. Femoral vein reconstruction in the management of chronic venous insufficiency. A 14-year experience. *Arch Surg.* 1982;117(12):1571–1579.
96. Lurie F, et al. Results of deep-vein reconstruction. *Vasc Surg.* 1997;31: 275–276.
97. Perrin M. Results of deep-vein reconstruction. *Vasc Surg.* 1997;31: 273–275.

98. Makarova NM, Lurie F, Hmelniker SM. Does surgical correction of the superficial femoral vein valve change the course of varicose disease? *J Vasc Surg.* 2001;33(2):361–368.
99. Goel RR, Abidia A, Hardy SC. Surgery for deep venous incompetence. *Cochrane Database Syst Rev.* 2015;(2):CD001097.
100. Guarnera G, Furgiuele S, Mascellari L, et al. External banding valvuloplasty of the superficial femoral vein in the treatment of recurrent varicose veins. *Int Angiol.* 1998;17(4):268–271.
101. Johnson ND, Querl LA, Flinn WR, et al. Late objective assessment of venous valve surgery. *Arch Surg.* 1981;116(11):1461–1466.
102. Eklof BG, Kistner RL, Masuda EM. Venous bypass and valve reconstruction: long-term efficacy. *Vasc Med.* 1998;3(2):157–164.
103. Taheri SA, et al. Indications and results of vein valve transplant. *J Cardiovasc Surg.* 1986;27:163–168.
104. Rai DB, Lerner R. Chronic venous insufficiency disease. Its etiology. A new technique for vein valve transplantation. *Int Surg.* 1991;76(3):174–178.
105. Sottiurai VS. Results of deep-vein reconstruction. *Vasc Surg.* 1997;31:276–278.

# Iliocaval Venous Obstruction: Surgical Treatment

YVES S. ALIMI SR. and OLIVIER HARTUNG

## SURGICAL TREATMENT OF ILOCAVAL VENOUS OBSTRUCTION 2112

### ETIOLOGY 2112

#### PREOPERATIVE EVALUATION 2113

History and Physical Examination 2113

Imaging 2114

#### INDICATIONS FOR SURGICAL TREATMENT 2114

#### GRAFTS IN THE VENOUS SYSTEM 2114

Venous Graft Materials 2115

Use of Arteriovenous Fistulae 2115

Anticoagulation 2116

Graft Surveillance 2116

#### SURGICAL PROCEDURES 2116

Cross-Pubic Venous Bypass (Palma Procedure) 2116

Technique 2116

Results 2117

#### Prosthetic Femorocaval, Iliocaval, and Inferior Vena Caval Bypasses 2117

Technique 2117

Results 2118

#### Combined Endovascular and Open Reconstructions 2119

#### Iliac Vein Decompression 2120

Technique 2120

### Results 2123

#### Suprarenal Inferior Vena Cava Reconstruction 2123

Technique 2123

Results 2123

#### Summary 2123

#### PELVIC CONGESTION SYNDROME 2124

Incidence 2124

Anatomy of the Pelvic Venous System 2124

Pathophysiology 2125

Clinical Findings 2125

Diagnosis 2125

DUPLEX SCANNING 2125

COMPUTED TOMOGRAPHIC AND MAGNETIC RESONANCE

VENOGRAPHY 2126

CONTRAST PHLEBOGRAPHY 2126

Differential Diagnosis 2127

#### Treatment 2127

Medical Treatment 2127

Conventional and Laparoscopic Surgery 2128

Endovascular Treatment 2128

TECHNIQUES 2128

#### CHAPTER ALGORITHMS 2130

## SURGICAL TREATMENT OF ILOCAVAL VENOUS OBSTRUCTION

The first successful venous reconstruction in a patient was reported more than 50 years ago by Warren and Thayer<sup>1</sup>; in the past 2 decades improvements in diagnosis, patient selection, surgical technique, and the availability of better graft materials have resulted in more frequently successful implantation of venous bypasses in patients.<sup>2</sup> More recently, endovascular treatment for iliac caval obstruction has progressed rapidly, and currently venous stenting is the primary choice for treatment of benign iliac or iliac caval venous occlusions. However, surgical treatment remains

an excellent option in cases in which endovascular techniques have failed or are not possible. The endovascular treatment for iliac caval obstruction is addressed in Chapter 161 (Iliac Venous Obstruction: Endovascular Treatment).

## ETIOLOGY

Deep venous thrombosis (DVT) is the most common cause of venous obstruction. Venous occlusion may also be due to trauma, radiation, external compression by retroperitoneal fibrosis or overlying arteries (May–Thurner syndrome),<sup>3,4–7</sup> benign, malignant, primary, or metastatic tumors<sup>8–10</sup>; cysts;

aneurysms; abnormally inserted muscle bands (popliteal vein entrapment)<sup>11</sup>; and fibrous bands or ligaments (soleal arch syndrome, femoral vein compression by the inguinal ligament<sup>12</sup>).

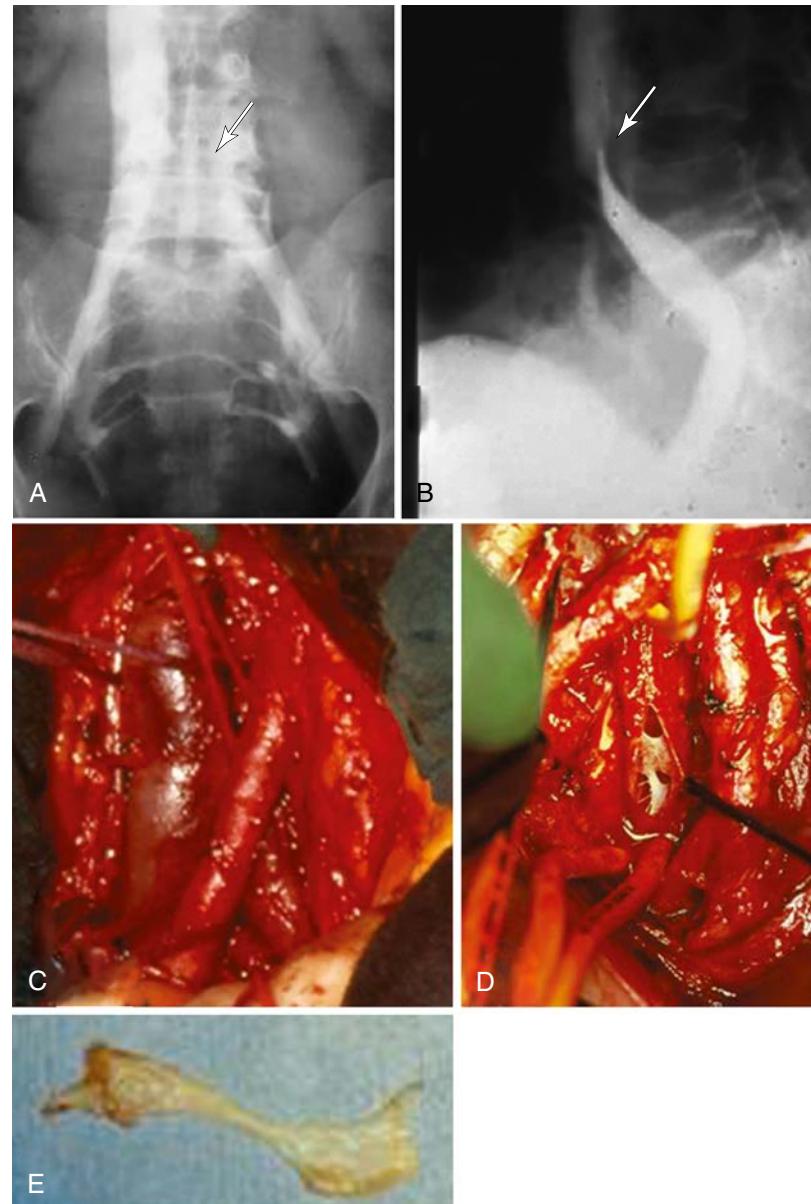
Compression of the left common iliac vein by the overriding right common iliac artery (May–Thurner syndrome) (Fig. 160.1) is considered an important cause of left iliofemoral venous thrombosis.<sup>4–7</sup> May and Thurner observed secondary changes, such as intraluminal webs or “spurs,” in the proximal left common iliac vein in 20% of 430 autopsies.<sup>3,4–7</sup> Other causes of iliofemoral and caval thrombosis include congenital anomalies, such as membranous occlusion of the suprahepatic inferior vena cava (IVC) with or without associated thrombosis of hepatic veins (Budd–Chiari syndrome),<sup>13</sup> aplasia, and hypoplasia of the iliofemoral veins as in Klippel–Trénaunay syndrome.<sup>14,15</sup>

## PREOPERATIVE EVALUATION

Preoperative evaluation in patients with iliofemoral and/or iliocaval venous obstruction should reveal the cause and functional significance of the obstruction and the extent and severity of associated venous incompetence. In at least two-thirds of patients with venous outflow obstruction, distal reflux due to valvular incompetence contributes greatly to development of chronic venous insufficiency (CVI).<sup>16</sup>

## History and Physical Examination

The history and physical examination, complemented by examination with a handheld Doppler instrument, should reveal signs and symptoms typical of venous congestion. Patients



**Figure 160.1** Compression of the Left Common Iliac Vein by the Right Common Iliac Artery (May–Thurner Syndrome). Anterior (A) and lateral (B) phlebograms. The arrow indicates compression of the vein by overriding artery. (C) Intraoperative view. (D) Intraoperative visualization of the webs inside the left common vein. (E) Intraluminal web after removal.

have lower extremity swelling and experience exercise-induced pain in the thigh muscles, referred to as venous claudication. This pain is described as a “bursting” pain in the thigh and sometimes the calf, which is relieved by rest and leg elevation.<sup>17</sup>

Signs of CVI, such as edema, varicose veins, skin changes, lipodermatosclerosis, eczema, and ulceration, should be noted. Distended varicose veins are present even in the supine patient with CVI, and suprapubic and abdominal wall collaterals develop in patients with pelvic occlusion. Bleeding from high-pressure varicosities is not infrequent. The swollen leg has a cyanotic hue, and bilateral swelling indicates bilateral iliofemoral or vena caval occlusion or systemic disease. In some patients, venous congestion results in hyperhidrosis and significant fluid loss through the skin. Associated chronic high-output or low-output lymphedema may also develop.<sup>18</sup>

Preoperative evaluation should identify risk factors for DVT (see Chs 146, Acute Deep Venous Thrombosis: Epidemiology and Natural History and 148, Acute Lower Extremity Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment). Associated chronic arterial occlusive disease and congenital venous malformations (Klippel–Trénaunay syndrome, Parkes Weber syndrome) should be excluded. Patients with membranous occlusion of the vena cava frequently also have evidence of hepatic failure, Budd–Chiari syndrome, and portal hypertension.<sup>13</sup>

## Imaging

Duplex ultrasound scanning (DUS) is the first test of choice to identify DVT. However, depending upon factors such as the presence of overlying bowel gas and increased body fat, the IVC and proximal iliac veins may be difficult to image in enough detail to guide further treatment. In these cases, computed tomographic venography (CTV) or magnetic resonance imaging (MRI) can be performed. These tests are also important in identifying causes of ilio caval venous thrombosis, including tumor, cyst, retroperitoneal fibrosis, and iliac venous compression.<sup>19</sup>

Abnormal DUS findings associated with ilio caval occlusion, such as absent flow in the iliac veins and loss of phasicity of flow in the distal veins, are discussed more fully in Chapters 25 (Vascular Laboratory: Venous Duplex Scanning) and 156 (Postthrombotic Syndrome: Natural History, Pathophysiology, and Etiology).

Ambulatory venous pressure measurements may suggest venous hypertension; measurements of arm–foot pressure differences, as described by Raju can also be used to quantitate venous hypertension. In their study a resting arm–foot pressure differential greater than 4 mm Hg was considered evidence for significant obstruction justifying venous reconstructions.<sup>20</sup> In potential candidates for proximal venous reconstruction, femoral and central venous pressure measurements are required in our practice to document the severity of iliac or ilio caval obstruction. Either a pressure difference of at least 5 mm Hg between the femoral and the central pressures in the supine patient or a twofold increase in femoral vein pressure after exercise indicates hemodynamically significant proximal stenosis or occlusion.

In patients being considered for venous reconstruction, we perform both ascending and descending catheter-based

phlebography to evaluate obstruction and associated valvular incompetence.<sup>21,22</sup> Femoral access is useful not only for descending phlebography and iliacavography but also for measuring femoral venous pressures. Iliocavography and abdominal venacavography through a brachial approach may also be necessary in some patients to visualize the vena cava proximal to the occlusion.

## INDICATIONS FOR SURGICAL TREATMENT

Prior to the development of endovascular techniques for the treatment of venous disease, surgery was the only option following failures of conservative management. However, with the development and success of advanced endovascular treatments (see also Ch. 161, Iliocaval Venous Obstruction: Endovascular Treatment),<sup>23–26</sup> surgery is now generally reserved for cases in which endovascular treatment fails or is deemed inappropriate. The severity of venous stenosis, the location and length of venous occlusion, the age of the thrombus, the nature of any external compression, the presence of underlying malignant disease, and the risks of surgical intervention also play a role in determining whether to attempt endovascular or direct surgical reconstruction. Currently, we first attempt endovascular treatment, alone or in combination with thrombolysis, surgical thrombectomy, or excision of old thrombus from the femoral veins, before a surgical bypass is recommended.

Proper patient selection is important; the ideal patient has unilateral iliac occlusion with minimal distal thrombus and valvular competence. Patients with severe infrainguinal post-thrombotic disease and valvular incompetence may have a decreased chance of success because the distal disease is not treated. In a series published by the Mayo Clinic, there was a trend toward a higher rate of graft occlusion in patients with infrainguinal reflux.<sup>27</sup>

## GRAFTS IN THE VENOUS SYSTEM

Grafts placed in the venous system undergo thrombosis more frequently than those implanted for arterial reconstruction, in part because flow in venous grafts is lower. Pressure in the venous system is low, and grafts can collapse under increased abdominal pressure or in tightly confined spaces, such as the area under the inguinal ligament and the retrohepatic space, or when tunneled through the diaphragm. Many patients with previous DVT have hypercoagulable states. The thrombogenic surface of the prosthetic graft also increases the risk of graft failure.<sup>27</sup>

As a result of extensive efforts made in the past decades, patency of grafts implanted in the venous circulation has improved considerably.<sup>28–41</sup> The availability of large-diameter autologous and prosthetic grafts, use of adjuncts such as a distal arteriovenous fistula, rigid external support of the grafts, perioperative and postoperative anticoagulation, the use of perioperative intermittent-compression pumps, and postoperative surveillance with duplex scanning all contribute to improved patency and clinical outcomes.

## Venous Graft Materials

Autogenous grafts for the femorofemoral, iliofemoral, and ilio caval locations have the best chance of long-term success. The great saphenous vein, because of its low thrombogenicity and suitability in terms of length, is the best choice when available. As a spiral or panel graft, it can be used for the reconstruction of large veins, although in our experience these grafts do not perform as well for iliocaval reconstructions as they do for superior vena caval replacement.<sup>21,22</sup> The contralateral superficial femoral vein, arm veins, and the jugular veins are other potential sources of autogenous grafts. Although harvesting of deep veins was initially believed to result in a high level of CVI in the lower extremity, more recent data suggest it is relatively benign in the majority of patients. The only factors found to be associated with venous morbidity following lower extremity deep vein harvest in a recent study were an ankle–brachial index less than 0.4 and a concurrent great saphenous vein harvest.<sup>42</sup>

The efficacy of cryopreserved vein or arterial grafts in the venous circulation has not been well studied. A few reports exist regarding their use in reconstruction of the superior vena cava and innominate veins.<sup>43</sup> Data at this point are insufficient to support the recommendation of these grafts for routine clinical use.

Of the available prosthetic materials, the expanded polytetrafluoroethylene (ePTFE) graft has been used most frequently for large vein replacement.<sup>3,8,9,10,21,22,44–50</sup> Because of the large diameter, sufficient length, immediate availability, and external ring or spiral support associated with relatively low thrombogenicity, ePTFE grafts continue to be the best choice for prosthetic replacement of large veins.

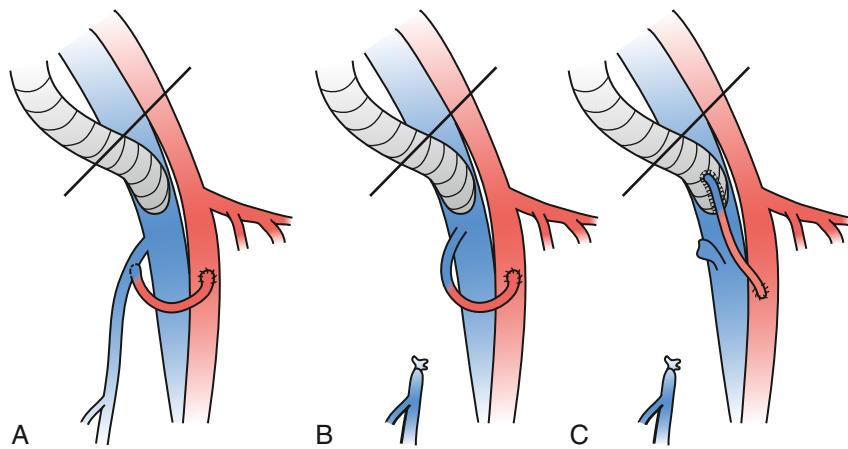
## Use of Arteriovenous Fistulae

Multiple studies have confirmed that a distal arteriovenous fistula, first suggested by Kunlin and Kunlin in 1953,<sup>33</sup> improves the patency of grafts placed in the venous system.<sup>27,28,31,36,37,51</sup> An arteriovenous fistula increases flow and decreases platelet and fibrin deposition in prosthetic grafts (Fig. 160.2).<sup>36</sup> Prosthetic grafts have significantly higher thrombotic threshold velocities than do autologous grafts and require higher flow to maintain patency.

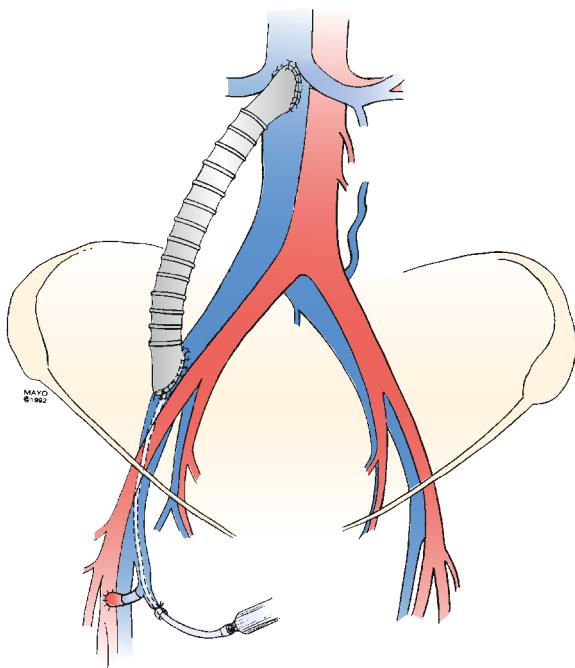
Disadvantages of an arteriovenous fistula include the longer operating time needed to create the fistula and the inconvenience of additional procedures to close the fistula at a later date. A potential side effect is elevated cardiac output caused by high fistula flow. In addition, high fistula flow can defeat the purpose of the operation by increasing venous pressure at the groin and causing more distal venous outflow obstruction. Experimental work revealed that to avoid deleterious effects on venous outflow from the leg, the optimal ratio between the diameters of the fistula and the graft should not exceed 0.3. Elevated intraoperative pressure in the femoral vein after placement of a fistula should be taken as a warning sign, and fistula diameter should be decreased by banding or other modifications.

The configuration and location of the fistula have also been the subject of much controversy. A large side branch of the great saphenous vein or the saphenous vein itself can be used to perform one anastomosis only. Most recently, we have placed the venous end of the arteriovenous fistula directly onto the hood of the venous graft at the distal anastomosis, using either a 4-mm vein as a free graft (saphenous vein or a large tributary) or a 4-mm ePTFE graft. The advantage of these is that flow can be calibrated with an electromagnetic flowmeter, and large flows (>300 mL/min) can then be avoided. The arterial anastomosis is usually made to the superficial femoral artery. The occlusion of the AV fistula is now currently performed endovascularly, by placing occlusion devices (coils, Amplatzer) in the fistula, through a contralateral arterial puncture. We also place a small polymeric silicone (Silastic) sheet around the fistula to prevent healing and to facilitate dissection of the fistula during a second procedure to occlude it, in case of endovascular failure. A 2-0 polypropylene suture is also tied loosely around the fistula, and its end is positioned in the subcutaneous tissue close to the incision for later identification. Intraoperative duplex scanning can be used later to identify the fistula. Percutaneous closure of the fistula with transcatheter embolization or a covered stent placed across the arterial side are also options.

At present, for all prosthetic grafts anastomosed to the femoral vein and all longer (>10 cm) iliocaval grafts, a femoral arteriovenous fistula is added to maintain patency (see Fig. 160.2). The fistula is left in place for at least 6 weeks after the operation, and patients without any side effects benefit from



**Figure 160.2** Different Types of Arteriovenous Fistulae Placed Distally to a Ringed Expanded Polytetrafluoroethylene (ePTFE) Femoral Venous Graft. The sphenofemoral junction is preserved with the use of either a branch of the great saphenous vein (A), or the main trunk of the great saphenous vein (B). (C) The sphenofemoral junction is divided and the main trunk of the great saphenous vein is directly anastomosed to the ePTFE graft.



**Figure 160.3** Illustration of a right iliac vein/inferior vena caval externally supported polytetrafluoroethylene graft. Note the arteriovenous fistula at the right groin and a 20-gauge catheter, which is introduced through a tributary of the saphenous vein for perioperative heparin infusion. (From Gloviczki P, Pairolero PC, Toomey BJ, et al. Reconstruction of large veins for nonmalignant venous occlusive disease. *J Vasc Surg*. 1992;16:750, with permission of Mayo Foundation.)

long-term fistula flow to prolong patency. For the Palma procedure (described later), we use a fistula selectively and take it down within 2 months after surgery.

### Anticoagulation

Intravenous heparin, at a dose of 50IU/kg, is given in surgery prior to cross-clamping, and anticoagulation is maintained during and after the procedure in most patients. We frequently administer low-dose heparin (500–800IU/h) locally through a small polyethylene catheter placed just distal to the anastomosis in the perioperative period (Fig. 160.3). This is continued until complete systemic heparinization is achieved by 48 hours after surgery. The catheter is then removed, heparinization is continued intravenously or by using low-molecular-weight heparin, and the patient begins oral anticoagulation therapy with warfarin.

An intermittent pneumatic compression pump, leg elevation, elastic bandages, and early ambulation are also used in the perioperative period to improve the success of venous reconstruction.<sup>52</sup> The patient is fitted with 30- to 40-mm Hg graduated-compression elastic stockings before discharge. Warfarin is continued in patients with autogenous grafts for at least 3 months. In most patients with prosthetic grafts or an underlying coagulation abnormality, oral anticoagulation is maintained indefinitely.

### Graft Surveillance

Intraoperative duplex scanning is performed in most patients to ensure patency, good flow, and lack of thrombus deposition. Direct pressure measurements are made before wound closure in every patient to document the hemodynamic benefit. In

venous or ePTFE conduits, fistula flow can be measured and calibrated with an electromagnetic flowmeter. If flow is higher than 300 mL/min, banding of the fistula is performed.

On the first postoperative day, we perform contrast phlebography through the catheter positioned at the distal anastomosis of the graft (see Fig. 160.3). Any stenosis or thrombosis detected at this time is revised during a reoperation. Postoperatively, grafts are observed with duplex scanning at 3 and 6 months and then twice yearly thereafter. Outflow plethysmography is also performed to document the level of hemodynamic impairment/improvement in the lower extremity. In symptomatic patients, contrast phlebography is usually performed to exclude graft stenosis.

## SURGICAL PROCEDURES

### Cross-Pubic Venous Bypass (Palma Procedure)

Initially described 40 years ago by Palma and Esperon<sup>53,54</sup> in Uruguay and popularized by Dale<sup>55</sup> in the United States, the Palma procedure has remained a useful technique for venous reconstruction in patients with unilateral iliofemoral outflow obstruction (Figs. 160.4 and 160.5). The operation requires a normal contralateral iliofemoral venous system to ensure venous drainage. Results have been better in patients with intact inflow, when the affected limb has no infrainguinal obstruction or deep venous incompetence.<sup>27,56</sup>

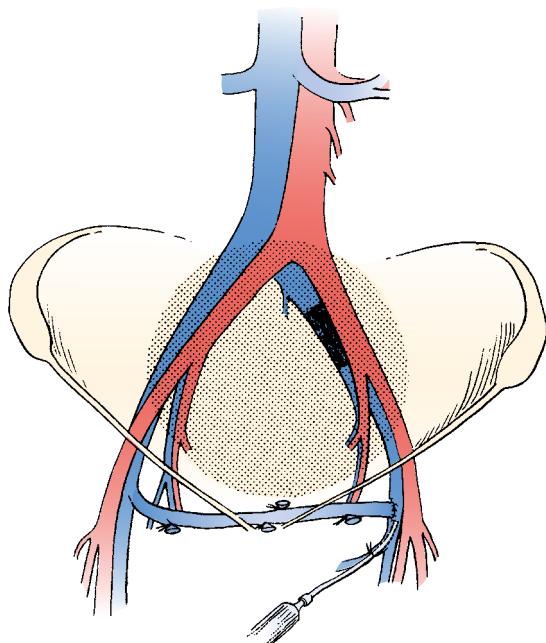
We favor this operation especially in young women who present with residual chronic iliac vein occlusion after acute left iliofemoral venous thrombosis which develops as a result of May–Thurner syndrome. The operation is indicated in patients who are not candidates for iliac vein stenting or in whom previous endovascular procedures have failed.

### Technique

The contralateral great saphenous vein is used in the classic Palma procedure (see Fig. 160.5). Preoperative imaging of the potential conduit with duplex scanning is recommended because varicose saphenous veins or veins smaller than 4 mm in diameter have poor chances of long-term success.

Endoscopic harvesting of a 25- to 30-cm segment of the contralateral saphenous vein ensures an excellent cosmetic result; otherwise, the vein can be dissected through two or three small skin incisions. It is divided in the distal thigh or calf and remains attached at the saphenofemoral junction. Tributaries are also ligated and divided.

The graft is gently distended and tunneled to the contralateral groin in a suprapubic, subcutaneous position. Dissection of the femoral vein on the affected side should be minimal; usually, only the anterior and lateral vein wall is freed for proximal and distal clamps or for a side-biting clamp to occlude the vein for the anastomosis. Excision of intraluminal fibrous bands after venotomy may be required. The anastomosis between the saphenous and femoral veins is performed in an end-to-side technique. If the vein is small, interrupted 5-0 or 6-0 sutures are preferred to permit later dilation of the vein and to avoid “purse-stringing” of the venous anastomosis. A small catheter



**Figure 160.4** Left-to-right femorofemoral venous bypass (Palma procedure) for left common iliac vein obstruction. A small polyethylene catheter can be placed through a side branch of the greater saphenous vein for immediate perioperative heparinization to improve chances of patency. (From Rhee RY, Gloviczki P, Luthra HS, et al. Iliocaval complications of retroperitoneal fibrosis. *Am J Surg*. 1994;168:179.)

can be placed through a tributary of the ipsilateral saphenous vein for immediate low-dose heparinization and postoperative phlebography (see Fig. 160.5). A temporary arteriovenous fistula can also be placed to improve flow and aid in achieving early patency.

If the traditional transposition results in significant kinking of the saphenous vein at the contralateral groin, free vein grafting should be considered, excising the saphenous vein along with a small rim of the common femoral vein and reimplanting it after a 180-degree turn. For autogenous graft material, the contralateral or even the ipsilateral saphenous vein (with lysis of any competent valves) or an arm vein can be used. When suitable autogenous conduit is not available, an 8- or 10-mm externally supported ePTFE graft is the best alternative (Fig. 160.6).<sup>48,57</sup>

## Results

Analysis of results of 433 operations published in 10 series revealed clinical improvement in 63% to 89% of patients (Table 160.1).<sup>27,44,48,54,55,58–63</sup> Reported patency rates ranged from 70% to 85%, but follow-up periods were variable and objective graft assessment with imaging was rarely performed in all patients. The largest series, 85 crossover venous bypasses, was reported by Husni.<sup>58</sup> At the last follow-up visits (6 months to 15 years postoperatively), 47 of 67 grafts were patent. Results in this study were improved when a temporary distal arteriovenous fistula was used. The patency rate of grafts implanted for extrinsic compression of the iliac vein without distal disease was 100%, as opposed to 67% in patients with post-thrombotic syndrome.<sup>58</sup> In a review of 50 consecutive operations

performed in 47 patients, Halliday and associates reported a cumulative patency rate of 75% at 5 years confirmed by phlebography. Clinical improvement was seen in 89% of patients.<sup>61</sup> Danza and colleagues reported somewhat better results with use of the saphenous vein as a free graft rather than as a transposition. Of 19 patients who underwent free saphenous vein grafting, 84% experienced either symptomatic relief or improvement versus 75% of 8 patients who underwent transposition.<sup>60</sup> Gruss<sup>64</sup> and Gruss and Hiemer<sup>48</sup> reported “long-term patency” (no time interval reported) in 22 of 26 grafts. On the basis of these results, Gruss recommended using externally supported ePTFE grafts with arteriovenous fistulae for all cross-femoral venous bypasses.<sup>48,64</sup>

Plethysmographic evidence of outflow obstruction was an independent predictor of clinical outcome in a report by AbuRahma and coworkers. Of their patients, 88% undergoing the Palma procedure who had abnormal preoperative maximum venous outflow showed significant clinical improvement, whereas 86% of those with normal preoperative maximum venous outflow had no improvement after surgery.<sup>59</sup>

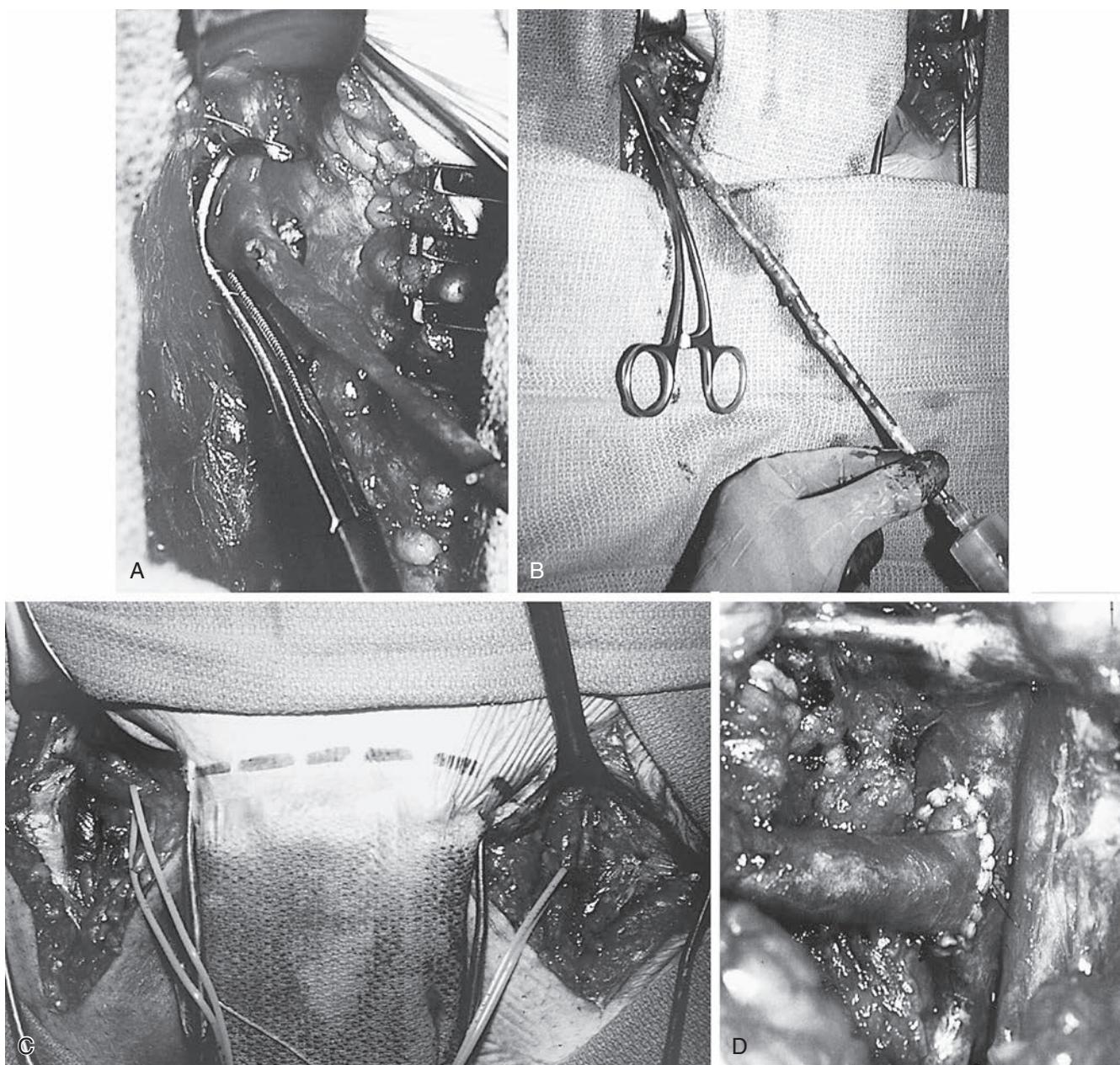
## Prosthetic Femorocaval, Iliocaval, and Inferior Vena Caval Bypasses

Anatomic in-line iliac or iliocaval prosthetic reconstruction can be performed for (1) unilateral disease when autogenous conduit for suprapubic grafting is not available or (2) bilateral iliac, iliocaval, or inferior vena caval occlusion. Extensive ilio-caval venous thrombosis secondary to inferior vena caval filters or tumors, as well as retroperitoneal fibrosis not responding to nonoperative therapy, are potential indications. Failure of previous endovascular attempts and occlusion after placement of multiple stents are also indications for bypass.

### Technique

The femoral vessels (for the arteriovenous fistula or for the site of the distal anastomosis) are exposed at the groin. The iliac vein or the distal segment of the IVC is exposed with a right oblique flank incision through a retroperitoneal approach. The vena cava at the level of the renal veins is best exposed through a midline or a right subcostal incision. The ascending colon is mobilized medially, and the vena cava is exposed. The infrarenal IVC is reconstructed with a 16- to 20-mm graft, the ilio caval segment usually with a 14-mm graft, and the femorocaval segment with a 10- to 12-mm graft. The arteriovenous fistula is constructed first in patients who undergo an iliocaval bypass (see Figs. 160.3, 160.7 and 160.8).

A short iliocaval bypass with a significant pressure gradient can be performed without an arteriovenous fistula. Reconstruction of the vena cava with a straight ePTFE graft, if inflow is good, is also usually performed without an arteriovenous fistula. In patients who undergo femorocaval bypass, we perform the proximal and distal anastomoses of the bypass first and then create the arteriovenous fistula before opening the graft. As discussed previously, we generally use a tributary of the great saphenous vein for the fistula. The operation is performed with the patient fully anticoagulated, and prior to closure, a small



**Figure 160.5** (A) Technique of Palma procedure: the contralateral saphenous vein is dissected, and its distal end divided in the thigh; then a vascular clamp is placed on the common femoral vein. (B) The vein is distended with papaverine solution. (C and D) The saphenous vein is tunneled to the left groin and anastomosed end to side to the common femoral vein. A femoral arteriovenous fistula is constructed and encircled with a Silastic sheath for easy identification for takedown 3 months later.

polyethylene catheter is placed to the level of the distal anastomosis to infuse low-dose heparin (500 IU/h).

### Results

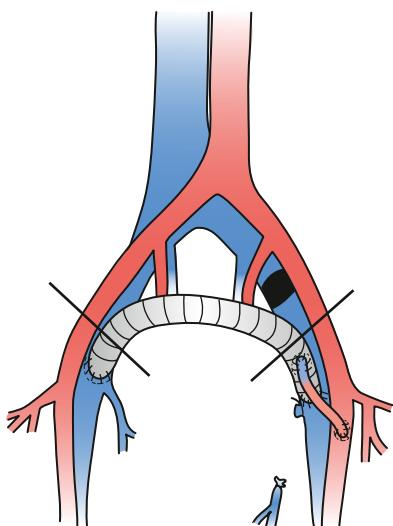
Experience with femorocaval or iliac caval bypass is limited; only a few series have been published (Table 160.2).<sup>22,27,46,47,65</sup> In a Mayo Clinic series of 17 such bypasses, primary and secondary patency rates at 5 years were 63% and 86%, respectively.<sup>27</sup>

Alimi and colleagues reported the results of eight iliac vein reconstructions with femorocaval or iliac caval bypasses for both acute and chronic obstructions. In four patients with chronic obstruction, three grafts were patent at last follow-up.<sup>46</sup> Eklof

and associates observed only one occlusion in five grafts followed for 14 to 22 months after surgery, in which bypass was combined with venous thrombectomy for acute DVT.<sup>66</sup> In 2003, the Mayo Clinic group published long-term results of femoroiliac, femorocaval, and iliac caval prosthetic bypasses. They observed 5-year secondary patency rates of 86% for femoroiliac and iliac caval bypasses and 57% for femorocaval bypasses. The only factor affecting long-term patency was the presence of May-Thurner syndrome.<sup>56</sup> We believe that all femorocaval or longer iliac caval grafts require the benefit of a distal arteriovenous fistula to maintain patency. Our policy now is to keep the fistula patent as long as possible.<sup>27,51</sup>

## Combined Endovascular and Open Reconstructions

The combination of long iliac vein occlusions with chronic thrombosis of the common femoral vein precludes effective venous stenting. In these patients, open surgical thrombectomy of the common femoral vein with excision of old thrombus and recanalized intimal strands can be combined with intraoperative iliac or iliofemoral vein stenting. We perform these procedures in a hybrid operating room. A saphenous vein or



**Figure 160.6** Diagram of a right-to-left expanded polytetrafluoroethylene femorofemoral crossover vein graft (Palma procedure). Note the fistula in the right groin, extending from the proximal superficial femoral artery to the hood of the graft. (From Jost CJ, Gloviczki P, Cherry KJ Jr, et al. Surgical reconstruction of iliofemoral veins and the inferior vena cava for nonmalignant occlusive disease. *J Vasc Surg*. 2001;33:320–328.)

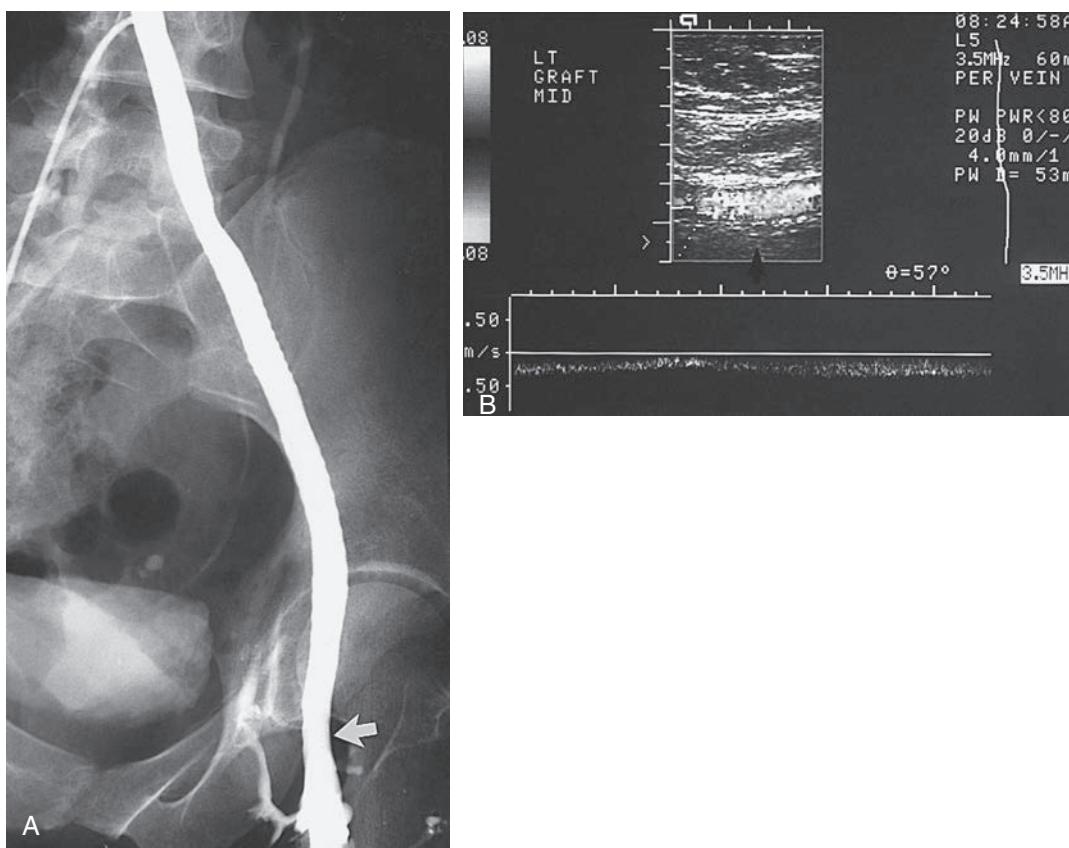
bovine pericardial patch can be used to close the defect after thrombectomy in the femoral vein (Figs. 160.9 and 160.10). Two-year patency rates of these hybrid reconstructions were published in a Mayo Clinic series, including four patients with stent placement extending into the common femoral vein patch and five patients with the stent terminated proximal to the common femoral patch. All of the latter experienced early thrombosis; two underwent further stenting into the common femoral vein at the time of revision. Two-year secondary patency in patients with common femoral vein extension ( $n = 6$ ) was 67% compared with 0% without common femoral vein stent ( $n = 3$ ).<sup>56</sup>

More recently, Comerota et al.<sup>67</sup> published a series of 31 patients with incapacitating post-thrombotic iliofemoral obstruction involving the common femoral vein who underwent hybrid operative procedure between 2008 and 2016. After a mean follow-up duration of  $14.4 \pm 2.9$  months (range, 10–29 months), primary and secondary patency at 12 months were 81% and 89.5%, respectively, the mean pre- and postoperative venous clinical score and Villalta score decreased from  $15.3 \pm 2.2$  to  $6.1 \pm 1.8$  ( $P < 0.01$ ), and from  $12.7 \pm 2.6$  to  $6.3 \pm 1.4$  ( $P < 0.01$ ), respectively, with significant improvement in quality of life. When comparing the first 17 patients with the last 14 patients, the rate of major complications decreased from 88% to 14%, which lead the authors to recommend routine preoperative axial imaging including venography through the popliteal vein, preoperative passage of a guide wire or catheter into the patent vena cava, placement of an ipsilateral popliteal vein sheath for intraoperative and postoperative anticoagulation, routine patch closure, routine arteriovenous fistulas, routine completion intravascular ultrasound and long-term anti-coagulation with warfarin to a target international normalized ratio of 3.0 to 4.0.

**TABLE 160.1** Published Results of Femorofemoral Crossover Bypass

First Author	Year	No. of Limbs	Follow-Up (Year)	Postoperative Imaging (%)	Patency Rate (%)	Clinical Improvement (%)	Graft Material
Palma <sup>54</sup>	1960	8	Up to 3	13	N/A	88	Vein
Dale <sup>55</sup>	1979	48	Up to 12	N/A	N/A	77	Vein
May <sup>44</sup>	1981	66	N/A	N/A	73	N/A	Vein
Dale <sup>63</sup>	1969	56	N/A	N/A	N/A	80	Veins
Husni <sup>58</sup>	1983	85	0.5–15	N/A	70	74	Vein ( $n = 83$ ) PTFE ( $n = 2$ )
Halliday <sup>61</sup>	1985	47	Up to 18	72	75 (5-year cumulative)	89	Vein
Danza <sup>60</sup>	1991	27	N/A	N/A	N/A	81	Vein
AbuRahma <sup>59</sup>	1991	24	5.5	100	75 (7-year cumulative)	63	Vein
Gruss <sup>48</sup>	1997	19	N/A	N/A	71	82 overall	Vein
		32	N/A	N/A	85		PTFE
Jost <sup>27</sup>	2001	18	2		Primary 77; secondary 83		Vein
		3			0		PTFE

PTFE, polytetrafluoroethylene.



**Figure 160.7** (A) Venogram 1.6 years after implantation in a 36-year-old female patient confirms widely patent 10-mm polytetrafluoroethylene graft. Arrow indicates site of the end-to-end femoral anastomosis. (B) This patient is free of symptoms 10 years after the operation with duplex evidence of graft patency.

Another series by Dumantepe et al.<sup>68</sup> gathered 157 patients treated between 2014 and 2017, with a 1-year primary and secondary bypass patency of 81% and 89.5%. The mean venous clinical severity score decreased from  $15.3 \pm 2.2$  to  $6.1 \pm 1.8$  ( $P < 0.001$ ) and the mean Villalta score dropped from  $12.7 \pm 2.6$  to  $6.3 \pm 1.4$  ( $P < 0.001$ ), with a significant improvement at 3 months of both the quality of life and the symptom severity score. Wound complications related to groin incisions were observed in 22.8% and lymphatic fistulas in 28.7% of patients.

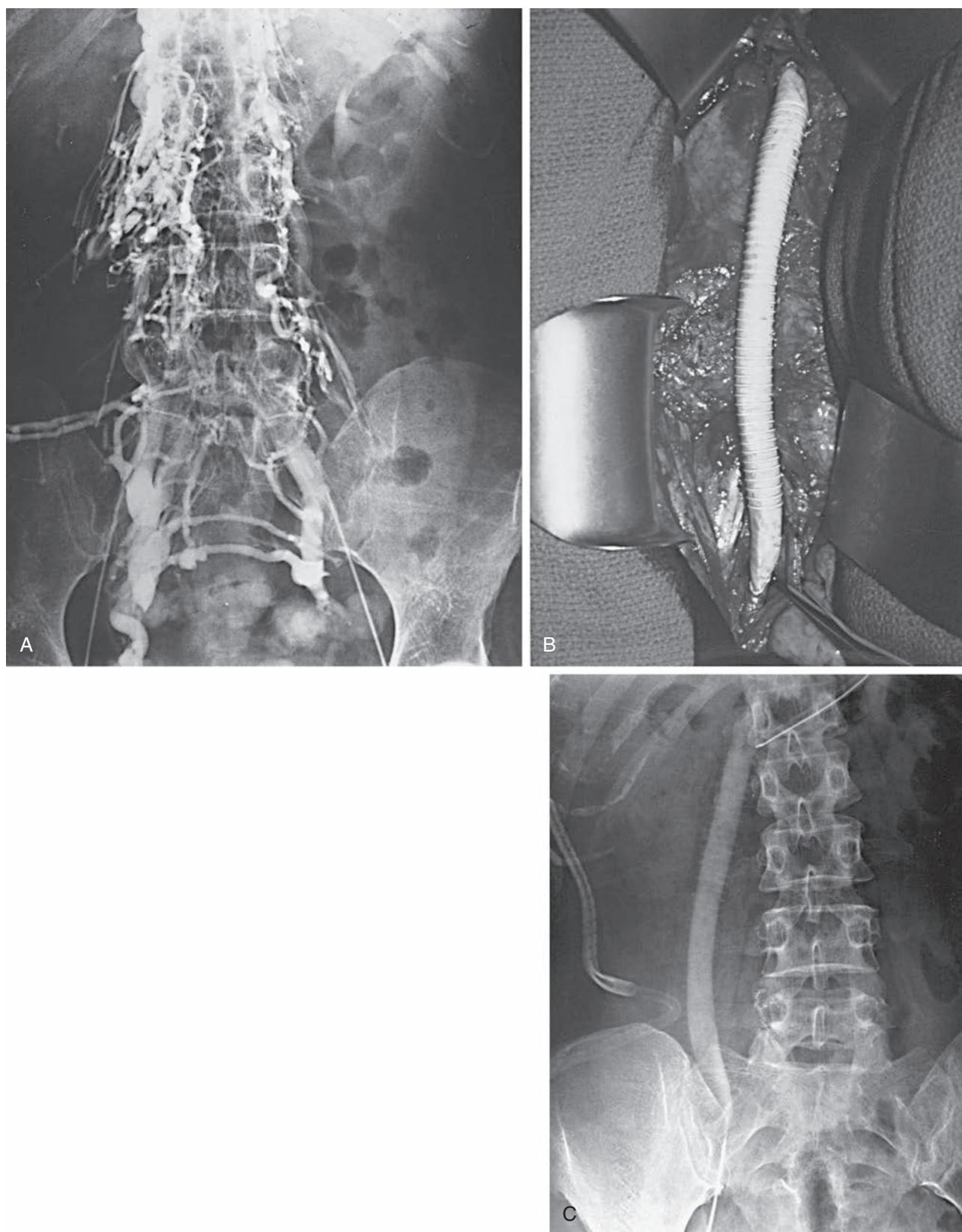
### Iliac Vein Decompression

Compression of the left iliac vein between the right common iliac artery (see Fig. 160.1) and the fifth lumbar vertebra was described first by McMurrich<sup>69</sup> in 1908 and later in much more detail in a large autopsy study by May and Thurner, who also recognized the clinical implications of the iliac "spurs" leading to acute DVT.<sup>4,70</sup> Cockett and Thomas coined the term *iliac vein compression syndrome* in 1965 and called attention to the obstructive symptoms in affected patients, who are often seen without clinical signs of previous DVT.<sup>5</sup> May–Thurner syndrome is observed more frequently in women between the second and fourth decades of life. Left lower extremity swelling, venous claudication, pain, and skin changes secondary to chronic stasis, including rare ulceration, may develop.<sup>3,5–7</sup>

An acute complication is left iliofemoral DVT. Some surgeons suggest repair of any lesion discovered,<sup>71–78</sup> but we advocate reconstruction only for symptomatic patients with previous iliofemoral DVT. Endovascular techniques with stenting are the first choice of treatment in most patients (see Ch. 161, Iliocaval Venous Obstruction: Endovascular Treatment). However, open surgery can be performed in patients in whom endovascular treatment has been unsuccessful or is considered inappropriate.

### Technique

The usual procedure is a Palma procedure. In patients with stenosis or short iliac occlusion, direct exploration of the vena caval bifurcation with the use of a variety of techniques to release the iliac venous obstruction has been recommended. The iliac vein is fully mobilized, and any external compressing bands are transected. Excision of intraluminal webs followed by vein or ePTFE patch angioplasty may be performed; other surgeons recommend transposition of the iliac artery behind the iliac vein.<sup>50,71</sup> Cormier and coworkers suggested transposition of the right common iliac artery into the left internal iliac artery to decompress the left common iliac vein.<sup>72</sup> Placement of a silicone elastic bridge over the iliac vein to prevent compression by the iliac artery, as suggested earlier, is not recommended.<sup>73</sup>



**Figure 160.8** (A and B) Extensive ilio caval obstruction in a 47-year-old patient treated with right ilio caval bypass with a right saphenous vein/common femoral artery arteriovenous fistula. (C) Postoperative venogram shows patent graft.

**TABLE 160.2** Published Results of Femorocaval/Iliocaval Bypass

First Author	Year	No. of Limbs	Follow-Up (Months)	Imaging (%)	Patency Rate (%)	Clinical Improvement (%)	Graft Material
Gloviczk <sup>22</sup>	1992	12	1–60	100	58	67	11 PTFE 1 Dacron
Husfeldt <sup>65</sup>	1981	4	4–30	100	100	100	PTFE
Dale <sup>47</sup>	1984	3	1–30	100	100	100	PTFE
Alimi <sup>46</sup>	1997	8	19.5 (mean)	100	88	88	PTFE
Jost <sup>27</sup>	2001	13	24		54		PTFE

PTFE, polytetrafluoroethylene.



**Figure 160.9** Combined Endovascular and Open Reconstruction for Chronic Iliofemoral Venous Occlusion. (A) Note old recanalized thrombus (arrow) in the common femoral vein. (B) The old thrombus was excised and the iliofemoral vein was stented with Wallstents (arrow). (C) The femoral vein was closed with bovine pericardial patch. (D) Postoperative venogram confirms widely patent iliofemoral vein.



**Figure 160.10** (A) Preoperative photograph of an 81-year-old patient with severe right lower extremity swelling and massive transudation of fluid due to right common iliac vein obstruction. Patient underwent a combined endovascular (iliac vein stenting) and open (thromboendo-venectomy of the common femoral vein). (B) Photograph 9 months after the operation confirmed excellent clinical results.

## Results

Akers and colleagues found that of 80 reported patients undergoing iliac vein decompression, 65 (81%) had significant improvement postoperatively.<sup>74</sup>

## Suprarenal Inferior Vena Cava Reconstruction

The most common reason to reconstruct the suprarenal IVC for benign disease is membranous occlusion of the IVC, which is frequently associated with occlusion of the hepatic veins (Budd–Chiari syndrome), subsequent portal hypertension, and liver failure (see Ch. 164, Portal Hypertension). Occlusion of the suprahepatic IVC usually does not always cause significant congestion of lower extremity veins, although leg edema and venous claudication may develop. If percutaneous transluminal balloon angioplasty, stenting, or transatrial dilation of the membranous occlusion has not been successful, and portosystemic shunting is not required, venacavostomy bypass is an effective technique to decompress the IVC. Most surgeons agree that an externally supported ePTFE graft is the best option.<sup>13,45,49,62</sup>

## Technique

The retrohepatic segment of the vena cava and the right atrium are exposed through a right anterolateral thoracotomy, with extension of the incision across the costal arch so that the peritoneal cavity is entered through the diaphragm. The liver is retracted anteriorly, and the paravertebral gutter is exposed together with the suprarenal segment of the IVC. The pericardium is opened anterior to the right phrenic nerve, and the right atrium is isolated. The IVC is cross-clamped with a partial-occlusion clamp above the renal vein, and a 16- to 18-mm

externally supported ePTFE graft is sutured end-to-side to the IVC. The graft is then passed parallel to the IVC to the right atrium or the suprahepatic IVC. The central anastomosis is performed after placement of a partial-occlusion clamp on the vena cava or the right atrium. Before completion of the anastomosis, air is carefully flushed from the graft to avoid air embolization.

An anterior approach was suggested by Kieffer and associates, who performed segmental replacement of the suprahepatic IVC using a short externally supported PTFE graft. Tunneling of a long cavoatrial graft anterior to the bile duct and under the left lobe of the liver was also reported (Fig. 160.11).<sup>49</sup>

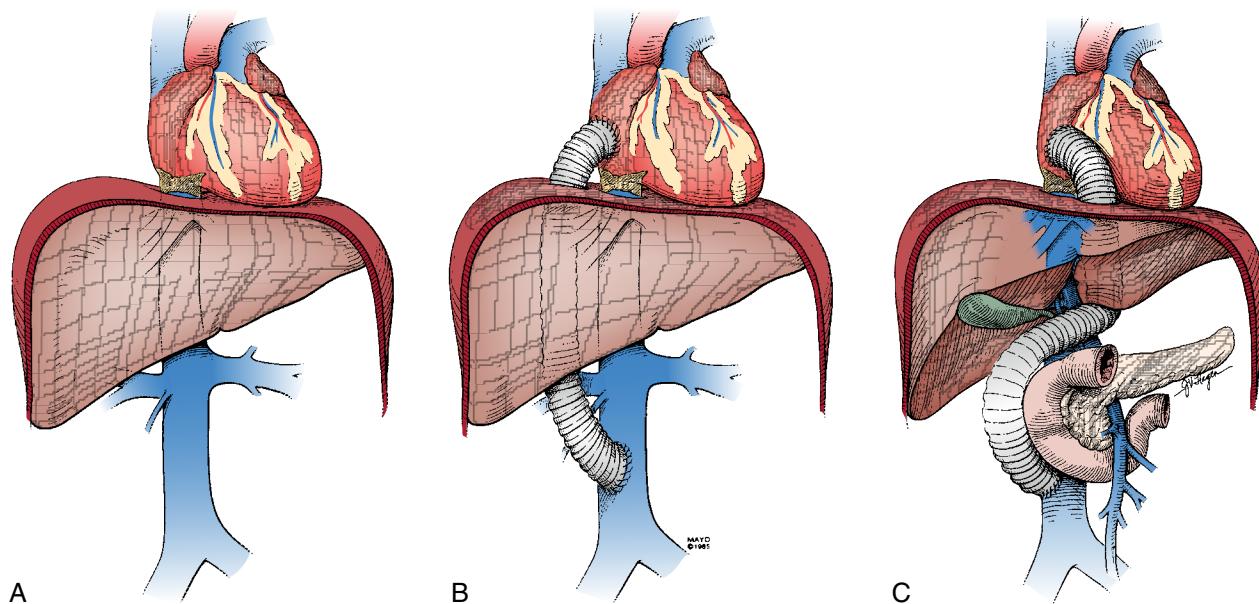
## Results

Wang and colleagues reported on 100 patients with Budd–Chiari syndrome, 12 of whom underwent cavoatrial bypasses. Clinical improvement with patent grafts was noted in 10 patients at a median follow-up period of 1.5 years after surgery.<sup>13</sup> In another series, Victor and colleagues reported patent grafts at 21 months to 6 years after the operation in five patients.<sup>62</sup>

Three cavoatrial grafts placed for nonmalignant disease were reported by the Mayo Clinic group: one patient with an ePTFE graft was asymptomatic at 10 years, a long Dacron graft became occluded at 3 years, and a spiral vein graft occluded within 1 year.<sup>27,56</sup>

## Summary

Progress in endovascular techniques has decreased the number of patients who are candidates for open surgical reconstruction for chronic occlusion of the iliofemoral veins or the IVC. Proper patient selection, attention to technical details during



**Figure 160.11** Different configurations of cavoatrial bypass performed for membranous occlusion of the inferior vena cava. Reinforced polytetrafluoroethylene graft can originate from the infrarenal (B) inferior vena cava and be routed behind the right lobe of the liver. Another potential position of the graft is behind the left lobe of the liver (C). (With permission of Mayo Foundation.)

surgery, selection of the appropriate graft, perioperative thrombosis prophylaxis, and close follow-up are important to achieve long-term success. The Palma procedure using the great saphenous vein provides predictable long-term success for patients with unilateral iliac vein occlusion. ePTFE grafting for iliac vein or IVC occlusion is also an effective tool in the treatment of carefully selected patients with advanced, symptomatic venous disease. Combined endovascular and open procedures will likely increase the success of reconstruction of the large veins in the future.

## PELVIC CONGESTION SYNDROME

The development of valvular incompetence and/or obstruction in the pelvic and gonadal veins may cause disabling symptoms, mainly in women of childbearing age; the disease is known as *pelvic congestion syndrome* (PCS). Although first described in 1857 by Richet<sup>79</sup> and given its name in 1949 by Taylor,<sup>80</sup> this pathology was recognized only recently as a frequent cause of chronic pelvic pain. It was defined by the VEIN-TERM consensus document as “pelvic pain, perineal heaviness, urgency of micturition and postcoital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices.”<sup>81</sup>

### Incidence

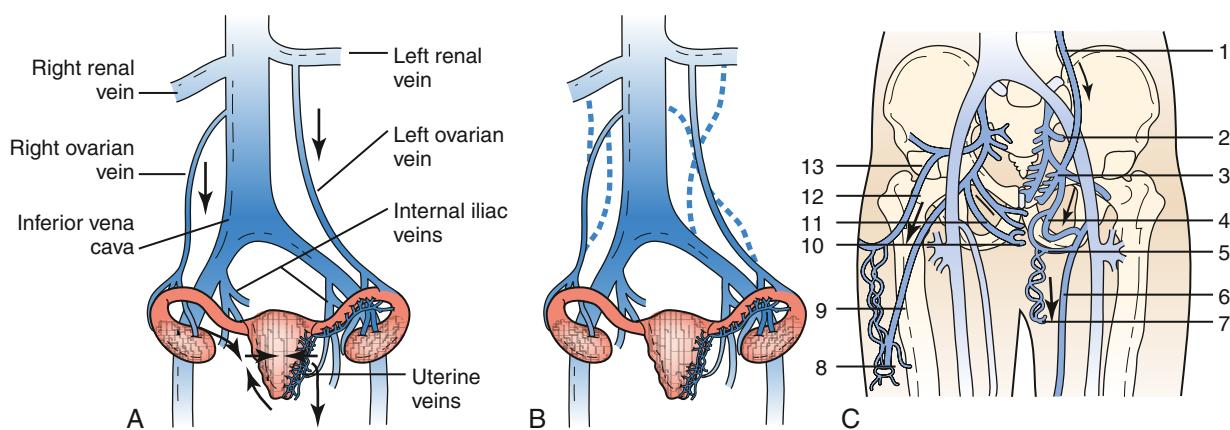
Pelvic venous incompetence (PVI) and varicose veins are found in 10% of women, and 15% of women between the ages of 18 and 50 years suffer from pelvic pain.<sup>82</sup> In a cohort of 148 patients with chronic pelvic pain, Soysal and coworkers noted that the incidence of PCS was 30%.<sup>83</sup> Belenky and colleagues found ovarian vein incompetence and varicosities in 9.9% of

the general female population, with 59% of this group experiencing symptoms of PCS.<sup>84</sup> However, because many of these symptoms can be caused by other pelvic diseases (endometriosis, uterine fibroma, pelvic cancer, etc.), initial gynecologic examinations are mandatory before reaching the diagnosis of PCS, even in the presence of pelvic varicose veins. PCS can also cause lower limb varicose veins in atypical locations or recurrence after surgical treatment.<sup>85</sup>

## Anatomy of the Pelvic Venous System

Pelvic structures are drained by both the internal iliac (hypogastric) and genital veins (Fig. 160.12).<sup>86</sup> The internal iliac vein rises near the upper part of the sciatic foramen, passes cranially posterior and medial to the internal iliac artery, and at the brim of the pelvis joins the external iliac to form the common iliac vein. Its tributaries correspond to branches of the internal iliac artery and are divided into parietal and visceral veins. Parietal tributaries are the superior and inferior gluteal, sciatic, sacral, ascending lumbar, and obturator veins. Visceral tributaries are the internal pudendal, middle hemorrhoidal, and vesicoprostatic plexuses in men and the uterine, gonadal, and vesicovaginal plexuses in women. Lepage and associates showed that in 27% of cases the internal iliac vein drains by means of two separated trunks.<sup>87</sup> In exceptional cases it can drain directly into the IVC. Valves are found infrequently in the internal iliac veins: 10% of cases in the main trunk and 9% in its tributaries.<sup>87</sup>

The ovarian veins form a plexus in the broad ligament near the ovary and uterine tube and communicate with the uterine plexus. They drain to the IVC on the right at an acute angle and on the left side to the LRV at a right angle. Anatomic variations can be present (see Fig. 160.12B). Multiple trunks can be present.<sup>88</sup> Observations based on vaginal ultrasound have



**Figure 160.12 Anatomy and Reflux of the Pelvic Veins.** (A) Anatomy. Black arrows indicate pathologic reflux in the bilateral ovarian veins and around the uterus, with varicosities developing on the left side of the uterus. (B) Anatomic variations of the ovarian veins, shown by dashed lines. (C) Internal iliac veins and their communications with the utero-ovarian plexus and thigh superficial veins: 1, ovarian vein; 2, internal iliac vein; 3, uterine vein; 4, obturator vein; 5, external pudendal vein; 6, great saphenous vein; 7, varicosity of the anteromedial aspect of the thigh; 8, varicosity of the posterolateral aspect of the thigh; 9, sciatic vein; 10, vulvar varicosity; 11, internal pudendal vein; 12, cystic and vaginal veins; 13, buttock veins. Multiple collaterals are present.

revealed that the normal average diameter of ovarian veins is less than 5 mm.<sup>89</sup> According to Stancati and coauthors, valves are present in these veins, mainly in the distal third.<sup>90</sup> However, Ahlberg and collaborators found no ovarian vein valves on the left side in 15% and on the right side in 6%.<sup>91</sup> The ovarian veins are connected with the utero-ovarian and salpingo-ovarian veins through the broad ligament and with the rectal, vaginal, and vesical veins.

## Pathophysiology

According to Greiner and Gilling-Smith,<sup>92</sup> pelvic varicose veins can be due to three different mechanisms:

- Type 1: reflux secondary to pelvic and genital (ovarian) vein incompetence. It is the most frequent etiology and of uncertain cause. However, it has been shown that hormonal factors contribute to varicose veins, and that these veins are exposed to high levels of hormones. Estradiol inhibits the reflex vasoconstriction of vessels and induces uterine enlargement with selective dilation of the ovarian and uterine veins mainly during pregnancy.<sup>93</sup> In one study, intravenous injection of dihydroergotamine in women with pelvic congestion and pain produced a 35% reduction in vein diameters veins associated with a decrease in pelvic blood flow that resulted in pain relief.<sup>94</sup> Moreover, cystic ovaries are frequently associated with pelvic varicose veins.<sup>94,95</sup>
- Type 2: secondary to obstruction of outflow. May-Thurner syndrome,<sup>96–98</sup> nutcracker syndrome,<sup>98,99</sup> left renal vein thrombosis, post-thrombotic disease involving the common iliac veins or the IVC (or both), and Budd-Chiari syndrome can all lead to the development of pelvic varicose veins via collateral pathways.
- Type 3: secondary to a local compression phenomenon. The main cause is endometriosis, but it can also be due to tumors, posttraumatic lesions, and sequelae of infections.

## Clinical Findings

PCS often develops in young women (late 20s to early 30s) who are multiparous,<sup>100</sup> but treatment occurs at a mean age of 41 years.<sup>101</sup> The condition often disappears after menopause.<sup>100</sup> These lesions are rare in men except in cases of varicocele and are often due to venous obstructive disease. PCS can be described as a highly variable combination of chronic (up to 6 months duration) pelvic pain (heaviness that increases during the day, mostly if the patient stays sitting or standing and when lifting, and can be relieved by the supine position), dyspareunia, dysmenorrhea, and urinary (dysuria, pollakiuria, bladder urgency), and rectal (constipation) symptoms. Symptoms occur predominantly on one side but can be bilateral. Hemorrhoids are frequently found in these patients.<sup>101</sup>

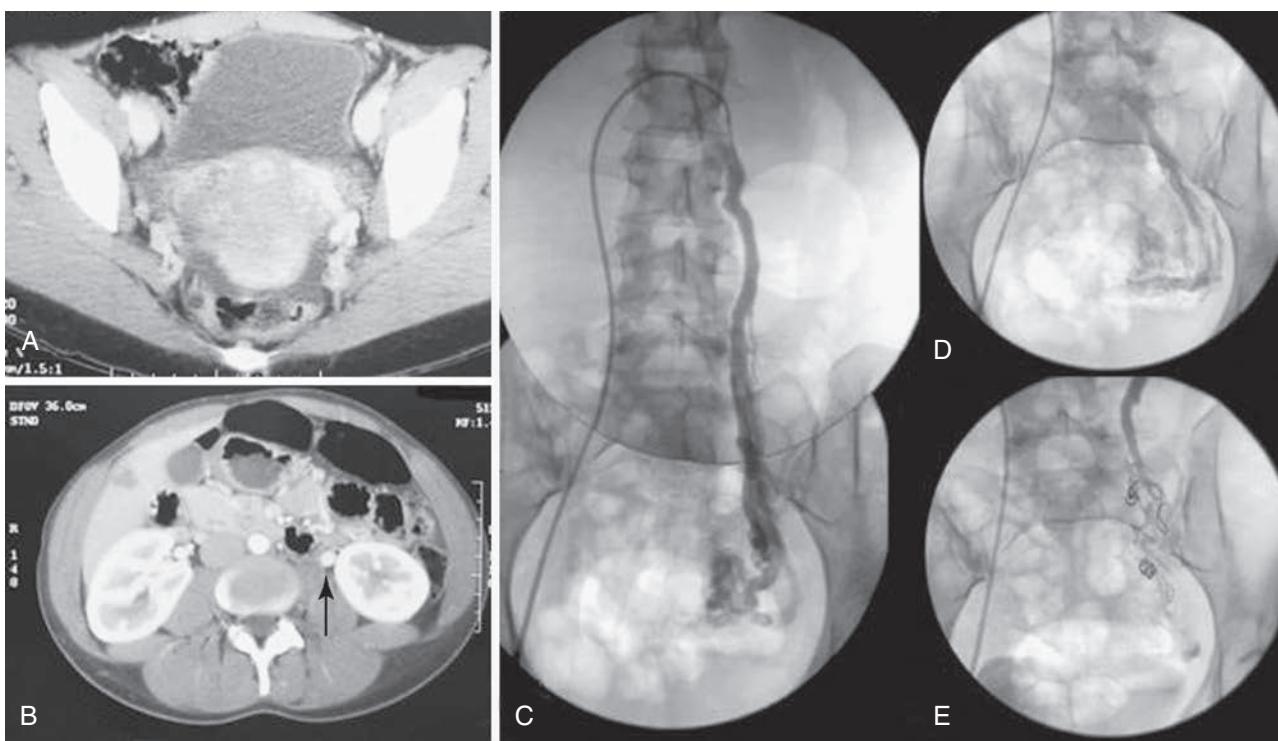
Clinical examination can reveal cervical motion; retrocervical, paracervical, uterine, and ovarian tenderness; uterine enlargement; and uterine retroversion. According to Beard and colleagues, the combination of tenderness on abdominal palpation over the ovarian point and a history of pain after sexual activity was 94% sensitive and 77% specific for discriminating pelvic congestion from other causes of pelvic pain.<sup>100</sup> Perineal (mainly vulvar) varicose veins can be associated with PCS and should be searched for clinically as well as in the past medical history (mainly during pregnancy). Lower extremity findings include superficial venous insufficiency, atypical varicose veins (buttock, posterior and lateral aspect of the thigh, etc.), and recurrence after procedures for varicose veins.<sup>101</sup>

## Diagnosis

### Noninvasive Investigations

#### Duplex scanning

A pelvic color DUS should be performed with transperitoneal 5-MHz and transvaginal probes after 3 days of a no-residue diet



**Figure 160.13** Woman with Pelvic Congestion Syndrome Secondary to Left Ovarian Vein Incompetence. (A) Pelvic varicose veins on computed tomography (CT) angiography. (B) CT angiogram showing left ovarian vein reflux. The vein is dilated and opacified early (*arrow*). (C) Selective phlebography of an incompetent left ovarian vein with periovarian varices. (D) Delayed phlebographic imaging showing the left internal and common iliac veins. (E) Results after embolization with foam and coils.

and an empty stomach.<sup>96</sup> Both the internal iliac and genital veins should be imaged to identify dilation and reflux, including imaging with the Valsalva maneuver. Pelvic varicose veins are defined as multiple dilated tubular structures around the uterus and ovary with venous Doppler signals and diameters larger than 5 mm.<sup>96</sup> The positive predictive value of a 6-mm-diameter ovarian vein for the diagnosis of PCS has been reported as 83.3%.<sup>102</sup> The obturator, sciatic, and internal pudendal veins should also be imaged. Collateral pathways, such as enlarged veins crossing the uterine myometrium, are often present. The common iliac veins, IVC, and renal veins should be imaged to search for venous obstruction. A lower extremity DUS can be obtained to search for valvular incompetence, which can be secondary to pelvic incompetence.

#### Computed tomographic and magnetic resonance venography

CTV or MR venography can be performed to confirm the presence of pelvic and genital varicose veins.<sup>103</sup> CTV should be timed for evaluation of the portal, genital, and renal veins, and separate imaging should be performed at later times for evaluation of the pelvic and iliocaval veins. Pelvic varices are imaged as dilated, tortuous, enhanced tubular structures around the uterus and ovary, with possible extension into the broad ligament and pelvic sidewall (Fig. 160.13A). They can also involve the paravaginal venous plexus. Rozenblit and associates define ovarian vein incompetence as opacification during the arterial phase of CT angiography and 7 mm or greater in maximum diameter (see Fig. 160.13B).<sup>104</sup>

On T1-weighted MRI, pelvic varicose veins have no signal intensity because of the flow void artifact; on gradient-echo MRI, varicose veins have high signal intensity. On T2-weighted MRI, they usually appear as an area of low signal intensity, although hyperintensity or mixed signal intensity may also be noted, possibly because of the relatively slow flow through the vessels. Two- and three-dimensional, T1-weighted gradient-echo sequences performed after the intravenous administration of gadolinium are the most effective sequences for demonstrating pelvic varicose veins.<sup>103,105,106</sup>

CT and MR venography examinations can also identify other sources of pelvic pain, mainly endometriosis. Images should be evaluated for venous obstructive disease. However, because these tests are performed in the supine position, they can underestimate venous pathology.

#### Contrast phlebography

This imaging technique is considered the “gold standard” for diagnosis and can be combined with interventions for treatment.<sup>107</sup> It is performed under local anesthesia via the common femoral or brachial vein approach,<sup>107,108</sup> and should image the four veins responsible for venous return from the pelvis: bilateral internal iliac and gonadal veins, as well as the common iliac veins, IVC and left renal vein in order to look for obstructive lesions. The study should be performed with and without a Valsalva maneuver. In case of suspected nutcracker syndrome, the renocaval pullback gradient should be measured. A 4-F or 5-F Cobra 2 catheter is commonly used to catheterize and

perform selective venography (see Figs. 160.13C, 160.14A and 160.15A). In some cases, a Simmons catheter is required for imaging of the right gonadal vein (Fig. 160.16A). In cases of a brachial approach, a multipurpose or a vertebral catheter can be helpful. Either approach can be used, but catheterization of the right ovarian vein is more often successful from the brachial approach (18% failure for brachial approach<sup>107</sup> vs. 58% failure through femoral approach<sup>108</sup>). Kim and associates advocate the use of balloon occlusion venography to image the internal iliac veins (7-F Berman wedge catheter [Arrow International, Reading, PA] inflated in the trunk of the internal iliac vein).<sup>109</sup>

According to Chung and Huh, criteria used for the phlebographic diagnosis of PCS caused by ovarian vein valvular incompetence are the following: ovarian vein larger than 5 mm in diameter (see Figs. 160.13C and 160.16A), retention of contrast medium in the ovarian vein for longer than 20 seconds, existence of congestion in the pelvic venous plexus, opacification of the internal iliac vein (see Fig. 160.13D), and/or filling of vulvovaginal and thigh varicosities. Each variable is assigned a value between 1 and 3, depending on the degree of abnormality, and a venogram score of 5 or higher indicates the presence of PCS.<sup>110</sup>

### Differential Diagnosis

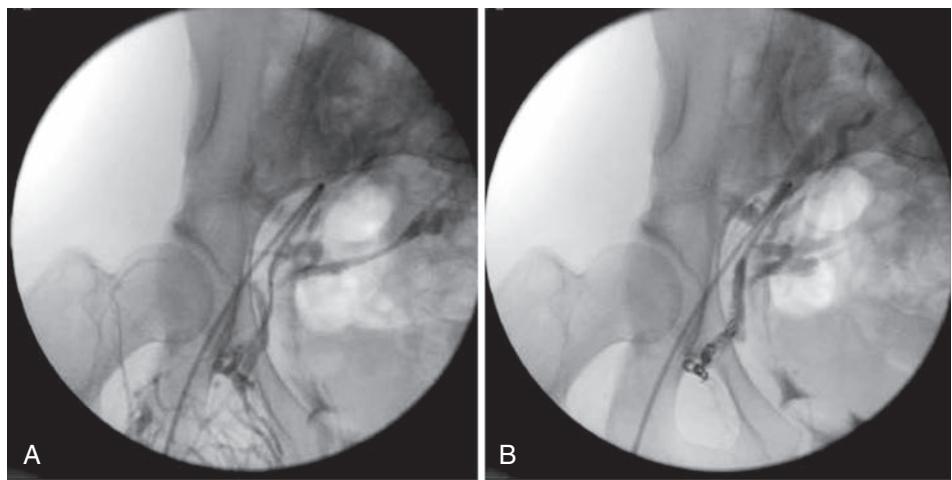
As suggested earlier, it is important to rule out nonvascular causes of pelvic pain, such as endometriosis, uterine

fibroma, pelvic cancer, or pudendal nerve compression. The diagnosis relies on analysis of the symptoms and on investigations. Pelvic ultrasound, CT, and MRI can be of considerable help, but sometimes a more extensive evaluation is required. Laparoscopy reveals pelvic varicose veins if performed in a feet-down position while limiting the pressure of peritoneal insufflation, and it may help to eliminate other pathologies.

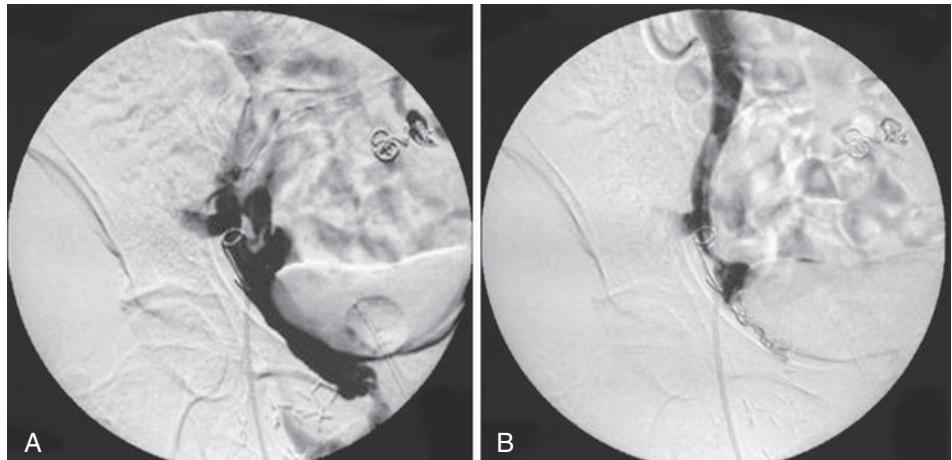
### Treatment

#### Medical Treatment

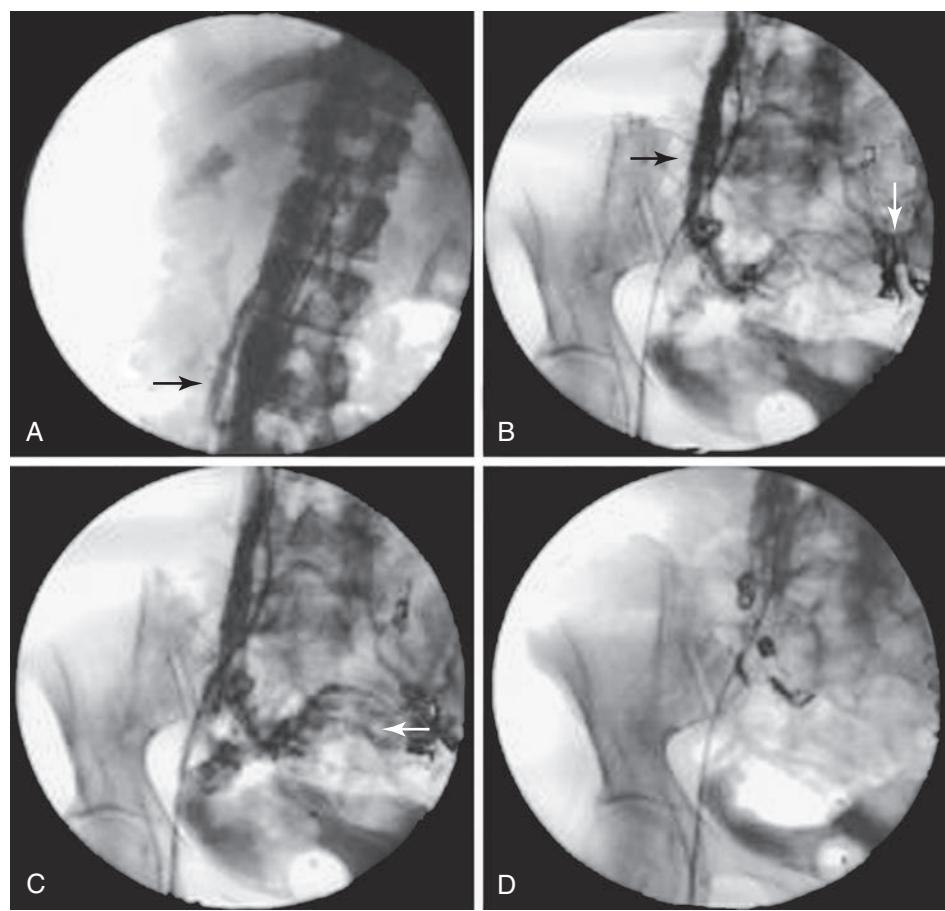
Medroxyprogesterone acetate (Provera, Upjohn Ltd, Kalamazoo, MI), 30 mg/day for 6 months, was shown to be effective in relieving the symptoms of PCS by Faquhar and coworkers, with 73% of women reporting at least 50% improvement, versus 33% of those treated with placebo.<sup>111</sup> However, this positive effect was not maintained 9 months after discontinuation of treatment. In a prospective randomized trial, Soysal and colleagues compared the efficacy of goserelin acetate (3.6 mg/month for 6 months) and medroxyprogesterone (30 mg/day for 6 months).<sup>83</sup> One year after treatment, goserelin had achieved a statistically significantly better result. Micronized purified flavonoid fraction (Daflon, Servier), 500 mg twice a day for 6 months, resulted in statistical improvement at the



**Figure 160.14** Patient with Varicose Vein Recurrence After Right Great Saphenous Vein Stripping. (A) Selective phlebography of the right obturator vein. (B) Results after treatment with foam and coils.



**Figure 160.15** Woman with Pelvic Congestion Syndrome. (A) Phlebography showing right vesicovaginal varicose veins. (B) Completion phlebography after treatment with foam and coils.



**Figure 160.16** Woman with Pelvic Congestion Syndrome Caused by Bilateral Ovarian Vein Reflux. (A) Selective phlebography of a large refluxing right ovarian vein with a Simmons catheter. (B) Result after sclerotherapy and embolization with foam and coils. (C) Late pelvic view showing periovarian varices (arrow). (D) Result after sclerotherapy and embolization with foam and coils.

end of treatment in a prospective randomized study.<sup>112</sup> Although these medications provide symptom relief, none have permanent effects once discontinued.

### Conventional and Laparoscopic Surgery

Different surgical techniques have been reported for the treatment of PCS, including ovarian and/or internal iliac vein ligation, ovarian and uterine artery and vein ligation, oophorectomy, and even total hysterectomy with bilateral salpingo-oophorectomy. Some of these techniques can be performed laparoscopically, but they remain invasive.<sup>113</sup> Despite the observation that bilateral oophorectomy combined with hysterectomy and hormone replacement therapy have been shown to be effective in patients who fail medical therapy,<sup>95</sup> this is an invasive option, which is not acceptable for women who want to become pregnant.

### Endovascular Treatment

#### Techniques

Endovascular therapy with embolization is now considered the first-line treatment for PCS in most patients. The procedure is performed under local anesthesia either together with diagnostic phlebography or as a separate procedure. After selective catheterization and contrast-enhanced study of the refluxing vein or veins, embolization is performed. “Rules” of the embolization technique include the following:

(1) the entire internal iliac vein should not be embolized, and (2) regarding the gonadal veins, embolization must be performed proximal to the last collateral to prevent recurrences. Embolization is mainly performed using coils (0.035 inch for 4-F or 5-F catheter and 0.018 inch for microcatheters, pushable or detachable, fibred or not). Vascular plugs can be used in cases of very large veins.<sup>114</sup> The number of devices used and the rate of recurrence can be reduced by the addition of foam sclerotherapy to embolization. Foam is prepared from sodium tetradecyl sulfate (Trombovar or Sotradecol) or Aetoxisclerol (polidocanol) and can be injected either before coiling or by using the sandwich technique (see Figs. 160.13E, 160.14B, 160.15B, and 160.16B). Foam is created using air or a 50/50 mixture of CO<sub>2</sub> and O<sub>2</sub> according to the Tessari method (see Ch. 155, Varicose Veins: Endovenous Ablation and Sclerotherapy).<sup>115</sup> With 3% polidocanol, we use up to 30 mL of foam. Other agents which have been used include n-butyl cyanoacrylate, ethylene vinyl alcohol copolymer, and sodium morrhuate combined with Gelfoam.<sup>109</sup>

When treating the internal iliac vein, Kim and coauthors recommended using balloon occlusion and avoiding embolization of the main trunk.<sup>109</sup> In addition, care must be taken to avoid embolization of the external iliac and common femoral veins.

In a prospective randomized study of 164 women with PCS, Chung and Huh compared ovarian vein embolization,

hysterectomy with bilateral oophorectomy and hormone replacement therapy, and hysterectomy with unilateral oophorectomy.<sup>110</sup> They showed that embolization was significantly more effective than the other two techniques. Asciutto et al. showed that using embolization, untreated patients had no improvement, whereas treated patients improved.<sup>116</sup> Regarding the technique, Monedero and coauthors reported 1186 cases of embolization for recurrent lower limb varicose veins caused by pelvic disease; they had better results with coils and the sandwich technique (coils plus 2% polidocanol or hydroxypolyethoxydodecane foam) than with the use of coils alone (95.6% rate of improvement vs. 76% at 6 months).<sup>107</sup> Literature review shows better results in series reporting embolization of all incompetent veins.

Complications of embolization with or without sclerotherapy are rare and include hematoma at the access site, extravasation of contrast corresponding to vein perforation, coil or glue embolization, DVT and pulmonary embolism, and transient cardiac arrhythmia.

PCS linked to ilio caval obstructive disease (mainly May–Thurner syndrome) should be treated by stenting of the obstructive lesions (the left common iliac vein).<sup>98,117</sup>

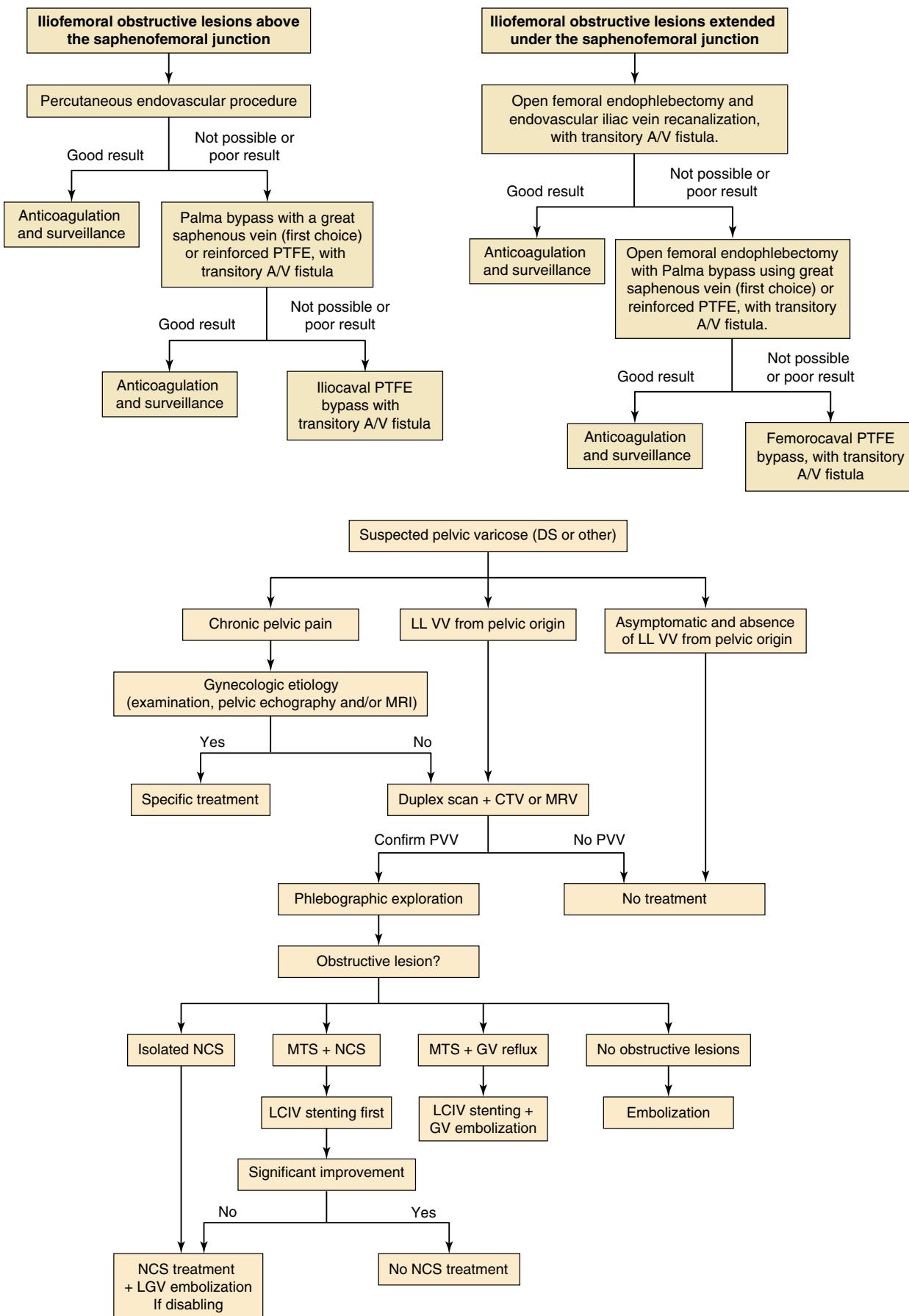
Clinical guidelines including recommendations for the treatment of PCS were recently published by the Society for Vascular Surgery and the American Venous Forum. These recommend that PCS and pelvic varices due to pelvic vein incompetence should be treated using coil embolization, plugs, or transcatheter sclerotherapy, used alone or together (grade 2B) (Table 160.3).<sup>118</sup>

**TABLE 160.3** Results of Embolization for Pelvic Congestion Syndrome

Series	N	Veins	Technique	Follow-Up (Months)	RESULTS (%)	
					Improved	Worsened
Capasso et al. <sup>119</sup>	19	OV	Enbucrilate and/or coils	15.4	74	
Tarazov et al. <sup>120</sup>	6	OV	Coils	24	100	
Machan et al. <sup>121</sup>	23	OV	Coils	15	78	
Cordts et al. <sup>122</sup>	9	OV	Coils + gelatin	13.4	100	
Cotroneo et al. <sup>123</sup>	22	OV	Coils	3	60	
Richardson et al. <sup>124</sup>	28	OV	Coils + foam	22.2	SS	
Maleux et al. <sup>125</sup>	41	OV	Enbucrilate + coils	19.9	68.2	
Scultetus et al. <sup>126</sup>	7	OV	Coils	27	43	
	6	IIVT	Coils		83	
	12	IIVT + OVR	Coils + OVR		83.4	
Bachar et al. <sup>127</sup>	6	OV	Coils	7.7	83	
Pieri et al. <sup>128</sup>	33	OV	3% STS	9	61	
Chung et al. <sup>110</sup>	52	OV	Coils	26.6	SS	
Kim et al. <sup>109</sup>	127	OV	Gelfoam + sodium morrhuate + coils	45	83	4
Lasry et al. <sup>129</sup>	30	OV ± IIVT	Coils	6	90	
Kwon et al. <sup>130</sup>	67	OV	Coils	40	82	
Creton et al. <sup>108</sup>	24	OV ± IIVT	Coils	36	76	
Gandini et al. <sup>131</sup>	38	OV	3% STS foam	12	100	0
Asciutto et al. <sup>116</sup>	35	OV and/or IIVT	Coils	45	Embolization >>>	
Laborda et al. <sup>132</sup>	202	OV ± IIVT	Coils	89% at 60	93	
Nasser et al. <sup>133</sup>	113	OV ± IIVT	Coils	12	100	0
Hocquelet et al. <sup>134</sup>	33	OV ± IIVT	Coils + foam	23	93	0
Monedero <sup>107</sup>	215	OV and/or IIVT	Coils + foam	6	90	
Ratnam <sup>135</sup>	218	OV and/or IIVT	Coils + foam	0.9M	95	
Hartung <sup>98</sup>	78	OV ± IIVT	Coils + foam	4	91	0

>>>, Embolization superior to other techniques. IIVT, internal iliac vein tributaries; OV, ovarian vein; OVR, ovarian vein resection; SS, statistically improved; STS, sodium tetradecyl sulfate.

## CHAPTER ALGORITHMS



DS, duplex-scan; LL VV, lower limb varicose veins; PVV, pelvic varicose veins; NCS, nutcracker syndrome; MTS, May-Thurner syndrome; LCIV, left common iliac vein; GV, gonadal vein; LGV, left gonadal vein

## SELECTED KEY REFERENCES

AbuRahma AF, Robinson PA, Boland JP. Clinical hemodynamic and anatomic predictors of long-term outcome of lower extremity venovenous bypasses. *J Vasc Surg.* 1991;14:635.

*Although an older publication, this paper points out the importance of hemodynamic factors in determining outcomes of cross-femoral bypasses.*

Daugherty SF, Gillespie DL. Venous angioplasty and stenting improve pelvic congestion syndrome caused by venous outflow obstruction. *J Vasc Surg Venous Lymphat Disord.* 2015;3:283–289.

*Recent retrospective study performed in two institutions of the diagnosis and management of PCS caused by venous outflow obstruction.*

Garg N, Gloviczki P, Karimi KM, et al. Factors affecting outcome of open and hybrid reconstructions for nonmalignant obstruction of iliofemoral veins and inferior vena cava. *J Vasc Surg.* 2011;53:383–393.

*More recent review of iliofemoral and caval bypasses including identification of factors which affect outcomes.*

Gloviczk P, Comerota AJ, Dalsing MC, et al. Society for Vascular Surgery; American Venous Forum. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the

Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(suppl 5):2S–48S.

*Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. Includes a section addressing the treatment of PCS.*

Gloviczk P, Pairolero PC, Toomey BJ, et al. Reconstruction of large veins for nonmalignant venous occlusive disease. *J Vasc Surg.* 1992;16:750.

*Large early experience with construction and outcomes following femoroiliac and inferior vena cava bypasses.*

Mahmoud O, Vikatmaa P, Aho P, et al. Efficacy of endovascular treatment for pelvic congestion syndrome. *J Vasc Surg Venous Lymphat Disord.* 2016;4:355–370.

*Recent review of efficacy of pelvic and gonadal vein embolization including multiple series with more than 1000 patients.*

Wang Z, Zhu Y, Wang S, et al. Recognition and management of Budd-Chiari syndrome: report of one hundred cases. *J Vasc Surg.* 1989;10:149.

*Good review of pathophysiology of Budd–Chiari syndrome coupled to appropriate treatment.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. Warren R, Thayer TR. Transplantation of the saphenous vein for post-phlebitic stasis. *Surgery*. 1954;35:867.
2. Bergan JJ, Yao JS, Flinn WR, McCarthy WJ. Surgical treatment of venous obstruction and insufficiency [review]. *J Vasc Surg*. 1986;3:174.
3. Rhee RY, Gloviczki P, Luthra HS, et al. Iliocaval complications of retroperitoneal fibrosis. *Am J Surg*. 1994;168:179.
4. May R, Thurner J. Ein Gefäßsporn in der Vena iliaca communis sinistra als Ursache der ubegend linksseitigen Beckenvenenthrombosen. *Ztsch Kreislaufforschung*. 1956;45:912.
5. Cockett FB, Thomas ML. The iliac compression syndrome. *Br J Surg*. 1965;52:816.
6. David M, Striffling V, Brenot R, et al. Syndrome de Cockett acquis: à propos de trois cas opérés dont deux formes inhabituelles. *Ann Chir*. 1981;35:93.
7. Steinberg JB, Jacocks MA. May-Thurner syndrome: a previously unreported variant. *Ann Vasc Surg*. 1993;7:577.
8. Dzinich C, Gloviczki P, van Heerden JA, et al. Primary venous leiomyosarcoma: a rare but lethal disease. *J Vasc Surg*. 1992;15:595.
9. Bower TC, Nagorney DM, Toomey BJ, et al. Vena cava replacement for malignant disease: Is there a role? *Ann Vasc Surg*. 1993;7:51.
10. Bower TC. Primary and secondary tumors of the inferior vena cava. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum*. London: Chapman & Hall; 1996:529–550.
11. Rich NM, Hughes CW. Popliteal artery and vein entrapment. *Am J Surg*. 1967;113:696.
12. Gullmo A. The strain obstruction syndrome of the femoral vein. *Acta Radiol*. 1957;47:119.
13. Wang Z, Zhu Y, Wang S, et al. Recognition and management of Budd-Chiari syndrome: report of one hundred cases. *J Vasc Surg*. 1989;10:149.
14. Gloviczki P, Stanson AW, Stickler GB, et al. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery*. 1991;110:469.
15. Jacob AG, Driscoll DJ, Shaughnessy WJ, et al. Klippel-Trenaunay syndrome: spectrum and management. *Mayo Clin Proc*. 1998;73:28.
16. Schanzer H, Skladany M. Complex venous reconstruction for chronic iliofemoral vein obstruction. *Cardiovasc Surg*. 1996;4:837.
17. Meissner MH, Eklof B, Smith PC, et al. Secondary chronic venous disorders. *J Vasc Surg*. 2007;46S:68S–83S.
18. Raju S, Furrh 4th JB, Neglén P. Diagnosis and treatment of venous lymphedema. *J Vasc Surg*. 2012;55:141–149.
19. Crowner J, Marston W, Almeida J, et al. Classification of anatomic involvement of the ilio caval venous outflow tract and its relationship to outcomes after ilio caval venous stenting. *J Vasc Surg Venous Lymphat Disord*. 2014;20(2):241–245.
20. Raju S. New approaches to the diagnosis and treatment of venous obstruction. *J Vasc Surg*. 1986;4:42.
21. Gloviczki P, Pairolero PC, Cherry KJ, Hallett JW. Reconstruction of the vena cava and of its primary tributaries: a preliminary report. *J Vasc Surg*. 1990;11:373.
22. Gloviczki P, Pairolero PC, Toomey BJ, et al. Reconstruction of large veins for nonmalignant venous occlusive disease. *J Vasc Surg*. 1992;16:750.
23. Raju S, Owen Jr S, Neglén P. The clinical impact of iliac venous stents in the management of chronic venous insufficiency. *J Vasc Surg*. 2002;35:8.
24. O'Sullivan GJ, Semba CP, Bittner CA, et al. Endovascular management of iliac vein compression (May-Thurner) syndrome. *J Vasc Intervent Radiol*. 2000;11:823.
25. Hurst DR, Forauer AR, Bloom JR, et al. Diagnosis and endovascular treatment of ilio caval compression syndrome. *J Vasc Surg*. 2001;34:106–113.
26. Juhan C, Hartung O, Alimi YS, et al. Treatment of nonmalignant obstructive ilio caval lesions by stent placement: mid-term results. *Ann Vasc Surg*. 2001;15:227.
27. Jost CJ, Gloviczki P, Cherry Jr KJ, et al. Surgical reconstruction of iliofemoral veins and the inferior vena cava for nonmalignant occlusive disease. *J Vasc Surg*. 2001;33:320.
28. Yamaguchi A, Eguchi S, Iwasaki T, Asano K. The influence of arteriovenous fistulae on the patency of synthetic inferior vena caval grafts. *J Cardiovasc Surg*. 1968;9:99.
29. Soyer T, Lempinen M, Cooper P, et al. A new venous prosthesis. *Surgery*. 1972;72:864.
30. Chiu CJ, Terzis J, Mac Rae ML. Replacement of superior vena cava with the spiral composite vein graft. *Ann Thorac Surg*. 1974;17:555.
31. Wilson SE, Jabour A, Stone RT, Stanley TM. Patency of biologic prosthetic inferior vena cava grafts with distal limb fistula. *Arch Surg*. 1978;113:1174.
32. Hobson 2nd RW, Wright CB. Peripheral side to side arteriovenous fistula. *Am J Surg*. 1978;126:411.
33. Kunlin K, Kunlin A. Experimental venous surgery. In: May R, ed. *Surgery of the Veins of the Leg and Pelvis*. Philadelphia: WB Saunders; 1979:37–75.
34. Hutschenreiter S, Vollmar J, Loeprecht H, et al. Reconstructive interventions of the venous system: clinical evaluation of late results using functional and vascular anatomic criteria. *Chirurgica*. 1979;50:555.
35. Fiore AC, Brown JW, Cromartie RS, et al. Prosthetic replacement for the thoracic vena cava. *J Thorac Surg*. 1982;84:560.
36. Gloviczki P, Hollier LH, Dewanjee MK, et al. Experimental replacement of the inferior vena cava: factors affecting patency. *Surgery*. 1984;95:657.
37. Plate G, Hollier LH, Gloviczki P, et al. Overcoming failure of venous vascular prostheses. *Surgery*. 1984;96:503.
38. Chan EL, Bardin JA, Bernstein EF. Inferior vena cava bypass: experimental evaluation of externally supported grafts and initial clinical application. *J Vasc Surg*. 1984;95:657.
39. Robison RJ, Peigh PS, Fiore AC, et al. Venous prostheses: improved patency with external stents. *J Surg Res*. 1984;36:306.
40. Koveker GB, Burkell WE, Graham LM, et al. Endothelial cell seeding of expanded polytetrafluoroethylene vena cava conduits: effects of luminal production of prostacyclin, platelet adherence, and fibrinogen accumulation. *J Vasc Surg*. 1988;7:600.
41. Akimaru K, Onda M, Tajiri T, et al. Reconstruction of the vena cava with the peritoneum. *Am J Surg*. 2000;179:289.
42. Modral JG, Sadjadi J, Ali AT, et al. Deep vein harvest: predicting need for fasciotomy. *J Vasc Surg*. 2004;39:387–394.
43. Jaus M, Macchiarini P. Superior vena cava and innominate vein reconstruction in thoracic malignancies: cryopreserved graft reconstruction. *Semin Thoracic Cardiovasc Surg*. 2011;23:330–335.
44. May R. The Palma operation with Gottlob's endothelium preserving suture. In: May R, Weber J, eds. *Pelvic and Abdominal Veins: Progress in Diagnostics and Therapy*. Amsterdam: Excerpta Medica; 1981:192–197.
45. Gloviczki P, Pairolero PC. Venous reconstruction for obstruction and valvular incompetence. *Perspect Vasc Surg*. 1988;1:75.
46. Alimi YS, DiMauro P, Fabre D, Juhan C. Iliac vein reconstructions to treat acute and chronic venous occlusive disease. *J Vasc Surg*. 1997;25:673.
47. Dale WA, Harris J, Terry RB. Polytetrafluoroethylene reconstruction of the inferior vena cava. *Surgery*. 1984;95:625.
48. Gruss JD, Hiemer W. Bypass procedures for venous obstruction: Palma and May-Husni bypasses, Raju perforator bypass, prosthetic bypasses, and primary and adjunctive arteriovenous fistulae. In: Raju S, Villavicencio JL, eds. *Surgical Management of Venous Disease*. Baltimore: Williams & Wilkins; 1997:289–305.
49. Kieffer E, Bahnini A, Koskas F. Nonthrombotic disease of the inferior vena cava: Surgical management of 24 patients. In: Bergan JJ, Yao JST, eds. *Venous Disorders*. Philadelphia: WB Saunders; 1991:501–516.
50. Lalka SG. Venous bypass graft for chronic venous occlusive disease. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum*. London: Chapman & Hall; 1996:446–470.
51. Menawat SS, Gloviczki P, Mozes G, et al. Effect of a femoral arteriovenous fistula on lower extremity venous hemodynamics after femorocalval reconstruction. *J Vasc Surg*. 1996;24:793.

52. Hobson 2nd RW, Lee BC, Lynch TG, et al. Use of intermittent pneumatic compression of the calf in femoral venous reconstruction. *Surg Gynecol Obstet.* 1984;159:284.
53. Palma EC, Riss F, Del Campo F, Tobler H. Tratamiento de los trastornos postflebiticos mediante anastomosis venosa safeno-femoral contralateral. *Bull Soc Surg Uruguay.* 1958;29:135.
54. Palma EC, Esperon R. Vein transplants and grafts in the surgical treatment of the postphlebitic syndrome. *J Cardiovasc Surg.* 1960;1:94.
55. Dale WA. Peripheral venous reconstruction. In: Dale WA, ed. *Management of Vascular Surgical Problems.* New York: McGraw-Hill; 1985:493–521.
56. Garg N, Gloviczki P, Karimi KM, et al. Factors affecting outcome of open and hybrid reconstructions for nonmalignant obstruction of iliofemoral veins and inferior vena cava. *J Vasc Surg.* 2011;53:383–393.
57. Lalka SG, Lash JM, Unthank JL, et al. Inadequacy of saphenous vein grafts for cross-femoral venous bypass. *J Vasc Surg.* 1991;13:622.
58. Husni EA. Reconstruction of veins: the need for objectivity. *J Cardiovasc Surg.* 1983;24:525.
59. AbuRahma AF, Robinson PA, Boland JP. Clinical hemodynamic and anatomic predictors of long-term outcome of lower extremity venous bypasses. *J Vasc Surg.* 1991;14:635.
60. Danza R, Navarro T, Baldizan J. Reconstructive surgery in chronic venous obstruction of the lower limbs. *J Cardiovasc Surg.* 1991;32:98–103.
61. Halliday P, Harris J, May J. Femoro-femoral crossover grafts (Palma operation): A long-term follow-up study. In: Bergan JJ, Yao JST, eds. *Surgery of the Veins.* Orlando: Grune & Stratton; 1985:241–254.
62. Victor S, Jayanthi V, Kandasamy I, et al. Retrohepatic cavoatrial bypass for coarctation of inferior vena cava with a polytetrafluoroethylene graft. *J Thorac Cardiovasc Surg.* 1986;91:99.
63. Dale WA, Harris J. Cross-over vein grafts for iliac and femoral venous occlusion. *Ann Surg.* 1969;168:319.
64. Gruss JD. Venous bypass for chronic venous insufficiency. In: Bergan JJ, Yao JST, eds. *Venous Disorders.* Philadelphia: WB Saunders; 1991:316–330.
65. Husfeldt KJ, May R, Weber J. Venous replacement with gore-tex prosthesis: experimental and first clinical results. In: Husfeldt KJ, May R, Weber J, eds. *Pelvic and Abdominal Veins: Progress in Diagnostics and Therapy.* Amsterdam: Excerpta Medica; 1981:249–258.
66. Eklof B, Broome A, Einarsson E. Venous reconstruction in acute iliac vein obstruction using ePTFE grafts. In: May R, Weber J, eds. *Pelvic and Abdominal Veins.* Amsterdam: Excerpta Medica; 1981:241–245.
67. Comerota AJ, Lurie F, Assi Z. The contemporary hybrid operative procedure for incapacitating post-thrombotic iliofemoral and vena cava obstruction improve procedural outcomes. *J Vasc Surg.* 2019;7:65–73.
68. Dumantepe M, Aydin S, Ökten M, Karabulut H. Endophlebectomy of the common femoral vein and endovascular iliac vein recanalization for chronic iliofemoral venous occlusion. *J Vasc Surg.* 2020;8(4):572–582.
69. McMurrich JP. The occurrence of congenital adhesions in the common iliac veins and their relation to thrombosis of the femoral and iliac veins. *Am J Med Sci.* 1908;135:342.
70. May R, Thurner J. The cause of predominantly sinistral occurrence of thrombosis of the pelvic veins. *Angiology.* 1957;8:419.
71. Taheri SA, Williams J, Powell S, et al. Iliocaval compression syndrome. *Am J Surg.* 1987;154:169–172.
72. Cormier JM, Fichelle JM, Vennin J, et al. Atherosclerotic occlusive disease of the superior mesenteric artery: late results of reconstructive surgery. *Ann Vasc Surg.* 1991;v;5(6):510–518.
73. Trimble C, Bernstein EF, Pomerantz M, Eiseman B. A prosthetic bridging device to relieve iliac venous compression. *Surg Forum.* 1975;23:249.
74. Akers DLJ, Creado B, Hewitt RL. Iliac vein compression syndrome: case report and review of the literature [see comments]. *J Vasc Surg.* 1996;24:477.
75. Rigas A, Vomvayannis A, Tsardakas E. Iliac compression syndrome. *J Cardiovasc Surg (Torino).* 1970;11:389.
76. Reasbeck PG, Reasbeck JC. Iliac compression syndrome: A myth, a rarity or a condition frequently missed? *N Z Med J.* 1983;96:383.
77. Welter HF, Becker HM. Therapy of the pelvic venous spur and postoperative follow-up. In: May R, Weber J, eds. *Pelvic and Abdominal Veins: Progress in Diagnostics and Therapy.* Amsterdam: Excerpta Medica; 1981:172.
78. Jaszcak P, Mathiesen FR. The iliac compression syndrome. *Acta Chir Scand.* 1978;144:133.
79. Richet NA. *Traite pratique d'anatomie medico-chirurgiale.* Paris: E. Chamerot, Librairie Editeur; 1857.
80. Taylor HC Jr. Vascular congestion and hyperemia: the effect on function in the female reproductive organs. Part I. Physiological basis and history of the concept. *Am J Obstet Gynecol.* 1949;57:211–230.
81. Eklof B, Perrin M, Delis KT, et al. American Venous Forum; European Venous Forum; International Union of Phlebology; American College of Phlebology; International Union of Angiology. Updated terminology of chronic venous disorders: the VEIN-TERM transatlantic interdisciplinary consensus document. *J Vasc Surg.* 2009;49:498–501.
82. Mathias SD, Kuppermann M, Liberman RF, et al. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. *Obstet Gynecol.* 1996;87:321–327.
83. Soysal ME, Soysal S, Vicdan K, Ozer S. A randomized controlled trial of goserelin and medroxyprogesterone acetate in the treatment of pelvic congestion. *Hum Reprod.* 2001;16:931–939.
84. Belenky A, Bartal G, Atar E, et al. Ovarian varices in healthy female kidney donors: incidence, morbidity and clinical outcome. *Am J Roentgen.* 2002;179:625–627.
85. Monedero JL, Ezpeleta SZ, Grimberg M, et al. Subdiaphragmatic venous insufficiency. Embolization treatment using mixed technique (coils and foam). *Phlebology.* 2004;45:269–275.
86. Gray H. *Henry. Anatomy of the Human Body* Philadelphia: Lea & Febiger; 1918. Bartleby.com; 2000.
87. LePage PA, Villavicencio JL, Gomez ER, et al. The valvular anatomy of the iliac venous system and its clinical implications. *J Vasc Surg.* 1991;14:678–683.
88. Lechter A, Lopez G, Martinez C, Camacho J. Anatomy of the gonadal veins: a reappraisal. *Surgery.* 1991;109:735–739.
89. Kennedy A, Hemingway A. Radiology of varices. *Br J Hosp Med.* 1990;44:38–43.
90. Stancati E, Criscenti SV, Ambrosio JD. Anatomy of the valves of human ovarian veins. *Br J Morphol Sci.* 2002;19:73–76.
91. Ahlberg NE, Bartley O, Chidekel N. Right and left gonadal veins: an anatomical and statistical study. *Acta Radiol Diagn.* 1966;4:595–601.
92. Greiner M, Gilling-Smith GL. Leg varices originating from the pelvis: diagnosis and treatment. *Vascular.* 2007;15:70–78.
93. Hodgkinson CP. Physiology of the ovarian veins during pregnancy. *Obstet Gynecol.* 1953;1:26–37.
94. Reginald PW, Beard RW, Kooner JS, et al. Intravenous dihydroergotamine to relieve pelvic congestion pain in young women. *Lancet.* 1987;15:351–353.
95. Beard RW, Kennedy RG, Gangar KF, et al. Bilateral oophorectomy and hysterectomy in the treatment of intractable pelvic pain associated with pelvic congestion. *Br J Obstet Gynaecol.* 1991;98:988–992.
96. Park SJ, Lim JW, Ko YT, et al. Diagnosis of pelvic congestion syndrome using transabdominal and transvaginal sonography. *Am J Roentgen.* 2004;182:683–688.
97. Hartung O, Otero A, Boufi M, et al. Mid-term results of endovascular treatment for symptomatic chronic non malignant ilio caval venous occlusive disease. *J Vasc Surg.* 2005;42:1138–1144.
98. Hartung O. Embolization is essential in the treatment of leg varicosities due to pelvic venous insufficiency. *Phlebology.* 2015;30(suppl 1):81–85.
99. Hartung O, Grisoli D, Boufi M, et al. Endovascular stenting in the treatment of pelvic vein congestion caused by nutcracker syndrome: lessons learned from the first five cases. *J Vasc Surg.* 2005;42:275–280.
100. Beard RW, Reginald PW, Wadsworth J. Clinical features of women with chronic lower abdominal pain and pelvic congestion. *Br J Obstet Gynaecol.* 1988;95:153–161.

101. Mahmoud O, Vikatmaa P, Aho P, et al. Efficacy of endovascular treatment for pelvic congestion syndrome. *J Vasc Surg Venous Lymphat Disord.* 2016;4:355–370.
102. Giacchetto C, Cotroneo GB, Marincola F, et al. Ovarian varicocele: ultrasonic and phlebographic evaluation. *J Clin Ultrasound.* 1990;18:551–555.
103. Coakley FV, Varghese SL, Hricak H. CT and MRI of pelvic varices in women. *J Comput Assist Tomogr.* 1999;23:429–434.
104. Rozenblit AM, Ricci ZJ, Tuvia J, Amis ES. Incompetent and dilated ovarian veins: a common CT finding in asymptomatic parous women. *Am J Roentgen.* 2001;176:119–122.
105. Kuligowska E, Deeds L, Lu K. Pelvic pain: overlooked and underdiagnosed gynaecologic conditions. *Radiographics.* 2005;25:3–20.
106. Asciutto G, Mumme A, Marpe B, et al. MR Venography in the detection of pelvic venous congestion. *Eur J Vasc Endovasc Surg.* 2008;36:491–496.
107. Monedero JL, Zubicoa Ezpeleta S, Castro Castro J, et al. Embolization treatment of recurrent varices of pelvic origin. *Phlebology.* 2006;21:3–11.
108. Creton D, Hennequin L, Kohler F, Allaert FA. Embolisation of symptomatic pelvic veins in women presenting with non-saphenous varicose veins of pelvic origin – three-year follow-up. *Eur J Vasc Endovasc Surg.* 2007;34:112–117.
109. Kim HS, Malhotra AD, Rowe PC, et al. Embolotherapy for pelvic congestion syndrome: long-term results. *J Vasc Interv Radiol.* 2006;17:289–297.
110. Chung MH, Huh CY. Comparison of treatments for pelvic congestion syndrome. *Tohoku J Exp Med.* 2003;201:131–138.
111. Faquhar CM, Rogers V, Franks S, et al. A randomized controlled trial of medroxyprogesterone acetate and psychotherapy for the treatment of pelvic congestion. *Br J Obstet Gynaecol.* 1989;96:1153–1162.
112. Simsek M, Burak F, Taskin O. Effects of micronized purified flavonoid fraction (Daflon) on pelvic pain in women with laparoscopically diagnosed pelvic congestion syndrome: a randomized crossover trial. *Clin Exp Obstet Gynecol.* 2007;34:96–98.
113. Mathis BV, Miller JS, Lukens ML, Paluzzi MW. Pelvic congestion syndrome: a new approach to an unusual problem. *Am Surg.* 1995;61:1016–1018.
114. Thors A, Haurani MJ, Gregio TK, Go MR. Endovascular intervention for pelvic congestion syndrome is justified for chronic pelvic pain relief and patient satisfaction. *J Vasc Surg Venous Lymphat Disord.* 2014;2:268–273.
115. Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. *Dermatol Surg.* 2001;27:58–60.
116. Asciutto G, Asciutto KC, Mumme A, Geier B. Pelvic venous incompetence: reflux patterns and treatment results. *Eur J Vasc Endovasc Surg.* 2009;38:381–386.
117. Daugherty SF, Gillespie DL. Venous angioplasty and stenting improve pelvic congestion syndrome caused by venous outflow obstruction. *J Vasc Surg Venous Lymphat Disord.* 2015;3:283–289.
118. Gloviczki P, Comerota AJ, Dalsing MC, et al. Society for Vascular Surgery; American Venous Forum. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53(suppl 5):2S–48S.
119. Capasso P, Simons C, Trotteur G, et al. Treatment of symptomatic pelvic varices by ovarian vein embolization. *Cardiovasc Interv Radiol.* 1997;20:107–111.
120. Tarazov PG, Prozorovskij KV, Ryzhkov VK. Pelvic pain syndrome caused by ovarian varices. Treatment by transcatheter embolization. *Acta Radiol.* 1997;38:1023–1025.
121. Machan L, Mowatt J, Hurwitz T, et al. Clinical outcome of women with chronic pelvic pain treated by ovarian vein embolization (abstract). *J Vasc Interv Radiol.* 1998;9(suppl):185.
122. Cordts PR, Eclavea MC, Buckley PJ, et al. Pelvic congestion syndrome: early clinical results after transcatheter ovarian vein embolization. *J Vasc Surg.* 1998;28:862–868.
123. Cotroneo AR, Di Stasi C, Tropeano G, et al. Percutaneous treatment of pelvic varicocele (abstract). *Radiology.* 1998;209(suppl):378–379.
124. Richardson GD, Beckwith TC, Myktyowycz M, Lennox AF. Pelvic congestion syndrome – diagnosis and treatment. *ANZ J Phlebol.* 1999;3:51–56.
125. Maleux G, Stockx L, Wilms G, Marchal G. Ovarian vein embolization for the treatment of pelvic congestion syndrome: long-term technical and clinical results. *J Vasc Interv Radiol.* 2000;11:859–864.
126. Scultetus AH, Villavicencio JL, Gillespie DL, et al. The pelvic venous syndromes: analysis of our experience of 57 patients. *J Vasc Surg.* 2002;36:881–888.
127. Bachar GN, Belenkay A, Greif F, et al. Initial experience with ovarian vein embolization for the treatment of chronic pelvic pain syndrome. *Isr Med Assoc J.* 2003;12:843–846.
128. Pieri S, Agresti P, Morucci M, de Medici L. Percutaneous treatment of pelvic congestion syndrome. *Radiol Med (Torino).* 2003;105:76–82.
129. Lasry JL, Coppe G, Balian E, Borie H. Pelvi-perineal insufficiency and varicose veins of the lower limbs: duplex Doppler diagnosis and endoluminal treatment in thirty females. *J Mal Vasc.* 2007;32:23–31.
130. Kwon SH, Oh JH, Ko KR, et al. Transcatheter ovarian vein embolization using coils for the treatment of pelvic congestion syndrome. *Cardiovasc Interv Radiol.* 2007;30:655–661.
131. Gandini R, Chiocchi M, Konda D, et al. Transcatheter foam sclerotherapy of symptomatic female varicocele with sodium-tetradecl-sulfate foam. *Cardiovasc Interv Radiol.* 2008;31:778–784.
132. Laborda A, Medrano J, de Blas I, et al. Endovascular treatment of pelvic congestion syndrome: visual analog scale (VAS) long-term follow-up clinical evaluation in 202 patients. *Cardiovasc Interv Radiol.* 2013;36:1006–1014.
133. Nasser F, Cavalcante RN, Affonso BB, et al. Safety, efficacy, and prognostic factors in endovascular treatment of pelvic congestion syndrome. *Int J Gynaecol Obstet.* 2014;125:65–68.
134. Hocquelet A, Le Bras Y, Balian E, et al. Evaluation of the efficacy of endovascular treatment of pelvic congestion syndrome. *Diagn Interv Imaging.* 2014;95:301–306.
135. Ratnam LA, Marsh P, Holdstock JM, et al. Pelvic vein embolisation in the management of varicose veins. *Cardiovasc Interv Radiol.* 2008;31:1159–1164.

# Iliocaval Venous Obstruction: Endovascular Treatment

ARJUN JAYARAJ and SESHADRI RAJU

INTRODUCTION 2132

PATHOLOGY 2133

INDICATIONS AND PATIENT SELECTION FOR ILOCAVAL VENOUS STENTING 2133

DIAGNOSIS 2135

TREATMENT 2135

Technique 2135

Recanalization of Chronic Total Occlusions 2139

Inferior Vena Cava Filters 2140

Anticoagulation 2140

STENT OCCLUSION 2140

Chronic Stent Malfunction 2141

Stent Surveillance 2142

OUTCOMES 2142

Morbidity and Mortality 2142

Patency 2142

Clinical Results 2143

Special Scenarios 2144

*Geriatric Group* 2144

*Obese Patients* 2146

*Lymphedema* 2146

*Iliac Vein Stenosis With Tandem Femoral Vein Occlusions* 2146

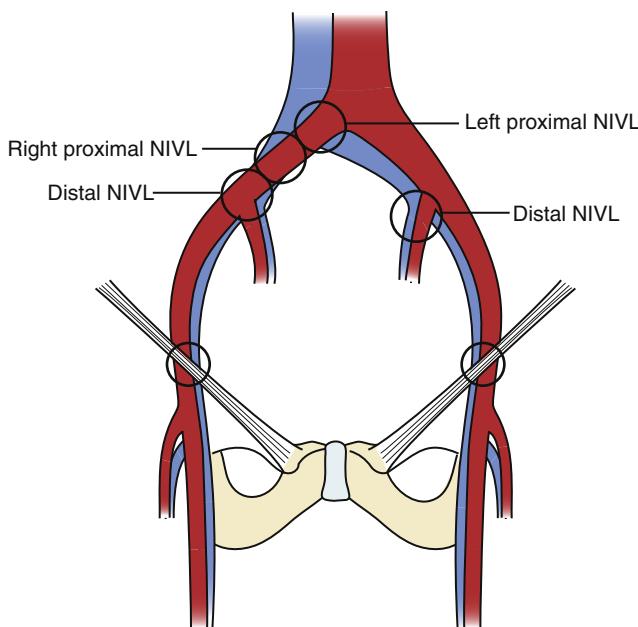
*Thrombosed Inferior Vena Cava Filter* 2146

## INTRODUCTION

A web-like lesion at the ilio caval junction was described by McMurrich, a Canadian physician, in 1908.<sup>1</sup> Recognition of the lesion now commonly known as May–Thurner syndrome (MTS), or iliac compression syndrome, evoked a series of controversies from the start. Initial debate involved the origin of the lesion: was it ontogenetic or acquired? Based upon the rarity of the lesion in embryos and infants, an acquired etiology is now generally accepted, although a few lesions occur at known fusion planes and could be classified as ontogenetic.<sup>2,3</sup> Since neovascularization is absent, post-thrombotic etiology is not likely. May and Thurner proposed that the lesions, which can range from increased wall thickness to intraluminal membranes, webs, and fibrous strands, result from the trauma of the repeated pulsations of the closely related artery. The name “iliac compression syndrome” is incomplete as compression is but one element of a complex lesion.

Later controversies arose concerning the high prevalence of MTS in the general population in silent form. Cockett reported that the lesion can be highly symptomatic in a select group, often young women of child-bearing age, with preferential involvement of the left lower extremity.<sup>4</sup> In some patients,

the lesion appeared to precipitate deep venous thrombosis of the extremity. Lea Thomas, a radiologist, developed specialized techniques to visualize the lesions with contrast, while recognizing that venographic sensitivity was only about 50%.<sup>5</sup> Modern imaging techniques have confirmed that iliac vein compression posterior to the crossing right common iliac artery is present in as much as two-thirds of the general population.<sup>6</sup> Recent use of intravascular ultrasound (IVUS) has shown the lesion to be present at more diverse locations in the pelvic venous anatomy (Fig. 161.1), and that it affects a much broader demographic than the narrow band recognized by Cockett and colleagues. IVUS has a sensitivity of >90% for the lesion.<sup>7</sup> Most lesions are silent, but symptoms ranging from swelling to venous ulcerations may be present. The lesion is best viewed as a permissive pathology, precipitating symptoms when a secondary insult to the limb, such as trauma, infection, or deep venous thrombosis (DVT) is superimposed. Post-thrombotic iliac vein stenoses resulting from DVT, either precipitated by a May–Thurner type of lesion or occurring *de novo*, are increasingly recognized. Specific relief of symptoms after percutaneous stent placement has largely silenced earlier critics who argued that the obstructive lesion, even when associated with collaterals, is a “natural anatomic variant” not requiring specific



**Figure 161.1** Common Sites of Iliac Vein Stenosis Seen on Intravascular Ultrasound Examination. The “classic” proximal nonthrombotic iliac vein lesion (NIVL) occurs in the left common iliac vein posterior to where it is crossed by the right common iliac artery. The distal lesion on the left side occurs posterior to the left hypogastric artery crossing. On the right side, both proximal and distal lesions underlie the right common iliac artery. Compression by the inguinal ligament is also a source of stenosis.

correction. Percutaneous iliac vein stenting has rendered earlier veno-venous bypass techniques all but obsolete, and these techniques are now reserved only for stent failures. IVUS technology has also exposed venous obstruction at the iliac level as a major cause of chronic venous disease (CVD).<sup>7,8</sup> The safety and efficacy of venous stenting have dramatically broadened the spectrum of CVD patients who can undergo treatment for this disease with clear clinical improvement. This represents a major treatment paradigm change. An unexpected finding in recent stent experience is the observation that patients with combined obstruction and reflux appear to benefit clinically even if the associated reflux remains untreated.<sup>8</sup>

## PATHEOLOGY

Two major types of iliocaval venous obstruction are recognized, nonthrombotic iliac vein lesions (NIVL), synonymous with MTS, and post-thrombotic iliac vein stenosis (PTS) resulting from a prior episode of DVT.<sup>9</sup> The relative incidence in major centers is roughly 50/50 but trending higher in favor of the post-thrombotic variety because of improved diagnosis of iliac vein DVT with modern imaging modalities. About 10% of cases are of the mixed type, as NIVL can precipitate thrombosis, and thrombus tends to add fibrosis to compression points in the vein during organization. NIVL lesions are typically subsegmental and focal, occurring in areas where compression by the overlying artery or ligament occurs (Fig. 161.1). PTS lesions are longer, involving one or more vein segments, with focal elements. A special form of long diffuse stenosis caused by

a post-thrombotic fibrous envelope surrounding the vein was first recognized by Rokitansky in autopsy studies. Milder forms of this type may not be recognizable in venograms without luminal measurements (Fig. 161.2). A focal lesion occurring in association with a Rokitansky stenosis will be underestimated as the adjacent reference segment for calculation of the stenosis is not normal but stenotic.

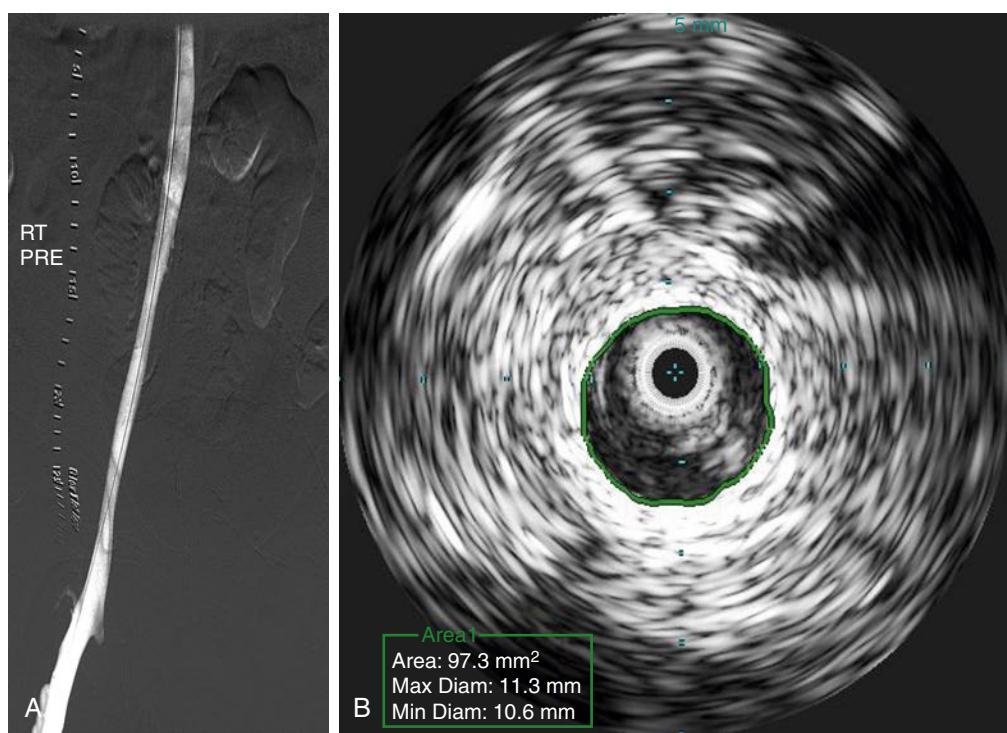
The majority of limbs with iliac vein obstruction will also have reflux below the inguinal ligament,<sup>10</sup> resulting in peripheral venous hypertension. Both the obstructive and reflux pathologies cause microvascular injury, which is sustained by the peripheral venous hypertension.<sup>11</sup> Recent studies have shown that central venous obstruction is more associated with elevated supine venous pressure while reflux is more associated with elevated venous pressures in the upright position. Ambulatory venous pressure which rises with increasing CEAP clinical class also worsens with increasing reflux and is less associated with obstruction.<sup>12,13</sup>

Venous collateralization is poorly understood. In many venous territories, alternative pathways already exist. They normally remain dormant as flow preferentially takes the course of the lower resistance main pathway. When the main channel is stenosed or occluded and the venous pressure rises, flow is diverted through these alternative routes. When the axial stenosis is stented, flow once again takes the lower resistance pathway and the collaterals “disappear.” Venographic collaterals can be demonstrated in about 30% of iliac vein stenoses.<sup>7,9</sup> Because of the geometric factor ( $r^4/L$ ) in the Poiseuille equation, an exponential number of collaterals are needed to equal the conductance of the normal iliac vein. For example, 256 collaterals, each 4 mm in size, are required to equal the conductance of a 16-mm common iliac vein. For this reason, it is rare for iliac vein lesions to be fully compensated by adequate collateralization. The exponential power of the geometric factor plays a role in venous resistance. The magnitude of its effects can be surprising. For example, a luminal stenosis of a mere 12% in the common iliac vein (16 mm to 14 mm) will nearly double the resistance, and hence, the pressure with the same flow.

Using isotope lymphangiography, lymphatic dysfunction can be demonstrated in ≈30% of limbs with CVD.<sup>14,15</sup> The injury occurs at the pre-collector level, presumably in association with the microcirculatory injury of CVD. Normalization of these scintigraphic abnormalities occurs in about 25% of limbs following iliac stenting (Fig. 161.3).

## INDICATIONS AND PATIENT SELECTION FOR ILOCAVAL VENOUS STENTING

CVD in general is a nonlethal disease and loss of limb is a rarity. There is no role for prophylactic treatment of silent lesions. If symptoms resulting from iliocaval stenosis or occlusion are present, conservative treatment with compression is the initial treatment modality. This modality will fail in 50% or more patients because of inefficacy or, more often,



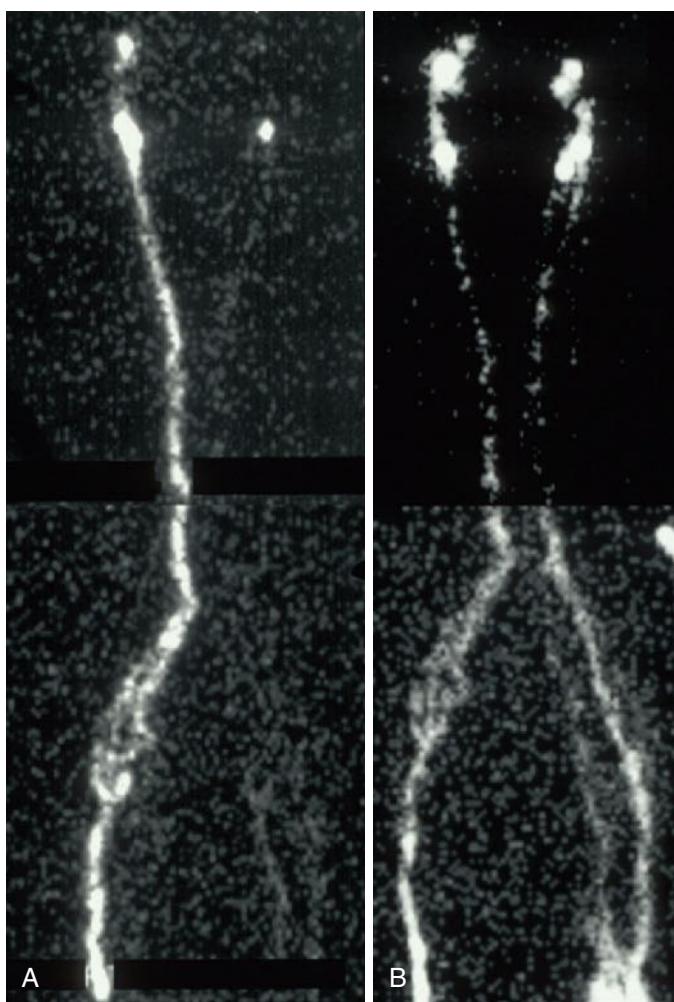
**Figure 161.2 Rokitansky Stenosis.** The long diffuse stenosis is not readily apparent on venography, which lacks an internal scale (A). On intravascular ultrasound examination (B) the maximum common iliac vein diameter is 11 mm with an area of 97 mm<sup>2</sup>, constituting a 50% area stenosis.

noncompliance with compression regimens.<sup>16</sup> The nature and cause of noncompliance is poorly understood. Intensive monitoring, education, and supervision have had no effect on the problem.<sup>17,18</sup> Iliac vein stenting may be carefully considered after failure of conservative treatment. Patients should be advised that this is not a “circulation problem” of the type that affects arteries, but a disease that usually manifests with only quality-of-life issues. Patients are often relieved by this information alone and are then able to make an informed decision regarding intervention.

In general, only patients with CEAP classes 3 to 6 are candidates for correction of iliocaval stenosis. Lesser clinical classes can occasionally be considered if they are thought to have venous claudication or the “venous hypertension syndrome.” Patients with venous hypertension syndrome have diffuse limb pain (not to be confused with local pain over varices) relieved by elevation of the limb and compression stockings. Some patients have learned that ambulation can provide pain relief due to lowering of the venous pressure by calf pump action. Atypical pain syndromes include venous claudication (particularly when climbing stairs), nocturnal leg cramps, restless legs, and dull, diffuse, achy limb pain at night even with the leg elevated. Lifestyle limitations and sleep deprivation from these atypical pain syndromes are appropriate indications for corrective intervention. Pain severity should be assessed by the visual analog scale (VAS). Venous clinical severity score (VCSS) is the current standard for complete clinical assessment (see Ch. 20, Clinical Evaluation of the Venous and Lymphatic Systems).

Special patient subsets who may benefit from stent correction of iliocaval venous stenosis include geriatric patients who cannot self-apply compression due to arthritis or frailty, obese patients with severe venous manifestations who are not candidates for weight reduction surgery, patients with recurrent cellulitis of the limb secondary to the obstructive lesions, and cases of acute iliac vein thrombosis caused by an underlying stenosis. Lysis of the acute thrombus will initially be required in combined acute/chronic lesions. It is best to wait for at least 2 months after lysis and pursue stenting selectively in patients who continue to remain symptomatic or have recurrence of symptoms following thrombolysis.

In another special category are limbs with swelling diagnosed as lymphedema. Too often, this diagnosis is based only on clinical impression without the benefit of isotope lymphangiography. “Classic” clinical features of lymphedema, such as dorsal foot hump, squaring of toes, and Stemmer sign, can be present in venous swelling as well, with or without associated lymphatic damage/dysfunction. A recent study that evaluated the diagnostic accuracy of clinical signs in comparison to lymphoscintigraphy found clinical signs of lymphedema to be unreliable in making a correct diagnosis of lymphedema in a third of patients. Conversely, in lymphoscintigraphy-confirmed lymphedema, only 17% had positive clinical signs. The study found venous obstruction as the most common cause of clinical signs in patients without lymphedema.<sup>19</sup> Considering the huge prevalence of CVD in western populations and the high incidence of associated lymphatic abnormalities, it is likely that lymphedema associated



**Figure 161.3** Venous Lymphedema. Note the absence of lymphatic activity in the left lower limb on lymphoscintigraphy (A). Activity recovers (B) after the underlying iliac venous stenosis is corrected with a stent.

with CVD (“venous lymphedema” or phlebolymphedema) is the most common type of secondary lymphedema in the United States, with a prevalence far exceeding either primary lymphedema or other secondary causes.

A diagnosis of lymphedema may consign the patient to lifelong, often ineffective conservative therapy. It is recommended that a correctible iliac vein stenosis be ruled out in individuals before a diagnosis of lymphedema is established for treatment purposes. After stent correction of a stenosis discovered by this approach, improvement in swelling can be expected, although to a lesser degree than in obstructed limbs without lymphatic abnormalities (see Fig. 161.3).

Associated reflux is often present in patients diagnosed with iliac vein obstruction. If the reflux is in the superficial system, saphenous ablation can be performed before iliac vein stenting, or it can be accomplished concurrently.<sup>20</sup> Patients with deep reflux should undergo iliac vein stenting first, as good results can be anticipated despite the residual reflux.<sup>21</sup> Deep reflux corrective procedures which currently require complex open techniques are reserved for the salvage of nonresponders to initial stenting.

## DIAGNOSIS

Venography has been the main imaging modality to diagnose iliac vein lesions. Transfemoral injection of contrast is required as adequate opacification of pelvic venous anatomy is often not obtained by pedal injection. Because iliac vein lesions are manifested as compression in the coronal (distal lesion) or the sagittal plane (proximal lesion), single plane views can be misleading (Fig. 161.4). However, subtle signs are often present to alert the astute observer (Fig. 161.5).

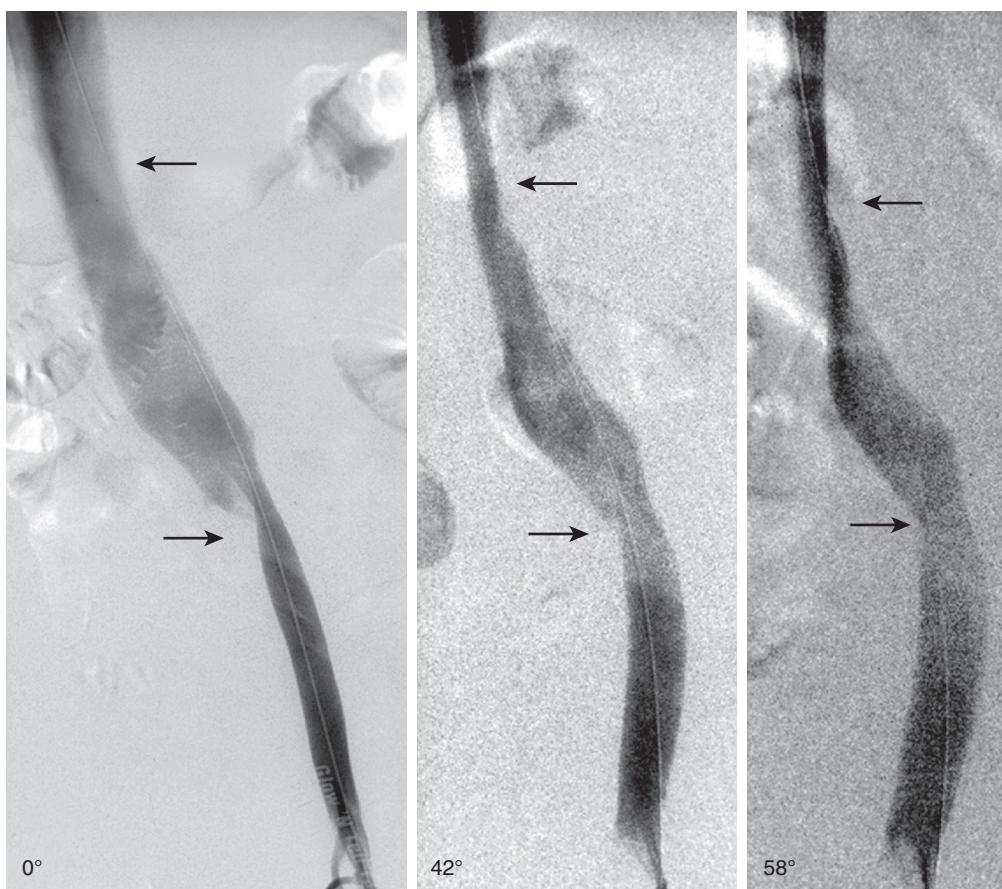
In a blinded comparison of IVUS and transfemoral venography in 155 limbs at our institution, the presence of a stenosis in the iliofemoral segments was altogether missed by venography in 19%.<sup>22</sup> Among those lesions visible with contrast, the degree of stenosis was significantly underestimated compared to IVUS ( $P < 0.001$ ). In addition, the level of the iliac confluence as determined by venography varied by as much as one vertebral body length compared to that identified using IVUS. The ideal upper and lower landing zones determined by venography agreed with IVUS guidance in only 15% and 26% of limbs, respectively.<sup>22</sup> Therefore, IVUS guidance during stent placement is preferred.<sup>22–24</sup> These procedural elements are crucial for technical success and outcome.

Imaging techniques (computed tomography venogram, magnetic resonance venogram, or duplex ultrasound) can be more definitive than venography for diagnosis, as lumen size at stenotic points can be measured by the intrinsic scale, which is not possible with venography. Recent studies have confirmed the ability of computed tomography venogram in diagnosing iliocaval venous obstruction by comparing it to IVUS.<sup>25,26</sup> At present, we consider IVUS the gold standard in the morphologic diagnosis of iliac vein lesions.

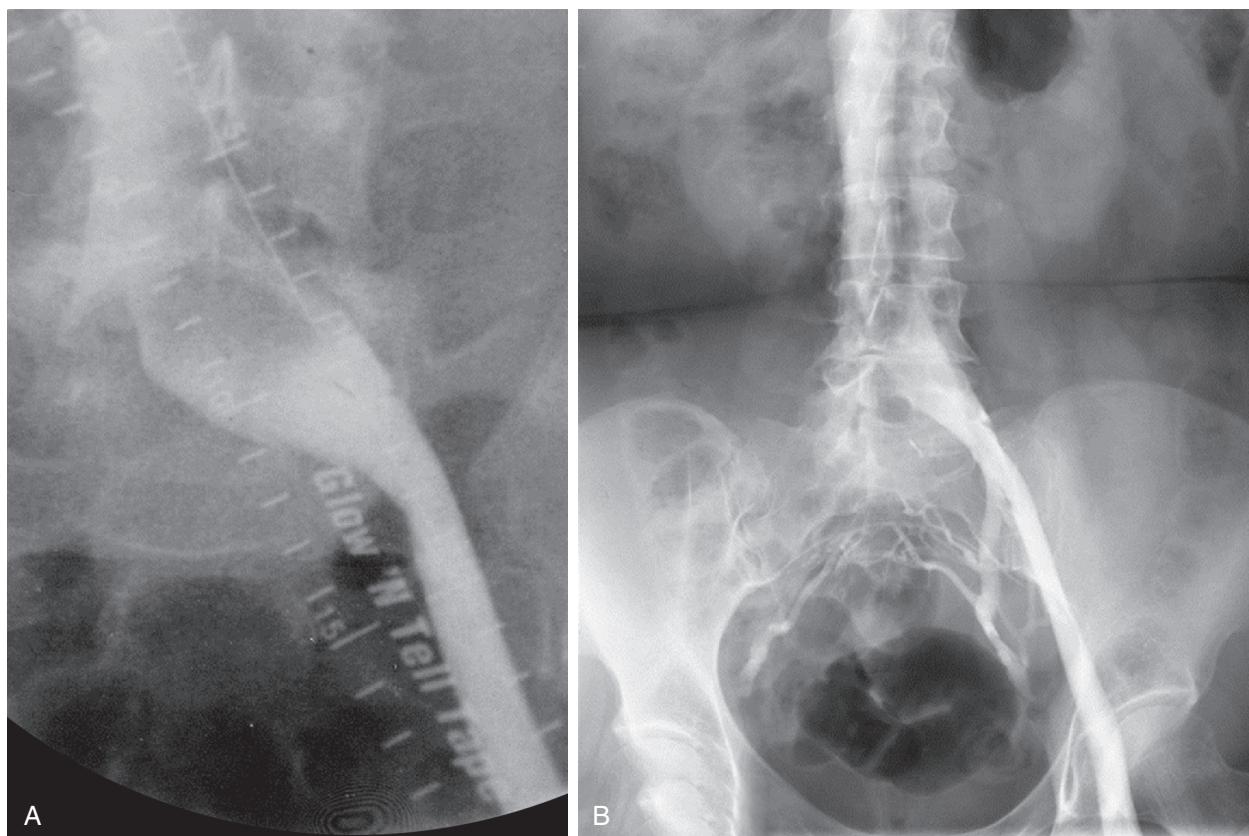
## TREATMENT

### Technique

A mid-thigh ipsilateral femoral vein access under ultrasound guidance is preferred. Access at superficial locations over bony points, as in arterial practice, is not necessary. Low venous pressure facilitates even deep access with few hematomas or other complications. A large sheath, typically 11F, is preferred for easy manipulation of inserted devices. The mid-thigh access allows enough room for the sheath to deploy stents below the inguinal ligament if needed. This approach has the advantages of the supine position, short distance to the lesion, and antegrade manipulation. Popliteal and internal jugular access are somewhat inferior, but can be used as backup sites. An optional on-table venogram may be performed for diagnostic and road-mapping purposes. The procedure can be performed solely with fluoroscopy and IVUS control without using contrast in the event of contrast allergy or renal dysfunction. IVUS examinations of the inferior vena cava (IVC), common iliac vein (CIV), external iliac vein (EIV), and common femoral vein (CFV) are carried out to identify lesions and appropriate landing sites. IVUS planimetry is used to measure areas. The degree of stenosis is best calculated using the expected normal



**Figure 161.4** Nonthrombotic iliac vein lesions are often two-dimensional rather than circumferential. In the example shown, the proximal lesion is not apparent on frontal projection ( $0^\circ$ ) but is revealed on lateral projections (←). The distal lesion apparent in the frontal view becomes hidden in oblique and lateral projections (→). The level of iliac confluence is not readily apparent in the frontal view.



**Figure 161.5** Venographic appearance of nonthrombotic iliac vein lesion: “island”-like appearance of the terminal common iliac vein (A). “Pancaking” (B) with collaterals.

Downloaded for Paing Myint (pmyint@gmail.com) at University of Pretoria from ClinicalKey.com by Elsevier on July 06, 2022. For personal use only. No other uses without permission. Copyright ©2022. Elsevier Inc. All rights reserved.

**TABLE 161.1**

## Optimal Iliofemoral Venous Segment Diameters/Areas

Vein	Diameter (mm)	Luminal Area (mm <sup>2</sup> )
CFV	12	125
EIV	14	150
CIV	16	200

CFV, common femoral vein; CIV, common iliac vein; EIV, external iliac vein.

area for the location (Table 161.1). Using the adjacent or contralateral lumen as a reference may result in underestimation of the stenosis; long diffuse narrowing of the lumen is present in an estimated 20% either alone or in association with focal stenosis.<sup>27</sup> It is important to keep in mind that venous hypertension can result with luminal area stenosis <50% secondary to changes in compliance.<sup>28</sup> In this regard it is imperative not to use a predetermined stenosis cutoff to determine stenting. Patients with disabling symptoms merit stenting even if the degree of stenosis is less than 50%. Predilation using large-caliber (16 to 18 mm) high-pressure balloons (14 to 16 atm) is routine. Because of the fibrous nature of iliac vein lesions, angioplasty alone is seldom effective as recoil is the rule. Large-caliber stents approximating the normal size of the iliofemoral segments should be used. The use of undersized stents is among the most common causes of iatrogenic stenosis with persistent symptoms (Fig. 161.6).

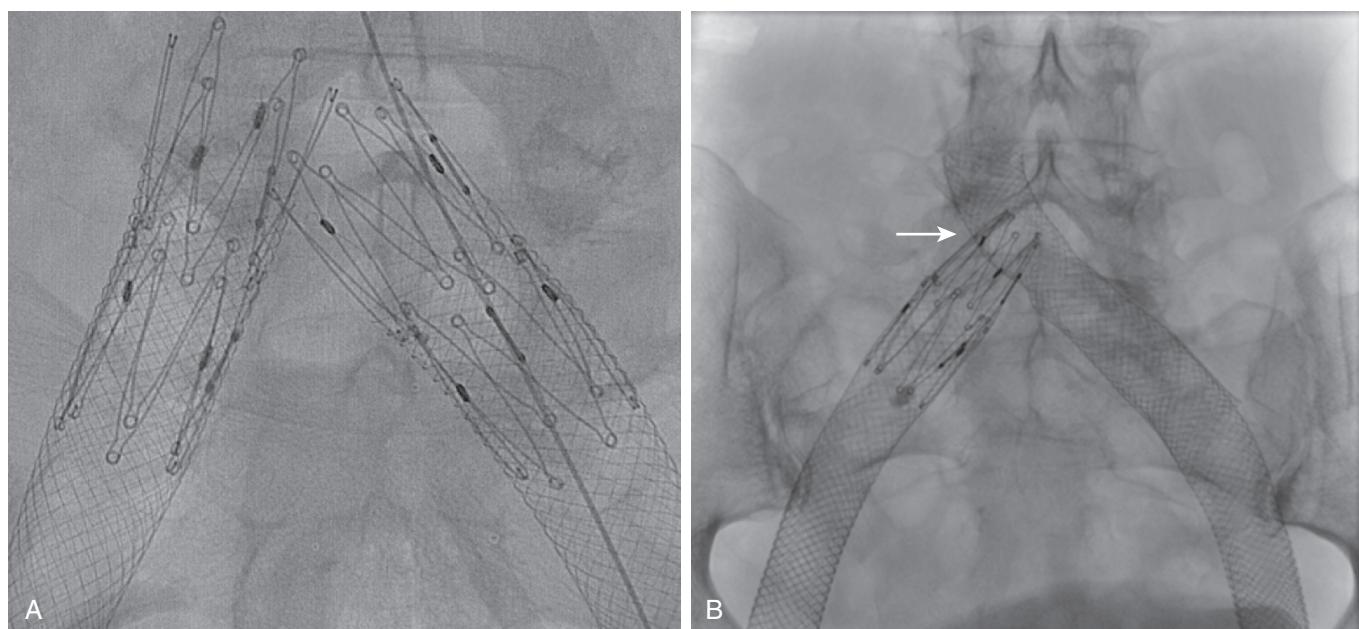
Treating the entire diseased segment or lesion in continuity with landing sites clear of disease is essential for successful outcomes. Skipping short segments of apparently normal vein is a source of potential recurrence. It appears that metal load is a lesser cause of stent thrombosis than uncovered lesions. From this perspective, a philosophy of liberal stent coverage rather than one of limited use should govern. Most limbs with post-thrombotic disease will require extension of the stent below the inguinal ligament into the common femoral vein. The stent end should remain above the orifice of the deep femoral vein, which provides adequate inflow in most instances to sustain the stent. Occasionally, the stent can be delivered into the deep femoral vein (via jugular, popliteal, or direct deep femoral access) if its ostium is involved in the post-thrombotic process. Stent fractures and erosions have been rare with stents crossing the joint crease, unlike arterial applications. Since the proximal lesion at the iliocaval confluence is spiral, incomplete stent coverage in this area is a common cause of residual symptoms. This tends to occur in procedures that are totally reliant on venographic control without the use of IVUS. The best upper and lower landing sites are chosen on IVUS views using the vertebral bodies and the femoral head as fluoroscopic markers. Extension of the iliac stent for a few centimeters into the IVC is generally required to traverse the proximal lesion in its entirety when Wallstents are exclusively used. An 18- or 20-mm stent dilated with 16- and 18-mm balloons, respectively, will accommodate most adults and provide a 2-mm reserve for extra dilation later if required. A Z-stent may be used proximally (within the Wallstent) for added radial strength under the artery, and to minimize jailing of the



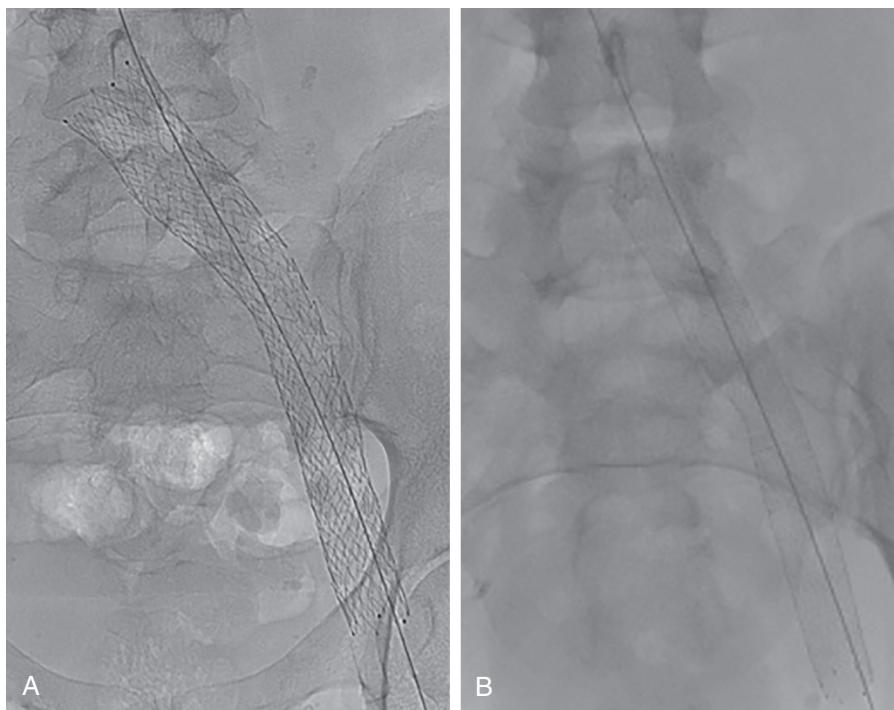
**Figure 161.6** An undersized 8-mm diameter stent (optimum 16 to 18 mm) was placed in the iliac vein (proximal arrow). Note the caliber of the stent is smaller than the common femoral vein (distal arrow). Placing an undersized stent results in an iatrogenic stenosis, which is difficult to correct.

contralateral iliac outflow (Fig. 161.7). The IVC Z-stent extension greatly simplifies bilateral simultaneous or sequential stenting by eliminating the need for difficult fenestration techniques to reconstruct the iliac confluence.<sup>29</sup> A significant reduction in contralateral DVT has been observed with the Z-stent extension compared to the Wallstent extension.<sup>30</sup> Use of appropriate size dedicated venous stents can be used in the same manner as Wallstent–Z-stent combination with regards to extension across the iliocaval confluence. Other principles of femoroiliocaval stenting discussed above should be borne in mind when utilizing the new stents. Dedicated venous stents currently approved for use by the FDA include Vici (Boston Scientific, Marlborough, MA) and Venovo (Bard, Tempe, AZ) (Fig. 161.8). Stenting the iliocaval confluence, particularly when there is bilateral disease, is an unsolved problem.<sup>31</sup> An ideal stent for the confluence is yet to be developed.

Post-dilation is carried out after stent deployment. IVUS planimetry is used to confirm that the stenosis has been corrected to achieve the recommended caliber shown in Table 161.1.<sup>22</sup> If not, a larger balloon up to the maximum-rated diameter of the stent is used to achieve the desired caliber. A completion venogram is performed to confirm patency and flow. The sheath is withdrawn slowly under ultrasound view until the tip exits the vein. A slight to-and-fro movement of the sheath confirms that it is outside the vein. A plug of Surgicel Fibrillar (Ethicon, Somerville, NJ) is loaded into the cylindrical plastic guard of the Seldinger needle.



**Figure 161.7** Z-Stent Inferior Vena Cava Extension of the Wallstent Stack. The widely spaced struts of the Z-stent minimize jailing of the contralateral iliac vein and allow easy bilateral sequential or staged iliac stenting (A). Fenestration techniques (B) are technically more demanding. In the example shown, a Z-stent has been used to scaffold the fenestrum created in the contralateral Wallstent (arrow). (From Raju S, Ward M, Jr., Kirk O. A modification of iliac vein stent technique. *Ann Vasc Surg.* 2014;28:1485–1492.)

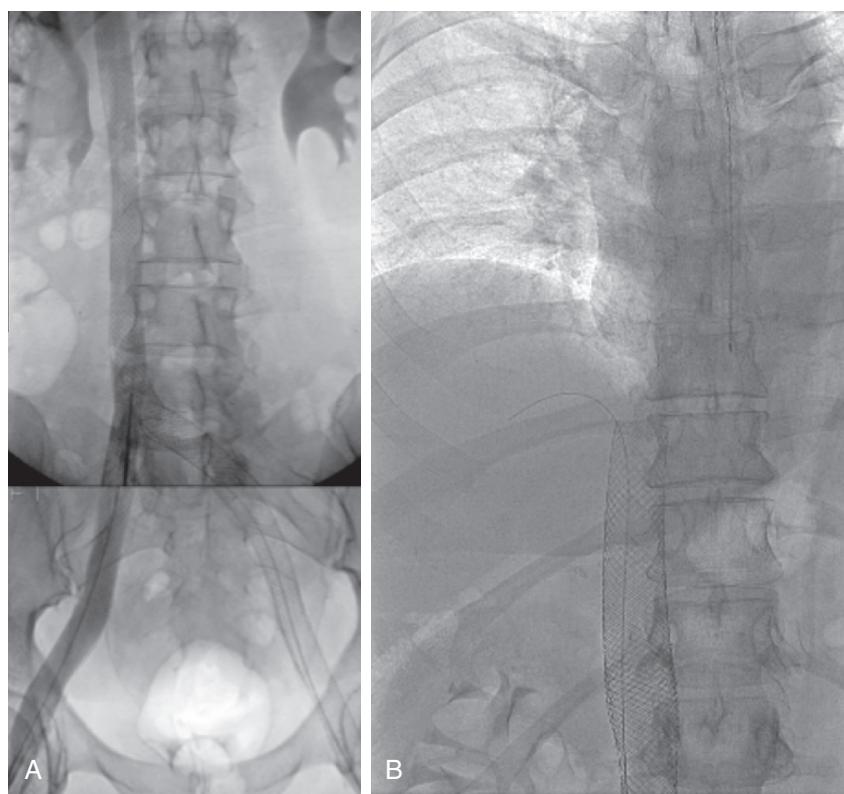


**Figure 161.8** Dedicated venous stents currently approved for use by the FDA. (A) Vici (Boston Scientific, Marlborough, MA). (B) Venovo (Bard, Tempe, AZ).

Using the obturator with the tip cut off, the hemostatic plug can be pushed into the sheath and delivered over the venotomy site before complete withdrawal of the sheath.

Recent data demonstrates that patients with bilateral chronic venous insufficiency symptoms should undergo initial

stenting of only the more symptomatic leg, since only 5% of patients with bilateral symptoms end up requiring stenting of the contralateral side. This is possibly from loss of collateral cross-pelvic channels (that cause overloading) post stenting of the ipsilateral side.<sup>32</sup>



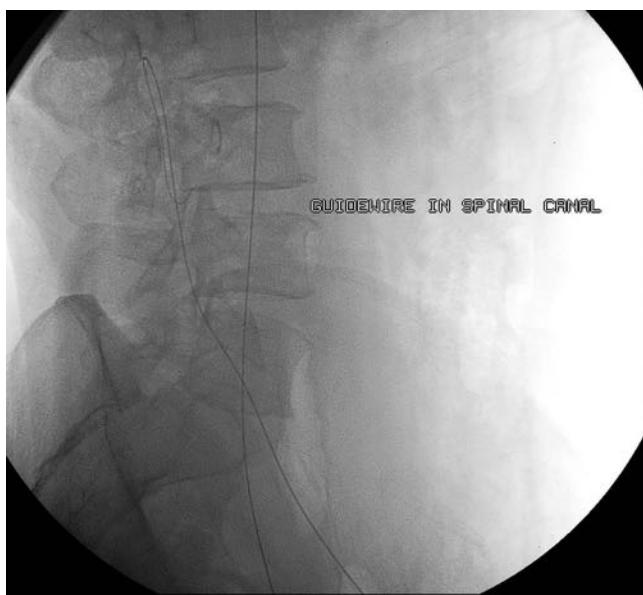
**Figure 161.9** Extensive recanalization of chronic total occlusions involving the inferior vena cava and both iliac veins. The stent stack extends to the common femoral vein below the inguinal ligament bilaterally (A). Stent erosions and fractures involving the Wallstent crossing joint creases are rare in venous applications. In (B), the Wallstent stack extends almost to the atrium.

## Recanalization of Chronic Total Occlusions

Once the province of complex open surgical procedures, chronic total occlusion (CTO) lesions have been found to be surprisingly amenable to percutaneous recanalization in an outpatient setting. Procedure success rates are in the range of about 85% for both iliac and IVC lesions.<sup>33,34</sup> Percutaneous recanalization of extensive occlusions involving both iliac veins and the IVC up to the right atrium have been reported in large case series (Fig. 161.9).<sup>33</sup> Most of these will have chronically occluded renal and hepatic drainage with alternate outflow already established. Few hepatic or renal complications after successful recanalization have been reported.

The recanalization process involves blind threading of a Glidewire through the trabeculated vein. Passage with the tip of the Glidewire rather than a loop is more often successful. Unlike in arterial CTO, no subendothelial or deeper dissection is performed. Venography, at least in the initial stages, is necessary to define the anatomy and provide a road map. Some CTO lesions that appear daunting on venography can be traversed with surprising ease. This is because contrast may not reach loosely trabeculated segments (often appearing as a “blush”) above short segments of more densely trabeculated vein. The use of angled-tip guiding catheters is standard. Specialized catheters for CTO crossing are helpful. The recanalization course should conform to the normal anatomic course of the occluded vessel. Off-course passage into collaterals or

perforations is easily recognized. Because of the low venous pressure and dense fibrous cover over CTO veins, free hemorrhage is rare. In case of perforation, the wire can simply be withdrawn and redirected without aborting the procedure. The passage of the wire into the vertebral canal through collaterals is a hazard if not recognized before balloon dilation. Since the abdominal IVC lies to the right of the vertebral column, passage of the wire in the midline is a clue to vertebral canal entry (Fig. 161.10). This can be checked by oblique or lateral fluoroscopic views. Once the entire CTO lesion is traversed, proper reentry into the open upper IVC or right atrium should be confirmed by venography or IVUS. Occasionally the wire passage may require predilation to allow passage of the 8.5-F IVUS catheter. Normally, the wire tract can be dilated to the desired caliber in a single pass. Stepwise dilation is not necessary as rupture/hemorrhage is very rare.<sup>35</sup> We recommend dilation to 24, 18, 16, and 14 mm for IVC, CIV, EIV, and CFV segments, respectively. To conserve supplies we use 18-mm balloons for all iliofemoral segments and have not encountered problems. Wallstents of corresponding size are then deployed. Small leaks and contrast extravasations are self-limiting once the low-resistance main pathway has been established by stent placement. Completion venography and IVUS planimetry are essential to ensure that a recanalized passage of adequate caliber without conduit defects has been established.

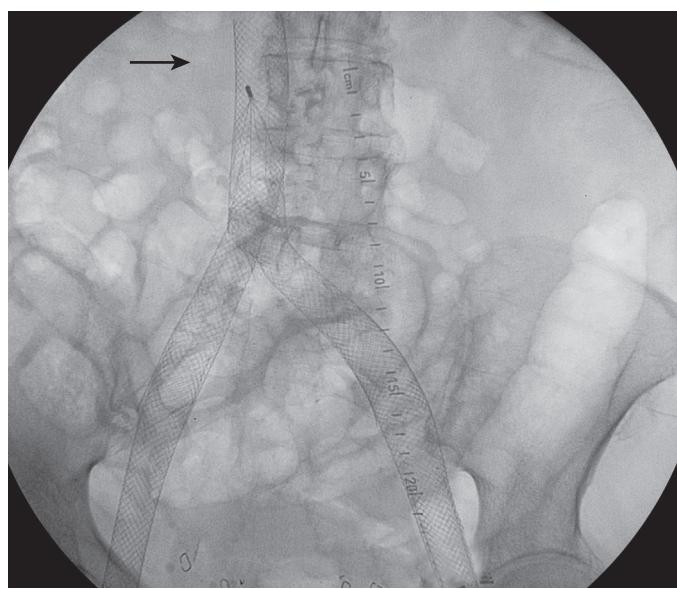


**Figure 161.10** Guidewire in the spinal canal visualized on lateral fluoroscopic views.

Inadequate inflow into stents is both a short-term and long-term threat to stent viability. There is presently no reliable way to assess inflow. Some stents with rapid washout of contrast have occluded, and others with sluggish flow have surprisingly remained patent. Intraoperative flow may be affected by extraneous factors, including the presence of the sheath obstructing inflow. Preoperative venographic assessments have not been reliable as more inflow channels become invisible once a low-resistance channel has been established by the stent. In extreme cases in which all the major named inflow pathways have become occluded and only multiple “twiggy” collaterals provide inflow, a temporary A-V fistula may be considered.

### Inferior Vena Cava Filters

Because of the recent liberal use of “ retrievable ” IVC filters, together with low retrieval rates, an increasing number of complications are currently seen with filter use. One of the more common complications is stenosis or thrombosis of the IVC near the filter. CTO of the IVC and one or both iliac veins produces swelling and pain of the extremities, which can be quite severe. Removal of the filter before recanalization is desirable, but retrieval of a filter encased in fibrous tissue is sometimes impossible. In such instances, the IVC filter can be crushed by balloon angioplasty and stented across using the recanalization technique described earlier (Fig. 161.11). Filters of many types (with the exception of the Mobin-Uddin filter) have been successfully treated in this fashion without adverse sequelae.<sup>33</sup> Permanent anticoagulation is desirable after stent exclusion of the filter as thromboembolic protection is lost. Migration of the compacted filter and vicious perforations remain a potential threat in these patients, and patients should be adequately warned during informed consent discussion.



**Figure 161.11** Recanalization and stenting of the inferior vena cava (IVC) and both iliac veins following thrombosis associated with an IVC filter (arrow) which has been compacted and stented across. Cumulative patency is excellent despite the extensive metal load.

### Anticoagulation

Perioperative anticoagulation is used for routine prophylaxis and because of intraoperative endothelial injury. Endothelial healing is complete by 6 weeks after injury.<sup>36</sup> It is believed that deployed stents are covered by pseudo-endothelium or are incorporated into the vein wall within this time frame. This means thrombogenicity of the stented segments will be governed by inherent risk factors and not the presence of a stent, *per se*. Thrombophilia does not appear to influence long-term stent patency with proper anticoagulation.<sup>35</sup>

Stent anticoagulation protocols vary widely among centers. In our practice, patients receive low-molecular-weight heparin (LMWH) in prophylactic dosage before the procedure and bivalirudin (75 mg single dose) intraoperatively. Some centers use more rigorous anticoagulation using activated clotting time per cardiac protocols. Post-procedure, LMWH is continued at a prophylactic dosage for 48 hours. Patients with NIVLs are discharged on aspirin 81 mg daily if there is no prior history of DVT. Stent thrombosis is extremely rare in this subset. PTS patients are discharged on aspirin as well, if the original DVT was provoked by an event that is no longer present. Long-term anticoagulation with warfarin or one of the new generation oral agents is instituted if there is thrombophilia, recurrent thrombosis, previous unprovoked thrombosis, stenting following recanalization or extensive stenting.

### STENT OCCLUSION

Acute thrombosis of stents (<30 days) is rare ( $\approx 1\%$ ) and occurs almost exclusively in PTS limbs, particularly following CTO recanalizations.<sup>34,37</sup> Thrombolysis usually restores durable patency. In other cases, a lesion at the stent inflow is responsible,



**Figure 161.12** Stent compression is unique to venous stents. Compression is difficult to appreciate on venography (A). Using intravascular ultrasound, an 18-mm stent can be seen to have been compressed to 8 mm (B).

as identified by IVUS. Stent extension to cover the inflow obstruction is required in addition to thrombolysis. In our experience, late occlusions (>30 days) occur in 2.1% of stented limbs, overwhelmingly (77%) in post-thrombotic limbs.<sup>38</sup> Both early and late occlusions in nonthrombotic disease are quite rare.<sup>37,38</sup>

### Chronic Stent Malfunction

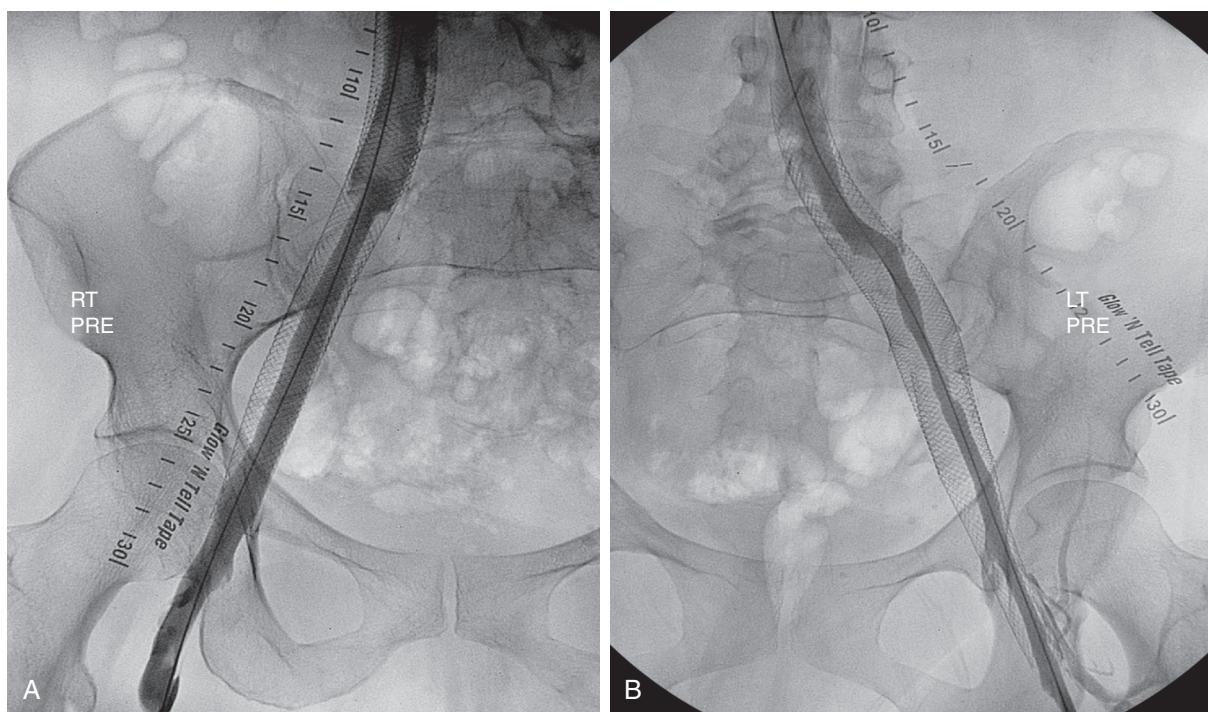
Chronic stent malfunction presents with residual or recurrent symptoms. Like any bypass conduit, stent malfunction is due to problems with inflow, outflow, the conduit itself, or a combination. There are some features unique to the venous stent.<sup>39</sup> Inflow/outflow problems are due to either missed or new lesions obstructing stent flow. Inadequate or partial coverage of the “classic” lesion at the iliocaval confluence during the original procedure is a common problem. This can be exacerbated by downward stent migration or foreshortening of the stent by the squeezing action of the partially covered lesion. A short (<2 cm) extension of the Wallstent into the IVC beyond the lesion can lead to coning of the upper end of the stent from compression by the nearby lesion. A small-caliber post-thrombotic IVC that was missed during the original procedure is an infrequent cause of stent malfunction, usually when IVUS planimetry was not used. Small-caliber IVC is not as well appreciated on venography as it lacks an internal scale. A normal adult infrarenal IVC has a transverse diameter of 17 to 24 mm on IVUS (smaller range in women). Area planimetry is not useful as the IVC is partially collapsed in most individuals.<sup>40</sup>

Inflow problems can occur when the distal lesion of the MTS (see Fig. 161.1) is missed during the initial procedure. This lesion is often not visible on venography or even

IVUS and requires “balloon-sizing” for detection.<sup>21</sup> New or missed post-thrombotic lesions can occur at the common femoral vein. When a short stent is used in the common iliac vein, extending only partially or not at all into the external iliac vein, a late stenosis (*de novo* stenosis) of unknown cause may develop in the external iliac vein after some years.

By far the most frequent causes of chronic stent malfunction are problems associated with the stent conduit itself. There are two major types: stent compression and in-stent restenosis (ISR) (Fig. 161.12).<sup>27</sup> Stent compression is unique to the venous system, wherein the stent is compressed from the outside, squeezing the lumen smaller than the original deployed caliber. The outside force is focal or diffuse fibrosis/restenosis of the stented segment. Stent compression is more resistant to balloon dilation than is ISR. In-stent restenosis occurring after iliac vein stenting is likely a different process from that affecting arterial stents. ISR that occurs early (<30 days) is probably mostly thrombus (thrombus lining/soft ISR) without cellular elements (Fig. 161.13). The thrombus lining is likely a result of sluggish flow in the now enlarged segment as the flow channel tends to modulate its caliber to correspond to the inflow. Anecdotal observation suggests that the thrombus lining may be cleared or reduced by instituting anticoagulation. It is also easily cleared at this stage by balloon maceration. After several months, this lining appears to be invested with fibrous elements (hard ISR) and is more difficult to clear by balloon dilation. Nonetheless, the majority can be cleared using aggressive high-pressure (14 to 16 atm) balloons.

Both stent compression and hard ISR are more common in PTS limbs, particularly after CTO recanalizations.<sup>41</sup> Progression of hard ISR from partial to total stent occlusion is very



**Figure 161.13** Venogram of an early in-stent restenosis (ISR) in an iliac stent (A). This likely occurs from thrombus build-up in the newly placed stent. The external iliac segment is commonly affected. (B) Venogram demonstrating late ISR in a severely post-thrombotic limb. The incidence and severity of ISR is higher in post-thrombotic limbs and is usually of the hard variety.

rare and appears to develop slowly over a period of years rather than in weeks or months. Most stent occlusions appear to be acute DVT events involving the stent, and differ from gradual progression of hard ISR to occlusion.<sup>38</sup>

### Stent Surveillance

The above description of stent malfunction makes it clear that routine stent surveillance protocols will improve outcomes. Our practice is duplex ultrasound (DUS) screening of the stent the day after placement, followed by DUS at 2 and 4 weeks post intervention to assess for acute stent occlusions and early thrombus lining (soft ISR). Later duplex surveillance intervals vary depending upon the original pathology. Lesions resulting from MTS are considered at low risk for occlusion and can be surveilled at 3- to 6-month intervals during the first year and less frequently thereafter. PTS lesions are more susceptible to stent malfunction and require quarterly surveillance during the first year and at least every 6 months thereafter. CTO recanalizations require even more intensive surveillance during the first year.

If symptoms fail to resolve or new symptoms develop, surveillance frequency should be modulated accordingly. Stent surveillance tends to promote follow-up continuity and probably reduces the number of patients “lost to follow-up.” The timing of reintervention in these cases of stent malfunction is based primarily on residual/recurrent symptoms except in rare instances in which stent occlusion appears to be imminent. We place patients with hard ISR

on cilostazol and optionally on prophylactic or therapeutic anticoagulation. The efficacy of these agents in venous stenting is undetermined.

## OUTCOMES

### Morbidity and Mortality

Endovenous correction of iliac and caval venous pathology can be done with minimal morbidity and mortality. In one large series of 982 stented limbs, access complications occurred in 0.4% despite the use of deep access sites. No procedure-related mortality occurred (30 days). DVT incidence was 3% over the 22 months of mean follow-up.<sup>37</sup> Multiple reviews of worldwide experience found femoroiliocaval stenting to be a safe and effective procedure with low morbidity across multiple procedures, including recanalization for chronic total venous occlusions (Tables 161.2 and 161.3).<sup>35,42</sup>

### Patency

Stent patency varies depending on underlying pathology. NIVL have excellent stent patency with very few failures compared to stenting carried out for post-thrombotic (PTS) lesions. Stent placement for the correction of stenosis has better secondary patency than do those performed for CTO. Neglen et al. noted primary and secondary cumulative stent patency of 79% and 100% for NIVL limbs, and 57% and 86%, respectively, for PTS limbs at the 6-year follow-up (Fig. 161.14). For

**TABLE 161.2** Patencies and Procedural Complications Following Iliocaval Stenting

First Author, Year	Case Mix: n (%)	CUMULATIVE PATENCY			Procedure Complications—n (%)
		Primary	Primary Assisted	Secondary	
Hartung, 2009	NIVL: 52/89 (58) PTS: 35/89 (39) Congenital: 2/89 (3)	83%  (Patency at 10 years)	89%	93%	Stent migration—2 Access site hematoma—2 Femoral artery tear—1 Contrast extravasation in CTO—2 Total—7 (8)
Knipp, 2007	PTS: 52/58 (90) NIVL: 6/58 (10)	38%  (Patency at 5 years)	63%	74%	Retained balloon—1 Stent migration—1 Groin hematoma—2 Retroperitoneal hematoma—1 Total—5 (9)
Meng, 2011	NIVL: 272/272 (100)	94%  (Mean follow-up of 4 years)	NA	NA	
Neglen, 2007	NIVL: 518/982 (53) PTS: 464/982 (47)	79%  (Patency at 6 years)	100% 80%	100% 86%	Femoral artery injury—4 Guidewire trapped in stent—1 Total—5 (0.5)
Ye, 2012	NIVL: 224 (100)	99%  (Patency at 4 years)	99%	99%	Local stent migration—3
<b>Chronic Total Occlusion</b>					
Kolbel, 2009	59	70%  (Patency at 5 years)	73%	80%	Access-site bleed—1 Perforation requiring transfusion—2 Total—3 (5)
Raju, 2009	139	32%  (Patency at 4 years)	58%	66%	Contrast-related transient rise in creatinine—1
Rosales, 2010	34	67%  (Patency at 2 years)	76%	90%	No major procedure related complication
Murphy, 2017	71 IVC filter occlusion: 38 Caval ligation/clipping: 4	52%  (Patency at 5 years)	85%	93%	Access site hematoma—1 Arterial pseudoaneurysm—1 Contrast related transient rise in creatinine—1 Total—3 (4)

CTO, chronic total occlusions; IVC, inferior vena cava; NIVL, nonthrombotic iliac vein lesions; PTS, post-thrombotic iliac vein stenosis.

CTO recanalization of iliocaval segments, cumulative primary and secondary patencies were 54% and 74%, respectively, at 48 months.<sup>37</sup> Murphy and colleagues from the same institution recently reported results of recanalization of CTO lesions involving the IVC and one or both iliac veins in 71 patients; primary and secondary patencies were 52% and 93%, respectively, at 60 months.<sup>33</sup> Worldwide results generally parallel these surprisingly good secondary stent patency rates for treatment of stenosis as well as CTO recanalization, as shown in Table 161.2. The lower primary patency reflects the need for re-interventional correction in post-thrombotic limbs to maintain performance.

## Clinical Results

Clinical results generally mirror the excellent patency of iliac vein stents (Table 161.3). Results reported by Neglen et al. are broadly representative. Cumulative rates of complete relief of pain and swelling were 65% and 32% with significant improvement (VAS  $\geq 3$ ; swelling  $\geq 1$  Gr) seen in 74% and 62%, respectively, at 5 years. Surprisingly, clinical results after iliac vein stenting appear to be good even if co-existing reflux is left uncorrected.<sup>8</sup> Raju and colleagues evaluated ulcer healing with iliac vein stenting in 192 limbs with and without reflux. The overall cumulative ulcer healing rate was

**TABLE 161.3** Clinical Outcomes and Complications Following Iliocaval Stenting

First Author, Year	Case Mix: n (%)	Clinical Outcomes	Clinical Complications—n (%)
Hartung, 2009	NIVL: 52/89 (58)	43/45 (96%) had improvement in pain; 31 (69%) had complete relief	Unrelated death—1
	PTS: 35/89 (39)	5/6 (83%) ulcers healed	DVT—5
	Congenital: 2/89 (3)	23/26 (89%) pelvic congestion improved; 15 (58%) cured	Total—6 (7)
Knipp, 2007	PTS: 52/58 (90)	80% had significant clinical improvement; 20% had no change	
	NIVL: 6/58 (10)		
Meng, 2011	NIVL: 272/272 (100)	84% had resolution of swelling 87% with skin pigmentation showed improvement 85% ulcers healed	
Neglen, 2007	NIVL: 518/982 (53)	Severe leg pain (VAS>5) decreased from 54% to 11%	No death
	PTS: 464/982 (47)	62% had cumulative total relief of pain	No pulmonary embolism
		Severe swelling (grade 3) decreased from 44% to 18%	DVT/stent thrombosis <30 days—14
		32% had cumulative total relief of swelling	DVT/stent thrombosis <30 days—23
		Cumulative ulcer healing 58%	Total—27 (4.5)
		Significant improvement in all categories	
Ye, 2012	NIVL: 224 (100)	Edema relief: 89% Ulcer healing: 82% Pain decreased from 4.3 to 0.4 (VAS) QOL significantly improved	No death No pulmonary embolism No DVT

**Chronic Total Occlusion**

Kolbel, 2009	66	Post-intervention 23% asymptomatic; 52% improved; 20% same; 6% worse	No pulmonary embolism  Stent thrombosis—14 (21)
Raju, 2009	139	79% had cumulative improvement in pain; 67% had complete relief	No death
		66% had cumulative improvement in swelling	DVT/stent thrombosis <30 days—10 <sup>a</sup>
		Cumulative healing of ulcers: 56%; complete relief in 32%	DVT/stent thrombosis >30 days—29 <sup>a</sup>
		QOL significantly improved	Contralateral thrombosis—3 Total—42 (30)
Rosales, 2010	32	Swelling and pain resolved in 32/34 (94%) 4/7 (57%) ulcers healed	Stent thrombosis—11 (34)
Murphy, 2017	60	66% had cumulative improvement in pain 41% had cumulative improvement in swelling Complete healing of ulcers in 78%	No death No pulmonary embolism Stent thrombosis 8/60 (13)

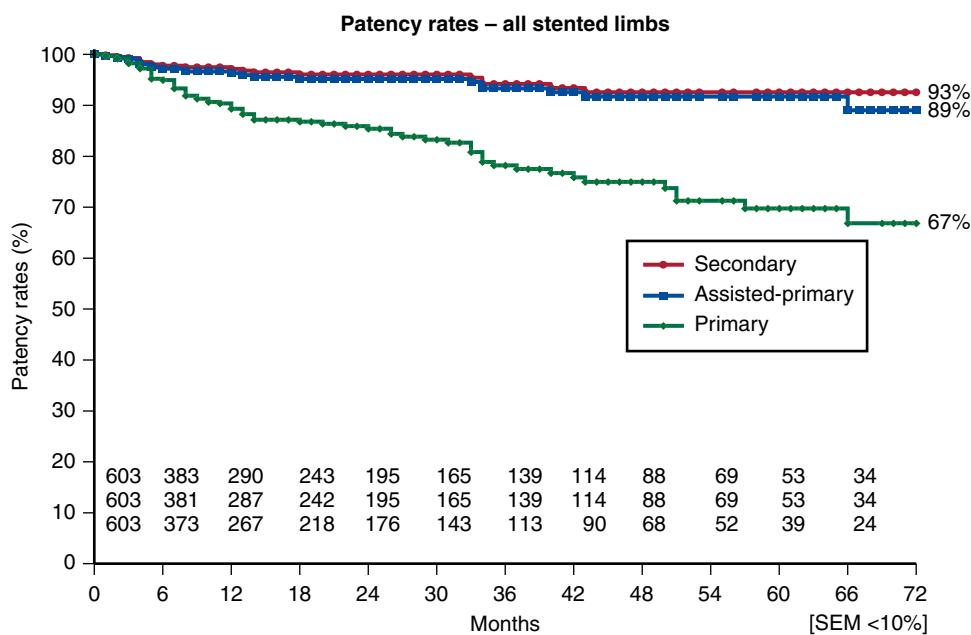
<sup>a</sup>Every stent thrombosis was considered a DVT.

DVT, deep vein thrombosis; NIVL, nonthrombotic iliac vein lesions; PTS, postthrombotic iliac vein stenosis; QOL, quality of life; VAS, visual analogue scale.

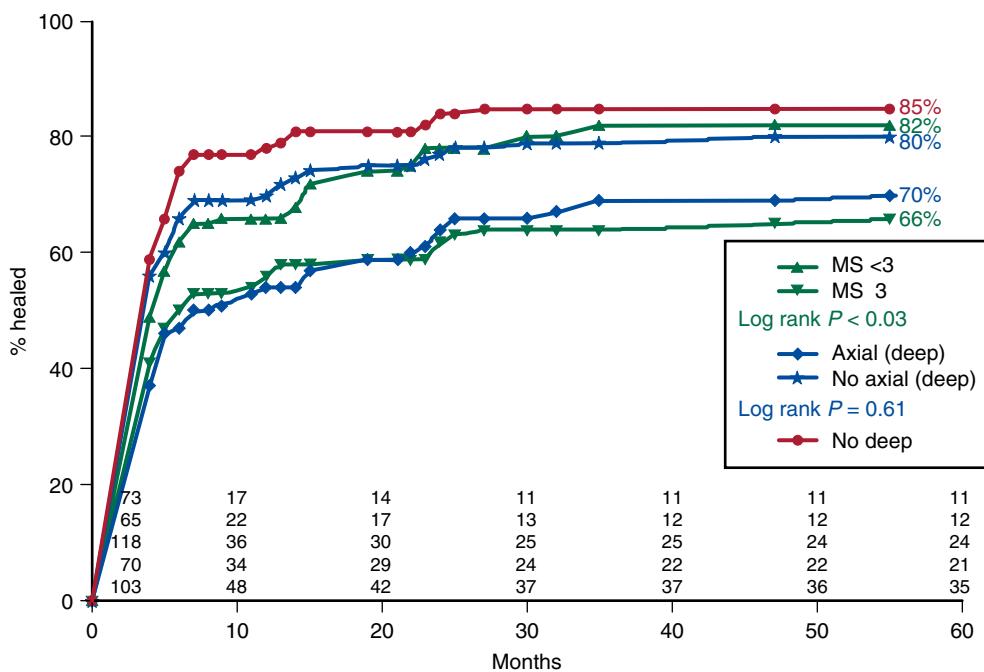
75% at 5 years (Fig. 161.15). Healing was better in limbs with NIVL (87%) compared to thrombotic limbs (66%). Ulcers <1-inch diameter had better healing rates than those with >1-inch diameter. Interestingly, the presence of axial deep reflux did not necessarily affect healing. However, limbs with reflux segment scores  $\geq 3$  had lower cumulative ulcer healing compared to limbs with reflux segment scores  $<3$ .<sup>21</sup>

**Special Scenarios****Geriatric Group**

Iliac vein stenting is a safe and effective option in the elderly (>80 years).<sup>43</sup> Many elderly patients are unable to apply compression because of frailty or arthritis. Ulceration or recurrent cellulitis requires frequent hospitalizations, often ending in institutionalization. On the other hand, percutaneous stent placement is



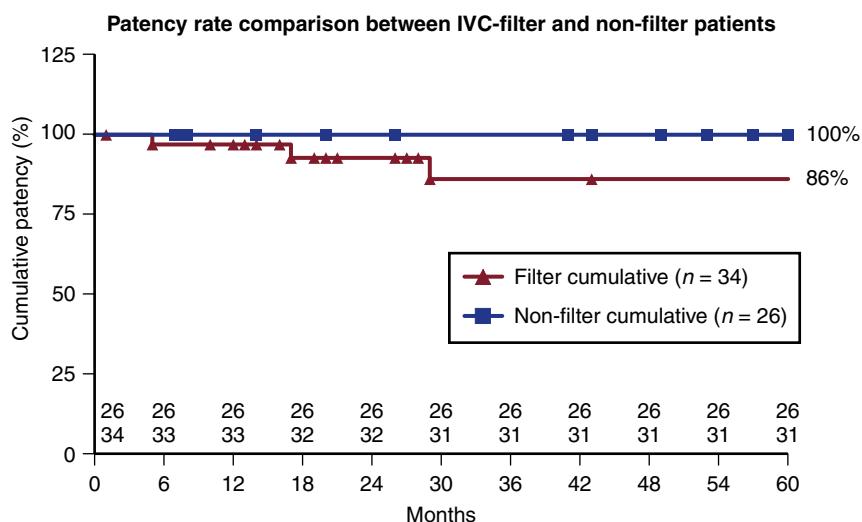
**Figure 161.14** Cumulative Patency Rates of Iliac Vein Stents (Thrombotic and Nonthrombotic Limbs). All of the stent occlusions occurred in post-thrombotic limbs and none in nonthrombotic limbs (NIVL) in this series. The secondary patency of NIVL in this series was a remarkable 100% (curve not shown). (From Neglen 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;46:979–990.)



**Figure 161.15** Cumulative Ulcer Healing in Limbs With and Without Deep Reflux. Note stable curve (few recurrences) after initial healing. There is no difference between limbs with and without axial reflux (blue). Cumulative healing (green) was lower ( $P < 0.03$ ) in limbs with three or more refluxing deep segments compared to those with less than 3 refluxing deep segments. The red curve represents limbs with isolated saphenous reflux treated by ablation. (From Raju S, Kirk OK, Jones TL. Endovenous management of venous leg ulcers. *J Vasc Surg Venous Lymphat Disord*. 2013;1:165–173.)

relatively well-tolerated. In a report of iliac vein stenting in 107 limbs in patients over the age of 80, there was no mortality; there was significant improvement of pain and swelling in 73% and 63%, respectively, at 6 years (cumulative data). Complete relief

of pain and swelling was observed in 43% and 25%, respectively. This study also noted relief from recurrent cellulitis in 70% of limbs, and 61% (cumulative) of ulcers healed at 6 years. Stockings were able to be discarded in 31% of patients.<sup>43</sup>



**Figure 161.16** Cumulative patency of stent recanalization of inferior vena cava chronic total occlusions (IVC CTO) with ( $n = 36$ ) and without ( $n = 24$ ) thrombosed filter. There is no difference in patency between the two subsets. Three limbs in which iliac vein stents occluded on one side with IVC patency maintained by the remaining iliac vein stent are counted as patent. (From Murphy EH, Johns B, Varney E, Raju S. Endovascular management of chronic total occlusions of the inferior vena cava and iliac veins. *J Vasc Surg Venous Lymphat Disord.* 2017;5:47–59.)

## Obese Patients

Iliocaval stenting has demonstrated benefit in CVD patients with a body mass index (BMI)  $>30$ . The incidence of bilateral CVD has been noted to be double in this subset in comparison to patients with BMI  $<30$  (28% vs. 14%;  $P < 0.01$ ).<sup>44</sup> Most have NIVL or PTS pathology, but venous compression can be caused by increased intraabdominal pressure from obesity.<sup>45</sup> Stenting in this group has been performed with good patency (86% secondary patency at 66 months). The clinical relief of pain, plus swelling and ulcer healing, is similar to nonobese patients.<sup>44</sup> The main treatment choice in these patients remains bariatric surgery; venous stenting can be considered if it is declined for medical or other reasons.

## Lymphedema

Secondary “venous lymphedema” can be seen in 16% to 30% of patients with CVD.<sup>14,15</sup> Careful attention must be paid to the diagnosis of obstructive venous lesions in this group as they may benefit from stent correction. Patients with secondary venous lymphedema have been noted to experience pain relief post stenting in a manner similar to their counterparts without lymphedema (83% vs. 87% at 40 months’ follow-up;  $P = 0.03$ ). Relief of swelling is somewhat less and occurs in 45% of limbs with lymphedema compared to 66% of limbs without ( $P < 0.01$ ).<sup>15</sup>

## Iliac Vein Stenosis With Tandem Femoral Vein Occlusions

Femoral vein occlusions are easily detected in CVD patients complaining of leg symptoms. The lesion often becomes the focus in contemplating treatment. Less obvious are associated iliac vein lesions that are not as easily detected. The occult iliac stenosis is often more severe, as recanalization/collateralization

in femoral occlusions is often satisfactory.<sup>46</sup> IVUS examination and iliac vein stenting may be considered in symptomatic limbs with tandem lesions. Good clinical relief has been reported with this approach.<sup>47</sup>

## Thrombosed Inferior Vena Cava Filter

Murphy and colleagues reported on their experience with stent recanalization of IVC CTO with occluded IVC filters with a mean follow-up of 4 years. There was no mortality or filter-related complications. Cumulative patency of the IVC stent ( $n = 34$ ) was 86% at 5 years, with good clinical relief (Fig. 161.16).<sup>33</sup>

## SELECTED KEY REFERENCES

- Murphy EH, Johns B, Varney E, Raju S. Endovascular management of chronic total occlusions of the inferior vena cava and iliac veins. *J Vasc Surg Venous Lymphat Disord.* 2017;5(1):47–59.
- Review of outcomes of stenting for management of occlusions of the iliocaval venous segments in 71 patients.
- Neglen 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(5):979–990.
- A comprehensive long-term study of clinical and stent-related outcome after venous stenting.
- Neglen P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. *J Vasc Surg.* 2002;35(4):694–700.
- The “gold standard” of IVUS to measure morphologic outflow obstruction is established.
- Raju S. Best management options for chronic iliac vein stenosis and occlusion. *J Vasc Surg.* 2013;57(4):1163–1169.
- Evidence summary addressing the diagnosis, management, and outcomes of stenting for iliocaval venous stenoses and occlusions.

Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. *J Vasc Surg.* 2006;44(1):136–143; discussion 144.

*The importance of the previously overlooked nonthrombotic iliac vein lesions (external compression) is pointed out.*

Raju S, Tackett Jr P, Neglen P. Reinterventions for nonocclusive iliofemoral venous stent malfunctions. *J Vasc Surg.* 2009;49(2):511–518.

*Review of and treatment of nonocclusive iliofemoral venous stent “malfunctions” in 137 patients following stenting for iliocaval venous stenoses and occlusions.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. McMurrich JP. The occurrence of congenital adhesions in the common iliac veins and their relation to thrombosis of the femoral and iliac veins. *Am J Med Sci.* 1908;135(8):342–346.
2. Ehrlich WE, Krumbhaar EB. A frequent obstructive anomaly of the mouth of the left common iliac vein. *Am Heart J.* 1943;26:737–750.
3. May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. *Angiology.* 1957;8(5):419–427.
4. Cockett FB. The iliac compression syndrome alias 'Iliofemoral thrombosis' or 'white leg'. *Proc Royal Soc Med.* 1966;59(4):360–361.
5. Thomas ML, Fletcher EW, Cockett FB, Negus D. Venous collaterals in external and common iliac vein obstruction. *Clin Radiol.* 1967;18(4):403–411.
6. Kibbe MR, Ujiki M, Goodwin AL, et al. Iliac vein compression in an asymptomatic patient population. *J Vasc Surg.* 2004;39(5):937–943.
7. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. *J Vasc Surg.* 2006;44(1):136–143; discussion 144.
8. Raju S, Darcey R, Neglen P. Unexpected major role for venous stenting in deep reflux disease. *J Vasc Surg.* 2010;51(2):401–408; discussion 408.
9. Neglen P, Raju S. Intravascular ultrasound scan evaluation of the obstructed vein. *J Vascular Surg.* 2002;35(4):694–700.
10. Johnson BF, Manzo RA, Bergelin RO, Strandness Jr DE. 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(2):307–312; discussion 313.
11. Pascarella L, Schonbein GW, Bergan JJ. Microcirculation and venous ulcers: a review. *Ann Vasc Surg.* 2005;19(6):921–927.
12. Raju S, Knight A, Lamanilao L, et al. Peripheral venous hypertension in chronic venous disease. *J Vasc Surg Venous Lymphat Disorders.* 2019;7(5):706–714.
13. Raju S, Knepper J, May C, et al. Ambulatory venous pressure, air plethysmography, and the role of calf venous pump in chronic venous disease. *J Vasc Surg Venous Lymphat Disord.* 2019;7(3):428–440.
14. Gloviczki P, Calcagno D, Schirger A, et al. Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. *J Vasc Surg.* 1989;9(5):683–689; discussion 690.
15. Raju S, JBr Furrh, Neglen P. Diagnosis and treatment of venous lymphedema. *J Vasc Surg.* 2012;55(1):141–149.
16. Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. *Ann Vasc Surg.* 2007;21(6):790–795.
17. Moffatt CJ. Perspectives on concordance in leg ulcer management. *J Wound Care.* 2004;13(6):243–248.
18. 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(5):629–636.
19. Jayaraj A, Raju S, May C, Pace N. The diagnostic unreliability of classic physical signs of lymphedema. *J Vasc Surg Venous Lymphat Disord.* 2019;7(6):890–897.
20. Neglen P, Hollis KC, Raju S. Combined saphenous ablation and iliac stent placement for complex severe chronic venous disease. *J Vasc Surg.* 2006;44(4):828–833.
21. Raju S, Kirk O, Jones T. Endovenous management of venous leg ulcers. *J Vasc Surg.* 2013;1:165–173.
22. Montminy ML, Thomasson JD, Tanaka GJ, et al. A comparison between intravascular ultrasound and venography in identifying key parameters essential for iliac vein stenting. *J Vasc Surg Venous Lymphat Disord.* 2019;7(6):801–807.
23. Gagne PJ, Tahara RW, Fastabend CP, et al. Venography versus intravascular ultrasound for diagnosing and treating iliofemoral vein obstruction. *J Vasc Surg Venous Lymphat Disord.* 2017;5(5):678–687.
24. Lau I, Png CYM, Eswarappa M, et al. Defining the utility of anteroposterior venography in the diagnosis of venous iliofemoral obstruction. *J Vasc Surg Venous Lymphat Disord.* 2019;7(4):514–521.e4.
25. Rossi FH, Kambara AM, Rodrigues TO, Rossi CBO, Izukawa NM, Pinto IMF, et al. Comparison of computed tomography venography and intravascular ultrasound in screening and classification of iliac vein obstruction in patients with chronic venous disease. *J Vasc Surg Venous Lymphat Disord.* 2020;8(3):413–422.
26. Jayaraj A, Raju S. Three-dimensional computed tomography venogram enables accurate diagnosis and treatment of patients presenting with symptomatic chronic iliofemoral venous obstruction. *J Vasc Surg Venous Lymphat Disord.* 2021;9(1):73–80.e1.
27. Raju S, Davis M. Anomalous features of iliac vein stenosis that affect diagnosis and treatment. *J Vasc Surg Venous Lymphat Disord.* 2014;2(3):260–267.
28. Raju S, Crim W, Buck W. Factors influencing peripheral venous pressure in an experimental model. *J Vasc Surg Venous Lymphat Disord.* 2017;5(6):864–874.
29. Raju S, Ward Jr M, Kirk O. A modification of iliac vein stent technique. *Ann Vascular Surg.* 2014;28(6):1485–1492.
30. Murphy EH, Johns B, Varney E, et al. Deep venous thrombosis associated with caval extension of iliac stents. *J Vasc Surg Venous Lymphat Disord.* 2017;5(1):8–17.
31. Neglen P, Darcey R, Olivier J, Raju S. Bilateral stenting at the ilio caval confluence. *J Vasc Surg.* 2010;51(6):1457–1466.
32. Jayaraj A, Noel C, Raju S. Contralateral limb improvement after unilateral iliac vein stenting argues against simultaneous bilateral stenting. *J Vasc Surg Venous Lymphat Disord.* 2020;8(4):565–571.
33. Murphy EH, Johns B, Varney E, Raju S. Endovascular management of chronic total occlusions of the inferior vena cava and iliac veins. *J Vasc Surg Venous Lymphat Disord.* 2017;5(1):47–59.
34. Raju S, Neglen P. Percutaneous recanalization of total occlusions of the iliac vein. *J Vasc Surg.* 2009;50(2):360–368.
35. Raju S. Best management options for chronic iliac vein stenosis and occlusion. *J Vasc Surg.* 2013;57(4):1163–1169.
36. Raju S, Perry JT. The response of venous valvular endothelium to auto-transplantation and in vitro preservation. *Surgery.* 1983;94(5):770–775.
37. Neglen 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(5):979–990.
38. Jayaraj A, Crim W, Knight A, Raju S. Characteristics and outcomes of stent occlusion after ilio caval stenting. *J Vasc Surg Venous Lymphat Disord.* 2019;7(1):56–64.
39. Raju S, Tackett Jr P, Neglen P. Reinterventions for nonocclusive iliofemoral venous stent malfunctions. *J Vasc Surg.* 2009;49(2):511–518.
40. Murphy EH, Arko FR, Trimmer CK, et al. Volume associated dynamic geometry and spatial orientation of the inferior vena cava. *J Vasc Surg.* 2009;50(4):835–842; discussion 842–843.
41. Neglen P, Raju S. In-stent recurrent stenosis in stents placed in the lower extremity venous outflow tract. *J Vasc Surg.* 2004;39(1):181–187.
42. Seager MJ, Busutil A, Dharmarajah B, Davies AH. Editor's Choice - A Systematic Review of Endovenous Stenting in Chronic Venous Disease Secondary to Iliac Vein Obstruction. *Eur J Vasc Endovasc Surg.* 2016;51(1):100–120.
43. Raju S, Ward M. Utility of iliac vein stenting in elderly population older than 80 years. *J Vasc Surg Venous Lymphat Disord.* 2015;3(1):58–63.
44. Raju S, Darcey R, Neglen P. Iliac-caval stenting in the obese. *J Vasc Surg.* 2009;50(5):1114–1120.
45. Padberg Jr F, Cerveira JJ, Lal BK, et al. Does severe venous insufficiency have a different etiology in the morbidly obese? Is it venous? *J Vasc Surg.* 2003;37(1):79–85.
46. Raju S, Fountain T, Neglen P, Devidas M. Axial transformation of the profunda femoris vein. *J Vasc Surg.* 1998;27(4):651–659.
47. Raju S, Ward Jr M, Davis M. Relative importance of iliac vein obstruction in patients with post-thrombotic femoral vein occlusion. *J Vasc Surg Venous Lymphat Disord.* 2015;3(2):161–167.

# Superior Vena Cava Occlusion and Management

MANJU KALRA, INDRANI SEN, HARALDUR BJARNASON, and PETER GLOVICZKI

## ETIOLOGY

2148

## CLINICAL PRESENTATION

2149

## DIAGNOSTIC EVALUATION

2149

Radiography 2149

Ultrasonography 2149

Radionuclide Imaging 2150

Computed Tomographic Angiography 2150

Magnetic Resonance Venography 2151

Contrast Venography 2152

## INITIAL TREATMENTS

2152

## INDICATIONS FOR INTERVENTIONAL TREATMENT

2152

## ENDOVENOUS TREATMENT

2153

## SURGICAL TREATMENT

2155

Graft Materials 2155

*Great Saphenous Vein Graft* 2155

*Femoral Vein Graft* 2156

*Spiral Saphenous Vein Graft* 2156

*Expanded Polytetrafluoroethylene Graft* 2156

*Other Grafts* 2157

## Surgical Technique

2157

## RESULTS

Results of Endovenous Treatment in Patients with Malignancy 2158

Results of Endovenous Treatment in Patients with Benign Superior Vena Cava Syndrome 2158

Complications, Restenosis, and Outcomes 2158

Results of Surgical Treatment 2159

Graft Surveillance 2161

## CONCLUSIONS

2162

In the United States each year about 15,000 patients develop symptoms of venous congestion of the head and neck due to occlusion of the superior vena cava (SVC) or innominate veins.<sup>1</sup> SVC syndrome is caused by malignant tumors of the lung and mediastinum in 60% of the cases.<sup>2</sup> The most frequent nonmalignant causes include placement of intravenous catheters, pacemaker wires, or mediastinal fibrosis.

Treatment for SVC syndrome involves creating outflow for the congested veins in the head and neck. Both endovascular and open surgical techniques are possible. Endovascular treatment for both acute and chronic SVC occlusion has become the first line of treatment for most patients because it is less invasive, and patients recover more quickly than following open surgery. Treatment in patients with advanced malignancy is frequently palliative, but for those with benign disease it is usually curative. Few areas of venous disease provide a more

satisfying experience for both the patient and the vascular specialist. Relief from severe, frequently incapacitating symptoms of venous congestion of the head and neck is almost instantaneous, and benefit is generally long lasting. In this chapter, we review the etiology, clinical presentation, and diagnostic evaluation of SVC syndrome, and present techniques and results for its treatment with endovascular and open surgical methods.

## ETIOLOGY

The first case of SVC obstruction described by William Hunter in 1757 was due to an aortic aneurysm. Aortic aneurysms remained the second most common cause of SVC syndrome after primary malignant thoracic tumors until the mid-1900s. Infectious causes such as tuberculous and syphilitic mediastinitis also

decreased markedly early in the 20th century. Lung cancer with mediastinal lymphadenopathy and primary mediastinal malignancy have become the most frequent causes of malignant SVC syndrome in the past three decades, constituting approximately 60% of cases.<sup>2–4</sup> Of these cases, nonsmall cell lung cancer is the cause in 50%, followed by small cell lung cancer (22%), lymphoma (12%), metastatic cancer (9%), germ cell cancer (3%), and thymoma (2%).<sup>1</sup> Other mediastinal malignant tumors leading to SVC syndrome include medullary or follicular carcinoma of the thyroid, teratoma, angiosarcoma, and synovial cell carcinoma.<sup>1–5</sup>

Benign disease is the cause of SVC syndrome in 40% of cases. Mediastinal fibrosis and granulomatous fungal disease, such as histoplasmosis, were formerly the most frequent benign causes. However, indwelling central venous catheters and cardiac pacemakers are now the most common benign cause.<sup>6–14</sup> Over 5 million central venous catheters and 170,000 pacemakers are now implanted annually in the United States and are associated with upper extremity or central deep venous thrombosis (DVT) in 7% to 33% of patients. SVC syndrome reportedly occurs in 1% to 3% of patients with central venous catheters and 0.2% to 3.3% of patients with implanted pacemakers.<sup>2</sup> Previous radiotherapy to the mediastinum, retrosternal goiter, and aortic dissection can also cause SVC syndrome. The risk of venous thrombosis is increased in patients with thrombophilia such as factor V Leiden mutation and deficiencies in circulating natural anti-coagulants, such as antithrombin III, protein S, and protein C.

## CLINICAL PRESENTATION

Signs and symptoms of venous congestion of the head, neck, and upper extremities are determined by the duration and extent of venous occlusive disease and the amount of collateral venous circulation that develops. Patients with SVC syndrome present with a feeling of fullness in the head and neck that is exacerbated when the patient bends over or lies flat in bed. The severity of disease can be graded by the number of pillows needed by the patient to sleep comfortably. Other symptoms include dyspnea on exertion, orthopnea, headache, dizziness, syncope, visual changes, confusion, and cough (Table 162.1).<sup>1,15,16</sup> Dilated neck veins and swelling of the face, neck, and eyelids are the physical signs most commonly seen (Fig. 162.1). Prominent chest wall collateral veins and ecchymosis and cyanosis of the face can occur. Although symptoms are usually localized to the head and neck, mild to moderate upper extremity swelling may also develop. In cases of malignant SVC syndrome, hemoptysis, hoarseness, dysphagia, weight loss, lethargy, and palpable cervical tumor or lymph nodes may be present. Patients with lymphoma may also present with fever and night sweats. In patients with end-stage renal disease (ESRD), asymptomatic SVC occlusion may be unmasked upon creation of an arteriovenous fistula (AVF), with rapid development of arm swelling and neck engorgement.

## DIAGNOSTIC EVALUATION

The diagnosis of SVC obstruction is usually suggested by a detailed history and physical examination. The diagnosis may be

**TABLE 162.1**

Signs and Symptoms of Superior Vena Cava Syndrome of Benign Etiology in 70 Patients

Symptoms	Number of Patients	%
Feeling of fullness in head or neck	61	87
Dyspnea on exertion or orthopnea	39	56
Headache	27	39
Dizziness or syncope	25	36
Visual problems	11	25
Cough	10	22
Nocturnal oxygen requirement	3	16
Protein losing enteropathy	1	2
Head and neck swelling	65	93
Large chest wall venous collaterals	40	57
Facial cyanosis	24	34
Arm swelling	23	33
Pleural effusion	2	3

From Rizvi AZ, Kalra M, Bjarnason H, Bower TC, Schleck C, Gловички P. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg*. 2008;47:372–380, with permission.

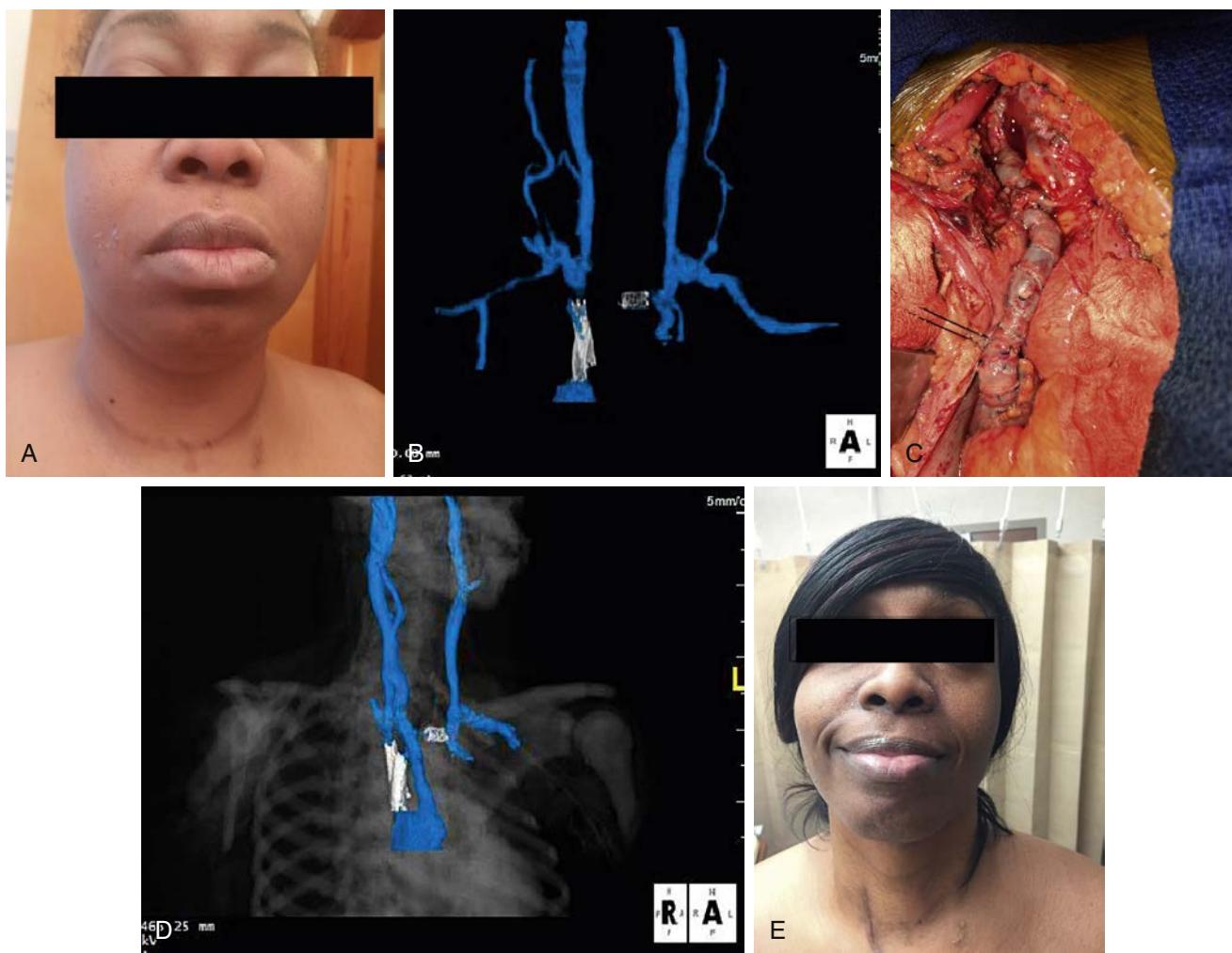
confirmed by a variety of tools, including plain radiographs, ultrasonography, computed tomography (CT), venography, and magnetic resonance imaging (MRI). The appropriate diagnostic study for an individual patient includes not only the demonstration of the underlying cause, but also the site and extent of obstruction as well as the routes of collateral venous circulation.

## Radiography

Plain film radiographs of the chest are readily available and often abnormal in patients with SVC obstruction. Most common findings include mediastinal widening, right hilar mass, pleural effusion, bilateral diffuse infiltrates, and upper lobe collapse. However, a normal radiograph of the chest does not preclude the diagnosis of SVC obstruction.<sup>1,4,17</sup> Occasionally, dilated collateral veins may be visible, especially enlargement of the azygos vein or superior intercostal vein (aortic nipple) draining the hemiazygos system. In more than 90% of patients a diagnosis of SVC syndrome can be made on the basis of clinical presentation and plain chest radiograph.<sup>16</sup>

## Ultrasonography

Duplex ultrasound (DUS) evaluation is an effective, noninvasive screening technique in the patient with suspected SVC obstruction. Although direct visualization of the SVC is not possible with transthoracic DUS, valuable information can be obtained. The subclavian and internal jugular veins are accessible to sonographic evaluation and can provide indirect evidence of SVC patency or obstruction. In the presence of



**Figure 162.1** (A) Recurrent severe symptomatic superior vena cava (SVC) syndrome in a 40-year-old woman following occlusion of prior kissing innominate vein stents. (B) CT venogram confirms thrombosis of the SVC and both innominate veins following placements of multiple central venous port-a-caths. (C) Right internal jugular vein–right atrial appendage spiral saphenous vein graft. (D) Postoperative CT venogram confirms graft patency. (E) Photograph of the patient 5 days after spiral vein graft placement. The clinical result is excellent 3 years after the operation.

SVC obstruction the normal respiratory flow variation caused by changes in intrathoracic pressure seen in patent subclavian veins is lost. This can be demonstrated by reduced or unchanged diameter and blood flow through the subclavian veins in response to respiratory maneuvers such as a sudden sniff or a Valsalva maneuver. Collateral vessels can be detected within the chest wall or in the mediastinum.

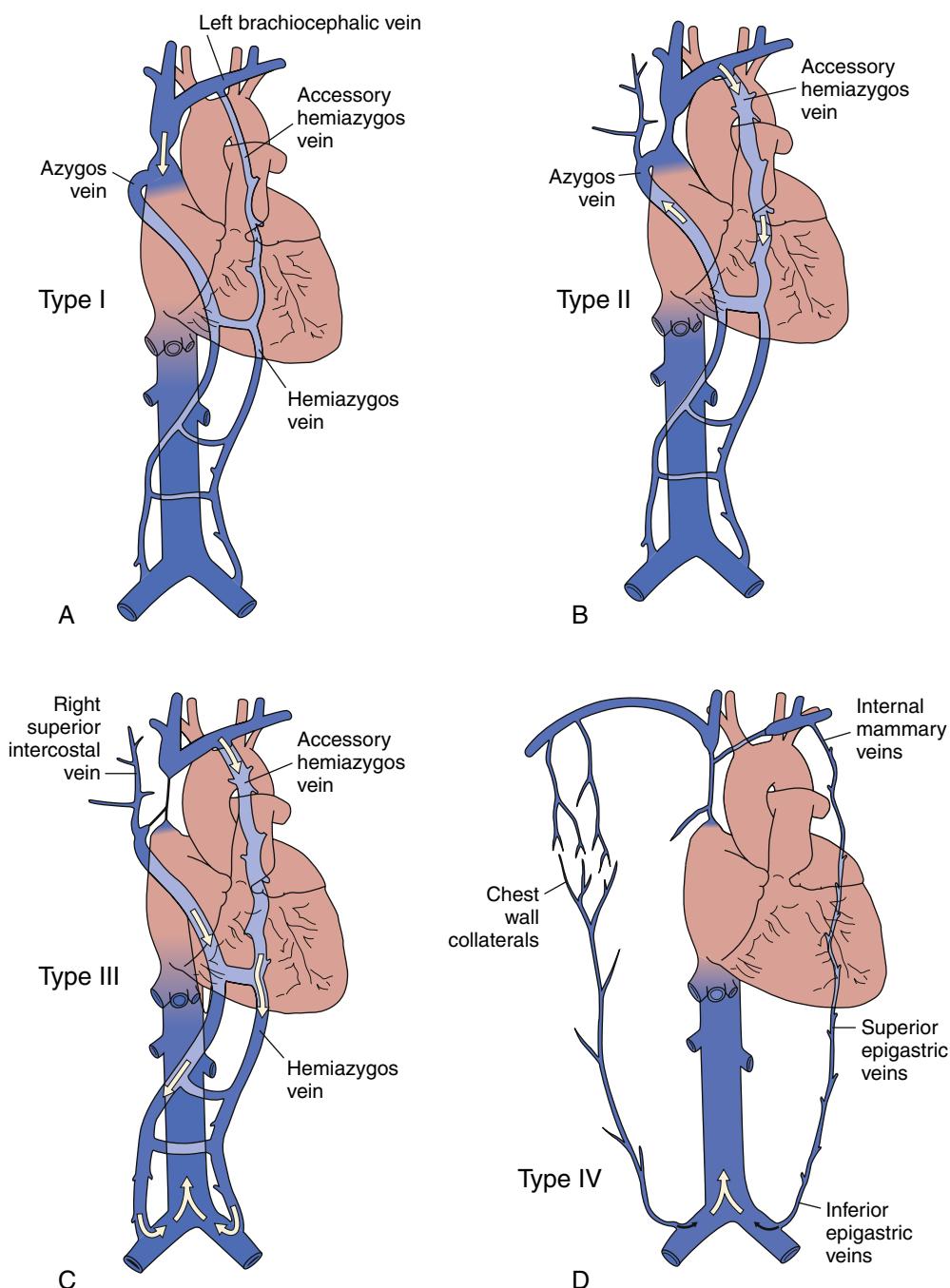
### Radionuclide Imaging

Radionuclide venography has been used in the diagnosis of SVC syndrome. A technetium 99m pertechnetate scan ( $^{99m}\text{Tc}$ ), performed with bilateral simultaneous injection of the radionuclide tracer into the arm veins, can not only demonstrate the presence of SVC obstruction and associated collateral pathways but also provide functional aspects of the SVC obstruction using time-density curves. An advantage is the potential usefulness as a follow-up examination in determining therapeutic response.<sup>18</sup> The disadvantage of radionuclide venography is the

lower-resolution anatomic detail and the inability to determine the cause of the SVC obstruction.

### Computed Tomographic Angiography

Computed tomographic angiography (CTA) has become the first line of diagnostic imaging due to its widespread availability, speed and ease of performance. It accurately depicts the location and extent of obstruction and can usually distinguish benign from malignant mediastinal disease.<sup>19–22</sup> Any mass or tumor is easily identified, and the central lines or pacemaker wires are well seen. CTA will also identify the collateral pathways, including the: (1) azygos–hemiazygos pathway, (2) internal mammary pathway, (3) lateral thoracic–thoracoepigastric pathway, and (4) vertebral pathway and small mediastinal veins. Less commonly, unusual shunts, including hepatic parenchyma (an intense focal enhancement in the medial segment of the left lobe of the liver) and pulmonary pathways are identified on CTA.<sup>23,24</sup>



**Figure 162.2** Venographic Classification of Superior Vena Cava (SVC) Syndrome According to Stanford and Doty. (A) Type I, High-grade SVC stenosis with normal direction of blood flow, but still normal direction of blood flow through the SVC and azygos veins. Increased collateral circulation through hemiazygos and accessory hemiazygos veins. (B) Type II, Greater than 90% stenosis or occlusion of the SVC, but patent azygos vein with normal direction of blood flow. (C) Type III, Occlusion of the SVC with retrograde flow in both the azygos and hemiazygos veins. (D) Type IV, Extensive occlusion of the SVC and innominate and azygos veins with chest wall and epigastric venous collaterals. (From Alimi YS, Głowiczki P, Vrtiska TJ, et al. 1998; Reconstruction of the superior vena cava: the benefits of postoperative surveillance and secondary endovascular interventions. *J Vasc Surg.* 27:298–299.)

## Magnetic Resonance Venography

The advantages of magnetic resonance venography (MRV) include the ability to demonstrate anatomic structures in multiple planes and to delineate the central venous chest veins and collateral vessels. MRV is a relatively noninvasive modality and

does not require the administration of iodinated contrast material. The disadvantage is its contraindication in patients with pacemakers and aneurysm clips as well as inability of patients with SVC syndrome to lie flat due to orthopnea. The recognition of problems using gadolinium in patients with renal

insufficiency decreased the utility of MRV; however, newer but significantly more expensive contrast agents such as Eovist (gadoteric disodium) and Multihance (gadobenate dimeglumine) are being introduced into practice.

## Contrast Venography

Venography was long considered the “gold standard” for accurate depiction of central venous obstruction and was routinely used as an anatomic roadmap before reconstructive surgery. Venography also depicts the presence and direction of venous collateral flow. It is performed by simultaneous injection of contrast material in bilateral superficial arm veins. Stanford and Doty<sup>25</sup> described four venographic patterns of SVC syndrome, each having a different venous collateral network depending on the site and extent of SVC obstruction (Fig. 162.2). Type I is partial; type II is complete or near-complete SVC obstruction with antegrade flow in the azygos vein; type III is 90% to 100% SVC obstruction with reversed azygos blood flow; and type IV is extensive mediastinal central venous occlusion with venous return occurring through the inferior vena cava (see Fig. 162.2).

It is important to remember that during upper extremity venography only veins and collateral pathways between the injection site and right atrium are visualized; the internal jugular veins frequently used as inflow for a surgical bypass are not visualized. More complete anatomic definition can be obtained effectively and noninvasively with CTV or MRV. In contemporary practice the role of conventional venography has shifted from a diagnostic modality to performance only during therapeutic endovascular treatment of SVC occlusion.

## INITIAL TREATMENTS

Conservative measures are used first in every patient to relieve symptoms of venous congestion and to decrease progression of venous thrombosis. These measures include elevation of the head during the night on pillows, modifications of daily activities by avoiding bending over, and avoidance of wearing constricting garments or a tight collar. Patients frequently need diuretic agents, at least temporarily, to decrease excessive edema of the neck and head.

Patients with acute SVC syndrome caused by malignant disease are generally treated with intravenous unfractionated or low-molecular-weight heparin, followed by long-term anticoagulation, to prevent recurrence and protect the collateral venous circulation. Thrombolytic treatment is considered in most patients with benign acute SVC syndrome, whereas those with chronic or malignant disease are candidates for treatment by endovascular stents, with or without thrombolytic treatment.

Symptoms of SVC syndrome caused by mediastinal malignancy frequently improve after irradiation, chemotherapy, or combination chemoradiation based on tumor histology.<sup>1</sup> Chen et al. treated 42 patients with malignant SVC syndrome using external beam radiotherapy and/or chemotherapy.<sup>3</sup> Symptoms of SVC syndrome resolved in 80% of the patients who

underwent radiotherapy, with a mean interval of 4 weeks.<sup>3</sup> Similar benefits of radiation or chemotherapy have been noted by others as well.<sup>26,27</sup> Since external compression by the tumor is the usual mechanism of caval occlusion in these patients, adjunctive endovascular treatment using stents, as discussed later, is the best technique to alleviate symptoms. Stenting of a severe SVC stenosis prior to commencing radiotherapy is indicated in order to prevent worsening of symptoms during the early stages from radiation-induced edema in the treatment field. A systematic Cochrane review by Rowell et al. evaluated two randomized and 44 nonrandomized studies addressing the treatment of SVC syndrome in patients with bronchial malignancy. Chemotherapy and/or radiotherapy relieved symptoms of SVC occlusion in 77% and 60% of patients with small cell and nonsmall cell lung cancer, respectively. Endovascular treatment with stenting, however, relieved symptoms in 95% patients and much more rapidly.<sup>27</sup>

## INDICATIONS FOR INTERVENTIONAL TREATMENT

The severe, incapacitating symptoms of SVC syndrome are frequently not alleviated by conservative measures. Up to one-fourth of malignant cases are resistant to radiochemotherapy, and even in cases where improvement occurs, symptomatic relief can require up to 3 weeks.<sup>27</sup> Further treatment options include endovenous or surgical intervention, depending upon the etiology and anatomy of the SVC lesion.

Endovenous treatment is considered the first choice for patients with malignant SVC obstruction because of the limited life expectancy. Surgical reconstruction should be contemplated only when the tumor is resectable, and life expectancy is greater than 1 year. Candidates for surgical reconstruction include those with lymphoma, thymoma, or metastatic medullary carcinoma of the thyroid gland.<sup>28–33</sup> In cases where endovascular treatment is not possible and major surgery is not indicated, extra-anatomic subcutaneous bypass between the jugular vein and the femoral vein using a composite saphenous vein graft is an alternative.<sup>34,35</sup>

In the past, patients with benign disease were treated with surgical replacement/bypass of the occluded SVC because of their longer life expectancy and the need for a durable reconstruction. However, as expertise and techniques have improved, most patients with benign SVC syndrome are considered for endovenous treatment first.<sup>15,36–42</sup> Surgical reconstruction is reserved for patients with extensive chronic venous thrombosis not anatomically suitable for endovascular treatment, and those with less extensive disease who have not benefited from endovascular attempts. Our group has performed reconstruction of the SVC for obstruction caused by granulomatous and idiopathic mediastinal fibrosis, central venous catheters, pacemaker electrodes, or ventriculoatrial shunt and in patients with antithrombin deficiency or idiopathic venous thrombosis.<sup>7,9,43,44</sup> The indications for reconstruction in patients with benign disease were similar in the reports by Doty et al.<sup>6</sup> and Moore et al.<sup>45</sup>

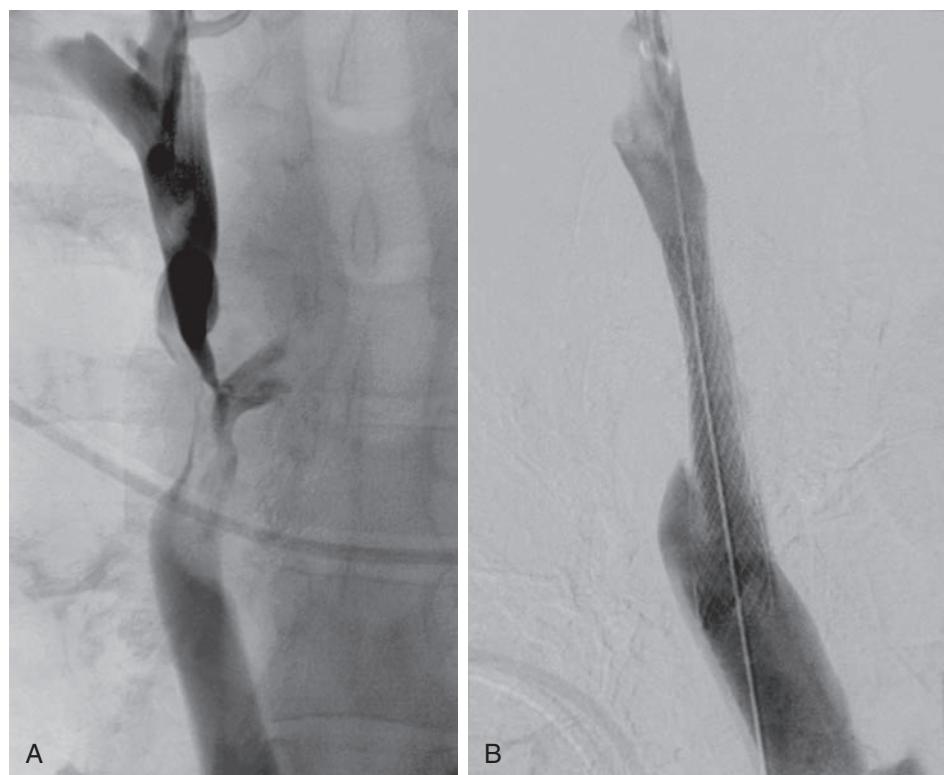
## ENDOVENOUS TREATMENT

The first percutaneous angioplasty for an SVC lesion in an adult was performed in 1986 by Sherry. The lesion was caused by a pacemaker wire.<sup>36</sup> Since then there has been tremendous progress in the endovenous treatment of SVC syndrome, with increasing technical and clinical success. Endovenous treatment provides patients with rapid symptomatic relief; however, long-term results of stents placed in young patients for benign lesions are still not well known, and rethrombosis or intimal hyperplasia can be significant. In spite of this, many clinicians now consider endovenous procedures first-line treatment in benign as well as malignant cases.<sup>15,27</sup>

Endovenous treatment includes percutaneous transluminal balloon angioplasty (PTA), stenting, and thrombolysis performed alone or in combination (Fig. 162.3). Following early interventions with angioplasty alone, it became evident that this often resulted in early restenosis due to the elastic/fibrotic nature of many SVC lesions, with or without external compression from mediastinal masses. The earliest stents deployed were Gianturco Z stents, self-expanding stents with hooks for fixation to prevent migration. They are easy to place, rigid, and do not shorten with deployment. The large stent interstices, however, are worrisome for allowing tumor ingrowth. Palmaz (Cordis Corporation, Miami, FL) balloon-expandable stents are ideally suited for short, focal fibrotic/compressive lesions because of their precise deployment and good radial force. Disadvantages include poor flexibility and availability only in short

lengths. In recent years, other self-expanding stents such as Wallstents (Boston Scientific Corp., Natick, MA), Smart stents (Cordis Endovascular, Warren, NJ), Protégé stents (ev3, Plymouth, MN), E\*Luminexx (Bard GmbH/Angiomed, Karlsruhe, Germany), Sinus-XL (OptiMed Medizinische Instrumente GmbH, Ettlingen, Germany), and Zilver Vena (Cook Medical Inc., Bloomington, IN) have been used more frequently for longer SVC stenoses because of flexibility and availability in multiple sizes. Occasional reports of covered stents are also available. Covered stents are effective to prevent ongoing hemorrhage if a patent vein is perforated during the procedure, and potentially to control tumor ingrowth. Some evidence suggests they require fewer reinterventions compared to bare metal stents.<sup>46,47</sup> Covered stents are commonly used primarily and include Gore Viabahn (Gore, Newark, DE) and iCast (Atrium, Dallas, TX) stents. We have noted encouraging results in a recent experience.<sup>48</sup> Thrombolysis may be performed alone for acute SVC thrombosis related to indwelling catheters or prior to angioplasty/stenting to lyse the thrombus and reveal underlying stenotic lesions for definitive treatment.

Endovascular intervention is performed under monitored local or general anesthesia depending upon the complexity of the lesion to be treated. The technique of endovenous repair involves ultrasound-guided percutaneous venous access of the common femoral vein and placement of 6- to 10-F sheaths, followed by crossing the stenotic/occlusive lesion with hydrophilic guide wires and catheters. The right internal jugular or an arm vein can be an alternate or additional venous access site



**Figure 162.3** (A) Venogram showing type II superior vena cava obstruction due to mediastinal fibrosis in a 31-year-old man. Successful placement of a Wallstent stent resulted in immediate resolution of symptoms. (B) The patient has since undergone balloon dilation for in-stent stenosis 11 months later and remains asymptomatic.

in patients with short focal lesions or if the lesion cannot be crossed from the femoral approach. Access of a hemodialysis AVF, if present, is also an option. Long sheaths extending to the site of occlusion can be helpful in providing the necessary support to cross the lesion. The PowerWire Radiofrequency Guidewire (Baylis Medical Company Inc., Montreal, Canada) has been reported to be useful in crossing thrombosed vessels.<sup>49</sup> Once wire access across the lesion is obtained, the hydrophilic wire can be exchanged for a stiff Amplatz (Boston Scientific) or Lunderquist (Cook Medical Inc.) wire, which is then used for PTA and/or stenting.

Primary PTA using 10- to 16-mm angioplasty balloons is performed followed by stenting. Venous stenoses can be very resistant, often requiring angioplasty with high-pressure balloons. The choice of stent is tailored to the etiology, degree, length, and tortuosity of the SVC stenosis, and more than one stent may be needed. Post-stenting balloon dilation is performed when a self-expanding stent or a stent graft is deployed (Fig. 162.4). When the confluence of the right and left brachiocephalic veins is involved in the primary lesion, or becomes so after caudal extension of stents within the SVC due to repeated stenoses, double barrel or parallel stents can be placed (see Fig. 162.4). Perforation can occur during the stenting process and if minor, manifesting as a small perivenous blush without hemodynamic changes, can be managed successfully with prolonged balloon inflation. Placement of a covered stent is required to control larger, more significant perforations, especially if associated with hemodynamic instability.<sup>50</sup> Rarely, SVC rupture can result in pericardial tamponade.

Rapid diagnosis and immediate ultrasound-guided pericardial drainage is necessary.<sup>50</sup>

Systemic anticoagulation with intravenous heparin (100 U/kg) is given prior to any catheter-based intervention. Thrombolysis may be performed alone for acute nonmalignant SVC thrombosis related to indwelling catheters or prior to angioplasty/stenting to remove the thrombus and unmask the underlying stenotic lesion for definitive treatment. The original agents used for thrombolysis (streptokinase and urokinase)<sup>51,52</sup> have been replaced with recombinant tissue plasminogen activator (t-PA), which is utilized by us almost exclusively.<sup>53</sup>

If thrombolysis is determined to be appropriate prior to PTA or stenting, a suitable length catheter with side holes is placed across the lesion for catheter-directed lytic therapy. Successful catheter-directed thrombolysis with or without pharmacomechanical thrombectomy has been reported in catheter-related thromboses and in malignant SVC occlusions.<sup>54</sup> Mechanical thrombectomy should be avoided/minimized within the mediastinum because of risk of precipitating cardiac arrhythmia. However, chronic occlusion with established collaterals in malignant SVC obstruction does not usually respond to lysis.<sup>55</sup>

Oral anticoagulation and/or antiplatelet therapy are routinely prescribed after SVC stenting for a minimum of 6 months. The need for post-procedure anticoagulation is individualized based on the cause of SVC syndrome. The majority of patients, especially those with malignancy and catheter-related thrombosis, receive oral anticoagulation for at least several months until the stent is lined with pseudointima and the risk of re-thrombosis decreases. Patients with mediastinal fibrosis are



**Figure 162.4** (A) Bilateral self-expanding kissing stents placement. (B) Post-stenting balloon dilation.

often treated with antiplatelet therapy alone. Both re-thrombosis following cessation of anticoagulation as well as excellent results without anticoagulation have been reported.<sup>56,57</sup>

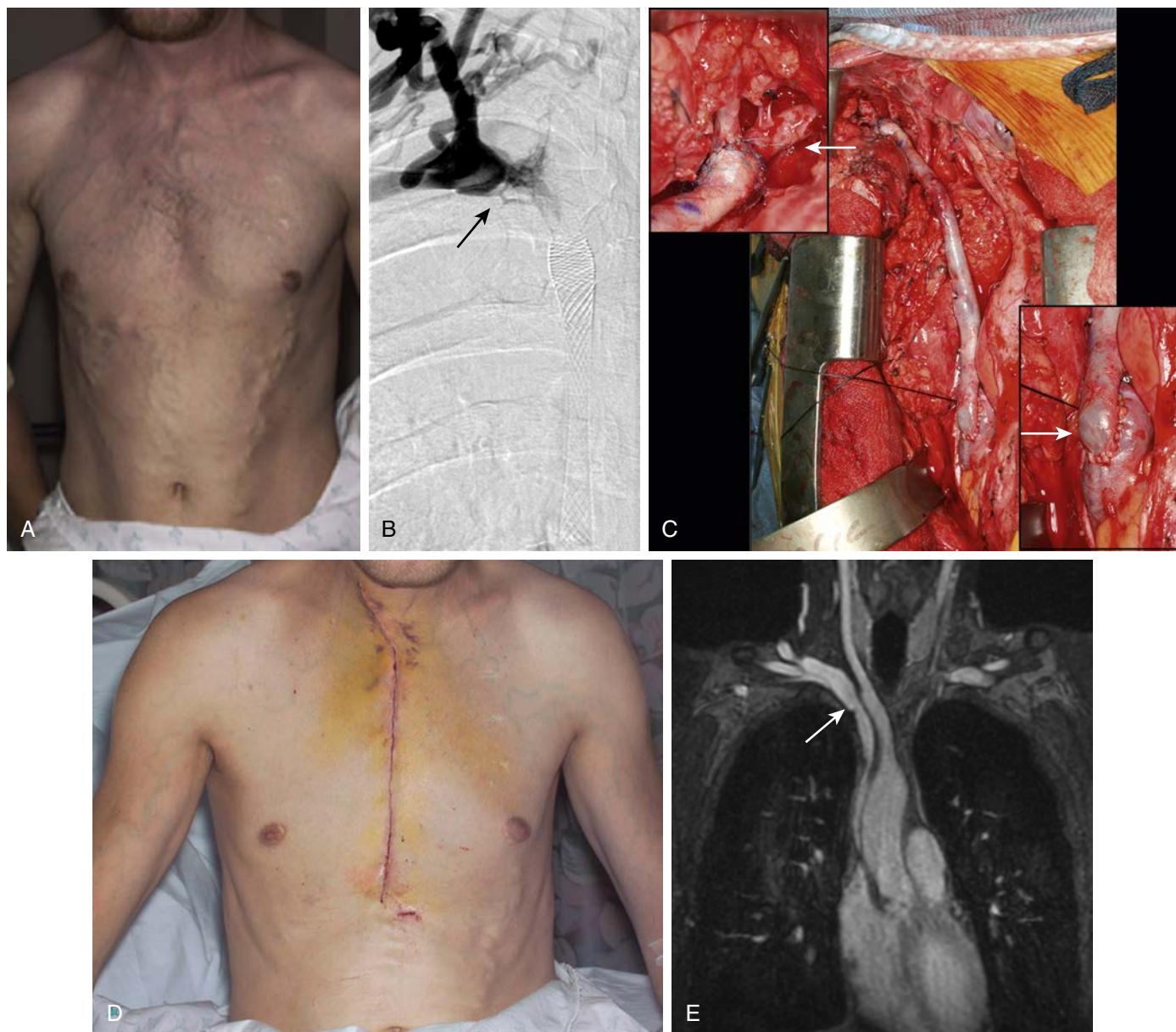
## SURGICAL TREATMENT

### Graft Materials

Grafting of large veins with autogenous graft has traditionally been difficult, because large-diameter autologous vein is not available to use as conduit.

### Great Saphenous Vein Graft

The great saphenous vein is usually not suitable for direct reconstruction because of poor size match. However, extra-anatomic reconstruction performed by connecting the external or internal jugular vein to the ipsilateral common femoral vein, using both great saphenous veins sutured together in an end-to-end fashion and tunneled subcutaneously, has been reported by several authors with good results.<sup>34</sup> To prevent external compression, Panneton et al. placed the composite saphenous vein graft from the right internal jugular to the femoral vein



**Figure 162.5** (A) Symptomatic recurrent superior vena cava (SVC) obstruction following occlusion of Wallstent, prominent abdominal and chest wall collaterals. (B) Venogram demonstrating occlusion till the peripheral vein, right IJV, and subclavian veins patent with large draining collaterals. (C) Bypass from right IJV–SCV confluence (*top inset*) to right atrial appendage (*bottom inset*) using femoral vein. (D) Postoperative symptom relief demonstrated by collapse of right chest wall and upper limb collaterals. (E) Magnetic resonance venogram 15 months after surgery confirms the graft (*white arrow*) to be widely patent.

inside an externally supported expanded polytetrafluoroethylene (ePTFE) graft.<sup>58</sup>

### Femoral Vein Graft

The femoral vein, or the femoropopliteal vein (FPV), is a good conduit to reconstruct the SVC. It has been used with success because of its excellent suitability in terms of size and length (Fig. 162.5).<sup>7,15</sup> However, if the patient has underlying thrombophilia, removal of a deep leg vein may result in deep vein thrombosis, lower extremity edema and discomfort. Compartment syndrome and chronic venous insufficiency following harvesting of longer segments of the femoropopliteal veins (FPV) have been reported.<sup>59,60</sup> These complications have been noted mostly when FPV grafts have been used for complex lower extremity arterial reconstruction with ischemia reperfusion likely contributing to the morbidity. In our experience with SVC reconstruction we have noted minimal side effects with harvest of the FPV. However, in young patients who undergo SVC reconstruction for benign disease, we still prefer using the great saphenous vein for a spiral saphenous vein graft (SSVG).

### Spiral Saphenous Vein Graft

The SSVG is autologous tissue with low thrombogenicity. Although its length is limited by the available saphenous vein segment, its diameter can be easily matched to that of the internal jugular or innominate vein (Fig. 162.6). This graft was first described in animal experiments by Chiu and colleagues,<sup>61</sup> and later in patients by Doty.<sup>62</sup> The technique used by the authors preparing the SSVG is illustrated in Figure 162.6.<sup>61</sup>

The saphenous vein is harvested, distended with papaverine–saline solution, and opened longitudinally. The valves are excised and the saphenous vein is wrapped around a 32- or 36-F polyethylene chest tube. The edges of the vein are sutured together with running 6-0 or 7-0 monofilament nonabsorbable sutures to form the SSVG conduit, interrupting the suture line at every three-quarter turn. The length of saphenous vein to be harvested to create a graft of sufficient length is determined according to the equation proposed by Chiu and coworkers ( $l = RL/r$ ;  $r$  and  $l$  = radius and length of saphenous vein,  $R$  and  $L$  = radius and length of SSVG).<sup>61</sup> Harvesting vein from the groin to the knee usually results in an SSVG approximately 10 cm long.

### Expanded Polytetrafluoroethylene Graft

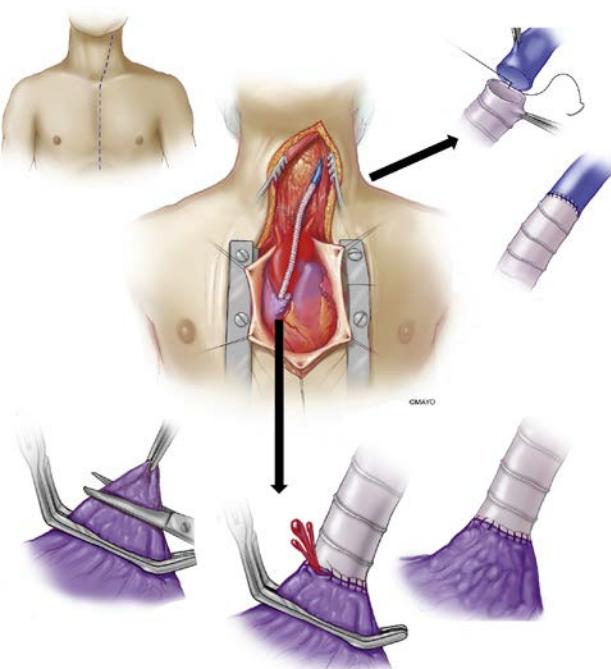
Of the available prosthetic grafts, externally supported ePTFE is used for large vein reconstruction almost exclusively (Fig. 162.7).<sup>9,61,63</sup> Short, large-diameter (10 to 14 mm) grafts have excellent long-term patency, because flow through the innominate vein usually exceeds 1000 mL/min. If the peripheral anastomosis is performed with the subclavian vein, venous inflow is significantly less, and the addition of an AVF in the arm is usually required to ensure graft patency. For an internal jugular–atrial appendage bypass, a large-diameter (12 mm) ePTFE graft is a suitable alternative if the spiral saphenous vein is not possible. An externally supported prosthetic graft is a good choice in patients with a tight mediastinum and for all patients



A

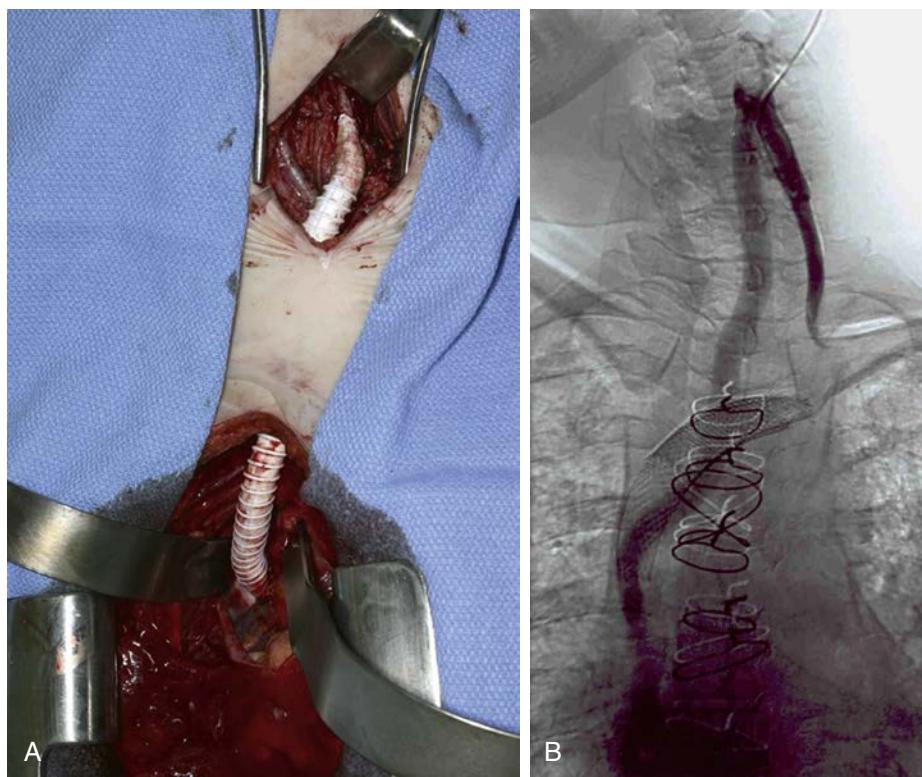


B



C

**Figure 162.6** (A) Technique for a spiral saphenous vein graft. The saphenous vein is opened longitudinally, valves are excised, the vein is wrapped around an argyle chest tube, and the vein edges are approximated with sutures. (B) A 15 cm-long spiral saphenous vein graft ready for implantation. (C) Technique of left internal jugular–right atrial spiral vein graft implantation. (From Gloviczki PG, Pairolero PC. Venous reconstruction for obstruction and valvular incompetence. In: Goldstone J, ed. *Perspectives in Vascular Surgery*, St. Louis: Quality Medical Publishing; 1988:75–93.)



**Figure 162.7** (A) Left internal jugular vein–atrial appendage externally supported expanded polytetrafluoroethylene graft. (B) Widely patent graft at 13 months after the operation.

with malignancy, because its stiffness prevents recurrent tumor from compressing the graft.

#### Other Grafts

Fresh iliacaval allograft homografts, cryopreserved femoral vein, aortic arch grafts, and grafts prepared from autogenous or bovine pericardium have also been used.<sup>64,65</sup>

#### Surgical Technique

The operation is performed under general anesthesia through a median sternotomy. If the internal jugular vein is used for inflow, the midline incision is extended obliquely into the neck along the anterior border of the sternocleidomastoid muscle on the appropriate side. The mediastinum is exposed, and biopsy of the mediastinal mass or resection of the tumor is performed before caval reconstruction. Once this is completed, the pericardial sac is opened to expose the right atrial appendage, which is used most frequently for the central anastomosis. If not involved in the fibrosing process, a patent SVC central to the occlusion can also be used for this purpose. The patient is therapeutically heparinized and a side-biting Satinsky clamp is placed on the right atrial appendage, which is opened longitudinally over a distance of 2 cm. Some trabecular muscle is excised to improve inflow, and an end-to-side anastomosis with the graft is performed using running 5-0 monofilament suture (see Fig. 162.6C). The graft is filled with heparinized saline before declamping the appendage, after placing the patient in Trendelenburg position and performing Valsalva maneuvers,

to prevent air embolization. The peripheral anastomosis of the graft is next performed to the internal jugular or innominate vein in an end-to-side or, preferably, an end-to-end fashion, often in a partial or total interrupted manner. Again, blood and air are flushed from the graft before establishing flow to prevent embolism. In patients with a very short graft from the innominate vein or a very long graft from the high internal jugular or subclavian vein, it is easier to complete the peripheral anastomosis first before the central anastomosis, so as to distend and position the graft to avoid kinking and determine appropriate length. Closure of the sternum needs to be performed with great care to not compress the low pressure venous graft at the thoracic inlet. Shaving or complete removal of the sternoclavicular junction may be necessary if excision of soft tissues and portions of the strap muscles does not result in sufficient space.

Although we have performed bifurcated SSVGs or prosthetic grafts to both internal jugular veins in a few patients, a single straight graft from the internal jugular or innominate vein is our current operative choice for SVC reconstruction. Because collateral circulation in the head and neck is almost always adequate, unilateral reconstruction is sufficient to relieve symptoms in most patients. If collateral circulation is felt to be inadequate, two separate bypasses are preferable to a bifurcated bypass. In malignant SVC occlusion when only part of the circumference of the SVC is invaded by the tumor, resection and caval patch angioplasty using prosthetic patch, bovine pericardium, or autogenous material, such as saphenous vein or pericardium, is also an option.

Postoperative anticoagulation is started 24 hours later with heparin, and the patient is discharged on an oral anticoagulation regimen. Patients with SSVGs or femoral vein grafts who have no underlying coagulation abnormality are maintained on anticoagulation for 3 months only. Those with underlying coagulation disorders and most patients with ePTFE grafts continue lifelong anticoagulation therapy.

## RESULTS

### Results of Endovenous Treatment in Patients with Malignancy

Initial attempts at treating SVC syndrome by endovascular means employed PTA alone. The earliest reports of SVC stenting in 1986/7 were in patients with malignant SVC occlusion; prompt relief of symptoms occurred and was maintained until death at 3 weeks to 6 months.<sup>38,39</sup> Relief of symptoms included “immediate” relief of headache and resolution of arm and face edema within 24 to 72 hours. These procedures were performed with Gianturco Z stents, which were subsequently modified by Rosch et al.<sup>39</sup> to create a multibody design that minimized stent migration. In the early 1990s occasional cases of stent deployment for pacemaker wire-induced thrombosis were reported, but repeated interventions were required to maintain patency in the short term.<sup>38,39,56</sup>

Nicholson et al. reported the largest study of endovenous interventions to that time in 75 patients with malignant SVC syndrome.<sup>66</sup> Symptomatic relief was achieved in all patients within 48 hours, and 90% remained symptom free until death. The authors compared SVC stenting with palliative radiation, and concluded that stenting had significantly greater efficacy. In a later study by Garcia Monaco et al.<sup>67</sup> dramatic symptomatic improvement was seen in 91% of 40 patients with malignant SVC syndrome following stenting, and was maintained in 83% during the course of the disease. Greillier et al.<sup>68</sup> reported complete resolution of symptoms more frequently in stented than in unstented patients with lung cancer (75% vs. 25%, respectively), as well as a lower relapse rate and longer time to relapse. Maleux et al. reported stenting in 78 patients with malignant SVC syndrome (large-bore Nitinol SE Zilver, Cook Medical), demonstrating 100% technical success rate and 89% primary patency at 12 months.<sup>69</sup> The recent development of large-caliber stents developed specifically for the SVC has also appeared to improve results.<sup>70,71</sup> Based on these data, endovenous treatment has become the first-line treatment for malignant SVC syndrome.<sup>72–75</sup>

### Results of Endovenous Treatment in Patients with Benign Superior Vena Cava Syndrome

Studies reporting on the treatment of benign SVC syndrome are scarce. We have reported our results of successful endovenous treatment of SVC syndrome of benign etiology in 28 of 32 patients, 19 with catheter-related thrombosis and 9 with mediastinal fibrosis.<sup>15</sup> Six patients underwent PTA and 22

underwent stenting; 5 procedures (2 PTA, 3 stents) were preceded by thrombolysis. Primary patency at 1 and 3 years was 70% and 44%, assisted primary and secondary patency rates at 3 years were 96% and 96%, respectively (see Fig. 162.8B). These were not significantly different from the patency of surgical reconstructions at our institution (Fig 162.8A). However, more re-interventions over longer periods of time occurred in the patients treated with endovascular procedures compared to those who underwent open surgery).<sup>15,76</sup> Other studies reported excellent technical success with secondary interventions required in approximately 10% of cases over 1 to 2 years.<sup>37,77</sup>

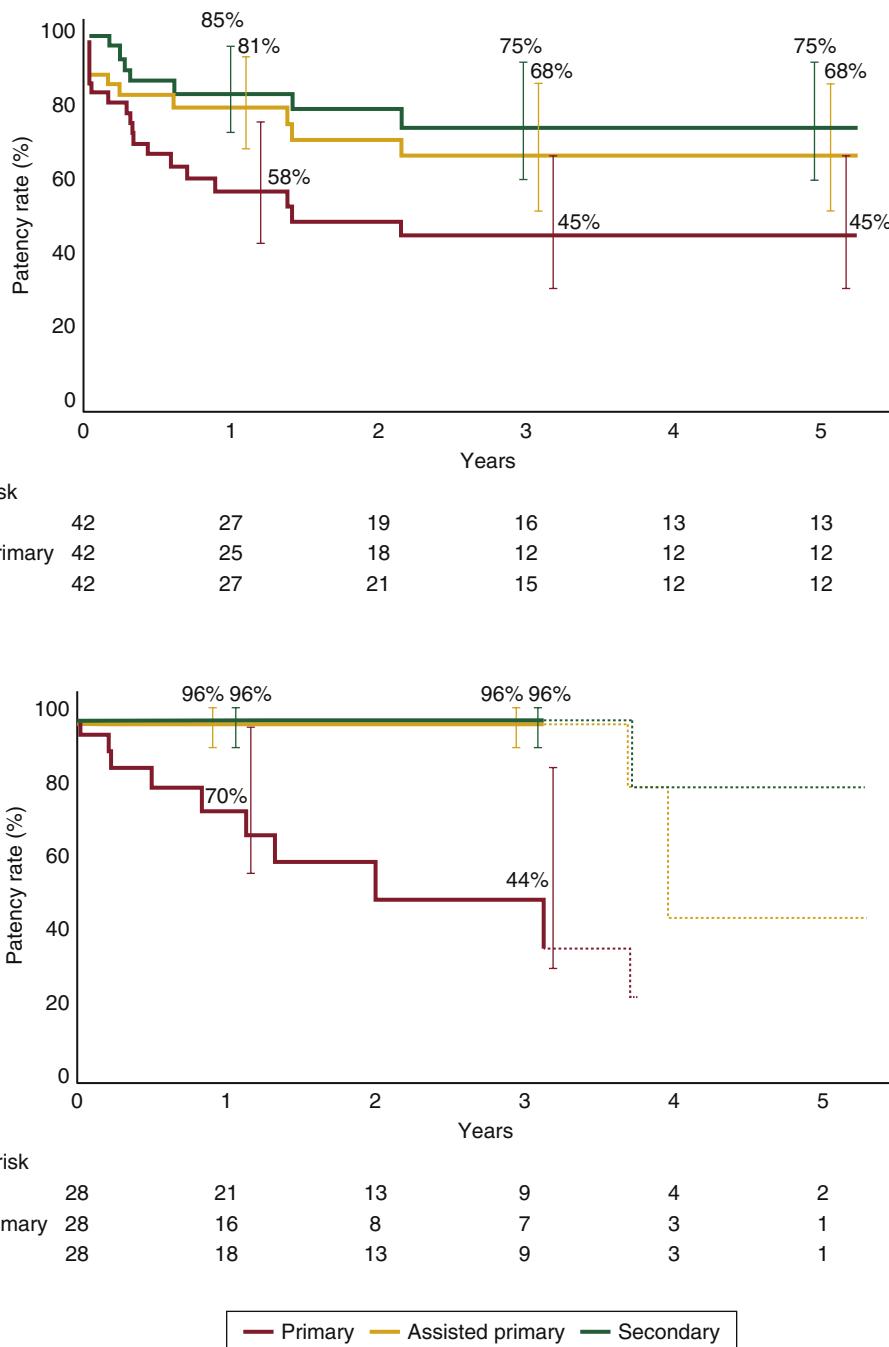
Additional studies provided evidence of the efficacy of thrombolysis followed by PTA and stenting in patients with benign SVC syndrome. Kee et al. reported on 27 patients treated with this technique. In the majority, successful lysis revealed underlying significant stenoses which were treated by stenting.<sup>54</sup> Although thrombolysis was generally safe, a Cochrane review concluded that when added to stenting, it resulted in increased morbidity compared to stenting alone.<sup>27</sup>

### Complications, Restenosis, and Outcomes

Most studies have emphasized the need for customizing treatment with a combination of thrombolysis, angioplasty, and stenting to achieve an initial technical success rate of 90% to 100% and secondary patency rates up to 85% at 1 year in small numbers of patients.<sup>41,54,55,78</sup> Barshes et al. reported 100% technical success and 96% symptomatic relief following stenting in patients with both benign and malignant SVC syndrome, with primary patency rates of 76% and 64% at 1 year, respectively.<sup>79</sup> However, to this date, prospective, randomized data comparing stent types or treatment algorithms does not exist. Oudkerk et al. compared outcomes between Gianturco and Wallstents, and reported the latter to be more prone to occlusion, possibly because of a closer weave and greater surface area of metal.<sup>80</sup>

Occlusion of stents because of protrusion of tumor between stent struts in patients with malignancy, as well as intimal hyperplasia, fibrosis, and extrinsic compression from mediastinitis, are real concerns following endovenous treatment. Restenosis usually results in recurrence of symptoms and necessitates repeat interventions, especially in patients with benign SVC syndrome (Fig. 162.9). Endovenous treatment is also associated with access site complications, bleeding related to thrombolysis/anticoagulation, stent migration, and cardiac tamponade from intrapericardial hemorrhage. The latter occurs infrequently, but has been reported after both PTA and stenting and necessitates urgent ultrasound-guided pericardiocentesis. We encountered this complication during repeat PTA in two patients.

Concerns regarding restenosis and symptomatic recurrence have led to the use of covered stents, based upon data suggesting that their use is associated with lower recurrence rates. In one study, Gwon et al. reported better cumulative patency with covered than uncovered stents (94% vs. 48%;  $P = 0.038$ ).<sup>46</sup> Over the last decade we have used covered stents selectively in the SVC, and placed them in 17/47 patients with benign



**Figure 162.8** (A) Cumulative primary, assisted primary, and secondary patency rates at 1, 3, and 5 years of open surgical reconstruction ( $n = 42$ ). Solid bars represent SEM <10%. (B) Cumulative primary, assisted primary, and secondary patency rates at 1 and 3 years of endovascular repair ( $n = 28$ ). Solid bars represent SEM <10%. (From Rizvi AZ, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg*. 2008;47(2):372–380.)

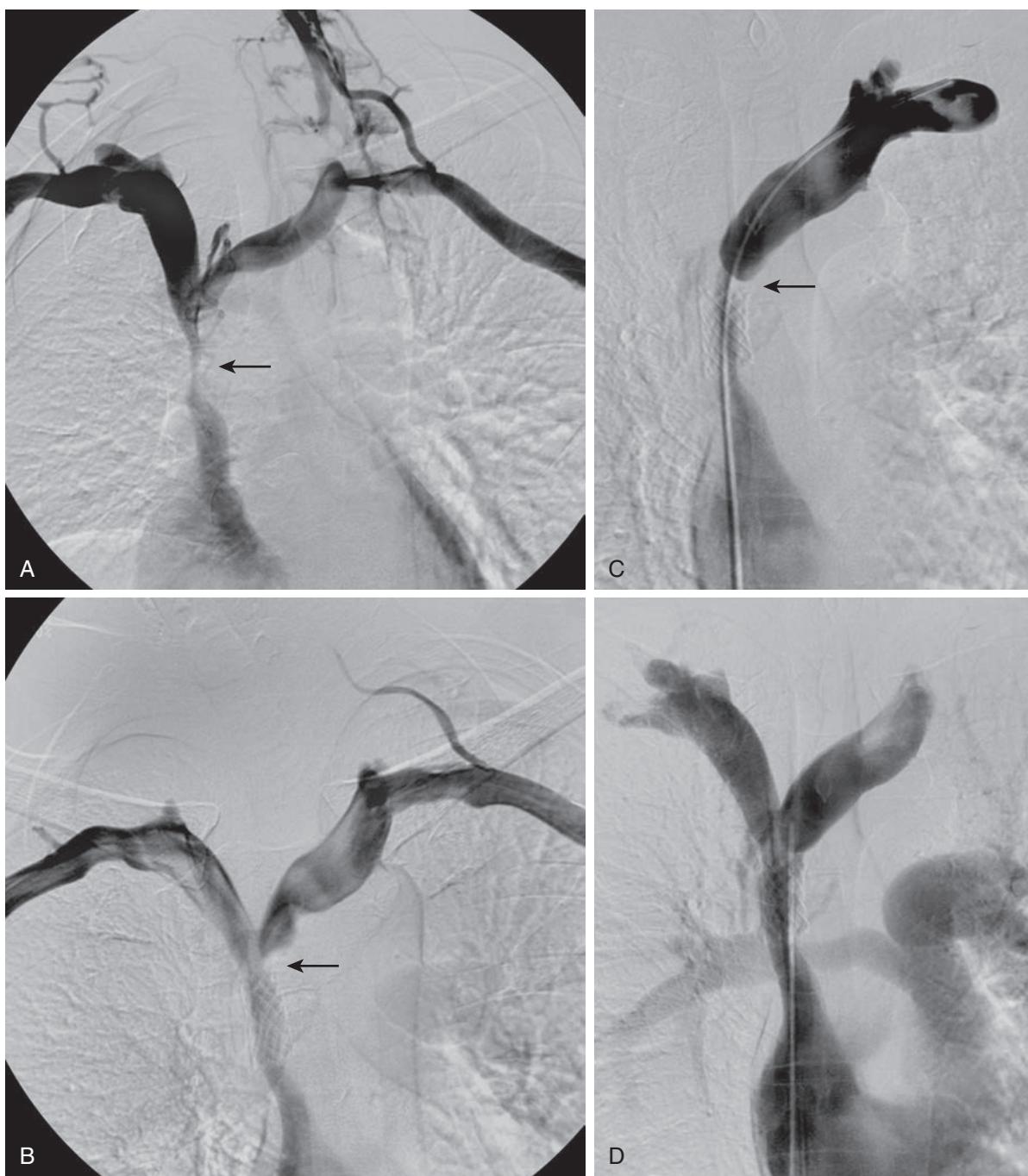
SVC syndrome.<sup>48</sup> Although not statistically significant, we observed a decreased rate of reintervention at 1 year in the group with covered stents (15%) versus those with uncovered stents (39%). These data are preliminary, but our experience mirrors the findings reported by Gwon et al.<sup>46,81,82</sup>

Despite the attraction of the minimally invasive nature of SVC stenting, the need for frequent, repeated reintervention remains a limiting factor in long-term success. Given the longevity of patients with benign SVC syndrome it is

not surprising that a fair number eventually opt for surgical treatment.

### Results of Surgical Treatment

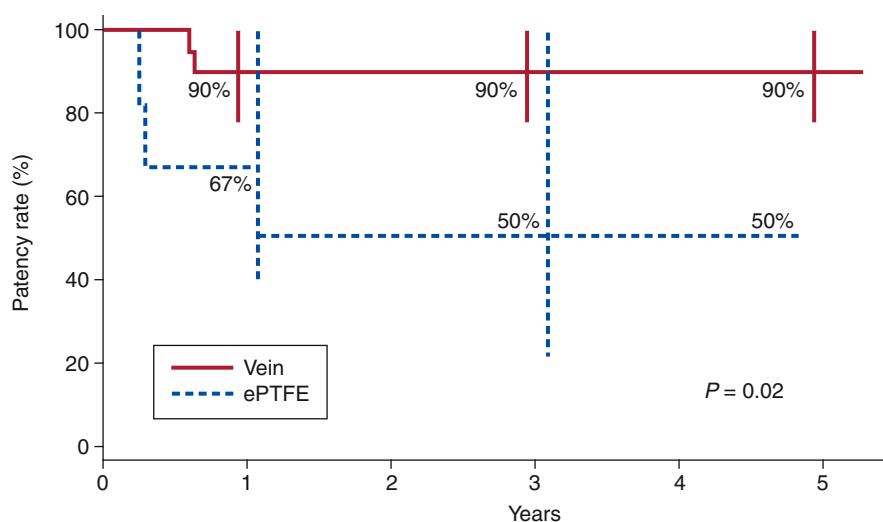
Open surgical treatment for SVC syndrome has excellent long-term results, but is now considered only after failure or inability to perform endovascular treatment. Outcomes depend on etiology, conduit, and the length of venous reconstruction.



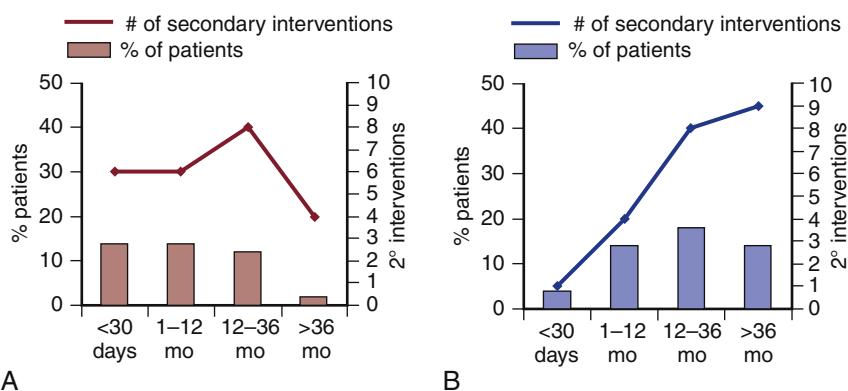
**Figure 162.9** (A) Venogram showing type II superior vena cava obstruction (arrow) due to mediastinal fibrosis in a 38-year-old man. Successful placement of a Palmaz stent resulted in immediate resolution of symptoms. (B) Venogram 14 months after stent placement shows high-grade stenosis of the left innominate vein proximal to the stent (arrow). This was successfully treated with balloon angioplasty. (C) Venogram 8 months later shows recurrence of stenosis (arrow). (D) Venogram following balloon angioplasty of stenosis of left innominate vein and stent shows widely patent stent. Patient has undergone two further balloon angioplasties over the next 10 months to maintain patency.

Of the autologous graft materials, experience with SSVG and femoral vein grafts has been the largest. Doty and colleagues reported on long-term results with 16 SSVGs used for benign SVC syndrome, demonstrating 88% patency and excellent clinical results at a mean follow-up of 10.9 years.<sup>62,83,84</sup> The authors' published experience includes 22/42 SVC reconstructions performed with SSVG, with 86% secondary patency at 5 years. Corresponding secondary patency of the entire cohort

that included 13 ePTFE, 6 femoral vein and 1 human allograft was 75% and clinical results were consistently good to excellent.<sup>15</sup> With the declaration of endovenous intervention as first-line therapy in all cases the frequency of open reconstructions has decreased proportionately. We have needed to perform only 15 additional open SVC reconstructions in the subsequent decade, however, the outcomes remain excellent with 91% secondary patency at 5 years.<sup>76</sup>



**Figure 162.10** Cumulative secondary patency rates of 23 vein grafts and 6 expanded polytetrafluoroethylene bypass grafts used for reconstruction of the superior vena cava. (From Kalra M, et al. Open surgical and endovascular treatment of superior vena cava syndrome caused by nonmalignant disease. *J Vasc Surg*. 2003;38:215–223.)



**Figure 162.11** (A) Treatment of benign superior vena cava syndrome. Secondary interventions required to maintain patency in (A), the open surgical group ( $n = 42$ ), and (B), the endovascular group ( $n = 28$ ). The bars represent the percentage of patients in each group and the line graphs represent total number of interventions. (From Rizvi AZ, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg*. 2008;47(2):372–380.)

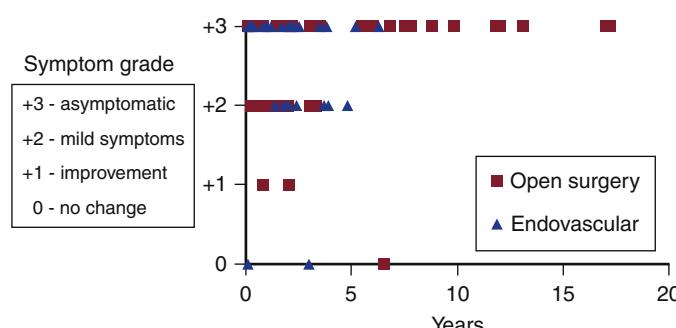
Increasing success with femoral vein as an arterial conduit has resurrected this autologous graft for large vein reconstructions as well.<sup>85</sup> All thirteen femoral vein grafts performed by our group thus far have remained patent. However, two of the thirteen patients developed mild but persistent swelling and venous claudication in the lower extremity from which the graft was harvested.<sup>15</sup>

In several series, ePTFE grafts implanted into the mediastinum have resulted in excellent patency. Darteville and associates observed continued patency in 20 of 22 ePTFE grafts at a mean follow-up of 23 months.<sup>30</sup> Moore et al. observed no graft occlusion at a mean follow-up of 30 months in 10 patients who underwent large central vein reconstruction.<sup>45</sup> In 8 of these 10 patients, an additional AVF in the arm was used to increase flow. Similar results have been reported in other studies.<sup>32,86,87</sup>

In our experience, some thrombus formation occurs even in patent ePTFE grafts, with occlusion occurring much more frequently in patients with longer ePTFE grafts in whom the distal anastomosis is performed with the internal jugular or the subclavian veins. Long-term patency is better in patients with innominate or SVC interposition grafts, and we now use ePTFE as a conduit only when the extent of the graft is limited to within the anterior mediastinum (Fig. 162.10).

### Graft Surveillance

Postoperative graft surveillance is important for maintenance of patency. DUS provides only indirect evidence of patency of an intrathoracic graft. Therefore CT or MRV is recommended before discharge and at 3 to 6 months and 1 year after surgery. In our experience, most graft stenoses presented within 1 to



**Figure 162.12** Grading of symptom relief at last clinical follow-up in patients undergoing open surgical reconstruction ( $n = 42$ ) or endovascular repair ( $n = 28$ ). (From Rizvi AZ, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg.* 2008;47(2):372–380.)

2 years after implantation, and half of these had mild stenoses on the first postoperative surveillance venogram (Fig. 162.11). In a recent systematic review of the literature on treatment, Sfyroeras et al. noted that endovascular is the first-line treatment for superior vena cava syndrome of benign etiology caused by intravenous devices, whereas surgery is most often performed for mediastinal fibrosis. Both treatments show good results regarding regression of the symptoms (Fig. 162.12),<sup>15</sup> and mid-term primary patency, with a significant incidence of secondary interventions.<sup>88</sup>

Regardless of the treatment modality, the discovery of restenosis was accompanied by recurrence of symptoms except in one instance. Similar outcomes have been reported by Doty and associates.<sup>84</sup> Based on these data, graft patency can be inferred based upon freedom from symptoms, and imaging after the first year need only be performed in symptomatic patients or in asymptomatic patients with known stenoses. Both endovascular therapy and open surgery have been used to treat graft stenoses, although endovascular treatment is more common.<sup>44</sup>

## CONCLUSIONS

The incidence of SVC syndrome is increasing with the growing use of indwelling catheters and pacemakers. The techniques

of endovascular treatment have been refined, and experience with their use has increased. Endovascular treatment is now an appropriate primary intervention in patients with SVC syndrome of both malignant and benign etiology. It is less invasive with lower morbidity than open surgical reconstruction, with equal midterm efficacy, albeit at the cost of multiple secondary interventions. Covered stents may prove to have improved patency compared to bare metal stents, although definitive data do not exist at this time. Endovascular therapy does not adversely affect the feasibility or patency of subsequent open surgical procedures. However, surgical treatment of SVC syndrome with spiral vein grafts or prosthetic grafts is effective, provides long-term relief, and remains an excellent option in patients who are not suitable for or fail endovascular treatment.

## SELECTED KEY REFERENCES

- Bacha EA, Chapelier AR, Macchiarini P, et al. Surgery for invasive mediastinal tumors. *Ann Thorac Surg.* 1998;66:234.
- A large retrospective analysis of 89 patients who underwent total or subtotal resection of a primary mediastinal tumor with resection and reconstruction of the SVC in 21 patients.*
- Gwon DI, Ko GY, Kim JH, et al. Malignant superior vena cava syndrome: a comparative cohort study of treatment with covered stents versus uncovered stents. *Radiology.* 2013;266:979–987.
- Cohort study comparing outcomes of covered versus uncovered stents used in malignant SVC syndrome.*
- Rizvi AZ, Kalra M, Bjarnason H, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg.* 2008;47:372.
- A comparative review of the results of surgical and endovascular treatment of SVC syndrome of benign etiology in 70 patients.*
- Wilson LD, Dettarbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. *N Engl J Med.* 2007;356:1862.
- Excellent contemporary review of the etiology, anatomy, and medical and surgical treatment of SVC syndrome caused by malignant disease.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

- Wilson LD, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. *New Engl J Med.* 2007;356(18):1862–1869.
- Rice TW, Rodriguez RM, Light RW. The superior vena cava syndrome: clinical characteristics and evolving etiology. *Medicine (Baltimore).* 2006;85(1):37–42.
- Chen JC, Bongard F, Klein SR. A contemporary perspective on superior vena cava syndrome. *Am J Surg.* 1990;160(2):207–211.
- Parish JM, Marschke Jr RF, Dines DE, Lee RE. Etiologic considerations in superior vena cava syndrome. *Mayo Clin Proc.* 1981;56(7):407–413.
- Yellin A, Rosen A, Reichert N, Lieberman Y. Superior vena cava syndrome. The myth—the facts. *Am Rev Respir Dis.* 1990;141(5 Pt 1):1114–1118.
- Doty DB, Doty JR, Jones KW. Bypass of superior vena cava. Fifteen years' experience with spiral vein graft for obstruction of superior vena cava caused by benign disease. *J Thorac Cardiovasc Surg.* 1990;99(5):889–895; discussion 895–896.
- Alimi YS, Gloviczki P, Vrtiska TJ, et al. Reconstruction of the superior vena cava: benefits of postoperative surveillance and secondary endovascular interventions. *J Vasc Surg.* 1998;27(2):287–299; 300–301.
- Francis CM, Starkey IR, Errington ML, Gillespie IN. Venous stenting as treatment for pacemaker-induced superior vena cava syndrome. *Am Heart J.* 1995;129(4):836–837.
- Gloviczki P, Pairolero PC, Toomey BJ, et al. Reconstruction of large veins for nonmalignant venous occlusive disease. *J Vasc Surg.* 1992;16(5):750–761.
- Grace AA, Sutters M, Schofield PM. Balloon dilatation of pacemaker induced stenosis of the superior vena cava. *Br Heart J.* 1991;65(4):225–226.
- Kastner RJ, Fisher WG, Blacky AR, Bacon ME. Pacemaker-induced superior vena cava syndrome with successful treatment by balloon venoplasty. *Am J Cardiol.* 1996;77(9):789–790.
- Lindsay HS, Chennells PM, Perrins EJ. Successful treatment by balloon venoplasty and stent insertion of obstruction of the superior vena cava by an endocardial pacemaker lead. *Br Heart J.* 1994;71(4):363–365.
- Spittell PC, Vlietstra RE, Hayes DL, Higano ST. Venous obstruction due to permanent transvenous pacemaker electrodes: treatment with percutaneous transluminal balloon venoplasty. *Pacing Clin Electrophysiol.* 1990;13(3):271–274.
- Sunder SK, Ekong EA, Sivalingam K, Kumar A. Superior vena cava thrombosis due to pacing electrodes: Successful treatment with combined thrombolysis and angioplasty. *American Heart J.* 1992;123(3):790–792.
- Rizvi AZ, Kalra M, Bjarnason H, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg.* 2008;47(2):372–380.
- Laguna Del Estal P, Gazapo Navarro T, Murillas Angoitia J, et al. [Superior vena cava syndrome: a study based on 81 cases]. *An Med Interna.* 1998;15(9):470–475.
- Spouge AR, Wilson SR, Wooley B. Abdominal sonography in asymptomatic executives: prevalence of pathologic findings, potential benefits, and problems. *J Ultrasound Med.* 1996;15(11):763–767; quiz 769–770.
- Mahmud AM, Teshima T, Isawa T, et al. Follow-up of patients with superior vena cava syndrome by functional analysis of radionuclide venography. *Nucl Med Commun.* 1998;19(5):417–426.
- Bashist B, Parisi A, Frager DH, Suster B. Abdominal CT findings when the superior vena cava, brachiocephalic vein, or subclavian vein is obstructed. *AJR Am J Roentgenol.* 1996;167(6):1457–1463.
- Kim HJ, Kim HS, Chung SH. CT diagnosis of superior vena cava syndrome: importance of collateral vessels. *AJR Am J Roentgenol.* 1993;161(3):539–542.
- Yamada T, Takahashi K, Shuke N, et al. Focal hepatic “hot spot” in superior vena cava obstruction: correlation between radiocolloid hepatic SPECT and contrast-enhanced CT. *Clin Nucl Med.* 1999;24(7):533–534.
- Yedlicka JW, Schultz K, Moncada R, Flisak M. CT findings in superior vena cava obstruction. *Semin Roentgenol.* 1989;24(2):84–90.
- Cihangiroglu M, Lin BH, Dachman AH. Collateral pathways in superior vena caval obstruction as seen on CT. *J Comput Assist Tomogr.* 2001;25(1):1–8.
- Furukawa A, Uchida K, Ishige Y, et al. Characterization of Propionibacterium acnes isolates from sarcoid and non-sarcoid tissues with special reference to cell invasiveness, serotype, and trigger factor gene polymorphism. *Microb Pathog.* 2009;46(2):80–87.
- Stanford W, Doty DB. The role of venography and surgery in the management of patients with superior vena cava obstruction. *Ann Thorac Surg.* 1986;41(2):158–163.
- Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus: a systematic review. *Clin Oncol (R Coll Radiol).* 2002;14(5):338–351.
- Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus. *Cochrane Database Syst Rev.* 2001;(4):CD001316.
- Herreros J, Glock Y, de la Fuente A, et al. [Superior vena cava compression syndrome. Our experience apropos of 26 cases]. *Ann Chir.* 1985;39(7):495–500.
- Bergeron P, Reggi M, Jausseran JM, et al. [Our experience with surgery of the superior vena cava]. *Ann Chir.* 1985;39(7):485–491.
- Darteville PG, Chapelier AR, Pastorino U, et al. Long-term follow-up after prosthetic replacement of the superior vena cava combined with resection of mediastinal-pulmonary malignant tumors. *J Thorac Cardiovasc Surg.* 1991;102(2):259–265.
- Gloviczki PBT, McKusick M, Pairolero PC. Superior vena cava syndrome: Endovascular and direct surgical treatment. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders.* London: Chapman & Hall; 1996:580–599.
- Magnan PE, Thomas P, Giudicelli R, et al. Surgical reconstruction of the superior vena cava. *Cardiovasc Surg.* 1994;2(5):598–604.
- Ricci C, Benedetti Valentini F, Colini GF, et al. [Reconstruction of the superior vena cava: 15 years' experience using various types of prosthetic material]. *Ann Chir.* 1985;39(7):492–495.
- Vincze K, Kulka F, Csorba L. Saphenous-jugular bypass as palliative therapy of superior vena cava syndrome caused by bronchial carcinoma. *J Thorac Cardiovasc Surg.* 1982;83(2):272–277.
- Graham A, Anikin V, Curry R, McGuigan J. Subcutaneous jugulofemoral bypass: a simple surgical option for palliation of superior vena cava obstruction. *J Cardiovasc Surg (Torino).* 1995;36(6):615–617.
- Sherry CS, Diamond NG, Meyers TP, Martin RL. Successful treatment of superior vena cava syndrome by venous angioplasty. *AJR Am J Roentgenol.* 1986;147(4):834–835.
- Qanadli SD, El Hajjam M, Mignon F, et al. Subacute and chronic benign superior vena cava obstructions: endovascular treatment with self-expanding metallic stents. *AJR Am J Roentgenol.* 1999;173(1):159–164.
- Charnsangavej C, Carrasco CH, Wallace S, et al. Stenosis of the vena cava: preliminary assessment of treatment with expandable metallic stents. *Radiology.* 1986;161(2):295–298.
- Rösch J, Uchida BT, Hall LD, et al. Gianturco-Rösch expandable Z-stents in the treatment of superior vena cava syndrome. *Cardiovasc Interv Radiol.* 1992;15(5):319–327.
- Solomon N, Wholey MH, Jarmolowski CR. Intravascular stents in the management of superior vena cava syndrome. *Cathet Cardiovasc Diagn.* 1991;23(4):245–252.
- Schindler N, Vogelzang RL. Superior vena cava syndrome. Experience with endovascular stents and surgical therapy. *Surg Clin North Am.* 1999;79(3):683–694. xi.
- Albers EL, Pugh ME, Hill KD, Wang L, Loyd JE, Doyle TP. Percutaneous vascular stent implantation as treatment for central vascular obstruction due to fibrosing mediastinitis. *Circulation.* 2011;123(13):1391–1399.
- Gloviczki P, Pairolero PC, Cherry KJ, Hallett Jr JW. Reconstruction of the vena cava and of its primary tributaries: a preliminary report. *J Vasc Surg.* 1990;11(3):373–381.
- Kalra M, Gloviczki P, Andrews JC, et al. Open surgical and endovascular treatment of superior vena cava syndrome caused by nonmalignant disease. *J Vasc Surg.* 2003;38(2):215–223.

45. Moore WHL, Rotsvcacy IBJ, Yao JST, eds. *Venous Disorders*. Philadelphia: WB Saunders; 1991:517–527.
46. Gwon DI, Ko GY, Kim JH, et al. Malignant superior vena cava syndrome: a comparative cohort study of treatment with covered stents versus uncovered stents. *Radiology*. 2013;266(3):979–987.
47. Anaya-Ayala JE, Smolock CJ, Colvard BD, et al. Efficacy of covered stent placement for central venous occlusive disease in hemodialysis patients. *J Vasc Surg*. 2011;54(3):754–759.
48. Haddad MM, Simmons B, McPhail IR, et al. Comparison of Covered Versus Uncovered Stents for Benign Superior Vena Cava (SVC) Obstruction. *Cardiovasc Intervent Radiol*. 2018;41(5):712–717.
49. Iafrati M, Maloney S, Halin N. Radiofrequency thermal wire is a useful adjunct to treat chronic central venous occlusions. *J Vasc Surg*. 2012;55(2):603–606.
50. Da Ines D, Chabrot P, Motreff P, et al. Cardiac tamponade after malignant superior vena cava stenting: Two case reports and brief review of the literature. *Acta Radiol*. 2010;51(3):256–259.
51. de Gregorio Ariza MA, Gamboa P, Gimeno MJ, et al. Percutaneous treatment of superior vena cava syndrome using metallic stents. *Eur Radiol*. 2003;13(4):853–862.
52. Williams DR, Demos NJ. Thrombosis of superior vena cava caused by pacemaker wire and managed with streptokinase. *J Thorac Cardiovasc Surg*. 1974;68(1):134–137.
53. Chan J, Rees CR, Song AK, Pham S. Usefulness of catheter-directed thrombolysis using alteplase in peripheral vascular occlusion. *Proc (Bayl Univ Med Cent)*. 2001;14(1):3–7.
54. Kee ST, Kinoshita L, Razavi MK, et al. Superior vena cava syndrome: treatment with catheter-directed thrombolysis and endovascular stent placement. *Radiology*. 1998;206(1):187–193.
55. Dib C, Hennebry TA. Successful treatment of SVC syndrome using isolated pharmacomechanical thrombolysis. *J Invasive Cardiol*. 2012;24(3):E50–E53.
56. Irving JD, Dondelinger RF, Reidy JF, et al. Gianturco self-expanding stents: clinical experience in the vena cava and large veins. *Cardiovasc Intervent Radiol*. 1992;15(5):328–333.
57. Rösch J, Bedell JE, Putnam J, Antonovic R, Uchida B. Gianturco expandable wire stents in the treatment of superior vena cava syndrome recurring after maximum-tolerance radiation. *Cancer*. 1987;60(6):1243–1246.
58. Panneton JM, Andrews JC, Hofer JM. Superior vena cava syndrome: relief with a modified saphenous bypass graft. *J Vasc Surg*. 2001;34(2):360–363.
59. Wells JK, Hagino RT, Bargmann KM, et al. Venous morbidity after superficial femoral-popliteal vein harvest. *J Vasc Surg*. 1999;29(2):282–289; discussion 289–291.
60. Modrall JG, Hocking JA, Timaran CH, et al. Late incidence of chronic venous insufficiency after deep vein harvest. *J Vasc Surg*. 2007;46(3):520–525; discussion 525.
61. Chiu CJ, Terzis J, MacRae ML. Replacement of superior vena cava with the spiral composite vein graft. A versatile technique. *Ann Thorac Surg*. 1974;17(6):555–560.
62. Doty DB. Bypass of superior vena cava: Six years' experience with spiral vein graft for obstruction of superior vena cava due to benign and malignant disease. *J Thorac Cardiovasc Surg*. 1982;83(3):326–338.
63. Meissner MH, Eklöf B, Smith PC, et al. Secondary chronic venous disorders. *J Vasc Surg*. 2007;46 Suppl S:68S–83S.
64. Jost CJ, Gloviczki P, Cherry Jr KJ, et al. Surgical reconstruction of iliofemoral veins and the inferior vena cava for nonmalignant occlusive disease. *J Vasc Surg*. 2001;33(2):320–327; discussion 327–328.
65. Marshall Jr WG, Kouchoukos NT. Management of recurrent superior vena caval syndrome with an externally supported femoral vein bypass graft. *Ann Thorac Surg*. 1988;46(2):239–241.
66. Nicholson AA, Ettles DF, Arnold A, et al. Treatment of malignant superior vena cava obstruction: metal stents or radiation therapy. *J Vasc Interv Radiol*. 1997;8(5):781–788.
67. García Mónaco R, Bertoni H, Pallotta G, et al. Use of self-expanding vascular endoprostheses in superior vena cava syndrome. *Eur J Cardiothorac Surg*. 2003;24(2):208–211.
68. Greillier L, Barlesi F, Doddoli C, et al. Vascular stenting for palliation of superior vena cava obstruction in non-small-cell lung cancer patients: a future 'standard' procedure? *Respiration*. 2004;71(2):178–183.
69. Maleux G, Gillardin P, Fieuws S, et al. Large-bore nitinol stents for malignant superior vena cava syndrome: factors influencing outcome. *AJR Am J Roentgenol*. 2013;201(3):667–674.
70. Fagedet D, Thony F, Timsit JF, et al. Endovascular treatment of malignant superior vena cava syndrome: results and predictive factors of clinical efficacy. *Cardiovasc Intervent Radiol*. 2013;36(1):140–149.
71. Mokry T, Bellemann N, Sommer CM, et al. Retrospective study in 23 patients of the self-expanding sinus-XL stent for treatment of malignant superior vena cava obstruction caused by non-small cell lung cancer. *J Vasc Interv Radiol*. 2015;26(3):357–365.
72. Urruticoechea A, Mesía R, Domínguez J, et al. Treatment of malignant superior vena cava syndrome by endovascular stent insertion. Experience on 52 patients with lung cancer. *Lung Cancer*. 2004;43(2):209–214.
73. Bierdrager E, Lampmann LE, Lohle PN, et al. Endovascular stenting in neoplastic superior vena cava syndrome prior to chemotherapy or radiotherapy. *Neth J Med*. 2005;63(1):20–23.
74. Lee-Elliott CE, Abubacker MZ, Lopez AJ. Fast-track management of malignant superior vena cava syndrome. *Cardiovasc Intervent Radiol*. 2004;27(5):470–473.
75. Chatzioannou A, Alexopoulos T, Mourikis D, et al. Stent therapy for malignant superior vena cava syndrome: should be first line therapy or simple adjunct to radiotherapy. *Eur J Radiol*. 2003;47(3):247–250.
76. Tallarita T, Kalra M, Bower T, et al. VESS29. Decreasing Incidence and Increasing Complexity of Open Reconstruction for Benign Superior Vena Cava Syndrome: 34-Year Single-Center Experience. *J Vasc Surg*. 2018;67(6):e71–e73.
77. Sheth S, Ebert MD, Fishman EK. Superior vena cava obstruction evaluation with MDCT. *AJR Am J Roentgenol*. 2010;194(4):W336–W346.
78. Rosenblum J, Leef J, Messersmith R, et al. Intravascular stents in the management of acute superior vena cava obstruction of benign etiology. *JPNEN J Parenter Enteral Nutr*. 1994;18(4):362–366.
79. Barshes NR, Annambhotla S, El Sayed HF, et al. Percutaneous stenting of superior vena cava syndrome: treatment outcome in patients with benign and malignant etiology. *Vascular*. 2007;15(5):314–321.
80. Oudkerk M, Kuijpers TJ, Schmitz PI, et al. Self-expanding metal stents for palliative treatment of superior vena caval syndrome. *Cardiovasc Intervent Radiol*. 1996;19(3):146–151.
81. Cho Y, Gwon DI, Ko GY, et al. Covered stent placement for the treatment of malignant superior vena cava syndrome: is unilateral covered stenting safe and effective? *Korean J Radiol*. 2014;15(1):87–94.
82. Gwon DI, Paik SH. Successful treatment of malignant superior vena cava syndrome using a stent-graft. *Korean J Radiol*. 2012;13(2):227–231.
83. Doty DB. Superior vena cava obstruction. *Mayo Clin Proc*. 1981;56(11):717–718.
84. Doty DB, Baker WH. Bypass of superior vena cava with spiral vein graft. *Ann Thorac Surg*. 1976;22(5):490–493.
85. Dhaliwal RS, Das D, Luthra S, et al. Management of superior vena cava syndrome by internal jugular to femoral vein bypass. *Ann Thorac Surg*. 2006;82(1):310–312.
86. Picquet J, Blin V, Dussaussoy C, et al. Surgical reconstruction of the superior vena cava system: indications and results. *Surgery*. 2009;145(1):93–99.
87. Wisselink W, Money SR, Becker MO, et al. Comparison of operative reconstruction and percutaneous balloon dilatation for central venous obstruction. *Am J Surg*. 1993;166(2):200–204; discussion 204–205.
88. Syroeras GS, Antonopoulos CN, Mantas G, et al. A review of open and endovascular treatment of superior vena cava syndrome of benign aetiiology. *Eur J Vasc Endovasc Surg*. 2017;53(2):238–254.

# Congenital Occlusion/ Absence of Inferior Vena Cava

MIKEL SADEK and GLENN R. JACOBOWITZ

## ASSOCIATION WITH DEEP VENOUS THROMBOSIS 2163

### EMBRYOGENESIS 2163

### PRESENTATION 2164

#### Clinical Diagnosis 2164

#### Imaging Modalities 2164

##### *Duplex Scan of the Lower Extremities and Pelvis* 2164

##### *Axial Imaging (Computed Tomography Venography and Magnetic Resonance Venography)* 2165

## *Venography* 2166

## MANAGEMENT 2166

### Acute Deep Venous Thrombosis with Mild Symptoms 2166

### Acute Deep Venous Thrombosis with Severe Symptoms (Leg Swelling, Venous Congestion) 2167

### Chronic Venous Insufficiency with Severe Symptoms (Tissue Compromise or Venous Ulceration) 2167

## SUMMARY 2168

Congenital absence of the inferior vena cava (AIVC) is a rare entity and is often first detected in the setting of an idiopathic deep venous thrombosis (DVT) of the lower extremity. The overall incidence of AIVC in the general population has been estimated to be 0.3% to 0.5%, but it may be present in up to 5% of patients under the age of 30 with idiopathic DVT. This incidence was first noted by Ruggeri et al. in 2001.<sup>1</sup> These authors noted that in their own review of published reports from 1966 to 1999, there were fewer than 10 cases of DVT in patients with AIVC. They also noted that this could have represented an underestimation, because the most common diagnostic imaging technique, the duplex scan, does not routinely include the abdominal veins. Indeed, dedicated abdominal duplex scanning or axial imaging is required to make the diagnosis.

It is likely that most cases of congenital absence of the IVC remain undiagnosed and are of little clinical consequence. However, it is the subset of patients presenting with an acute DVT that increases the complexity of management.

## ASSOCIATION WITH DEEP VENOUS THROMBOSIS

Several authors have noted an association of AIVC with DVT, particularly in young males.<sup>1–6</sup> Congenital AIVC may create a low-flow state, making the lower extremity more susceptible

to DVT, and thrombophilias, such as factor V Leiden or homocysteinemia, may increase the risk further.<sup>2,3</sup> Halparin et al. evaluated a pediatric population and noted that congenital AIVC does not seem to present with symptoms of DVT until at least the second decade of life. The authors suggest that for the anomaly to manifest as DVT, a second “hit” is required, consistent with the multifactorial etiology of DVTs.<sup>4</sup> Venous collaterals appear to be able to compensate for the lack of a normal IVC but fail when the demands for venous drainage exceed the capacity of the collateral veins, with DVT then occurring via a mechanism of stasis. Factors in the pediatric and adolescent population that may increase the demand for venous drainage include strenuous physical activity, a growth spurt, or the presence of inherited or acquired thrombotic risk factors. Acquired factors include immobilization, trauma, surgery, malignancy, vascular catheterization, smoking, or the use of oral contraceptives.<sup>4</sup>

## EMBRYOGENESIS

AIVC may be associated with other congenital abnormalities, including atrial septal defects, polysplenia, or dysgenesis of the lungs.<sup>5,6</sup> The complex embryogenesis of the IVC begins at week 6, as it develops from three pairs of primitive veins, the supracardinal, subcardinal, and postcardinal veins. These veins form collaterals and connections during development but then regress, leading to a single continuous channel, the IVC.<sup>7</sup>

The IVC can be divided into four segments, the hepatic, prerenal, postrenal, and renal collar. These segments arise from the primitive veins. The supracardinal vein gives rise to the postrenal IVC as well as the hemiazygos and azygos veins. The subcardinal vein gives rise to the prerenal portion, and the renal collar is formed from the subcardinal and supracardinal segments. Hepatic sinusoids form the hepatic segment.<sup>7</sup> It has been proposed that AIVC may be caused by dysgenesis of this complex process or by an interruption of the process by an intrauterine insult.<sup>8,9</sup> The most common types of IVC anomalies are isolated left IVC, double IVC, atresia or agenesis of a segment or the total IVC, and azygos or hemiazygos continuation of the IVC (Figs. 163.1–163.3).<sup>10</sup> Regression of the right supracardinal vein with persistence of the left supracardinal vein results in a left IVC. If both the left and right supracardinal veins persist, there will be a double IVC. Atresia of a segment

of the IVC or total IVC atresia is caused by failure of anastomosis of one (segmental AIVC) or multiple (total AIVC) segments of the IVC.<sup>10,11</sup>

## PRESENTATION

AIVC may be noted incidentally, or it may present with complications such as venous thromboembolic disease and associated sequelae.

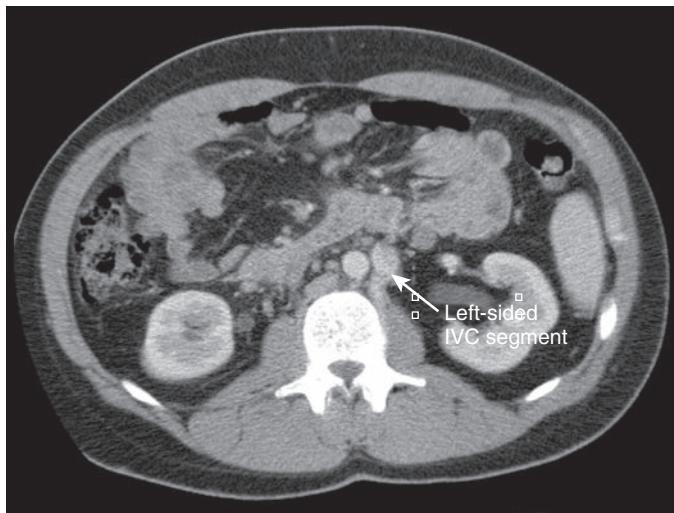
### Clinical Diagnosis

Diagnosis of congenital absence or occlusion of the IVC relies on a high index of suspicion. For example, young patients (<40 years) are considered to be at lower risk for DVT. Therefore, in a young person with an unprovoked DVT, evaluation for hypercoagulability might be accompanied selectively by imaging for congenital anomalies of the deep venous system. This may hold true in even more particular circumstances, such as young patients presenting with extensive bilateral iliofemoral thrombosis or with physical exam findings of extensive collateralization (i.e., abdominal wall varicosities). As noted previously, up to 5% of individuals between 20 and 40 years of age who develop a DVT may have an underlying congenital anomaly of the IVC.<sup>1</sup>

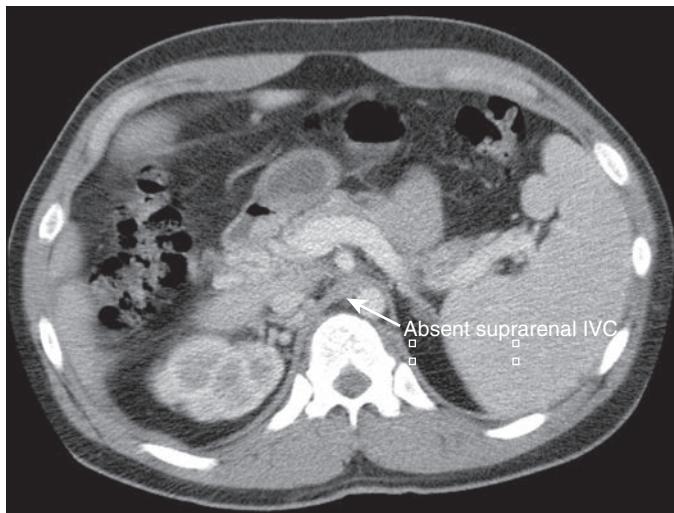
### Imaging Modalities

#### Duplex Scan of the Lower Extremities and Pelvis

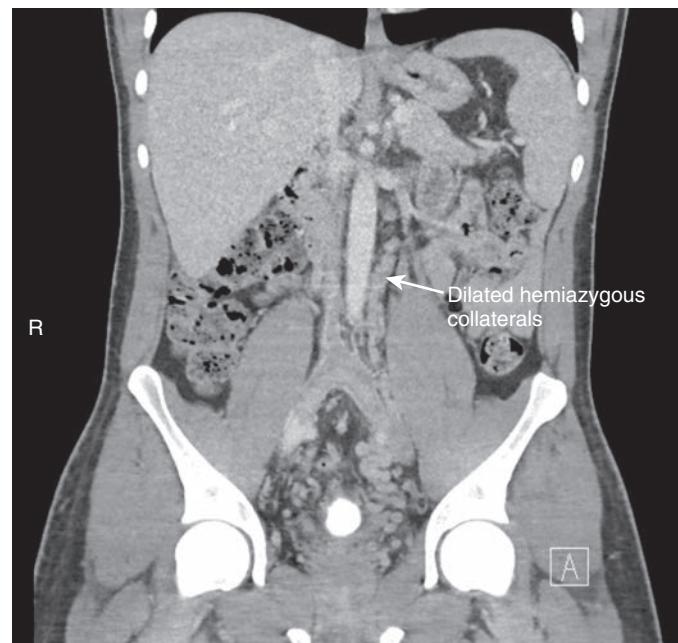
In most cases the initial study of choice is the lower extremity venous duplex. With regard to the deep venous system, duplex may identify direct or indirect signs related to central venous obstruction. In the setting of chronic venous hypertension,



**Figure 163.1** Computed tomography scan demonstrating left-sided infrarenal inferior vena cava (IVC) with an absent suprarenal IVC.



**Figure 163.2** Computed tomography scan demonstrating an absent suprarenal inferior vena cava (IVC).



**Figure 163.3** Coronal image of computed tomography scan showing hemiazygous continuation of an absent inferior vena cava.

where the more peripheral deep veins exhibit damaged valves, significant reflux may be present in the iliac, femoral, popliteal, or tibial veins.<sup>12</sup> Even in the setting of competent deep veins, there may be signs suggestive of a central obstruction, such as diminished or absent respiratory phasicity.<sup>13</sup> There may also be evidence of chronic DVT in the iliofemoral and popliteal veins, such as a contracted, thick-walled, hyperechoic lumen, with possible recanalization.<sup>12</sup> In addition, due to the significant burden placed on the lower extremity's venous system in the setting of AIVC, reflux may develop in the superficial or perforator veins. Significant superficial collateral networks emanating from the abdominal wall or the pelvis may also be identified by duplex ultrasound. Lastly, direct insonation of the iliocaval segments may show absence of flow or complete absence of the segments themselves. The disadvantage of duplex is that it is highly operator-dependent and dependent on patient-specific factors such as size, bowel gas, and patient cooperation.<sup>12</sup> Once clinical suspicion for severe iliocaval disease is present and duplex ultrasound corroborates the clinical findings, confirmatory imaging is typically required. This would be performed most commonly with noninvasive axial imaging, such as computed tomography venography (CTV) or magnetic resonance venography (MRV). Invasive methodologies, such as venography and intravascular ultrasound (IVUS), may also be used.

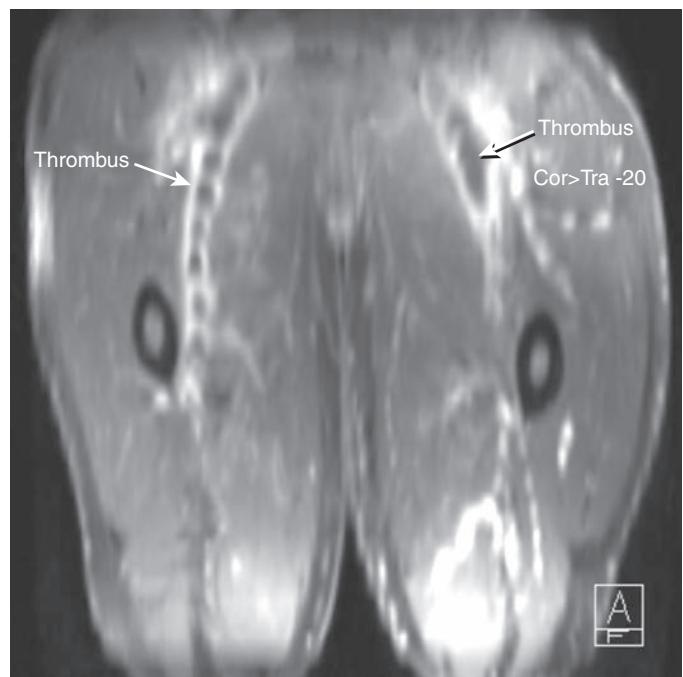
### Axial Imaging (Computed Tomography Venography and Magnetic Resonance Venography)

CTV and MRV help to diagnose and to characterize the anomalous anatomic variants associated with AIVC. Both modalities have advantages and disadvantages. Each identifies the distribution of DVT in the central veins.

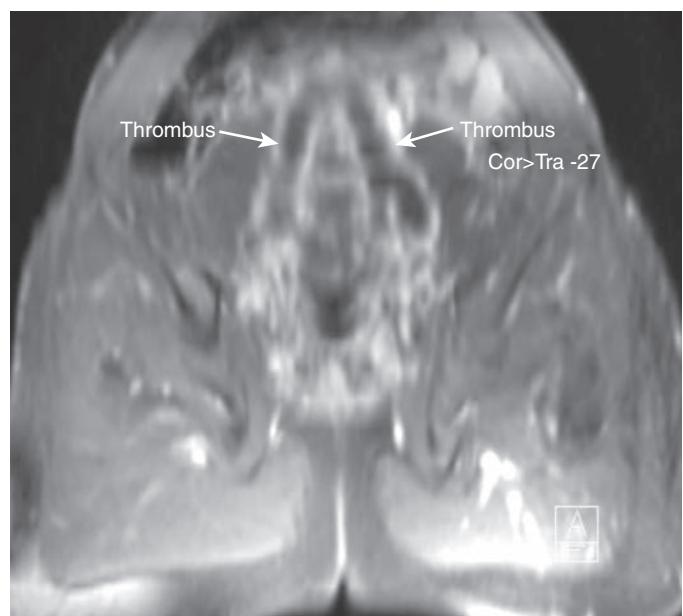
For CTV, one significant potential complication is contrast-induced nephropathy; therefore, this modality should be used judiciously in patients presenting with chronic kidney disease. This may be especially true in patients with renal aplasia, which has a known association with congenital AIVC.<sup>14</sup> Also, should the patient proceed to intervention, the potential for renal insult from the intraprocedural contrast, or from the thrombectomy techniques themselves, should be taken into account.<sup>15</sup> In addition, CT scans contribute to the cumulative long-term risk of radiation, which may be of greater consideration in evaluating younger patients.<sup>16</sup> Patients with significant reactions or allergies to iodinated contrast may be precluded from utilizing this modality. With regard to image quality, the timing and acquisition of CTV are variable, and this variability may be exaggerated in patients with AIVC.

There are advantages to using CTV. It allows for the rapid acquisition of images and is readily available in most centers. In addition, if a patient has known metal implants, there is substantially less artifact with the use of CTV as compared with MRV, and the intraluminal contents of stented vasculature can be evaluated more readily.<sup>16</sup>

MRV has the advantage of lack of radiation. With regard to evaluation of the vasculature, the gadolinium may dwell longer than the iodinated contrast utilized for the CTV; therefore, the vasculature may be evaluated more completely over prolonged time intervals (Figs. 163.4–163.6).<sup>17</sup> This allows for a more

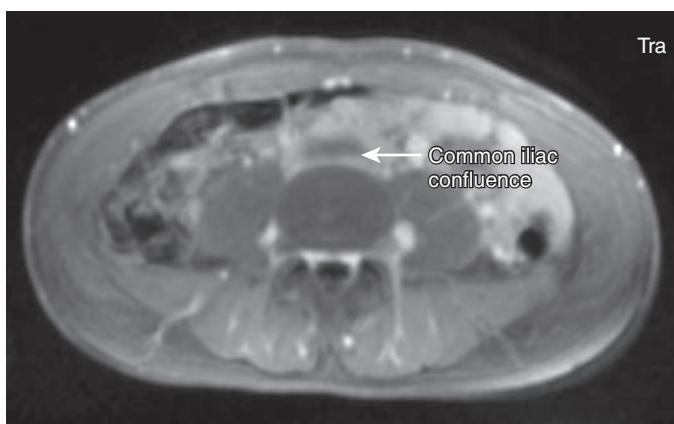


**Figure 163.4** Magnetic resonance venogram demonstrating acute thrombosis of the bilateral femoral veins in the setting of an absent inferior vena cava.



**Figure 163.5** Magnetic resonance venogram demonstrating acute thrombosis of the bilateral iliac veins in the setting of an absent inferior vena cava.

complete assessment of the venous circulation and the ability to obtain time-resolution images. These may provide critical information about collateral circulation and patterns of flow. Another possible advantage of MRV may be the ability to estimate the chronicity of the DVT.<sup>18</sup> In the elective setting MRV may be the preferred modality, given the improved filling of the vasculature and the possibility for improved time resolution.<sup>19</sup> Disadvantages to obtaining an MRV include strict contraindications in patients with certain metal implants, such as pacemakers. Moreover, patients with advanced (stages IV–V)



**Figure 163.6** Magnetic resonance venogram demonstrating acute thrombosis of the confluence of the iliac veins in the setting of an absent inferior vena cava.

chronic kidney disease are at risk for nephrogenic systemic fibrosis (NSF) with the administration of gadolinium.<sup>20</sup> There are time-of-flight sequences that do not utilize intravenous contrast agents; however, the resolution of these images is often suboptimal for full delineation of the vasculature. Lastly, the degree of stenosis may be overestimated by MRV owing to the way in which the image is acquired, with the associated flow voids.<sup>21</sup>

### Venography

Venography is considered the gold standard for direct visualization of the venous vasculature. It serves most commonly as an adjunctive study to noninvasive imaging modalities. The procedure itself allows for direct visualization of flow through the axial and collateral pathways. Multiple projections may be required, and selective catheterization may help to further delineate anatomy and flow (Fig. 163.7). IVUS is used frequently as an adjunct to confirm anatomy, to obtain accurate sizing, and to assess for post-treatment patency.

## MANAGEMENT

Owing to the absence of the IVC and the commensurate lack of axial flow, there is a lower risk for the development of pulmonary emboli in the setting of DVT, although enlarged collaterals may serve as a route for distal embolization.<sup>19</sup> Therefore, the indications for treatment are more commonly based on the presenting lower extremity signs and symptoms. The patient may be asymptomatic at presentation, or there may be signs and symptoms of an acute process, such as an acute DVT, or a chronic process, such as the stigmata of chronic venous insufficiency. Truly emergent presentations are rare because patients have already developed a significant collateral network that compensates in the setting of an acute process.<sup>22</sup>

### Acute Deep Venous Thrombosis with Mild Symptoms

Conventional treatment for an acute DVT with mild symptoms consists of anticoagulation with the use of graduated compression stockings.<sup>22</sup> In the case of AIVC, the goal of



**Figure 163.7** Venogram of segmental atresia of the infrarenal inferior vena cava.

anticoagulation is to prevent further propagation of thrombus, particularly into patent collateral networks that are contributing to venous return. Because of the presence of a fixed anatomic defect, the general recommendation is to treat with lifelong anticoagulation.<sup>3</sup> Warfarin and low-molecular-weight heparin may be utilized. The direct oral anticoagulants (DOACs) such as apixaban, rivaroxaban, edoxaban, and dabigatran are attractive alternatives due to their convenience.<sup>23</sup> With regard to graduated compression, evidence suggests that it may not prevent the development of a postthrombotic syndrome; however, it may help patients in whom the postthrombotic syndrome has already been diagnosed.<sup>24</sup>

There should be a discussion with the patient regarding invasive management for the treatment of iliofemoral acute DVT.<sup>25</sup> The relevant invasive treatments include catheter-directed thrombolysis, pharmacomechanical thrombectomy, and percutaneous mechanical thrombectomy, with or without adjunctive catheter-directed lytic therapy (see Chs. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment and 161, Iliocaval Venous Obstruction: Endovascular Treatment).

Interventional treatments are typically reserved for patients with severe symptoms, and should be offered in the acute phase (i.e., less than 2–4 weeks). They should be utilized to treat the iliofemoral veins or the remnant IVC directly. In certain instances, the congenital anomaly leads to thrombus formation in the renal or hepatic veins, and they may be treated as well.<sup>25</sup> Important tools in ensuring restoration of luminal patency of the treated veins include performing venography in multiple oblique projections as well as IVUS to assess for full resolution

of thrombus. Restoration of adequate inflow is predicated on restoration of flow from a patent femoral or profunda femoris vein into a patent iliac venous system.

The restoration of outflow is the clear obstacle in the setting of the congenital AIVC. Often, the outflow collateral network that has developed over time, perhaps communicating with the azygos system, is robust enough to maintain patency with the assistance of long-term anticoagulation.<sup>26</sup>

The use of pharmacomechanical thrombectomy may expedite treatment and limit the dosage of the chosen lytic agent (see Chs. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment and 161, Iliocaval Venous Obstruction: Endovascular Treatment). Level 1 evidence supporting the invasive management of acute iliofemoral DVT has been a source of controversy. The primary outcomes that are commonly evaluated include anatomic patency of the iliofemoral veins as well as freedom from the development of postthrombotic syndrome. The first randomized trial to evaluate the long-term outcomes for the treatment of iliofemoral venous thrombosis was the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) study.<sup>27</sup> This study compared the treatments of anticoagulation alone to the use of catheter-directed lytic therapy. At the 5-year time point there was an improvement in iliacaval patency from 47% to 66% ( $P = 0.012$ ) in patients treated with lytic therapy and an improvement in the freedom from development of postthrombotic syndrome from 41% to 55% ( $P = 0.047$ ). Subsequently, a Cochrane database review showed that catheter-directed thrombolysis improved iliofemoral venous patency and reduced the incidence of postthrombotic syndrome by approximately one-third.<sup>25</sup>

Most recently, the ATTRACT trial randomized 692 patients to anticoagulation alone versus percutaneous intervention with pharmacomechanical thrombectomy with or without adjunctive angioplasty/stenting. The incidence of bleeding complications was higher in the percutaneous intervention group (1.7% vs. 0.3%,  $P = 0.049$ ). The incidence of moderate-to-severe post-thrombotic syndrome on 24-month follow-up was slightly less in the percutaneous intervention group (24% vs. 18%,  $P = 0.04$ ). Improvement in quality of life did not differ significantly between the two groups, and the conclusion of the manuscript was that percutaneous intervention did not lower the risk of postthrombotic syndrome but did increase the risk for major bleeding.<sup>28</sup>

The most significant risk of interventional therapies using thrombolytic agents is the risk of minor or major bleeding, which ranges from 5% to 10%.<sup>21</sup> Considering the lack of evidence to support the invasive management of iliofemoral DVT, particularly in the setting of mild symptoms, a full assessment of the risks, benefits, and alternatives must be undertaken, and treatment should be individualized.

### Acute Deep Venous Thrombosis with Severe Symptoms (Leg Swelling, Venous Congestion)

In patients who present with more severe symptoms, the risk-benefit ratio for invasive management is altered, and progressively more so as the pathology approaches limb-threatening stages. Fortunately, this situation is rare in the setting of

congenital AIVC, given that the compensatory collateral pathways have matured over time. Nonetheless, debilitating acute limb swelling and the presentations of phlegmasia cerulea dolens, phlegmasia alba dolens, or even venous gangrene are possible. In these settings, the focus of treatment is rapid restoration of deep venous circulation for limb-salvage purposes.

The aforementioned techniques and principles remain unchanged except that pharmacomechanical thrombectomy would be favored compared with isolated catheter-directed therapy given that it restores luminal patency more rapidly. Open venous thrombectomy may also be considered (see Chs. 149, Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment, 160, Iliocaval Venous Obstruction: Surgical Treatment, and 161, Iliocaval Venous Obstruction: Endovascular Treatment).<sup>27</sup>

### Chronic Venous Insufficiency with Severe Symptoms (Tissue Compromise or Venous Ulceration)

In the setting of refractory symptoms of chronic venous insufficiency, the initial consideration should be to ensure that the iliofemoral veins are patent using the techniques described previously (venography and intravascular ultrasound). If there is evidence of chronic disease peripheral to the congenitally absent IVC, there may be a role for venography with or without angioplasty. Although stenting is used widely in the treatment of iliofemoral venous lesions, the success of stenting is predicated on a widely patent conduit with adequate inflow and outflow. In the setting of AIVC, the risk of thrombosis may be prohibitive with regards to iliofemoral venous stenting.

As a last resort in a patient with debilitating chronic venous insufficiency, and after confirming that the peripheral veins are patent, an open venous reconstruction or complex endovascular reconstruction may be warranted.<sup>29</sup> The majority of the literature as it relates to open reconstruction of the IVC is in the setting of oncologic resections (see Ch. 195, Vascular Reconstruction in Oncologic Surgery).<sup>30</sup> The principles of adequate inflow, outflow, and conduit still require strict adherence. Preoperative axial imaging is critical for operative planning; it can identify the extent of the defect and the presence of abdominal wall collaterals, which, if injured or ligated during surgery, can lead to excessive bleeding.

For open reconstruction, autologous tissue is the preferred conduit, because lifelong anticoagulation may not be needed as it would be for synthetic grafts. Aortic and IVC homografts have both been utilized.<sup>31</sup> In depopulated homografts there does not appear to be a concern for rejection; however, some authors report placing patients on immunosuppression for up to one year post-procedure.<sup>32</sup> Another theoretical complication is aneurysmal degeneration; however, this has not been observed in patients undergoing reconstruction of the IVC. The configuration of the proximal and distal anastomoses (end-to-end or end-to-side) is determined by the anatomy. An arteriovenous fistula may be created to ensure adequate inflow; however, in one series of three patients undergoing arteriovenous fistula construction concomitant with IVC reconstruction, high-output cardiac

failure occurred in two of the three patients. The fistulas were all ligated accordingly.<sup>33</sup> Although the data for open IVC reconstructions are limited, anecdotal reports suggest the potential for long-term patency.<sup>31,32</sup> Overall, the clinical success of any open reconstruction is predicated on continued and diligent conservative management with anticoagulation and compression.

With the advent of improved intra-procedural imaging, and advances in endovascular technique and technologies, endovascular reconstructions for AIVC may be undertaken in select circumstances. Case reports have described variations in treatment from stenting the azygous vein outflow to creation of a neocava using sharp recanalization techniques with adjunctive stenting.<sup>34,35</sup> These treatments are rather novel and require significant

expertise, creativity, and extensive preoperative planning. Patient selection remains the cornerstone for successful outcomes.

## SUMMARY

It is likely that most cases of congenital absence or occlusion of the IVC remain undiagnosed and, if asymptomatic, are considered of little clinical importance. However, this diagnosis should be considered in young patients with idiopathic DVT, particularly if bilateral and extensive. In association with extensive iliofemoral DVT and/or thrombophilia, management of this condition can be challenging. Based on the severity of presenting symptoms, thrombolysis may be considered in these

**TABLE 163.1**

Clinical Data Characterizing Inferior Vena Cava Agenesis Associated with Deep Venous Thrombosis in 62 Reported Cases and 10 Patients

Reference	Number of Patients	M/F Sex Ratio	Mean Age (Years)	DVT Localization (Side)	Risk Factors	Precipitating Factor	Treatment
17	1	0/1	12	1 Unilateral (right)	None	None	Prolonged VKA, elastic stockings
37	9	8/1	29 (19–57)	6 Bilateral	None	None	7 Prolonged VKA, elastic stockings (>6–72 months) 2 VKA (6 months)
1	4	3/1	19	2 Bilateral, 2 Unilateral (right)	None	None	Prolonged VKA, elastic stockings
4	1	0/1	39	Bilateral	None	None	Prolonged VKA, folic acid supplementation, elastic stockings
34	1	1/0	37	NR	None	None	Stenting of hemiazygos outflow, elastics stockings
35	1	0/1	29	Bilateral	Budd–Chiari syndrome	None	Pharmacomechanical thrombectomy, creation of “neocava” with stents, anticoagulation, elastic stockings
38	5	3/2	25	1 Bilateral, 4 Unilateral (left)	1 Oral contraception, 2 Travel >4 h	2 Major physical activity	3 Prolonged VKA, 2 thrombolysis VKA, 5 elastic stockings
39	1	1/0	14	1 Unilateral (left)	None	None	Prolonged VKA, elastic stockings
40	2	1/1	17	2 Unilateral (right)	None	1 Major physical activity	Thrombolysis, prolonged VKA, elastic stockings
41	4	2/2	27	3 Bilateral, 1 Unilateral (NR)	1 Oral contraception	None	Prolonged VKA, elastic stockings
42	1	0/1	40	1 Unilateral (right)	None	Major physical activity	Prolonged VKA, elastic stockings
43	1	1/0	22	Unilateral (right)	None	NR	Prolonged VKA, elastic stockings
44	1	1/0	26	Unilateral (left)	None	Major physical activity	Prolonged VKA, elastic stockings
45	1	1/0	21	Unilateral (left)	None	None	No information available
46	1	1/0	39	Unilateral (left)	None	None	VKA for 1 year and elastic stockings

**TABLE 163.1**

Clinical Data Characterizing Inferior Vena Cava Agenesis Associated with Deep Venous Thrombosis in 62 Reported Cases and 10 Patients—cont'd

Reference	Number of Patients	M/F Sex Ratio	Mean Age (Years)	DVT Localization (Side)	Risk Factors	Precipitating Factor	Treatment
47	1	0/1	67	Bilateral	None	None	Prolonged VKA, elastic stockings
48	1	1/0	62	Unilateral (right)	None	None	Prolonged VKA, elastic stockings
11	1	1/0	44	Unilateral (left)	None	None	Prolonged VKA, elastic stockings
49	1	1/0	49	Bilateral	NR	NR	Prolonged VKA, elastic stockings
50	1	1/0	30	Bilateral	None	None	Prolonged VKA, elastic stockings
51	1	1/0	41	Unilateral (right)	None	None	Venous bypass, prolonged VKA
52	1	0/1	48	NR	None	None	Prolonged VKA, elastic stockings
53	1	1/0	17	Unilateral (left)	None	None	Thrombolysis, 6 months LMWH
25	1	1/0	32	Unilateral (right)	None	None	Prolonged VKA, elastic stockings
54	1	1/0	37	Unilateral	None	None	Prolonged VKA
55	1	1/0	21	Bilateral	None	None	Thrombolysis, prolonged VKA, elastic stockings
56	1	1/0	27	Bilateral	None	None	Prolonged VKA, elastic stockings
57	1	1/0	18	Unilateral (right)	Behcet disease	None	Prolonged VKA
58	1	1/0	26	Infrarenal portion of IVC	None	None	Prolonged VKA
59	1	0/1	23	Unilateral (right)		Pregnancy, preeclampsia	Prolonged VKA, elastic stockings
60	1	1/0	19	Bilateral	None	None	Prolonged VKA
61	1	1/0	50	Unilateral (left)	1 Travel ≥4 h	None	Prolonged VKA
62	1	1/0	54	Unilateral (right)	None	None	Prolonged VKA
63	1	1/0	22	Right pelvic collateral vein	None	None	Prolonged VKA
64	1	0/1	17	Bilateral	None	None	Prolonged VKA (>1 year)
65	1	1/0	14	Unilateral (right)	None	None	Prolonged VKA
66	1	1/1	33.34	2 Unilateral (right)	Knee trauma	None	NR
67	1	1/0	8.5	Unilateral (right)	None	None	VKA 8 months
68	1	0/1	18	Pelvic DVT Bilateral	1 Oral contraception	None	Prolonged VKA
69	1	0/1	26	Bilateral	None	None	Prolonged VKA
70	1	1/0	20	Pelvic DVT	None	None	Prolonged VKA
71	2	1/1	24.28	1 Unilateral 1 Bilateral	None	None	1 prolonged VKA 1 VKA (12 months)

*Continued*

**TABLE 163.1**

Clinical Data Characterizing Inferior Vena Cava Agenesis Associated with Deep Venous Thrombosis in 62 Reported Cases and 10 Patients—cont'd

Reference	Number of Patients	M/F Sex Ratio	Mean Age (Years)	DVT Localization (Side)	Risk Factors	Precipitating Factor	Treatment
72	1	1/0	18	1 Unilateral	None	None	Prolonged VKA
73	10	8/2	25	6 Bilateral 4 Unilateral	1 Travel ≥4 h	8 Major physical activity	9 prolonged VKA, elastic stockings; 1 VKA (25 months)
<b>TOTAL</b>	<b>72</b>	<b>53/19</b>	<b>29.6 ± 13.2</b>	<b>28 Bilateral 4 Unilateral 28 Bilateral 40 Unilateral 1 NR 2 Right pelvic collateral vein 1 Infrarenal portion of IVC</b>	<b>3 Oral contraception 4 Travel ≥4 h 1 Knee trauma 1 Bedridden for 2 days</b>	<b>13 Major physical activity</b>	<b>56 Prolonged VKA 7 VKA (&lt;3 years) 1 LMWH (6 months) 5 thrombolysis 1 bypass</b>

DVT, Deep venous thrombosis; F, female; LMWH, low-molecular-weight heparin; M, male; NR, not reported; VKA, vitamin K antagonist.

Reprinted with permission from Lambert M, Marboeuf P, Midulla M, et al. Inferior vena cava agenesis and deep vein thrombosis: 10 patients and review of the literature. *Vasc Med*. 2010;15(6):451–459.<sup>73</sup>

patients, with an endpoint of restoring baseline venous flow to previously established venous collaterals. Long-term anticoagulation is often indicated, particularly if thrombophilia is identified. Table 163.1 summarizes the presentation and treatments of recent publications.

*Literature review of cases to date where patients with inferior vena cava agenesis were treated for deep venous thrombosis. In more recent years, patients with more severe symptoms were treated with both anticoagulation and thrombolysis.*

Lamparello BM, et al. Congenital anomaly of the inferior vena cava and factor V Leiden mutation predisposing to deep vein thrombosis. *Vasc Health Risk Manag*. 2014;10:609–613.

*Association of thrombophilia and congenital absence of the inferior vena cava as predisposing factors for deep venous thrombosis.*

Man L, Hendricks N, Maitland H, et al. IVC agenesis: a rare cause of deep vein thrombosis. *J Thromb Thrombol*. 2016;41(3):541–543.

*Summary of inferior vena cava agenesis as a rare cause of deep venous thrombosis.*

Ruggeri M, et al. Congenital absence of the inferior vena cava: a rare risk factor for idiopathic deep-vein thrombosis. *Lancet*. 2001;357(9254):441.

*One of the first reviews of congenital absence of the inferior vena cava with an estimate of overall incidence in the general population.*

Sagban TA, Scharf RE, Wagenhäuser MU, et al. Elevated risk of thrombophilia in agenesis of the vena cava as a factor for deep vein thrombosis. *Orphanet J Rare Dis*. 2015;10:3.

*Case report with literature review of catheter-directed thrombolysis for severe, symptomatic deep vein thrombosis in the setting of congenital absence of the inferior vena cava.*

Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev*. 2014;1:CD002783.

*Meta-analysis demonstrating the efficacy of catheter-directed thrombolysis for acute deep venous thrombosis.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## SELECTED KEY REFERENCES

Enden T, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31–38.

*Largest study to date randomizing patients with acute iliofemoral deep venous thrombosis to anticoagulation alone versus catheter-directed thrombolysis for long-term prevention of postthrombotic syndrome.*

Ganguli S, Kalva S, Oklu R, et al. Efficacy of lower-extremity venous thrombolysis in the setting of congenital absence or atresia of the inferior vena cava. *Cardiovasc Intervent Radiol*. 2012;35(5):1053–1058.

*Series of six patients treated with thrombolysis for deep venous thrombosis in the setting of congenital absence of the IVC.*

Garg K, Cayne N, Jacobowitz G. Mechanical and pharmacologic catheter-directed thrombolysis treatment of severe, symptomatic, bilateral deep vein thrombosis with congenital absence of the inferior vena cava. *J Vasc Surg*. 2011;53(6):1707–1710.

*Elevated risk of thrombophilia in agenesis of the vena cava as a factor for deep vein thrombosis.*

Halparin J, Monagle P, Newall F. Congenital abnormalities of the inferior vena cava presenting clinically in adolescent males. *Thromb Res*. 2015;135(4):648–651.

*Series demonstrating the association between congenital absence of the inferior vena cava and unprovoked deep venous thrombosis in adolescent males.*

Lambert M, Marboeuf P, Midulla M, et al. Inferior vena cava agenesis and deep vein thrombosis: 10 patients and review of the literature. *Vasc Med*. 2010;15(6):451–459.

## REFERENCES

1. Ruggeri M, et al. Congenital absence of the inferior vena cava: a rare risk factor for idiopathic deep-vein thrombosis. *Lancet*. 2001;357(9254):441.
2. Parsa P, et al. Congenital agenesis of inferior vena cava: a rare cause of unprovoked deep venous thrombosis. *Ann Vasc Surg*. 2015;29(5):1017.e15–1017.e18.
3. Garg K, Cayne N, Jacobowitz G. Mechanical and pharmacologic catheter-directed thrombolysis treatment of severe, symptomatic, bilateral deep vein thrombosis with congenital absence of the inferior vena cava. *J Vasc Surg*. 2011;53(6):1707–1710.
4. Yun SS, et al. Deep venous thrombosis caused by congenital absence of inferior vena cava, combined with hyperhomocysteinemia. *Ann Vasc Surg*. 2004;18(1):124–129.
5. Schneider JG, et al. Recurrent deep venous thrombosis caused by congenital interruption of the inferior vena cava and heterozygous factor V Leiden mutation. *J Intern Med*. 2002;252(3):276–280.
6. Halparin J, Monagle P, Newall F. Congenital abnormalities of the inferior vena cava presenting clinically in adolescent males. *Thromb Res*. 2015;135(4):648–651.
7. Dellavalle A, Ribichini F, Steffenino G. Unsuspected infrahepatic interruption of inferior vena cava associated with floppy mitral valve, mitral valve prolapse, and severe mitral regurgitation. *Chest*. 1994;106(5):1626–1628.
8. Matsuoka T, et al. Anomalous inferior vena cava with azygos continuation, dysgenesis of lung, and clinically suspected absence of left pericardium. *Chest*. 1990;97(3):747–749.
9. Debing E, et al. Congenital absence of inferior vena cava. *Eur J Vasc Surg*. 1993;7(2):201–203.
10. Basile A, et al. Embryologic and acquired anomalies of the inferior vena cava with recurrent deep vein thrombosis. *Abdom Imaging*. 2003;28(3):400–403.
11. Ramanathan T, Hughes TM, Richardson AJ. Perinatal inferior vena cava thrombosis and absence of the infrarenal inferior vena cava. *J Vasc Surg*. 2001;33(5):1097–1099.
12. Sarlon G, et al. Congenital anomalies of inferior vena cava in young patients with iliac deep venous thrombosis. *Ann Vasc Surg*. 2011;25(2):e265.e5–e265.e8.
13. Barleben A, Bandyk DF. Surveillance and follow-up after revascularization for critical limb ischemia. *Semin Vasc Surg*. 2014;27(1):75–81.
14. Labropoulos N, Leon Jr LR. Duplex evaluation of venous insufficiency. *Semin Vasc Surg*. 2005;18(1):5–9.
15. Harvey HB, Brink JA, Frush DP. Informed consent for radiation risk from CT is unjustified based on the current scientific evidence. *Radiology*. 2015;275(2):321–325.
16. Umeoka S, et al. Vascular dilatation in the pelvis: identification with CT and MR imaging. *Radiographics*. 2004;24(1):193–208.
17. Yang DM, et al. Time-resolved MR angiography for detecting and grading ovarian venous reflux: comparison with conventional venography. *Br J Radiol*. 2012;85(1014):e117–e122.
18. Baekgaard N, et al. Thrombus age is ideally measured by history or MRV prior to thrombus removal. *Phlebology*. 2015;30(1 suppl):20–26.
19. Cho BC, et al. Congenital absence of inferior vena cava as a rare cause of pulmonary thromboembolism. *Yonsei Med J*. 2004;45(5):947–951.
20. Daftari Besheli L, et al. Current status of nephrogenic systemic fibrosis. *Clin Radiol*. 2014;69(7):661–668.
21. Vessie EL, et al. A practical guide to magnetic resonance vascular imaging: techniques and applications. *Ann Vasc Surg*. 2014;28(4):1052–1061.
22. Comerota AJ, Gravett MH. Iliofemoral venous thrombosis. *J Vasc Surg*. 2007;46(5):1065–1076.
23. Comerota AJ, Aldridge SC. Thrombolytic therapy for deep venous thrombosis: a clinical review. *Can J Surg*. 1993;36(4):359–364.
24. Kahn SR, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383(9920):880–888.
25. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev*. 2014;(1):CD002783.
26. Enden T, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31–38.
27. Vedantham S, Goldhaber SZ, Julian JA, et al. ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med*. 2017;377(23):2240–2252.
28. Augustinos P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. *Circulation*. 2004;110(9 suppl 1):I27–I34.
29. Rodriguez LE, et al. Symptomatic iliofemoral deep venous thrombosis treated with hybrid operative thrombectomy. *J Vasc Surg Venous Lymphat Disord*. 2015;3(4):438–441.
30. Etkin Y, et al. Successful venous repair and reconstruction for oncologic resections. *J Vasc Surg Venous Lymphat Disord*. 2016;4(1):57–63.
31. Garg K, et al. Delayed reconstruction with cryopreserved vein of an iatrogenically ligated inferior vena cava. *J Vasc Surg Venous Lymphat Disord*. 2014;2(1):74–76.
32. Billing JS, et al. Aortic arch homograft as a bypass conduit for superior vena cava obstruction. *Ann Thorac Surg*. 2003;76(4):1296–1297.
33. Scali ST, Beck AW, DeMartino RD, et al. Endovascular management of congenital atresia of the infrarenal IVC. *Vasc Endovascular Surg*. 2010;44(3):234–236.
34. Haskal ZJ, Potosky DR, Twaddell WS, et al. Percutaneous endovascular creation of an inferior vena cava in a patient with caval agenesis, Budd-Chiari syndrome, and iliofemorocaval thrombosis. *J Vasc Interv Radiol*. 2014;25(1):63–69.
35. Hardwigsen J, et al. Leiomyosarcoma of the retrohepatic portion of the inferior vena cava: clinical presentation and surgical management in five patients. *J Am Coll Surg*. 2005;200(1):57–63.
36. Gayer G, Luboshitz J, Hertz M, et al. Congenital anomalies of the inferior vena cava revealed on CT in patients with deep vein thrombosis. *AJR Am J Roentgenol*. 2003;180:729–732.
37. Obernosterer A, Aschauer M, Schnell W, Lipp RW. Anomalies of the inferior vena cava in patients with iliac venous thrombosis. *Ann Intern Med*. 2002;136:37–41.
38. Gil RJ, Pérez AM, Arias JB, et al. Agenesis of the inferior vena cava associated with lower extremities and pelvic venous thrombosis. *J Vasc Surg*. 2006;44:1114–1116.
39. Dean SM, Tytle TL. Acute right lower extremity iliofemoral deep venous thrombosis secondary to an anomalous inferior vena cava: a report of two cases. *Vasc Med*. 2006;11:165–169.
40. Chee YL, Culligan DJ, Watson HG. Inferior vena cava malformation as a risk factor for deep venous thrombosis in the young. *Br J Haematol*. 2001;114:878–880.
41. D'Aloia A, Faggiano P, Fiorina C, et al. Absence of inferior vena cava as a rare cause of deep venous thrombosis complicated by liver and lung embolism. *Int J Cardiol*. 2003;88:327–329.
42. Vucicevic Z, Degoricija V, Alfirevic Z, Sharma M. Inferior vena cava agenesis and a massive bilateral iliofemoral venous thrombosis. *Angiology*. 2008;59:510–513.
43. Evanchuk DM, Von Gehr A, Zehnder JL. Superficial venous thrombosis associated with congenital absence of the inferior vena cava and previous episode of deep venous thrombosis. *Am J Hematol*. 2008;83:250–252.
44. Stratopoulos C, Pitsios C, Valenti P, et al. Medical Image. Deep vein thrombosis due to absence of inferior vena cava. *N Z Med J*. 2006;119:U2288.
45. Simon RW, Amann-Vesti BR, Pfammatter T, Koppensteiner R. Congenital absence of the inferior vena cava: a rare risk factor for idiopathic deep-vein thrombosis. *J Vasc Surg*. 2006;44:416.
46. Takehara N, Hasebe N, Enomoto S, et al. Multiple and recurrent systemic thrombotic events associated with congenital anomaly of inferior vena cava. *J Thromb Thrombolysis*. 2005;19:101–103.
47. Suh HJ, Kim WT, Kim MY, Cho YK. Combined anomaly of the right hepatic lobe agenesis and absence of the inferior vena cava: a case report. *Korean J Radiol*. 2008;9(suppl):S61–S64.
48. Salgado Ordóñez F, Gavilán Carrasco JC, Bermúdez Recio FJ, et al. Absence of the inferior vena cava causing repeated deep venous thrombosis in an adult – a case report. *Angiology*. 1998;49:951–956.

49. Shah NL, Shanley CJ, Prince MR, Wakefield TW. Deep venous thrombosis complicating a congenital absence of the inferior vena cava. *Surgery*. 1996;120:891–896.
50. Dougherty MJ, Calligaro KD, DeLaurentis DA. Congenitally absent inferior vena cava presenting in adulthood with venous stasis and ulceration: a surgically treated case. *J Vasc Surg*. 1996;23:141–146.
51. Bass JE, Redwine MD, Kramer LA, Harris Jr JH. Absence of the infrarenal inferior vena cava with preservation of the suprarenal segment as revealed by CT and MR venography. *AJR Am J Roentgenol*. 1999;172:1610–1612.
52. Sánchez Fernández GL, Reiss UM, de Alarcón PA. Risk of thrombosis with anomalies of the inferior vena cava and factor V Leiden. *Pediatr Blood Cancer*. 2008;50:731.
53. Timmers GJ, Falke TH, Rauwerda JA, Huijgens PC. Deep vein thrombosis as a presenting symptom of congenital interruption of the inferior vena cava. *Int J Clin Pract*. 1999;53:75–76.
54. Tsuji Y, Inoue T, Murakami H, et al. Deep vein thrombosis caused by congenital interruption of the inferior vena cava – a case report. *Angiology*. 2001;52:721–725.
55. Kondo Y, Koizumi J, Nishibe M, et al. Deep venous thrombosis caused by congenital absence of the inferior vena cava: report of a case. *Surg Today*. 2009;39:231–234.
56. Kara M, Ozçakar L, Eken G, Ozen G, Kiraz S. Deep venous thrombosis and inferior vena cava agenesis causing double crush sciatic neuropathy in Behcet's disease. *Joint Bone Spine*. 2008;75:734–736.
57. Cizginer S, Tatlı S, Girshman J, et al. Thrombosed interrupted inferior vena cava and retroaortic left renal vein mimicking retroperitoneal neoplasm. *Abdom Imaging*. 2007;32:403–406.
58. Ilijic M, Ivanisevic M, Djelmis J, et al. Postportal deep-vein thrombosis revealing agenesis of the inferior vena cava. *Eur J Obstet Gynecol Reprod Biol*. 2007;131:235–236.
59. Motwani J, Rose PE, Shatwell W. An unusual case of venous thromboembolism. *Br J Haematol*. 2005;128:1.
60. Clayburgh DR, Yoon JD, Cipriani NA, Ricketts PA, Arora VM. Clinical problem-solving. Collateral damage. *N Engl J Med*. 2008;359:1048–1054.
61. Iqbal J, Nagaraju E. Congenital absence of inferior vena cava and thrombosis: a case report. *J Med Case Rep*. 2008;2:46.
62. Moulding FJ, Roach SC, Hanbidge AE. Thrombosed pelvic collateral veins resulting from anomalous inferior vena cava: a mimicker of acute appendicitis. *AJR Am J Roentgenol*. 2005;184:703–704.
63. Oterdoom DL, de Jong BM, Hoogland PV, Groen RJ. Transient cauda equina compression syndrome and headache caused by internal vertebral venous plexus engorgement in a teenage female with vena cava inferior agenesis and iliac vein thrombosis. *J Neurol Neurosurg Psychiatry*. 2007;78:1283–1284.
64. Waseem M, Aslam M, Kumar K, Hernandez W. An adolescent with thigh pain. *Pediatr Emerg Care*. 2008;24:768–770.
65. Rose SS, Ali Y, Kumar A, et al. Deep venous thrombosis caused by inferior vena cava atresia and hereditary thrombophilia. *Am J Med Sci*. 2009;337:67–70.
66. Ismail EA, Azab AF, Jayappa S, Al-Qattan H. Congenital absence of the infrahepatic segment of the inferior vena cava with deep venous thrombosis in an 8.5-year-old boy. *Pediatr Int*. 2010;52:e117–e120.
67. Nichols JL, Gonzalez SC, Bellino PJ, Bieber EJ. Venous thrombosis and congenital absence of inferior vena cava in a patient with menorrhagia and pelvic pain. *J Pediatr Adolesc Gynecol*. 2010;23:e17–e21.
68. Dudeck O, Zeile M, Poellinger A, et al. Epidural venous enlargements presenting with intractable lower back pain and sciatica in a patient with absence of the infrarenal inferior vena cava and bilateral deep venous thrombosis. *Spine*. 2007;32:E688–E691.
69. Sandercoe GD, Brooke-Cowden GL. Developmental anomaly of the inferior vena cava. *ANZ J Surg*. 2003;73:356–360.
70. Siragusa S, Anastasio R, Falaschi F, et al. Congenital absence of inferior vena cava. *Lancet*. 2001;357:1711.
71. Parma M, Belotti D, Marinoni S, Pogliani EM. Congenital absence of the inferior vena cava and genetic coagulation abnormalities: a rare associated risk factor for recurrent idiopathic deep vein thrombosis. *Clin Appl Thromb Hemost*. 2003;9:347–348.
72. Lambert M, Marboeuf P, Midulla M, et al. Inferior vena cava agenesis and deep vein thrombosis: 10 patients and review of the literature. *Vasc Med*. 2010;15(6):451–459.

# Portal Hypertension

MARK A. ADELMAN and JOANELLE LUGO

## INTRODUCTION 2171

### PATHOPHYSIOLOGY 2171

### CLASSIFICATION 2172

  Extrahepatic Presinusoidal Obstruction 2172

  Intrahepatic Presinusoidal Obstruction 2172

  Intrahepatic Sinusoidal and Postsinusoidal Portal Hypertension 2172

  Extrahepatic Postsinusoidal Obstruction 2173

  Arteriovenous Fistulae 2173

### CLINICAL PRESENTATION 2173

### COMPLICATIONS OF PORTAL HYPERTENSION 2173

  Variceal Formation and Hemorrhage 2173

  Ascites 2173

  Encephalopathy 2174

  Hepatorenal Syndrome 2174

  Hepatopulmonary/Portopulmonary Syndromes 2174

### DIAGNOSIS 2174

  Laboratory Evaluation 2174

  Upper Gastrointestinal Endoscopy 2174

  Liver Biopsy 2174

  Duplex Scanning 2175

  Computed Tomography Angiography 2175

  Percutaneous Angiography 2175

## NONSURGICAL TREATMENT OF PORTAL HYPERTENSION AND ITS COMPLICATIONS 2175

### Prevention and Treatment of Variceal Bleeding 2175

*Primary Prophylaxis* 2175

  NONSELECTIVE BETA BLOCKADE 2175

  ENDOSCOPIC VARICEAL BAND LIGATION 2175

  ENDOSCOPIC SCLEROTHERAPY 2175

*Acute Variceal Hemorrhage* 2175

  VASOPRESSIN 2176

  SOMATOSTATIN/OCTREOTIDE 2176

  BALLOON TAMPOONADE 2176

  BALLOON-OCCCLUDED ANTEGRADE AND RETROGRADE TRANSVENOUS OBLITERATION 2176

  TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT 2176

*Secondary Prophylaxis* 2177

### Treatment of Ascites 2178

*Treatment of Encephalopathy* 2178

### Hepatic and Portal Vein Recanalization 2179

## SURGICAL TREATMENT OF PORTAL HYPERTENSION 2179

  Liver Transplantation 2181

### CHAPTER ALGORITHM 2182

## INTRODUCTION

Portal hypertension (PHT) occurs when there is an abnormal increase in pressure in the veins that carry blood from the visceral organs to the liver. This can be explained by Ohm's law, where the change in pressure is equal to the flow times the resistance ( $P = Q \times R$ ). Therefore, the pressure can be increased by increasing the flow or increasing the resistance. Normal portal pressure is between 5 and 10 mm Hg. Clinically significant portal hypertension (PHT) occurs at pressures of 10 mm Hg above systemic venous pressure. Both intrahepatic and portocollateral resistance can increase vascular resistance when compared to the low resistance of a normal liver.<sup>1</sup>

## PATHOPHYSIOLOGY

PHT occurs as the result of an increase in portal flow, an obstruction to portal circulation resulting in increased intrahepatic resistance, or both. An increase in intrahepatic resistance is seen due to narrowing of the vascular lumina from distortion of sinusoidal structures and regenerative nodule formation in the cirrhotic liver. Hepatic stellate cells have also been shown to play a role in the development of increased intrahepatic resistance due to their enhanced contractility and the development of intrahepatic vasoconstriction. In normal conditions, they regulate sinusoidal blood flow by the balance between vasoconstrictors and vasodilators. In the cirrhotic liver there is a decrease in vasodilators and an increase in vasoconstrictors,

as well as an increase in fibrosis, which promotes overall intrahepatic vasoconstriction and an increase in portal pressure.<sup>2,3</sup>

Portal blood flow is increased by vasodilation in the splanchnic vasculature. While the liver experiences vasoconstriction of the intrahepatic vessels, the splanchnic vessels are affected by endogenous vasodilators and a decrease in reactivity to vasoconstrictors. This is the main cause of the increase in portal blood flow seen in cirrhosis. Splanchnic vasodilation is compensated by an increase in heart rate and cardiac output early on, but eventually results in arterial hypotension. The arterial hypotension in turn activates high-pressure baroreceptors and the sympathetic nervous system. This causes the release of vasoconstrictors which affect the peripheral but not the splanchnic vessels, leading to a hyperdynamic circulation. Collaterals form to connect the high-pressure portal veins with the low-pressure systemic veins and develop into gastroesophageal varices. Shunting of blood into the systemic system occurs, resulting in hepatic encephalopathy.<sup>2</sup>

## CLASSIFICATION

PHT is classified according to anatomic location, as extrahepatic, intrahepatic, and posthepatic. Posthepatic causes include veno-occlusive disease and cardiac conditions. These categories are further subdivided according to their relationship to sinusoids within the liver (Table 164.1).

### Extrahepatic Presinusoidal Obstruction

Presinusoidal extrahepatic obstruction is most commonly caused by thrombosis of the portal vein. Portal vein thrombosis occurs in both children and adults. In children, the most common cause is infectious, such as appendicitis or omphalitis. In adults, there are multiple causes, including hypercoagulable states, inflammatory diseases, complications of medical interventions, malignancy, and most commonly cirrhosis. Portal vein thrombosis occurs with an incidence of 0.6% to 22% in adult patients with these conditions.<sup>4</sup>

### Intrahepatic Presinusoidal Obstruction

Intrahepatic presinusoidal obstruction occurs from fibrosis and compression of portal venules, which subsequently restrict portal flow. This can be seen with hepatic fibrosis, sarcoidosis, chronic arsenic exposure, Wilson disease, hepatoportal sclerosis, primary biliary cirrhosis, schistosomiasis, and myeloproliferative disorders. Wilson disease is a hereditary disorder of copper metabolism, in which copper accumulates in hepatocytes due to an inability to excrete copper into the biliary system.

Schistosomiasis is the most common cause of PHT in third world countries. It occurs from ova deposition in portal vein walls, resulting in a granulomatous inflammatory reaction that causes fibrosis and restriction of portal blood flow. The mechanism of action in myeloproliferative disorders involves deposition of cellular material into the portal zones. In sarcoidosis the deposition of sarcoid granulomas within the portal vein leads to its obstruction and increase in portal blood flow.<sup>5,6</sup>

**TABLE 164.1** Causes of Portal Hypertension

#### Presinusoidal

*Portal vein thrombosis*

Omphalitis

Pancreatitis

Trauma

Malignancy

Hypercoagulable states

#### Other

Polycythemia vera

Biliary atresia

Schistosomiasis

Sarcoidosis

Wilson disease

Congenital hepatic fibrosis

#### Sinusoidal

Cirrhosis

Toxic hepatitis

#### Postsinusoidal

Cirrhosis

Hemachromatosis

#### Veno-occlusive disease

Budd-Chiari syndrome

Hepatic vein webs

Malignant obstruction

Hypercoagulable states

#### Cardiac

Congestive heart failure

Constrictive pericarditis

### Intrahepatic Sinusoidal and Postsinusoidal Portal Hypertension

Sinusoidal hypertension results from alcoholic, viral, and toxic hepatitis. Postsinusoidal obstruction is caused by alcoholic liver disease, postnecrotic cirrhosis, and hemochromatosis. Together, sinusoidal and postsinusoidal hypertension resulting in cirrhosis are the most common causes of PHT in the Western world. The mechanism of action is mechanical obstruction of portal blood flow by regenerating hepatic nodules and cirrhotic bands in the liver. In addition to the effects on the hepatic sinusoids, these phenomena can also damage presinusoidal and postsinusoidal structures. The normal architecture becomes distorted.

Cirrhosis also results in increases in hepatic blood flow. The liver generates multiple arteriovenous shunts and collaterals, which lead to nearly 33% of blood flow bypassing functional hepatocytes. This causes an increase in cardiac output and diminished systemic resistance, therefore elevating hepatic wedge

pressure and portal liver pressure. Moreover, since a third of portal blood is shunted away from functioning hepatocytes, the cirrhotic patient develops impaired hepatic function.<sup>1–3</sup>

## Extrahepatic Postsinusoidal Obstruction

Extrahepatic postsinusoidal obstruction results from hepatic vein thrombosis and cardiac disease. Precipitating factors for hepatic vein thrombosis include malignancies, trauma, pregnancy, and oral contraceptives. Hepatic vein occlusion also occurs in Budd–Chiari syndrome, which in turn is associated with myeloproliferative disorders and hypercoagulable states.<sup>1–3</sup>

## Arteriovenous Fistulae

Arteriovenous fistulae cause PHT by increasing flow in the portal circulation. As the disease progresses to fibrosis and obstruction of the presinusoidal spaces, PHT is exacerbated. Arteriovenous fistulae can be caused by percutaneous transhepatic manipulation or penetrating trauma. They can also be associated with splenic fistulae from splenic artery aneurysms, sarcoidosis, Gauche disease, and myeloid metaplasia.<sup>1–3</sup>

## CLINICAL PRESENTATION

Physical examination findings consistent with liver disease include ascites, spider angiomas, palmer erythema, gynecomastia, enlarged abdominal wall collateral veins (caput medusae), and muscle wasting. Encephalopathy, asterixis, and fatigue may also be present. In many cases, variceal bleeding constitutes the initial presentation.<sup>7–9</sup>

## COMPLICATIONS OF PORTAL HYPERTENSION

### Variceal Formation and Hemorrhage

The formation of portal–systemic collaterals is seen when portal pressures reach 10 to 12 mm Hg above systemic venous pressures. Due to elevated portal pressures and increased splanchnic blood flow diverted from the portal to the systemic system, the vascular resistance of the collateral beds increases. Although it is lower than the obstructed portal system, it is still higher than normal portal pressure. This phenomenon explains why the formation of portal–systemic collaterals does not normalize the elevated portal pressures.<sup>10</sup>

Varices are mainly the result of dilation and dysfunction of the preexisting embryonic connections between the portal and systemic venous systems, but formation of new blood vessels via neoangiogenesis also occurs. These new vessels are abnormal, with marked hyperplasia and hypertrophy of their walls. The left gastric vein arising from the portal vein and the short gastric veins arising from the splenic vein are the vessels most often affected.<sup>10</sup>

Esophageal varices form when the left gastric vein becomes dilated, and both esophageal and gastric varices form as a result of dysfunction and dilation of the short gastric

veins. These vessels divert portal blood flow into the azygos venous system via the venous plexus of the lamina propria and submucosa of the esophagus and stomach. Esophageal varices form from the distal to proximal esophagus and can be divided into four zones: the gastric, palisade, transitional, and truncal zones. The transitional zone is defined as the 2 cm above the gastroesophageal junction and extends superiorly for another 2 cm; it is the zone most susceptible to bleeding. Gastric varices can be divided into type I and type II, where type I are gastric varices that extend above the cardia as esophageal varices and type II are isolated to the stomach, most commonly on the fundus.<sup>10</sup>

Varices can also be seen on the abdominal wall from collateralization between the left portal vein and the systemic system via periumbilical veins in the falciform ligament. The physical exam finding associated with this is known as caput medusae.

Esophageal and gastric varices are present in roughly 50% of cirrhotic patients at the time of diagnosis, and the incidence increases to 90% of patients with long-term follow-up. Rupture with bleeding occurs from small varices (<5 mm) in 7% of patients over a 2-year period, and in 30% of patients with large varices over the same period.<sup>9</sup> The mortality rate after the first bleed reaches 35%, and 60% of patients rebleed within the first year. Each additional bleed carries a mortality rate of 20%.<sup>1,11</sup>

The most widely accepted explanation as to why varices bleed is the explosion hypothesis. It suggests that when the hydrostatic pressure inside varices increases to above 10 mm Hg, variceal dilation, and a decrease in wall thickness occurs. Ruptures occur when the tension in the expanding wall can no longer be countered by wall tension (Law of LaPlace). The critical hepatic venous pressure gradient is 12 mm Hg. In the presence of varices, pressures above 12 mm Hg are associated with a significant risk of variceal bleeding; however, the magnitude above this value does not necessarily correlate with risk of hemorrhage. Medical therapy and interventions are aimed at keeping the hepatic venous pressure gradient below 12 mm Hg; pressures below this level are associated with minimal risk of bleeding.<sup>10</sup>

### Ascites

Ascites occur in up to 80% of patients with PHT. With the increase in portal pressure, Starling forces drive fluid out of vessels and into the interstitial space, causing ascites. Low oncotic pressure resulting from the hypoalbuminemia manifested by cirrhotic patients also occurs, exacerbating the problem. In addition, the lymphatic system typically becomes overwhelmed.<sup>5</sup>

The accumulation of ascites places patients at risk for spontaneous bacterial peritonitis (SBP). In the past, approximately 75% of these infections were attributed to Gram-negative aerobic bacteria, suggesting the gastrointestinal tract as the source. However, more recent data show that up to one-third of cases are associated with Gram-positive bacteria.<sup>12,13</sup> Approximately 30% of patients with ascites require hospital admission at some point for antimicrobial treatment of SBP. Its presence is associated with increased mortality in cirrhosis.<sup>14</sup>

## Encephalopathy

Hepatic encephalopathy refers to any neuropsychiatric dysfunction caused by liver disease. The symptoms are broad, ranging from subclinical to coma or death. Due to malfunctioning hepatocytes and portosystemic shunting, increased levels of ammonia and glutamine derived from ammonia occur in the arterial system. These cause dysfunction of astrocytes in the brain as well as mitochondrial dysfunction, ultimately resulting in alterations of cerebral function, cerebral edema, and potentially cerebral herniation. These changes are graded by the West Haven Criteria. Grades I and II include mild symptoms such as changes in cognition, altered sleep patterns, mood changes (anxiety or euphoria), mild disorientation, asterixis, and increasing apathy and drowsiness. Grades III and IV consist of somnolence or coma.<sup>7,15</sup>

Encephalopathy occurs in 30% to 40% of patients with decompensated liver failure and is associated with an increase in mortality.<sup>7</sup> It is thought that obstruction of blood flow in the liver together with the development of collaterals result in the shunting of neuroactive peptides into the systemic circulation. It is considered a reversible disorder; early recognition can prevent progression.<sup>16</sup>

## Hepatorenal Syndrome

Hepatorenal syndrome (HRS) occurs when renal function is decreased in the presence of cirrhosis and ascites. It is considered a “diagnosis of exclusion”; therefore, other causes of renal dysfunction must be ruled out to confirm its presence. Clinically it presents as oliguria, hyponatremia, and low urinary sodium output. It can occur rapidly (deterioration of renal function within 2 weeks) or as a more chronic disorder. Rapid deterioration is associated with a poor prognosis; only 10% of patients survive hospitalization.<sup>17</sup>

## Hepatopulmonary/Portopulmonary Syndromes

These syndromes are defined as combinations of PHT, pulmonary hypertension, pulmonary vasodilation/shunting, and impaired oxygenation. They present with clubbing, dyspnea, and deoxygenation induced by the upright position. In general, mortality is the result of liver failure rather than pulmonary complications.<sup>18</sup>

## DIAGNOSIS

### Laboratory Evaluation

The initial evaluation of liver disease should include an arterial blood gas, lactate, complete blood count, International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, factor V level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), amylase, lipase, magnesium, phosphorous, creatine kinase, and comprehensive metabolic panel. Ammonia levels are

commonly obtained, although they have not been shown to correlate well with neurologic abnormalities.<sup>9</sup> The results of these studies in conjunction with the history of onset and physical examination findings can help determine whether liver dysfunction is acute or chronic, and determine its severity.<sup>19</sup>

Specific testing for etiology should also be included in the diagnostic evaluation, including viral hepatitis immunology, human immunodeficiency virus (HIV), ceruloplasmin, serum copper, antinuclear antibody, and a toxicology screen.<sup>19</sup>

A decrease in serum testosterone has been seen in up to 90% of men with cirrhosis, and low testosterone levels are associated with an increase in mortality. The conversion rates of testosterone to estradiol are significantly increased in men with cirrhosis, while the overall plasma production rates of estradiol and clearance rates of estradiol remain similar to men without cirrhosis. These findings may be responsible for the physical examination findings described previously and are associated with liver failure. However, data supporting the specific mechanisms of action are lacking.<sup>20,21</sup>

## Upper Gastrointestinal Endoscopy

Endoscopy is critical in the evaluation of patients with PHT to diagnose and evaluate varices, and should be performed in all patients with varices, regardless of whether they have bled. After an episode of bleeding, it is recommended that repeat endoscopy be performed every 3 to 6 months. Endoscopy can also diagnose gastropathy, gastritis, ulceration, and mucosal lacerations.<sup>8,11,22</sup>

## Liver Biopsy

Liver biopsy can determine the etiology of liver disease as well as its acuity. Although the necessity of biopsy is controversial, determining the cause of PHT through biopsy is useful in guiding treatment. Pathologic features of cirrhosis include rounding of edges seen on low power with remodeling of hepatic architecture causing nodularity, loss of terminal hepatic venules in parenchyma between portal tracts, spacing between portal tracts, portal veins and hepatic veins, increase in vascular channels within areas of scar and fibrous tissue, and evidence of hepatocyte regeneration. Plasma cells at the portal/septal interface can be seen in chronic hepatitis B infections. Mallory–Denk bodies are seen with alcoholic liver disease, but are also present in Wilson disease, drug-induced liver disease, and primary biliary cirrhosis.<sup>23</sup> Mallory–Denk bodies (MDB) are eosinophilic cytoplasmic inclusion bodies that hover near the hepatocyte nucleus. The clinical and prognostic significance of MDBs is not entirely clear, but their accumulation is reversible with removal of the causal agent, such as abstaining from alcohol. Therefore, if seen on biopsy, consideration may be given to postponing elective procedures to allow the liver time to heal.<sup>24,25</sup> Chronic schistosomiasis results in a characteristic “pipistem” fibrosis and may demonstrate calcified eggs and periportal granulomas; the acute infection will demonstrate live eggs surrounded by eosinophils.<sup>23</sup>

## Duplex Scanning

Duplex scanning is a simple and effective way to determine portal vein patency. It can also determine direction of flow through the portal vein. This information is imperative in pre-operative planning for TIPS, shunt procedures, and liver transplant. It is also a key surveillance tool after these procedures to confirm portal vein patency.<sup>26,27</sup>

## Computed Tomography Angiography

Computed tomography angiography (CTA) can be performed in the setting of normal renal function to determine portal vein patency and provide clues to the chronicity of thrombus, if present. CTA can also identify other pathologic features of liver disease such as nodularity of liver parenchyma and the presence of malignancy.<sup>27</sup>

## Percutaneous Angiography

Transhepatic percutaneous portal venography is necessary for evaluation of anatomy of the portal vein prior to surgical shunting procedures. It can be achieved by evaluating the venous phase following selective catheterization of the celiac and superior mesenteric arteries. The procedure is used to define the portal tributaries as well the portal hepatic wedge pressure, which quantifies the presence and severity of PHT. It can also be useful in determining the extent of cirrhosis. In advanced cirrhosis, the network of dense collaterals and dilation of the hepatic artery will become apparent on angiogram, as will reversal of flow in the portal vein.<sup>28-30</sup>

# NONSURGICAL TREATMENT OF PORTAL HYPERTENSION AND ITS COMPLICATIONS

The goal of treatment of PHT is to prevent and/or control complications, in particular variceal bleeding, ascites, and encephalopathy.

## Prevention and Treatment of Variceal Bleeding

Prevention and treatment of variceal bleeding is divided into primary prophylaxis (treatment to prevent bleeding before it occurs), treatment of acute variceal hemorrhage, and secondary prophylaxis (treatment after a bleeding episode to prevent a second one).

### Primary Prophylaxis

Preferred options for primary prophylaxis include nonselective beta blockade, endoscopic variceal band ligation (EVBL), and endoscopic sclerotherapy.

### Nonselective beta blockade

Propranolol has been used in the prevention of both primary and recurrent variceal bleeding. It is a nonselective beta-blocker;

it is thought that by reducing cardiac output and thereby systemic pressure, it reduces portal venous pressure. Nonselective beta blockers are recommended in patients with small varices and high risk of bleeding and in all patients with large varices. The decision as to which nonselective beta-blocker is better is unclear, but there is some evidence that carvedilol may offer added benefits over propranolol. Beta blockade in the treatment of acute bleeding episodes has not been studied.<sup>11,31</sup>

### Endoscopic variceal band ligation

EVBL is indicated as primary prophylaxis in patients with medium and large esophageal varices and a high risk of bleeding. In those without high bleeding risk, the efficacy is similar to that of prophylaxis with nonselective beta blockade alone. EVBL has risks of esophageal perforation, pain, and bleeding; therefore, most physicians recommend beta blockade in patients at low risk for bleeding unless contraindicated.<sup>11</sup> Repeat endoscopy is recommended every 3 to 6 months.<sup>32</sup>

### Endoscopic sclerotherapy

Endoscopic sclerotherapy is recommended in patients with gastric varices as primary prophylaxis. In these patients, the efficacy is greater than prophylaxis with beta-blockers. Adverse events are rare but include pulmonary and cerebral embolization.<sup>11</sup>

Cyanoacrylate sclerotherapy has been used for treatment of bleeding gastric ulcers in patients with decompensated cirrhosis who are not candidates for transjugular intrahepatic portosystemic shunt (TIPS) procedures. Cyanoacrylate causes polymerization and hardening upon contact with blood. In published studies, it has been shown to stop bleeding in 93% of these patients; early rebleeding occurred in only 7%. No postprocedural complications were seen.<sup>33</sup> Recently, the safety and efficacy of using coils in addition to cyanoacrylate to prevent systemic embolization of the polymer was studied in a randomized controlled trial. Lobo and colleagues found no statistically significant benefit to adding coils to the polymer due to a small sample size, but there was a greater tendency for embolization using the traditional technique.<sup>34</sup>

Endoscopic sclerotherapy is as effective as endoscopic variceal ligation in the treatment of high-risk patients with esophageal varices as prophylaxis and in the acute setting of variceal hemorrhage.<sup>32,35</sup> In one study, both techniques were effective as prophylaxis in 80% of high-risk patients.<sup>35</sup> Another study demonstrated that the use of either technique achieved complete control of active bleeding in 100%.<sup>32</sup>

### Acute Variceal Hemorrhage

Acute variceal hemorrhage will stop spontaneously in 40% to 50% of patients. This is thought to be secondary to hypovolemia and subsequent splanchnic vasoconstriction.<sup>36</sup> Because of this, transfusions should be given sparingly to avoid rebleeding.

Treatments used to control active hemorrhage include vasoactive agents such as vasopressin, somatostatin, and octreotide, balloon tamponade, EVBL, and/or endoscopic sclerotherapy (described previously), balloon-occluded retrograde transvenous obliteration (BRTO), and TIPS.

## Vasopressin

Vasopressin was formerly considered first-line therapy for active bleeding from varices, and has been shown to control bleeding in 60% to 80% of cases. Moreover, it is the only medication shown to decrease mortality.<sup>36</sup> Its use leads to decreased portal flow and, in turn, decreased hepatic flow. However, its vasoconstrictive effects can lower cardiac output; it is therefore used in conjunction with other pharmacologic agents that increase cardiac output without reducing the positive effects of decreased portal flow.<sup>37</sup> Terlipressin is a synthetic analog of vasopressin that has also been shown to be effective in controlling variceal bleeding and improving survival. Terlipressin has a longer half-life than vasopressin and is recommended to be dosed intermittently. Intermittent versus continuous infusion was recently compared in a randomized controlled trial which found that continuous infusion may be more effective than intermittent infusion in preventing treatment failure and rebleeding in patients with variceal bleeding. A larger study is needed for confirmation, but this study suggests a change to the current infusion protocol may be indicated.<sup>38</sup>

## Somatostatin/Octreotide

Somatostatin and octreotide have the same effects as vasopressin in lowering splanchnic blood flow, but have fewer side effects. Somatostatin is a tetradecapeptide derived from the hypothalamus, and octreotide is a synthetic analog of somatostatin. Octreotide has a longer half-life than somatostatin (100 vs. 2 minutes). Both have been shown to control bleeding and decrease portal venous pressure. Somatostatin appears to produce less cardiac compromise when compared to vasopressin.<sup>5</sup>

## Balloon tamponade

Balloon tamponade is effective in controlling acute variceal hemorrhage. A tube with one or two inflatable balloons is inserted into the stomach; the balloon or balloons are then inflated to compress gastric and esophageal varices. The technique originated in the 1950s, and the balloons are named after their developers, Linton–Nachlas and Sengstaken–Blakemore. The Sengstaken–Blakemore tube is composed of two balloons, one to control esophageal varices and the second to control gastric varices, as well as a port to suction gastric contents. It has been shown to control initial hemorrhage in up to 95% of patients and results in permanent cessation of bleeding in 40% to 50%.<sup>39,40</sup> The Minnesota tube is a variation of the Sengstaken–Blakemore tube that includes an additional lumen to suction esophageal secretions.

The use of balloon tamponade is generally reserved for patients unresponsive to medical therapy and is thought to be a bridge to more permanent control such as endoscopic banding, sclerotherapy, or surgery.<sup>40</sup> Complications associated with its use include aspiration pneumonia, airway obstruction, tube migration, and esophageal ulceration and rupture.<sup>41</sup> To some extent these can be avoided by using indirect laryngoscopy with a glidescope to position the tube properly.<sup>42</sup>

## Balloon-occluded antegrade and retrograde transvenous obliteration

Endoscopic treatments can be used in conjunction with BRTO in the management of large, high-flow gastric varices when bleeding cannot be controlled by these treatments alone or by TIPS. The goal of the therapy is to occlude portosystemic collaterals that exist between the stomach and the renal vein (“gastrorenal shunts”) using a systemic transvenous access such as the common femoral vein. Esophageal varices should be treated prior to utilizing BRTO. Portal vein patency should be evaluated prior to BRTO, as the presence of an occluded portal vein may mean that the gastrorenal shunts constitute the primary outflow for mesenteric and splenic veins. In this situation, occlusion of the shunts may cause mesenteric venous hypertension.

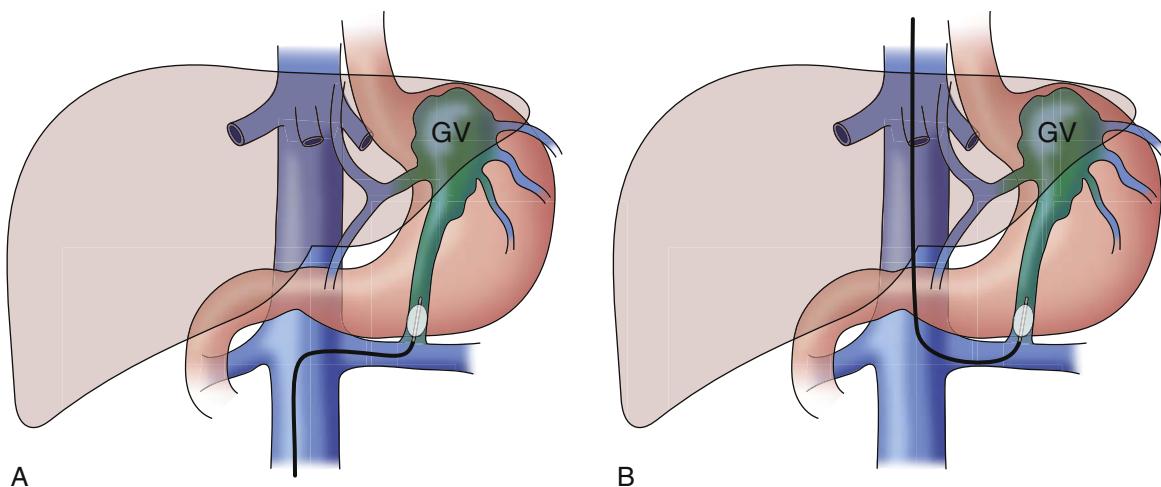
The procedure is performed using an occlusion balloon inserted percutaneously from the common femoral vein into the outflow of the gastrorenal shunt, resulting in occlusion of the tract (Fig. 164.1). Venography can be performed to define the extent of the outflow tract and varices. A sclerosing agent such as sodium tetradecyl sulfate or polidocanol is then injected into the varices and outflow track via a microcatheter advanced next to the occlusion balloon. The presence of the balloon allows the sclerosant to dwell longer and prevents reflux into the systemic or portal system. Balloon occlusion is maintained 4 to 24 hours, and re-imaging is then performed prior to balloon deflation to confirm obliteration. The efficacy is 91% to 100% in patients with gastrorenal shunts. However, it can result in increased PHT and esophageal varices if they are not treated first.<sup>11,43</sup>

Balloon-occluded antegrade transvenous obliteration (BATO) can also be used alone to treat bleeding gastric varices or with BRTO if it fails. The goal of BATO is to occlude portosystemic collaterals from the portal system via the gastric veins or to occlude them in an antegrade fashion. BATO utilizes a portal venous approach in one of three ways, percutaneous transhepatic obliteration, an existing TIPS, or trans-ileocolic vein obliteration. The percutaneous transhepatic obliteration approach is technically similar to that of performing a percutaneous transhepatic cholangiogram, except that the target is the portal vein rather than the bile ducts. TIPS is only utilized if already present, or if the planned treatment for the patient includes TIPS. Trans-ileocolic vein obliteration is used mainly to treat mesenteric varices and is rarely done.

The technique for BATO (Fig. 164.2) is similar to BRTO. When a TIPS is present, BATO can be used routinely with BRTO as the portal vein access is already established.<sup>44</sup> BATO has been shown to increase the technical success of BRTO alone from 84%–98% to 98%–100%.<sup>45</sup>

## Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunts, commonly referred to as TIPS, are performed for refractory variceal bleeding and refractory ascites.<sup>46,47</sup> The TIPS procedure (Figs. 164.3 and 164.4) has been well described, and in high volume institutions, the technical success reaches 97%. The rate of major



**Figure 164.1** Balloon-Occluded Retrograde Transvenous Obliteration (BRTO). Illustration demonstrating the basic transfemoral (A) and transjugular (B) approaches for conventional BRTO of gastric varices (GV). BRTO is approaching the GV from the systemic venous side. Balloon-occluded antegrade transvenous obliteration is approaching the gastric varices from the portal venous side. (From Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol.* 2012;15(3):203–225.)

complications is low (<3%). The procedure is initiated via either internal jugular vein using ultrasound guidance. The right hepatic vein is then selected with a 5-F curved catheter, as it has the best trajectory for portal vein access. The left or middle hepatic veins can also be used, but are technically more difficult. A balloon catheter is used to perform a wedged hepatic venogram to opacify the portal vein target. The catheter is then aimed toward the portal vein. A 10-F guide catheter is directed against the hepatic vein wall, and a locked trocar stylet and 5-F catheter are passed through the liver parenchyma and into the portal vein target. The stylet is removed, and the 5-F catheter is aspirated to confirm placement into the portal vein with adjustment as necessary. Once there is blood return, contrast is used to confirm placement. A guide wire is then advanced into the portal vein, and the access set and 10-F guide catheter are advanced into the portal system. Once in place, the inner components of the set are removed and a marker catheter is used to define the anatomy of the splenic and mesenteric vessels. The larger sheath is then also withdrawn leaving the marker catheter for pressure measurements. The large sheath is passed over a wire into the portal vein once again and is used to aid in deployment of a covered stent graft across the newly created channel. After deployment, the stent is angioplastied. Repeat pressure measurements are taken to confirm a decrease in the portosystemic gradient to less than 12 mm Hg.<sup>48</sup>

The hepatic venous pressure gradient can be used as a predictor of rebleeding after an episode of acute bleeding. A hepatic venous pressure gradient  $\geq 20$  mm Hg is associated with failure of treatment, greater transfusion requirements, more admissions to the intensive care unit (ICU), and decreased survival. Early TIPS placement in high-risk patients reduces

treatment failure, in hospital mortality, and 1-year mortality.<sup>49</sup> These patients have better outcomes with prophylactic TIPS performed after an initial acute variceal bleed to prevent further complications from rebleeding.<sup>46</sup>

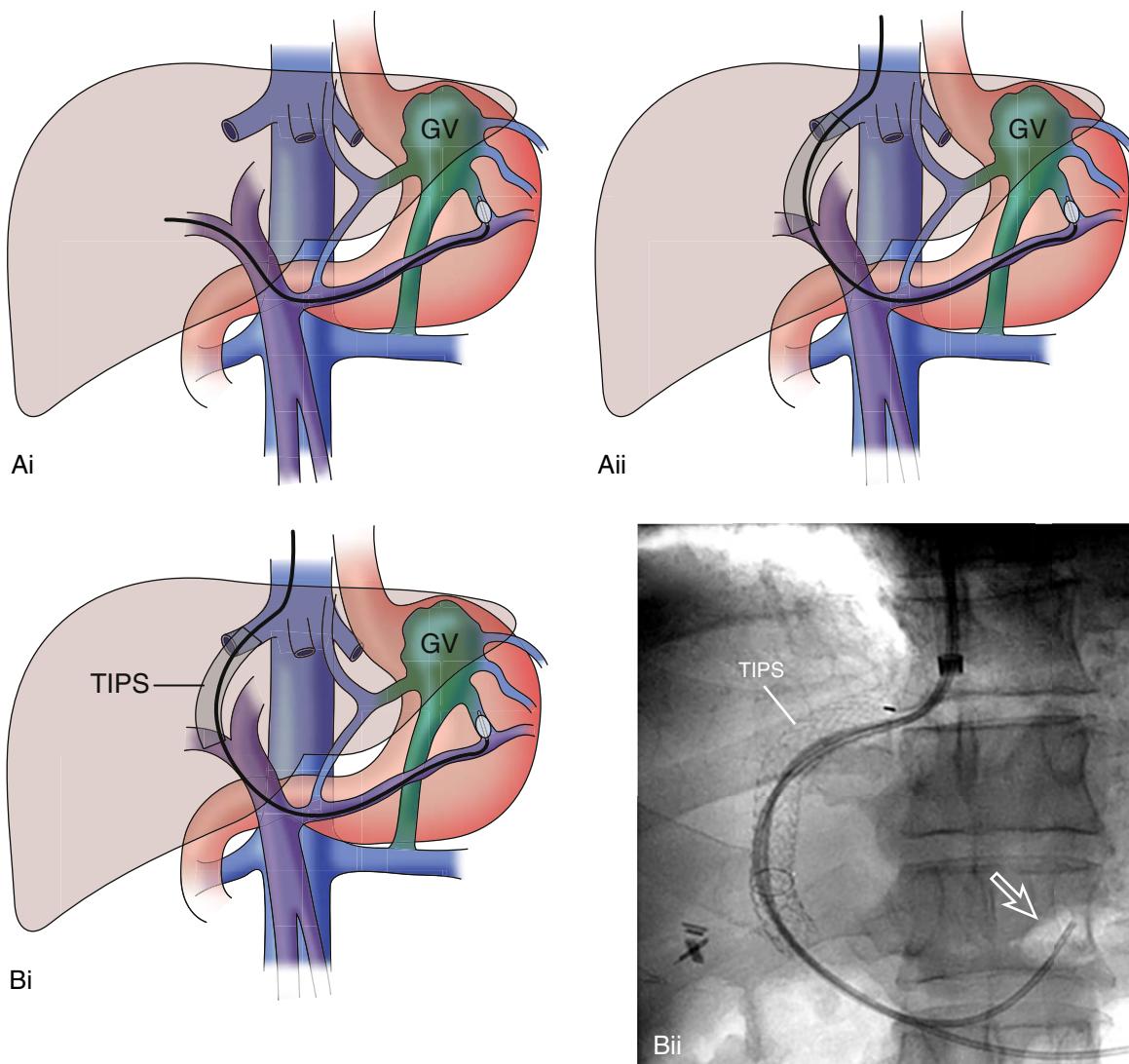
In the event of gastric and ectopic variceal bleeding, TIPS has been shown to stabilize and prevent rebleeding after acute gastric bleeding and has a lower recurrence rate than BRTO. However, in cases of refractory gastric bleeding, BRTO can be used subsequently to embolize larger gastric veins, which facilitates flow toward the TIPS. BRTO can be used primarily in the treatment of gastric varices if patients are not candidates for TIPS due to hepatic encephalopathy or marginal liver function. In general, the literature lacks direct comparisons of TIPS to BRTO in the treatment of gastric varices. Severity of PHT, hepatic reserve, and complications of liver cirrhosis should be considered when deciding which procedure to proceed with in the management of gastric varices.<sup>50</sup>

Recently, there has been a report of using paclitaxel-coated balloons to treat in-stent stenosis after TIPS. This technology is promising in terms of improving secondary patency.<sup>51</sup>

### Secondary Prophylaxis

Mortality associated with rebleeding of varices approaches 40%, and most commonly occurs within the first 5 days after the initial episode. Without adequate prophylaxis, the risk of rebleeding approaches 80% at 1 year.<sup>52</sup>

The mainstays of therapy for secondary prophylaxis to prevent rebleeding are nonspecific beta blockade and EVBL. The combination of both treatments is more efficacious than either treatment alone, resulting in a rebleeding rate of less than 50%.<sup>9</sup> TIPS has been shown to reduce rebleeding by approximately



**Figure 164.2** (A) Balloon-occluded antegrade transvenous obliteration (BATO). Illustration demonstrating BATO and its subclassification into percutaneous transhepatic obliteration (PTO; panel *Ai*) and trans-TIPS (transjugular intrahepatic portosystemic shunt; panel *Aii*) obliteration. (B) Illustration demonstrating trans-TIPS BATO (panel *Bi*) and a fluoroscopic image of a trans-TIPS BATO (panel *Bii*). The illustration depicts the BATO balloon in the posterior gastric vein and the fluoroscopic image demonstrates an air-filled BATO balloon (*open arrow*) occluding the left gastric vein (coronary vein). *GV*, gastric varices. (From Saad WE, Kitasono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol.* 2012;15(3):203–225.)

30% compared with endoscopic treatment alone, but is associated with increased encephalopathy.<sup>53</sup>

### Treatment of Ascites

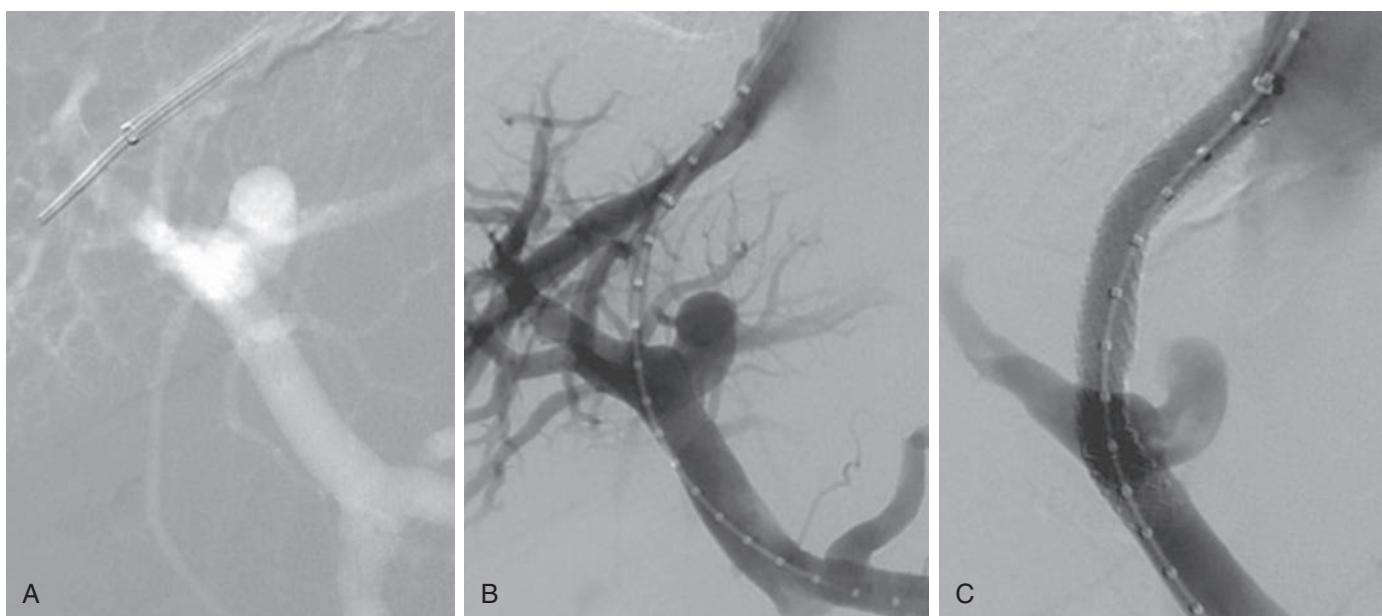
Spironolactone and furosemide remain the most commonly used treatments for ascites, given their efficacy and lack of adverse consequences. Initial doses are 100 mg of spironolactone and 40 mg of furosemide daily; these can be increased to a maximum of 400 mg and 160 mg, respectively. Spironolactone alone is effective in promoting weight loss, but the addition of furosemide is protective against hyperkalemia. Patients in

whom these medications are ineffective or not tolerated are candidates for paracentesis or TIPS.<sup>9</sup>

### Treatment of Encephalopathy

Encephalopathy is treated by correcting inciting conditions, including variceal bleeding, infection, and electrolyte imbalances, and by restricting the production and absorption of ammonia. Lactulose is effective in preventing ammonia absorption and increasing fecal nitrogen excretion.<sup>54</sup>

Neomycin is also effective in the treatment of encephalopathy, but side effects (nephrotoxicity and ototoxicity) limit its use.<sup>55</sup>



**Figure 164.3** Determining the Shunt Length. (A) Wedged CO<sub>2</sub> contrast portogram. (B) Portography with additional contrast injection through 10-F sheath located at the right hepatic vein-inferior vena cava junction to measure required length of endograft. (C) Portography after 7 cm covered length Viatorr endograft deployed. (Schematic of transjugular intrahepatic portosystemic shunt [TIPS] – Figure 2 from Keller FS, Farsad K, Rosch J. The transjugular intrahepatic portosystemic shunt: technique and instruments. *Tech Vasc Interv Radiol.* 2016;19:2–9.)

## Hepatic and Portal Vein Recanalization

In patients with PHT complicated by portal or hepatic vein thrombosis, recanalization of these veins has the potential to reduce symptoms and complications. A retrospective study performed in the United Kingdom reported the results of endovascular recanalization of the hepatic vein in patients with Budd–Chiari syndrome.<sup>56</sup> The study evaluated outcomes in 63 patients treated with venoplasty of the hepatic vein ± stent placement over a 27-year period. The efficacy of the treatment was compared with a previous report using TIPS published by the same investigators.<sup>57</sup> Access was established via the femoral or internal jugular vein. In the event the hepatic vein could not be accessed via the inferior vena cava, a percutaneous transhepatic approach was used. Once the wire was in place, it was snared using the jugular approach, and the rest of the procedure performed from the jugular route. A large balloon catheter was used to dilate the obstructed hepatic vein. If balloon dilation was ineffective, a bare metal stent was deployed. Technical success was reported as 100%, with symptom resolution in 73%. Patency rates were similar between the patients undergoing recanalization and the historical TIPS group, ranging from 70% to 90% at 1 year and 60% to 80% at 10 years. Survival rates were also similar, but procedural complications (9.5% vs. 27.1%) and hepatic encephalopathy (0% vs. 18%) were significantly lower in patients treated with vein recanalization. The authors concluded that TIPS should be reserved for failure of recanalization.<sup>56</sup>

Portal vein recanalization has also been used in conjunction with TIPS to improve candidacy for liver transplant in patients with portal vein thrombosis. The procedure is performed via access from the internal jugular and splenic veins. After the

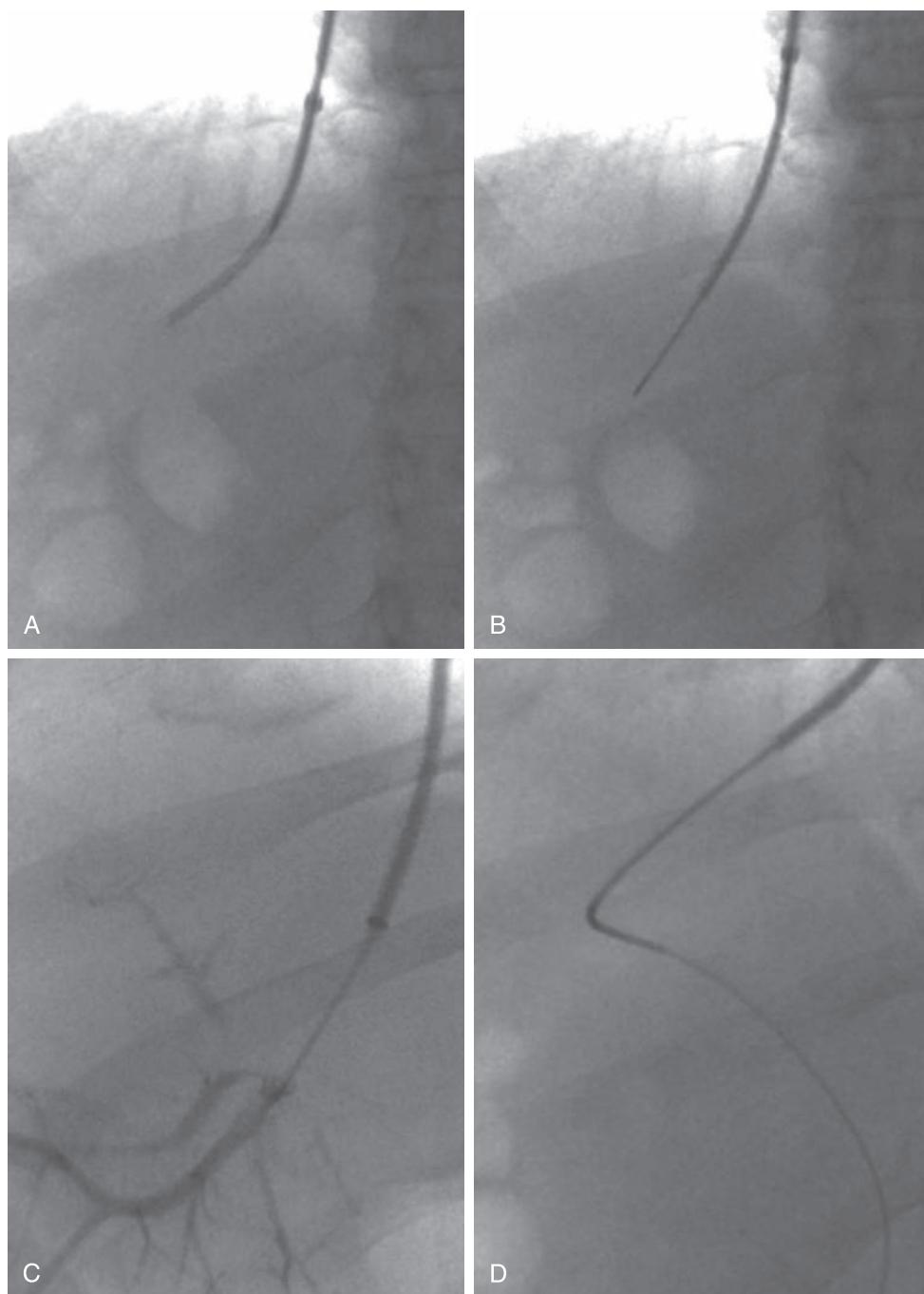
TIPS stent is deployed, the confluence of the stent and the portal vein is venoplastied. This technique generally opens the portal vein without further intervention. Embolization of existing varices and/or splenorenal shunts is sometimes performed to improve patency of the portal vein.

In one study, the initial success rate approached 100%, and the patency rate was 92% at 17 months. Twenty-three of 61 patients enrolled in the study underwent successful liver transplantation.<sup>58</sup>

## SURGICAL TREATMENT OF PORTAL HYPERTENSION

Portosystemic bypasses were first used to treat variceal bleeding with promising results; the recurrence rate was less than 3%.<sup>59</sup> These bypasses were then studied as prophylaxis to prevent variceal bleeding. However, prophylactic shunting did not demonstrate a benefit over medical therapy in survival rates, and demonstrated an increase in the incidence of severe hepatic encephalopathy when compared with medical therapy alone. Because of this, surgical shunting is not recommended as prophylaxis.

Portosystemic shunting has also been studied with respect to quality of life and survival. Studies demonstrated that while the rebleeding rate was greatly reduced, there was no long-term survival benefit.<sup>60</sup> In emergency situations with acutely bleeding varices, portosystemic shunting has been shown to stop bleeding and prevent rebleeding. However, mortality is high, and it is generally not recommended given the efficacy of non-surgical options.<sup>61,62</sup>



**Figure 164.4** Portal Vein Access Under Fluoroscopy. (A) Transjugular intrahepatic portosystemic shunt (TIPS) set in resting position in right hepatic vein. (B) TIPS set rotated anteriorly with stylet and 5-F catheter extended. (C) Test injection of contrast material to confirm position of 5-F catheter in portal circulation. (D) Guide wire in superior mesenteric vein with tip of 5-F catheter in main portal vein. (C, Adapted from Saad, ed. “The TIPS Procedure: Technique” in Portal Hypertension, 3rd ed., 2016, with permission from Thieme. D, Figure 5 from Keller FS, Farsad K, Rosch J. The transjugular intrahepatic portosystemic shunt: technique and instruments. *Tech Vasc Interv Radiol.* 2016;19:2–9.)

There are two types of shunts: selective and nonselective shunts. A selective shunt preserves blood flow to the portal vein while decompressing esophageal varices. Nonselective shunts drain all portal blood flow to the caval system. The most commonly performed selective shunt is a distal spleno-renal shunt. Nonselective shunts include the portacaval shunt and mesocaval shunt. Selective shunting procedures were initially proposed

in an attempt to lower the incidence of hepatic encephalopathy and liver failure associated with nonselective shunts, and early results demonstrated promise.<sup>63</sup>

Portacaval shunts can be performed in end-to-side and side-to-side fashion. The benefit of one technique over the other has not been demonstrated.<sup>64</sup> Anatomic limitations include the diameter of the portal vein as well as a history of portal vein

thrombosis and recanalization. The portal vein should be at least 1.0 cm in diameter, and previous thrombosis/recanalization is a relative contraindication, as rethrombosis rates are high in these patients. The approach can be via a midline incision or a right upper quadrant subcostal incision. The duodenum is mobilized, and the IVC is exposed to the level of the hepatic veins. The portal vein is mobilized from the surrounding bile duct and hepatic artery and controlled. If performing an end-to-side anastomosis, the portal vein is divided, and the hepatic end ligated. The IVC is then clamped with a side-biting clamp, and the portal vein is anastomosed to the IVC. Portal pressures should be measured and decrease by at least 50%. In the side-to-side anastomosis, a greater length of both the IVC and portal vein is exposed to bring the two vessels in proximity for the anastomosis. Portal pressures should decrease by 50% after it is completed. An effective side-to-side portacaval shunt can also be created with a large diameter expanded polytetrafluoroethylene (ePTFE) graft.<sup>65</sup>

Mesocaval shunts have been used in cases of refractory variceal bleeding to control hemorrhage, as well as in patients with massive ascites, an obliterated portal vein, extreme obesity, and Budd–Chiari syndrome.<sup>66–68</sup> Mesocaval shunts are technically easier to perform than portacaval shunts. The procedure is performed via a midline laparotomy. The transverse colon is elevated and retracted superiorly, and the small bowel is retracted inferiorly to expose the root of the small bowel mesentery. The root of the transverse mesocolon is opened to expose the superior mesenteric vessels. The superior mesenteric vein (SMV) lies anterior to the artery. The surface of the IVC is then found in the retroperitoneum after mobilizing the duodenum. The IVC is isolated to allow for placement of a side-biting clamp. A bypass is then created between the SMV and the IVC using a large-caliber (18 to 20 mm) prosthetic graft. The IVC anastomosis is created first. When the shunt is opened, portal pressure should decrease by 50%, and there should be a palpable thrill within the graft.<sup>67</sup>

Selective shunting refers to creation of the distal splenorenal shunt. The goal of this shunt is to decompress esophageal varices without diverting portal–splanchnic flow. The procedure is performed via a bilateral subcostal incision. The splenic vein is identified by opening the lesser sac. The right gastroepiploic vein is divided, and the short gastric veins are preserved. The pancreas is rotated anteriorly to expose the splenic vein in its entirety; connections to the pancreas are ligated. The renal vein is isolated by dividing the ligament of Treitz and rotating the fourth portion of the duodenum inferiorly. The splenic vein is then divided, and the portion attached to the SMV ligated. A side-biting clamp is placed on the renal vein, and an end-to-side anastomosis is created between the splenic vein and the renal vein. Pressure measurements are then taken from the SMV, renal and splenic veins. The splenic vein pressure should decrease by 60% to 70%, allowing for preferential drainage of the esophageal varices. All collaterals between the portal–azygous and portal–mesenteric system must be also be divided, and care must be taken to divide the left gastric vein, umbilical vein and falciform ligament as well.<sup>61</sup>

Several randomized controlled studies evaluated the efficacy of the selective distal splenorenal shunt compared with the

nonselective portacaval shunt for the management of patients with PHT and bleeding from esophageal varices. In one study, 88% of patients maintained portal hepatic flow in the selective shunt group compared with 5% in the nonselective group. Hepatic function was preserved and encephalopathy improved in the selective shunt group. There was no difference in rebleeding or survival between the two groups.<sup>69</sup> The findings of a second study showed that patients undergoing distal splenorenal shunts had a statistically significant lower incidence of hepatic encephalopathy and liver failure when compared with the nonselective group (18.7% and 62.5%, respectively). Both perioperative and late mortality were reduced in the selective shunt group.<sup>63</sup> In a third study, encephalopathy was decreased in the selective shunt group, but there was no difference in late mortality between the selectively shunted and nonselectively shunted groups.<sup>70</sup> Findings of other studies have mostly confirmed a lower rate of encephalopathy in selectively shunted patients, but whether a significant difference in mortality exists between the two groups remains unclear.<sup>71–73</sup>

There have been many studies comparing portosystemic shunting to endoscopic therapy for treatment of variceal bleeding in patients with cirrhosis and PTH. Twenty-two trials were included in a review from the Cochrane database. Shunt procedures significantly reduced the risk of rebleeding when compared with endoscopic therapy, but significantly increased acute hepatic encephalopathy and chronic encephalopathy. There were no differences in mortality and duration of hospital stay.<sup>74</sup>

TIPS was compared with selective distal splenorenal shunting in a randomized trial for control of variceal bleeding. There were no significant differences in rebleeding, first encephalopathic event, or survival at 2 and 5 years between the groups, but thrombosis, stenosis, and reintervention rates were significantly higher in the TIPS group (82% vs. 11%). The authors concluded that treatment choice should depend on available resources and expertise.<sup>75</sup>

Endoscopic sclerotherapy was compared with portacaval shunting in a randomized trial in cirrhotic patients presenting with acutely bleeding esophageal varices. Both techniques controlled active bleeding in most patients, but surgery was significantly more effective in terms of permanent control of bleeding (100% vs. 20% respectively), episodes of encephalopathy, and overall survival.<sup>76</sup>

A retrospective study compared outcomes of surgical shunts versus TIPS for the treatment of complicated PTH over a 20-year period. Shunt failure occurred more frequently after TIPS (16 of 31 vs. 6 of 31), and “shunt failure free” and overall survival rates were higher in the surgically treated patients.<sup>77</sup>

Taken together, the results of these studies suggest the continued benefit and role of operative shunting in the acute and long-term management of bleeding varices and PHT.

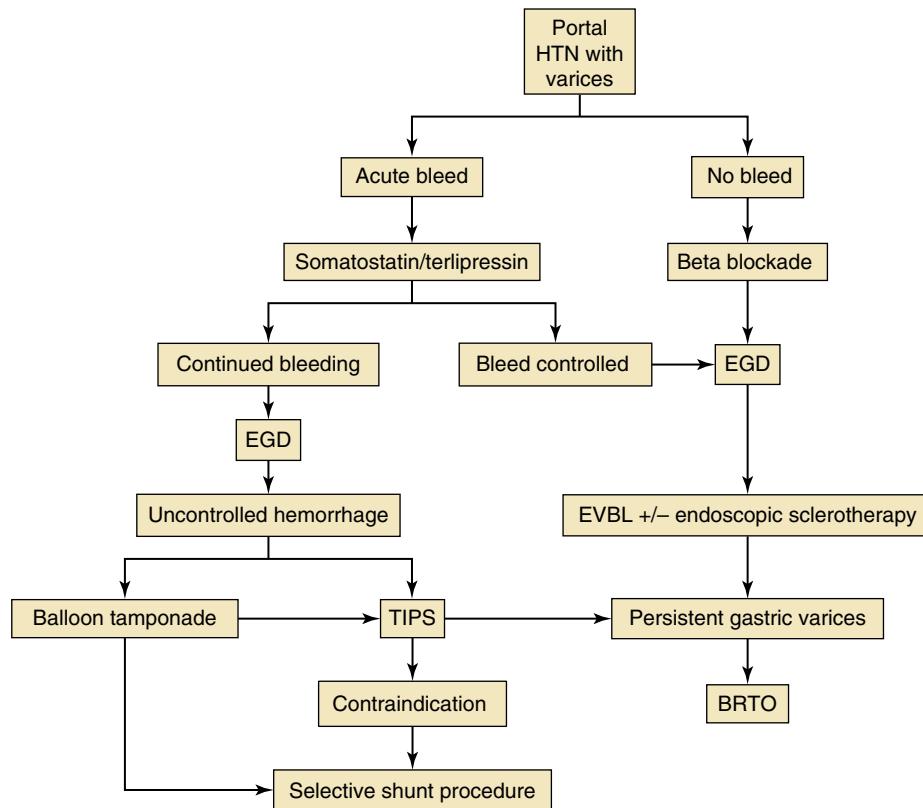
## Liver Transplantation

Liver transplantation is indicated for end-stage liver disease and not necessarily for management of PTH or variceal bleeding. However, transplantation may be the endpoint of

treatment for these patients. In general, the available data suggest that patients who undergo surgical shunt for variceal bleeding have higher survival rates after transplantation

than patients treated with endoscopic procedures. In some patients, surgical shunting appeared to eliminate the need for transplantation.<sup>78–80</sup>

## CHAPTER ALGORITHM



## SELECTED KEY REFERENCES

Bloom S, Kemp W, Lubel J. Portal hypertension: pathophysiology, diagnosis, and management. *Intern Med J*. 2015;45:16–26.

*Recent overview of PHT and its complications.*

Hosokawa I, Adam R, Allard MA, et al. Outcomes of surgical shunts and transhepatic jugular intrahepatic portasystemic stent shunts for treatment of complicated portal hypertension. *Br J Surg*. 2017;104:443–451.

*Recent comparison of surgical stents and TIPS, and how surgical shunts fit into treatments for PHT in the current environment.*

Nobuyuki T, Yoshitaka T, Tsutsumi M. Management of gastroesophageal varices in cirrhotic patients: current status and future directions. *Ann Hep*. 2016;15:314–325.

*Recent review of all available techniques for the treatment of variceal bleeding.*

Orloff MJ, Isenberg JI, Wheeler HO, et al. Liver transplantation in a randomized controlled trial of emergency treatment of acutely bleeding esophageal varices in cirrhosis. *Transplant Proc*. 2010;42:4101–4108.

*Use of liver transplantation in the treatment of variceal bleeding.*

Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade tranvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol*. 2012;15:203–225.

*Description of new techniques of BRTO and BRAO.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. Gupta TK, Chen L, Groszmann RJ. Pathophysiology of portal hypertension. *Clin Liver Dis.* 1997;1(1):1–12.
2. Seo YS, Shah VH. Pathophysiology of portal hypertension and its clinical links. *J Clin Exp Hepatol.* 2011;1(2):87–93.
3. Iwakiri Y. Pathophysiology of portal hypertension. *Clin Liver Dis.* 2014;18:281–291.
4. Radovich PA. Portal vein thrombosis and liver disease. *J Vasc Nursing.* 2000;XVIII(1):1–5.
5. Kravetz D, Bosch J, Teres J, et al. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal hemorrhage. *Hepatology.* 1984;4(3):442–446.
6. Fatemi N, Sarkar B. Molecular mechanism of copper transport in wilson disease. *Environ Health Perspect.* 2002;110(5):695–698.
7. Ferro JM, Viana P, Santos P. Management of neurologic manifestations in patients with liver disease. *Curr Treat Options Neurol.* 2016;18:37.
8. Kim SH, Keum B, Jeen YT, Chun HJ. Hepatobiliary and pancreatic: caput medusae. *J Gastroenterol Hepatol.* 2014;29:1952.
9. Bloom S, Kemp W, Lubel J. Portal hypertension: pathophysiology, diagnosis and management. *Intern Med J.* 2015;45:16–26.
10. Berzigotti A, Escorsell A, Bosch J. Pathophysiology of variceal bleeding in cirrhotics. *Ann Gastroenterol.* 2001;14(3):150–157.
11. Nobuyuki T, Yoshitaka T, Tsutsumi M. Management of gastroesophageal varices in cirrhotic patients: current status and future directions. *Ann Hep.* 2016;15(3):314–325.
12. Bert F, Noussair L, Lambert-Zechovsky N, Valla D. Viridans group streptococci: an underestimated cause of spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Eur J Gastroenterol Hepatol.* 2005;17:929–933.
13. Cholongitas E, Papatheodoridis GV, Lahanas A, et al. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. *Liver Int.* 2005;25:57–61.
14. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Dig Dis.* 2016;34:382–386.
15. Nirajan-Azadi AM, Araz F, Patel YA, et al. Ammonia level and mortality in acute liver failure: a single-center experience. *Ann Transplant.* 2016;21:479–483.
16. Waghraj A, Waghraj N, Mullen K. Management of covert hepatic encephalopathy. *J Clin Exp Hepatol.* 2015;5(S1):S75–S81.
17. Wadei HM, Mai MI, Alisan N, Gonwa TA. Hepatorenal syndrome: pathophysiology and management. *Clin J Am Soc Nephrol.* 2006;1:1066–1079.
18. Grace JA, Angus PW. Hepatopulmonary syndrome: update on recent advances in pathophysiology, investigation, and treatment. *J Gastroenterol Hepatol.* 2013;28:213–219.
19. Cardoso FS, Marcelino P, Bagulho L, Karvellas CJ. Acute liver failure: an up-to-date approach. *J Crit Care.* 2017;39:25–30.
20. Sinclair M, Grossman M, Gow P, Angus PW. Testosterone in men with advanced liver disease: abnormalities and implications. *J Gastroenterol Hepatol.* 2015;30:244–251.
21. Baker HWG, Burger HG, Kretser DM, et al. A study of endocrine manifestations of hepatic cirrhosis. *Quarterly J Med.* 1976;XLV(177):145–178.
22. Dong MH, Saab MD. Complications of cirrhosis. *Dis Mon.* 2008;54:445–456.
23. Ma C, Brunt EM. Histopathologic evaluation of liver biopsy for cirrhosis. *Adv Anat Pathol.* 2012;19(4):220–230.
24. Eckhauser F, Appelman H, O'Leary T. Hepatic pathology as a determinant of prognosis after portal decompression. *Am J Surg.* 1980;139:105–112.
25. Nuttli T, McGoey RR. Altered mental status, alcohol abuse, and hyperammonemia. *J La State Med Soc.* 2014;166:46–48.
26. Zierler RE. *Strandness's Duplex Scanning in Vascular Disorders.* 4th ed. Lippincott Williams & Wilkins; 2009.
27. Valla DC, Condat B. Portal vein thrombosis in adults: pathophysiology, pathogenesis and management. *J Hepatology.* 2000;32:865–871.
28. Zubarev PN, Alent'ev SA, Belevitin AB, Kotiv BN. Digital subtraction arteriopertigraphy in the examination of patients with the portal hypertension syndrome. *Vestn Khir Im I I Grek.* 1997;156(3):81–85.
29. Okuda K, Takayasu K, Matsutani S. Angiography in portal hypertension. *Gastroenterol Clin North Am.* 1992;21(1):61–83.
30. Nordlinger BM, Nordlinger DF, Fulenwider JT, et al. Angiography in portal hypertension – clinical significance in surgery. *Am J Surg.* 1980;139:132–141.
31. Burroughs A, Jenkins W, Sherlock S. Controlled trial of propranolol for the prevention of recurrent variceal hemorrhage in patients with cirrhosis. *N Engl J Med.* 1983;309:1539–1542.
32. Ali SM, Wu S, Xu H, et al. A prospective study of endoscopic injection sclerotherapy and endoscopic variceal ligation in the treatment of esophageal varices. *J Laparoendosc Adv Surg Tech.* 2017;27(4):333–341.
33. Lizardo-Sanchez L, Burdick J, Trotter JF. Safety and efficacy of 2-octylcyanoacrylate in the management of patients with gastric and duodenal varices who are not candidates for transjugular intrahepatic portosystemic shunts. *Proc (Bayl Univ Med Cent).* 2016;29(4):371–373.
34. Lobo MRA, Chaves DM, De Moura DTH, et al. Safety and efficacy of EUS-guided coil plus cyanoacrylate versus conventional cyanoacrylate technique in the treatment of gastric varices: a randomized controlled trial. *Arg Gastroenterol.* 2019;56(1):99–105.
35. Svoboda P, Kantorova I, Kozumplik L, Marsova JA. Prospective randomized controlled trial of sclerotherapy vs ligation in the treatment of high-risk esophageal varices. *Surg Endosc.* 1999;13(6):580–584.
36. Chen YL, Ghali P. Prevention and management of gastroesophageal varices in cirrhosis. *Int J Hepatol.* 2012;2012:750150.
37. Mols P, Hallemans R, Van Kuyk M. Hemodynamic effects of vasopressin alone and in combination with nitroprusside in patients with liver cirrhosis and portal hypertension. *Ann Surg.* 1984;199:176–181.
38. Jha SK, Mishra M, Jha A, Dayal VM. Comparison of continuous versus intermittent infusions of terlipressin for control of acute variceal bleeding in patients with portal hypertension: An open-label randomized controlled trial. *Indian J Gastroenterol.* 2018;37(4):313–320.
39. Feneyrou B, Hanana J, Daures JP, Prioton JB. Initial control of bleeding from esophageal varices with the sengstaken-blakemore tube. Experience in 82 patients. *Am J Surg.* 1988;155(3):509–511.
40. Greenwald B. The minnesota tube – its use and care in bleeding esophageal and gastric varices. *Gastroenterol Nurs.* 2004;27(5):212–217.
41. Christensen T, Christensen T. The implementation of a guideline of care for patients with a sengstaken-blakemore tube in situ in a general intensive care unit using transitional change theory. *J Int Crit Care Nur.* 2007;23:234–242.
42. Schlichting AB, Gardner-Gray JM, Hurst G. Novel use of glidescope indirect laryngoscopy for insertion of a minnesota tube for variceal bleeding. *J Emerg Med.* 2015;49(1):40–42.
43. Saad WE. Balloon-occluded retrograde transvenous obliteration of gastric varices: concept, basic technique, and outcomes. *Semin Interv Radiol.* 2012;29:118–128.
44. Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol.* 2012;15(3):203–225.
45. Arai H, Abe T, et al. Efficacy of balloon-occluded retrograde transvenous obliteration, percutaneous transhepatic obliteration and combined techniques for the management of gastric fundal varices. *World J Gastroenterol.* 2006;12:3866–3873.
46. Smith M, Durham J. Evolving Indications for TIPS. *Tech Vasc Interv Radiol.* 2016;19:36–41.
47. Bizollon T, Dumortier J, Jouisse C, et al. Transjugular intra-hepatic portosystemic shunt for refractory variceal bleeding. *Eur J Gastroenterol Hepatol.* 2001;13:369–375.
48. Keller FS, Farsad K, Rosch J. The transjugular intrahepatic portosystemic shunt: technique and instruments. *Tech Vasc Interv Radiol.* 2016;19:2–9.
49. Monescillo A, Martinez-Lagares F, Ruiz-del-Arbol L, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology.* 2004;40(4):793–801.

50. Saad WE, Darcy MD. Transjugular intrahepatic portosystemic shunt (TIPS) versus balloon-occluded retrograde transvenous obliteration (BRTO) for the management of gastric varices. *Semin Intervent Radiol.* 2011;28(3):339–349.
51. Marticorena Garcia SR, Langmann M, Schnorr B, et al. Use of paclitaxel-coated balloon catheter dilation to reduce in-stent restenosis in transjugular intrahepatic portosystemic shunt (TIPS). *Röfo.* 2016;188(4):374–380.
52. Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. Portal hypertension and gastrointestinal bleeding. *Semin Liver Dis.* 2008;28:3–25.
53. Boyer TD. Transjugular intrahepatic portosystemic shunt: current status. *Gastroenterology.* 2003;124:1700–1710.
54. Poh Z, Chang PE. A current review of the diagnostic and treatment strategies of hepatic encephalopathy. *Int J Hepatol.* 2012;2012:480309.
55. Rueff B, Benhamou J. Management of gastrointestinal bleeding in cirrhotic patients. *Clin Gastroenterol.* 1975;4:426–438.
56. Tripathi D, Sunderraj L, Vemala V, et al. Long term outcomes following percutaneous hepatic vein recanalization for Budd Chiari syndrome (BCS). *Liver Int.* 2017;37(1):111–120.
57. Tripathi D, Macnicholas R, Kothari C, et al. Good clinical outcomes following transjugular intrahepatic portosystemic stent-shunts in Budd-Chiari syndrome. *Aliment Pharmacol Ther.* 2014;39:846–872.
58. Thornburg B, Deai K, Hickey R, et al. Portal vein recanalization and transjugular intrahepatic portosystemic shunt creation for chronic portal vein thrombosis: technical considerations. *Tech Vasc Interv Radiol.* 2016;19:52–60.
59. Grace ND, Muench H, Chalmers TC. The present status of shunts for portal hypertension in cirrhosis. *Gastroenterology.* 1966;50(5):684–691.
60. Rikkers LF. Operations for management of esophageal variceal hemorrhage. *West J Med.* 1982;136:107–121.
61. Smith RB, Warren WD. Selective distal splenorenal shunt for bleeding esophageal varices. *Annu Rev Med.* 1975;26:229–234.
62. Sarfey IJ, Carter JA, Welch HF. Analysis of operative mortality after portal decompressive procedures in cirrhotic patients. *Am J Surg.* 1980;140(2):306–311.
63. Busuttil RW, Brin B, Tompkins RK. Matched control study of distal splenorenal and portacaval shunts in the treatment of bleeding esophageal varices. *Am J Surg.* 1979;138:62–67.
64. Reynolds TB, Hudson NM, Mikkelsen WP, et al. Clinical comparison of end to side and side to side portacaval shunt. *N Engl J Med.* 1966;274(13):706–710.
65. Hermann RE. Shunt operations for portal hypertension. *Surg Clin North Am.* 1975;55(5):1073–1087.
66. Descottes B, Lachachi F, Maisonneuve F, et al. Long-term results of mesocaval shunts with polytetrafluoroethylene grafts. *Int Surg.* 2008;93(5):268–273.
67. Drapanas T, LoCicero J, Dowling JB. Hemodynamics of the interposition mesocaval shunt. *Ann Surg.* 1975;181(5):523–531.
68. Cameron JL, Zuidema GD, Smith GW, et al. Mesocaval shunts for the control of bleeding esophageal varices. *Surgery.* 1979;85(3):257–262.
69. Rikkers LF, Rudman D, Galambos JT, et al. A randomized controlled trial of the distal splenorenal shunt. *Ann Surg.* 1978;188(3):271–280.
70. Langer B, Rotstein LE, Stone RM, et al. A prospective randomized trial of the selective distal splenorenal shunt. *Surg Gynecol Obstet.* 1990;150(1):45–48.
71. Conn HO, Resnick RH, Grace ND, et al. Distal splenorenal shunt vs. portal-systemic shunt: current status of a controlled trial. *Hepatology.* 1981;1(2):151–160.
72. Millikan WJ, Warren WD, Henderson JM, et al. The emory prospective randomized trial: selective versus nonselective shunt to control variceal bleeding. *Ann Surg.* 1985;201(6):712–721.
73. Harley HA, Redeker AG, Reynolds TB, et al. Results of a randomized trial of end to side portacaval shunt and distal splenorenal shunt in alcoholic liver disease and variceal bleeding. *Gastroenterology* 1986;91(4):802–809.
74. Khan S, Tudur-Smith C, Williamson P, Sutton R. Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. *Cochrane Database Syst Rev.* 2006;18(4):CD000553.
75. Henderson JM, Boyer TD, Kutner MH, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systemic shunt for variceal bleeding: a randomized trial. *Gastroenterology.* 2006;130:1643–1651.
76. Orloff MJ, Isenberg JI, Wheeler HO, et al. Randomized trial of emergency endoscopic sclerotherapy versus emergency portacaval shunt for acutely bleeding esophageal varices in cirrhosis. *J Am Coll Surg.* 2009;209(1):25–40.
77. Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol.* 2012;15(3):203–225.
78. Henderson JM. Liver transplantation for portal hypertension. *Gastroenterol Clin N Am.* 1992;21(1):197–213.
79. Bismuth H, Adam R, Raccuia JS. Liver transplantation in the treatment strategy of portal hypertension. *Chirurg.* 1995;66(6):574–581.
80. Orloff MJ, Isenberg JI, Wheeler HO, et al. Liver transplantation in a randomized controlled trial of emergency treatment of acutely bleeding esophageal varices in cirrhosis. *Transplant Proc.* 2010;42:4101–4108.

# Nutcracker Syndrome

JOVAN N. MARKOVIC and CYNTHIA K. SHORTELL

INTRODUCTION 2183

BACKGROUND 2184

Prevalence, Demographics and Risk Factors 2184

Anatomy 2184

DIAGNOSIS 2185

Clinical Presentation 2185

Imaging 2187

MANAGEMENT 2188

Open Surgery for Anterior Nutcracker Syndrome 2189

Open Surgery for Posterior Nutcracker Syndrome 2191

Endovascular Treatment of Nutcracker Syndrome 2191

SUMMARY 2192

CHAPTER ALGORITHM 2193

## INTRODUCTION

*"The left renal vein as it lies between the aorta and the superior mesenteric artery resembles a nut between the jaws of a nutcracker."*

J.C.B. Grant, 1937

Nutcracker syndrome (NCS) is a rare clinical entity characterized by outflow obstruction from the left renal vein (LRV) into the inferior vena cava (IVC) caused by reduction of the LRV diameter either due to extrinsic compression of the LRV by surrounding anatomic structures (most commonly between the aorta and the overlying superior mesenteric artery (SMA)) or due to stretching and traction on the LRV.<sup>1–5</sup> Regardless of the etiology, the above-mentioned anatomical aberrations of the renocaval venous territory lead to an increase in the venous pressure distal to the LRV obstruction with subsequently impaired venous drainage from the left kidney (due to LRV hypertension) and/or pelvis (secondary to the gonadal vein reflux).

Colloquially this pathological anatomic configuration has been referred to as NCS if presenting with a constellation of symptoms, or "nutcracker phenomenon" (NCP) if LRV compression is found incidentally in otherwise asymptomatic patients.<sup>6–8</sup> It's worth noting that the existence of a true clinical syndrome may be disputed by some authors. This is largely due to the following facts: some degree of the LRV compression by the SMA is physiologic<sup>9</sup>, surgical ligation of the LRV during aortic procedures is usually well tolerated, and patients with LRV stretched taut over an aortic aneurysm are rarely symptomatic.<sup>9–14</sup>

Traditionally, different terminology has been used to describe this anatomic scenario, including "LRV entrapment syndrome," or "mesoaortic compression" of the LRV.<sup>15–23</sup> However, the unique phrasing of this anatomic phenomenon was originally coined after the anatomist Grant likened compression of the LRV between the aorta and SMA to that of a nut in a nutcracker in pathologic specimens from the 1930s.<sup>24</sup> Clinical reports of the syndrome were initially reported by the Egyptian urologists El-Sadr and Mina in 1950<sup>25</sup> and followed by venographic characterization by Chait et al. in 1971, who first coined the term "nutcracker".<sup>26</sup> It was eventually in 1972 when Dr. de Schepper, a Belgian radiologist, named the disorder as "nutcracker syndrome" and yielded further interest in the disease process after associating the LRV compression with pelvic/perirenal varicosities, and hematuria.<sup>27</sup> Initial reports proposing surgical repair through transposition of the LRV were described shortly thereafter by Pastershank in 1974.<sup>28</sup> These initial publications have given rise to numerous small case series and intermittent case reports in the timeframe since.

There remains a paucity of larger studies and thus no consensus exists over the optimal management of NCS, including patient selection and procedure of choice. As a result, there remains much controversy regarding the optimal diagnostic and therapeutic approach to NCS. Largely, this can be attributed to several factors, including the rarity of NCS, the nonuniformity in patient symptomatology with diagnostic uncertainty and concomitant delays in diagnosis, varying opinions of the optimal surgical approach and lack of consensus data on the durability and longevity of these different approaches, and the involvement of a number of specialists and subspecialists in the care of these patients.

Only case series/reports... ↓ evidence & consensus

This chapter focuses on the anatomic, diagnostic, and therapeutic strategies utilized to approach this rare, albeit challenging, vascular disorder.

## BACKGROUND

### Prevalence, Demographics and Risk Factors

The exact prevalence of NCS is unknown primarily due to an absence of unified diagnostic criteria and variability of presenting symptom(s). Although not limited to a specific gender or age range, based on data from several studies it is thought that NCS is more prevalent in females and the young patients (second and third decade of life), with a secondary peak in middle age adults.<sup>22,29</sup> However, further studies have shown that NCS is equally prevalent among male and female patients,<sup>30</sup> and that it can affect older patients, as well.<sup>29</sup>

Radiologic studies demonstrated a 10.4% prevalence of NCP on evaluation of abdominal computed tomographic (CT) scans performed for other indications, with no difference in the prevalence of NCP by gender alone.<sup>31</sup> Owing to causes elaborated upon later, a lower BMI has been shown to have a correlation with NCS.<sup>32</sup> A large proportion of the nutcracker literature includes patients of Asian origin, although it should be noted that no true population-based studies have been performed to determine if there are any ethnic, racial and/or geographic risk factors for NCS. Finally, with the exception of a single case report in which NCS was found in two young siblings, data from the current body of literature shows no evidence of genetic hereditary link in the inheritance of this disorder.<sup>33</sup>

### Anatomy

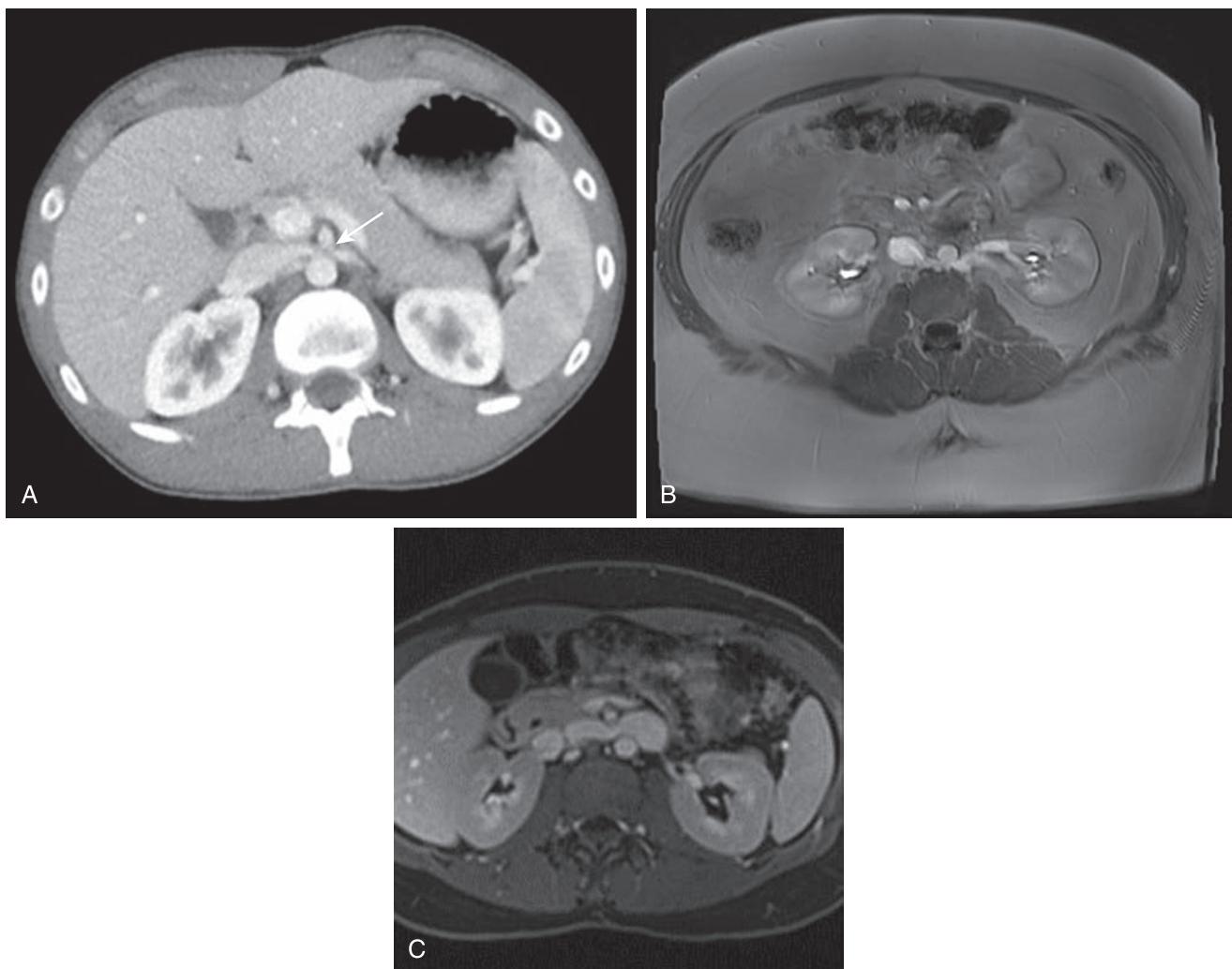
Based on underlying anatomy there are two main types of NCS. The most common type, anterior NCS, refers to compression of the LRV between the abdominal aorta and the SMA, as mentioned above (Fig. 165.1A).<sup>34</sup> In posterior NCS the LRV is in retro-aortic position and is compressed between the abdominal aorta and the vertebral column (Fig. 165.1B). There is also atypical NCS caused by very rare anatomic variants including the compression of the LRV and IVC as they pass between the aorta and the SMA in patients with left-sided IVC (Fig. 165.1C). A number of other anatomic variations pertinent to the anatomy and angulation of the SMA may also result in symptomatic compression of the LRV, although whether they can be truly considered as causes of the NCS is controversial. These include compression by pancreatic neoplasms, paraaortic lymphadenopathy, retroperitoneal tumors, an overarching testicular artery, fibrolymphatic tissue or "webs" between the SMA and aorta, as well as compression of larger veins by a gravid uterus.<sup>1,34–36</sup> The normal distance between the SMA and aorta has been noted to average 4 to 5 mm at the level of the LRV. LRV diameters average approximately  $1.2 \pm 0.2$  cm (1.1 cm proximal segment; 1.2 cm distal segment) in cadaveric studies, with ultrasound studies showing slightly smaller diameters of LRV size (4–5 mm) in patients without NCS.<sup>37–39</sup>

Anterior NCS can result in dilation and engorgement of the gonadal vein, as well as a preponderance of pelvic collaterals that can be visualized with cross-sectional or angiographic imaging. It is very important to note that a recent study has shown that gonadal vein diameter may not correlate with gonadal venous reflux in patients with pelvic venous congestion syndrome not related to renal vein compression.<sup>40</sup> Dos Santos et al. demonstrated that many normally sized ovarian veins exhibit pathologic reflux, and some large ovarian veins are competent. The authors measured diameters of 34 ovarian veins (17 right, 17 left) using digital subtraction venography. The findings were compared with previously diagnosed reflux (by transvaginal DUS) in 16 out of these 34 veins (47.1%). Data showed that the mean diameters of the non-refluxing and refluxing veins were 7.2 mm (range 3–13 mm) and 8.5 mm (range 4–13 mm), respectively, with no statistically significant difference ( $P = 0.204$ ) among groups.<sup>40</sup> Based on these findings the accuracy for diagnosis of ovarian venous reflux based on vein diameter is less than 56%, which approximates the probability of random guessing (50%). Whether or not these findings can be extrapolated to patients with NCS is not clear, nevertheless these findings do underscore the importance of clinical features, rather than radiologic findings alone, to make the diagnosis of NCS.

Anatomically, there are a variety of explanations as to the mechanism of SMA compression of the LRV, including a more acute angle between the aorta and SMA (<16 degrees; normal range: 35–40 degrees), which is often attributed to a paucity of retroperitoneal or mesenteric fat, wasting of the paraspinal muscles, as well as profound weight loss.<sup>36,41</sup> However, according to other studies that used magnetic resonance angiography (MRA) the sagittal plane angle between the SMA and the abdominal aorta needs to be less than 35 degrees for a definitive NCS diagnosis.<sup>42</sup> Similar with these findings, Kim et al. demonstrated, by comparing CT results with LRV venography and measurement of the pressure gradients between the LRV and IVC, that sagittal plane angle <39 degrees on CT had high sensitivity and specificity for detecting symptomatic NCS with respective rates of 92% and 89%.<sup>43</sup>

The paucity of retroperitoneal fat correlates well with the observation that NCS is oftentimes seen in those with a particularly thin body habitus.<sup>44</sup> Posterior ptosis of the left kidney resulting in abnormal angulation and subsequent stretching and traction of the LRV has also been implicated as a possible cause of LRV narrowing and subsequent hypertension.<sup>45</sup> Additional anatomic variants resulting in anterior NCS include aberrant branching of the SMA and an abnormal, particularly cephalad course of the LRV.<sup>37,44,45</sup>

Although prior studies have demonstrated that posterior NCP may be similar in prevalence to anterior NCP,<sup>31</sup> there are far fewer reports in the literature of the management of posterior NCS patients, although their symptomatology is noted to be no different from that of their anterior NCS counterparts.<sup>5</sup> In truth, a retro-aortic LRV remains an uncommonly observed anatomic phenomenon, with a recent study showing a prevalence of 0.77% to 3.18%, with only a minority of cases being symptomatic (6.5%).<sup>46–48</sup>



**Figure 165.1** Cross-sectional imaging demonstrating (A) anterior nutcracker syndrome with compression of the left renal vein (arrow) between the aorta and superior mesenteric artery as observed by computed tomography; (B) posterior nutcracker syndrome with a retro-aortic renal vein as observed by magnetic resonance imaging; and (C) compression of the left-sided IVC by the SMA and the aorta. *IVC*, inferior vena cava; *SMA*, superior mesenteric artery.

A combined anterior and posterior NCS has also been reported as a result of the LRV duplication (the **circumaortic renal vein**).<sup>31,49</sup> This is a rare anatomic variant of the LRV where the vein has both antero- and retro-aortic segment on its course to the IVC (with reported incidence of 0.3–5.7%).<sup>50</sup> This anatomic variant can be prone to the compression of the anterior LRV segment between the aorta and SMA, while the posterior LRV segment is compressed by the aorta against the vertebral column resulting in symptoms secondary to the LRV hypertension and/or gonadal vein reflux.<sup>46</sup> Lastly, **right-sided NCS**, although possible, is even more infrequently reported in the literature and oftentimes results from the condition of **left-sided IVC** and the unique combination of **left-sided IVC, hemiazygos continuation, and persistent left SVC**.<sup>51</sup>

## DIAGNOSIS

The pathophysiologic mechanism(s) that leads to development of symptoms in NCS has been questioned by many, stemming

from the fact that NCP exists, by definition, without symptomatology. Further skepticism around the syndrome and pathophysiology is generated by the fact that the LRV is stretched in instances of a “prominent aorta” and in abdominal aortic aneurysms (AAAs), as well as the fact that the LRV is often ligated without apparent detrimental effect during AAA repair. Although uncertain, **hypotheses as to why NCS does not occur in these scenarios include** a genetic propensity to the development of venous wall weakness, along with the timeframe with which collaterals are allowed to develop in NCS versus acutely as in AAA.<sup>52</sup> In addition, other similar venous compression syndromes, most notably May–Thurner syndrome, may be found incidentally without clinical sequelae.

## Clinical Presentation

For didactic purposes, regardless of underlying anatomy, the clinical presentation in patients with NCS can be correlated with the following **two hemodynamic aberrations**:

① hypertension in the LRV with subsequent renal pathology; and  
 ② gonadal vein reflux (induced by the LRV hypertension) with subsequent pelvic venous disorders. The LRV has an important role in pelvic venous outflow, as anatomically it represents the most caudal outflow point (prior to the IVC) for a complex venous system with major contribution from the gonadal vein, which in turn interconnects distally with the internal iliac veins, and the common femoral vein. These three drainage territories are multiply interconnected with frequent cross-pelvic drainage. Pelvic venous disorders can arise from reflux in the ovarian and/or internal iliac veins that can lead to pelvic varicosities and associated symptoms.

This venous network also plays an important role as collateral circulation in the setting of the gonadal vein reflux induced by the LRV hypertension, and may in certain cases explain absence of symptoms in some patients with LRV obstruction. In this subgroup of patients, the draining capacity of the above-mentioned venous network is not exceeded by adding an influx of venous blood from the refluxing gonadal vein, and compensation by collateral networks may result in alternate but overall sufficient venous blood outflow from the gonadal vein via the iliac venous system, without subsequent development of symptom(s). However, the threshold for exceeding the compensatory capacity of collateral circulation may be lowered as a result of increased venous pressure secondary to distal obstruction in the collateral network such as in patients with compression of the left common iliac vein by the right common iliac artery (May–Thurner syndrome). It is also possible that increased venous flow in the common iliac vein (caused by additional venous influx from refluxing gonadal vein) leads to enlargement of the common iliac vein diameter, which increases the risk of its compression by the overlying right common iliac artery. The combination of this increased venous blood volume and obstruction of the common iliac vein outflow due to extrinsic compression results in a hemodynamic environment that may lead to decompensation of collateral venous pathways and development of pelvic symptoms characterized by venous congestion caudal to the common iliac vein. This is the rationale behind the premise that stenting of the common iliac vein will lead to improvement of symptoms associated with ovarian vein reflux and pelvic venous disorders.

The constellation of signs and symptoms that has traditionally defined NCS (Table 165.1) is quite variable, and it is this variety along with ambiguity of symptomatology that has led to diagnostic uncertainty and delays in diagnosis. The most commonly reported symptoms have traditionally been left flank pain coupled with either gross or microscopic hematuria.<sup>53</sup> As compression of the LRV progresses over time and pelvic collaterals form, a number of symptoms related to pelvic congestion syndrome (PCS) may develop, such as dyspareunia, dysuria, and/or dysmenorrhea. Physical exam findings may include lower extremity, posterior thigh, and gluteal varicosities, varicocele in men (typically left sided), as well as vulvar/labial varices in females. It should be noted that there are no true physical exam findings that are pathognomonic for NCS.<sup>30</sup> However, a constellation of any of the previous findings in

**TABLE 165.1** Clinical Features of Nutcracker Syndrome

Highly Suspicious	Possibly Related
Hematuria	Dyspareunia
Gross	Dysmenorrhea
Microscopic	Dysuria
Left flank pain	Varices
	Vulvar
	Scrotal (Varicocele)
	Lower extremity
	Gluteal
	Proteinuria
	Abdominal pain

concert with hematuria and flank pain are strongly suggestive for the diagnosis of NCS.

Hematuria is the most commonly described symptom of NCS<sup>2,30</sup> and can be either gross or microscopic in presentation, oftentimes resulting in further workup for uro-genital causes of hemorrhage. Microscopic hematuria is several times more common in presentation than gross hematuria.<sup>54</sup> Authors have described hematuria that may be isolated to the left ureteral orifice on cystoscopy, although hematuria in concert with flank pain can be due to a variety of causes that must be excluded prior to the diagnosis of NCS. The pathophysiology resulting in hematuria is not completely understood but thought to revolve around the obstruction of LRV outflow, with subsequent LRV hypertension leading to the diffusion of red blood cells and proteins into the glomerular filtrate.<sup>55,56</sup> In addition, LRV hypertension has been postulated to result in the development of thin-walled varices and valveless collaterals which are prone to rupture into the neighboring collecting system itself, resulting in microhematuria or in more severe cases macrohematuria, or in the communication of dilated venous sinuses with adjacent renal calices.<sup>57,58</sup> Orthostatic proteinuria has likewise been described as a common finding in patients with confirmed NCS, and NCS was once thought to result in chronic fatigue syndromes in children.<sup>59</sup>

Symptoms of pain are ascribed to the passage of blood or clots through the collecting system<sup>1</sup> and as such are typically isolated to the left flank given the propensity of NCS to affect the left side. However, more generalized abdominal pain has been demonstrated in NCS, and left flank pain has likewise been ascribed to the gonadal vein syndrome, in which abdominal or flank pain radiates to the posteromedial thigh and buttock.<sup>1,60</sup> In addition, although the two clinical entities are often confused, nutcracker anatomy (i.e., LRV compression) may be a cause of PCS, in which the accumulation of blood in the pelvis from reflux or obstruction of gonadal, gluteal, or periuterine veins results in a chronic pain syndrome associated with perineal or vulvar varices.<sup>61</sup> This pain is manifested as dyspareunia, dysmenorrhea, and/or dysuria, none of which are typical presentations of NCS. We should also note that symptoms such as scrotal/vulvar varices and pain are exacerbated with standing, physical activity, or orthostasis, because this position results in increased venous filling and distension of collateral drainage pathways.<sup>52,60</sup> In 2018 Li et al. published

a study that evaluated a cohort of 3042 patients with testicular varicocele due to dilatation of the pampiniform venous plexus.<sup>62</sup> This study showed that 858 (28.21%) patients with varicocele had co-existing NCS.<sup>62</sup>

## Imaging

If there is clinical suspicion of LRV compression further imaging should be performed to exclude nonvascular etiologies of LRV compression, as well as to further define the anatomy of the LRV obstruction. This is due to the fact that potentially treatable etiologies of LRV compression such as neoplasm require referral to a specialist other than a vascular surgeon. The utility of imaging adjuncts in the diagnosis is proven, although a dedicated clinical history is of utmost importance and the decisions for NCS diagnosis and therapy should be based upon the correlation of presenting symptoms with imaging findings. Historically, multiple imaging studies were frequently obtained during the evaluation of a patient with clinically suspected NCS, but ultimately venography was typically pursued as the confirmatory diagnostic modality since it allows venocaval pressure gradient measurement and in real time it determines venous reflux into gonadal and pelvic collaterals. It is very important that venogram is performed carefully to avoid injection under excessive pressure into the LRV, which can cause "artificial" flow in the gonadal vein, and be erroneously interpreted as gonadal vein reflux. To this end, injection of the contrast in the left renal artery with delayed imaging of venous outflow is extremely helpful.

Some authors favor initial use of left renal venography with measurement of the gradient between the LRV and IVC, but this has been supplanted by noninvasive cross-sectional imaging modalities. Although there is some controversy in terms of which imaging modality is preferentially used in the initial diagnosis, both catheter-based and cross-sectional imaging are needed as they provide different diagnostic information, as outlined later.

Oftentimes, duplex ultrasonography (DUS) serves as the initial imaging modality if NCS is suspected, because it is non-invasive, lacks radiation exposure, and is readily available across most institutions. Ultrasound has the advantage of being able to delineate vascular anatomy and determine basic flow and velocity characteristics of the LRV. However, this modality is limited by patient anatomy and habitus, overlying bowel gas, and interoperator variability. Used by an experienced practitioner, DUS has demonstrated a sensitivity and specificity of 78% and 100%, respectively, in diagnostic accuracy for NCS and has been noted to be particularly useful when coupled with the observation of gonadal and retroperitoneal collateral veins, which demonstrate characteristic aberrant flow in a retrograde direction from the LRV.<sup>63</sup> However, this observation has limited clinical applicability due to the fact that the presence of collaterals occurs only after long-standing NCS and hence may not be detected early in the course of the syndrome. Absolute diameter size criteria of the LRV as observed during DUS has been noted by several authors to be of particular diagnostic futility, because larger LRV diameters can be variants of normal

and limited by the sonographers' interpretation, patient positioning, and/or hydration status.<sup>64,65</sup> However, particular utility of DUS has been observed when the diagnostic criteria uses the ratios between anteroposterior diameters and flow velocities at the narrowed proximal and distended distal portions of the LRV, comparing the two to obtain a ratio ( $>5.0$ ) diagnostic of NCS.<sup>63</sup> The five-fold increase in flow velocity is associated with relatively high sensitivity (80%) and specificity (95%) for NCS.<sup>66</sup> Another useful ultrasonographic parameter is post-stenotic peak velocity determined by Doppler spectral analysis which normally exceeds 100 cm/s.<sup>39</sup> However, errors are relatively frequent in DUS examination due to upright versus supine positioning with subsequent changes in mesoaortic angles, variation of vessel diameter during systole and diastole, as well as intrinsic errors in measurement of velocities and flows.<sup>67,68</sup> Others have used the ratio of the anteroposterior diameter of the LRV between the most dilated and the most narrow portions as diagnostic criteria in adults ( $>3.7$ ) and children ( $>4.3$ ).<sup>69</sup> However, it should be noted that children may form a special group of NCS patients because they in many cases don't require intervention, owing to the eventual development of mesenteric and retroperitoneal fat. This allows for the widening of the mesoaortic angle and subsequent relief of LRV compression, resolution of hematuria, and improvement in LRV to velocity/flow ratios.<sup>54</sup> In addition, early DUS results were obtained in concert with venography to confirm diagnoses because there was uncertainty and lack of data behind the validity and applicability of DUS in diagnosis at the time of studies. Currently, DUS remains an adjunct for diagnosis in combination with other, cross-sectional imaging modalities, as described next.

In the current era, axial imaging with magnetic resonance imaging (MRI) or contrast CT has gained increasing importance in the initial imaging workup of NCS.<sup>50</sup> The utility of these tests is comparable and can demonstrate a characteristic "beak sign" (as defined by narrowing of the LRV in a triangular shape between the SMA and aorta), as well as the unique circumstance of the retro-aortic/circumaortic LRV, retroperitoneal masses, pelvic or periaortic collaterals, and dilation of the gonadal vessels.<sup>70</sup> Critically important in axial imaging is the visualization of pelvic collaterals. If none are present, then the diagnosis of NCS is essentially eliminated as the cause of the patient's symptoms. According to one study, beak sign as delineated by CT imaging demonstrated the highest diagnostic accuracy as compared with LRV hilar/aortomesenteric diameter ratio and mesoaortic angle ( $<41$  degrees), with a sensitivity of 91.7% and specificity of 88.9%.<sup>71</sup> Other diagnostic cutoff values have been established using CT with three-dimensional reconstruction, including an LRV hilar–aortomesenteric cutoff ratio of 4.9 and a  $<41$ -degree angle between the SMA and aorta as measured by imaging.<sup>72</sup> By analyzing and comparing CTA and CTV scans of 33 NCS patients (97.0% female; age  $46.2 \pm 3.3$  years [mean  $\pm$  SD]) and 103 patients without NCS, Hangge et al. identified a strong correlation between the degree of LRV compression and NCS diagnosing.<sup>11</sup> Data showed that both specificity and sensitivity for NCS were 91% when pre-compression to compression ratio greater than 2.25 was used.

When a cutoff greater than 3.0 was used, sensitivity and specificity were 85% and 100%, respectively.<sup>11</sup> Multi-logistic regression analysis from the same study demonstrated that higher degree of the LRV compression was associated with hematuria ( $P = 0.01$ ), proteinuria ( $P = 0.002$ ) and abdominal pain ( $P = 0.007$ ), but not left flank pain ( $P = 0.06$ ).<sup>11</sup>

MRI yields similar anatomic assessment as CT without the use of contrast media or radiation exposure and can also give unique insight regarding obstruction of flow in the LRV, which is seen with compression of the vessel observed in NCS.<sup>73</sup> In a prospective study that included 40 pediatric patients (9 males, 31 females; age  $15.6 \pm 2.34$  years [mean  $\pm$  SD]) with NCS symptoms and ultrasonographically confirmed compression of the LRV, Er et al. evaluated MRI imaging efficacy and compared different MRI sequences in the diagnosis and follow-up of patients with NCS.<sup>74</sup> Data from this study showed that a noncontrast MRI, using T-2 True Fast Imaging with Steady-State Free Precession sequence, had an incremental value in the accurate diagnosis and follow-up of NCS patients.<sup>74</sup>

Axial imaging alone does not provide the necessary hemodynamic data for the diagnosis of NCS – namely, whether reflux into the gonadal and pelvic circulation is present and severe. **Venography** allows for the measurement of the renocaval pressure gradient (i.e., “pullback”), while also allowing for the visualization of mesoaortic-induced LRV narrowing (in case of anterior NCS), dilation of the LRV, reflux and opacification into the collateral pelvic network (including the gonadal, lumbar, adrenal, and other veins), and the sluggish passage of contrast through the LRV (Fig. 165.2).<sup>70</sup> Many of the criteria for venographic diagnosis/confirmation of NCS arise from an initial study performed by Zerhouni et al., which demonstrated a renocaval gradient of 0 to 3 mm Hg in a normal population.<sup>75</sup> However this work had significant limitations that stemmed from a low number of patients and selection of patients (three patients with varicocele) and was subsequently challenged by Beinart,<sup>57</sup> who demonstrated that 98% of normal subjects had a renocaval pressure gradient less than 1 mm Hg, with later studies demonstrating a range of renocaval pressure gradients, yielding subsequent debate as to the utility of absolute cutoff values for pressure gradients versus symptomatology. A standard of sorts was established when Nishimura and colleagues demonstrated a cutoff value of  $\geq 3$  mm Hg as diagnostic of LRV hypertension, which was observed in concert with hematuria and opacification of collaterals in their cohort,<sup>76</sup> and subsequently propagated by Takebayashi et al.<sup>63</sup> In the study by Takebayashi, left renocaval pressure gradients were defined as: normal ( $< 1$  mm Hg), borderline hypertensive (1–3 mm Hg), and hypertensive ( $\geq 3$  mm Hg).<sup>63</sup> However, as noted in other studies, the renocaval gradient may range from 3 to 10 mm Hg in normal patients, and in those with NCS these values range from 2 to 14 mm Hg, representing an overlap and area of diagnostic uncertainty if one were to attempt to diagnose NCS by the renocaval pressure gradient alone.<sup>37,72</sup> It should also be noted that in those with long-standing NCS, the high renocaval gradient typically observed may not be present, due to compensation by collateral circulation and decompression of the proximal LRV obstruction, which can result in low gradient



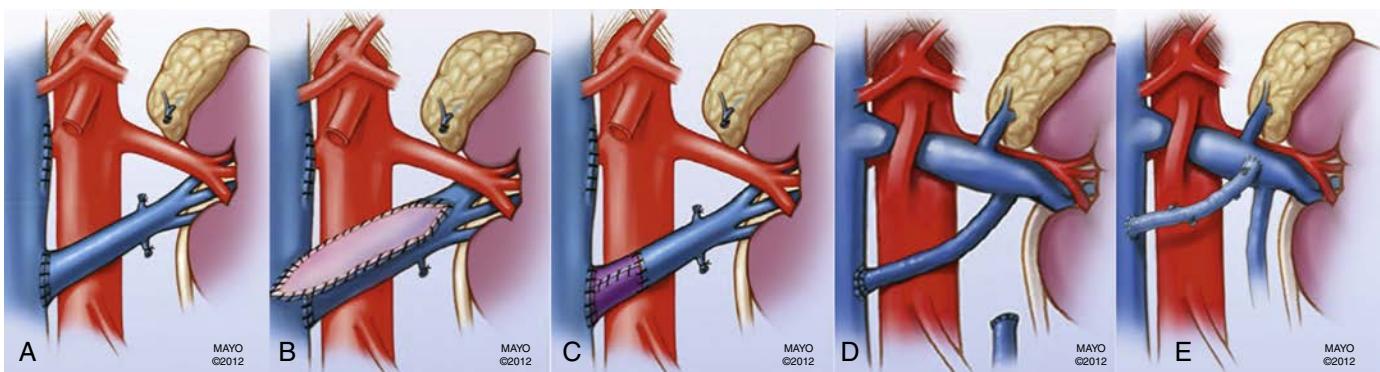
**Figure 165.2** Selective Left Renal Venography Demonstrating Characteristic Findings in Anterior Nutcracker Syndrome. Note the vast network of perirenal and pelvic collateral vessels, a dilated and incompetent gonadal vein (long arrow), and stagnant flow in the left renal vein (short arrow).

values. In addition, these values may be erroneous in the face of positioning and hydration status.<sup>21,37</sup>

Historically, other imaging modalities have been reported, such as intravenous urography, retrograde pyelography, and IVC phlebography, although they are not of current diagnostic utility and hence will not be described here. Cystoscopy, which many patients receive as part of the diagnostic workup for hematuria of unknown cause, is efficacious in localizing hematuria to the left ureteral orifice and hence the left side. However, no features on cystoscopy are pathognomonic for NCS, and as such, this invasive technique remains only indirectly diagnostic, and used for exclusion of other causes of hematuria.

## MANAGEMENT

The major goal of NCS treatment is the reduction and ideally the elimination of the LRV hypertension (and resulting gonadal vein reflux if present), regardless of which treatment modality is selected. Although the prompt recognition of the symptomatology and the subsequent diagnosis of NCS are important, patient selection and the operative strategy used are both critical to patient outcomes. Currently, there remains a marked lack of concordance regarding when/which patients should be treated and the optimal operative technique. The mere presence of radiographic compression (i.e., “bird beak”) is not a sufficient indication to operate, with requirements including hematuria, the presence of collaterals, and pelvic and/or flank pain (see Chapter Algorithm). Ideally, interventions are directed toward reducing the hypertensive state of the LRV



**Figure 165.3** Operative Strategies for the Management of Nutcracker Syndrome. (A) Left renal vein transposition. (B) Left renal vein transposition with patch angioplasty. (C) Left renal vein transposition with saphenous vein cuff. (D) Gonadal vein transposition. (E) Saphenous vein bypass. (From Erben Y, Gloviczki P, Kalra M, et al. Treatment of nutcracker syndrome with open and endovascular interventions. *J Vasc Surg Venous Lymphat Disord*. 2015; 3:389–396.)

induced by its compression, but as authors have noted, many procedures are performed as a result of symptoms of unrelenting and disabling pain or gross hematuria resulting in anemia.<sup>77,78</sup> We have elected not to describe the “conservative” management of NCS because this treatment strategy is more suited to children presenting with hematuria and found to have NCS, as further development and weight gain can, as mentioned, result in widening of the acute aortomesenteric angle and hence relief of LRV compression. In 2019, Miro et al. confirmed this strategy to be clinically acceptable by publishing a review of their experience in the management of pediatric patients with NCS over a period of 18 years.<sup>79</sup> They reported that out of a total of 21 patients the vast majority (19 patients, 90.5%) were male, with an average age at presentation of 11.7 years.<sup>79</sup> The mean follow-up period was 52.3 months. The authors recommended use of abdominal ultrasound to visualize the aortomesenteric junction in patients with persistent severe varicocele or with intermittent macroscopic hematuria and that catheter venography should be used only in inconclusive cases. They concluded that a long period of conservative treatment is appropriate for pediatric patients with NCS who do not have persistent symptoms or clinical decompensation.<sup>79</sup>

## Open Surgery for Anterior Nutcracker Syndrome

Numerous operative techniques have been used to treat anterior NCS in an open fashion. These have included LRV transposition ± patch venoplasty, patch venoplasty alone, LRV transposition with a saphenous vein cuff, gonadal vein transposition, saphenous vein bypass, gonado-caval bypass, gonado-iliac bypass, resection of fibrous tissue with placement of a “wedge” at the aortomesenteric angle, SMA transposition, left renal autotransplantation, nephrectomy, external stenting of the LRV, and nephropexy.<sup>35,45,80–83</sup> In this section, we describe the most commonly performed open surgical techniques.

The most commonly reported technique to surgically manage anterior NCS is LRV transposition (Fig. 165.3A).<sup>77</sup> This technique is performed transabdominally via a midline

mini-laparotomy, with cephalad and rightward retraction of the small bowel, entrance into the retroperitoneum inferior to the transverse mesocolon<sup>84</sup> and subsequent mobilization of the LRV. This technique requires ligation of the gonadal vein, and frequently ligation of the adrenal and lumbar veins as additional mobilization of the LRV becomes necessary. Following systemic heparin administration and clamping of the IVC, the LRV is transected proximally and is reimplanted caudally into the lateral aspect of the IVC by creating a tension free end-to-side anastomosis. Prior to clamp removal the proximal opening in the IVC is closed using continuous suture. In some instances a saphenous vein patch or cuff may be required with transposition of the LRV (Fig. 165.3B). This is especially important in the case of long-standing NCS, when permanent fibrotic distortion of the LRV may occur secondary to the sequelae of LRV hypertension on the endogenous structure of the vessel wall. A great saphenous vein patch, despite a requirement for an additional incision in the lower extremity, is preferred as it is typically readily available in this younger cohort (i.e., not expended from prior cardiovascular surgery, not affected by superficial venous disease) and carries a lower risk for infection versus synthetic graft material. Similarly, a vein cuff may be needed to gain the additional length required in order to reimplant the left renal vein lower on the inferior vena cava.

Patch venoplasty without LRV transposition is not frequently reported in the literature but is an option in those for whom transposition is not feasible owing to a short LRV, an “overstretched” LRV, or in instances where the extrinsic compression of the LRV would not be alleviated by merely transposing the vein.<sup>72</sup> Overstretching of the LRV is a unique scenario likely resulting from a prominent aorta (as seen in AAA) or an extremely ptotic kidney. Likewise, if the anatomic limitations of the LRV transposition result in an anastomosis in which tension is unavoidable, a tension-free anastomosis can be created by employing a saphenous vein cuff directly to the IVC (Fig. 165.3C).

An additional surgical alternative is gonadal vein transposition (Fig. 165.3D). This technique is feasible and in many cases of NCS it may be the only possible surgical option.<sup>85</sup>

Relatively frequently the refluxing gonadal vein is markedly dilated, and through division of this vessel low in the pelvis, venous reflux that contributes to pelvic congestion can be relieved or eliminated. Additional advantages of this approach include the fact that it can be used to treat patients with posterior and atypical NCS, avoids renal vein clamping or transection, requires only a single anastomosis, and avoids saphenous vein harvest with subsequent incision(s) in the lower extremity. For this technique to be used, the gonadal vessel must be large enough in diameter (approximately 75% or greater of the LRV diameter) to effectively decompress the LRV and the segment of the gonadal vein prior to its branching distally in the pelvis must be long enough to reach the IVC without tension.<sup>85,86</sup> These features of the gonadal vessel are determined by preoperative imaging and confirmed intraoperatively. Gonadal vein transposition is performed through a mini-laparotomy, with Kocherization and cephalad retraction of the viscera, with exposure of the retroperitoneum allowing for intraoperative confirmation of the feasibility of this approach (assessment of the gonadal and renal veins). If the gonadal vein size and length are adequate, mobilization of the gonadal vein with ligation of small side branches is performed to yield enough length to transpose the vessel. Following this, the gonadal vein is transected distally in the pelvis and tunneled posterior to the inferior mesenteric vein. Heparin is administered, and a partially occlusive ("side-biting") clamp is used on the IVC with proximal control obtained on the gonadal vein. Next, a tension free end-to-side anastomosis of the gonadal vein to the IVC is created with simple running suture. After release of clamps, Doppler assessment of the venous flow of the transposed gonadal vein and the newly created anastomosis is performed. Postoperatively, we recommend routine administration of anticoagulation with low-dose heparin (i.v. 250 IU/h). When the patient is able to tolerate PO intake, i.v. anticoagulation is transitioned to oral anticoagulation for next 30 days (coumadin, apixaban or rivaroxaban). Following this we recommend lifelong aspirin (81 mg/day).

Owing to advantages and the technical feasibility of gonadal vein transposition to anterior, posterior and atypical NCS, this has become our preferred strategy for the surgical management of NCS. In the largest case series to date from our institution (18 patients; 17 (94.4%) females), Gilmore et al. showed that GVT was a safe and effective treatment modality for selected NCS patients.<sup>87</sup> During a median follow-up of 178 days, complete symptom relief, partial symptom relief, and transient symptom relief were achieved in 11 patients (61.1%), 4 patients (22.2%), and 2 patients (11.1%), respectively. One patient in the study had no improvement of symptoms. There were no major perioperative complications or mortality during the follow-up period. Given that GVT had comparable safety and efficacy to other described surgical procedures this treatment modality should be considered as a treatment of choice for appropriately selected patients.<sup>87</sup> The relatively limited dissection during operation (in comparison to LRV transposition), including mitigation of necessity for transection and/or manipulation of the LRV with subsequent potential for thrombosis and/or anastomotic stenosis and risk to the kidney, no

leg incision (for the great saphenous vein harvest) and need for only a single anastomosis, coupled with excellent technical and clinical outcomes (decreased morbidity and hospital stay), have led our institutional practice pattern to prefer a "gonadal vein transposition first" type strategy, in patients where transposition is technically feasible as determined by anatomic features, described previously.

Another surgical strategy for the treatment of either anterior or posterior NCS is that of saphenous vein bypass (Fig. 165.3E), which like gonadal vein transposition avoids clamping or transecting the LRV. Great saphenous vein bypass is used in those infrequent situations where transposition of either the LRV or gonadal vein is not feasible. However, in addition to requiring saphenous vein harvest, this procedure requires two anastomoses and clamping of the LRV.

Finally, there are reports of a novel surgical technique that involves the robotic-assisted LRV transposition. Although initial results are promising, evidence pertinent to robotic-assisted surgery is based on a small number of case reports, therefore more studies with a larger number of patients are necessary for more accurate assessment of this relatively novel treatment modality.<sup>88,89</sup> Proponents of robotic-assisted surgery suggest that increase of the range of motion for instrument apposition, the enhanced vision of operative field, and the surgeon's comfort represent its biggest benefits over traditional laparoscopic surgery.<sup>88–90</sup>

Outcomes with open surgery for anterior NCS are well documented and overall yield clinically acceptable outcomes. In one of the larger cohorts, Erben et al. from the Mayo Clinic retrospectively reviewed 37 consecutive patients (36 treated with open surgery) and reported outcomes of using an "LRV transposition-first" strategy over a 20-year period.<sup>77</sup> An average length of hospital stay was  $4.5 \pm 2.7$  days (median  $\pm$  SD). At long-term follow-up ( $36.8 \pm 52.6$  months ([median  $\pm$  SD], range: 1–219 months), the authors reported a recurrence rate of 8.3%.<sup>77</sup> Data also showed that 22.2% of patients required endovascular and open re-intervention due to stenosis and occlusion. At 2-year follow-up, respective rates for primary, primary assisted primary, and secondary patency were 74%, 97%, and 100%.<sup>77</sup> Freedom from re-intervention at 12 and 24 months was 76% and 68%, respectively. Data from this study suggested that patency of LRV reconstruction is best achieved with addition of saphenous vein patch and saphenous venous cuff to optimize venous outflow and to decrease tension of the transposed LRV, respectively.<sup>77</sup> There were no cases of major perioperative complications, renal failure, or mortality.<sup>77</sup>

Other postoperative complications of open surgical procedures for NCS are relatively uncommon and include deep venous thrombosis, retroperitoneal hematoma, paralytic ileus, and the development of chylous ascites.<sup>78,91</sup> The perioperative mortality rate is exceedingly low, likely due to a young and otherwise morbidity-free patient population. We recommend that, in the postoperative phase, 30 days of anticoagulation with novel agents or warfarin should be instituted, with further benefit potentially derived from additional antiplatelet agents (aspirin, clopidogrel), although this has not been examined in the literature to date.

## Open Surgery for Posterior Nutcracker Syndrome

Posterior NCS is challenging from an open surgical perspective because the retro-aortic position of the LRV means that the LRV must be anteriorly transposed if using LRV transposition. Dissection in the narrow window between the vertebral column and aorta poses particular hazard from difficulty to visualize lumbar, perirenal, and other collateral vessels. Additional difficulties may result from neglected or unseen damage to the numerous lymphatic vessels along the aorta in the retroperitoneum, mandating careful ligation to prevent lymph leak and its subsequent morbidity. Much like renal vein transposition as described previously for anterior NCS, anterior LRV transposition may also require a vein patch in the face of long-standing, fibroproliferative disease. In addition, careful attention must be paid because the retro-aortic LRV is particularly friable and prone to damage during its dissection and mobilization.<sup>72</sup> Successful laparoscopic techniques for LRV transposition in anterior and posterior NCS have been described by Hartung et al.<sup>92,93</sup> but are not recommended for routine application, owing to the expertise required to perform a delicate anastomosis in a minimally invasive fashion.

In 2018, Park et al. published a systematic review of literature that included only patients with posterior NCS.<sup>94</sup> They found that when intervention is indicated, open surgery is still the most commonly utilized treatment option. Predictably, data were extrapolated based on a small number of cases (total of 22) due to the low prevalence of posterior NCS, and therefore their findings should be interpreted with caution and in the context of each individualized patient's presentation.

Other strategies used for the open surgical management of posterior NCS include saphenous vein bypass, aortic transposition, as well as gonadal vein transposition.<sup>95</sup> Again, much as in the scenario for anterior NCS, gonadal vein transposition (if technically feasible) has the potential to obviate most of the hazards of dissection in the area of the renal vein. This is magnified in the instance of a retro-aortic LRV. The approach to performing gonadal vein transposition is the same as in anterior NCS.

Complications for the open treatment of posterior NCS are the same as those for anterior NCS. Although a retro-aortic renal vein may be a more frequent anatomic variant than originally thought,<sup>47</sup> treatment of symptomatic posterior NCS is rarely reported in the literature and is limited to case reports and intermittent case series.<sup>4,5,92,95–104</sup> As such, there remains a marked lack of long-term follow-up and description of patient outcomes, with no consensus as to optimal treatment strategies.

## Endovascular Treatment of Nutcracker Syndrome

As with virtually all vascular pathologies, endovascular treatment modalities for NCS treatment have been proposed and utilized. However, as with other compressive entities (i.e., thoracic outlet syndrome, May–Thurner syndrome), endovascular

options have been met with limited success. Initially described by Neste et al. in 1996,<sup>105</sup> the utility of endovascular therapy involves stenting of the LRV. The bulk of the available data describing endovascular treatment of NCS is in the form of case reports.<sup>91,106–109</sup> Relatively recently several larger case series have been described as well.<sup>110,111</sup> Wang et al. reported the results of LRV stenting in 30 NCS patients.<sup>111</sup> At median three years' follow-up (range 12 to 80 months) there was symptomatic improvement in all the patients. However, two patients presented with stent protrusion into the IVC during 1 year's follow-up. As the patients remained asymptomatic at 49 and 56 months' follow-up, the authors have chosen close monitoring over stent removal or surgery for the management of the LRV stent protrusion.<sup>111</sup>

In a case series reported by Chen et al., 61 patients underwent LRV stenting with a median follow-up of 66 months.<sup>110</sup> The authors reported an overwhelmingly positive response in terms of technical success and symptom resolution, as well as a low perioperative complication rate. Complications included maldeployment of a stent requiring open reintervention and stent migration to the right atrium, which was particularly troublesome as it mandated open cardiac surgery. The authors report that the ideal stent should have the properties of high radial strength, conformability, and minimal shrinkage in length, all of which allow for ideal stent positioning.<sup>110</sup> In fact, the propensity for these devices to migrate in this location has led some authors to recommend both the oversizing and positioning of stents from the first division of the LRV.<sup>72</sup> Unfortunately, recent larger series using an "endovascular first" strategy to the treatment of NCS, with longer follow-up times, have demonstrated a 6.7% migration rate of stents, which is higher than initially hypothesized using midterm follow-up data.<sup>107</sup>

In 2019, Avgerinos et al. reported the use of endovascular stenting in 18 patients including five patients with previously failed transposition of the LRV.<sup>112</sup> At a follow-up time of  $41.4 \pm 26.6$  months (mean  $\pm$  SD) 72.2% patients had symptom resolution or improvement. In three patients treated for previously unsuccessful LRV transposition, symptoms persisted after stenting as well, and two of them ultimately required renal autotransplantation. The third patient underwent restenting and was free of restenosis at 52.5 months with partial resolution of symptoms. Overall primary and assisted primary patency rates were 85.2% and 100%, respectively, at 24 months' follow-up and no patient experienced stent migration.<sup>112</sup>

The largest series to date, evaluating 75 patients (49 males, 26 females) who underwent LRV stenting, once again raised concerns regarding stent migration.<sup>113</sup> During a mean 55 months of follow-up (range, 6–126 months) five (6.6%) patients had stent migration, including one each into the right atrium and right ventricle (requiring stent extraction with open cardiac surgery), two into the IVC and one into the proximal LRV. Despite relatively high numbers of stent migration there was no statistically significant difference in relevant anatomical and hemodynamic parameters (the anteroposterior diameter and peak velocity of the aortomesenteric portion and the renal hilum of the LRV) between patients with and without stent migration. However, the authors suggested that diameter of

the stents is a key factor associated with stent migration. Four migrated stents were 14 mm × 40 mm and one was 10 mm × 40 mm.<sup>113</sup> This accentuates the need for venous stents suitable for use in the renal veins.

Given that these stents can migrate to the right-sided circulation or lungs, the high migration rate, as reported, is quite worrisome. The types of endovascular devices used in the larger case series are overwhelmingly self-expanding and include the Wallstent, Palmaz, SmartControl, and self-expanding SMART stents. Other complications from endovascular therapy for NCS include in-stent thrombosis and fracture. Stent protrusion into the IVC, which was initially thought to be concerning, is considered to be safe by others.<sup>91</sup> Antiplatelet medications are a necessity in the postoperative period to minimize the risk of thrombotic complications in relation to the stent.

Despite the report of adequate long-term outcomes using an “endovascular-first” strategy to treat NCS,<sup>107</sup> a major limitation of studies favoring this strategy remains the absence of direct comparisons between open and endovascular therapy for NCS performed in the same era at a single institution, raising additional concerns about the durability of these procedures. In addition, a significant majority of stents described in the current body of literature are stents designed (and intended) for arterial morphology and arterial flow hemodynamic. Moreover, as the cohort of patients treated for NCS are oftentimes in their second or third decades of life, the duration of imaging follow-up required has yet to be established and remains lifelong at this time. Although there are many limitations to this technology as described previously, with the recent expansion of dedicated venous stents in chronic venous insufficiency patients (notably for ileocaval outflow obstruction) it is reasonable to expect that an increased number of dedicated venous stents will be used in patients with NCS in the future with a potential to become a suitable treatment alternative to open surgery.

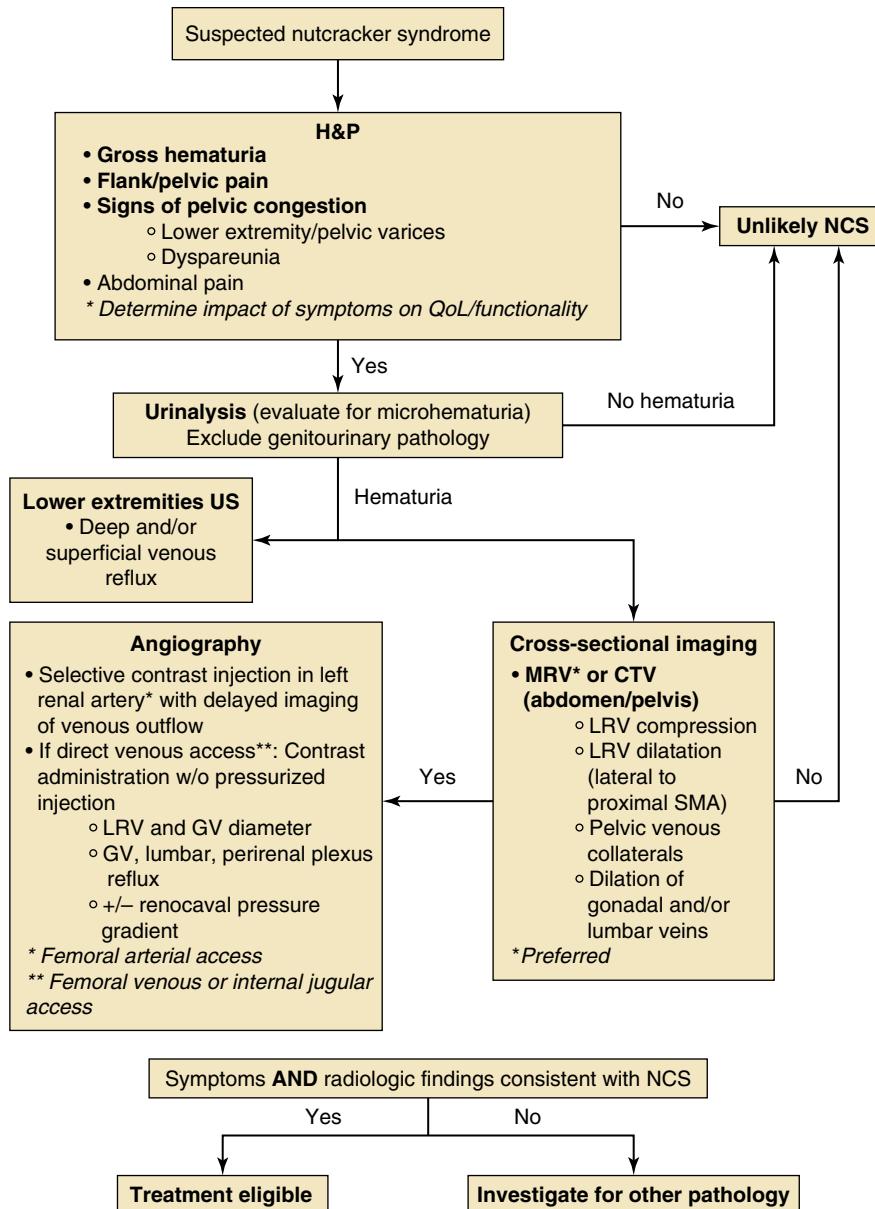
Lastly, based on the premise that each of the above-described treatment modalities has strengths and limitations,

some practitioners are using a “hybrid” approach by combining open surgical and endovascular technique. Although initial data are promising, due to a very small number of patients, more experience is needed for deriving scientifically meaningful conclusion pertinent to hybrid approach technical feasibility, safety and efficacy.<sup>114,115</sup>

## SUMMARY

Management of patients with NCS continues to evolve. NCS has much potential to inflict lifestyle-limiting morbidity in the form of debilitating pain, hematuria, and disfiguring varices in the lower extremities and scrotal/vulvar region. This syndrome is the result of anatomic compression or overstretching of the LRV, with much speculation as to the reasons it may occur in some but not others with anatomic LRV outflow compromise. NCS is often misdiagnosed or at best is diagnosed in its later stages, after the development of renal venous hypertension, which when it becomes symptomatic mandates operative and/or endovascular repair. Although currently there is no gold standard diagnostic test for NCS patients, diagnosis is most efficiently achieved through dedicated clinical examination and characteristic findings on cross-sectional imaging and venography. Therefore, a decision to intervene is based on a combination of clinical presentation, radiologic findings and patient preference. Although there are a variety of operative strategies applicable to this condition, much of this is dictated by the subclass of NCS (anterior or posterior), as well as intraoperative anatomy. Relief of pain and hematuria is frequently achieved with decompression of the LRV. Endovascular strategies have been used and reported more frequently in the recent era, although long-term data are still necessary to prove their safety and efficacy. In the near future, we can expect that further development and use of dedicated venous stents will result in increased safety (primarily pertinent to mitigation of risk for stent migration) and in improved clinical outcomes associated with endovascular treatment of NCS patients.

## CHAPTER ALGORITHM



Algorithm for the diagnosis and management of NCS. CTA, computer tomography with angiography; LRV, left renal vein; MRV, magnetic resonance venography; NCS, nutcracker syndrome.

## SELECTED KEY REFERENCES

Beinart C, Sniderman KW, Saddekni S, et al. Left renal vein hypertension: a cause of occult hematuria. *Radiology*. 1982;145(3):647–650.

*Early series describing the development of left renal vein hypertension and hematuria associated with nutcracker syndrome.*

Chen S, Zhang H, Shi H, et al. Endovascular stenting for treatment of Nutcracker syndrome: report of 61 cases with long-term followup. *J Urol*. 2011;186(2):570–575.

*Large (61 patients) contemporary series describing outcomes of endovascular treatment for nutcracker syndrome.*

El-Sadr AR, Mina E. Anatomical and surgical aspects in the operative management of varicocele. *Urol Cutaneous Rev*. 1950;54(5):257–262.

*One of the earliest reports of nutcracker syndrome.*

Erben Y, Gloviczki P, Kalra M, et al. Treatment of nutcracker syndrome with open and endovascular interventions. *J Vasc Surg Venous Lymphat Disord*. 2015;3(4):389–396.

*Large series reporting outcomes of surgical transposition of the left renal vein.*

Pastershank SP. Left renal vein obstruction by a superior mesenteric artery. *J Can Assoc Radiol*. 1974;25(1):52–54.

*First report describing transposition of the left renal vein for treatment of nutcracker syndrome.*

Said SM, Gloviczki P, Kalra M, et al. Renal nutcracker syndrome: surgical options. *Semin Vasc Surg*. 2013;26(1):35–42.

*Comprehensive review which includes methodology for diagnosis of nutcracker syndrome using CT-derived angles.*

Velasquez CA, Saeyeldin A, Zafar MA, et al. A systematic review on management of nutcracker syndrome. *J Vasc Surg Venous Lymphat Disord*. 2018;6(2):271–278.

*The most recent systematic review that summarizes diagnostic and treatment modalities in the management of nutcracker syndrome.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. Kurklinsky AK, Rooke TW. Nutcracker phenomenon and nutcracker syndrome. *Mayo Clin Proc.* 2010;85(6):552–559.
2. Velasquez CA, Saeeldin A, Zafar MA, et al. A systematic review on management of nutcracker syndrome. *J Vasc Surg Ven Lymphat Disord.* 2018;6(2):271–278.
3. Alaygut D, Bayram M, Soylu A, et al. Clinical course of children with nutcracker syndrome. *Urology.* 2013;82(3):686–690.
4. Ali-El-Dein B, Osman Y, Shehab El-Din AB, et al. Anterior and posterior nutcracker syndrome: a report on 11 cases. *Transplant Proc.* 2003;35(2):851–853.
5. Skeik N, Gloviczk P, Macedo TA. Posterior nutcracker syndrome. *Vasc Endovasc Surg.* 2011;45(8):749–755.
6. Liebl R. Nutcracker phenomenon or nutcracker syndrome? *Nephrol Dial Transplant.* 2005;20(9):2009.
7. Shin JI, Lee JS. Nutcracker phenomenon or nutcracker syndrome? *Nephrol Dial Transplant.* 2005;20(9):2015.
8. Shin JI, Lee JS. Nutcracker. *Lancet.* 2005;365(9478):2177–2178.
9. Yun SJ, Lee JM, Nam DH, et al. Discriminating renal nutcracker syndrome from asymptomatic nutcracker phenomenon using multidetector computed tomography. *Abdom Radiol (NY).* 2016;41(8):1580–1588.
10. Dunphy L, Penna M, Tam E, El-Kafsi J. Left renal vein entrapment syndrome: nutcracker syndrome. *BMJ Case Rep.* 2019;2019(12):e230877.
11. Hangge PT, Gupta N, Khurana A, et al. Degree of left renal vein compression predicts nutcracker syndrome. *J Clin Med.* 2018;7(5):107.
12. Hanif MO, Aggarwal S. Left renal vein obstruction. *StatPearls.* Treasure Island, FL: StatPearls Publishing; 2020.
13. Orczyk K, Wysiadecki G, Majos A, et al. What each clinical anatomist has to know about left renal vein entrapment syndrome (nutcracker syndrome): a review of the most important findings. *Bio Med Res Int.* 2017;2017:1746570.
14. Peterson J, Hage AN, Diljak S, et al. Incidental anatomic finding of celiacomesenteric trunk associated with ‘nutcracker phenomenon,’ or compression of the left renal vein. *Am J Case Rep.* 2017;18:1334–1342.
15. Koshimichi M, Sugimoto K, Yanagida H, et al. Newly-identified symptoms of left renal vein entrapment syndrome mimicking orthostatic disturbance. *World J Pediatr.* 2012;8(2):116–122.
16. Orczyk K, Labetowicz P, Lodzinski S, et al. The nutcracker syndrome. Morphology and clinical aspects of the important vascular variations: a systematic study of 112 cases. *Int Angiol.* 2016;35(1):71–77.
17. Ragazzi M, Milani G, Edefonti A, et al. Left renal vein entrapment: a frequent feature in children with postural proteinuria. *Pediatr Nephrol.* 2008;23(10):1837–1839.
18. Sugimoto K, Fujita S, Miyazawa T, et al. Pediatric left renal vein entrapment syndrome diagnosed by 99mTc-albumin-conjugate scintigraphy. *Nephron Clin Pract.* 2012;122(3–4):122–126.
19. Tago M, Katsuki NE, Hirakawa Y, Yamashita SI. Asymptomatic nutcracker phenomenon: entrapment of the left renal vein shown by CT without left flank or pelvic pain, or macroscopic haematuria. *BMJ Case Rep.* 2020;13(1):e233867.
20. Vianello FA, Mazzoni MB, Peeters GG, et al. Micro- and macroscopic hematuria caused by renal vein entrapment: systematic review of the literature. *Pediatr Nephrol.* 2016;31(2):175–184.
21. Barnes RW, Fleisher HL 3rd, Redman JF, et al. Meso-aortic compression of the left renal vein (the so-called nutcracker syndrome): repair by a new stenting procedure. *J Vasc Surg.* 1988;8(4):415–421.
22. Rudloff U, Holmes RJ, Prem JT, et al. Meso-aortic compression of the left renal vein (nutcracker syndrome): case reports and review of the literature. *Ann Vasc Surg.* 2006;20(1):120–129.
23. Yang WJ, Liu YP, Yang FS. Meso-aortic compression of left renal vein revealed by multidetector computed tomography: nutcracker syndrome. *Emerg Med J.* 2007;24(9):636.
24. Grant JCB. *Methods of Anatomy.* Baltimore, MD: Williams & Wilkins; 1937:158.
25. El-Sadr AR, Mina E. Anatomical and surgical aspects in the operative management of varicocele. *Urol Cutaneous Rev.* 1950;54(5):257–262.
26. Chait A, Matasar KW, Fabian CE, Mellins HZ. Vascular Impressions on the uterus. *Am J Roentgenol.* 1971;111(4):729–749.
27. de Schepper A. [“Nutcracker” phenomenon of the renal vein and venous pathology of the left kidney]. *J Belge de Radiologie.* 1972;55(5):507–511.
28. Pastershank SP. Left renal vein obstruction by a superior mesenteric artery. *J Canad Assoc Radiol.* 1974;25(1):52–54.
29. Mahmood SK, Oliveira GR, Rosovsky RP. An easily missed diagnosis: flank pain and nutcracker syndrome. *BMJ Case Rep.* 2013;2013:bcr2013009447.
30. He Y, Wu Z, Chen S, et al. Nutcracker syndrome--how well do we know it? *Urology.* 2014;83(1):12–17.
31. Poyraz AK, Firdolas F, Onur MR, Kocakoc E. Evaluation of left renal vein entrapment using multidetector computed tomography. *Acta Radiologica.* 2013;54(2):144–148.
32. Ozkurt H, Cenker MM, Bas N, et al. Measurement of the distance and angle between the aorta and superior mesenteric artery: normal values in different BMI categories. *Surg Radiol Anat.* 2007;29(7):595–599.
33. Matsukura H, Arai M, Miyawaki T. Nutcracker phenomenon in two siblings of a Japanese family. *Pediatr Nephrol.* 2004;20(2):237–238.
34. Radisic MV, Feldman D, Diaz C, Froment RO. Unexplained hematuria during pregnancy: right-sided nutcracker phenomenon. *Int Urol Nephrol.* 2006;39(3):709–711.
35. Ariyoshi A, Nagase K. Renal hematuria caused by “nutcracker” phenomenon: A more logical surgical management. *Urology.* 1990;35(2):168–170.
36. Menard MT. Nutcracker syndrome: when should it be treated and how? *Perspect Vasc Surg Endovasc Ther.* 2009;21(2):117–124.
37. Hohenfellner M, Steinbach F, Schultz-Lampel D, et al. The nutcracker syndrome: new aspects of pathophysiology, diagnosis and treatment. *J Urol.* 1991;146(3):685–688.
38. Satyapal KS, Rambiritch V, Pillai G. Morphometric analysis of the renal veins. *Anatom Record.* 1995;241(2):268–272.
39. Kim SH, Cho SW, Kim HD, et al. Nutcracker syndrome: diagnosis with Doppler US. *Radiology.* 1996;198(1):93–97.
40. Dos Santos SJ, Holdstock JM, Harrison CC, et al. Ovarian Vein Diameter Cannot Be Used as an Indicator of Ovarian Venous Reflux. *Eur J Vasc Endovasc Surg.* 2015;49(1):90–94.
41. Arima M, Hosokawa S, Ogino T, et al. Ultrasonographically demonstrated nutcracker phenomenon: Alternative to angiography. *Int Urol Nephrol.* 1990;22(1):3–6.
42. Zhang H, Li M, Jin W, et al. The left renal entrapment syndrome: diagnosis and treatment. *Ann Vasc Surg.* 2007;21(2):198–203.
43. Kim KW, Cho JY, Kim SH, et al. Diagnostic value of computed tomographic findings of nutcracker syndrome: correlation with renal venography and renocaval pressure gradients. *Eur J Radiol.* 2011;80(3):648–654.
44. Wendel RG, David Crawford E, Hehman KN. The “nutcracker” phenomenon: an unusual cause for renal varicosities with hematuria. *J Urol.* 1980;123(5):761–763.
45. Shokeir AA, El-Diasty TA, Ghoneim MA. The nutcracker syndrome: new methods of diagnosis and treatment. *Br J Urol.* 1994;74(2):139–143.
46. Shaper KR, Jackson JE, Williams G. The nutcracker syndrome: an uncommon cause of haematuria. *Br J Urol.* 1994;74(2):144–146.
47. Heidler S, Hruby S, Schwarz S, et al. Prevalence and incidence of clinical symptoms of the retroaortic left renal vein. *Urologia Int.* 2015;94(2):173–176.
48. Aljabri B, MacDonald PS, Satin R, et al. Incidence of major venous and renal anomalies relevant to aortoiliac surgery as demonstrated by computed tomography. *Ann Vasc Surg.* 2001;15(6):615–618.
49. Panagar AD, Subhash RLP, Suresh BS, Nagaraj DN. Circumaortic left renal vein—a rare case report. *J Clin Diagn Res.* 2014;8(3):111–112.
50. Ahmed K, Sampath R, Khan MS. Current trends in the diagnosis and management of renal nutcracker syndrome: a review. *Eur J Vasc Endovasc Surg.* 2006;31(4):410–416.
51. Yildiz AE, Cayci FS, Genc S, et al. Right nutcracker syndrome associated with left-sided inferior vena cava, hemiazygos continuation

- and persistant left superior vena cava: a rare combination. *Clin Imag*. 2014;38(3):340–345.
52. Sculetus AH, Villavicencio JL, Gillespie DL. The nutcracker syndrome: its role in the pelvic venous disorders. *J Vasc Surg*. 2001;34(5):812–819.
  53. Russo D, Minutolo R, Iaccarino V, et al. Gross hematuria of uncommon origin: The nutcracker syndrome. *Am J Kidney Dis*. 1998;32(3):e3.1–e3.4.
  54. Shin JI, Park JM, Lee SM, et al. Factors affecting spontaneous resolution of hematuria in childhood nutcracker syndrome. *Pediatr Nephrol*. 2005;20(5):609–613.
  55. MacMahon HE, Latorraca R. Essential Renal Hematuria. *J Urol*. 1954;71(6):667–676.
  56. Pytel A. Renal Fornical Hemorrhages: Their Pathogenesis and Treatment. *J Urol*. 1960;83(6):783–789.
  57. Beinart C, Sniderman KW, Saddekni S, et al. Left renal vein hypertension: a cause of occult hematuria. *Radiology*. 1982;145(3):647–650.
  58. Low AI, Matz LR. Haematuria and Renal Fornical Lesions. *Br J Urol*. 1972;44(6):681–691.
  59. Ekim M, Özçakar ZB, Fitoz S, et al. The “nutcracker phenomenon” with orthostatic proteinuria: case reports. *Clin Nephrol*. 2006;65(04):280–283.
  60. Coolsaet BLRA. Ureteric pathology in relation to right and left gonadal veins. *Urology*. 1978;12(1):40–49.
  61. O’Brien MT, Gillespie DL. Diagnosis and treatment of the pelvic congestion syndrome. *J Vasc Surg*. 2015;3(1):96–106.
  62. Li S, Liu Q, Wang J, et al. Association between left renal vein entrapment and varicocele recurrence: a cohort study in 3042 patients. *Scient Rep*. 2018;8(1):10534.
  63. Takebayashi S, Ueki T, Ikeda N, Fujikawa A. Diagnosis of the nutcracker syndrome with color Doppler sonography: correlation with flow patterns on retrograde left renal venography. *Am J Roentgenol*. 1999;172(1):39–43.
  64. Wolfish NM, McLaine PN, Martin D. Renal vein entrapment syndrome: frequency and diagnosis. A lesson in conservatism. *Clin Nephrol*. 1986;26(2):96–100.
  65. Buschi AJ, Harrison RB, Norman A, et al. Distended left renal vein: CT/sonographic normal variant. *Am J Roentgenol*. 1980;135(2):339–342.
  66. Cardarelli-Leite L, Velloni FG, Salvadori PS, et al. Abdominal vascular syndromes: characteristic imaging findings. *Radiol Bras*. 2016;49(4):257–263.
  67. Taylor KJ, Holland S, Doppler US. Part I. Basic principles, instrumentation, and pitfalls. *Radiology*. 1990;174(2):297–307.
  68. Fitoz S, Ekim M, Ozçakar ZB, et al. Nutcracker syndrome in children. *J Ultra Med*. 2007;26(5):573–580.
  69. Park SJ, Lim JW, Cho B-S, et al. Nutcracker syndrome in children with orthostatic proteinuria. *J Ultra Med*. 2002;21(1):39–45.
  70. Butros SR, Liu R, Oliveira GR, Ganguli S, Kalva S. Venous compression syndromes: clinical features, imaging findings and management. *Br J Radiol*. 2013;86(1030):20130284.
  71. Kim KW, Cho JY, Kim SH, et al. Diagnostic value of computed tomographic findings of nutcracker syndrome: Correlation with renal venography and renocaval pressure gradients. *Eur J Radiol*. 2011;80(3):648–654.
  72. Said SM, Gloviczki P, Kalra M, et al. Renal nutcracker syndrome: Surgical options. *Sem Vasc Surg*. 2013;26(1):35–42.
  73. Wong HI, Chen MCY, Wu CS, et al. The usefulness of fast-spin-echo T2-weighted MR imaging in Nutcracker syndrome: a case report. *Korean J Radiol*. 2010;11(3):373–377.
  74. Er A, Uzunlulu N, Guzelbey T, et al. The nutcracker syndrome: The usefulness of different MRI sequences for diagnosis and follow-up. *Clin Imag*. 2019;55:144–147.
  75. Zerhouni EA, Siegelman SS, Walsh PC, White RI. Elevated pressure in the left renal vein in patients with varicocele: preliminary observations. *J Urol*. 1980;123(4):512–513.
  76. Nishimura Y, Fushiki M, Yoshida M, et al. Left renal vein hypertension in patients with left renal bleeding of unknown origin. *Radiology*. 1986;160(3):663–667.
  77. Erben Y, Gloviczki P, Kalra M, et al. Treatment of nutcracker syndrome with open and endovascular interventions. *J Vasc Surg Venous Lymphat Disord*. 2015;3(4):389–396.
  78. Reed NR, Kalra M, Bower TC, et al. Left renal vein transposition for nutcracker syndrome. *J Vasc Surg*. 2009;49(2):386–393; discussion 393–394.
  79. Miro I, Serrano A, Perez-Ardavin J, et al. Eighteen years of experience with pediatric nutcracker syndrome: the importance of the conservative approach. *J Pediatr Urol*. 2020;16(2):218.e1–218.e6.
  80. Shaper KRL, Jackson JE, Williams G. The nutcracker syndrome: an uncommon cause of haematuria. *Br J Urol*. 1994;74(2):144–146.
  81. Thompson PN, Darling RC, Chang BB, Shah DM, Leather RP. A case of nutcracker syndrome: Treatment by mesoaoortictransposition. *J Vasc Surg*. 1992;16(4):663–665.
  82. Stewart BH, Reiman G. Left renal venous hypertension “nutcracker” syndrome. *Urology*. 1982;20(4):365–369.
  83. Amaral J, Honjo O, Hannick JH, et al. In situ gonadal vein valvulotomy and side-to-side gonado-iliac bypass for the management of nutcracker syndrome in an adolescent with a solitary kidney and absence of pelvic congestion. *Urology*. 2019;126:200–203.
  84. Denchev B, Domuschieva E, Jelev G, et al. Surgical treatment of a patient with nutcracker syndrome via transposition of the left renal vein. *EJVES Short Rep*. 2018;41:10–12.
  85. Markovic J, Shortell C. Right gonadal vein transposition for the treatment of anterior nutcracker syndrome in a patient with left-sided inferior vena cava. *J Vasc Surg Venous Lymphat Disord*. 2016;4(3):340–342.
  86. Miler R, Shang EK, Park WM. Gonadal vein transposition in nutcracker syndrome. *Ann Vasc Surg*. 2018;46:205:e13–e16.
  87. Gilmore BF, Benrashid E, Geersen D, Shortell CK. Gonadal vein transposition is a safe and effective treatment of nutcracker syndrome. *J Vasc Surg Venous Lymphat Disord*. 2021;9(3):712–719.
  88. Chau AH, Abdul-Muhsin H, Peng X, et al. Robotic-assisted left renal vein transposition as a novel surgical technique for the treatment of renal nutcracker syndrome. *J Vasc Surg Cases Innov Tech*. 2018;4(1):31–34.
  89. Wang P, Jing T, Qin J, et al. Robotic-assisted Laparoscopic Transposition Of The Left Renal Vein For Treatment Of The Nutcracker Syndrome. *Urology*. 2015;86(6):e27–28.
  90. van der Schatte Olivier RH, Van’t Hullenaar CD, Ruurda JP, Broeders IA. Ergonomics, user comfort, and performance in standard and robot-assisted laparoscopic surgery. *Surg Endoscopy*. 2009;23(6):1365–1371.
  91. Hartung O, Grisoli D, Boufi M, et al. Endovascular stenting in the treatment of pelvic vein congestion caused by nutcracker syndrome: lessons learned from the first five cases. *J Vasc Surg*. 2005;42(2):275–280.
  92. Hartung O, Barthelemy P, Berdah SV, Alimi YS. Laparoscopy-assisted left ovarian vein transposition to treat one case of posterior nutcracker syndrome. *Ann Vasc Surg*. 2009;23(3):413.e13–16.
  93. Hartung O, Azghari A, Barthelemy P, et al. Laparoscopic transposition of the left renal vein into the inferior vena cava for nutcracker syndrome. *J Vasc Surg*. 2010;52(3):738–741.
  94. Park JH, Lee GH, Lee SM, et al. Posterior nutcracker syndrome - a systematic review. *Vasa*. 2018;47(1):23–29.
  95. Li X, Ji C, Guo H. Abdominal aortic transposition as a treatment alternative for posterior nutcracker syndrome. *Int J Urol*. 2012;19(11):1043–1044.
  96. Allam SR, Livingston TS, Kalaria V, et al. Posterior nutcracker syndrome: an infrequent cause of hematuria. *Kidney Int*. 2014;85(4):985–986.
  97. Chen Y, Xing J, Liu F. Left renal vein transposition is effective for posterior nutcracker syndrome. *Int J Clin Exp Med*. 2014;7(12):5925–5927.

98. Deser SB, Onem K, Demirag MK, Buyukalpelli R. Surgical treatment of posterior nutcracker syndrome presented with hyperaldosteronism. *Int Cardiovasc Thor Surg.* 2016;22(5):682–684.
99. Granata A, Clementi A, Floccari F, et al. An unusual case of posterior nutcracker syndrome. *Clin Exp Nephrol.* 2014;18(4):670–671.
100. Marone EM, Psacharopulo D, Kahlberg A, et al. Surgical treatment of posterior nutcracker syndrome. *J Vasc Surg.* 2011;54(3):844–847.
101. Quinones-Baldrich WJ. Posterior nutcracker syndrome in a child. *J Vasc Surg.* 2015;61(2):511.
102. Syed F, Lam Q, Maharjan N, et al. Diagnosis and successful surgical management of posterior nutcracker syndrome in a patient with loin pain hematuria. *J Ark Med Soc.* 2015;111(12):254–256.
103. Zhang X, Wang S, Wei J. Prosthetic left renocaval bypass for posterior nutcracker syndrome. *Indian J Surg.* 2015;77(Suppl 1):103–105.
104. Shah D, Qiu X, Shah A, Cao D. Posterior nutcracker syndrome with left renal vein duplication: An uncommon cause of hematuria. *Int J Surg Case Rep.* 2013;4(12):1142–1144.
105. Neste MG, Narasimham DL, Belcher KK. Endovascular stent placement as a treatment for renal venous hypertension. *J Vasc Intervent Radiol.* 1996;7(6):859–861.
106. Park YB, Lim SH, Ahn JH, et al. Nutcracker syndrome: intravascular stenting approach. *Nephrol Dialysis Transplant.* 2000;15(1):99–101.
107. Quevedo HC, Arain SA, Abi Rafeh N. Systematic review of endovascular therapy for nutcracker syndrome and case presentation. *Cardiovasc Revasc Med.* 2014;15(5):305–307.
108. Chiesa R, Anzuini A, Marone EM, et al. Endovascular Stenting for the Nutcracker Phenomenon. *J Endovasc Ther.* 2001;8(6):652–655.
109. Feng K-K, Huang C-Y, Hsiao C-Y, et al. Endovascular stenting for nutcracker syndrome. *J Chin Med Assoc.* 2013;76(6):350–353.
110. Chen S, Zhang H, Shi H, et al. Endovascular stenting for treatment of Nutcracker syndrome: report of 61 cases with long-term followup. *J Urol.* 2011;186(2):570–575.
111. Wang X, Zhang Y, Li C, Zhang H. Results of endovascular treatment for patients with nutcracker syndrome. *J Vasc Surg.* 2012;56(1):142–148.
112. Avgerinos ED, Saadeddin Z, Humar R, et al. Outcomes of left renal vein stenting in patients with nutcracker syndrome. *J Vasc Surg Venous Lymphat Disord.* 2019;7(6):853–859.
113. Wu Z, Zheng X, He Y, et al. Stent migration after endovascular stenting in patients with nutcracker syndrome. *J Vasc Surg Venous Lymphat Disord.* 2016;4(2):193–199.
114. Jayaraj A, Gloviczki P, Peeran S, Canton L. Hybrid intervention for treatment of the nutcracker syndrome. *J Vasc Surg Cases.* 2015;1(4):268–271.
115. Stawiarski K, Wosnitza M, Erben Y. A novel hybrid left renal vein transposition and endovascular stenting technique for the treatment of posterior nutcracker syndrome. *J Vasc Surg Cases Innovat Tech.* 2017;3(3):142–145.

# Venous Aneurysms and their Management

VICTOR J. DAVILA and SAMUEL R. MONEY

## INTRODUCTION 2195

### LOWER EXTREMITY VENOUS ANEURYSMS 2196

#### Lower Extremity Superficial Venous Aneurysms 2196

#### Lower Extremity Deep Venous Aneurysms 2196

### ABDOMINAL VENOUS ANEURYSMS 2198

#### Inferior Vena Cava 2198

### Visceral Venous Aneurysms 2198

### UPPER EXTREMITY AND INTERNAL JUGULAR VENOUS ANEURYSMS 2200

#### Upper Extremity Superficial Venous Aneurysms 2200

#### Upper Extremity Deep Venous Aneurysms 2200

#### Jugular Venous Aneurysms 2200

### CONCLUSION 2201

## INTRODUCTION

Aneurysms are abnormal dilations of blood vessels and occur most commonly in arteries. Venous aneurysms are rare but have been reported throughout the veins in the body, including the extremities, head and neck, and abdomen.

When defining venous aneurysms, Gillespie et al. state: “The definition of a venous aneurysm has been controversial. A venous aneurysm is best described as a solitary area of venous dilation that communicates with a main venous structure by a single channel, and it must have no association with an arteriovenous communication or a pseudoaneurysm. Most importantly, it should not be contained within a segment of a varicose vein.”<sup>1</sup> In general, venous aneurysms can be defined as an area of dilation 2 to 3 times the surrounding normal vein.<sup>1,2</sup> They are rare and generally asymptomatic; thus, the true incidence is unknown.

Venous aneurysms can be classified as primary (congenital) or secondary (acquired). Primary aneurysms are caused by a weakness in the venous wall secondary to inherited conditions such as Klippel–Trénaunay syndrome, neurofibromatosis 1 (NF-1), and Parkes Weber syndrome (discussed more fully in Chapter 171, Congenital Vascular Malformations: Surgical Management).<sup>3</sup> Secondary venous aneurysms arise from etiologies such as trauma, inflammation, degenerative processes, mechanical stress, and venous hypertension. Some case reports describe a correlation between pregnancy and venous aneurysm formation, but no causative factors have been elucidated.<sup>4</sup> Scientific publications identify the presence of estrogen

receptors in venous vascular tissue, and although it is tempting to hypothesize causality, this has not been established.<sup>5–7</sup>

Histologically, the intima of venous aneurysms may be thickened and fibrosed. In addition, the media may be attenuated or absent and display a paucity or total lack of smooth muscle cells. Matrix metalloproteinases (MMPs) have been noted to be expressed at higher levels in venous aneurysms compared with normal venous tissue. The established relationship between MMPs and arterial aneurysms is long standing, but more research is needed to document this relationship in venous aneurysms.<sup>8</sup>

Clinically, patients with venous aneurysms are usually asymptomatic; however, complications can occur and include thrombosis, embolization, rupture, local mass effects with or without edema, and localized pain or tenderness. Diagnosis may be made with physical examination in the case of superficial venous aneurysms; however, they are often misdiagnosed as soft tissue masses or even hernias.<sup>1</sup> Diagnostic confirmation can be performed using duplex ultrasound (DUS), computed tomography, or magnetic resonance imaging. Venography is not indicated for primary diagnosis. A thorough history should be elicited from the patient, specifically inquiring about family history of aneurysmal or connective tissue disease and any recent or remote trauma to the region. In addition, physical examination should identify any sequela of arteriovenous fistula, with imaging studies performed if needed.

Treatment of venous aneurysms is performed on a case-by-case basis because there are few evidence-based studies to guide treatment. In general, conservative management is indicated for small and/or asymptomatic aneurysms. Surgical treatment

for large aneurysms or those associated with complications consists of tangential aneurysmectomy, aneurysm resection with primary anastomosis, aneurysm resection with interposition grafting, or ligation of the affected venous segment. There is no standard endovascular treatment, but endovascular modalities have been successfully implemented in select patients.<sup>9–11</sup>

## LOWER EXTREMITY VENOUS ANEURYSMS

### Lower Extremity Superficial Venous Aneurysms

Superficial venous aneurysms are usually visible and present as painless masses, often misdiagnosed as soft tissue masses. Depending on the location, these aneurysms can be confused with hygromas, or even inguinal or femoral hernias.<sup>1</sup> Thorough physical examination may identify a superficial venous aneurysm because the mass is more resistant to compression in the dependent position compared with when the extremity is elevated. DUS can definitively make the diagnosis. Saphenous vein aneurysms have been diagnosed during operative procedures for what were thought to be varicose veins preoperatively. Venous aneurysms on the dorsum of the foot have been described and are usually asymptomatic. Interestingly, all case reports of pedal venous aneurysms involve young women.<sup>12</sup>

Treatment of superficial venous aneurysms involves ligation and excision after ensuring that the deep venous system is intact. If the aneurysm is near the saphenofemoral junction, traditionally a high ligation should also be performed. Hamman et al. described their experience with endovenous thermal ablation of incompetent saphenous veins with associated aneurysms. They treated 15 limbs in 13 patients who had saphenous vein aneurysms within 20 mm of the saphenofemoral or saphenopopliteal junction. Venous segments were considered aneurysmal if they were greater than 20 mm in the greater saphenous vein and greater than 15 mm in the small saphenous vein. High ligation was concomitantly performed if the aneurysms were greater than 30 mm in greatest dimension. The authors reported no instances of endovenous heat-induced thrombosis class 2–4, deep vein thrombosis, or pulmonary embolism.<sup>13</sup>

Aneurysms of perforating veins in the lower extremity have been described only rarely. This may be secondary to the lack of specific symptoms. Ultrasound is diagnostic when the size of the perforating venous aneurysms exceeds 9 mm. Although these aneurysms are located below the deep fascia, they are included in the superficial venous aneurysm section because they are often treated the same way superficial refluxing veins are treated – subfascial ligation with or without aneurysm excision. Aneurysms are excised if they are symptomatic. Labropoulos et al. also noted that these aneurysms are usually fusiform and recommended treatment if perforating vein treatment was undertaken. That group found no relation between the sizes of perforating vein aneurysms and the severity of chronic venous disease.<sup>14</sup>

### Lower Extremity Deep Venous Aneurysms

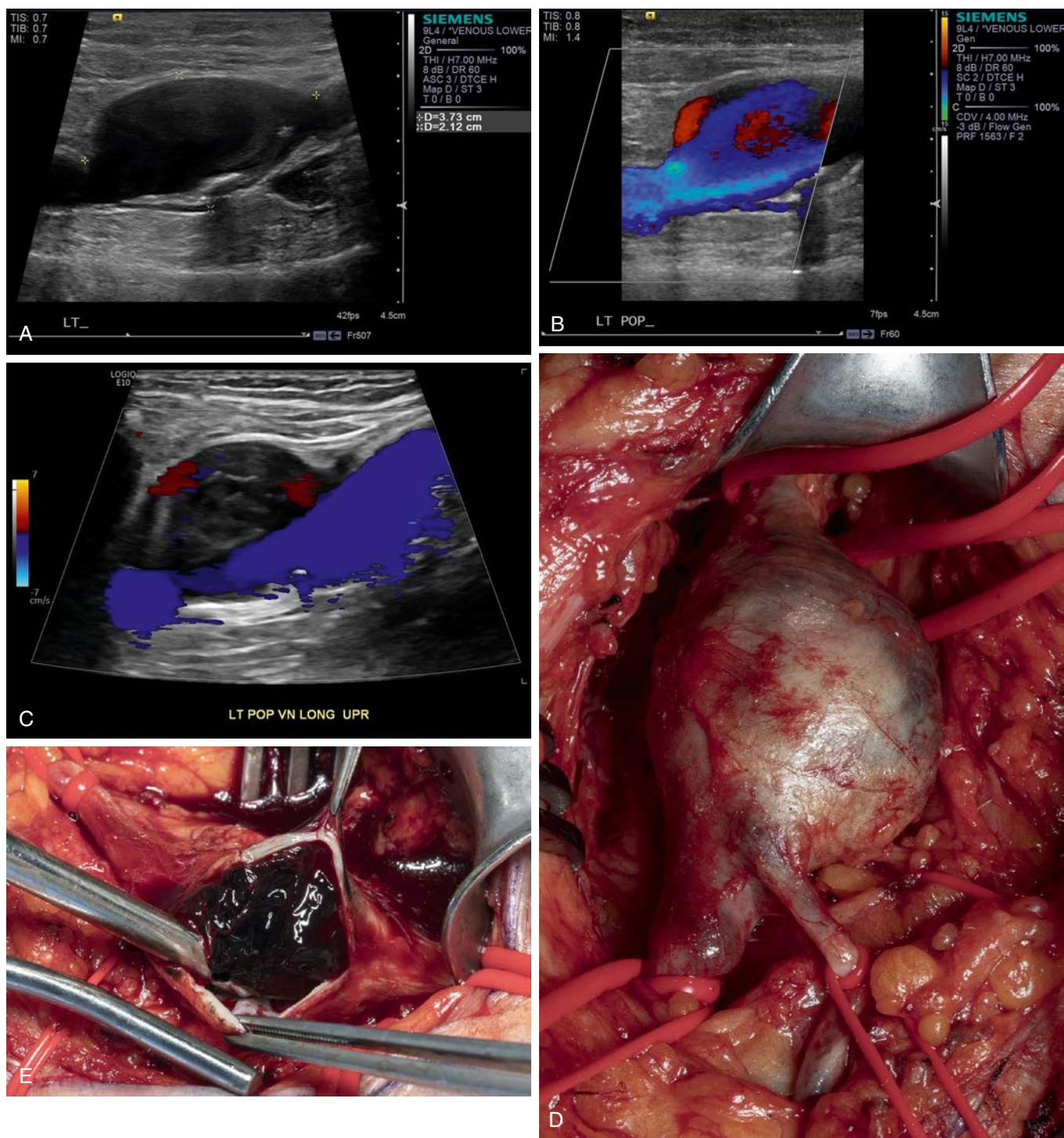
Popliteal venous aneurysms (Fig. 166.1) are the most commonly reported and best studied of all venous aneurysms. Evidence from previous studies suggests that popliteal venous

aneurysms are more commonly associated with complications than aneurysms in the superficial system. These complications include thrombosis, pulmonary embolism, localized pain and swelling, more diffuse lower extremity swelling, and symptoms of chronic venous disease. In one of the largest case series, 24 cases of popliteal venous aneurysm were identified; all patients presented with thromboembolic disease. Seventy-one percent presented with pulmonary embolism.<sup>15</sup> Other studies have shown that most popliteal venous aneurysms (45%–80%) are discovered incidentally during work-up after patients have suffered a pulmonary embolism.<sup>16,17</sup>

Noppeneij et al. described their retrospective analysis of 39 patients treated for popliteal venous aneurysms from 1992 to 2018. Their treatment algorithm consisted of evaluation for popliteal venous aneurysm size and turbulent flow within the aneurysm sac. Generally, patients with aneurysms larger than 20 mm also had turbulent flow and thus were offered resection. There were 4 of 29 patients who did not have turbulent flow in an aneurysm greater than 20 mm. These were noted to be stable without evidence of thrombus formation during the surveillance period. Patients with aneurysms less than 20 mm were split evenly between those with turbulent flow ( $n = 5$ ) and those without turbulent flow ( $n = 5$ ). All 5 patients with turbulent flow and 1 patient without turbulent flow (patient preference) were reconstructed. The 4 patients without turbulent flow were noted to have stable aneurysm size without evidence of thrombus during the surveillance period.<sup>18</sup>

Asymptomatic patients with aneurysms less than 20 mm can be serially monitored with ultrasound to evaluate for progression. Symptomatic patients, particularly those who have suffered a pulmonary embolus, should be treated regardless of aneurysm size. Anticoagulation alone is not considered sufficient treatment for popliteal venous aneurysms. Patients can develop thrombus when therapeutically anticoagulated even when no thrombus was identified on initial diagnosis. Thrombus burden localized to the popliteal venous aneurysm has been shown to predispose to pulmonary embolus even when patients are therapeutically anticoagulated.<sup>19,20</sup> Surgical reconstruction is preferred in these cases and consists of tangential aneurysmectomy with lateral venorrhaphy, aneurysm resection with primary anastomosis, interposition grafting with saphenous vein, or spiral saphenous vein interposition grafting.<sup>21</sup> If no other option is available, a synthetic bypass can be used, but postoperative thrombosis is more common. Tangential aneurysmectomy with lateral venorrhaphy (Fig. 166.2) is the preferred method of reconstruction.<sup>22</sup> Inferior vena cava (IVC) filter placement and catheter-directed lysis should be considered on a case-by-case basis, taking into account patient-specific variables such as ability to tolerate anticoagulation and concomitant extent of ipsilateral deep venous thrombosis. Patients are routinely placed on anticoagulation for 3 to 6 months after all procedures.

Another method for popliteal venous aneurysm repair is described by Beaulieu et al. Closed plication of the aneurysm is accomplished by tangential plication with pledgeted suture. This method was performed in nine patients with reasonable outcomes. The benefits include no routine postoperative anticoagulation and avoiding the need for proximal and distal control of the aneurysm. Limitations include contraindication



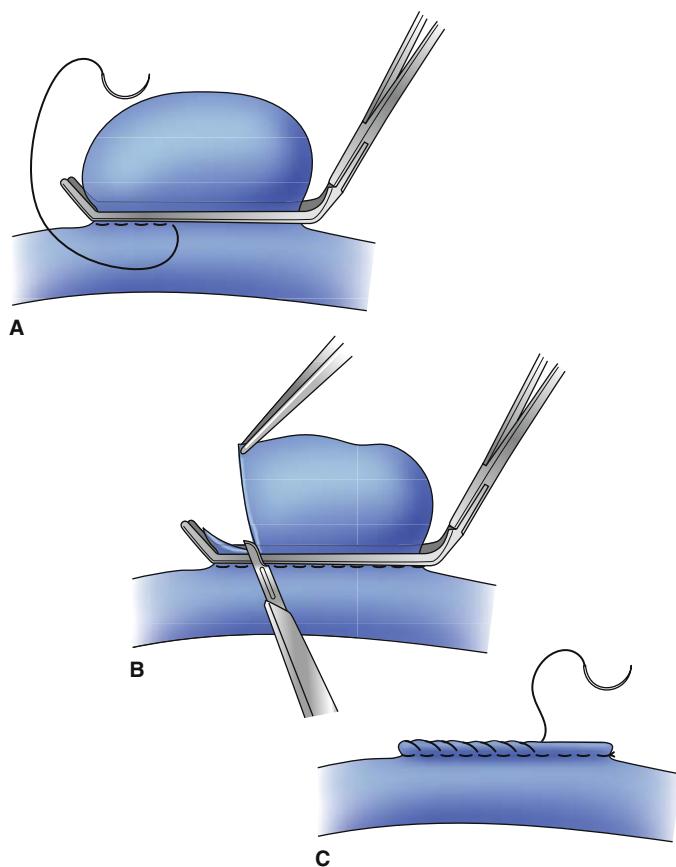
**Figure 166.1** (A) Ultrasound image demonstrating turbulent flow in popliteal venous aneurysm. (B) Color flow image demonstrating turbulent flow in popliteal venous aneurysm. (C) Ultrasound image demonstrating thrombus in popliteal venous aneurysm. (D) Intraoperative photo of dissected popliteal venous aneurysm. (Photo: Nathan M. Wallace). (E) Intraoperative photo of luminal thrombus in popliteal venous aneurysm. (Photo: Nathan M. Wallace). (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.).

in the setting of mural thrombus and the utilization of prosthetic material (pledget). The authors did not experience a deep surgical site infection in their series.<sup>23</sup>

Due to their rarity, few studies exist to guide the treatment of femoral and common femoral venous aneurysms. We believe that, extrapolating from the popliteal venous aneurysm literature, symptomatic aneurysms should be treated surgically and asymptomatic venous aneurysms can be monitored for

increase in size and/or development of intraluminal thrombus if they are small on discovery.

Iliac vein aneurysms are rare. Rupture was reported in one case of a large external iliac vein aneurysm.<sup>15</sup> More commonly these aneurysms are asymptomatic and discovered incidentally or during evaluation for other pathology such as pulmonary embolism. Zarrintan et al. performed a review of 50 iliac vein aneurysms in the literature. Gender differences were noted in



**Figure 166.2** (A) Illustration of technique of tangential aneurysmectomy with lateral venorrhaphy. Clamp is placed at base of aneurysm without compromising lumen of popliteal vein. Vein walls are approximated by undersewing clamp with running horizontal mattress suture. (B) Aneurysm is resected flush with vascular clamp. (C) Second, reinforcing running stitch is placed, approximating vein wall edges external to mattress suture. (From Aldridge SC, Cometota AJ, Katz ML, et al. Popliteal venous aneurysm: report of two cases and review of the world literature. *J Vasc Surg*. 1993;18:708–715.)

presentation with men more commonly presenting with limb swelling or pain (41.9%) and venous insufficiency (12.9%), while women were most commonly asymptomatic (35.3%). Males also tended to present with a history of trauma (12.9%) while women had a higher prevalence of associated May-Thurner syndrome. The authors also noted a higher incidence of aneurysms found on the left side and more commonly in the external iliac vein followed by the common iliac vein.<sup>24</sup>

Treatment is best accomplished with tangential aneurysmectomy and lateral venorrhaphy. Ligation of the iliac vein leads to a high rate of chronic lower extremity edema and post-thrombotic syndrome and should be avoided. Aneurysms associated with arteriovenous fistula are likely best managed with covered stenting of the arterial system followed by venous aneurysm resection.

## ABDOMINAL VENOUS ANEURYSMS

### Inferior Vena Cava

The normal caliber of the IVC is 1.5 to 3.7 cm, and the IVC is considered aneurysmal when it exceeds 5 cm. Fewer than 60 case reports addressing IVC aneurysms have been published, which make these rare entities.<sup>25</sup> Clinically, IVC aneurysms are rarely symptomatic and often discovered incidentally on

cross-sectional imaging performed for other reasons. In a previous report the most common presentation was ilio caval thrombosis, which occurred in 19%.<sup>26</sup> Gradman and Steinberg created a classification system (Fig. 166.3) defining types of IVC aneurysms, which is shown as follows<sup>27</sup>:

- Type 1: suprahepatic aneurysms without obstruction.
- Type 2: aneurysms located above or below the hepatic veins with obstruction.
- Type 3: infrarenal aneurysms without obstruction.
- Type 4: miscellaneous aneurysms.

Although this classification system is not intuitive, it helps to guide management.<sup>27</sup>

Type 1 aneurysms can usually be observed with no adverse outcomes. Types 2, 3, and 4 aneurysms are prone to thrombosis or embolization and, for this reason, are usually treated. Surgical repair is the most common treatment, either tangential excision with venorrhaphy or resection with interposition bypass grafting.<sup>26</sup>

### Visceral Venous Aneurysms

Venous aneurysms in the visceral veins, including the portal, mesenteric, and renal systems, are extremely rare. In the only recent systematic analysis, 98 case reports were identified, including 198 aneurysms in 176 patients. The majority of aneurysms were in the portal vein (191 of 198 aneurysms).

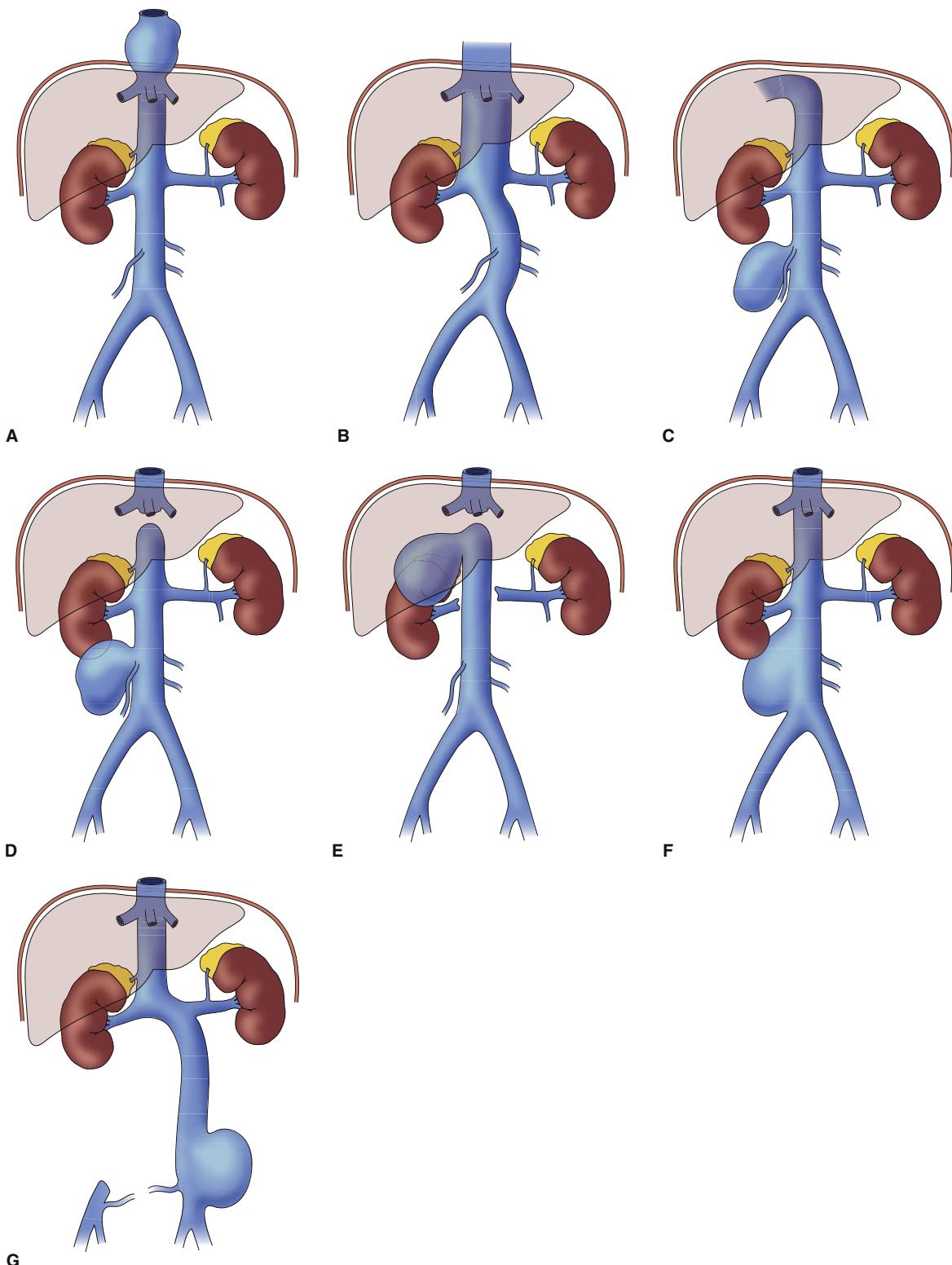
Portal venous aneurysms are defined as a portal vein with a diameter greater than 15 mm, or greater than 19 mm in cirrhotic patients.<sup>28</sup> In the studies reported, one-half of patients presented with nonspecific abdominal pain, 30% were asymptomatic with incidental aneurysm discovery, and 20% of patients presented with thrombosis.<sup>29,30</sup> Rupture was rare.

The congenitally aneurysmal portal vein is thought to arise from incomplete regression of the right primitive distal vitelline vein. Acquired portal vein aneurysms form secondary to portal hypertension, trauma, pancreatitis, or local malignancy with venous wall invasion.<sup>31</sup>

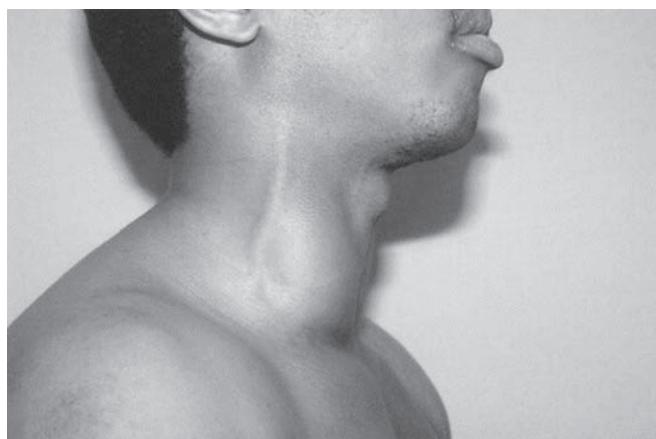
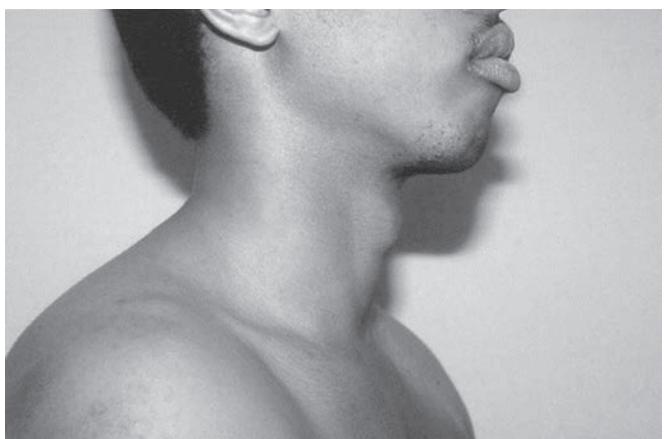
Treatment is indicated in portal venous aneurysms greater than 3 cm or smaller aneurysms with complications (rupture, thrombosis, pain, rapid enlargement) in appropriate surgical candidates. Patients without portal hypertension do well with tangential aneurysmectomy and aneurysmorrhaphy, although extensive perioperative bleeding can occur. In patients with concomitant portal hypertension, the treatment should address this underlying condition either through portovenous shunting or liver transplantation. Regression is rare but has been reported.<sup>26</sup>

Mesenteric vein aneurysms are extremely rare and have presented as asymptomatic masses discovered incidentally, or following the development of abdominal pain or thrombosis. In a review published in 2004, 10 cases were identified. The most common presenting symptom was abdominal pain.<sup>32</sup> The majority were treated conservatively, although there is a report of a catastrophic outcome following rupture.<sup>33</sup> It is recommended that surgical treatment be performed in symptomatic patients, or asymptomatic patients with aneurysms greater than 3 cm.

Splenic vein aneurysms are much less common than splenic artery aneurysms, and they have been shown to occur secondary to arterial aneurysm rupture into the splenic vein.<sup>30,34</sup> Treatment is aimed at symptomatic patients, women of childbearing age, or aneurysm size greater than 3 cm.



**Figure 166.3** (A) Type I aneurysm showing suprahepatic location without obstruction in inferior vena cava (IVC). (B) Type I aneurysm in perihepatic location with left-sided IVC. (C) Type II aneurysm showing suprarectal interruption of IVC with infrarenal IVC aneurysm. (D) Type II aneurysm with intrahepatic interruption of IVC and infrarenal IVC aneurysm. (E) Type II aneurysm with intrahepatic interruption of IVC, intrahepatic IVC aneurysm, and entry of renal veins into azygous and hemizygous system. (F) Type III infrarenal IVC aneurysm without venous obstruction. (G) Type IV aneurysm of iliac vein with left-sided IVC. (From Gradman WS, Steinberg F. Aneurysm of the inferior vena cava: case report and review of the literature. *Ann Vasc Surg*. 1993;7:347–353.)



**Figure 166.4** Under Valsalva maneuver, aneurysms of the internal jugular vein may become alarmingly large (*right panel*). However, their course is usually benign, and surgical excision is rarely indicated. (From Gillespie DL, Villavicencio JL, Gallagher C, et al. Presentation and management of venous aneurysms. *J Vasc Surg*. 1997;26:5:845–852.)

Renal vein aneurysms are also rare. In a systematic review, five cases were identified. In three cases, abdominal pain was the presenting symptom; the other two patients were asymptomatic. Surgical repair involving aneurysmectomy or nephrectomy was performed in the symptomatic patients.<sup>29</sup>

Renal vein aneurysms can be confused with distended renal veins, particularly on the left side. The diagnosis of an aneurysm must not be confused with the nutcracker syndrome. In addition, investigation of a spontaneous splenorenal shunt should be entertained in patients with portal hypertension because this may also contribute to left renal vein dilation.

## UPPER EXTREMITY AND INTERNAL JUGULAR VENOUS ANEURYSMS

Upper extremity and jugular venous aneurysms also occur in both the deep and superficial venous systems. They are thought to be less common than venous aneurysms in the lower extremities; in one series, they constituted 23% of 39 aneurysms diagnosed in 30 patients.<sup>1</sup>

### Upper Extremity Superficial Venous Aneurysms

Superficial venous aneurysms in the upper extremities often present with pain and/or swelling, but a significant proportion are asymptomatic. In these cases, they are often misdiagnosed and treated as soft tissue masses, with the diagnosis only being made at the time of surgery. This can be avoided with a thorough physical examination which includes compression of the mass with the extremity in both the dependent and elevated positions, and changes can be noted during a Valsalva maneuver. There should be differential filling (fast vs. slow) of the mass depending on the position of the extremity (dependent vs. elevated). DUS scanning is diagnostic and should be routinely used.

Surgical treatment should be directed at symptomatic aneurysms or if the patient desires excision for cosmetic reasons. DUS performed immediately before incision is beneficial in identifying all feeding vessels which can then be targeted early

in the procedure before the aneurysm sac is excised. The procedure can usually be carried out under local anesthesia.

Pseudoaneurysms frequently develop in arteriovenous fistulae created for hemodialysis access. These are discussed in Chapter 178 (Hemodialysis Access: Nonthrombotic Complications).

### Upper Extremity Deep Venous Aneurysms

Brachial, axillary, and subclavian venous aneurysms are seldom symptomatic and usually present as a painless slowly enlarging mass. If a mass is visible through the skin, physical examination during Valsalva will show enlargement of the mass. In most cases, DUS is diagnostic. Cross-sectional imaging may be considered if adjacent structures are thought to be compromised or for operative planning.

Upper extremity deep venous aneurysms are rarely reported in the literature, and no evidence-based treatment algorithm exists. Although they have been reported to be less likely to be associated with complications, a few case reports have demonstrated pulmonary embolization from these aneurysms.<sup>35,36</sup> Others have reported cases of deep upper extremity venous aneurysms causing localized discomfort.<sup>37</sup> With this in mind, the authors recommend that symptomatic aneurysms be treated with aneurysmectomy and venous reconstruction as needed. Asymptomatic aneurysms can be surgically treated in appropriate risk patients, or serially observed for any change in size or occurrence of symptoms.

### Jugular Venous Aneurysms

Venous aneurysms of the jugular veins (Fig. 166.4) are usually asymptomatic and frequently misdiagnosed. The differential diagnosis includes any soft tissue mass of the head and neck, such as lipoma, lymphangioma, malignancy, hematoma, or cystic structures. Congenital venous aneurysms of the external and internal jugular veins presenting in childhood have been described. These aneurysms may also present in adults, although this is rare. There are case reports of patients with NF-1 being predisposed to developing jugular venous aneurysms. Treatment of these aneurysms involves surgical resection and

is performed most commonly for cosmetic purposes because they rarely lead to pulmonary embolization.<sup>38</sup> Ligation of the feeding vessels with aneurysmectomy is frequently performed as long as there is good contralateral venous drainage. Spontaneous regression of a jugular venous aneurysm after 24 months in a 2-year-old has been described.<sup>39</sup>

## CONCLUSION

Venous aneurysms are rare. They are usually discovered incidentally on cross-sectional imaging or in the work-up for pulmonary embolus. Although no randomized controlled trials are available, best treatment involves surgical consideration for large or symptomatic venous aneurysm, and observation of small and asymptomatic aneurysms. Tangential aneurysmectomy with lateral venorrhaphy is generally the preferred surgical procedure. More studies of these rare entities are needed to develop better treatment algorithms.

## SELECTED KEY REFERENCES

Gillespie DL, Villavicencio JL, Gallagher C, et al. Presentation and management of venous aneurysms. *J Vasc Surg*. 1997;26(5):845–852.

*Good overview of systemic venous aneurysm presentation and management.*

Gradman WS, Steinberg F. Aneurysm of the inferior vena cava: case report and review of the literature. *Ann Vasc Surg*. 1993;7:347–353.

*Seminal article on inferior vena cava aneurysms which includes a proposed classification scheme and management algorithm.*

Johnstone JK, Fleming MD, Gloviczki P, et al. Surgical treatment of popliteal venous aneurysms. *Ann Vasc Surg*. 2015;29:1084–1089.

*Good retrospective review and review of literature regarding popliteal venous aneurysm presentation and management.*

Laurenzi A, Ettorre GM, Raffaella Lionetti. Portal vein aneurysm: what to know. *Dig Liver Dis*. 2015;47:918–923.

*Review of literature regarding portal venous aneurysms. Diagnosis and treatment algorithms are discussed.*

Montero-Baker MF, Branco BC, Leon Jr LL. Management of inferior vena cava aneurysm. *J Cardiovasc Surg*. 2015;56:769–774.

*Overview of inferior vena cava aneurysm management and meta-analysis of literature.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

1. Gillespie DL, Villavicencio JL, Gallagher C, et al. Presentation and management of venous aneurysms. *J Vasc Surg.* 1997;26(5):845–852.
2. McDevitt DT, Lohr JM, Martin KD, et al. Bilateral popliteal vein aneurysms. *Ann Vasc Surg.* 1993;7:282e6.
3. Bartline PB, McKellar SH, Kinikini DV. Resection of a large innominate vein aneurysm in a patient with neurofibromatosis type 1. *Ann Vasc Surg.* 2016;30:157.e1–157.e5.
4. Burnley HM, McCormick D, Hurren J, et al. Primary venous dissecting aneurysm arising during pregnancy: a case report and review of the literature. *J Clin Pathol.* 2003;56:634–635.
5. Haas E, Meyer MR, Schurr U, et al. Differential effects of 17beta-estradiol on function and expression of estrogen receptor alpha, estrogen receptor beta, and GPR30 in arteries and veins of patients with atherosclerosis. *Hypertension.* 2007;49:1358–1363.
6. Hodges YK, Tung L, Yan XD, et al. Estrogen receptors alpha and beta prevalence of estrogen receptor beta mRNA in human vascular smooth muscle and transcriptional effects. *Circulation.* 2000;101:1792–1798.
7. Pang Y, Dong J, Thomas P. Progesterone increases nitric oxide synthesis in human vascular endothelial cells through activation of membrane progesterone receptor-alpha. *Am J Physiol Endocrinol Metab.* 2015;308:E899–E911.
8. Irwin C, Synn A, Kraiss L, et al. Metalloproteinase expression in venous aneurysms. *J Vasc Surg.* 2008;48(5):1278–1285.
9. Ross CB, Schumacher PM, Datillo JB, et al. Endovenous stent-assisted coil embolization for a symptomatic femoral vein aneurysm. *J Vasc Surg.* 2008;48(4):1032–1036.
10. Ibrahim WH, Bassurrah HM. Endovascular management of splenic arteriovenous fistula with giant venous aneurysmal dilatation. *Ann Vasc Dis.* 2012;5(4):439–444.
11. Ueda T, Murata S, Yamamoto A, et al. Endovascular treatment of post-laparoscopic pancreatectomy splenic arteriovenous fistula with splenic vein aneurysm. *World J Gastroenterol.* 2015;21(25):7907–7910.
12. Casian D, Culic V. Primary aneurysm of the medial marginal vein of the foot. *Case Rep Vasc Med.* 2015;2015:374691.
13. Hamann SAS, van der Velden SK, De Maeseneer MGR. Safety and effectiveness of endovenous thermal ablation for incompetent saphenous veins with an aneurysm close to the junction. *Eur J Vasc Endovasc Surg.* 2019;58(2):244–248.
14. Labropoulos N, Comito M, De Zolt P, et al. Management of perforator vein aneurysms in the lower extremities. *J Vasc Surg Venous Lym Dis.* 2015;3:270–275.
15. Park JS, Kim JY, Kim M, et al. Ruptured aneurysm of the external iliac vein. *J Vasc Surg Venous Lym Dis.* 2016;4:92–94.
16. Johnstone JK, Fleming MD, Głowiczki P, et al. Surgical treatment of popliteal venous aneurysms. *Ann Vasc Surg.* 2015;29:1084–1089.
17. Sandstrom A, Reynolds A, Jha P. Popliteal vein aneurysm: a rare cause of pulmonary emboli. *Ann Vasc Surg.* 2017;38:315.e15–315.e17.
18. Noppeneij T, Kopp R, Pfister K, et al. Treatment of popliteal vein aneurysms. *J Vasc Surg Venous Lymphat Disord.* 2019;7(4):535–542.
19. Nasr W, Babbitt R, Eslami MH. Popliteal vein aneurysm: a case report and review of literature. *Vasc Endovasc Surg.* 2007;41:551–555.
20. Aldridge SC, COmerota AJ, Katz ML, et al. Popliteal venous aneurysm: report of two cases and review of the world literature. *J Vasc Surg.* 1993;18:708–715.
21. Yamamoto Y, Kimura K, Takago S, et al. Aneurysm resection interposed with a spiral saphenous vein graft in a patient with a popliteal venous aneurysm with thrombosis. *J Vasc Surg Venous Lymphat Disord.* 2019;7(6):898–901.
22. Johnstone JK, Fleming MD, Głowiczki P, et al. Surgical treatment of popliteal venous aneurysms. *Ann Vasc Surg.* 2015;29:1084–1089.
23. Beaulieu RJ, Boniakowski AM, Coleman DM, et al. Closed plication is a safe and effective method for treating popliteal venous aneurysm. *J Vasc Surg Venous Lymphat Disord.* 2021;9(1):187–192.
24. Zarrintan S, Tadayon N, Kalantar-Motamed SMR. Iliac vein aneurysms: a comprehensive review. *J Cardiovasc Thorac Res.* 2019;11(1):1–7.
25. Montero-Baker MF, Branco BC, Leon Jr LL. Management of inferior vena cava aneurysm. *J Cardiovasc Surg.* 2015;56:769–774.
26. Lall P, Potineni L, Dosluoglu HH. Complete spontaneous regression of an extrahepatic portal vein aneurysm. *J Vasc Surg.* 2011;53:206–208.
27. Gradman WS, Steinberg F. Aneurysm of the inferior vena cava: case report and review of the literature. *Ann Vasc Surg.* 1993;7:347–353.
28. Doust BD, Pearce JD. Grey-scale ultrasonic properties of the normal and inflamed pancreas. *Radiology.* 1976;120:653–657.
29. Sfyroeras GS, Antoniou GA, Drakou AA, et al. Visceral venous aneurysms: clinical presentation, natural history, and their management: a systematic review. *Eur J Vasc Endovasc Surg.* 2009;38:498–505.
30. Ueda T, Murata S, Yamamoto A, et al. Endovascular treatment of post-laparoscopic pancreatectomy splenic arteriovenous fistula with splenic vein aneurysm. *World J Gastroenterol.* 2015;21(25):7907–7910.
31. Gallego C, Velasco M, Marcuello P, et al. Congenital and acquired anomalies of the portal venous system. *Radiographics.* 2002;22:141–159.
32. Wolosker N, Zerati AE, Nishinari K, et al. Aneurysm of superior mesenteric vein: case report with 5-year follow-up and review of the literature. *J Vasc Surg.* 2004;39:45961.
33. Smith TJ, Morehouse DL. Superior mesenteric vein aneurysm rupture. *Vasc Endovascular Surg.* 2011;45(6):559–560.
34. Ibrahim WH, Bassurrah HM. Endovascular management of splenic arteriovenous fistula with giant venous aneurysmal dilatation. *Ann Vasc Dis.* 2012;5(4):439–444.
35. Choi ST, Park HS, Lee YH, et al. A thrombotic primary venous aneurysm of an upper extremity causing pulmonary emboli after it was squeezed. *Ann Vasc Surg.* 2015;29:836.e9–836.e13.
36. Wallace JR, Baril DT, Chaer RA. Upper extremity venous aneurysm as a source of pulmonary emboli. *Ann Vasc Surg.* 2013;27:240.e5–240.e8.
37. McCready RA, Bryant MA, Divelbiss JL, et al. Subclavian venous aneurysm: case report and review of the literature. *J Vasc Surg.* 2007;45:1080–1082.
38. Khashram M, Walker PJ. Internal jugular venous aneurysm. *J Vasc Surg Venous Lym Dis.* 2015;3:94.
39. Zhang C, Li H, Guo X, et al. Clinical diagnosis and treatment of internal jugular venous aneurysms. *Ann Vasc Surg.* 2020;62:497.e7–497.e12.

# Lymphedema: Evaluation and Decision Making

STANLEY G. ROCKSON

## PATOPHYSIOLOGY 2202

### CLASSIFICATION AND STAGING 2203

Primary Lymphedema 2203

Classification by Age at Onset and Inheritance 2203

Classification by Morphology 2203

Classification by Anatomy 2203

Classification by Clinical Setting 2205

Secondary Lymphedema 2205

Cancer 2205

Filariasis 2206

Other Causes 2206

Clinical Staging 2206

### CLINICAL PRESENTATION 2207

History 2207

Signs and Symptoms 2207

Edema 2207

Skin Changes 2207

Pain 2207

## Complications 2207

Infection 2207

Malnutrition and Immunodeficiency 2207

Malignant Tumors 2207

## DIAGNOSIS 2208

Physical Examination 2208

Testing 2208

Lymphoscintigraphy 2208

Advanced Imaging 2210

Direct Contrast Lymphangiography 2210

Differential Diagnosis 2211

Systemic Causes 2211

Venous Insufficiency 2211

Vascular Malformation 2212

Lipedema 2212

Other Causes 2212

## DECISION MAKING 2213

## PROSPECTS FOR MOLECULAR THERAPY 2213

Lymphedema is the term used to characterize the various pathological conditions in which there is progressive accumulation of protein-enriched interstitial fluid. Collectively, these forms of edema arise as a consequence of relative impairment of lymphatic vascular function. Lymphatic vascular insufficiency can result from either primary or acquired (secondary) lymphatic defects. Cryptogenic forms of lymphedema are often presumed to represent primary lymphatic dysfunction. Although impaired lymphatic function can manifest as visceral pathology, particularly in the respiratory or gastrointestinal organs, it is upper or lower extremity edema, with or without visceral involvement, that is the most common presentation of lymphatic impairment.

## PATOPHYSIOLOGY

Impairment of lymphatic outflow leads to the pathologic consequences of lymphedema. In high-input failure, such as that which occurs in venous edema, increased pressure at the venous end of the capillary leads to the accentuated production of interstitial fluid through increased capillary filtration; if the production of lymph exceeds the maximal transport capacity of the lymphatic conduits, lymphedema will ensue, even if these structures are anatomically and functionally normal. By contrast, low-output failure ensues when some pathologic condition compromises lymphatic flow. Lymph stasis can accompany lymphatic hypoplasia or aplasia, functional insufficiency of anatomic absence of lymphatic valves, or, conceivably, blunted lymphatic contractility.<sup>1</sup> Because

the lymphatic circulation is responsible for the return of interstitial fluid and protein to the central circulation, lymph stasis creates an accumulation of protein and cellular metabolites in the extracellular space; with the ensuing increase in tissue colloid osmotic pressure, there is water accumulation and elevation of the interstitial hydraulic pressure (see Ch. 10, Lymphatic Pathophysiology).

Impaired lymphatic transport leads to the accumulation of hyaluronan and other glycoproteins within the extracellular space. This is followed by a secondary increase in the fibroblast, keratinocyte, and adipocyte content of the affected tissues along with the accumulation of mononuclear cells, including macrophages. Ultimately, an increase in collagen deposition occurs, typically accompanied by an overgrowth of connective tissue and adipose elements in the skin and subcutaneous tissue.<sup>2</sup> Although the contributory mechanisms are still not well understood, there is a tendency for these processes to lead to progressive subcutaneous fibrosis.

## CLASSIFICATION AND STAGING

Standard clinical classifications distinguish lymphedema on the basis of cause (primary versus secondary). Primary lymphedema is further classified on the basis of genetics (familial versus sporadic) and time of onset (congenital, praecox, tarda).<sup>3–5</sup> Although these systems are useful for categorizing lymphedema, they do not address the clinical severity of the disease and are usually not relevant to therapy. More recent classifications focus on the clinical stage of lymphedema or emphasize the causal anatomic or functional lymphatic abnormality, in an attempt to predict natural history and to identify the best therapeutic approach.<sup>1,6,7</sup>

### Primary Lymphedema

The prevalence of the heritable causes of primary lymphedema is difficult to ascertain, and estimates vary substantially. Primary lymphedema is thought to occur in approximately 1 of every 6000 to 10,000 live births. On the basis of data collected by the Rochester group study, it affects 1.15 per 100,000 persons younger than 20 years.<sup>8</sup> Females are affected 2- to 10-fold more commonly than males, and the incidence peaks between the ages of 12 and 16 years.<sup>1,9</sup>

Of 125 patients with primary lymphedema treated at the Mayo Clinic, 97 (78%) were female and 28 (22%) were male, yielding a female-to-male ratio of 3.5:1.<sup>10</sup> The ratio of unilateral to bilateral lymphedema was 3:1. Congenital lymphedema occurred more frequently in males than in females. In these patients, the edema was usually bilateral and involved the entire lower extremity. In contrast, the typical patient with lymphedema praecox was female and had unilateral involvement, with swelling usually extending only to the knee.

Primary lymphedema represents a heterogeneous group of disorders; therefore, its classification schemes are numerous. Affected individuals can be classified by age at onset, morphology, or clinical setting.

### Classification by Age at Onset and Inheritance

The term *congenital* is applied when lymphedema is present at birth or is recognized within the first year of life. *Lymphedema*

*praecox* most commonly appears at the onset of puberty, but it may be delayed until the third decade of life. *Lymphedema tarda* typically begins after the age of 35 years.

**Congenital.** Congenital lymphedema can occur in a sporadic fashion; however, when clusters of cases occur in families, an *autosomal dominant* pattern of transmission is frequently observed.<sup>11</sup> In addition to isolated causal mutations, there is a strong association between intrauterine and congenital lymphatic dysfunction and the presence of chromosomal abnormalities, including *Turner syndrome*, *Klinefelter syndrome*, and *trisomy 21*, among others. In congenital lymphedema, the swelling can involve only a single lower extremity, but edema of multiple limbs, the genitalia, and even the face can be seen. Bilateral leg swelling and involvement of the entire lower extremity are more likely in congenital cases than in other forms of primary lymphedema.<sup>10</sup>

**Lymphedema Praecox.** Lymphedema praecox is the most common form of primary lymphedema, accounting for up to 94% of cases in large series. The name *Meige disease* has historically been reserved for a specific familial form of lymphedema and typical onset at puberty. Lymphedema praecox displays a marked gender imbalance, with an estimated 10:1 female-to-male prevalence.<sup>2</sup> The edema is usually unilateral, and is limited to the foot and calf in the majority of patients.<sup>10</sup> Estrogenic hormones may play a role in the pathogenesis of this form of primary lymphedema.<sup>10</sup>

**Lymphedema Tarda.** Lymphedema tarda is relatively less common. Appearing after the age of 35 years, it typically accounts for an estimated 10% of cases of primary lymphedema.

### Classification by Morphology

It has been suggested that a morphologic classification of primary lymphedema might provide more useful prognostic information than classification by age at onset (Fig. 167.1).<sup>2</sup> This alternative classification scheme relies on an anatomic description of the lymphatic vasculature.<sup>3,11</sup>

**Aplasia.** In aplasia, no collecting vessels can be identified.

**Hypoplasia.** In hypoplasia, a diminished number of vessels are seen.

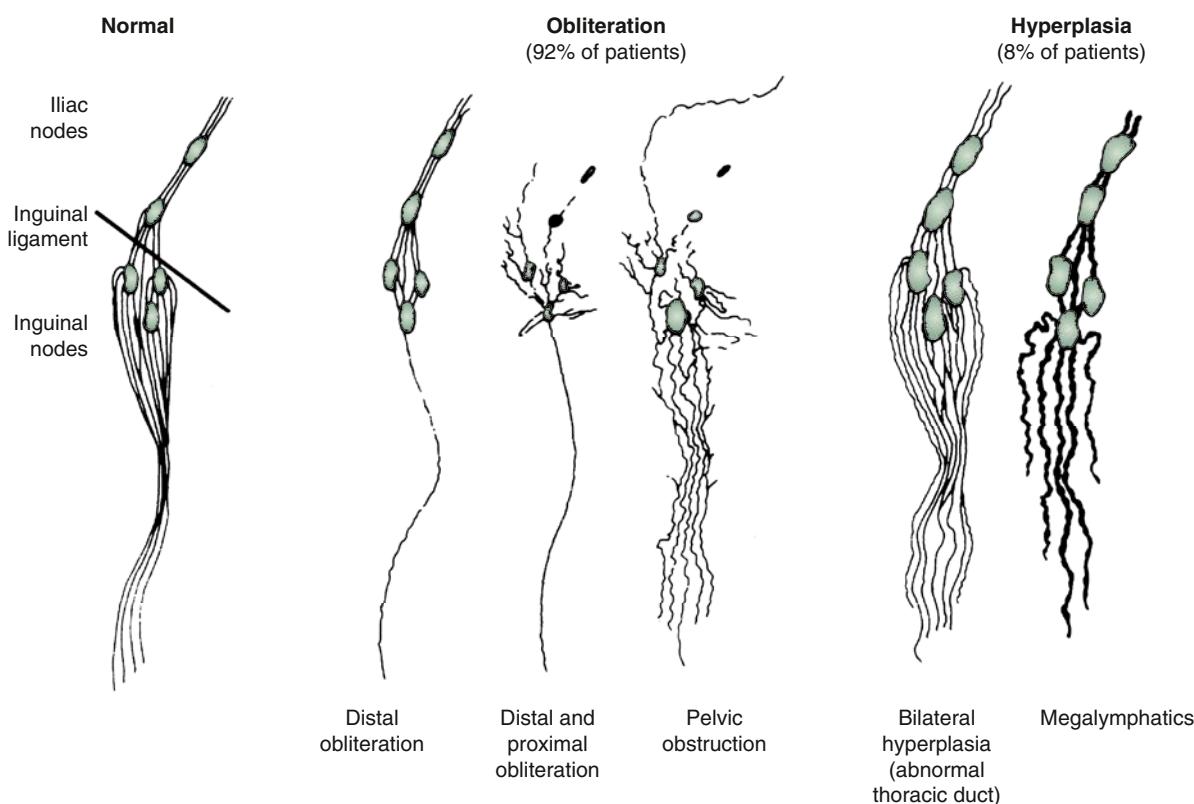
**Numerical Hyperplasia.** In numerical hyperplasia (as defined by Kinmonth et al.<sup>3</sup>), an increased number of vessels are seen.

**Hyperplasia.** In addition to an increase in number, the vessels have valvular incompetence and display tortuosity and dilatation (megalymphatics, lymphangiectasia). Megalymphatics and lymphatic hyperplasia are less common than hypoplasia or aplasia. This pattern demonstrates a male predominance. These patients most often have unilateral edema involving the entire lower extremity (Fig. 167.2). Cutaneous angiomas and chylous reflux can also be seen. Megalymphatics are associated with a greater extent of involvement and a worse prognosis.

### Classification by Anatomy

Aplasia and hypoplasia have a different natural history, depending on whether they involve the distal or proximal portion of the leg.

**Distal Obstruction.** Approximately one-third of all cases result from agenesis, hypoplasia, or obstruction of the distal lymphatic vessels, with relatively normal proximal vessels



**Figure 167.1** Lymphangiographic patterns of lymphatic morphology in a normal lower limb and in patients with different types of primary lymphedema. Obliteration of the lymphatic pathways may be due to aplasia, hypoplasia, or obstruction of the lymphatic channels and nodes.



**Figure 167.2** Primary lymphedema of the right leg caused by hyperplasia of the lymphatics and valvular incompetence. Mid-calf skin vesicles contain a milky fluid because of lymphangiectasia and reflux of chyle.

(see Fig. 167.1).<sup>11</sup> In these cases, the swelling is usually bilateral and mild, and females are affected much more frequently than males. The prognosis is good. In general, after the first year of symptoms, there is little extension in the same limb or to uninvolved extremities. Although the maximal extent of involvement is established early in the disease in about 40% of patients, the girth of the limb continues to increase. Distal hypoplasia or aplasia of the lymphatics most often correlates with the presence of bilateral peripheral edema of the lower extremities. Familial occurrence, female predominance, and indolent progression characterize this pattern of lymphatic disturbance.

**Proximal Obstruction.** In more than half the cases, the defect primarily involves obstruction of the proximal lymphatics or nodes, with an absence of distal lymphatic involvement. Pathologic studies reveal intranodal fibrosis.<sup>12</sup> In these cases, the swelling tends to be unilateral and severe; there may be a slight female predominance.<sup>11</sup> In patients with proximal involvement, the extent and degree of the abnormality are likely to progress, potentially requiring surgical intervention. Initially uninvolved distal lymphatic vessels may become obliterated over time. A minority of patients have a pattern of bilateral hyperplasia of the lymphatic channels. In these less common forms of primary lymphedema, there is a slight male predominance. When isolated proximal obstructive hypoplasia is observed, clinical involvement of the entire limb is more likely, with relentless worsening of edema.



**Figure 167.3** (A) Adult patient with congenital lymphedema. In addition to the bilateral arm lymphedema depicted, she has edema of both legs and the face. (B) Upper extremities of this patient's 18-year-old son, who has a similar distribution of lymphedema. This is an example of Milroy disease.

## Classification by Clinical Setting

Alternatively, primary lymphedema can be classified by abnormal phenotype or associated clinical anomalies.<sup>13</sup>

**Inheritance.** Although sporadic cases of primary lymphedema are more common,<sup>11</sup> there is a significant tendency for congenital lymphedema to cluster in families (Fig. 167.3). A familial predisposition for congenital lymphedema, ultimately determined to have an autosomal dominant form of inheritance with variable penetrance, was first described by Milroy in 1892.<sup>14</sup> He reported "hereditary edema" affecting 22 individuals in 1 family over 6 generations. Although Milroy studied not only congenital lymphedema but also the praecox and tarda variants of the syndrome that bears his name, lymphedema praecox is better known as Meige disease.<sup>15</sup>

In general, congenital lymphedema with recessive forms of inheritance is less common than that with dominant forms of inheritance.<sup>11,16,17</sup> Nevertheless, the list of heritable lymphedema-associated syndromes is long and growing.<sup>18–20</sup> Primary lymphedema has been described in association with various forms of chromosomal aneuploidy, such as Turner and Klinefelter syndromes; with various dysmorphic genetic anomalies, such as Noonan syndrome and neurofibromatosis; and with a variety of as yet unrelated disorders, such as yellow nail syndrome, intestinal lymphangiectasia, generalized lymphatic anomaly (formerly known as lymphangiomatosis), and arteriovenous malformation.<sup>21–26</sup> The association of lymphedema with vascular anomalies underscores the common developmental origin of the lymphatic and blood vasculature. Clinicians and scientists have recently refined a classification algorithm for primary lymphatic anomalies. This decision tree can be utilized to narrow the diagnostic scope of primary lymphedema and to guide genetic testing and management.<sup>20</sup>

**Associated Disorders.** Numerous disorders are associated with heritable forms of lymphedema. Increasingly, these disorders have yielded to chromosomal mapping techniques. Lymphedema-cholestasis, or Aagenes syndrome, has been mapped to

chromosome 15q.<sup>27</sup> In several family cohorts of Milroy disease, it has been determined that the disorder reflects missense inactivating mutations in the tyrosine kinase domain of vascular endothelial growth factor receptor 3 (VEGFR-3),<sup>28,29</sup> thus suggesting the likelihood that this condition reflects an inherited defect in lymphatic vasculogenesis. Several additional lymphedema syndromes have recently lent themselves to successful genetic mapping.<sup>28</sup> Mutations in FOXC2 have subsequently been associated with a wide variety of primary lymphedema presentations.<sup>30</sup> Similarly, a more unusual form of congenital lymphedema, hypotrichosis–lymphedema–telangiectasia, has been ascribed to both recessive and dominant inheritance of mutations in the transcription factor gene SOX18.<sup>31</sup> It is plausible that further elucidation of the molecular pathogenesis of these diseases linked to FOXC2 and SOX18 mutations will lead to enhanced insights into the mechanisms of normal and abnormal lymphatic development.

## Secondary Lymphedema

Acquired (secondary) lymphedema is the most commonly encountered form of lymphatic dysfunction (Fig. 167.4). In the United States, iatrogenic causes predominate among the acquired forms of lymphedema owing to the common occurrence of lymphatic trauma after surgery or radiotherapy for cancer.<sup>9,32</sup>

### Cancer

Of the various clinical settings that predispose patients to lymphedema, treatment of breast cancer is most commonly associated with acquired lymphatic insufficiency (of the upper extremity). Lymph node dissection and adjuvant radiation therapy independently and synergistically predispose to lymphatic vascular insufficiency.<sup>21</sup> According to the most recent estimates, 6% to 30% of breast cancer survivors experience clinically significant arm lymphedema after axillary intervention. Despite the benefits of recent surgical and



**Figure 167.4 Chronic Acquired Lymphedema of the Lower Extremities.** Note severe skin changes (A) and swelling of the foot (B) associated with squaring of the toes (Stemmer's sign) and the typical peau d'orange. (C) Severe lymphedema with subcutaneous lymph cysts and chronic verrucous superinfection.

radiotherapeutic enhancements, the problem of lymphedema has not been eradicated.<sup>18</sup>

Similar lymphatic sequelae are encountered in the lower extremities and pelvis after interventions for gynecologic or urologic malignant neoplasms. Malignant melanoma can cause either upper or lower extremity lymphedema when radical dissection is required in the axilla or groin, respectively.

### Filariasis

Filariasis, caused by infestation with parasites such as *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, is by far the most frequent cause of secondary lymphedema in third-world countries. Of the estimated 90.2 million people in the world who are infected, more than 90% have bancroftian filariasis.<sup>33</sup> The disease is most frequent in subtropical and tropical countries such as China, India, and Indonesia. It is transmitted by various types of mosquitoes, and transmission is closely related to poor urban sanitation.<sup>34</sup>

Perilymphatic inflammation and fibrosis, and sclerosis of the lymph nodes are caused by the indwelling adult worms. Lymph node fibrosis, reactive hyperplasia, and dilatation of the lymphatic collecting channels are caused by the worm products, by physical injury to the valves and vessel walls caused by the live worms, and by the immune response of the host.<sup>35</sup> Eosinophilia is found in the peripheral blood smear, and microfilariae can be demonstrated in peripheral nocturnal blood, centrifuged urine sediment, or lymphatic fluid.<sup>36</sup>

Filarial lymphedema rapidly develops into grossly incapacitating elephantiasis that is extremely difficult to treat.

### Other Causes

Lymphedema can also be acquired from other types of lymphatic vascular trauma, including burns and large or

circumferential wounds to the extremity. Additional causes of acquired lymphedema include pregnancy, bacterial and fungal infections, infections after snake or insect bites, contact dermatitis, and rheumatoid arthritis.<sup>9</sup> Autoimmune destruction of the lymphatics has been hypothesized but not directly demonstrated.

### Clinical Staging

Existing guidelines for the grading of lymphedema are limited.<sup>37</sup> Because none of the classification schemes addresses the clinical stage of the disease, in 1985 the Working Group of the 10th International Congress of Lymphology suggested staging chronic lymphedema, regardless of cause. A latent, subclinical stage and three clinical grades were established,<sup>38</sup> and each grade was subclassified as mild, moderate, or severe:

- **Latent Phase:** Excess fluid accumulates and fibrosis occurs around the lymphatics, but no edema is apparent clinically.
- **Grade I:** Edema pits on pressure and is reduced largely or completely by elevation; there is no clinical evidence of fibrosis.
- **Grade II:** Edema does not pit on pressure and is not reduced by elevation; moderate to severe fibrosis is evident on clinical examination.
- **Grade III:** Edema is irreversible and develops from repeated inflammatory attacks, fibrosis, and sclerosis of the skin and subcutaneous tissue. This is the stage of lymphostatic elephantiasis.

The advantage of this classification is that it permits the evaluation of treatment effectiveness and the comparison of different treatment modalities. One drawback is that appropriate staging may be difficult in some cases without a biopsy of the subcutaneous tissue.

## CLINICAL PRESENTATION

### History

A careful history frequently reveals the cause of the swelling and suggests the diagnosis of lymphedema. A family history that is positive for leg swelling may indicate familial lymphedema. The development of painless leg swelling in a teenage girl without any identifiable cause strongly suggests primary (idiopathic) lymphedema. A history of diarrhea and weight loss is a clue to mesenteric lymphangiectasia, whereas intermittent drainage of milky fluid from skin vesicles indicates reflux of chyle. In patients with secondary lymphedema, the cause of limb swelling should be evident from the history, such as previous lymph node dissection, irradiation, tumor, trauma, or infection. In patients who have traveled in tropical countries, filariasis is suspected. Although the causes of primary and secondary lymphedema are different, the clinical presentation and characteristic physical findings are frequently similar.

### Signs and Symptoms

The clinical signs and symptoms of lymphedema largely depend on the duration and severity of the disease.

#### Edema

Initially, the interstitial space is expanded by an excess accumulation of relatively protein-rich fluid. The swelling produced by the fluid collection is typically soft, is easily displaced with pressure (pitting edema), and may substantially decrease with elevation of the limb. In the lower extremities, the edema typically extends to the distal aspects of the feet, resulting in the characteristic “square toes” seen in this condition. Stemmer’s sign is positive when the skin at the base of the second toe becomes inelastic to the point that the examiner’s fingers cannot cause the skin to tent. The dorsum of the forefoot can be involved, resulting in the typical appearance of a “buffalo hump.” During a period of years, the limb may take on a woody texture as the surrounding tissue becomes indurated and fibrotic.

#### Skin Changes

In the early stage of lymphedema, the skin usually has a pinkish red color and a mildly elevated temperature owing to the increased capillary blood flow in the skin. In long-standing lymphedema, the skin becomes thick and shows areas of hyperkeratosis, lichenification, and development of peau d’orange. The term pigskin reflects the reactive changes of the dermis and epidermis in response to the chronic inflammation caused by lymphatic stasis.<sup>2</sup> Recurrent chronic eczematous dermatitis or excoriation of the skin may occur, but frank ulcerations are rare. Unlike the situation in venous stasis, the skin maintains a higher degree of hydration and elasticity in lymphedema, and ischemic changes due to high skin tension and disruption of the circulation to the skin and subcutaneous tissue are rare.<sup>39</sup>

Additional skin changes in chronic lymph stasis, primarily in patients with hyperplasia of the lymphatics and valvular incompetence, include verrucae or small vesicles, which

frequently drain clear lymph (lymphorrhea). In patients with lymphangiectasia and reflux of chyle, drainage from the vesicles is milky (chylorrhea; see Fig. 167.2).

Primary lymphedema may be associated with yellow discoloration of the nails.<sup>2,39,40</sup> In the yellow nail syndrome, pleural effusion is also present. The pale yellow color of the nails is most likely caused by impaired lymphatic drainage. Severe clubbing, transverse ridging, friability, and decreased rate of nail growth are also observed.<sup>41,42</sup>

#### Pain

Although some aching or heaviness of the limb is a frequent complaint, intense pain is rare. If a patient with lymphedema complains of marked pain, infection or neuritic pain in the area of scar tissue or radiation treatment should be suspected. Other possible causes of leg swelling, such as venous edema or reflex sympathetic dystrophy, should also be considered (see the later discussion in Differential Diagnosis).

### Complications

#### Infection

The propensity for recurrent soft tissue infection is one of the most troublesome aspects of long-standing lymphedema.<sup>43</sup> Accumulated fluid and proteins provide a good substrate for bacterial growth. Lymphatic dysfunction impairs local immune responses, which plays a permissive role in the propagation of bacterial and fungal invasion. Furthermore, once it is established, soft tissue infection exacerbates the existing lymphatic dysfunction, sometimes irreversibly. With recurrent infection, there is progressive damage of lymphatic capillaries. In primary lymphedema, the reported infection rate is as high as 31%.<sup>10</sup> In all chronic lower extremity edema patients, the lifetime prevalence of cellulitis is estimated to be in excess of 35%.<sup>44</sup>

The clinical presentation of soft tissue infection in lymphedema varies substantially – from the acute manifestation of rapidly progressive infection to only modest exacerbations of edema accompanied by subtle cutaneous erythema in the absence of fever. Recurrent attacks of cellulitis can damage the existing cutaneous lymphatics, exacerbate the skin disease, and further aggravate existing edema.

#### Malnutrition and Immunodeficiency

Lymphangiectasia with protein-losing enteropathy or chylous ascites or chylothorax may result in severe loss of proteins, long-chain triglycerides, cholesterol, and calcium.<sup>45,46</sup> Loss of lymphocytes, immunoglobulins, polypeptides, and cytokines, coupled with impaired immune trafficking through the lymphatic vasculature, results in a state of immunodeficiency that decreases the patient’s ability to resist infections or, potentially, malignant disease.<sup>47</sup>

#### Malignant Tumors

In rare cases, chronic lymphedema of any cause may be complicated by the development of malignant tumors in the involved limb. Lymphangiosarcoma after long-standing secondary lymphedema, originally described by Stewart and Treves,<sup>48</sup>

is a rare malignant disease that frequently results in limb loss or even death. Lymphangiosarcoma is manifested as multicentric lesions with bluish nodules, sclerotic plaques, or bullous changes. Other malignant tumors that appear with increased frequency in lymphedematous limbs include Kaposi sarcoma, squamous cell carcinoma, malignant lymphoma, and melanoma.

## DIAGNOSIS

In most cases of advanced, sustained lymphedema, the characteristic clinical presentation, history, and physical findings establish the diagnosis with near certainty.<sup>49</sup> In more subtle presentations, it may be difficult to distinguish primary lymphedema from other edematous conditions. Additional objective data may be required to confirm the presence of impaired lymphatic flow or the typical pattern of abnormal fluid distribution within tissues. The diagnosis is more difficult to establish in the early stages of disease, particularly when edema is mild or intermittent.

## Physical Examination

The physical examination of a patient with lymphedema should include inspection for cutaneous and subcutaneous fibrosis and peau d'orange and attempts to elicit the pathognomonic Stemmer sign, in which the examiner is unable to tent the skin of the interdigital webs, based on the characteristic loss of cutaneous elasticity in lymphedema (see Fig. 167.4). In some cases, particularly early in the disease, the pitting edema of this condition may be indistinguishable from other local or systemic causes of edema.

## Testing

Objective documentation of lymphatic dysfunction is sometimes useful. Available tests include isotopic lymphoscintigraphy, near infrared fluorescent lymphatic imaging, indirect and direct lymphography, lymphatic capillaroscopy, magnetic resonance imaging, axial tomography, and ultrasonography. Direct lymphography is rarely used today and should be restricted to those patients who are potential candidates for lymphatic surgery. Lymphatic capillaroscopy is available only in specialized centers.

### Lymphoscintigraphy

Isotopic lymphoscintigraphy is a reliable and reproducible method for the confirmation of a lymphedema diagnosis.<sup>50,51</sup> A radiolabeled macromolecular tracer is injected intradermally or subdermally within one of the interdigital spaces of the affected limb. The lymphatic transport of the radiolabeled macromolecule is tracked with a gamma camera. The biokinetic behavior of interstitially applied colloid particles depends on their surface charge and particle size. Particles with small diameters are absorbed into capillaries, whereas those in the 10-nm range, such as antimony trisulfide (Sb<sub>2</sub>S<sub>3</sub>), are absorbed into the lymphatic system. The time needed for activity to appear

in the regional lymph nodes varies according to the physical characteristics of the imaging agent. For example, small particles such as technetium Tc99m-labeled human serum albumin may appear in the pelvic nodes within 10 minutes,<sup>52</sup> whereas relatively large agents, including rhenium and Sb2S3 colloid, should arrive within 30 minutes to 1 hour,<sup>53</sup> respectively. In most centers, 99mTc-Sb<sub>2</sub>S<sub>3</sub> or 99mTc-labeled human serum albumin is used for lymphoscintigraphy,<sup>50,54–56</sup>

**Interpretation.** Lymphoscintigraphy provides a semi-quantifiable assessment of lymphatic function as well as visualization of major lymphatic trunks and lymph nodes. The data can be recorded in a standardized report format, which is helpful for creating reproducible reports when many physicians review these tracings. A sample report form, shown in Figure 167.5, is an adaptation of one proposed by Kleinhans and colleagues for the estimation of a transport index.<sup>57</sup>

In normal limbs, lymphoscintigraphy shows several lymph vessels as the tracer is visualized along the anteromedial aspect of the leg. The injection site, because of the relatively large tracer dose given, does not show details, and no information about lymph distribution in the feet is obtainable. Several lymph channels may be identified in the calf. In the thigh, however, the lymph vessels run close to each other, and separate activity in each larger channel is seldom seen on lymphoscintigrams (Fig. 167.6).

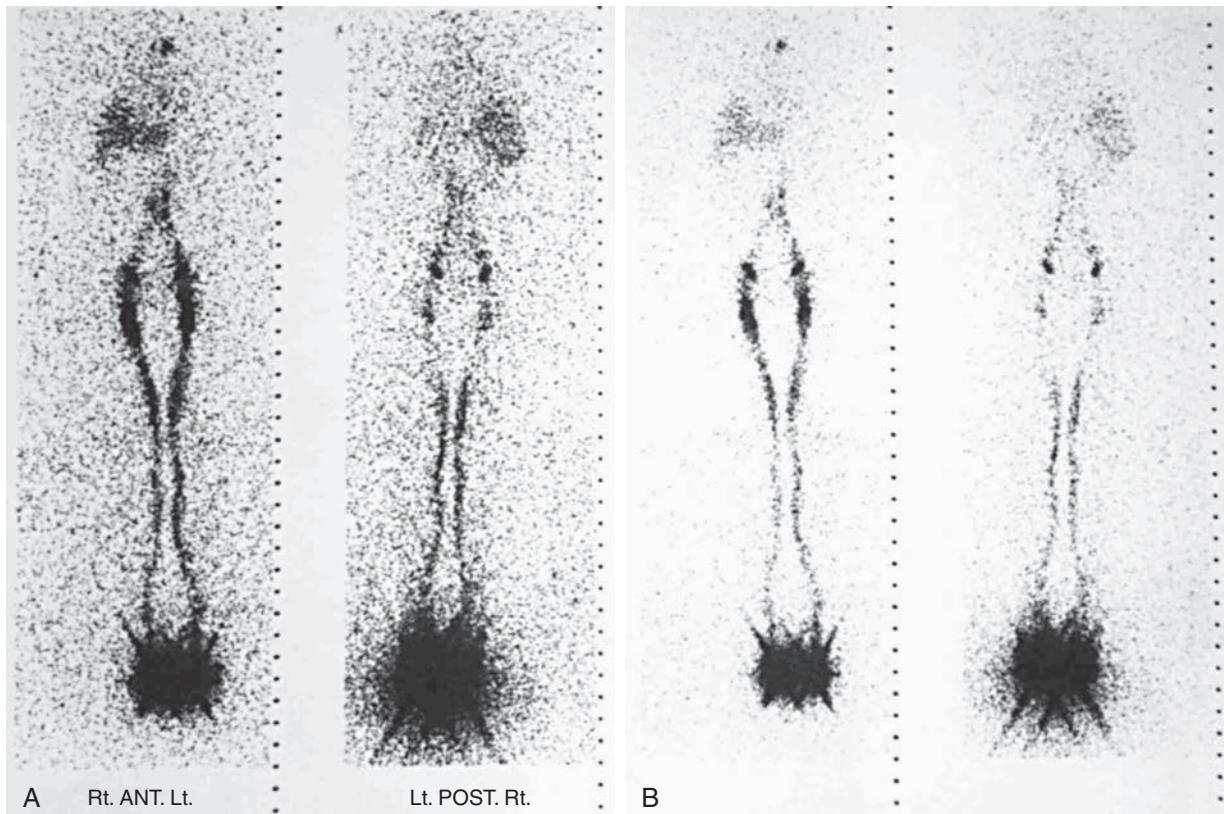
Tracer activity is clear in the inguinal lymph nodes by 60 minutes (range, 15–60 minutes). A faint hepatic uptake, activity in the bladder, and faint traces in the para-abdominal nodes are visible at 1 hour. Three-hour images show intense uptake in the liver; symmetrical and good uptake in the lymph nodes of the groin, pelvis, and abdomen; and occasionally a tracer focus in the left supraclavicular area at the site of the distal thoracic duct.

The qualitative interpretation of images has resulted in moderate sensitivity and excellent specificity for the diagnosis of lymphedema.<sup>55</sup> Quantitative lymphoscintigraphy, with measurement of lymphatic clearance, may improve the detection of early disease,<sup>50</sup> but the results obtained in some studies have been equivocal.<sup>54,55</sup> Neither the image pattern nor the quantitative parameters can reliably distinguish primary from secondary lymphedema.<sup>54,56</sup>

**Lymphedema.** Typical abnormalities observed in lymphedema include dermal backflow (Fig. 167.7), absent or delayed transport of tracer,<sup>58</sup> crossover filling with retrograde backflow, and either absent or delayed visualization of lymph nodes. In primary lymphedema, channels are obliterated or absent; in a smaller percentage of cases, they become ectatic and incompetent. The asymmetry or delayed appearance of radiocontrast material in the proximal nodal tissue can be used as a semiquantitative measure of the severity of lymphatic vascular insufficiency. The density of subcutaneous accumulation of radiotracer (dermal backflow) can also be quantitated, as can the ratio of radioactivity in ipsilateral versus contralateral nodal tissues in the setting of unilateral limb edema. Quantitation has the greatest utility in predicting the likelihood of a beneficial response to therapeutic intervention.

Patient's Initials _____								
Clinic Number _____ Date _____								
LYMPHOSCINTIGRAPHY DATA EVALUATION								
<input type="checkbox"/> Arms <input type="checkbox"/> Legs								
IMAGE	1 Hr		3 Hr		6 Hr		24 Hr	
	R	L	R	L	R	L	R	L
Lymph transport kinetics: 0 = no delay, 1 = rapid, 3 = low-grade delay, 5 = extreme delay, 9 = no transport								
Distribution pattern: 0 = normal, 2 = focal abnormal tracer, 3 = partial dermal, 5 = diffuse dermal, 9 = no transport								
Lymph node appearance time: Minutes								
Assessment of lymph nodes: 0 = clearly seen, 3 = faint, 5 = hardly seen, 9 = no visualization								
Assessment of lymph vessels: 0 = clearly seen, 3 = faint, 5 = hardly seen, 9 = no visualization								
Abnormal sites of tracer accumulation (describe)								

**Figure 167.5** Evaluation Form for Calculation of the Lymphatic Transport Index. (Modified from Kleinhans E, Baumeister RG, Hahn D, et al. Evaluation of transport kinetics in lymphoscintigraphy: follow-up study in patients with transplanted lymphatic vessels. *Eur J Nucl Med.* 1985;10:349. Courtesy Springer-Verlag.)



**Figure 167.6** Anterior and posterior images in two intensity settings from a total-body scan with a dual-headed gamma camera. **(A)** Normal lymphoscintigram. **(B)** Higher intensity settings in the same patient. A large area of high activity and scatter is seen at the feet, where the injection was made. The single well-outlined band in each leg represents the main lymphatic channels. The lymph nodes in the groin and liver, the pelvic and para-aortic nodes, and an area at the site of the upper thoracic duct, are visualized.

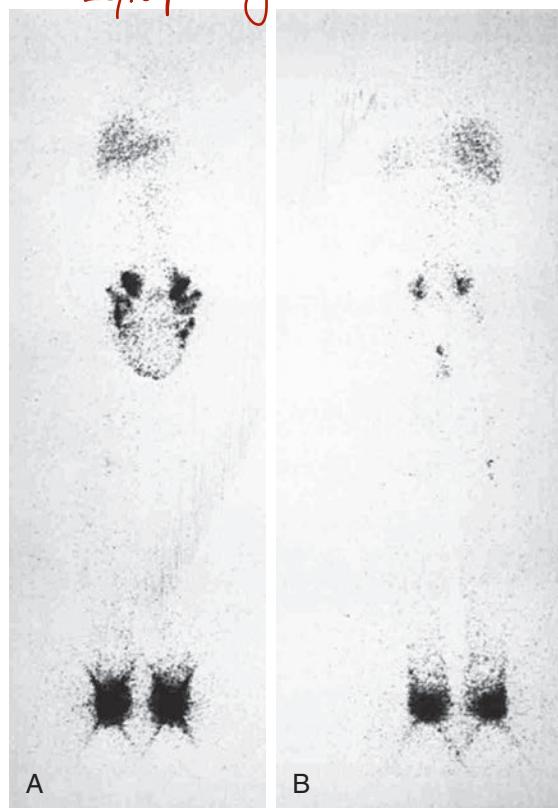
*Lymphedema.*

**Figure 167.7** Radionuclide Lymphoscintigraphy in Chronic Bilateral Lower Limb Lymphedema. The study demonstrates a dramatic degree of dermal backflow, suggesting the presence of lymphatic hypertension and valvular incompetence.

**Lymphangiectasia.** Scintigraphic findings in lymphangiectasia consist of dilated lymph channels with only mild or no delay in lymph transport (Fig. 167.8). Colloid injected into the unaffected lower extremity may reflux into the affected lymphedematous leg because of lymphatic valvular incompetence. Similar reflux of the colloid may be seen in the dilated mesenteric lymphatics (Fig. 167.9) or in the retroperitoneum, perineum, or scrotum. Ruptured lymphatics cause extravasation of the colloid into the abdominal cavity or the chest in patients with chylous ascites or chylothorax. The images are generally not helpful in determining the exact site of the lymphatic leak.

### Advanced Imaging

Lymphedema is typically confined to the epifascial space of the skin and subcutaneous tissue, sparing muscle. This characteristic absence of muscle involvement produces distinctive changes that can be observed with computed tomography (CT) or magnetic resonance imaging (MRI). These typical imaging features facilitate the differentiation of lymphedema from other edematous entities. In lymphedema, the images reveal a characteristic honeycomb distribution of edema within the epifascial structures along with thickening of the skin. In venous edema, both the epifascial and subfascial compartments are affected, whereas in lipedema, there is fat accumulation without fluid. MRI is also helpful in the identification of lymph nodes and enlarged lymphatic trunks and in the differentiation of various potential

*Lymphangiectasia.*

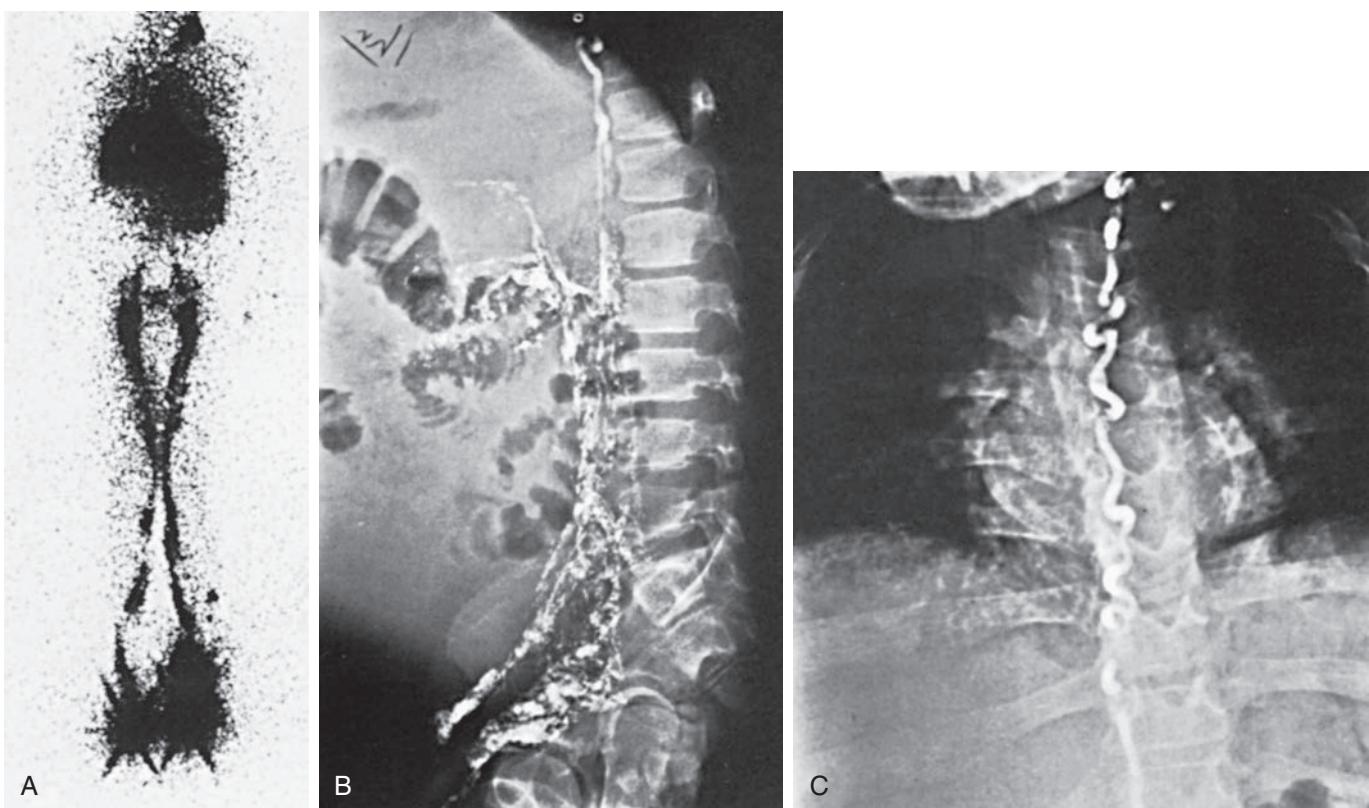
**Figure 167.8** Bilateral leg scintigraphy with anterior (A) and posterior (B) views in a 24-year-old man outlines the swollen scrotum in the 6-hour image. Colloid reflux resulted from dilation and valvular incompetence of the lymphatics.

causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI can complement the functional assessment provided by lymphoscintigraphy.<sup>58</sup>

The development and growing utilization of physiologic surgeries such as lymphaticovenous anastomosis (LVA) and vascularized lymph node transfer (VLNT) has necessitated advanced imaging for characterization of lymphatic anatomy and lymphatic function.<sup>59</sup> Indocyanine green lymphography (ICG-L) may be used preoperatively to identify lymphatic vessels and to predetermine the locations for LVA incisions.<sup>60</sup> However, this technique has a limited depth of penetration and deep lymphatic vessels are not well visualized. Magnetic resonance imaging lymphography (MRL) with intracutaneous administration of an MR contrast agent allows for assessment of both superficial and deep lymphatic vasculature.<sup>61</sup> Additionally, MRL allows for detailed channel morphology, number, depth, and trajectory as well as precise anatomic location of dermal backflow.<sup>62</sup> Interpretation of MRL might be confounded by venous uptake of the gadolinium-based agent. Intravenous administration of ferumoxytol may be used to mask the venous contamination.<sup>63</sup> Quantitative measures of lymphatic transit in PET/MR lymphography have been demonstrated to correlate with clinical severity staging. However, this technique is not readily available.<sup>64</sup>

### Direct Contrast Lymphangiography

Contrast lymphangiography is used primarily before reconstructive lymphatic surgery. Imaging is accomplished through the direct



**Figure 167.9** Lymphoscintigram of an 18-year-old man with lymphangiectasia, protein-losing enteropathy, and chylous ascites. Note the large leg lymphatics (A) and reflux of colloid into the mesenteric lymph vessels (B), filling almost the entire abdominal cavity. Note the large thoracic duct (C).

injection of iodine-based, lipid-soluble agents into the subcutaneous lymphatics, which are first identified by the subcutaneous injection of dye (methylene blue) and then cannulated. Contrast lymphography poses distinct technical difficulties and may, in fact, exacerbate lymphatic malfunction through the accumulation and pooling of the oil-based contrast medium. For these reasons, its use should be limited to preoperative evaluation in specialized centers. Direct contrast lymphography can be adapted to selective interventions in lymphatic patients.<sup>65</sup>

## Differential Diagnosis

The differential diagnosis frequently includes lipedema; a lipodystrophy that typically causes symmetrical enlargement of the lower extremities, particularly in obese females; and venous insufficiency, a hydrostatic cause of lower extremity edema. In lipedema there may be a component of pitting edema; but in contradistinction to lymphedema, there is sparing of the feet despite pronounced enlargement of the calves and thighs. Venous stasis has relatively distinctive cutaneous attributes, including chronic deposits of hemosiderin in the skin. The patient's history and the clinical setting often determine the degree to which chronic venous insufficiency plays a role in the differential diagnosis. However, even when the clinical setting and physical examination suggest the presence of venous stasis, the accompanying venous hypertension may chronically elevate the lymphatic load and thus predispose to the secondary development of lymphatic edema. In practice, therefore,

such patients often have a mixed lymphatic-venous form of chronic edema. The term "phlebolymphedema" is sometimes used to describe this association.

## Systemic Causes

During the evaluation of patients with chronic limb swelling, a systemic cause should be excluded first. Underlying cardiac diseases, such as congestive heart failure, chronic constrictive pericarditis, and severe tricuspid regurgitation, are the most frequent systemic causes leading to pitting or bilateral leg swelling. Hepatic or renal failure, hypoproteinemia, malnutrition, and endocrine disorders (myxedema) are other possible causes of leg swelling. Allergic reactions, hereditary angioedema, and idiopathic cyclic edema are rare systemic causes that should be considered. Chronic use of diuretics may lead to generalized swelling that most frequently affects the extremities and the face. Other drugs that may cause swelling include corticosteroids, some antihypertensive drugs, and anti-inflammatory agents.

## Venous Insufficiency

Among the local or regional causes of limb swelling, chronic venous insufficiency is much more common than lymphedema. In some patients with chronic iliac or iliocaval obstruction, massive swelling of the entire extremity can develop (Fig. 167.10). The usual causes of proximal venous occlusion are



**Figure 167.10** Right leg swelling due to venous insufficiency, caused by chronic iliofemoral venous thrombosis.

deep venous thrombosis or external compression of the vein by tumor or retroperitoneal fibrosis. Whereas lymphedema is usually painless, venous hypertension results in marked pain and cramps after prolonged standing or at the end of the day. Patients with proximal venous obstruction may complain of typical claudication, which is manifested as throbbing pain in the thigh or calf while walking. The pain improves with rest, although elevation of the extremity provides the fastest relief. The presence of varicosity, pigmentation, induration, or venous ulcers makes the diagnosis of venous insufficiency easier. Chronic inflammation in the subcutaneous tissue due to venous stasis may result in destruction of the collecting lymph channels; a mixed venous-lymphatic edema (phlebolymphedema) develops in these patients.

## Vascular Malformation

Patients with congenital vascular malformations frequently have a larger than normal extremity that may be difficult to distinguish from lymphedema (Fig. 167.11). An increase in the length of the affected extremity, the presence of atypical lateral varicosity, and a port-wine stain with underlying developmental abnormality of the deep venous system are characteristic of Klippel-Trénaunay syndrome.<sup>66</sup> Although hypertrophy of the soft tissues and bones is caused by an abnormality in mesenchymal development, congenital lymphedema may also be present in these patients. In patients with high-shunt, high-flow arteriovenous malformations, the extremity is larger than normal and frequently longer as well.<sup>67</sup> A bruit and thrill are



**Figure 167.11** Left leg edema associated with a congenital vascular malformation (Klippel-Trénaunay syndrome).

present, the superficial veins are dilated and frequently pulsatile, and the distal arterial pulses may be diminished.

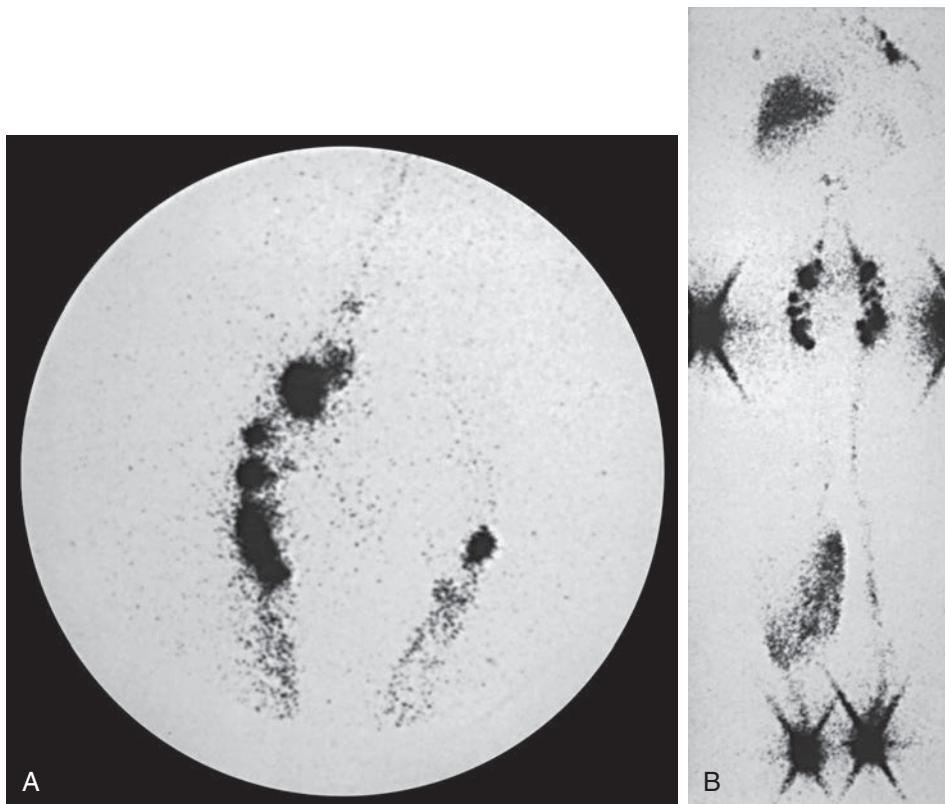
## Lipedema

Lipedema is characterized by deposition of a large amount of fatty tissue in the subcutaneous layers. Most of these patients have morbid obesity; some, mostly females, have fat deposition localized to the lower half of the body. Evaluation of the lymphatic system with lymphoscintigraphy or lymphangiography shows essentially normal findings. More recently, there has been a demonstration of elevated levels of platelet factor 4 (PF4/CXCL4) across the spectrum of lymphatic disease, including lipedema patients, supporting the existing evidence that lipedema arises as a consequence of lymphatic dysfunction.<sup>68</sup>

## Other Causes

Trauma and subsequent reflex sympathetic dystrophy may result in painful swelling of the extremity. Because of disuse, a varying degree of osteoporosis can be observed, and increased sympathetic activity occurs in the limbs of these patients. The swelling is usually the result of high-output lymphatic failure, and increased lymphatic transport may be demonstrated on lymphoscintigraphy (Fig. 167.12). Baker cyst, soft tissue tumor, hematoma, and inflammation such as tenosynovitis or arthritis are additional local causes of limb swelling that should be considered in the differential diagnosis of lymphedema.

Poncet-Weber → + AVF



**Figure 167.12** Lymphoscintigraphy in high-output lymphatic failure due to reflex sympathetic dystrophy of the right leg. (A) Fast lymphatic transport in the affected right leg compared with the normal left leg is evident in the image of the inguinal nodes 20 minutes after injection. (B) Total-body image at 3 hours shows a dermal pattern on the right, but no evidence of proximal lymphatic obstruction.

## DECISION MAKING

Clinical examination of the patient frequently reveals the correct cause of limb swelling. Initial laboratory examinations should include routine blood tests to look for signs of renal or hepatic failure, eosinophilia, or hypoproteinemia. Urinalysis may indicate proteinuria. Once a systemic cause of edema is excluded, the local or regional cause should be confirmed.

Patients at risk for the development of secondary lymphedema (e.g., cancer survivors) pose a distinct challenge for decision making because there is an imperative to recognize the evolving condition at its earliest stages. Within the last decade, there has been introduction of a new technology, bioimpedance spectroscopy, that provides the requisite sensitivity and specificity to detect stage 0 disease.<sup>69</sup> Increasingly, this technique, which is rapidly and efficiently performed at the bedside, will have applicability to the serial monitoring of the patient's treatment response as well.<sup>70</sup> There may also be an evolving role for prospective analysis of body fluids to determine lymphedema risk-in-evolution.<sup>71</sup>

Venous duplex scanning confirms or excludes venous occlusion or valvular incompetence in the leg. CT has become routine for most adult patients with leg swelling to exclude underlying malignant disease. MRI provides the most accurate information in patients with clinical signs of congenital vascular malformation, soft tissue tumor, or retroperitoneal fibrosis.

Lymphoscintigraphy is the test of choice for the confirmation of lymphedema, and a normal finding on lymphoscintigraphic examination essentially excludes the diagnosis of lymphedema. Patients with chronic venous insufficiency may

have abnormal results on lymphoscintigraphic examination, with delayed transport because of mixed lymphatic and venous edema. As mentioned earlier, direct contrast lymphangiography should be performed selectively and should not be part of the routine evaluation of patients with chronic limb swelling. Increasingly, near-infrared fluorescent lymphography is incorporated into the pre-surgical evaluation of lymphedema, when reconstructive approaches are contemplated.<sup>72</sup>

For all patients with chronic lymphedema, conservative management through physical means is the mainstay of therapy. Current indications and patient selection for conservative and surgical therapies of both primary and secondary lymphedema are discussed in detail in Chapters 168 (Lymphedema: Nonoperative Treatment) and 169 (Lymphedema: Surgical Treatment).

## PROSPECTS FOR MOLECULAR THERAPY

Although current therapeutic strategies for lymphedema effectively reduce excess volume, minimize complications, and optimize function, the disease currently lacks a cure. For these reasons, there has been an emphasis on the possible application of effective molecular therapies. Among these, one of the most exciting prospects is therapeutic lymphangiogenesis, a molecular approach based on growing insights into the mechanisms of lymphatic vascular development.

Among the biological factors that initiate and regulate the growth of vascular structures, the vascular endothelial growth factor (VEGF) family plays a central role.<sup>73,74</sup> VEGF-C and

VEGF-D direct the development and growth of the lymphatic vasculature in embryonic and postnatal life by binding to VEGFR-3 receptor, which is nearly exclusively expressed on lymphatic endothelia.<sup>75,76</sup> In transgenic mice that overexpress VEGF-C, the lymphatic vessels demonstrate a hyperplastic, proliferative response, with secondary cutaneous changes.<sup>77</sup> Exogenous administration of VEGF-C upregulates VEGFR-3, leading to a lymphangiogenic response.<sup>78,79</sup>

These molecular observations have helped elucidate the mechanisms that contribute to disease expression in the most common heritable form of lymphedema, the autosomal dominant condition known as Milroy disease. In many affected family cohorts, this disease has been linked to the *FLT4* locus, encoding VEGFR-3.<sup>80</sup> Disease-associated alleles contain missense mutations that inactivate the tyrosine kinase signaling mechanism, thereby preventing downstream cellular activation. It is believed that the mutant form of the receptor is not only functionally inactive but also excessively stable, serving as a potential “sink” for activating ligands. Thus, the normal signaling mechanism is blunted, leading to hypoplastic development of lymphatic vessels.<sup>81,82</sup>

The prospects for therapeutic lymphangiogenesis in human lymphedema have been underscored by the recent description of a mouse model of inherited limb edema that features a mutation in the VEGFR-3 signaling mechanism and a pathologic process that resembles human disease.<sup>75</sup> In this model, therapeutic overexpression of VEGF-C with use of a viral vector induces the generation of new functional lymphatics and the amelioration of lymphedema. Similarly, in a rodent model of acquired postsurgical lymphatic insufficiency (resembling postmastectomy lymphedema), the exogenous administration of human recombinant VEGF-C restores lymphatic flow (as assessed by lymphoscintigraphy),<sup>83,84</sup> increases lymphatic vascularity, and reverses the hypercellularity that characterizes the untreated lymphedematous condition.

Patients with lymphatic and complex vascular malformations frequently present clinically with an important component of peripheral lymphedema. Management of such patients has entered the molecular arena: in vascular malformation, there is growing utilization of mTOR inhibition to stabilize and reverse the vascular presentation. Recent investigations have shown the potential of targeted small molecule modulators of cellular pathways in the treatment of these patients.<sup>85</sup>

Recent investigations of human and experimental lymphedema have increasingly explored the inflammatory substrate of the disease.<sup>86</sup> Among others, the mechanistic role of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) has been identified in the molecular pathogenesis of lymphedema.<sup>86</sup> Antagonism of LTB<sub>4</sub> biosynthesis has been shown to ameliorate experimental lymphedema<sup>87</sup>; furthermore, a pilot clinical investigation of ketoprofen, a lipoxygenase antagonist, has shown human clinical benefit.<sup>88</sup>

Intensive future investigation will be required to verify the therapeutic potential of such approaches and to establish dose-response relationships and the durability of the therapeutic response. In the context of therapeutic lymphangiogenesis, as with other forms of angiogenic therapy, the relative virtues of growth factor therapy versus gene therapy must be established.<sup>89</sup>

## SELECTED KEY REFERENCES

- Cambria RA, Gloviczki P, Naessens JM, Wahner HW. Noninvasive evaluation of the lymphatic system with lymphoscintigraphy: a prospective, semiquantitative analysis in 386 extremities. *J Vasc Surg*. 1993;18:773.
- Description of the techniques and interpretation of upper and lower extremity lymphoscintigraphic studies in normal patients and in those with various lymphatic disorders.*
- Cornish BH, Chapman M, Hirst C, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology*. 2001;34:2–11.
- Prospective demonstration of the high positive predictive value of bioimpedance spectroscopy in the early diagnosis of lymphedema.*
- Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *J Clin Invest*. 2014;124(3):915–921.
- The evolving mechanistic concepts in lymphatic disease are reviewed.*
- Rockson SG, Keeley V, Kilbreath S, et al. Cancer-associated secondary lymphoedema. *Nat Rev Dis Primers*. 2019;5:22.
- State-of-the-art review defining the clinical spectrum, etiology, evaluation, and treatment of secondary, cancer-associated lymphedema.*
- Rockson SG, Miller LT, Senie R, et al. American Cancer Society Lymphedema Workshop. Workgroup III: diagnosis and management of lymphedema. *Cancer*. 1998;83(Suppl American):2882–2885.
- Position statement of the American Cancer Society on the diagnostic evaluation and management of upper extremity lymphedema secondary to the treatment of breast cancer.*

A complete reference list can be found online at [www.expertconsult.com](http://www.expertconsult.com).

## REFERENCES

- Browse N, Stewart G. Lymphedema: pathophysiology and classification. *J Cardiovasc Surg.* 1985;26:91–106.
- Schirger A. Lymphedema. *Cardiovasc Clin.* 1983;13:293–305.
- Kinmonth JB, Taylor GW, Tracy GD, Marsh JD. Primary lymphoedema; clinical and lymphangiographic studies of a series of 107 patients in which the lower limbs were affected. *Br J Surg.* 1957;45:1–9.
- Kinmonth J. The lymphoedemas: general considerations. In: Kinmonth J, ed. *The lymphatics: surgery, lymphography and diseases of the chyle and lymph systems.* London: Edward Arnold; 1982:83.
- Allen E. Lymphedema of the extremities: classification, etiology and differential diagnosis: a study of three hundred cases. *Arch Intern Med.* 1934;54:606.
- Browse NL. The diagnosis and management of primary lymphedema. *J Vasc Surg.* 1986;3:181–184.
- Browse NI, et al. Primary lymphedema. In: Ernst C, ed. *Current therapy in vascular surgery.* Philadelphia: BC Decker; 1987:454.
- Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am.* 1981;245:54–63.
- Rockson SG. Lymphedema. *Am J Med.* 2001;110:288–295.
- Smeltzer D, Stickler G, Schirger A. Primary lymphedema in children and adolescents: a follow-up study and review. *Pediatrics.* 1985;76:206–218.
- Wolfe JH, Kinmonth JB. The prognosis of primary lymphedema of the lower limbs. *Arch Surg.* 1981;116:1157–1160.
- Mendoza E, Schmid-Schonbein GW. A model for mechanics of primary lymphatic valves. *J Biomech Eng.* 2003;125:407–414.
- Rockson S. Syndromic Lymphedema: keys to the kingdom of lymphatic structure and function? *Lymph Res Biol.* 2003;1:181–183.
- Milroy W. An undescribed variety of hereditary edema. *N Y Med J.* 1892;56:505.
- Milroy W. Chronic hereditary edema: Milroy's disease. *JAMA.* 1928;91:1172–1174.
- Lewis JM, Wald ER. Lymphedema praecox. *J Pediatr.* 1984;104:641–648.
- Dahlberg PJ, Borer WZ, Newcomer KL, Yutuc WR. Autosomal or X-linked recessive syndrome of congenital lymphedema, hypoparathyroidism, nephropathy, prolapsing mitral valve, and brachytelephalangy. *Am J Med Genet.* 1983;16:99–104.
- Radhakrishnan K, Rockson SG. The clinical spectrum of lymphatic disease. *Ann NY Acad Sci.* 2008;1131:155–184.
- Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *J Clin Invest.* 2014;124:915–921.
- Gordon K, Mortimer PS, van Zanten M, et al. The St George's Classification Algorithm of Primary Lymphatic Anomalies. *Lymphat Res Biol.* 2021;19(1):25–30.
- Mucke J, Hoepffner W, Scheerschmidt G, et al. Early onset lymphoedema, recessive form – a new form of genetic lymphoedema syndrome. *Eur J Pediatr.* 1986;145:195–198.
- Henriksen HM. Turners's syndrome associated with lymphoedema, diagnosed in the newborns. *Z Geburtshilfe Perinatol.* 1980;184:313–315.
- White SW. Lymphedema in Noonan's syndrome. *Int J Dermatol.* 1984;23:656–657.
- Venencie PY, Dicken CH. Yellow nail syndrome: report of five cases. *J Am Acad Dermatol.* 1984;10:187–192.
- Wheeler ES, Chan V, Wassman R, et al. Familial lymphedema praecox: Meige's disease. *Plast Reconstr Surg.* 1981;67:362–364.
- Abe R, Kimura M, Airosaki A, et al. Retroperitoneal lymphangiomyomatosis with lymphedema of the legs. *Lymphology.* 1980;13:62–67.
- Bull LN, Roche E, Song EJ, et al. Mapping of the locus for cholestasis-lymphedema syndrome (Aagenes syndrome) to a 6.6-cM interval on chromosome 15q. *Am J Hum Genet.* 2000;67:994–999.
- Karkkainen MJ, Ferrell RE, Lawrence EC, et al. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet.* 2000;25:153–159.
- Irrthum A, Karkkainen MJ, Devriendt K, et al. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. *Am J Hum Genet.* 2000;67:295–301.
- Finegold DN, Kimak MA, Lawrence EC, et al. Truncating mutations in FOXC2 cause multiple lymphedema syndromes. *Hum Mol Genet.* 2001;10:1185–1189.
- Irrthum A, Devriendt K, Chitayat D, et al. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. *Am J Hum Genet.* 2003;72:1470–1478.
- Brayton KM, Hirsch AT, O'Brien PJ, et al. Lymphedema prevalence and treatment benefits in cancer: impact of a therapeutic intervention on health outcomes and costs. *PLoS One.* 2014;9:e114597.
- Mak JW. Epidemiology of lymphatic filariasis. *Ciba Found Symp.* 1987;127:5–14.
- Chernin E. The disappearance of bancroftian filariasis from Charleston, South Carolina. *Am J Trop Med Hyg.* 1987;37:111–114.
- Case T, Leis B, Witte M, et al. Vascular abnormalities in experimental and human lymphatic filariasis. *Lymphology.* 1991;24:174–183.
- Dandapat MC, Mohapatro SK, Dash DM. Management of chronic manifestations of filariasis. *J Indian Med Assoc.* 1986;84:210–215.
- O'Donnell Jr TF, Allison GM, Iafrati MD. A systematic review of guidelines for lymphedema and the need for contemporary intersocietal guidelines for the management of lymphedema. *J Vasc Surg Venous Lymphat Disord.* 2020;8:676–684.
- Casley-Smith J, Foldi M, Ryan T, et al. Summary of the 10th International Congress of Lymphology Working Group Discussions and Recommendations, Adelaide, Australia. *Lymphology.* 1985;18:175–180.
- Chant AD. Hypothesis: why venous oedema causes ulcers and lymphoedema does not. *Eur J Vasc Surg.* 1992;6:427–429.
- Samman PD, White WF. The "Yellow Nail" Syndrome. *Br J Dermatol.* 1964;76:153–157.
- Taylor JS, Young JR. The swollen limb: cutaneous clues to diagnosis and treatment. *Cutis.* 1978;21:553–560.
- Fields CL, Roy TM, Ossorio MA, Mercer PJ. Yellow nail syndrome: a perspective. *J Ky Med Assoc.* 1991;89:563–565.
- Quirke M, Ayoub F, McCabe A, et al. Risk factors for nonpurulent leg cellulitis: a systematic review and meta-analysis. *Br J Dermatol.* 2017;177:382–394.
- Burian EA, Karlsmark T, Franks PJ, et al. Cellulitis in chronic oedema of the lower leg: an international cross-sectional study. *Br J Dermatol.* 2021;185(1):110–118.
- Servelle M. Congenital malformation of the lymphatics of the small intestine. *J Cardiovasc Surg (Torino).* 1991;32:159–165.
- Kinmonth JB, Cox SJ. Protein-losing enteropathy in lymphoedema. Surgical investigation and treatment. *J Cardiovasc Surg (Torino).* 1975;16:111–114.
- Randolph GJ, Ivanov S, Zinselmeyer BH, Scallan JP. The lymphatic system: integral roles in immunity. *Annu Rev Immunol.* 2017;35:31–52.
- Stewart NJ, Pritchard DJ, Nascimento AG, Kang YK. Lymphangiosarcoma following mastectomy. *Clin Orthop.* 1995:135–141.
- Rockson SG, Miller LT, Senie R, et al. American Cancer Society Lymphedema Workshop. Workgroup III: Diagnosis and management of lymphedema. *Cancer.* 1998;83:2882–2885.
- Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. *Radiology.* 1988;167:729–735.
- Szuba A, Shin WS, Strauss HW, Rockson S. The third circulation: radio-nuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med.* 2003;44:43–57.
- Devoogdt N, Pans S, De Groef A, et al. Postoperative evolution of thickness and echogenicity of cutis and subcutis of patients with and without breast cancer-related lymphedema. *Lymphat Res Biol.* 2014;12:23–31.
- Stewart G, Gaunt JI, Croft DN, Browse NL. Isotope lymphography: a new method of investigating the role of the lymphatics in chronic limb oedema. *Br J Surg.* 1985;72:906–909.

54. Vaqueiro M, Gloviczki P, Fisher J, et al. Lymphoscintigraphy in lymphedema: an aid to microsurgery. *J Nucl Med.* 1986;27:1125–1130.
55. Gloviczki P, Calcagno D, Schirger A, et al. Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. *J Vasc Surg.* 1989;9:683–689; discussion 690.
56. Cambria RA, Gloviczki P, Naessens JM, Wahner HW. Noninvasive evaluation of the lymphatic system with lymphoscintigraphy: a prospective, semiquantitative analysis in 386 extremities. *J Vasc Surg.* 1993;18:773–882.
57. Kleinhans E, Baumeister RG, Hahn D, et al. Evaluation of transport kinetics in lymphoscintigraphy: follow-up study in patients with transplanted lymphatic vessels. *Eur J Nucl Med.* 1985;10:349–352.
58. Mitsumori LM, McDonald ES, Wilson GJ, et al. MR lymphangiography: How I do it. *J Magn Reson Imaging.* 2015;42:1465–1477.
59. Forte AJ, Boczar D, Huayllani MT, et al. Targeted therapies in surgical treatment of lymphedema: a systematic review. *Cureus.* 2019;11:e5397.
60. Unno N, Inuzuka K, Suzuki M, et al. Preliminary experience with a novel fluorescence lymphography using indocyanine green in patients with secondary lymphedema. *J Vasc Surg.* 2007;45:1016–1021.
61. Mills M, van Zanten M, Borri M, et al. Systematic review of magnetic resonance lymphangiography from a technical perspective. *J Magn Reson Imaging.* 2021;53(6):1766–1790.
62. Pons G, Clavero JA, Alomar X, et al. Preoperative planning of lymphaticovenous anastomosis: The use of magnetic resonance lymphangiography as a complement to indocyanine green lymphography. *J Plast Reconstr Aesthet Surg.* 2019;72:884–891.
63. Neligan PC, Kung TA, Maki JH. MR lymphangiography in the treatment of lymphedema. *J Surg Oncol.* 2017;115:18–22.
64. Long X, Zhang J, Zhang D, et al. Microsurgery guided by sequential preoperative lymphography using (68)Ga-NEB PET and MRI in patients with lower-limb lymphedema. *Eur. J Nucl Med Mol Imaging.* 2017;44:1501–1510.
65. Pieper CC, Hur S, Sommer CM, et al. Back to the Future: Lipiodol in Lymphography – From Diagnostics to Theranostics. *Invest Radiol.* 2019;54:600–615.
66. Gloviczki P, Stanson AW, Stickler GB, et al. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery.* 1991;110:469–479.
67. Gloviczki P. Arteriovenous fistulas and vascular malformations. In: Ascher E, ed. *Haimovici's vascular surgery.* 5th ed. Malden, MA: Blackwell Publishing; 2004 991.
68. Ma W, Gil HJ, Escobedo N, et al. Platelet factor 4 is a biomarker for lymphatic-promoted disorders. *JCI Insight.* 2020;5(13):e135109.
69. Cornish BH, Chapman M, Hirst C, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology.* 2001;34:2–11.
70. Cornish B, Bunce I, Ward L, et al. Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. *Breast Cancer Res Treat.* 1996;38:169–176.
71. Lin S, Kim J, Lee MJ, et al. Prospective transcriptomic pathway analysis of human lymphatic vascular insufficiency: identification and validation of a circulating biomarker panel. *PLoS One.* 2012;7:e52021.
72. Narushima M, Yamamoto T, Ogata F, et al. Indocyanine green lymphography findings in limb lymphedema. *J Reconstr Microsurg.* 2016;32:72–79.
73. Olofsson B, Jeltsch M, Eriksson U, Alitalo K. Current biology of VEGF-B and VEGF-C. *Curr Opin Biotechnol.* 1999;10:528–535.
74. Veikkola T, Karkkainen M, Claesson-Welsh L, Alitalo K. Regulation of angiogenesis via vascular endothelial growth factor receptors. *Cancer Res.* 2000;60:203–212.
75. Joukov V, Pajusola K, Kaipainen A, et al. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. *EMBO J.* 1996;15(2):290–298.
76. Kaipainen A, Korhonen J, Mustonen T, et al. Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development. *Proc Natl Acad Sci USA.* 1995;92:3566–3570.
77. Jeltsch M, Kaipainen A, Joukov V, et al. Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. *Science.* 1997;276:1423–1425.
78. Oh SJ, Jeltsch MM, Birkenhager R, et al. VEGF and VEGF-C: specific induction of angiogenesis and lymphangiogenesis in the differentiated avian chorioallantoic membrane. *Dev Biol.* 1997;188:96–109.
79. Enholm B, Karpanen T, Jeltsch M, et al. Adenoviral expression of vascular endothelial growth factor-C induces lymphangiogenesis in the skin. *Circ Res.* 2001;88:623–629.
80. Gordon K, Varney R, Keeley V, et al. Update and audit of the St George's classification algorithm of primary lymphatic anomalies: a clinical and molecular approach to diagnosis. *J Med Genet.* 2020;57(10):653–659.
81. Karkkainen MJ, Petrova TV. Vascular endothelial growth factor receptors in the regulation of angiogenesis and lymphangiogenesis. *Oncogene.* 2000;19:5598–5605.
82. Karkkainen MJ, Saaristo A, Jussila L, et al. A model for gene therapy of human hereditary lymphedema. *Proc Natl Acad Sci USA.* 2001;98:12677–12682.
83. Szuba A, Skobe M, Karkkainen M, et al. Therapeutic lymphangiogenesis with human recombinant VEGF-C. *FASEB J.* 2002;16:U114–U130.
84. Cheung L, Han J, Beilhack A, et al. An experimental model for the study of lymphedema and its response to therapeutic lymphangiogenesis. *BioDrugs.* 2006;20:363–370.
85. Kalwani NM, Rockson SG. Management of lymphatic vascular malformations: a systematic review of the literature. *J Vasc Surg Venous Lymphat Disord.* 2021;9(4):1077–1082.
86. Jiang X, Nicolls MR, Tian W, Rockson SG. Lymphatic dysfunction, leukotrienes, and lymphedema. *Annu Rev Physiol.* 2018;80:49–70.
87. Tian W, Rockson SG, Jiang X, et al. Leukotriene B4 antagonism ameliorates experimental lymphedema. *Sci Transl Med.* 2017;9(389):eaal3920.
88. Rockson SG, Tian W, Jiang X, et al. Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema. *JCI Insight.* 2018;3(20):e123775.
89. Rockson SG. Experimental lymphedema: can cellular therapies augment the therapeutic potential for lymphangiogenesis? *J Am Heart Assoc.* 2012;1:e003400.

# Lymphedema: Nonoperative Treatment

ALBEIR Y. MOUSA, RAMEZ MORCOS, and MIKE BROCE

INTRODUCTION	2215
BACKGROUND	2216
PREVENTIVE MEDICINE	2216
Patients at Risk	2216
Edema Preventive Measures	2218
MECHANICAL REDUCTION OF LIMB SWELLING	2219
Complex Decongestive Therapy	2219
<i>Manual Lymphatic Drainage</i>	2220
<i>Compression Bandaging</i>	2220
<i>Compression Garments</i>	2221
<i>Nonelastic Compression</i>	2223
<i>Sequential Pneumatic Compression</i>	2223
<i>Pressure Level</i>	2224
<i>Exercise</i>	2225

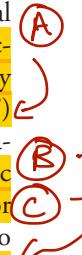
Skin Care and Nail Care	2225
Therapeutic Approach Based on Clinical Stages	2225
Level of Evidence	2225
SURGICAL TREATMENT	2225
Physiological Intervention	2225
Excisional Procedures	2225
OTHER TREATMENT	2226
SUPPORTING EVIDENCE	2226
COMPLICATIONS	2227
Skin Infections	2227
Malignancy	2227
Psychological Impairment	2227
INSURANCE ROLE	2228
IDEAL OUTPATIENT LYMPHEDEMA CLINIC	2228
HELPFUL RESOURCES	2228

## INTRODUCTION

In this chapter, we examine the lymphatic system (Fig. 168.1) and its malfunction with a focus on current nonoperative treatments. The diagnosis and surgical treatment of lymphedema are discussed in other chapters. It is important to know that pathology of the lymphatic system is linked mainly to lipid and protein malabsorption, accumulation of protein-rich interstitial fluid, and the inability to return lymph to the systemic circulation leading to the development of lymphedema. Since there is no cure for lymphedema, treatment strategies focus on methods to reduce limb swelling and prevent secondary infections. A variety of mechanical therapies that share the common goals of reducing limb volume and preventing recurrence serve as the cornerstones of current contemporary management. Other components of nonoperative management include skin hygiene, appropriate clothing, avoidance of trauma, and compression techniques and physiotherapy. Other treatment modalities are discussed briefly, including, pharmacotherapy, laser therapy, and gene therapy. Failure to manage chronic

lymphedema may result in devastating limb swelling with increased morbidity, decreased quality of life and productivity,<sup>1</sup> increased risk of infection, and even rarely late-onset malignancy. Lastly, we briefly discuss the psychological status of the patients, insurance concerns, and what would be considered the ideal lymphedema clinic.

In general terms, lymphedema is the result of an imbalance between the production and transport of lymph,<sup>2-4</sup> which leads to an accumulation of protein-rich fluid in the interstitial spaces. This imbalance may be the result of increased production of lymph which exceeds the maximal transport capacity of normal lymphatic conduits (so-called “high-input failure”) such as occurs in the setting of venous hypertension. Alternatively, congenital absence or deficiency of normal lymphatic channels or damage to lymph vessels by infection, surgery or radiation, may reduce the capacity of the lymphatic system to handle even a normal volume of lymph production (“low output failure”). In either case, the net effect is an accumulation of extracellular, protein-rich interstitial fluid that may lead to a cascade of inflammatory changes culminating in progressive,



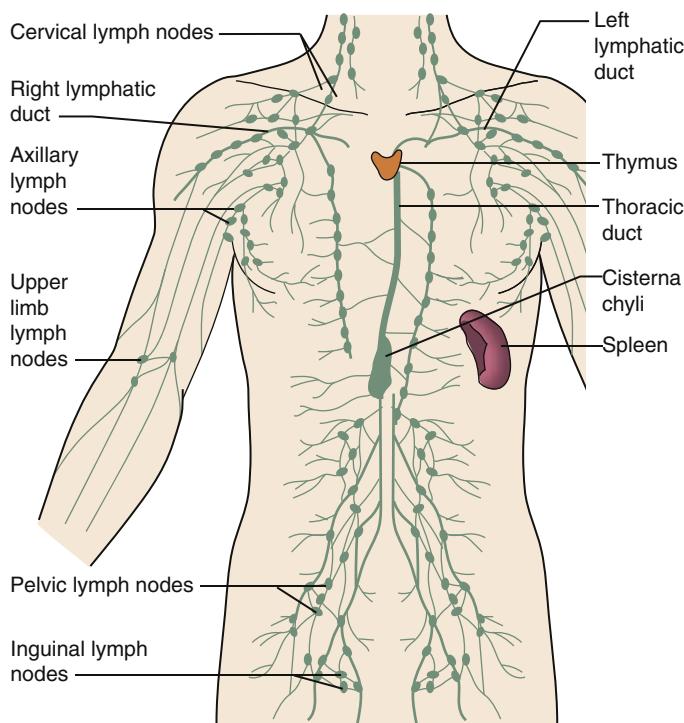


Figure 168.1 Lymphatic System.

irreversible subcutaneous fibrosis. Given the central role of the lymphatic system in potent immune responses, lymphedema results in increased risk for infection and rarely, late-onset malignancy.

Lymphedema is classified as primary or secondary. Primary lymphedema is typically related to developmental aplasia, hypoplasia, agenesis, or fibrosis of the lymphatic system. Congenital primary lymphedema is usually recognized in the first year of life and is more common in boys than girls. When primary lymphedema appears before the age of 35, it is called "lymphedema praecox." If it appears after the age of 35, then it is referred to as "lymphedema tarda."<sup>5</sup> Both lymphedema praecox and tarda are 2 to 10 times more common in females than males.

Secondary lymphedema is much more common than primary lymphedema and is most frequently related to lymph node dissection, radiation, traumatic injury or malignancy (Fig. 168.2). Of note, chronic venous disease (CVD) is a common cause of secondary lymphedema and it is called venous lymphedema<sup>6</sup>; it is sometimes misdiagnosed as primary lymphedema leading to suboptimal treatment.<sup>7</sup>

## BACKGROUND

The diagnosis of lymphedema can usually be based on history and physical examination. The clinical history should include age of onset, areas of involvement, the progression of symptoms, family history, past medical history including any related surgery, travel, trauma, and radiation. The physical exam should focus on the distribution, severity, and character of edema. The International Society of Lymphology describes, Stage I lymphedema as characterized by soft pitting edema that

is largely reversible with elevation. Stage II is irreversible, characterized by fibrosclerotic changes, inflammation, hardening, or thickening, along with non-pitting edema. Stage III or lymphostatic elephantiasis is characterized by an extreme increase in the size and texture of the skin often with typical papillomas and/or deep skin folds. Stemmer's sign describes the inability to pick up a fold of skin at the base of the second toe due to the loss of skin elasticity. A prominent transverse crease across the front of the ankle is common. Peau d'orange (literally "skin of the orange") describes the cutaneous edema typical of lymphatic obstruction. Duplex ultrasound of the venous system is appropriate to rule out the presence of venous pathology. Chronic venous hypertension may lead to the accumulation of interstitial fluids that increase the workload on the lymphatic system to adequately drain the interstitial fluid resulting in a mixed disease called venous lymphedema.<sup>2</sup> Lymphoscintigraphy is both sensitive and specific for lymphedema. Conservative treatment with repeat lymphoscintigraphy is recommended for a patient with an initial negative study and high clinical suspicion of lymphedema (Fig. 168.3).<sup>8</sup> Another classification method considers the malignant versus benign features of the lymphedema (Fig. 168.4).

The approach most often used to classify lymphedema is the Common Terminology Criteria for Adverse Events v3.0, which was developed for grading adverse events in the context of clinical trials.<sup>9</sup> This grading system provides not only objective measures (inter-limb discrepancy in volume or circumference), but also subjective and clinical assessments for lymphedema diagnosis (Table 168.1).

There are other rare forms of lymphedema such as Meige disease (which has autosomal dominant inheritance, a familial type of lymphedema praecox associated with distichiasis),<sup>3,4,10,11</sup> Milroy disease (which has autosomal dominant with incomplete penetrance),<sup>5</sup> and yellow nail syndrome (which is a rare disorder that occurs after the age of 50 but the juvenile form has been reported. Although the etiology remains unclear, there is a role of the lymphatic impairment. The syndrome is diagnosed when the triad of yellow nail discoloration, lower limb lymphedema, and pulmonary manifestations (a chronic cough, bronchiectasis, pleural effusion) coexist. Usual treatment is oral vitamin E, antifungal, surgical removal of the pleural effusion, along with lymphedema treatment.<sup>7</sup>

esashes  
from  
lymphatic  
glands

## PREVENTIVE MEDICINE

### Patients at Risk

Identifying patients who are at risk is the essential step for preventive medicine. In undeveloped countries, *Wuchereria bancrofti* is the most common cause of lymphedema and filariasis. The effort to decrease the transmission in endemic areas may decrease the incidence of lymphedema; the mass administration of diethylcarbamazine plus ivermectin significantly decreased lymphatic filariasis.<sup>12,13</sup> It was reported that higher doses of albendazole did not improve the result, but on the other hand, was associated with more severe side effects. It was

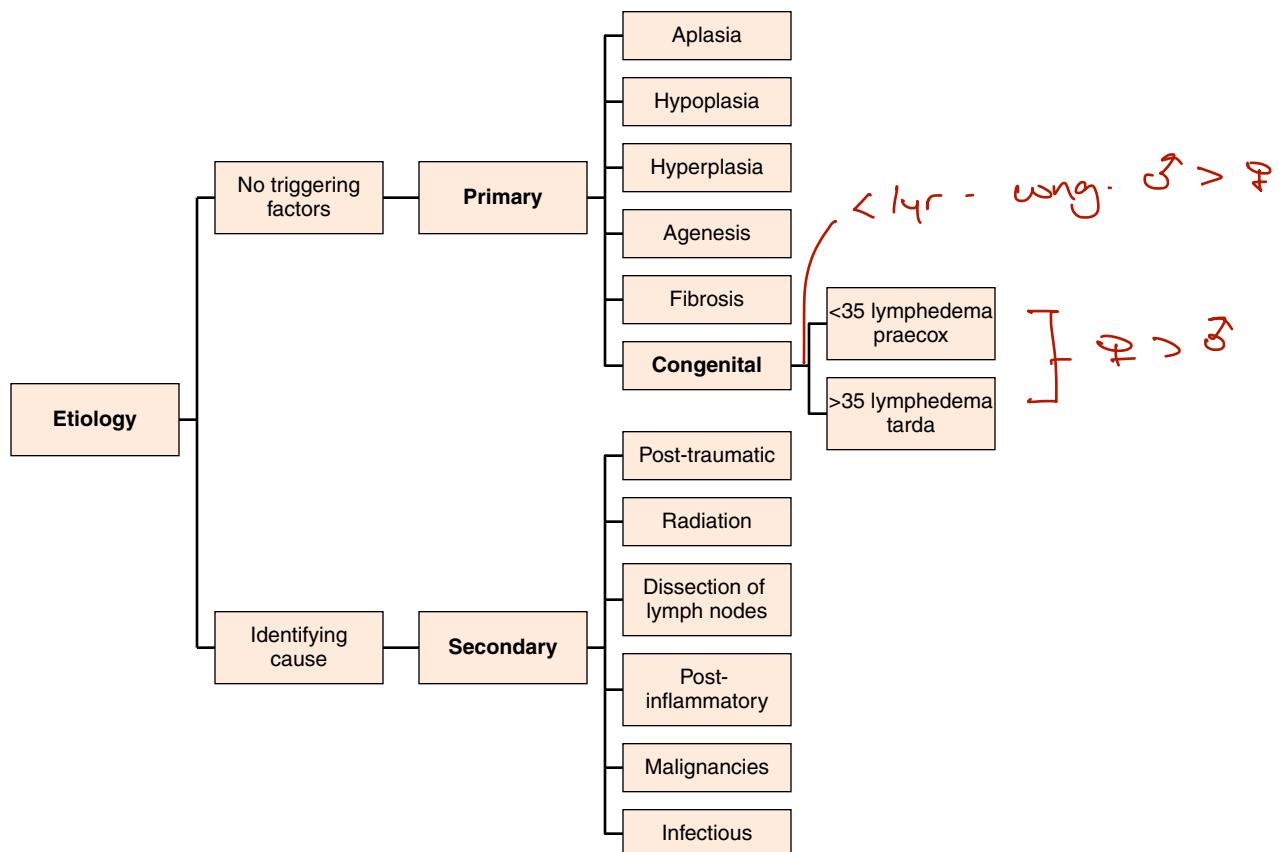


Figure 168.2 Lymphedema Etiology.

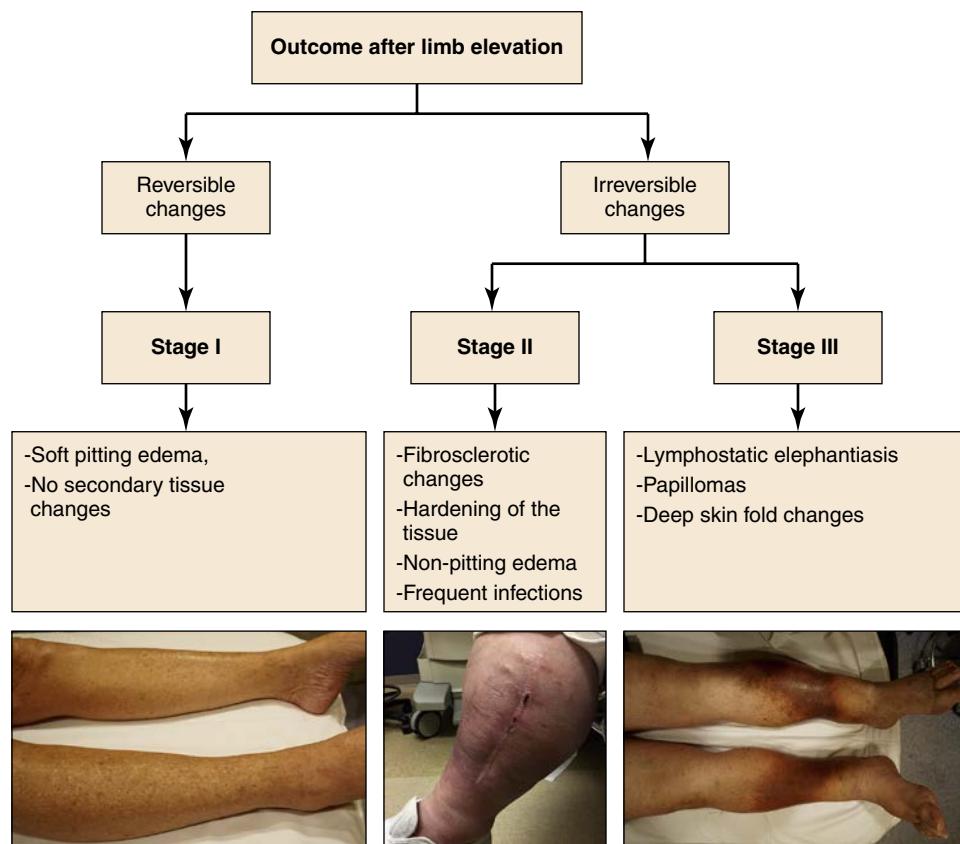


Figure 168.3 Diagnosis, Classification, and Clinical Features.

Malignant lymphedema	Benign lymphedema
-Sudden onset -Rapid progression -Pain -Paresthesia, paresis or paralysis -Skin changes -Dilated superficial veins	-Usually unilateral -Normal skin color (except with stage III) -Positive Stemmer sign -No pain -No paresis/paralysis (except with radiation damage, stroke, etc.) -Dorsum of hand/foot involved with swelling -Deep natural skin folds

Figure 168.4 Malignant vs. Benign Features.

**TABLE 168.1** Common Terminology Criteria for Adverse Events (CTCAE) • *Different grading system*

Grade	Inter-Limb Discrepancy	Visible Difference
I	5%–10%	Swelling or obscuration of anatomic architecture on close inspection; pitting edema
II	10%–30%	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour
III	More than 30%	Gross deviation from normal anatomic contour; interfering with activities of daily living
IV	Progression to malignancy (e.g., lymphangiosarcoma); amputation indicated; disabling lymphedema	

suggested that alternative regimens could be useful in the later stages of existing programs or to achieve elimination more rapidly in areas where programs have yet to start.<sup>14</sup>

In developed countries, there are two groups of patients who are at high risk of developing lymphedema. The first group contains patients who undergo **radiation of a lymph node group and/or surgical lymphadenectomy** as part of cancer treatment. Efforts to spare lymph nodes during cancer treatment have proven to be effective in reducing the incidence of lymphedema. For instance, for patients with breast cancer, the standard of care in staging has evolved from dissection of 2nd ± 3rd level axillary lymph nodes to performing sentinel lymph node biopsy, followed by complete dissection only if nodal metastases are detected; this approach has reduced the incidence of lymphedema by approximately 80%.<sup>15–18</sup> Similarly, the use of sentinel lymph node biopsy to identify lymph nodes involved by metastatic melanoma has significantly reduced the need for extensive inguinal and pelvic lymphadenectomy and has also reduced potential lower extremity lymphedema. Interestingly, it also has been reported that being obese or overweight may place women at risk for developing lymphedema following

breast cancer treatment,<sup>19</sup> and is considered a major risk factor for lymphedema.<sup>20,21</sup> It is also worth noting that **BMI over 50,<sup>9</sup> the extent of local surgery, local radiation, delayed wound healing, and tumor-related lymphatic obstruction** are also risk factors that exacerbate the risk of lymphedema development in patients being treated for breast cancer.<sup>12</sup>

The second high-risk group is patients with **recurrent cellulitis**; a damaged lymphatic system that undermines the system's functional capacity and eventually causes lymphedema. Recurrent cellulitis may cause **permanent irreversible lymphatic compromise**. Other forms of chronic infection can cause sufficient inflammation to damage the lymphatics.<sup>22</sup> However, because lymphedema is the strongest risk factor for cellulitis,<sup>23,24</sup> at times it is difficult to distinguish between cellulitis as the initial presentation of previously subclinical lymphedema or independently caused lymphedema. The low-grade chronic inflammation produced by rosacea could be caused by the lymphedema of facial structures, particularly the eyelids. The goal of starting **prophylactic antibiotics** for this group is necessary to prevent recurrent infection. The aim of current therapy should be directed at **resolving acute infections and the prevention of recurrent episodes of cellulitis** (Fig. 168.5).<sup>25</sup>

Patients with a history of fungal infection, including candidiasis and tinea, should use **topical antifungal medications**. Routine use of **topical clotrimazole cream (1%)** or miconazole nitrate lotion or cream (2%) is sufficient for most patients. Oral fluconazole or itraconazole may be needed for recalcitrant or extensive infection. No studies have definitively addressed the efficacy of these treatments in terms of documenting a decreased incidence of lymphedema in those patients.

## Edema Preventive Measures

It has been reported that **lifestyle modifications**, such as changes in diet and increased exercise, have helped to decrease the progression of lymphedema.<sup>26,27</sup> In terms of preventive care, several self-care measures can be practiced to decrease lymphedema, including maintaining **daily skin hygiene** (e.g., the limbs should be washed regularly with soap and water) and it is important to **avoid trauma**; either of these can be the nidus of infections.

Other lifestyle or daily habits include **elevating the affected limb**, modifying dietary intake to include **less salt and more protein**, wearing **properly fitted compression stockings**, and walking and performing **aerobic exercises to promote lymphatic flow**. It is important to monitor and measure limb volume as an objective parameter during the follow-up with patients with lymphedema.<sup>28</sup>

Exercise helps to decrease lymphedema swelling; during the **contraction phase of the muscle, the lymph gets pushed to an alternative lymph node through the lymph vessels**.<sup>29,30</sup> Historically, patients at risk for developing lymphedema have been advised against "overusing" their at-risk body parts for fear of triggering lymphedema. This recommendation is based on anecdotal associations of the initial onset of lymphedema with episodes of vigorous exercise or sustained, repetitive use of the at-risk extremity. Recommendations against exercise have recently been tempered and re-phrased, based on the results of

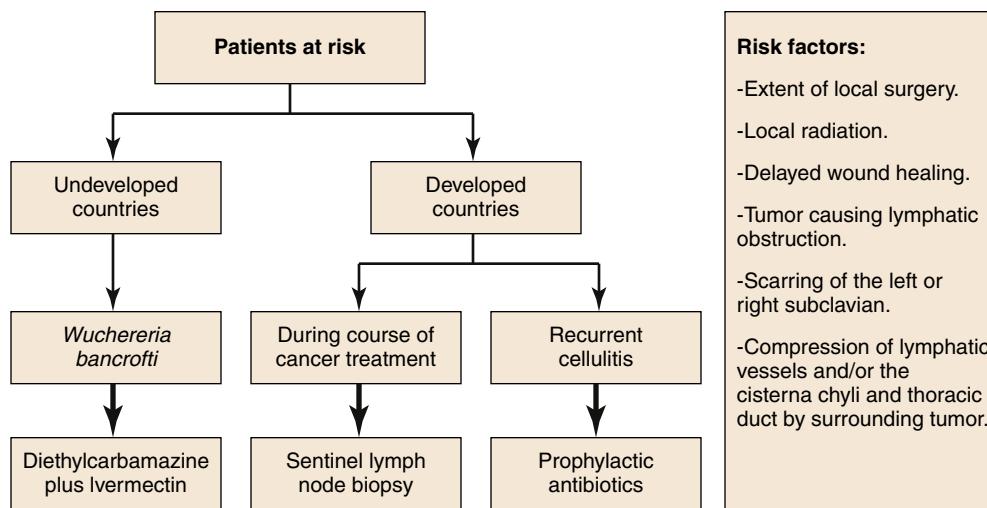


Figure 168.5 Preventive Medicine.

	<b>Skin hygiene</b>		<b>Clothing precautions</b>		<b>Trauma avoidance</b>		<b>Fungal infection control</b>
<ul style="list-style-type: none"> <li>-Wash daily</li> <li>-Apply moisturizer</li> </ul>		<ul style="list-style-type: none"> <li>-Wear cooling fabrics</li> <li>-Avoid synthetics</li> <li>-Wear loose-fitting garments</li> </ul>		<ul style="list-style-type: none"> <li>-Treat cuts, scrapes, and puncture wounds immediately with cleansing and topical antibiotic cream</li> </ul>		<ul style="list-style-type: none"> <li>-Apply topical antifungal agents on a scheduled or intermittent basis as needed</li> </ul>	
	<b>Limb elevation</b>		<b>Dietary</b>		<b>Exercise</b>		<b>Compression stocking</b>
<ul style="list-style-type: none"> <li>-Elevated bed positioning</li> <li>-Periodic daily elevation</li> </ul>		<ul style="list-style-type: none"> <li>-Monitoring fluid intake</li> <li>-Weight management</li> <li>-Low sodium meals</li> <li>-High protein</li> </ul>		<ul style="list-style-type: none"> <li>-Aerobic</li> <li>-Gentle resistive</li> <li>-Stretching exercises</li> </ul>		<ul style="list-style-type: none"> <li>-Obtain a correct fit</li> </ul>	

Figure 168.6 Edema Preventive Measures.

several randomized controlled trials.<sup>31,32</sup> These trials revealed that a gentle, incremental program of full-body resistive training, started at a low level and increased gradually, did not increase the incidence of lymphedema among at-risk breast cancer survivors, and might have been protective. Similar trials have yet to shed light on the risk–benefit profile of exercise in lower extremity lymphedema. An international study LIMP-PRINT (Lymphoedema IMpact and PRevalence-INTernational) sought to evaluate the size and impact of lymphedema and chronic edema in different countries and health services across the world. That study highlighted that prevalence of chronic edema varied according to the facility type, ranging from 5.0% to 66.1%.<sup>13</sup>

Exercise routines should include **combinations of lymphedema remedial exercises** (e.g., active, repetitive, non-resistive motion of the involved body part) along with three main types of exercise (i.e., aerobic, strength, and flexibility). Other possible types of exercise could be considered but have not been adequately studied in people with lymphedema (e.g., Pilates, yoga, Tai Chi, Qigong, aquatic exercise, trampoline rebounding, breathing exercises, and relaxation). Finally, patients should avoid exposure to extreme heat or cold, at least to the extent that tissue injury may occur, such as a burn or frostbite (Fig. 168.6).<sup>33</sup>

## MECHANICAL REDUCTION OF LIMB SWELLING

Currently, there is no cure for lymphedema, and management is based on a series of lifelong physical therapies.<sup>1</sup> Practitioners at lymphedema centers or clinics should set specific goals tailored to each patient, while at the same time base treatment on the stage and grade of the lymphedema. The aim of the treatment and goals should be to **minimize limb diameter, decrease edema, maintain skin integrity, prevent infection, and encourage patients to use self-care to monitor their skincare and weight reduction**.

### Complex Decongestive Therapy

The standard of care for lymphedema is commonly referred to as **complex decongestive therapy (CDT)**. CDT was popularized in Europe by Földi et al.,<sup>34</sup> Kasseroller,<sup>35</sup> and Leduc et al.,<sup>36</sup> as well as Casley-Smith<sup>37</sup> in Australia, and was later introduced to the United States in the early 1990s; CDT continues to be **first-line therapy for stage II and III lymphedema**. CDT's success has been documented worldwide.<sup>38–42</sup> It is the combination of four components and two phases.

The components are: (1) manual lymphatic drainage; (2) compression bandaging; (3) compression garments; and (4) compression devices. Volume reductions were reported after the use of compression garments, pumps, and manual lymphatic drainage. However, the greatest improvements were reported when these treatments were combined in a treatment program.<sup>43</sup>

The two phases are:

1. Initial or reductive phase (phase I); the aim to reduce the size of the affected area and to emphasize proper skincare.
2. Maintenance phase (phase II), which begins immediately after phase I; the main aim is to maintain the gains made during phase I, and requires life-long self-maintenance.

Although very successful, CDT requires a large investment of time from the therapist and patient. Therapists must be specially trained to perform standardized techniques of manual lymph drainage (MLD) and complex multilayered wrapping. Currently, the treatment is offered in specialized practices, but other programs are becoming more widely available. In the United States, there is a voluntary certification process that involves documentation of training, logging treatment hours, and a certification examination to ensure competence. This effort was initiated and coordinated by the Lymphology Association of North America (LANA). Certified therapists are listed on LANA's website,<sup>44</sup> which can be searched by name, state, or zip code. Although phase I CDT can achieve abrupt and dramatic reductions in limb volume, long-term success requires ongoing phase II home-based program maintenance. Without consistent adherence to the program, a patient's lymphedema volume will re-accumulate. The multi-week intensive treatment program also may be limited by insurance coverage in the United States; modified programs, often with inferior outcomes, maybe a patient's only option. An alternative program that utilizes home compression bandaging and exercise may achieve comparable results to conventional CDT in some patients with milder (e.g., stage II) lymphedema. Patient compliance and adherence to the therapy is normally 60% to 70%, which in turn, requires trained therapists to have an average volume reduction of 50%.<sup>40,45</sup> It is worth mentioning a recent pilot study to compare the short-term effects of hyperbaric oxygen therapy (HBO) and CDT in 10 patients with breast cancer-related lymphedema, who were divided into two groups and received 10 treatments over 2 weeks. Patients who received combined therapy HBO+CDT showed better parameters as measured by bioimpedance spectroscopy. There was no difference in circumference of the upper limbs nor quality-of-life questionnaire results.<sup>14</sup>

### Manual Lymphatic Drainage

First developed by Emil Vodder in 1936,<sup>46</sup> the theory behind MLD is to apply gentle pressure to the skin to stretch the superficial lymphatics, to enhance the contraction and sequestration of lymphatic vessels, and to help the unidirectional flow of lymph to relieve congestion and to minimize subsequent subcutaneous fibrosis. MLD is performed in a series of steps. Before MLD is started, it is beneficial to divide the trunk into six areas (see Fig. 168.1), which correlate to the drainage territories of

the cervical, axillary, and inguinal lymph node beds. Treatment is first initiated by massaging an intact section adjacent to the section that includes the affected limb or body part to prepare the area to receive congested lymph. This maneuver has been shown to redirect lymph fluid toward functioning lymphatic territories.<sup>47</sup> Practiced in this fashion, MLD has been shown to redirect lymph toward functioning lymphatic territories.<sup>47</sup> MLD techniques are particularly of great interest when treating body parts that are not conducive to sustained compression (e.g., face, breast, genitalia, and trunk) (Fig. 168.7). The evidence from a recent systematic review and other studies have shown improvement when combining MLD with compression bandages in treating lymphedema; however, the evidence did not support using MLD by itself – independent from CDT for limb volume reduction.<sup>48–50</sup> Yet, Moseley et al. reported that MLD alone did contribute to improvement in self-reported symptoms when used in the palliative care setting.<sup>2,51</sup> Also, there is some evidence that there are several benefits to practicing standard manual massage with a new device, Linforoll.<sup>52</sup>

Another recent study comparing MLD to CDT showed no significant differences ( $P = \text{NS}$ ) in the five measurement levels of the arm circumference at the 5th week and 3rd month with a similar improvement in shoulder ROM, pain, tightness, and heaviness sensations in both groups ( $P < 0.05$ ).<sup>15</sup> Others have recommended prophylactic implementation of MLD to prevent secondary lymphedema in patients with breast cancer.<sup>16</sup>

### Compression Bandaging

Elastic wrapping is the principal compression technique used in phase I CDT. Short-stretch bandages have been reported to be very effective in the initial management of arm lymphedema.<sup>53,54</sup> The wrapping requires: (1) tubular bandage lining; (2) foam, polyester, or cotton under the cast padding; (3) digit bandages; and (4) multiple layers of short bandages with limited stretchability when pulled. A recent study described the use of upper extremity compression sleeves among breast cancer survivors whose arm volumes increased by 3% from baseline. Normalization of arm volumes was achieved for the majority of patients after 4 weeks of sleeve use and was maintained for an average follow-up of 4 months. At 1 year following diagnosis, lymphedema incidence was reduced relative to previously reported rates.<sup>55</sup> The goal is to create an internal pump-like action. Two different types of pressures are produced by the bandaging: (1) the low resting pressure (20 to 30 mm Hg),<sup>56</sup> which is the result of short-stretch bandages on the patient during resting; and (2) the high working pressure, which is the result of short-stretch bandages on the patient during muscle contraction. The resulting cycling between high working pressures and low resting pressure under the bandages in the interstitial fluid areas mimics the action of a pump, which assists the unidirectional flow of lymph to be transported away from the congested area. Inelastic multi-component compression (ICM) bandages normally applied by specialized medical staff are considered the standard of care treatment for compression therapy related to lymphedema of the extremities. However, there are new adjustable compression wraps (ACWs), which can be self-applied by patients. To date, the ACWs have been



**Figure 168.7** Manual Lymphatic Drainage.

mainly recommended during the maintenance phase; however, this could be a step toward self-management during the initial treatment phase as well.<sup>57</sup> The technique of applying the elastic wrap is important to achieve an effective compression gradient; short-stretch bandages must be applied with low-to-moderate tension using more layers at the ends of the extremities.<sup>3,58-61</sup> During phase I CDT, low-stretch wraps are worn 24 hours a day (except when the patient is receiving a massage or bathing). In the maintenance phase, a compression garment is worn during the day, and the wraps continue to be worn at night. Compression bandaging is always a part of the phase I CDT. Some individuals with more severe forms of lymphedema may need to use home compression bandaging long-term as part of phase II. Although somewhat debatable, especially in the past, heating combined with compression bandaging was deemed

effective treatment for chronic lymphedema with dermatolymphangioadenitis.<sup>62</sup>

### Compression Garments

Compression garments are normally used during all phases of lymphedema treatment, including prophylaxis in at-risk patients. Strict adherence to the daily use of properly fitting and appropriately graduated elastic compression garments are the key components to maintaining limb size for most patients. Fitted elastic knit two-way low-stretch compression garments generate greater pressures more distally than proximally to maintain unidirectional lymphatic flow.<sup>5,63</sup> Normally, compression garments deliver about 20 to 50 mm Hg of pressure (Table 168.2).<sup>2,5</sup> Generally speaking, the highest compression that can be tolerated by the patient is likely to be the most beneficial.<sup>5</sup>

Wearing compression bandages or garments that are too tight, restrictive, or not fitting properly may worsen limb condition. When fitted correctly and when properly worn, compression garments may reduce swelling (Fig. 168.8).<sup>51</sup> Support garments come in a variety of sizes, compression strengths, and materials; the different features may be selected to meet

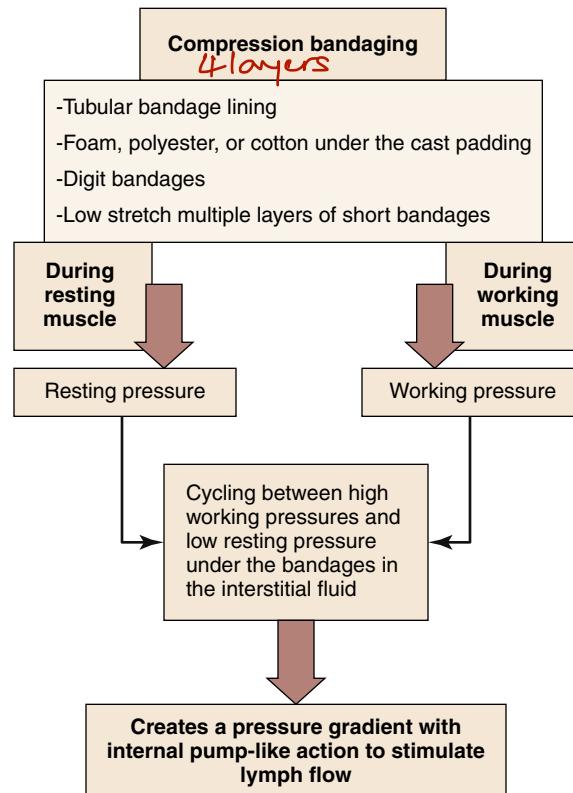
**TABLE 168.2**

## Compression Garments and their Associated Pressure

Type	Garment Pressure
Over-the-counter	7–15 mm Hg. Not graduated
Anti-embolism	15–20 mm Hg. Graduated
Chronic venous insufficiency or lymphedema	20–30, 30–40, 40–50, and 50–60 mm Hg
Patients with comorbidities	20–30 mm Hg or less
Upper extremity	20–30 mm Hg
Lower limbs with recalcitrant chronic lymphedema	30–40 mm Hg

the unique needs and dimensions of individual patients (Figs. 168.9 and 168.10). Although off-the-shelf prefabricated garments may fit many limbs, custom stockings may be necessary for significant swelling or an unusual shape. Compression garments should be replaced every 3 to 6 months. Contraindications for the use of compression garments include arterial insufficiency, acute cardiac failure, extreme limb shape distortion, very deep skin folds, extensive skin ulceration, severe peripheral neuropathy, and lymphorrhea.<sup>64</sup> There is a lack of evidence suggesting a positive or negative effect from compression garment use during exercise. The results from current and previous research suggest the recommendation that garments must be worn during exercise is questionable, and its application requires an individualized approach.<sup>65</sup>

Stocking length is frequently an issue. As a general rule, stockings should be long enough to cover the edematous portion of the limb, but patient preference and physical limitations have to be considered. In general, knee-high or thigh-high compression garments with removable proximal pressure support (e.g., biking shorts, sport leotards) are better tolerated than full-length garments. Patient input in selecting among the

**Figure 168.8** Compression Bandaging.