

Proximal Lower Extremity Chronic Venous Outflow Obstruction: Recognition and Treatment

By Peter Neglén and Seshadri Raju

As postthrombotic disease becomes better understood, the importance of venous outflow obstruction is recognized increasingly. It appears that obstruction of the iliac vein is particularly important and results in more severe symptoms than more distal segmental blockages. Unfortunately, no accurate invasive or noninvasive test for the evaluation of obstruction is available. In fact, it is not known what degree of venous stenosis should be considered hemodynamically "critical." Thus, currently it is impossible to detect borderline obstructions of potential hemodynamic significance. A high index of suspicion must be maintained. The diagnosis relies on clinical signs and symptoms, and treatment must be based on results of morphologic investigations such as transfemoral phlebography or, preferably, intravascular ultrasonography. Percutaneous iliac venous balloon dilation and insertion of a stent offers a safe and efficient method to correct pelvic venous obstruction. It is less invasive and relatively safer than open surgery and can, therefore, be offered to a larger group of patients. Furthermore, initial percutaneous management does not preclude subsequent bypass or reflux surgery. Although the technique is recent and follow-up relatively short, there is cautious optimism that this treatment will be useful and replace bypass surgery for iliac venous obstruction.
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THE INTRODUCTION of minimally invasive endovascular techniques has revolutionized the management of patients with thrombotic and nonthrombotic iliac vein obstructive lesions. It has largely replaced open surgery for this condition and offers a safe and efficient alternative for many patients. Based on the promising clinical results after treatment, the role and importance of proximal venous obstruction in chronic venous insufficiency (CVI) also are being reevaluated. This has led to a renewed interest in the nature and pathophysiology of venous obstruction and in tests for the detection of hemodynamically significant lesions. It is now clear that experience based on arterial obstructive disease cannot necessarily be directly transferred to the venous system. However, many issues regarding diagnosis, indications for treatment, and appropriate outcome measures remain unresolved.

THE IMPORTANCE OF VENOUS OBSTRUCTION

Although the pathophysiology of CVI is complex and has several contributing factors, reflux caused by valvular incompetence often has been emphasized as the most important underlying factor. Other important aspects, including venous outflow obstruction, a poor calf muscle pump, low compliance, and geometrical changes of the flow channels largely have been ignored. Most lower extremity outflow obstructions are related to absent or poor recanalization after an episode of acute

deep vein thrombosis (DVT). An obstructive component predominates in approximately one third of these limbs, and a combination of reflux and obstruction is present in 55% of symptomatic patients.^{1,2} In comparison with either abnormality alone, the combination of reflux and obstruction is associated with the highest levels of venous hypertension and the most severe symptoms.^{3,4} Rather than focusing solely on venous reflux, the importance of venous outflow obstruction must be recognized in treating the postthrombotic limb.

ETIOLOGY

Deep venous thrombosis is the most common cause of iliac vein obstruction. The iliac vein is the common outflow tract of the lower extremity, and chronic obstruction of this segment results in more severe symptoms than distal segmental blockages.⁵⁻⁷ Collateralization of the femoral-popliteal segment is facilitated by duplicated veins, direct connections to the profunda vein, saphenopopliteal connections, and deep muscular tributaries in the thigh. More distal obstructions, thus, are better compensated. In contrast, collateral formation after ileofemoral obstruction is relatively poor. Only

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20% to 30% of iliac veins completely recanalize after thrombosis. The majority of occluded iliac veins only partially recanalize and develop varying degrees of collaterals.^{8,9}

Benign or malignant tumors, retroperitoneal fibrosis, iatrogenic injury, irradiation, cysts, and aneurysms also may cause iliac obstruction. "Primary," nonthrombotic iliac vein obstruction (May-Thurner syndrome¹⁰ or iliac vein compression syndrome¹¹) also has been described and appears to be a more common cause of venous obstruction than previously recognized. In our experience treating more than 400 obstructed limbs, approximately 40% had nonthrombotic obstruction as defined by the absence of historical, ultrasonographic, or venographic evidence of a previous thrombosis. Stenosis of the proximal common iliac vein typically results from compression by the right common iliac artery with secondary band or web formation.¹² However, 15% of limbs with primary disease have stenosis of both the common and external iliac veins.¹³ Such extensive stenosis could conceivably follow a subclinical thrombosis initiated at the vessel crossing that then propagated distally into the external iliac vein. Conversely, limbs with obvious postthrombotic disease may have had an underlying iliac vein compression resulting in an iliofemoral vein thrombosis.¹⁴ Whatever the chain of events, isolated iliac vein obstruction should be considered in patients complaining of leg pain and swelling and having an absent history of previous DVT or other venous disease.

SYMPTOMATOLOGY

Although symptoms of CVI may vary greatly, the more severe manifestations of stasis ulceration often have been emphasized. However, it is our experience that a substantial number of patients with ambulatory venous hypertension complain of disabling limb pain and swelling without skin changes.¹⁵ Symptomatic venous occlusion classically has been associated with dramatic symptoms including swelling, signs of stasis, and typical exercised-induced "bursting" thigh pain relieved by only rest and elevation of the limb for several minutes (venous claudication). This probably is an overly simplistic view. Certainly patients with chronic venous insufficiency may describe a less distinct pain and discomfort with decreased quality of life and moderate disability. These symptoms

are not always improved by compression stockings or venous valve repair. In these patients it is possible that the symptoms may be attributed to outflow obstruction.

HEMODYNAMIC TESTS

The largest obstacle to the diagnosis, treatment, and assessment of outcome is the inability to adequately characterize the hemodynamic significance of a venous obstruction. Algorithms for evaluating patients with chronic venous insufficiency often completely omit tests for outflow obstruction. Unfortunately, there is no accepted "gold standard" for quantifying the hemodynamic significance of an obstructive lesion, and there currently is no reliable noninvasive study for preoperative evaluation. Duplex Doppler and plethysmography are helpful in the diagnosis of acute venous obstruction. However, ultrasound findings and outflow fractions obtained by air and strain gauge plethysmography are unreliable in chronic obstruction and play a limited role. Although abnormal plethysmographic findings may indicate outflow obstruction, significant blockage may be present with a normal examination.¹⁶⁻¹⁸ Even invasive pressure measurements, such as the hand/foot pressure differential and pressure increase with reactive hyperemia, and indirect resistance calculations are insensitive and do not define the level of obstruction.¹⁶

The venous circulation is a low-pressure, low-velocity, and large-volume vascular system compared with the high-pressure, high-velocity, and small-volume arterial system. The venous pressure in such a system is a function not only of resistance to flow (degree of obstruction and collateral formation), but also depends to a higher degree on flow velocity and volume. Unfortunately, it is not known how much resting venous flow has to be increased to detect a hemodynamically significant stenosis and how to do it in a reproducible manner. This has important implications for the development of tests evaluating outflow obstruction. Pull-through pressure differentials and pressure increases with exercise or hyperemia are much lower with venous than arterial obstructions.¹⁹⁻²¹ Small pressure increases at rest may be associated with significant obstruction. Current definitions of significant venous pressure changes are largely arbitrary. Currently, supine pull-through gradients greater than 2 to 3 mm Hg at rest or a gradient exceeding 2 to 5 mm Hg in comparison with the

contralateral femoral pressure are accepted as evidence of significant obstruction. The prevailing rule is that the femoral venous pressure increase with exercise should be at least 5 mm Hg to warrant intervention. However, it is difficult, especially during surgery, to increase venous outflow sufficiently to detect a hemodynamically relevant obstruction in the supine position. We have attempted to increase flow in the supine position by inducing hyperemia with ischemic cuff occlusion, ankle exercise, and intraarterial papaverin injection, and in the erect position by toe stands.^{22,23} None of these methods seems to be accurate. Although a positive test result may indicate hemodynamic significance, a normal test result does not exclude it. Thus, it is currently impossible to detect potentially important borderline obstructions.

Significant vascular obstructions often are defined as stenoses of greater than 70% to 80%, a concept derived from observations on the arterial system. However, these conclusions may not be applicable in the venous system because there are many fundamental differences. The effects of the venous obstruction are upstream (lack of emptying) rather than downstream (lack of perfusion). The signs and symptoms of venous obstruction, thus, are different. A proximal arterial stenosis does not become significant until it meets and exceeds the level of the high downstream peripheral resistance. In contrast, an iliac vein lesion must exceed only a low downstream resistance and may become significant at a substantially lesser degree of stenosis. The contralateral veins converge beyond an iliac vein stenosis, which may mitigate any pressure gradient at rest.²⁴ Furthermore, the geometrical form of an obstruction may change the pattern of blood flow. A slitlike narrowing of the venous lumen, even with no alteration in cross-sectional area, may increase resistance to flow. This may explain why relatively minor degrees of compression may affect blood flow in the left iliac vein. Finally, the hemodynamic significance of an iliac vein stenosis may be influenced by the degree of collateralization. Venous collaterals can be considered either an indicator of significant obstruction or as a compensatory mechanism bypassing and neutralizing the obstruction. The factors responsible for and mechanisms of collateral formation are unclear. However, arm or foot venous pressures may be abnormal despite impressive collateralization.²⁵ Thus, it

is not known at what degree a venous stenosis should be considered hemodynamically "critical."

MORPHOLOGIC INVESTIGATIONS

Phlebography is the time-honored method of imaging venous outflow tract morphology. Performed as an ascending or antegrade transfemoral investigation, it may show the site of obstruction and the presence of collaterals. Although proximal obstruction seems to be more important hemodynamically, a distal obstruction still may constitute a major hemodynamic outflow obstruction. Neither the anatomic location, extent and degree of an obstruction, nor the number and size of collateral vessels seen on phlebography are reliable guides to hemodynamic severity.²⁶

Intravascular ultrasonography (IVUS) appears to better delineate the extent and degree of stenosis than phlebography.^{27,28} IVUS can detect clearly lesions that are not obvious on single plane transfemoral venography. Injection of contrast dye can hide details, such as intraluminal webs, which are revealed by IVUS. Ultrasonography can differentiate between axial collateral formation in proximity to a postthrombotic vein and intraluminal trabeculation. External venous compression and any associated luminal deformity also can be visualized directly. Most importantly, IVUS appears superior to standard single plane venography for estimating the morphologic degree of iliac vein stenosis. Preoperative transfemoral single plane phlebograms were considered "normal" in 19% of postthrombotic and 28% of nonthrombotic limbs with obstruction on IVUS.¹³ On average, the transfemoral venogram significantly underestimated the degree of stenosis by 30%. Phlebography also was less accurate in detecting obstructions of greater than 70% compared with IVUS. Although multiple views may improve the accuracy of transfemoral venography, this currently is not standard practice. In lieu of adequate hemodynamic tests, IVUS evaluation currently is the best available method for diagnosing clinically significant chronic iliac vein obstruction.

SURGICAL TREATMENT

Before the introduction of percutaneous endovascular venous balloon dilation and stent insertion, open surgery was the only alternative to conservative management. Short nonocclusive stenoses as encountered in the iliac vein compression

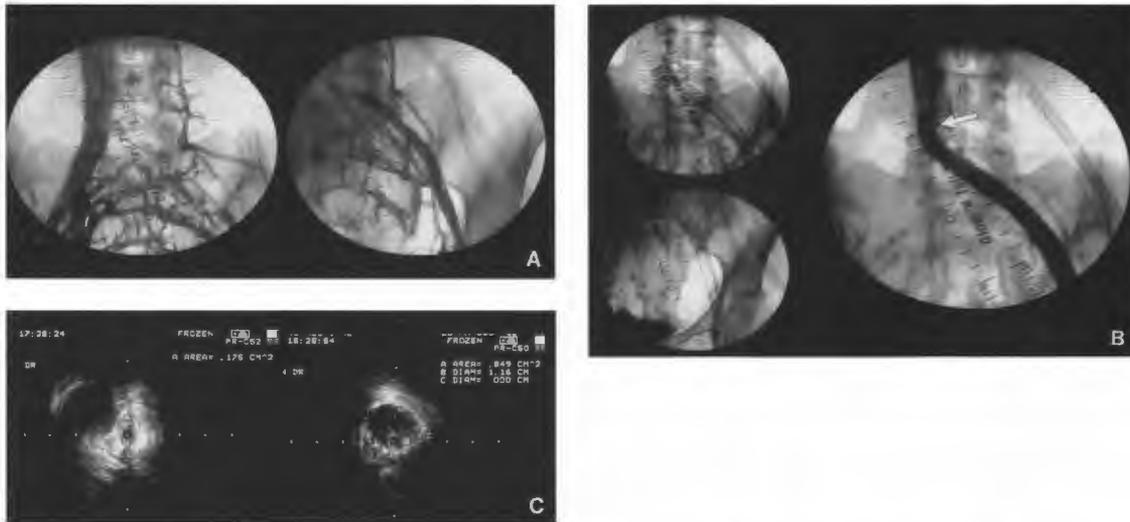


Fig 1. (A) Intraoperative transfemoral ascending phlebogram before balloon dilation and stenting in a patient with chronic thrombotic obstruction. Note filling of the ascending lumbar vein and transpelvic collateral circulation. (B) Status after insertion of 2 overlapping stents (diameter 12 mm) placed well into the inferior vena cava (IVC) and covering the entire left iliac vein (left). Flow through the iliac vein to the IVC (proximal end of stent at arrow) is uninterrupted, and no collateral circulation is visualized. (C) IVUS investigation before (left) and after (right) insertion of stent. Note an area increase from 0.175 to 0.849 cm². Reprinted with permission.¹³

syndrome have been managed with right iliac artery transposition and iliac vein patch angioplasty. Complete iliac vein occlusions required either a femoral-femoral or femoral-iliac bypass using saphenous vein or a polytetrafluoroethylene (PTFE) graft. To ensure patency, bypass surgery often is combined with a temporary or permanent arteriovenous fistula and lifelong anticoagulation.

The magnitude of these surgical procedures, as well as the risks associated with long-term anticoagulation, requires selection of only patients with the most severe postthrombotic symptoms. Strict criteria, including severe disabling symptoms and markedly increased venous pressure levels, are used. This has restricted surgical treatment to a minority of symptomatic patients.

The crossover bypass has been reported to be durable and to provide good symptom relief. "Clinical" (not phlebographic) patency has ranged from 67% to 95% at a maximum follow-up of 3 years.²⁹⁻³¹ However, most series include a small number of patients and lack consistent venographic follow-up, which appears to be the only reliable method to show patency. Clinical improvement is not necessarily related to graft patency.

ENDOVASCULAR TREATMENT

Percutaneous iliac venous balloon dilation and insertion of a stent has made it possible to correct pelvic vein obstruction with a less-invasive alternative (Figs 1 and 2). An endovascular approach has been utilized successfully to treat residual iliac vein stenosis after thrombolysis for acute DVT; complete occlusions and partial obstructions in chronic postthrombotic disease; nonthrombotic chronic iliac vein compression syndrome; and stenoses of other etiologies. There are few sizable series with acceptable follow-up reported in the literature, and the majority of these have not differentiated among various etiologies.

O'Sullivan et al³² reported a 1-year patency of 79% in a retrospective analysis of 39 patients. Almost half of the patients presented with acute DVT and were treated after successful thrombolysis, and half presented with chronic symptoms. Discounting initial technical failures, stented patients had a 1-year patency of 92% and 94% in the respective groups. The clinical results in the stented limbs were excellent. A similar group of 18 patients were reported by Hurst et al.¹⁸ Six limbs were treated after disobliteration of an acute DVT. The primary patency rates at 12 and 18 months were 79% and 79%, respectively. Most patients

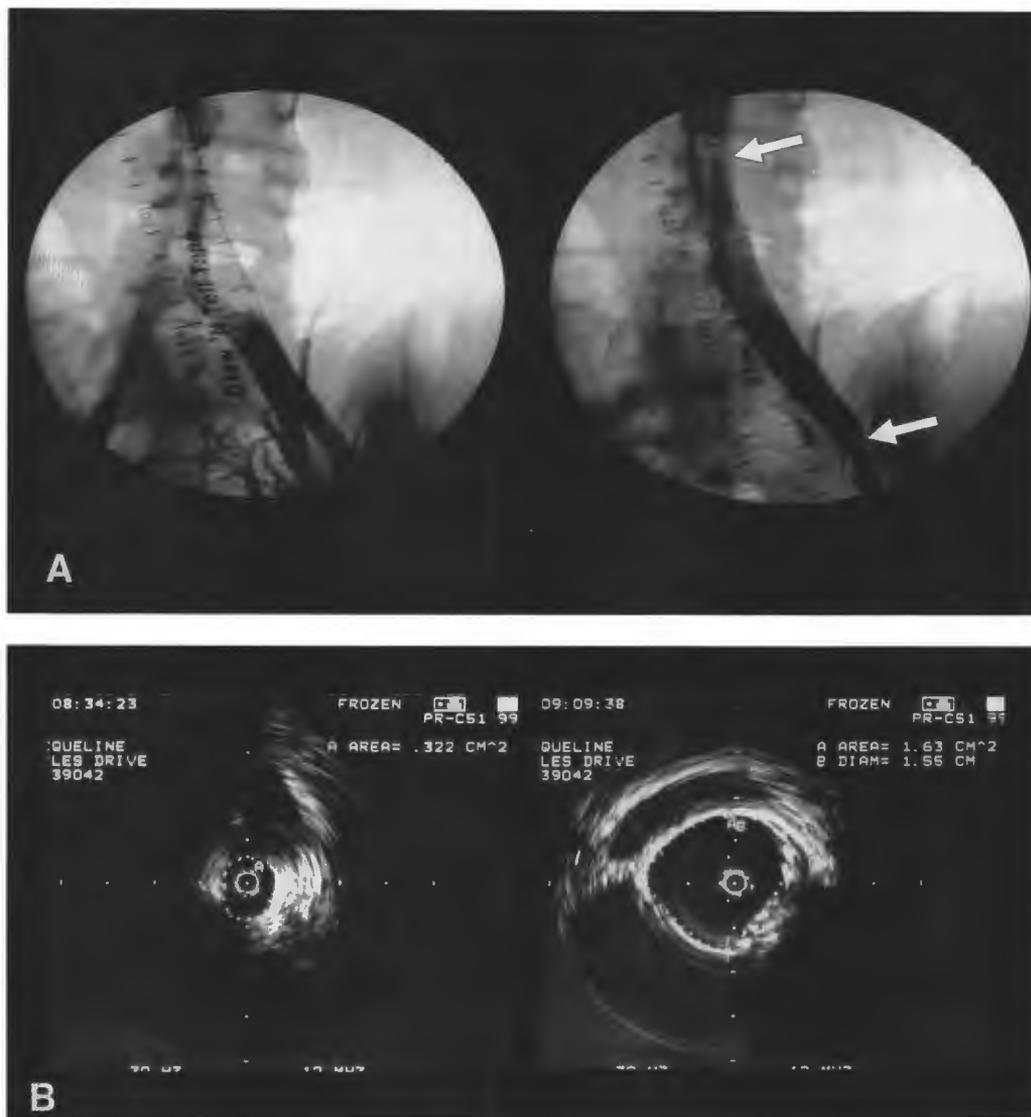


Fig 2. (A) Intraoperative transfemoral ascending phlebogram before (left) and after (right) balloon dilation and insertion of stent (16 mm) in a patient with nonthrombotic disease (iliac vein compression syndrome). The translucent common iliac vein with collaterals is typical. No collateral circulation is visualized after stenting (stent extended between arrows). (B) IVUS investigation before (left) and after (right) insertion of stent. Note an area increase from 0.322 to 1.63 cm². Reprinted with permission.¹³

(13 of 18) had resolution or substantial improvement of leg swelling and pain. However, 5 patients (28%) continued to have pain despite resolution of swelling and widely patent stents on venography. Binkert et al³³ reported 100% patency at an average follow-up time of 3 years in 8 patients. Symptoms resolved or substantially improved in most patients.³³

In a different group of patients, Nazarian et al³⁴ reported a 1-year primary assisted patency rate of

66% in 29 iliac obstructions. Patient selection likely accounts for the lower patency rate in this series. Thirteen patients had complete occlusions, 16 of which were caused by malignancy. Interestingly, few occlusions occurred after 6 months, and the patency rate remained the same at 1 and 4 years follow-up. The same group also has reported 1-year primary and secondary patency rates of 50% and 81%, respectively in a mixed population of 56 patients with iliac obstruction caused by

malignancy, trauma, pregnancy, and postoperative stenosis.³⁵

Our own experience of more than 400 stented pelvic veins includes only patients with chronic nonmalignant occlusions without any pretreatment thrombolysis, thrombectomy, or mechanical disobliteration of acute DVT. As discussed below, substantial technical modifications were made after our initial experience in stenting 29 limbs.²⁷ These limbs have, therefore, been excluded from the analysis presented here. Details of 304 limbs undergoing iliac vein stenting for correction of chronic stenosis between December 1997 and November 2000 have been presented previously.³⁶ The obstruction was considered nonthrombotic ("primary") in 142 limbs and postthrombotic in 162 limbs. Two-year primary and primary-assisted/secondary patency rates as documented by transfemoral phlebography were 71% and 97%, respectively. Stented limbs with "primary" disease appeared to fare better than those with postthrombotic obstruction (cumulative primary patency rate 90% and 70% at 2 years, respectively).¹³

Complication rates associated with endovascular intervention are minimal and comprise mostly cannulation site hematomas. A few cases of retroperitoneal hematoma requiring blood transfusion have been described.^{18,27} The use of ultrasound-guided cannulation and collagen plug closure largely have abolished these problems. We have not seen any procedure-related complications after introduction of these modifications, and mortality has been nil. Thus, it appears that balloon dilation and stenting of iliac vein obstructions is a safe, minimally invasive method associated with few complications, no mortality, and acceptable short- to intermediate-term patency.

CLINICAL RESULTS

As alluded to above, reports describing patency rates suggest clinical improvement in most patients (>90%) after balloon angioplasty and stenting.^{32,33} Hurst et al¹⁸ showed resolution or substantial improvement of symptoms in 72% of limbs. Patients with chronic venous insufficiency may complain of symptoms varying from mild swelling and diffuse discomfort to disabling pain, stasis dermatitis, and ulceration. Among these, only ulcer healing and recurrence rates have been used to assess outcome after treatment for CVI, and most other important parameters have been ignored.

Recently, a number of quality-of-life questionnaires, validated for assessment of chronic venous insufficiency, have been used to evaluate the benefit of interventions.³⁷ Swelling may be assessed by physical examination (grade 0, none; grade 1, pitting, not obvious; Grade 2, ankle edema; grade 3, obvious swelling involving the limb), or by water plethysmography. The level of pain may be measured by a visual analogue scale.³⁸

Unfortunately, few published studies have applied these criteria to the treatment of venous outflow obstruction. Adopting these criteria in a prospective evaluation of stented patients with iliac vein obstruction,^{13,27,36} we have found that the incidence of ulcer healing was 68% and that the cumulative rate of ulcer-free survival at 2 years was 62%.³⁶ Despite the frequent presence of valvular incompetence, no subsequent reflux procedure was performed when the ulcer remained healed during the observation period. Median swelling and pain severity scores decreased significantly (grade 2 to 1 and 4 to 0, respectively). The number of limbs free of objective swelling increased significantly from 12% to 47% and limbs free of any pain increased from 17% to 71%. Using a quality-of-life questionnaire assessing subjective pain, sleep disturbance, morale and social activities, routine and strenuous physical activities, significant improvement was noted in all major categories after venoplasty and stenting.

The ulcer itself can be a source of pain and local swelling apart from that caused by the iliac vein stenosis. However, the improvement in pain and swelling was significant in both ulcerated and non-ulcerated limbs. The preintervention level of pain was similar in both groups, highlighting the importance of nonulcer pain and swelling in limbs with symptomatic iliac vein obstruction. Interestingly, patients with recurrent venous obstruction also had recurrence of their symptoms after a symptom-free period.

Thus, the clinical outcome is favorable in the intermediate term. The results clearly indicate significant relief of symptoms after dilation and stenting of an iliac vein obstruction, even in the presence of persistent reflux. The results also *ex juvantibus* indicate that outflow obstruction is a more important and frequent component of CVI than previously recognized.

TECHNIQUE

Although venous balloon dilation and stenting is a minimally invasive procedure, some important aspects need to be emphasized. The detailed technique is described elsewhere.^{13,27,32} Angioplasty and stenting of the venous system should be considered a different procedure than that in the arterial system. It has been shown previously that simple balloon dilation leads to early restenosis, and immediate recoil of the iliac vein has been observed intraoperatively in the majority of limbs.³⁹⁻⁴¹ Stenting therefore is advised in all cases. Use of ultrasound guidance for femoral vein access has eliminated complications related to inadvertent arterial puncture and multiple cannulation attempts. IVUS is invaluable, both as a diagnostic tool in defining the degree and extent of obstructive lesions and as an intraoperative tool to direct stent deployment.

If a stenosis is near the confluence of the common iliac veins, the stent should be placed well into the IVC. If not, the stent is frequently "squeezed" distally, and a proximal restenosis may develop.²⁷ This IVC placement does not seem to impair flow from the contralateral limb and has not resulted in contralateral DVT even when the stent has occluded ipsilaterally. Neither a "kissing" balloon technique at the confluence of the common iliac veins nor insertion of bilateral stents is necessary. A large stent (14 to 16 mm) is recommended, and the stented area always should be redilated after insertion to achieve good wall apposition as evaluated by IVUS. In contrast to the artery, the vein seems to accept extensive dilation without clinical rupture. No clinical rupture of the vein has been reported so far, even when complete occlusions have been dilated to a diameter of 14 to 16 mm. It is important to cover the entire obstruction as outlined by IVUS to decrease the risk of restenosis. One might be inclined to insert as short a stent as possible; however, it is better to overstent than understent a lesion in terms of length. Short skip areas between 2 stents should be avoided. The occlusion rate is related to incomplete treatment rather than the length of stent or

metal load. Postoperatively, we have limited medication to 81 mg of aspirin daily started immediately after the procedure and continued indefinitely. Only patients on warfarin preoperatively for a prior DVT and thrombophilia were anticoagulated postoperatively.

CONCLUSION

Venous balloon angioplasty and stenting appears to be a safe, simple, and efficient method to treat ilio caval venous obstruction, at least in the short to intermediate term. An immediate or late failure of the procedure does not preclude later open surgery to correct the obstruction. Subsequent valve repair for associated reflux also may be performed when necessary. Unfortunately, no accurate noninvasive or invasive test for evaluation of obstruction is available at this time. Until such tests are developed, appropriate patient selection relies on clinical signs and symptoms as well as a high index of suspicion. The final diagnosis and treatment must be based on morphologic investigations. Transfemoral phlebography, or preferably IVUS, play an important role in the diagnosis of ilio caval venous obstruction and should be utilized more widely in the evaluation of patients with CVI. Compared with open surgery, venous balloon angioplasty and stenting is a minimally invasive procedure associated with few risks. It may, therefore, be offered to and benefit a larger group of patients with chronic venous insufficiency. However, some caveats have to be stated. The technology is relatively new, and follow-up is limited. The long-term effects of stents in the venous system are not known, including the potential development of neointimal hyperplasia. Several more years of monitoring are required to assess the efficacy and safety of this therapeutic modality in CVI. However, patients in the early part of our experience now have undergone follow-up beyond 3 years. The clinical benefits appear to be maintained without precipitous degradation. Based on preliminary experience, there is cautious optimism that iliac venous stent placement will be a useful modality in the management of patients with CVI.

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