Central Venous Pathologies: Treatments and Economic Impact

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ABSTRACT: Chronic venous insufficiency (CVI) is responsible for significant costs to society in the form of medical and surgical treatment and, importantly, unmeasurable lost work productivity due to pain and disability. Symptomatic chronic central vein obstruction, a cause of CVI, is potentially treatable using open surgical and endovascular techniques to restore vessel patency. Although upper extremity central vein obstruction often requires an open surgical procedure for durable relief, endovascular stents have proven remarkably useful for iliofemoral disease.

Containment of healthcare resources requires accurate diagnosis, durable treatment modalities, and appropriate patient selection so that therapy is targeted to those individuals most likely to benefit. In this regard, identification of appropriate lesions should be based on intravascular ultrasound and 3-dimensional imaging studies. Treatment with dedicated venous stents offers the potential for long-term symptomatic improvement and increased work productivity when used in a well-defined, anatomically appropriate population with significant, symptomatic CVI.

BACKGROUND

Central venous pathologies include thrombotic and nonthrombotic causes of venous obstruction in the large central veins that drain the upper and lower extremities.[1] Whether primarily thrombotic, compressive, or malignant, lesions of the central veins produce outflow obstruction that culminates in symptomatic chronic venous insufficiency, post-thrombotic syndrome, and occasionally, pulmonary embolism. Advanced venous disease is said to affect approximately six million individuals in the United States alone.[2]

Upper and lower extremity central vein obstructions are distinct clinical entities with different etiologies, symptoms, and sequelae. Upper extremity obstruction occurs from malignancy, thoracic outlet syndrome, or indwelling central venous catheters that cause luminal thrombus and scar formation. Malignant upper extremity central vein obstruction is commonly found in the mediastinum, obstructing the brachiocephalic veins and/or the superior vena cava. Symptoms often include those related to compression of other structures, such as finger numbness and tingling from a compressed subclavian artery, hoarseness due to compressed phrenic and recurrent laryngeal nerves, and other sequelae often found with a Pancoast tumor.[3] Although primary vascular malignancies occur, most of these cases occur from extravascular malignancies such as non-small cell lung cancer (50%), small cell lung cancer (22%), lymphoma (12%), and metastatic lesions (9%).[4] Less frequent malignant causes of superior vena caval obstruction include germ cell cancers, thymoma, and mesothelioma.

Nonmalignant upper extremity central vein obstruction occurs from venous thoracic outlet syndrome or indwelling catheters, which are often placed for hemodialysis, and pacemaker wires.[5] Venous obstruction from compression at the thoracic outlet, often initiated by extreme effort, remains a surgical problem, and venous stents have not performed well at this location.[6]

This review discusses chronic venous disease with a focus on central vein pathologies of the legs, specifically the iliofemoral venous segment. Specific attention is paid to prevalence, diagnostic and treatment modalities, proper patient selection, and the economic burden to society. For clarity, venous disease with symptoms lasting more than 14 days will be identified by the term chronic venous insufficiency (CVI). Although it is possible for CVI patients to have symptoms without central vein obstruction, the scope of this review will be limited to those with venous obstruction and symptoms of pain, edema, skin changes, or ulceration.

PREVALENCE OF CHRONIC VENOUS DISEASE

CVI is widespread, with a prevalence that far exceeds that of symptomatic peripheral arterial disease. Depending on the study and the definitions used, CVI exclusive of varicose veins is found in 1% to 10% of the population (Table 1).[7-14] In a seminal study of 2,215 randomly selected current and former employees of the University of California, San Diego, Criqui and colleagues identified functional disease of the deep veins in 11.3% of men and 7.8% of women.[7] The prevalence of functional deep vein disease increased with age, from 6.9% in patients younger than age 50 to 11.3% in those aged 70 and older. Deep

AUTHOR	YEAR	COUNTRY	SAMPLE SIZE	PREVALENCE	
				MEN	WOMEN
Coon[9]	1973	United States	6,389	3.1%	4.0%
Da Silva[10]	1974	Switzerland	4,376	8.7%	9.6%
Widmer[11]	1978	Switzerland	4,529	7.0%	6.0%
Franks[12]	1992	England	1,338	4.7%	4.0%
Komsuoglu[13]	1994	Turkey	850	1.4%	6.0%
Ruckley[14]	2002	Scotland	1,566	2.3%	1.3%
Criqui[7]	2003	United States	2,211	7.8%	5.3%

Table 1.
Prevalence of chronic venous insufficiency excluding varicose veins. Data modified from Rabe et al.[7,9-14]

venous disease was more common in Caucasians than in other ethnicities, with a prevalence of 10.3% in Caucasians, 6.2% in Hispanics, 6.9% in African Americans, and 8.8% in Asians. In a multivariable analysis of the same data, the odds-ratio for functional deep vein disease was 0.69 for women (reference = men), 1.54 for people aged 70 and older (reference = age < 50), and 0.66 and 0.72 for Hispanics and African Americans, respectively (reference = Caucasians).[15]

A subsequent analysis of the San Diego study population identified risk factors for severe clinical findings, etiology, anatomy, and pathophysiology (the CEAP classification) of venous disease in men and women. In men, age, family history of venous disease, larger waist circumference, laborer occupation, and smoking were statistically significant predictors of severe CVI, whereas increased diastolic blood pressure was protective. In women, age, family history, larger waist circumference, long periods of standing, flat feet or small arches, leg injuries, multiparity, and a history of cardiovascular disease were predictors, but African American ethnicity was protective.[15]

ECONOMIC BURDEN OF CHRONIC VENOUS DISEASE

Symptomatic CVI affects society in two ways. First, severely symptomatic disease interferes with the patient's ability to perform a broad spectrum of job functions, including those that involve prolonged standing or sitting and especially those that require physical labor. Second, the treatment of CVI requires frequent outpatient visits for wound care and, when severe, costly hospitalizations and interventions.

A prospective French study found that the principal costs for treating venous ulcers were attributed 48% to wound care, 33% to medications, and 16% to hospitalizations. The cost of treating a patient's venous ulcer was reported to be €101/week in Sweden and €184/week in Germany (between $101/week and $222/week in U.S. dollars).[16,17] At the time of these studies, the total expenditures for venous ulcers accounted for approximately 2% of the national healthcare budget in Western Europe and the United States.[8,18,19]

A 2010 publication by Rabe and Pannier reported the CVI healthcare expenditures using data principally from the Bonn Vein Study. Treatment of CVI was more common in females than males (31% vs 12.7%, respectively). Not unexpectedly, the use of compression stockings rose from 7.3% in CEAP-score C1 patients (those with telangiectasies or reticular veins) to 81.8% in C5-6 patients (those with healed or active ulcers). Surgical intervention was necessary in only 3.1% of C1 patients, rising to 36.4% in those with C5-6 symptomatology. Tabulation of the costs from the German official statistical calculations showed that, excluding treatment for varicose veins, the healthcare cost for treating diseases of the veins and lymphatics was approximately €1.4 million in 2006, or about 1.6% of the annual budget of the Ministry of Health and Social Security.[8]

With respect to lost work productivity, a study by McGuckin et al. estimated that venous ulcers accounted for 2 million lost work days annually in the United States.[20] A French study found that approximately 7% of the working population is out of work at any given time due to venous disease. The impact to French society was ₣320 million (€48,783,685) annually in lost productivity.[20]

TREATMENT OF ILIOFEMORAL VEIN OBSTRUCTION

The information presented in the previous sections documents the high prevalence of CVI, which accounts for significant societal costs related to both treatment and losses from decreased occupational productivity and disability. Identification of the precise proportion of symptomatic CVI population with iliofemoral outflow obstruction, the segment of the population most amenable to venous stenting, remains elusive. Looking forward, physicians must be able to clearly and objectively differentiate patients with anatomic obstruction severe enough to warrant definitive treatment so that interventions are performed on patients with good prospects for symptomatic relief.

Before the 1990s, treatment of venous obstructive disease was relegated to open surgical procedures. Venous bypass with autogenous conduit (either the saphenous vein femoro-femoral crossover, the rarely performed autogenous in-line femoro-iliac/caval bypass, or prosthetic femoro-iliac/caval procedures) were fraught with low rates of patency. Creation of a temporary arteriovenous fistula to improve flow and discourage early thrombosis can be considered a de facto declaration of unacceptably low patency rates of venous bypass procedures. In the best hands, venous bypass patency rates at 1 year are around 75% for autogenous conduits and as low as 50% for prosthetic grafts.[22-25] Today, endovascular interventions have all but eliminated the need for open surgical reconstruction. Other than hybrid procedures (e.g., principally localized endophlebectomy at the common femoral vein that can improve inflow to an endovascular intervention),[26,27] current indications for open surgical bypass are limited to failed endovascular procedures, trauma, and malignancy.

The definitive endovascular treatment of iliofemoral venous obstruction was pioneered by Raju and Neglen.[28] Beginning with an initial clinical experience in the late 1990s and first reported in 2000, these clinicians led the way in using metallic stents to percutaneously resolve symptomatic large vein obstruction. They showed that excellent results could be achieved with a minimally invasive approach and identified intravascular ultrasound (IVUS) as an important diagnostic tool for screening venous lesions appropriate for intervention and gauging the intraprocedural adequacy of stent deployment.[29]

The 15 years following Raju and Neglen's work witnessed a slow acceptance of venous stenting for obstructive lesions.[30-35] Most of the studies during this time used the braided Elgiloy WALLSTENT (Boston Scientific); although it is not approved in the United States for the treatment of iliofemoral venous occlusion, it is the best choice for endovascular venous intervention in the hands of most venous interventionalists. Patency rates of venous stents were excellent, approaching between 80% and 90% at 1 year.[33,36-38] Reported patency rates were better when stenting nonthrombotic lesions (e.g., those that occur in May-Thurner syndrome) compared with the longer, more diffuse post-thrombotic lesions that develop after deep vein thrombosis.

These studies confirm that venous stenting is effective in the restoration of iliofemoral venous patency. Newer stent designs dedicated to the treatment of venous lesions hold promise for precise deployment and long-term reductions in restenosis and occlusion.[34,35,38,39]

CHOOSING THE PROPER PATIENTS FOR VENOUS STENTING

With the introduction of any new therapy, initial caution is often followed by unjustified enthusiasm. Venous stenting is no different. After confirmation of acceptable patency rates, venous interventionalists sought to employ this tool in their patients—particularly since no definitive therapy existed before stenting. The enthusiasm to treat patients with venous stenting helped stimulate commercial interest in the development of dedicated venous stents. However, the widespread use of venous stents without defining exactly which patients benefited most from the therapy was problematic. Further, the diagnostic insensitivity of standard contrast venography for assessing nonthrombotic lesions risked overuse of the therapy. Intravascular ultrasound solved some of these issues, as have 3-dimensional (3D) imaging modalities such as computed tomography and magnetic resonance venography. The recently published VIDIO study documented the importance of IVUS in identifying anatomic lesions appropriate for intervention.[40,41] Using IVUS as the reference, venography underestimated the severity (percent diameter reduction) of venous lesions by an average of 11% (Figure 1).[40] Moreover, IVUS identified significant lesions missed by venography in 26% of cases. When correlated with symptom resolution after stenting, patients with lesions exceeding approximately 50% area reduction in preintervention IVUS had significantly better clinical outcomes compared to those with milder lesions.[41]

Failure of symptom resolution after venous stenting can result from an improper diagnosis of the main cause of symptoms. A significant psychological overlay is found in many patients with

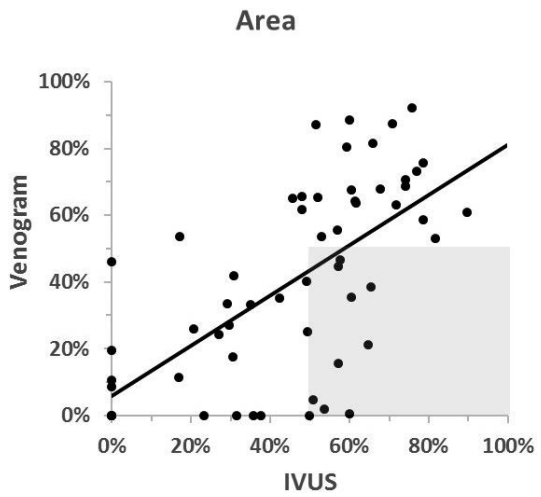

Figure 1.
Correlation between target lesion severity (% diameter reduction) by venography and intravascular ultrasound (IVUS). The gray shaded area identifies lesions of > 50% diameter reduction on IVUS but < 50% by three-view venography. Reprinted with permission.[40]

venous disease.[42,43] In a 2013 publication, Amsler, Rabe, and Blättler reported an analysis of 1,978 patients from the Bonn Vein Study followed for a mean of 6.6 years.[44] The Psychic versus Somatic Venous Disease Questionnaire (PsySoVDQ), a 9-item survey, was administered to distinguish true somatic symptoms from those of psychological origin. The PsySoVDQ score was divided into a somatic component (SC) and a psychic component (PC). After excluding patients with CEAP classification ≥ C4 from the analysis, an elevated PC score was observed in 43.4% of 1,095 patients with CEAP 0-1 and 34.2% of 705 patients with CEAP 2-3 (Table 2). An elevated PC score was associated with female sex, younger age, and lower body mass index. Patients with CEAP 0-1 had higher PC scores than those with CEAP 2-3. The authors concluded that the PsySoVDQ provides a tool to identify patients who have a significant psychic component to their symptoms.[44] The unstated conclusion is that such patients might be less likely to benefit from venous interventions. These findings, however, do not take into account the exclusion of the severely symptomatic CEAP 4-6 cohort from the analysis—a group that would be predicted to have a greater propensity for anatomic venous disease.

PROSPECTS FOR THE FUTURE AND COMMERCIAL IMPLICATIONS

Iliofemoral venous stenting is applicable only in a minority of the CVI population. The large proportion of patients with isolated superficial venous disease, deep venous reflux in the absence of obstruction, or iliofemoral obstruction but mild symptoms can be treated effectively with conservative antithrombotic therapies or with superficial vein ablation.

The subset of patients with severe symptoms and significant anatomic lesions of the iliofemoral segment comprise the population appropriate for venous stenting. Dedicated venous stents, when available, should be used instead of stents designed for the arterial circulation.[45] Furthermore, 3D imaging modalities should be used in the diagnosis and treatment of central venous lesions.[40]

Many unanswered questions remain. A stent's radial force and flexibility are opposing design features with clinical tradeoffs. Stents with greater radial force may be associated with greater pain during deployment, more straightening of the vein segment, and a higher risk of stent fracture over time. By contrast, stents with lower radial force may be more susceptible to external compression and suffer the

CEAP	N	BVS SYMPTOMS	SOMATIC COMPONENT		PSYCHIC COMPONENT	
			SC = 0	SC ≥ 1	PC = 0	PC ≥ 1
CEAP 0-1	1,095	501 (45.8%)	767 (70.0%)	328 (30.0%)	620 (56.6%)	475 (43.4%)
CEAP 2-3	705	461 (65.4%)	359 (50.9%)	346 (49.1%)	464 (65.8%)	241 (34.2%)
All	1,800	962 (53.4%)	1,126 (62.6%)	674 (37.4%)	1,084 (60.2%)	716 (39.8%)

Table 2.
Somatic and psychic scores by CEAP classification in the Bonn Vein Study (BVS). Modified from Amsler, Rabe, and Blättler.[44] CEAP: clinical-etiology-anatomy-pathophysiology classification for venous disorders; SC: somatic component of Psychic versus Somatic Venous Disease Questionnaire (PsySoVDQ); PC: psychic component of PsySoVDQ

hemodynamic shortcomings of an elliptical rather than a round cross-sectional profile after deployment. In addition, the optimal postprocedure antithrombotic regimen remains poorly defined and likely to be different in nonthrombotic versus post-thrombotic cases.

The clarification of these issues and those not yet identified will markedly affect the commercial use of venous stents. Market penetration of stent technology into the less-severe CEAP categories will depend on long-term results. Practitioners will avoid the use of stents in less severely symptomatic patients if the risk of long-term complications is high, either from the stent itself or from an antithrombotic regimen necessary to sustain patency. Lastly, the increasing identification of right-sided nonthrombotic lesions at the external and internal iliac vein confluence could dramatically increase the use of venous stents, raising yet another question about the timing of bilateral treatment.

CONCLUSION

In summary, CVI is responsible for significant costs to society related to treatment and lost work productivity. The use of diagnostic modalities such as IVUS and 3D imaging studies identify patients who will benefit the most from venous intervention. Treatment with dedicated venous stents has the potential to achieve improved outcomes, and the upcoming release of data from current regulatory trials is eagerly awaited.

KEY POINTS

- Chronic venous insufficiency is a common condition that is responsible for significant costs to society, including high treatment costs and lost work productivity.
- Stents have provided a minimally-invasive treatment for patients with central vein obstruction, and the newer dedicated venous stents hold great potential to further improve outcomes.
- Imaging studies that include intravascular ultrasound should be used to evaluate the appropriateness and the anatomic location of central vein interventions.

Conflict of Interest Disclosure:
Dr. Ouriel is an employee of and holds equity in Syntactx, a contract research organization that receives research funding from a variety of companies with diagnostic and therapeutic products for venous disease.

Keywords:
chronic venous insufficiency, central vein obstruction, venous stents

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