Residual Symptoms After Superficial Lower Extremity Venous Ablation

by Luis A. Dibos, MD, FACS

It is generally accepted that endovenous laser (EVL), and radiofrequency (RF) ablation have become the gold standard in the treatment of superficial lower extremity venous insufficiency. Several prospective randomized trials on the results of these treatment modalities compared with vein stripping and high ligation show significant clinical superiority of the less invasive procedures.

Patients with chronic lower extremity venous insufficiency classically present with complaints of leg fatigue, aching, itching, and some element of edema. In more advanced cases, large varicosities, venous stasis changes of the skin, and ulcerations may develop. Duplex ultrasound evaluation of these patients usually reveals significant reflux in the Greater and Lesser Saphenous vein and may involve several accessory veins, tributaries and perforator veins. An element of deep reflux is present in about 20-25% of patients with superficial venous insufficiency.\textsuperscript{1} In the absence of superficial femoral or popliteal vein reflux, common femoral vein reflux is generally benign, and in most cases, resolves after ablation of the refluxing Great Saphenous Vein.\textsuperscript{2} The overwhelming majority of these patients show significant improvement in their symptoms after ablation of their incompetent veins. These results are usually immediate and good 5 year data has been obtained, with over 85% reflux free and vein occlusion rates.\textsuperscript{3}

A subset of patients, despite adequate treatment of their superficial venous insufficiency, will have residual symptoms. It is critical to obtain an initial extensive medical history from all patients to exclude any other potential cause for their symptoms. Edema in particular has multiple etiologies. Caution must be exercised in recommending ablation procedures in these patients prior to addressing potential medical causes of edema. Control of hypertension, diabetes, and CHF are paramount prior to performance of any ablation therapy. Even if venous reflux is the only cause for the edema, resolution may take some time, and use of compression...
The Use of Pentoxifylline in Venous Disease

by Alejandro Arnez, MD

Pentoxifylline (also known as Pentopak, Pentoxy, and Trental) is a xanthine derivative hemorheologic agent. At a dose of 400 mg PO TID, in addition to local care and compression and/or Intermittent Pneumatic Compression, it is recommended in patients with venous leg ulcers.

The pharmacologic effect of pentoxifylline improves the rheology of blood flow in the microcirculation by altering the flexibility of the erythrocyte’s cell membrane as well as leukocyte deformability and neutrophil activation and adhesion. Eight randomized studies were tabulated by a Cochrane review evaluating pentoxifylline versus placebo in patients with venous leg ulcers, using objective measurements of wound healing. There was uniform observation that pentoxifylline improved wound healing.1

More recent physiological investigation has shown that the pressure in the veins of the lower limb remains raised in patients with venous ulceration during ambulation, whereas in normal subjects the pressure in superficial veins falls to a low level. This elevated pressure appears to cause damage to the superficial capillaries in the skin, culminating in the production of venous ulceration.

More recently it has been proposed that accumulation of white blood cells may result in capillary damage and that the collected white cells might release free radicals and inflammatory mediators which are actively responsible for tissue injury.2

Mechanism of Ulcerations

Fibrin Cuffs:

Browse and Burnand proposed that oxygen diffusion into the tissues of the skin was restricted by a pericapillary fibrin cuff that they had observed histologically.3 They suggested that increased capillary pressure as a consequence of the raised venous pressure results in an increased loss of plasma proteins through the capillary wall. This includes fibrinogen which polymerizes to provide the “fibrin cuff” that may be seen around capillaries in the skin, using both histochemical and immunohistochemical methods.

Measurements of protein loss from capillaries showed that fibrinogen was quantitatively the most important plasma protein leaking into the tissues in patients with venous disease. Subsequent measurements of fibrinolysis have shown that patients with venous disease have reduced fibrinolytic activity in the blood and veins which might explain why the fibrin cuff persists.4 In this theory of ulceration, the role of the fibrin cuff in restricting the supply of oxygen to the tissues is central. There is no published evidence to prove that fibrin provides a barrier to oxygen diffusion.

Use of Pentoxifylline as Pharmacological Treatment

The objective of the treatment is to reverse the damaging effect of venous hypertension by enhancing fibrinolysis.

Pentoxifylline down-regulates polymorphonuclear neutrophils resulting in much lower likelihood of adhesion and activation.5 In a multi-center study in which 82 patients were entered, pentoxifylline has been shown to result in much better healing rates of ulcers than placebo.6 It has been recommended that this drug may be useful for the treatment of resistant ulcers7

A study containing 200 nondiabetic patients with venous leg ulcers > 1cm for longer than 2 months randomized to pentoxifylline 400mg TID vs. placebo; at 6 months, pentoxifylline group members nonsignificantly were more likely to have ulcers healed (64% vs. 52%) (BMJ 319:875, 1999–JW/AFP)

In a systematic review of 8 trials involving 547 patients comparing pentoxifylline vs. placebo or placebo plus compression for venous leg ulcers, pentoxifylline was associated with significantly better rates of healing than placebo or placebo + compression (Lancet 358:1550, 2002–JW). Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor which raises intracellular cAMP, activates PKA, inhibits TNF-alpha and leukotriene synthesis, and reduces inflammation and innate immunity.8

Peak plasma levels of the parent compound are reached within 0.4-0.8 hours and 1-1.6 hours for active metabolites (Metabolite I, Metabolite V) after administration, plasma levels are 5-8 times greater than pentoxifylline. The half life and under-the-blood-level time of accumulation or cytochrome p450 induction following multiple doses. Almost totally urinary excretion showed no parent drug found, having as the main biotransformation product the Metabolite V.

Biodisponibility is near 100% for oral dosage, food intake before the drug administration showed delay in absorption but does not affect the total absorption. No studies have been performed in patients with renal or hepatic dysfunction.

Other Uses

- Pentoxifylline is also indicated in the treatment of intermittent claudication, vascular dementia and stroke prevention.9
- It has been shown to reduce mortality in acute alcoholic and non-alcoholic steatohepatitis, presumably through its ability to inhibit TNF-alpha. Pentoxifylline's anti-TNF properties indicates it for treatment of alcoholic liver disease.10
- A study demonstrated the possible use of pentoxifylline administered in conjunction with vitamin E for reducing the extent of fibrotic lesions induced by radiation therapy for breast cancer.11
- Pentoxifylline is also being investigated for the causative treatment of endometriosis.12
- It is also indicated for the treatment of Peyronie’s disease.13

References:
2. Colindoga Smith PJS, The Yale Journal of Biology and Medicine (1993), 47-59, Pathogenesis of Chronic Venous Insufficiency and Possible Effects of Pentoxifylline. College of Medicine, University of Iowa, Iowa City, Iowa and Middlesex School of Medicine,The Middlesex Hospital, London, UK.
12. Song H, Li Y, Clarke J, Shi G. “Pentoxifylline versus medical therapies for diabetic women with endometriosis”. Cochrane Database Syst Rev. 2009 Jul 8 (2):CD007777. Li Du Weil China Second University Hospital, Sichuan University, No. 21, Third Part of Ren Min Nan Road, Chengdu, Sichuan, China, 810041
the right common iliac artery. Many of these may be seen. The gold standard, however, is intravascular ultrasound (IVUS). Even with Venography, which used to be the standard, as many as 30% of lesions may be missed, and in cases where stenosis is diagnosed, the degree of stenosis is underestimated. Venography is now reserved as a roadmap for stenting once the lesion has been identified with IVUS.

The majority of obstructive lesions, whether primary or secondary, may be successfully treated with endovenous stenting. The results have been excellent, both angiographically, as well as clinically. In most studies, there was either complete resolution or substantial improvement of symptoms in close to 80% of patients, as well as an improvement in the Venous Clinical Severity Score (from 8.5 to 2), and Venous Disability Scores (from 2 to 0).

For the practicing clinician, there must be a strong index of suspicion for venous outflow obstruction, especially in advanced cases of venous disease. A negative non invasive test should not exclude further diagnostic tests. Stenting of the obstructive lesion is minimally invasive, compared to older surgical techniques, and has yielded excellent results.

References:
5. May R, Thurner J. Cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. Angiology 1957

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stockings is mandatory until complete resolution is achieved. Patients with persistent pain despite successful ablations may have to be ruled out for scleroderma or other connective tissue disorders, as well as for neurological disorders.

If symptoms persist after superficial ablation, despite control of medical comorbidities, proximal or outflow venous obstruction must be considered. This is especially true in patients with symptoms out of proportion to the clinical findings, and in patients with advanced venous disease (skin changes, ulcerations).

Obstruction of the venous outflow tract (common femoral, external and common iliac vein, and IVC) may be caused by thrombotic (incomplete recannulization after DVT), and nonthrombotic causes, with the former being most prevalent. Only 20% of iliac veins with DVT will fully recanalize with anticoagulation as the sole treatment. The remaining veins will only partially recanalize and lead to different degrees of obstruction. Most of these involve the external and common iliac veins.

Non-thrombotic (primary) obstruction is usually due to external compression on the veins from crossing arteries or ligaments, and also from intraluminal webs or septations. The most well known external compression syndrome is May-Thurner8 or Cockett’s9 syndrome, in which the left common iliac vein is compressed by the right common iliac artery. Many of these primary lesions remain silent until a secondary or additional insult precipitates symptoms (permissive pathology). These secondary insults include trauma, obesity, seated orthostasis in the elderly, DVT, edematogenic medications, secondary reflux, joint surgery, lymphedema, and post menopausal hormonal changes.

Diagnosis of these obstructive lesions is difficult with non invasive methods, although with newer Duplex technology, in expert hands, some of them may be seen. The gold standard, however, is intravascular ultrasound (IVUS). Even with Venography, which used to be the standard, as many as 30% of lesions may be missed, and in cases where stenosis is diagnosed, the degree of stenosis is underestimated. Venography is now reserved as a roadmap for stenting once the lesion has been identified with IVUS.

Nicos Labropoulos, PhD, RVT Joins CVR as New Director of Research and Medical Education

We are proud to announce that Nicos Labropoulos, PhD, DIC, RVT, one of the foremost experts in vascular medicine, has joined Center for Vein Restoration as our new Director of Research and Medical Education.

Dr. Labropoulos’ name is well known in vascular medicine circles. He is Professor of Surgery and Director of the Non-Invasive Vascular Laboratory, Department of Surgery at the Stony Brook University Medical Center in Stony Brook, New York. His clinical interests and areas of expertise include non-invasive vascular imaging, ultrasound-guided vascular procedures, pathophysiology and diagnosis of venous thromboembolism, chronic venous disease and diagnosis and prevention of atherosclerosis.

He has served on the editorial boards of several medical journals, including Journal of Vascular Surgery, Annals of Vascular Surgery, and Vascular and Endovascular Surgery. He also has served as a reviewer for 20 medical journals, including the New England Journal of Medicine, Lancet, British Journal of Medicine, and Archives of Surgery. He also has been a Traveling Fellow of the Royal Society of Medicine, along with being an award-winning, international scientific presenter. He has given over 500 invited lectures and has been visiting professor in many medical centers in US and other countries. He has edited four vascular books, over 50 book chapters and more than 200 publications in peer reviewed medical and surgical journals.

Dr. Labropoulos also serves on the boards of the International Vascular Foundation and the Institute of Vascular Diseases, two non-profit organizations providing education and humanitarian work. He also has served as a member and panel expert of the National Quality Forum and the Joint Commission for the Accreditation of Health Organizations.

He trained in vascular medicine and earned his PhD from University of London. He is a member of many vascular societies in US and many other countries. Dr. Labropoulos speaks English, Spanish, Portuguese and Greek.
We are pleased to announce the opening of our 16th Center for Vein Restoration location, in Sterling Heights, Michigan. The center is led by physician Rachel Sussman, D.O. Located in the east side of the Metro Detroit area, the clinic serves patients primarily in Macomb, Oakland and Wayne Counties.

“I take great pride in providing my patients with the highest standard of care,” said Dr. Sussman, whose parents were also both physicians. “Each patient receives an individualized treatment plan based on their unique presentation and needs.”

Dr. Sussman is board certified in Phlebology and Family Medicine. She is a member of the American College of Phlebology, Michigan Osteopathic Association and the American Osteopathic Association.

She came to medicine later in life, first completing a B.A. in English at the University of Michigan, Ann Arbor and pursuing graduate studies in speech and language pathology. She later earned her medical degree from Michigan State College of Osteopathic Medicine and completed a Family Medicine residency at Ingham Regional Medical Center in Lansing, Michigan.

She transitioned her career to venous medicine in 2007 after receiving extensive training in the comprehensive management of vein disease in addition to extensive ultrasound diagnostic training.

The clinic is located at 43184 Dequindre Road (at 19 Mile Road), Suite 202. Contact our team by phone at (586) 997-0999, or online via our website at www.centerforvein.com.

The Compression Stocking Test

by Khanh Nguyen, DO

How many times do you hear “I hate compression stockings?” Well, I will proclaim that “I love compression stockings.” Sure, they may be hard to get on, difficult to wear in the summer, and not so complimentary to a nice dress. However, to a physician, I think they are great. This is why:

Compression stockings help to increase venous blood circulation by providing graduated pressure in the lower extremities. This is accomplished by having the tightest constriction at the ankles, and gradually becoming less constrictive towards the knees and thighs. Effectively, this improves venous flow and improves venous symptoms. Whenever I’m not sure of the cause of a patient’s symptoms, I go to my special, low-technology, cost-effective test: compression stockings. Many times, if a patient returns with improvement in their symptoms with stockings, they likely will improve significantly with surgical intervention.

So, the next time you are caught with vague lower extremity symptoms and not sure if the patient has venous disease or not, why not try compression stockings? If they improve, you may have your answer.

How to Prescribe Stockings

The perfect prescription for a patient really is the one that alleviates the patient’s symptoms without compromising arterial function. A patient’s ABI (Ankle Brachial Index) must be >0.8 mm Hg per leg to wear compression stockings. More often than not, 20-30 mm of Hg is a reasonable starting compression.

It is also crucial that compression stockings are properly sized. Typically, four measurements are made when prescribing stockings: 1) ankle circumference, 2) calf circumference, 3) upper thigh circumference and 4) length of the entire lower leg to the thigh.

By knowing these basics behind prescribing compression stockings, you will improve the success rate of your patients wearing them.
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Autumn is a time of change, renewal and anticipation of things to come. This certainly holds true for Center for Vein Restoration, where we are proud to announce several exciting developments.

First, we continue to grow. We’ve opened our 16th location, in Sterling Heights, Michigan – now our second Michigan location. As always, we’re excited to utilize our expertise and experience in vein health to help our patients look better, feel better and, ultimately, live better.

Second, we’re proud to announce that one of the most prominent experts in the field of vein health has joined our advisory board: Nicos Labropoulos, PhD, RVT. You can read more about Dr Labropoulos in this newsletter.

Third, we continue to fulfill our promise to educate the public on vein health, helping them see that varicose veins and spider veins are not simply normal signs of aging, but in fact are related to venous insufficiency, a previously overlooked and undiagnosed condition. To that end we’re getting out in the community more, sponsoring popular radio programs, and exhibiting at health fairs and even bridal events.

Finally, on the medical front, we continue to offer our CME courses in venous insufficiency and exhibit at conferences, such as the recent Maryland Academy of Physicians Assistants conference and the Maryland Academy of Family Physicians 2011 Annual Convention. We look forward to continuing this outreach to better help us connect with clinicians and address your questions on diagnosis and treatment options for your patients.

Thank you as always for reading the Venous Review. We hope you find these articles educational and interesting.

Regards,

Robert C. Kiser, DO, MSPH
Editor