PHLEBOLYMPHOLOGY

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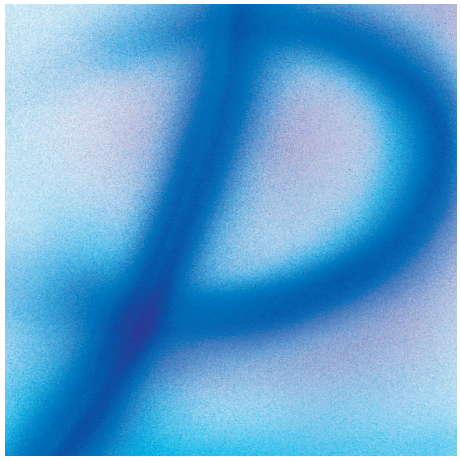

Vol 19 • No.2 • 2012 • p57-104

History of venous surgery (3) ..... PAGE 59
Michel PERRIN (Lyon, France)

Factors to identify patients at risk for progression of chronic venous disease: have we progressed? ..... PAGE 68
Mieke FLOUR (Leuven, Belgium)

Benefit of Daflon 500 mg in the reduction of chronic venous disease–related symptoms ..... PAGE 79
Maja LENKOVIC (Rijeka, Croatia)

Pelvic vein incompetence: a review of diagnosis and treatment ..... PAGE 84
Giuseppe ASCIUTTO (Malmö, Sweden)

Randomized controlled trial in the treatment of varicose veins ..... PAGE 91
Bo EKLÖF (Helsingborg, Sweden) and Michel PERRIN (Lyon, France)

AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, news, and a congress calendar.

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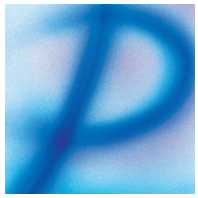
Phlebolymphology

CONTENTS

PHLEBOLYMPHOLOGY



EDITORIAL

Hugo PARTSCH (Vienna, Austria) **Page 58**

PHLEBOLOGY

History of venous surgery (3) **Page 59**

Michel PERRIN (Lyon, France)

Factors to identify patients at risk for progression of chronic venous disease: have we progressed? **Page 68**

Mieke FLOUR (Leuven, Belgium)

Benefit of Daflon 500 mg in the reduction of chronic venous disease–related symptoms **Page 79**

Maja LENKOVIC et al. (Rijeka, Croatia)

Pelvic vein incompetence: a review of diagnosis and treatment **Page 84**

Giuseppe ASCIUTTO (Malmö, Sweden)

Randomized controlled trial in the treatment of varicose veins **Page 91**

Bo EKLÖF (Helsingborg, Sweden) and Michel PERRIN (Lyon, France)

CONGRESS

Congress and conference calendar **Page 100**

Note from the Editorial Manager.

The two latest issues were erroneously numbered (respectively, Vol 19 (4) and Vol 20 (1), instead of Vol 18 (4) and Vol 19 (1)). The present issue reverts to the correct numbering.

Hugo Partsch
Editor in Chief

Dear Readers,

This very special issue of Phlebolymphology *contains review articles providing a wealth of information that is rarely found in textbooks or in journals.*

Much more than a look back at the historical developments of venous surgery, the third and last chapter of the "history of venous surgery" written by ***Michel Perrin*** *is a comprehensive and beautifully illustrated article on the state of the art of modern venous surgery and its role in deep venous disease. The reader will surely sense that this subject is still very close to the heart of the author, who worked in this field for many years and was one of its early pioneers.*

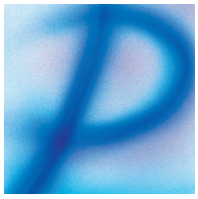
Mieke Flour*, from the University of Leuven in Belgium, has written a fantastic review on a complex issue of high clinical relevance: the identification of risk factors for the progression of venous disease. Since longitudinal studies focusing on the spontaneous course of venous pathology are widely lacking, this subject is of the utmost importance to the evaluation of the long-term outcome of different treatment regimes. In a fascinating and comprehensive article, the author leads us from clinical and hemodynamic risk factors to genetic and racial factors, including gene polymorphism, and then on to the biomarkers that characterize inflammation and endothelial dysfunction. Apart from the very nice picture of the author, the article contains no illustration; however, it provides a bunch of very relevant and carefully selected references.*

Maja Lenkovic*, from the Dermatological University Clinic in Croatia, reports on the clinical effects of Daflon 500 mg in patients with various venous disorders. A total of 1212 patients were enrolled in this open trial, including 115 patients with recurrent or recalcitrant leg ulceration, of which 13% were healed after 6 months of adjunctive treatment with Daflon 500 mg.*

Giuseppe Asciutto *from the University Hospital Malmö-Lund, Sweden, reviews the clinical aspects, etiology, diagnosis, and treatment options for pelvic vein incompetence, an often underestimated clinical entity that has gained interest in everyday practice. Spanish pioneers like Leal Monedero and Zubicoa are not mentioned in the long reference list because—unfortunately—they do not publish in English. However, their work was included in the interesting article written by J.F. van Cleef, published in* Phlebolymphology *in the first issue of 2011.*

Lastly, to conclude this issue of Phlebolymphology, a joint article by ***Bo Eklöf****, Sweden, and* ***Michel Perrin****, France, contains the second part of the overview on "randomized controlled trials in the treatment of varicose veins." (The first part was published in the last issue of* Phlebolymphology*). What great work, so much more instructive than any meta-analysis!*

Enjoy your reading!



History of venous surgery (3)

This is the last of the 3 chapters that make up a "History of Venous Surgery." In the previous issues of *Phlebolymphology* (Vol. 18, no. 3 and no. 4, 2011), an overview was presented of varicose vein surgery from the ancient Egyptians to the 20th century. In the present issue, the history continues with venous surgery other than varicose vein surgery.

Michel PERRIN

Vascular surgery, Lyon, France

Venous surgery other than varicose vein surgery

TREATMENT OF DEEP VEIN THROMBOSIS OF THE LOWER AND UPPER LIMBS DURING THE ACUTE PHASE.

Lower limbs

1. Thrombectomy

Thrombectomy is the resection of a blood clot and was the first surgical procedure performed in the treatment of acute deep vein thrombosis (*Figure 21*). In the lower limb, this procedure is attributed to the German surgeon Läwen in 1937. In principle, thrombectomy has three objectives: prevention of pulmonary embolism, treatment of the thrombosis itself, and prevention or limiting of sequelae, and postthrombotic syndrome. Combined with anticoagulant therapy, which made it possible, but also in competition with it, thrombectomy was recommended in France by Leriche, and then Fontaine, after the Second World War. It was favorably received by a few surgical teams, but did not enjoy total support by all vascular specialists. Subsequently, because of the availability of medical therapies and new techniques, the objectives of thrombectomy were called into question.

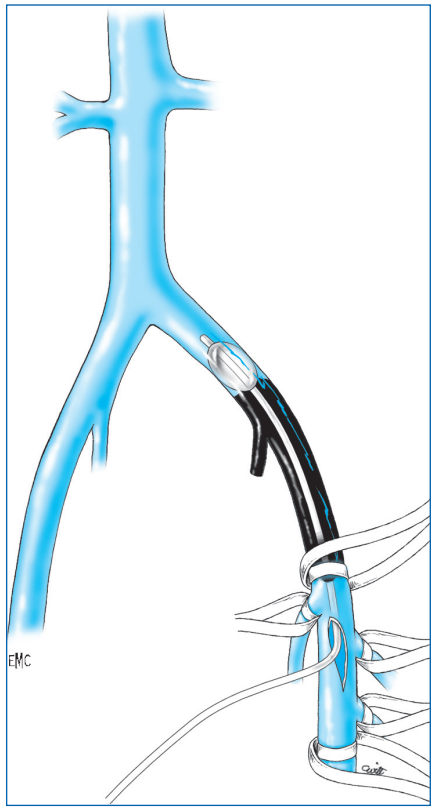


Figure 21. *Thrombectomy of the iliac venous axis with a Fogarty catheter*

Source: Perrin M, Nicolini P. Traitement des thromboses veineuses profondes des membres inférieurs par fibrinolyse in situ et thrombectomie. EMC (Elsevier Masson SAS, Paris), Techniques chirurgicales - Chirurgie vasculaire, 43-167, 2001.

2. Fibrinolysis

In fibrinolysis, a fibrinolytic agent is administered to a patient with a thrombosis and activates plasminogen in the blood. The fibrinolytic agent

Keywords:
aneurysm, history, obstruction, reflux, venous malformations, venous surgery, venous thrombosis

Phlebolymphology. 2012;19(2):59-67.

converts fibrinogen into fibrin, which lyses blood clots in a process of fibrinolysis or thrombolysis.

In 1968, the first treatment was reported in Scandinavia (Robertson). The fibrinolytic agent was delivered by intravenous infusion, which had the disadvantage of delivering the fibrinolytic agent to the thrombus in a nontargeted manner and carried the risk of bleeding.

Fibrinolysis *in situ* was introduced in 1991 (Okrent, USA). Its principle consists of delivering the fibrinolytic agent with a catheter in contact with, or even in, the thrombus. This explains why fibrinolysis in situ is more effective with lower doses, thus decreasing the risk of bleeding.

3. Thrombectomy via an intravenous device inserted transcutaneously.

The principle is to insert into the venous lumen, at a distance from the thrombosis, a catheter with a specific mechanism so as to break up the clot and suck it out. This mechanical action can be combined with fibrinolysis (*Figure 22*).

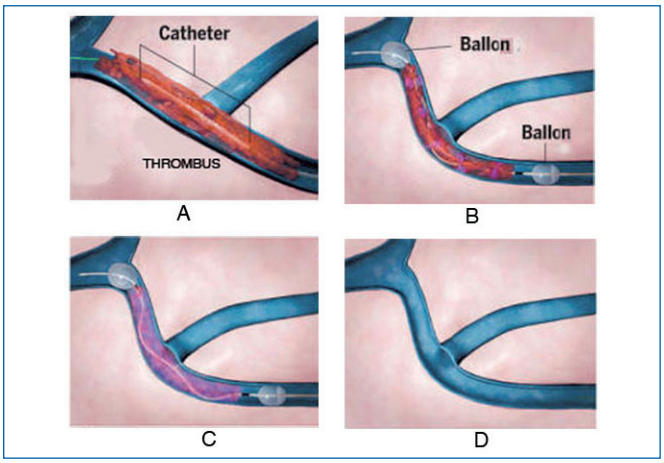


Figure 22. *Mechanical thrombectomy + fibrinolysis.*
A. The catheter is inserted over a guide wire into the thrombotic deep vein. B. Two balloons are inflated upstream and downstream of the clot to prevent embolism during the following phase of surgery. C. A fibrinolytic agent is injected between the 2 balloons while a monitor produces an oscillating movement on the central guide wire to break up the clot. D. The catheter and the guide wire are removed at the end of the procedure.

4. Caval barriers

One of the major complications of a lower limb deep vein thrombosis is the migration of a blood clot from a lower limb vein into the pulmonary arteries. The result is a pulmonary embolism, of variable severity but which can be fatal. To prevent this type of complication, the first interventions in the early 20th century involved venous ligation downstream of the thrombus, generally of the inferior vena cava. Subsequently, pericaval clips were used to divide the venous lumen into several channels (Adams - De Weese, USA, 1958). This maintained the venous circulation but prevented the migration of large emboli (*Figure 23*).

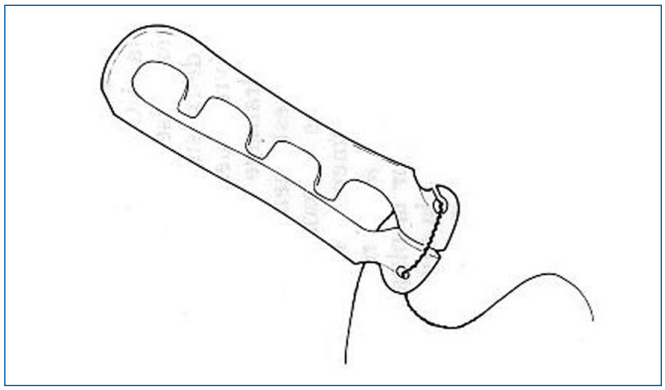


Figure 23. *Adams De Weese filter placed around the vena cava thus segmenting the lumen thus allowing passage of blood but not of large emboli.*

Subsequently, clips were replaced by placement of an endovenous filter. The first such filter was based on the same therapeutic principle: it was inserted via a peripheral vein but without open surgery of the inferior vena cava, and thus was much less invasive. It was developed and used by L. Greenfield (USA) in 1972 *(Figure 24 A)*. Since then, many such filters have been

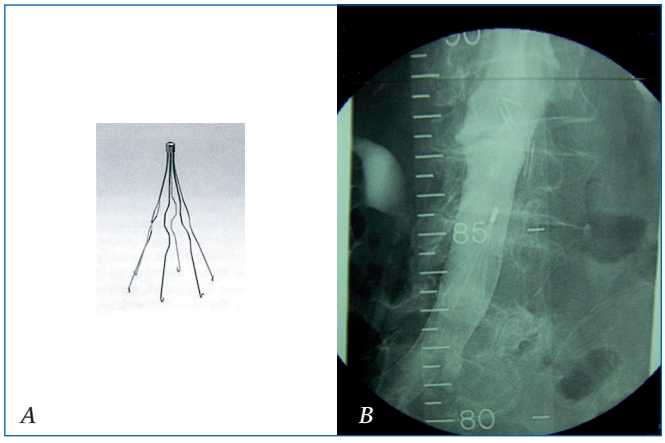


Figure 24. *A. Greenfield filter inserted percutaneously into the venous lumen at a distance from the inferior vena cava is placed in the latter to prevent passage of large emboli related to a lower limb deep vein thrombosis.*
B. Venogram of an optional inferior vena cava filter.

developed. Using ultrasound guidance, they can be inserted during a bedside procedure. Lastly, insofar as the risk of a pulmonary embolism can be transient, temporary or removable filters (*Figure 24 B*) have been developed.

Upper limbs

Even though a deep vein thrombosis in the arm is much less frequent than in the leg, the first venous thrombectomy was performed on the upper limb in 1910 by Schepelmann, a German surgeon. Only axillary and subclavian vein thromboses, that is, veins at the root of the upper limb, require surgery according to some authors, in particular US doctors. Just as in the lower limb, thrombolysis in situ has now replaced thrombectomy.

From the time of Paget (1866) and von Schrötter (1901), it has been known that a thrombosis of the subclavian vein can be associated with compression of vasculo-nervous structures at the junction of the thorax and the upper limb in the area between the clavicle and the first rib. Under these circumstances, an additional procedure is performed—when treatment of a venous thrombosis with thrombolysis has been chosen—removal of compression by partial resection of the clavicle (A. De Weese, USA, 1971) or removal of the first rib (Ross, USA, 1984).

SURGERY FOR TREATMENT OF REFLUX AND/OR OBSTRUCTION OF THE INTERNAL ILIAC AND GONADAL VEINS

It must be kept in mind that these abnormalities can be responsible for various disorders with a chronic course, for chronic venous disease, and gynecological, and urinary disorders (pelvic venous insufficiency syndrome).

Obstructive syndromes

Venous occlusion is defined as the existence of a complete blockage, while partial or total blockage of the venous lumen is referred to as obstruction. Only deep vein obstruction results in pathophysiological abnormalities, depending on its location. Generally, obstruction of a distal vein has no effect and, in particular, it is in the lower limb that obstruction of a proximal vein is harmful, in particular that of the iliac vein and the caval vein. Such obstruction may be related to a lesion of the venous lumen, most often postthrombotic syndrome, but may also be due to external compression of the vein by a tumor or an organ.

Initially, and according to the principles of arterial surgery, the bypass technique was used. The first venous bypass procedure was performed in 1948 by a Uruguayan surgeon, E. C. de Palma, who used the GSV as a vascular substitute to compensate for obstruction of the iliac vein. Subsequently, prosthetic materials have also been used.

Apart from obstruction related to cancer, where it may be necessary to resect the vein and to replace it, within the last 10 years, treatment with an endovenous stent has become the preferred technique. In fact, this technique involves dilatation of the stenotic area, or rechanneling in the case of an occlusion, performed by inflating a balloon catheter. This catheter is inserted over a guide wire using a transcutaneous approach by venipuncture of a distant vein. Once the obstruction site has been removed or the vein rechanneled by the balloon, the stent is positioned in the lumen of the vein to prevent repeat stenosis (*Figures 25, 26 A, B*). This type of endoluminal surgery is less invasive than open surgery such as bypass grafting.

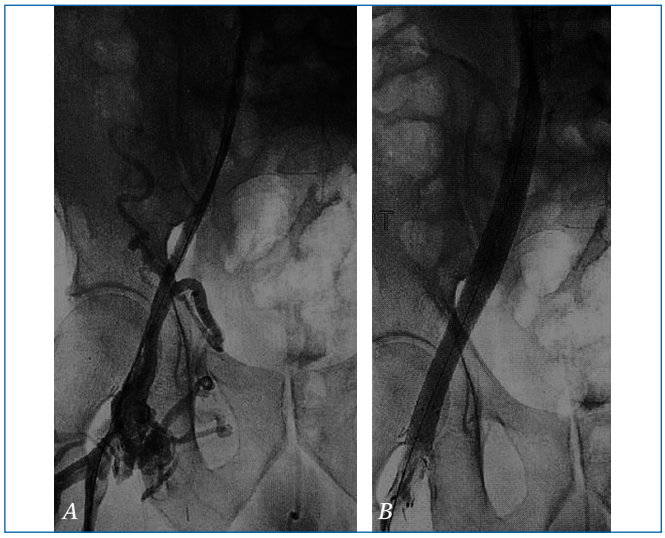


Figure 25. *Treatment of postthrombotic obstruction of the iliac vein by stent placement.*
A. Venography in a patient who presented with postthrombotic right iliac vein obstruction. Note the irregular appearance and narrowing of the venous lumen.
B. The vein has resumed its normal diameter after balloon dilatation and stent placement. Both the balloon and stent are clearly visible in the postoperative venography.

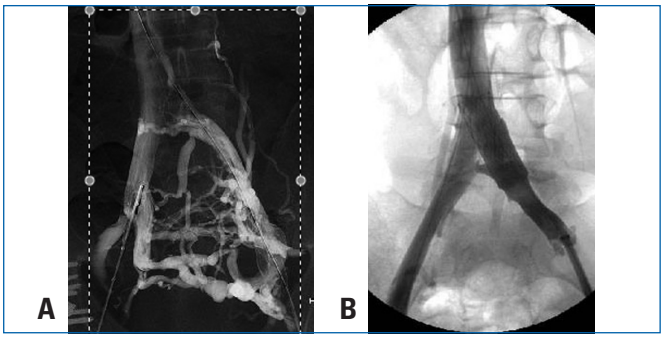


Figure 26. *A. Phlebography by bi-femoral catheterization with primary compression of the left iliac vein.*
A. Shunt circulation was developed by the presacral venous plexus, the left paralumbar vein and the anastomotic network of the left iliac axis into the right iliac axis.

Source: Courtesy: J. Leal Monedero and S. Ezpeleta Zubicoa.

B. Same patient after stent placement.

Source: Courtesy: J. Leal Monedero and S. Ezpeleta Zubicoa.

Reflux syndromes

We will only discuss the deep veins, since reflux into the superficial veins corresponds to varicose veins. This reflux can involve the lower limb veins and pelvic veins.

1. Reflux syndromes in the lower limb

When it extends from the groin to the calf, it produces a constant, major increase in venous pressure which is especially deleterious. As in the case of an obstruction, the etiology may be primary, secondary, or congenital.

Regarding primary etiology, the valve can be identified and the procedure is called a valvuloplasty. The first such procedure was performed in 1968 by R. Kistner (Hawaii, USA), the pioneer of deep vein reflux surgery. Different valvuloplasty techniques have subsequently been proposed. In internal valvuloplasty, the vein is opened and the valve is identified under direct visual control (*Figure 27*). In external valvuloplasty, the vein is repaired without opening it (*Figure 28*).

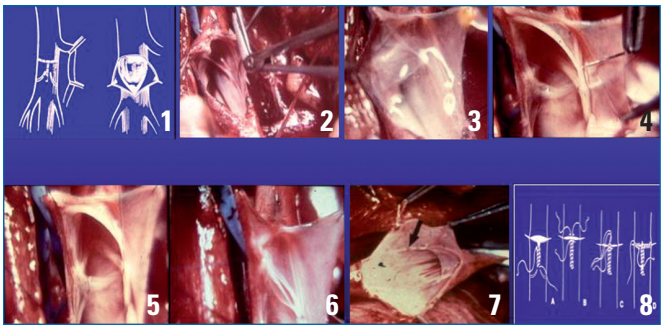


Figure 27. *Internal valvuloplasty of a valve in a deep vein. From left to right and from top to bottom: Dotted line tracing and opening of the vein by a T-incision (venotomy). (3) In the incised vein, the valve is identified and appears translucent. (4) Valvular repair is carried out by stretching its free borders with over-and-over sutures. After the repair has been completed, the 2 free borders of the valves (6-7) are now in contact, and the valve is again competent. Closure of the vein with sutures.*

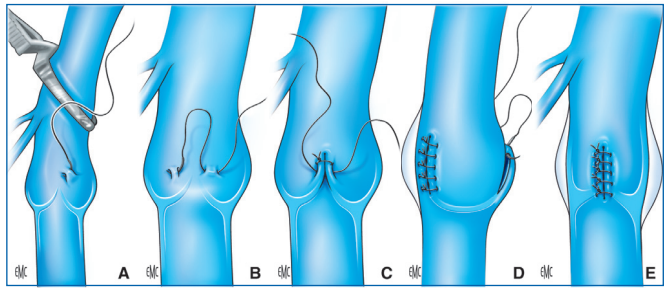


Figure 28. *External valvuloplasty of a valve in a deep vein. As in internal valvuloplasty, the procedure consists of stretching the 2 free borders of the valves. To do this, separate sutures are placed on the venous wall at the 2 commissures of the valve.*

Source: Maleti O, Lugli M, Perrin M. Chirurgie du reflux veineux profond. EMC (Elsevier Masson SAS, Paris), Techniques chirurgicales - Chirurgie vasculaire, 43-163, 2009.

Among secondary etiologies where the cause identified is postthrombotic syndrome, the valve is destroyed by the thrombosis and cannot be repaired. Among congenital causes, the valves may be absent or atrophied, and thus the same holds true. Therefore, other surgical techniques have to be used:

- Transplantation of a venous valvular segment. In 1982, Taheri (USA) and Raju (USA) proposed using the humeral and axillary veins which have a functional valve and can be collected undamaged and transplanted into the lower limb (*Figure 29*).

- Transposition consists of transposing the vein that is the site of reflux onto another lower limb vein, below its competent valve (*Figure 30*). R. Kistner (USA) invented this technique in 1982.

- The creation of a neovalve using venous tissue from the patient was proposed by P. Plagnol (France) in 1999 and by O. Maleti (Italy) in 2002 (*Figures 31A, B*). Bio-prosthetic valves are currently being assessed.

2. Gonadal and/or pelvic vein reflux syndromes

In women, these can cause gynecological disorders such as pelvic congestion syndrome (H. Taylor, USA, 1949),

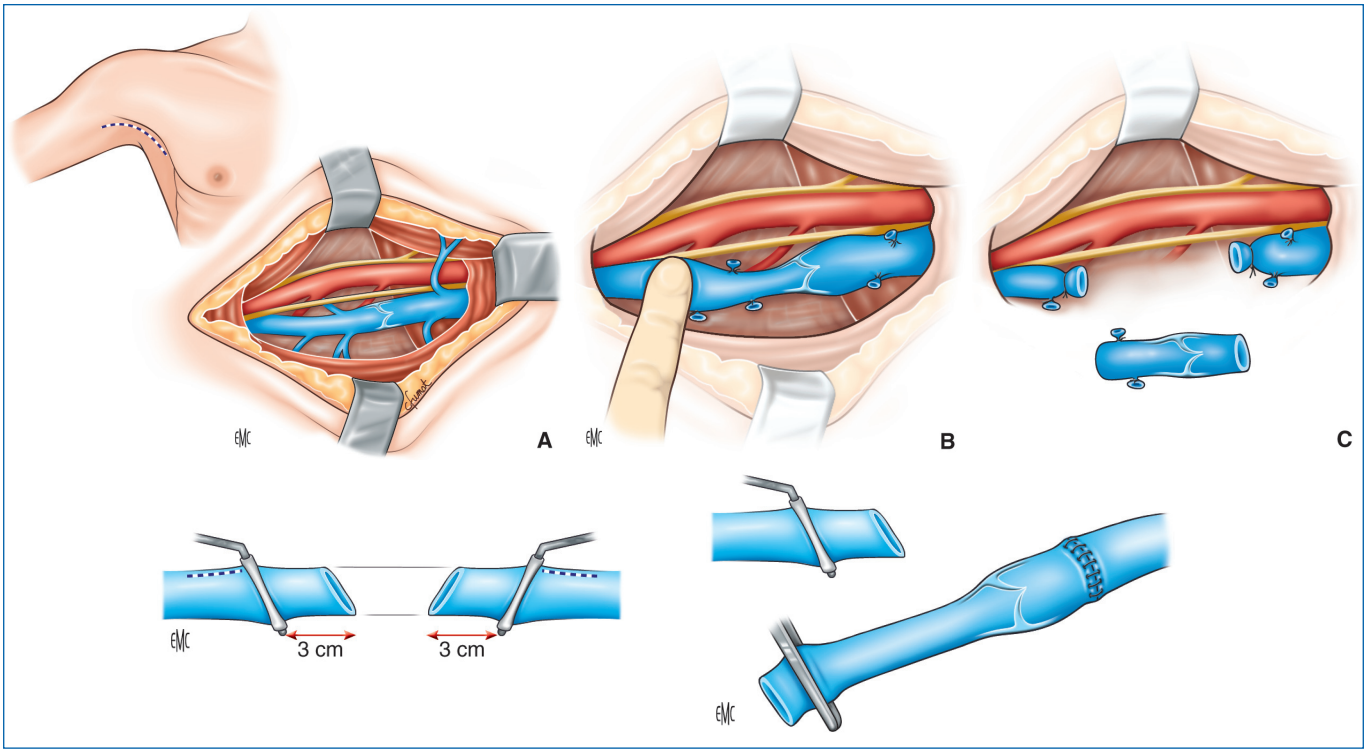


Figure 29. *Transplantation of a venous valvular segment.*
From top to bottom:
A, B, C: A segment of axillary vein is collected after verifying that it has a competent valve. An equivalent length of vein presenting reflux is resected. The venous valvular segment is transplanted. Here, only the proximal anastomosis has been performed; the distal anastomosis will restore continuity of the venous axis. Thus, a competent valve is placed in the venous axis that is the site of the reflux.

Source: Maleti O, Lugli M, Perrin M. Chirurgie du reflux veineux profond. EMC (Elsevier Masson SAS, Paris), Techniques chirurgicales - Chirurgie vasculaire, 43-163, 2009.

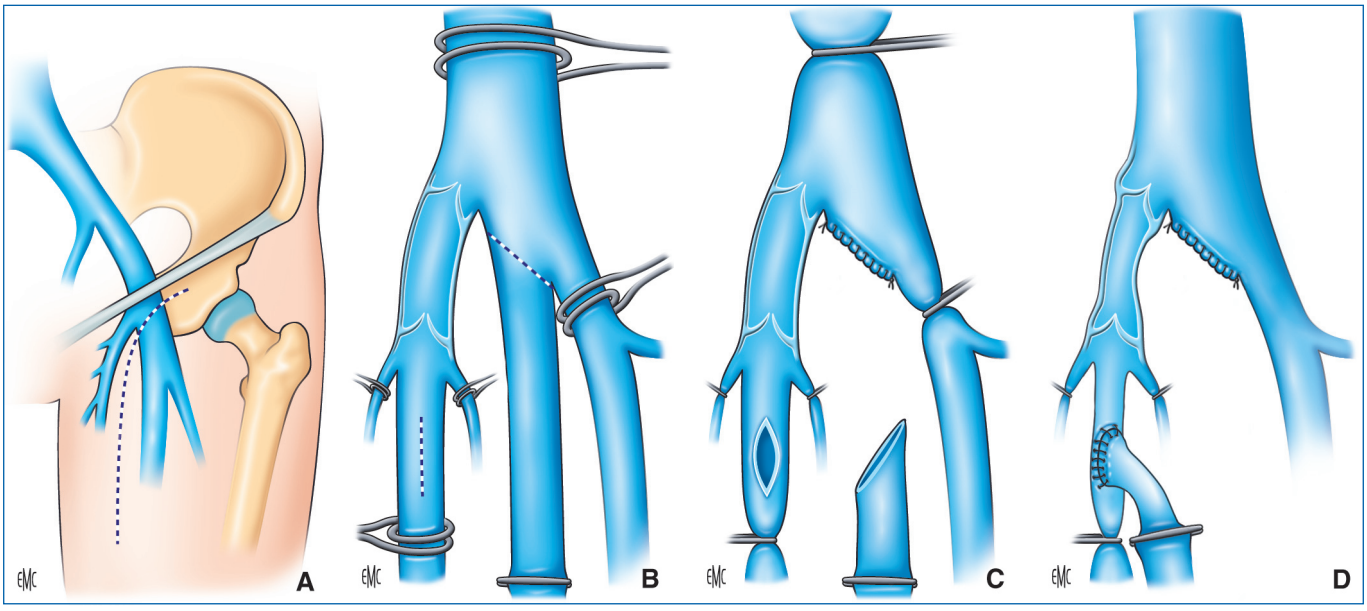


Figure 30. *Transposition.*
The femoral vein presents reflux in the middle segment. The vein located to the left is the great saphenous vein which has competent terminal and subterminal valves. The incompetent femoral vein is transposed below the competent valves of the great saphenous vein.

Source: Maleti O, Lugli M, Perrin M. Chirurgie du reflux veineux profond. EMC (Elsevier Masson SAS, Paris), Techniques chirurgicales - Chirurgie vasculaire, 43-163, 2009.

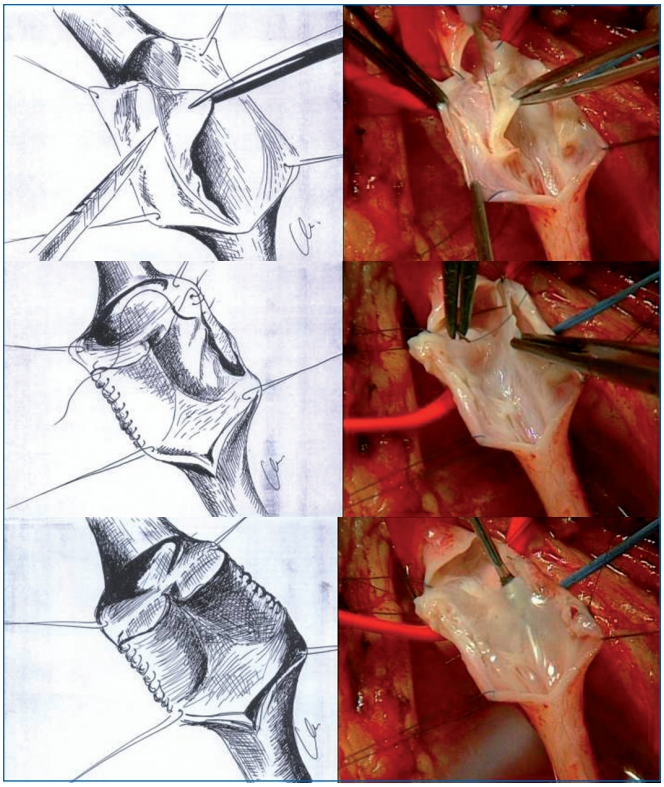


Figure 31A. *Creation of a bicuspid neovalve (Maleti's technique) From top to bottom:*
- After opening the vein a few centimeters along its axis, the operator divides its wall on one side into two layers.
- This detachment stopped in the middle allows construction of a sac which corresponds to a valve in a normal subject.
-The same technique is performed on the other side thus creating a valve with 2 valvular cusps.

Courtesy: O.Maleti MD

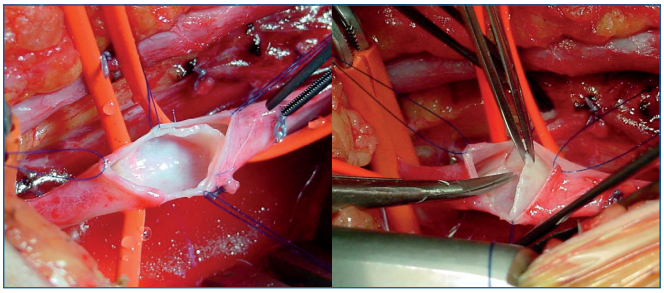


Figure 31B. *Creation of a monocuspid neovalve (Maleti's technique).*
- On the left. Postthrombotic thickened venous wall.
- On the right. A monocuspid valve was created by separation from the wall.

Courtesy: O.Maleti MD

vulvar or perineal varices, and lower limb varicose veins. In men, gonadal vein reflux causes dilatation of the testicular veins and can cause infertility. Such reflux can be treated with sclerotherapy, but in cases of major reflux, surgical ligation of the gonadal or pelvic veins is performed. Currently, coil embolization of refluxing veins and sclerotherapy are used in combination. This procedure, proposed by R. Edwards (USA) in 1993, obliterates the veins where reflux occurs (*Figures 32 A, B*).

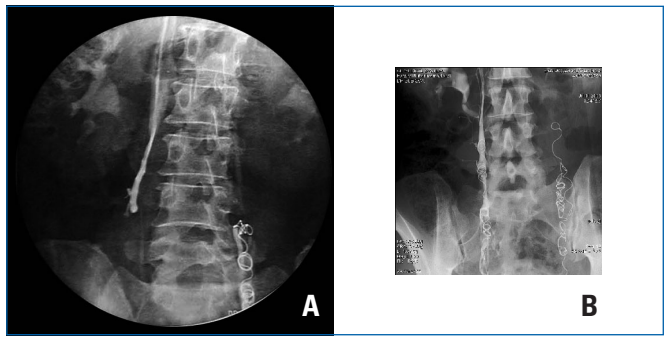


Figure 32. *A. Selective venography of the right gonadal vein demonstrating reflux. The left gonadal vein has been embolized (with sclerosing foam + coil embolization).*

Courtesy: J. Leal Monedero and S. Ezpeleta Zubicoa.

B. Same patient after bilateral embolization of the gonadal veins.

Courtesy: J. Leal Monedero and S. Ezpeleta Zubicoa.

SURGERY OF VENOUS ANEURYSMS

A venous aneurysm is defined as an increase in the size of a vein equal to at least twice the normal diameter of the vein considered. It is difficult to identify the date and the author of the first surgical treatment of a venous

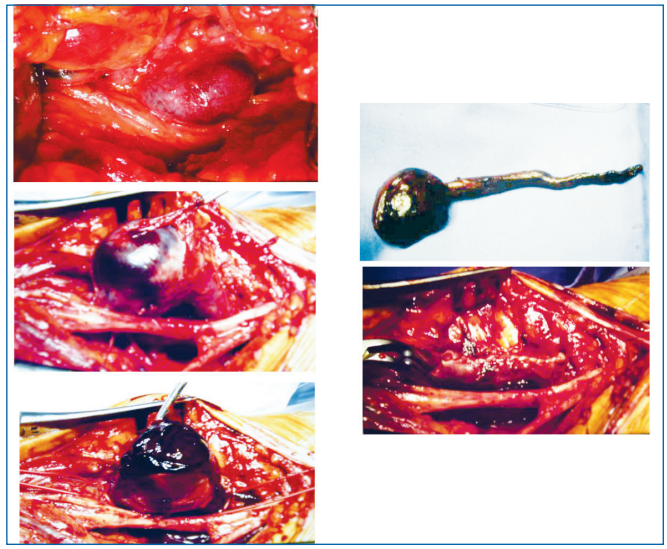


Figure 33. *Open surgery of a venous aneurysm.*
The aneurysm contains a large thrombus. After resecting the aneurysmal sac, continuity of the venous axis is restored by closing the vein with a suture.

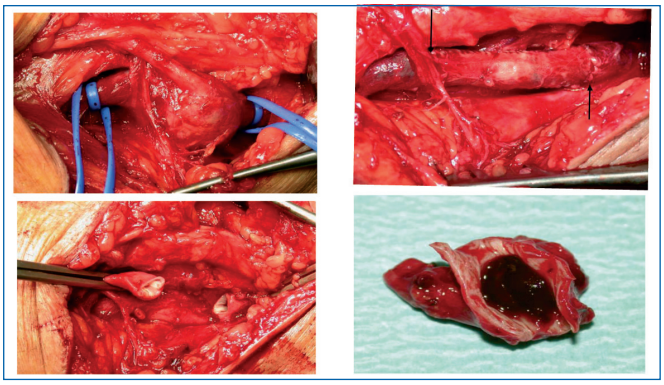


Figure 34. Open surgery of a venous aneurysm. If the aneurysm occupies the entire circumference of the vein, the operator proceeds differently, but by suturing the vein end to end, continuity of the venous axis is also restored.

aneurysm. A rare disorder, venous aneurysm is most often located in the popliteal vein. It is agreed that aneurysms should be treated with open surgery depending on their morphology and on whether or not there are blood clots in the aneurysm sac. After resecting the aneurysm, venous continuity is restored whenever possible (*Figures 33, 34*).

SURGERY TO TREAT THE "NUTCRACKER SYNDROME"

This term refers to disease resulting from compression of the left renal vein between the aorta and the superior mesenteric artery, in a nutcracker-like configuration, which accounts for its name (*Figure 35*). Such compression can cause lumbar pain, hematuria, and pelvic congestion syndrome by reflux of the left gonadal

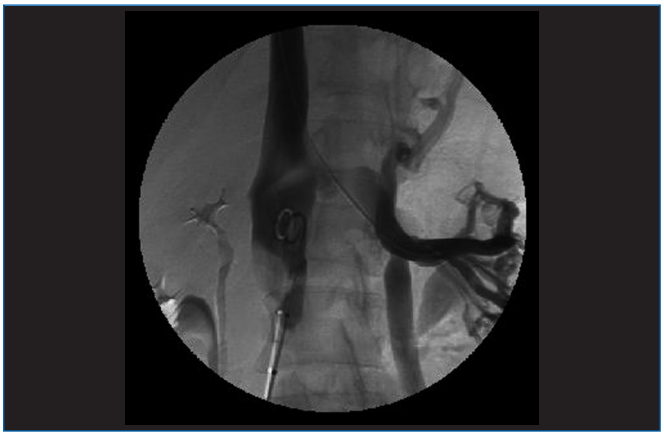


Figure 35. Nutcracker syndrome. Selective venography with compression of the left renal vein with an incompetent gonadal vein.

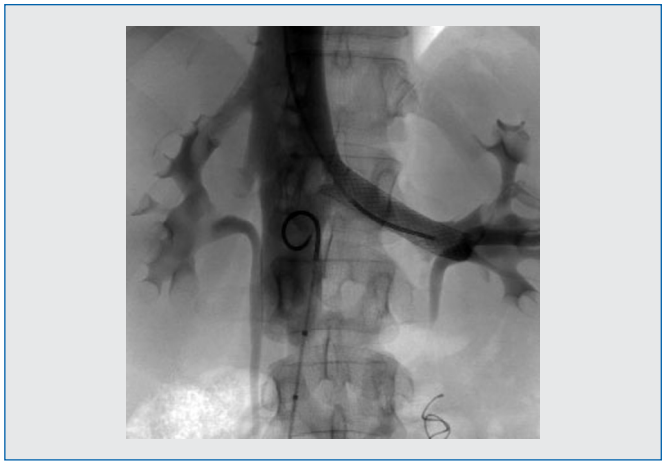


Figure 36. Nutcracker syndrome. Stenting of the left renal vein.

vein. Although surgical treatment is rarely indicated, many techniques have been proposed. First, open surgery techniques are used to eliminate compression, either by reimplanting the left renal vein or the kidney itself, or by performing a venous bypass. More recently, the nutcracker syndrome has been treated with endovenous stents (M. G. Neste USA, 1996) (*Figure 36*).

SURGERY FOR CONGENITAL VENOUS MALFORMATIONS

Congenital venous malformations in their severe form remain the most serious challenge in phlebology. Within the last 20 years, a relatively precise consensus has been reached regarding classification, thus making it possible to divide such malformations into two groups: venous and arteriovenous malformations, with the latter being most severe. Historically, surgery, sclerotherapy, and embolization have been used separately or in combination. Pioneers associated with advances in this field include (in alphabetical order) S. Belov (Bulgaria), P. O. Burrows (USA), J. Y. Kim (Korea), B. B. Lee (Korea), D. A. Loose (Germany), E. E. Scott (USA), D. E. Szilagy (USA), J. L. Villavicencio (USA), W. Yakes (USA). Currently, there is agreement on combined use of different surgical methods after multidisciplinary meetings.

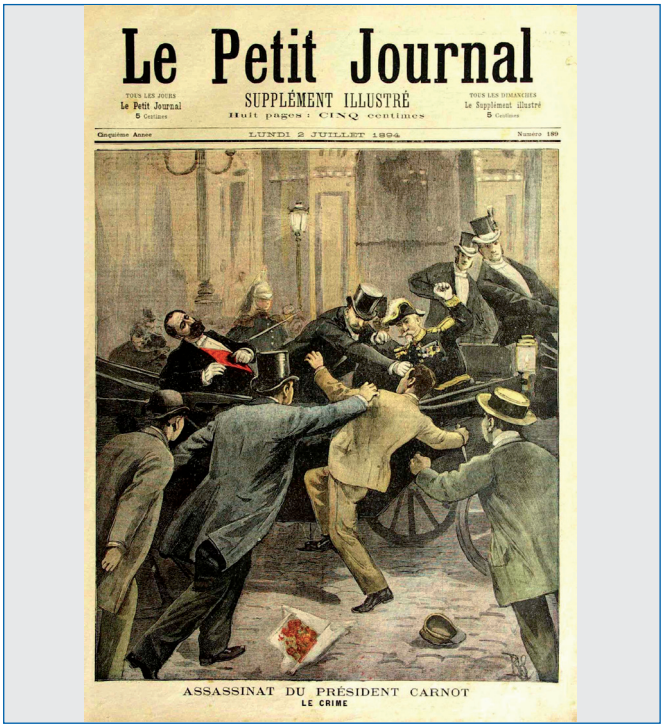
SURGERY FOR VENOUS TUMORS

Primary venous tumors develop in the venous wall. They are rare and can be benign or malignant and are

treated by resection of the vein with possible restoration of venous continuity depending on tumor location. Secondary tumors are an extension of an adjacent cancer or metastatic spread of cancer or a distant cancer. Surgery is used to treat them in some cases. Historically, it has been observed that surgery to remove a tumor prolongs survival following traditional vascular reconstruction procedures.

SURGERY FOR VENOUS TRAUMA AND WOUNDS

This type of surgery has benefited from advances in intensive care and vascular reconstructive surgery, both in terms of survival as well as absence of sequelae. As a historical footnote, the French president Sadi Carnot died in Lyon in 1884 from a torn portal vein after he was stabbed in the abdomen by an immigrant anarchist, Sante Geronimo Cesario (*Figure 37*). A. Carrel, the French surgeon who trained in Lyon and then immigrated to the USA and who later received the Nobel Prize, wrote that if at that time it had been possible to repair blood vessels, a field in which he distinguished himself, the president would have survived. In 1947 the famous Spanish matador Manuel Laureano Rodríguez Sánchez, also known as Manolete, died of an injury to the femoral vein after having been impaled by the bull "Islero" from Don Eduardo II's cattle ranch. His name was subsequently associated with a special type of high pass maneuver with the cape used in bullfighting known as the "manoletina" where the bull charges behind the bullfighter into his red "muleta" (*Figure 38*).


Le Petit Journal

SUPPLÉMENT ILLUSTRÉ

Huit pages : CINQ centimes

LUNDI 2 JUILLET 1894

ASSASSINAT DU PRÉSIDENT CARNOT

LE CRIME

Figure 37. *The assassination of the French President Sadi Carnot in an open horse-drawn carriage, as depicted on the front page of an illustrated supplement in "Le Petit Journal," a French daily newspaper of the time.*

Figure 38. *The famous "manoletina" pass created by Manolete is a high pass maneuver where the bull charges behind the bullfighter into his red "muleta."*

The Korean and Vietnam wars enabled military surgeons to better codify the veins that had to be reconstructed from those that had to be ligated (N. Rich, USA).

CONCLUSIONS AND FUTURE PERSPECTIVES

It is not within the scope of this paper on the history of venous surgery to discuss the advantages and disadvantages of the different methods, their results and their indications, all the more so since the speed with which new techniques are introduced would quickly make this document obsolete. A few comments are, however, warranted.

Surgery in the broader sense based on its etymological definition is increasingly less invasive, and this has transformed the quality of life of patients postoperatively.

It is likely that a certain number of venous disorders no longer require surgery insofar as their pathogenesis is better elucidated and because medical therapy will have an increasingly larger role, whether used separately or in combination with surgery.

Lastly, economic considerations will definitely have an impact on the future course of venous disease. The efficacy of treatment will have to take into account the cost-to-benefit ratio.

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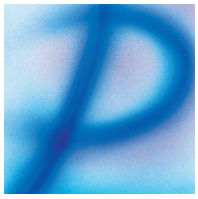

Factors to identify patients at risk for progression of chronic venous disease: have we progressed?

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SUMMARY

This article will review the literature concerning the risk factors that identify C2, C3, C4 patients, according to the clinical, etiological, anatomical, pathophysiological (CEAP) classification, who are at risk for progression to C6.

Evidence concerning the risk factors for progression of chronic venous disease (CVD) is weak. There are no known hemodynamic methods to identify which patient with primary CVD and limbs with C-class 2 to 4 will develop leg ulcers. Duplex ultrasound scanning parameters of interest would be the anatomic extent and distribution of reflux and obstruction, and the quantification of reflux, measured at set time intervals in prospective long-term studies with a large sample size. History and physical examination should focus on the appearance of new signs during the interval period, but cannot reliably identify those patients in whom venous reflux changes develop over time. To detect clinical progression, these patients need to be followed up using clinical severity scores, which are more sensitive than the C-classification. Primary venous incompetence should be differentiated from secondary incompetence because the two conditions differ in pathophysiology, management, and prognosis.

Some clinical risk factors and clinical signs that warrant early intervention in patients with varicose veins have been detected, but it will probably be difficult to perform the required prospective longitudinal studies, cross-cultural whenever possible, to evaluate the influence of such clinical factors on disease progression. Alternative ways need to be found.

There are gene polymorphisms and biomarkers that identify patients at high risk for progression to ulceration. In addition, genetic variations may differ across ethnic groups. Additional studies are needed to show if sex, age, ethnicity, and environment influence disease progression.

Keywords:
chronic venous disease, risk factors, venous incompetence

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So far there are no available specific inflammatory mediators for CVD or reliable methods for assessment of endothelial function. Data regarding the deterioration of ankle mobility, calf muscle pump function, and patient activity need to be correlated with progression of the disease or with reversal under treatment, in order to use them to rate the progression of venous disease. If factors for disease progression in patients with primary CVD could be identified, a modification of these factors, if feasible, may prevent development of venous ulcer.

EVIDENCE ON THE RISK FACTORS FOR PROGRESSION OF CHRONIC VENOUS DISEASE.

The natural history (progression) of CVD remains poorly understood: only a few longitudinal studies have been reported, and much of the available information is from cross-sectional studies.

Among patients awaiting surgery, nearly one third of those with venous reflux had progression in CEAP clinical stage and/or duplex ultrasound scanning. The great saphenous vein and tributaries were the anatomic sites most often affected by a change, either as extension of preexisting reflux (in antegrade and retrograde fashion) or as reflux in a new segment.[1]

In a prospective 7-year follow-up of patients with both superficial and deep venous reflux, deterioration in clinical class was shown in most of the limbs at the end of the observation period. Limbs that underwent a superficial or deep venous procedure remained stable or improved over time; those that underwent elastic compression alone had worsening hemodynamic and clinical status.[2]

The Bochum study was a large cohort investigation in Germany exploring the natural history of preclinical (C0) and early stages (C1) of the development of varicosities and the behavior of venous calf pump function from childhood to adulthood in subjects with healthy veins. Telangiectasias and reticular veins were noted early on, independently of the presence of reflux. Large varicosities appeared in older subjects, often preceded by reflux in the saphenous veins.[3]

The Bonn Vein Study I, conducted in 2000, involved 3072 participants of the general population of the city of Bonn and two rural townships, aged 18 to 79 years (1350 men, 1722 women).[4] In the follow-up study (Bonn Vein Study II) 6.6 years later, the same population was investigated again. The incidence of progress to chronic venous insufficiency (C3-C6) was approximately 2.0% per year. In a multivariate analysis, the main risk factors for developing severe stages (C4-C6) were age, hypertension, and obesity.

Reflux may develop at one or more locations, and can progress in a retrograde or antegrade manner, or in both directions. The progression of CVD is more rapid in postthrombotic limbs when compared with those with primary CVD. Poor prognostic factors for progression to advanced CVD include the combination of reflux and obstruction, ipsilateral recurrent deep venous thrombosis (DVT), and multisegmental involvement. People receiving no etiologic treatment are at greater risk for venous disease progression.[5]

There are no validated risk factors for disease progression.

There are no studies on how to identify patients with primary CVD who will develop more severe symptoms, complications, or recurrence following treatment. Kostas and co-workers evaluated the long-term (5 years) characteristics of CVD progression and its correlation with the modification of specific risk factors. The contralateral (normal) limb of 73 patients undergoing varicose vein surgery for unilateral varicosities was prospectively evaluated using physical and color duplex examination and classified by CEAP. In about half of patients, CVD (reflux development and clinical deterioration) developed in the contralateral, initially asymptomatic, limb in 5 years. In these patients, obesity, orthostatism, and noncompliance with the use of elastic stockings were independent risk factors for CVD progression, but estrogen therapy and multiparity were not.[6]

Data on risk factors for progression to postthrombotic syndrome following deep venous thrombosis

In secondary CVD, occurrence of postthrombotic syndrome after an episode of acute DVT is related to both failure of recanalization (with persistent venous obstruction), and the development of valvular incompetence. Progression from asymptomatic cosmetic varicose veins (C2) to symptomatic stages with pain, edema, skin changes, and ulceration has been shown to be more pathogenic than previously thought, and to have a high prevalence and a broad demographic spectrum in patients with CVD. Moreover,

nonthrombotic iliac vein lesions are commonly found in the asymptomatic general population.[7]

Risk factors have been identified in ulcer recurrence that may be helpful

It is important to correct the underlying disorder in patients with established venous ulcer disease in order to prevent recurrence. Residual iliofemoral vein obstruction, residual deep incompetence, particularly axial deep reflux, residual or recurrent superficial reflux, and persistent venous hypertension have been identified as risk factors for ulcer recurrence.[8,9]

Conclusion

There are no known hemodynamic methods to identify which patients with primary CVD and limbs with C-class 2 to 4 will develop leg ulcers. Duplex ultrasound scanning parameters of interest would be the anatomic extent and distribution of reflux and obstruction, and the quantification of reflux, measured at set time intervals in prospective long-term studies with a large sample size. History and physical examination should focus on the appearance of new symptoms during the interval period, but cannot reliably identify those patients in whom venous reflux changes develop over time. To detect symptomatic progression, these patients need to be followed up using clinical severity scores, which are more sensitive than the C-classification. Primary venous incompetence should be differentiated from secondary postthrombotic venous incompetence because the two conditions differ in pathophysiology, management, and prognosis. Primary venous incompetence is recognized to be a slowly progressive disorder that may advance to C4-C6 manifestations over time in up to 20% or more of the older population.

If factors for disease progression in patients with primary CVD could be identified, a modification of these factors, if feasible, may prevent development of venous ulcer.[10]

Neglen pointed out that it is necessary first to develop a protocol for CVD investigation for clinical practice, and then introduce a more sophisticated protocol for longitudinal research in CVD. Additional methods of studying venous hemodynamics and the microcirculation should also be used in longitudinal studies. With regard to primary CVD, it is essential to identify measurements that predict progression from C-class 2-4 to active leg ulcers.[11]

CLINICAL RISK FACTORS AND CLINICAL SIGNS THAT WARRANT EARLY INTERVENTION IN PATIENTS WITH VARICOSE VEINS

Studies of risk factors for developing varicose veins have largely yielded inconsistent results. Much of the variation between studies is probably related to differences in definitions, in population sampling techniques (age, race, occupation, sex), and in assessment/measurement methods. References mention risk factors identified from several types of data sources: clinical investigations, especially in larger population samples, histological studies of the vein wall, and evaluation of treatment outcomes. The current belief is that both environmental and genetic factors are associated with the development of varicose veins.

Clinical factors

Trunk varicose veins occur very commonly with increasing age.[4,12,13] Risk due to a positive family history has been investigated and confirmed by Cornu-Thénard and several others.[14,15]

A genetic predisposition may be present, but evidence for this and for a mode of inheritance is lacking.[16]

Genetic twin studies in Germany[17,18] and England[19] indicated a strong genetic influence on varicosities and on venous function, and the data strongly suggest that the FOXC2 gene on chromosome 16 is implicated in the development of varicose veins in the general population.

In women, obesity has been associated with the presence of varicose veins but it appears to be an aggravating factor rather than a primary cause; the evidence is inconsistent. Many studies consider body mass index to be more important in females than in males. However, obesity seems to play a more important role in the development of severe clinical signs of CVD, possibly due to functional more than to anatomical insufficiency.[12,13,20]

Female sex is a universally cited risk factor, while large geographical differences suggest strong environmental influences. In most studies undertaken so far, CVD has been found to be more prevalent among women than among men, although the difference was small. A different timing of disease in the two sexes was observed

by Fiebig[18] in terms of the mean age at disease onset, with females showing first symptoms of CVD at 30.8 years of age, compared with 36.8 years for males.

Pregnancy (multiparity) is an established risk factor or aggravating factor for the development of varicose veins. The use of hormones, eg, birth control pills, is not universally accepted as a risk factor. Smoking affects the vascular wall and has an impact on endothelial cell function and behavior. As for several other cultural and behavioral habits, their role as risk factors for the development of varicose veins is difficult to prove.[13,20]

Compared with women without clinical signs in the Framingham Study, women with varicose veins were more often obese, had lower levels of physical activity, higher systolic blood pressure, and were older at menopause. For men, varicose veins coexisted with lower levels of physical activity and higher smoking rates. These results suggest that increased physical activity and weight control may help prevent varicose veins among adults at high risk, and reduce the overall risk of atherosclerotic cardiovascular disease as well.[13]

Prolonged standing has been cited as a risk factor, but the data should be interpreted with caution given the difficulty in measuring levels of posture and because of potential bias in selection of the study population.

In the Bonn Vein Study II, "sensation of swelling" significantly increased the risk for the development of chronic venous insufficiency (CVI).[4] Clinical signs (eg, corona phlebectatica and other skin changes) may warrant early intervention to prevent later ulcer formation. The risk of ulceration is related to the severity of varicosities and venous insufficiency, and is increased following deep vein thrombosis (incompetence). However, the risks may also be increased in those who smoke, are obese, and have restricted ankle movement and reduced calf muscle pump power.[20]

There are studies showing that mechanical dysfunction of the calf muscle pump may enhance the development of leg ulceration.[21] It will therefore be important to investigate ankle range of motion, calf muscle pump function, and patient activity in relation to progression of disease. The data that are presently available need to be correlated with progression of the disease.[13,20,22]

Histopathology

Clinically observed thickening of the vessel wall appears to be associated with an increase of thick and disorganized collagen bundles and fragmentation of elastic fibers. Similar alterations of extracellular matrix are found in the vein wall and skin of C2 patients.[23]

Treatment outcome

Follow-up duplex scanning after aggressive treatment of superficial venous disease showed improvement or complete reversal of deep venous insufficiency in the majority of patients as reported by Ahmad. Only 28% of patients receiving less aggressive treatment showed improvement in their reflux valve closure time; the remaining 72% were unchanged or showed deterioration.[24]

Conclusion

It will probably be difficult to perform the needed prospective longitudinal studies, cross-cultural whenever possible, to evaluate the influence of these clinical factors on disease progression. An alternative way is to find unique features in limbs with already established ulcers (C6) as compared with limbs with lower severity venous disease (C2 to C4).[11]

GENE POLYMORPHISMS AND BIOMARKERS THAT IDENTIFY PATIENTS AT HIGH RISK FOR PROGRESSION TO ULCERATION

Varicose veins without skin changes have a prevalence of approximately 20% in Northern and Western Europe, while advanced CVI affects about 3% of the population. Among the many who have varicose veins (C2), only 10% will develop a venous ulcer. Genetic risk factors are thought to play an important role in the etiology of both varicose veins without skin changes and of venous ulcer. Clinical as well as hemodynamic parameters (including duplex scanning, plethysmography, or both) fail to predict ulcer appearance.

1) Genetic factors may play a role in the etiology and progression to advanced CVD (see above), but there is a need to establish biobanks and blood banks for subsequent analysis in longitudinal studies.[11]

2) Some data are available on gene polymorphisms and biomarkers that may identify patients at high risk for progression to ulceration.

It has been suggested that tumor necrosis factor-alpha (TNF-α) gene polymorphism is associated with increased susceptibility to venous leg ulceration,[25] but some authors refute a direct link between these two findings since the A allele of the -308 G/A single nucleotide polymorphism (SNP) in the promoter region of the TNF-α gene might be a factor for venous leg ulcer susceptibility. However, their data suggest that this association is secondary and that the primary association is probably with obesity.[26] Estrogen receptor beta (ER-β) polymorphism is associated with impaired healing in the elderly, reportedly predisposing individuals to venous ulceration.[27]

Studies on single nucleotide polymorphisms of the fibroblast growth factor receptor 2 (FGFR-2) gene indicate a genetic alteration in the FGFR-2 gene which is present significantly more often in CVI patients with chronic nonhealing wounds.[28]

Studies on hemochromatosis suggest that there could be a pathophysiological role of iron deposition, iron trafficking genes, and transglutaminases in venous leg ulcer, resulting in a strong genetic component in ulcer pathogenesis. A relationship has been described between the C282Y polymorphism in the hemochromatosis (HFE) gene and venous ulceration. In such cases, a simple C282Y blood genetic test demonstrated a more than 6-fold increase in specificity in predicting ulcer development (98%; CI 95%, 92.8–99.7), while ulcer onset occurs almost 10 years earlier in patients carrying the H63D variant.[29]

Studies on thrombophilia: In patients with chronic venous leg ulceration, MacKenzie defined the prevalence of thrombophilia, and determined whether this is associated with medical history or with duplex scan evidence of DVT. Despite no previous DVT (duplex/history), patients with ulcers have a 2 to 30 times higher prevalence of thrombophilia (41%) compared with the general population. Certain thrombophilias (antithrombin deficiency) may be a risk factor for ulcer development. But in this study, in patients with chronic venous leg ulceration, there was no difference in DVT rates between those with and without thrombophilia.[30]

Venous thrombosis and inflammation are closely related. In an assessment of whether there is a relation between genetic modifiers of the inflammatory response and the risk of venous thrombosis, Pieroni et al concluded that cytokine gene polymorphisms did not significantly influence venous thrombotic risk.[31]

3) Some studies are in progress, like the genome-wide association studies approach that identify relevant patterns of numerous SNPs to predict future disease states and evaluate gene patterns that relate to multiple phenotypes of complex diseases. Sex, age, ethnicity, and environment seem to influence strongly the penetrance of disease.[29]

4) There is a need for additional large cross-sectional and longitudinal studies on the natural history of primary CVD including systematic population-based searches for CVD susceptibility genes and factors that could be regarded as prognostic markers in CVD progression to ulcer formation.[11]

DIFFERENCES IN SKIN TYPE OR METABOLISM OR RACE THAT MAY PLACE PATIENTS AT INCREASED RISK OF ULCERATION

Some publications indicate sociodemographic differences in the risk of progression of CVI.

A study in West London collected details on age, sex, and ethnic background of all patients who attended for treatment of leg ulceration over a one-year period.[32] While the overall estimate of ulcer prevalence was 1.02 per 1000 population, there was a significantly higher proportion of whites suffering from leg ulceration compared with South Asians (Indian subcontinent background): odds ratio of 4.43 (95%; CI, 1.94-10.13; *P*=0.0004). Because of selection bias, the authors conclude that either there is a real difference in prevalence or South Asians do not attend the clinic for treatment.

In the San Diego cross-sectional study of a multiethnic sample of more than 2000 men and women between 1994 and 1998, the authors report that women had more superficial functional disease, whereas men had more deep functional disease. CVD increased with age, and non-Hispanic Whites had more venous insufficiency than did Hispanics, African Americans, or Asians.[33]

Humoral or genetic factors responsible for disease progression to ulcer formation are related to thrombosis and to inflammation. Hyperhomocysteinemia is

recognized as one of many risk factors for venous thrombosis, and for the development and progression of CVI, and is present in about 65% of patients with CVI. In the publication of Sam et al, a strong relationship was observed between mild to moderately elevated plasma homocysteine concentration and increasing severity of venous disease (C6> C5 > C4). The authors suggest that these data confirm the 'multihit' hypothesis suggesting that various inherited and acquired factors act in concert to raise individuals above the thrombotic threshold. Prevalence of the C677T MTHFR mutation (methylene tetrahydrofolate reductase) was higher in complicated C4-C6 disease (20%) than in uncomplicated C2-C3 disease (10%), and overall more patients (15%) were homozygous, compared with an estimated 5% of the healthy white population.[34]

Genetic variations that affect chronic inflammation may differ across ethnic groups. SNPs in cytokine genes affect cytokine levels and the degree of inflammation. Genetic variants, specifically SNPs in cytokine genes can affect cytokine production and, therefore, may in part modulate the inflammatory response.[35]

USE OF ELEVATED IL-6, A UNIVERSAL MARKER OF INFLAMMATION, IN IDENTIFYING PATIENTS AT RISK FOR PROGRESSION OF VENOUS DISEASE

It is generally agreed that universal markers such as IL-6 are elevated, but it is uncertain whether or not they indicate progression of the disease. It would be of value to identify biomarkers signaling an increased risk of ulcer formation.

IL-6 occupies a central place in the inflammatory response. It is produced and released into the systemic circulation from many different cells in the body, including endothelial cells, fibroblasts, subcutaneous adipose tissue, as well as from cells of the immune system. The levels correlate with body mass index and percent body fat. It is the only cytokine that can stimulate the synthesis of all the acute phase proteins involved in the inflammatory response. As a universal marker IL-6 is not specific to, or diagnostic in, progression of venous disease.

Genetic polymorphism influences the plasma levels of IL-6 (GG allele carriers have IL-6 levels twice those of individuals with the CC allele).

In a prospective cohort study of representative community residents aged 71 years and older, Purser reported that geographical segregation could influence the level of IL-6.[36] Results showed that socially disadvantaged environments may influence IL-6, a biomarker of age-associated inflammation: being older, African American, taking more prescription drugs, having a body mass index greater than 30, consuming greater levels of alcohol, and being a current smoker were all strong and important individual level predictors of elevated IL-6.

Several biomarkers reflect functional activation of monocyte-macrophages and damage to the endothelial structure related to venous stasis and venous hypertension.

The elevated plasma levels of several inflammatory mediators (TNF-α, IL-1β, IL-6, IL-10, IL-8, IL-12p70) are also risk determinants for venous thrombotic disease.[37]

Many studies have investigated the relation between venous stasis, functions of the vascular and perivascular anatomic structure, venous endothelium, and circulating leukocytes. Their results revealed elevated baseline production of inflammatory markers in patients with varicose veins, and that induced venous occlusion (cuff inflation) further augmented the levels of all cytokines in the study series, especially in patients with varicose veins. The authors believe that the study shows functional activation of monocyte-macrophages related to venous stasis as a consequence of venous hypertension. Cell response damages the endothelial structure and may represent an important element in the pathophysiology of CVI.[38]

Fox published a systematic review of clinical studies that have examined the association between inflammation and venous thrombosis, specifically: the value of inflammatory markers in predicting the future development of venous thrombosis; test characteristics of markers of inflammation in the diagnosis of acute venous thrombosis; and the effect of venous thrombosis on blood levels of inflammatory markers. Results show

that plasma C-reactive protein levels do not appear to predict risk of future venous thrombosis.[39]

Christiansen confirmed that IL-6 is not a marker for disease progression. Between August 1995 and June 1997, blood was collected from 66 140 people in the second Norwegian Health (cohort) Study of Nord-Trondelag (HUNT2). A total of 506 cases were registered with a first venous thrombosis. Levels of IL-1β, IL-6, -8, -10, -12p70 and TNF-α were measured in the baseline sample. Authors did not find evidence for a relationship between venous thrombosis and an altered inflammatory profile. The results from this population sample suggest that an altered inflammatory profile is more likely to be a result rather than a cause of venous thrombosis, although short-term effects of transiently elevated levels cannot be ruled out.[40]

As for wound healing, although a large number of parameters have been shown to be differentially expressed between healing and nonhealing wounds, no single or combination of biomarkers has been demonstrated to accurately reflect wound progression on a single patient basis.[41]

ASSESSMENT OF ENDOTHELIAL DYSFUNCTION

Although the etiology of varicose veins remains partly unknown, recent studies have focused on endothelial cell integrity and function. Current evidence suggests the multifactorial origin of primary CVD, leading to tissue remodeling of the venous wall with changes in the microcirculation and dermis.

Markers of endothelial cell dysfunction have been shown to be of prognostic significance in predicting vascular events. They are linked to (can result from and/or contribute to) many disorders characterized by micro- or macrovascular pathology, they are an early marker of the development of vascular changes, and can pre-date clinically obvious vascular pathology by many months or years. In this context, elevated markers of endothelial cell dysfunction are found in association with aging, venous disorders (spontaneous venous thromboembolism, venous hypertension, reduction of shear stress, and varicosis), but also with many other disease entities, including endocrinopathies (diabetes type 1, type 2 and their complications, thyroid disease, obesity, metabolic syndrome, and sleep apnea syndrome), and in arterial pathology (hypertension, hypercholesterolemia and atherosclerosis, plaque rupture, infarction or heart failure, recurrent stroke), in connective tissue diseases, and smoking or exposure to air pollution.

Endothelial function testing may have great potential prognostic value for the detection of cardiovascular disease, but the available tests are not to be used in routine clinical assessment: no available test to assess endothelial cell dysfunction has sufficient sensitivity and specificity to be used in clinical practice. Most of the studies are observational. The optimal methodology for investigating the multifaceted aspects of endothelial dysfunction is still under debate.

Three types of testing for endothelial dysfunction are used: vascular reactivity tests, systemic plasma markers, and immunostaining of histological specimens. Most authors would agree that wall dilation and valve incompetence in primary CVD are related to venous endothelial dysfunction. Varicose vein patients demonstrate imbalances in the humoral mediators of vasoconstriction and venous dilatation.

1) Vascular reactivity tests are the most widely used methods in the clinical assessment of endothelial function: they are noninvasive and evaluate the peripheral macrocirculation (conduit arteries) or microcirculation (resistance arteries and arterioles).[42]

2) Systemic plasma markers of endothelial damage and repair (endothelial cell injury, endothelial cell activation) have only a very limited role in the assessment of individual patients (as a result of biological availability or assay variability).

- Measurements of nitric oxide biology: Plasma levels of nitric oxide, a potent mediator of vascular relaxation, may be modulated in venous disease.

- Humoral mediators of vasoconstriction and venous dilatation: Varicose vein patients show imbalances in the humoral mediators of vasoconstriction and venous dilatation. Plasma levels of endothelin-1 are increased in those with varicose veins and rise disproportionately in response to venous stasis with low vessel tone.

- Pro- and anti-inflammatory cytokines: Chronic venous hypertension leading to endothelial cellular injury and activation can be associated with an inflammatory

reaction and leukocyte recruitment in venous valves, a process that may lead to their dysfunction, reflux, and upstream elevation of venous pressure.

- Adhesion molecules (ICAM-1, VCAM-1, E-selectin, vWF, soluble P-selectin, CD40 ligand) reflect early stages of leukocyte-endothelium interactions. Although these are generally considered pathogenetic in venous disease, Ghaderian found no major differences in ICAM-1 or E-selectin expression in varicose vein specimens compared with controls.[43]

- Leukocyte recruitment and endothelium interaction (monocytes and macrophages) for which one of the markers, HIF-1α (the transcription factor hypoxia-inducible factor-1α), is elevated in some cases with varicosis. Some authors suggest that this supports the hypothesis of hypoxia in varicose veins. The factor is increased by prolonged mechanical stretch or by increases in vein wall tension.[44]

- Soluble markers are in fact mixtures of true soluble molecules with membrane-bound forms such as endothelial microparticles, which are heterogeneous and distinctive in phenotypic markers and procoagulant properties: phenotype analysis can distinguish endothelial cell activation from apoptosis. Endothelial microparticle-monocytes conjugates were found to enhance transendothelial migration of leukocytes in vitro and to be a marker of several inflammatory diseases. Elevated endothelial microparticles are not diagnostic of venous disease progression or inflammation.[45]

- Enzymatic activity: MMP-1, -2, -8, and -9 and TIMP-1, -2, and -3 are increased in both high and low venous pressure regions. The degree of extracellular matrix remodeling of the venous wall and valve leaflets correlates with the morphologic findings of macroscopic lesions with changes in the microcirculation and in the dermis. MMP-2 is said to induce venous relaxation / to inhibit contraction of the inferior vena cava.[46]

- Plasma thrombomodulin (TM) is considered to be a marker of endothelial injury. The relationship of soluble TM with thrombosis is complex: there is no difference in the prevalence of the 3 TM genotypes between thrombosis cases and controls (in 2 cohort studies). There was no difference in age-adjusted mean values of sTM by genotype, no associations of age-adjusted sTM or TMA455V genotype with overall venous thromboembolism or with thrombosis (any subtype).[47]

3) Histopathology: immunostaining and RT-PCR reveal alterations of the intima, like focal intimal discontinuity and denudation of endothelium in varicose veins.[43] Recent evidence suggests that changes in the vein wall may precede valvular dysfunction. Areas of intimal hyperplasia and smooth muscle cell proliferation are often noted in varicose veins, although regions of atrophy are also present. The total elastin content in varicose as opposed to nonvaricose veins is reduced; changes in overall collagen content are uncertain.[44]

More studies to identify markers of endothelial dysfunction of prognostic value are necessary.

Recommendations

Longitudinal studies will be necessary to evaluate the factors responsible for disease progression. In addition the genetic and humoral mediators of endothelial dysfunction present in limbs with primary CVD and disease progression should be identified.[11]

RELIABILITY OF ANKLE MOBILITY, CALF MUSCLE PUMP FUNCTION, AND PATIENT ACTIVITY IN RATING THE PROGRESSION OF VENOUS DISEASE

Physiologic deterioration of calf muscle pump function at the end of the day was reported using both photoplethysmography and air plethysmography. Although the variance was relatively limited, these findings suggest that venous return from the limb deteriorates with prolonged upright activity.[48] Musculoskeletal changes impact on the hemodynamics of the calf muscle pump and it is not always easy to distinguish between cause and effect.[49]

When measuring ankle range of motion using goniometry, there was an association with significantly reduced range in all grades of venous insufficiency (C2-C6).[22] Limbs with CVI have a limited ankle range of motion that decreases with increasing severity of clinical symptoms; this decreased range of motion is associated with, and may contribute to, poor calf pump function.[50]

With increased severity of CVI this mechanical dysfunction of the calf muscle pump results in sustained ambulatory venous hypertension.[51]

Changes in nerve and muscle function and range of motion may affect gait and ambulation: either causal in disease formation, or leading to a worsening or progression of disease symptomatology.[21]

In CVI and venous hypertension, muscle changes have been observed on biopsy specimens of the gastrocnemius muscle,[52] but these are not correlated with progression of disease: histopathology study revealed morphologic changes suggesting that disuse, denervation, and ischemia may contribute to changes in muscle function.

NB. Several cofactors may contribute to, or worsen, CVD: Local tissue destruction in CVI develops in conjunction with damage to peripheral nerves, which has been demonstrated in both clinical and immunohistochemical studies. Nerve involvement may result in neuropathic pain and muscle dysfunction, alterations in mobility may lead to gait alterations and decrease in range of motion, all affecting calf muscle pump function, and so contribute to the pathogenesis of venous ulcers.[21]

More than two-thirds of leg ulcer patients have an impaired calf muscle pump, which is regarded as causal to the development of the ulceration.[53] Air plethysmography, by assessing muscle pump function, has been shown to reliably predict prognosis of venous ulcers. Patients with clinically evident CVI were evaluated to relate the degree of insufficiency (measured by air plethysmography, color duplex) and calf muscle pump dysfunction to venous ulceration. Legs with active venous ulcers had significantly poorer calf muscle pump function than those with healed ulcers or with no history of ulceration. Thus, CVI is a necessary but not sufficient cause of ulceration, and a deficiency of the calf muscle pump is significantly related to the severity of venous ulceration.[53]

Apart from known risk factors (as longer ulcer duration, large surface area, ankle brachial pressure index <0.85), dysfunction of calf muscle pump has been correlated with delayed healing or nonhealing of leg ulceration despite adequate compression treatment. In this study a calf/ankle circumference ratio of less than 1.3, a fixed ankle joint, and reduced ankle range of motion were the only independent parameters associated with nonhealing.[54]

The data that are presently available need to be correlated with progression of the disease or with reversal under treatment. Prospective controlled studies have assessed improvement of venous hemodynamics or ulcer healing following supervised exercise programs directed to improve calf pump function, muscle strength, and endurance. This confirms positive results obtained after a few months in terms of hemodynamic parameters, calf muscle pump, and concomitant osteoarthritis. Physical rehabilitation and gait training can potentially improve healing rates, or help decrease recurrences in patients affected by stage C6. The benefits of this conditioning were maintained for at least 3 months.[22,51,55,56]

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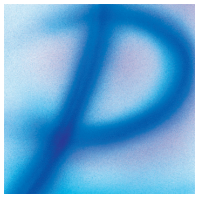

Benefit of Daflon 500 mg in the reduction of chronic venous disease–related symptoms.

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SUMMARY

Background: Lower limb symptoms have frequently been associated with increased severity of venous disease. In clinical practice they are reported by patients at all stages of chronic venous disease. This study assessed the contribution of Daflon 500 mg in improving venous symptoms and promoting venous ulcer healing in patients with primary chronic venous disease.

Methods: Patients aged ≥18 years, with at least 3 symptoms (including pain, sensation of heaviness in the legs, sensation of swelling, and night cramps), assigned to clinical classes C0 to C6 of the Clinical (severity)–Etiology–Anatomy–Pathophysiology (CEAP) classification following leg examination (recording the highest CEAP class for each patient), and presenting either with or without venous reflux, but not with obstruction, were included in the trial and received Daflon 500 mg 2 tablets per day for 6 months.

Results: Between month 3 and month 6, there was a significant ($P<0.05$) improvement in patients' symptoms (sensations of heaviness in the legs, swelling, pain, and cramps) following treatment with Daflon 500 mg. After 6 months, 13% of recalcitrant ulcers had healed, which was deemed satisfactory by the health care team.

Selected abbreviations and acronyms

CEAP Clinical (severity)–Etiology–Anatomy–Pathophysiology
CVD chronic venous disease
MPFF micronized purified flavonoid fraction
PCVD primary chronic venous disease
VAD venoactive drug

Keywords:
chronic venous disease, edema, micronized purified flavonoid fraction, pain, venous symptoms

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INTRODUCTION

The term "chronic venous disease" (CVD) refers to any long-standing morphological and functional abnormality of the venous system that manifests with symptoms and/or signs indicating the need for investigation and/or care.[1]

Primary chronic venous disease (PCVD) includes patients presenting with reflux but not with obstruction. Signs of PCVD may be present on clinical examination. The venous signs that are visible manifestations of CVD are described in the Clinical (severity)–Etiology–Anatomy–Pathophysiology (CEAP) classification and include dilated veins (telangiectasia, reticular veins, varicose veins), leg edema, skin changes, and ulcers.[2] According to this classification, clinical signs are categorized into seven classes ranging from C0 to C6.[2] Affected limbs may either be symptomatic (S) or asymptomatic (A), regardless of their clinical class. A review of the literature shows that the most common symptoms of PCVD are tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itchy skin, restless legs, and leg tiredness/fatigue. Although not pathognomonic, these symptoms may be suggestive of CVD, particularly if they are exacerbated by heat, vary during the course of the day, and are relieved with leg rest and/or elevation.[1] The presence of venous signs and/or (noninvasive) laboratory evidence is required to attribute these symptoms to PCVD.

PCVD encompasses the full spectrum of signs and symptoms associated with classes C0 to C6. (*Table I*)

Venoactive drugs (VADs) belong to several different chemical classes. The majority of them are plant-derived compounds, like benzopyrones, saponins, anthocyanins, proanthocyanidins, and *Ginkgo biloba*,[3] while some are produced by chemical synthesis, like calcium dobesilate, benzarone, and naftazone. (*Table II*)

Micronized purified flavonoid fraction (MPFF, Daflon® 500 mg), an oral VAD consisting of 90% micronized diosmin and 10% flavonoids expressed as hesperidin, diosmetin, linarin, and isorhoifolin,[4] improves venous tone and lymphatic drainage, and reduces capillary hyperpermeability by protecting the microcirculation from inflammatory processes.[5] Recent research has highlighted the central role of inflammation in the progression of PCVD and elucidated some of the processes involved.[6] Daflon 500 mg is the only currently available drug to have shown an anti-inflammatory effect in acute venous hypertension, in a model induced by the creation of a venous fistula in rats.[7] In this model, treatment with Daflon 500 mg reduced reflux flow in a dose-dependent manner.[7] In addition, Daflon 500 mg reduced the release of inflammatory mediators such as oxygen free radicals, prostaglandins, and thromboxane in animal models of ischemia reperfusion.[8] In MPFF, the absorption of diosmin is improved by its micronization to particles with a diameter <2µm.[9]

Clinical class	Description
C0	No visible or palpable signs of venous disease
C1	Telangiectases or reticular veins • Telangiectases defined by dilated intradermal venules <1 mm in diameter • Reticular veins defined by dilated, non palpable, subdermal veins ≤3 mm in diameter
C2	Varicose veins distinguished from reticular veins by a diameter of 3 mm or more
C3	Edema
C4	Changes in skin and subcutaneous tissue secondary to CVD divided into 2 subclasses to better define the differing severity of venous disease • C4a, Pigmentation or eczema • C4b, Lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer

Source. Eklöf et al. *J Vasc Surg.* 2004;40:1248-1252. ©2004, Society for Vascular Surgery.

Table I. *Revised CEAP clinical classification of chronic venous disease of the lower limb.*[2]

Group	Substance	Origin
α-Benzopyrones	Coumarin	Melilot *(Melilotus officinalis)* Woodruff *(Asperula odorata)*
γ-Benzopyrones (flavonoids)	Diosmin	Citrus spp. *(Sophora japonica)*
	Micronized purified flavonoid fraction	*Rutaceae aurantiae*
	Rutin and rutosides	*Sophora japonica*
	O-(b-Hydroxyethyl)-rutosides (troxerutin, HR)	*Eucalyptus spp.* *Fagopyrum esculentum*
Saponins	Escin	Horse chestnut seed extracts *(Aesculus hippocastanum L)*
	Ruscus extract	Butcher's broom *(Ruscus aculeatus)*
Other plant extracts	Anthocyanins	Bilberry *(Vaccinium myrtillus)*
	Proanthocyanidins (oligomers)	Red vine leaf extract Maritime pine *(Pinus maritimus)*
	Extracts of Ginkgo, heptaminol, and troxerutin	*Ginkgo biloba*
	Total triterpene fraction	*Centella asiatica*
Synthetic products	Calcium dobesilate	Synthetic
	Benzarone	Synthetic
	Naftazone	Synthetic

Source: Ramelet et al. *Varicose veins and telangiectasias.* Paris, France: Elsevier; 2004. © 2004, Elsevier.

Table II. *Classification of the main venoactive drugs.*[3]

Given the comprehensive evidence about it, we chose to use Daflon 500 mg in our trial assessing the contribution of a pharmacological treatment in symptom improvement, venous edema reduction, and venous ulcer healing in patients with PCVD.

MATERIAL AND METHODS

From January 2007 to December 2009, we enrolled outpatients consulting for venous leg problems in the outpatient clinic of the dermatovenerology ward of the Clinical Hospital Center Rijeka, Rijeka, Croatia.

Patients, aged ⩾18 years, with at least 3 symptoms (including sensation of heaviness in the legs, sensation of swelling, and night cramps), assigned to clinical classes C0 to C6 of the CEAP classification following leg examination (recording the highest CEAP class for each patient), and presenting either with or without venous reflux, but not with obstruction, were included in the study. They received Daflon 500 mg 2 tablets per day for 6 months. For all CEAP clinical classes, the end point was the disappearance of clinical symptoms.

In addition to Daflon 500 mg 2 tablets per day, patients with active venous ulcers (class C6) underwent standard therapy, which consisted of elastic bandages and silver-releasing foam dressings, as adjunctive treatment. Complete wound reepithelisation was considered successful healing. Symptoms were assessed after 3 and 6 months of therapy. The percentage of healed ulcers was determined after 6 months of treatment.

RESULTS

A total of 1212 patients showing no obstruction on pocket Doppler ultrasound were enrolled in the trial. Most patients (90.1%) were women and the average patient age was 53.5 years (ranging from 28 years to 79 years). The majority of patients were assigned to the C0, C1 or C2 stages of the CEAP classification (42.90%), 34.5% to either the C3 or C4 stages, and 22.6% to either

the C5 or C6 stages. The majority of patients had an occupation that required them to stand or sit for sustained periods of time. All patients reported sensations of heaviness, pain, and nocturnal cramps that were unresponsive to elastic bandage.

Based on our analysis, symptoms like sensations of heaviness, pain, nocturnal cramps, and edema disappeared in 60.2%, 62.5%, and 73% of patients, respectively, after 6 months of therapy with Daflon 500 mg. (*Figure 1*).

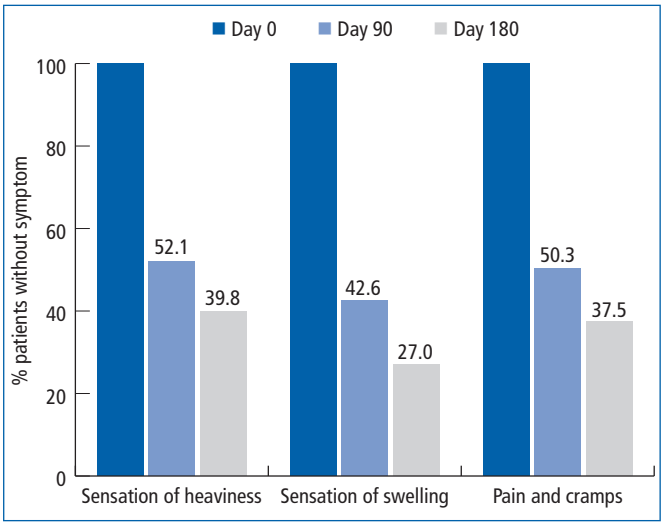

Figure 1. *Percentage (%) of patients belonging to classes C0 to C6 of the clinical CEAP classification with sensations of heaviness, sensations of swelling, venous pain, and night cramps at baseline (D0) and after 3- and 6-month treatment with Daflon 500 mg (respectively at D90 and Day 180; the P value for each symptom was <0.05).*

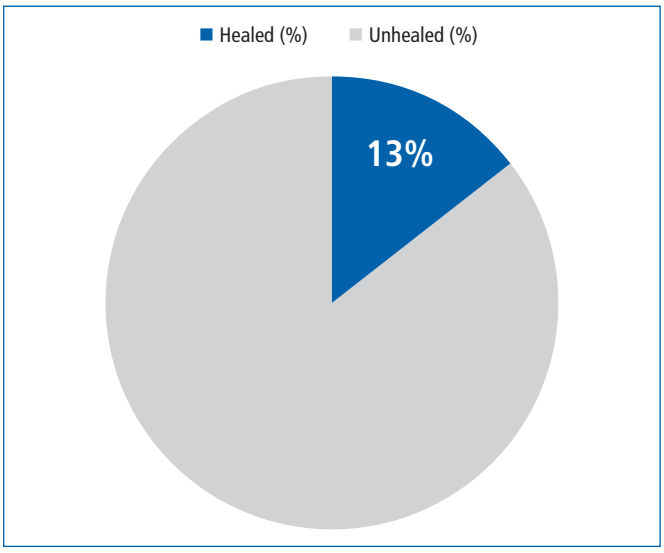

Figure 2. *Percentage (%) of C6 patients with healed or unhealed ulcers following 6-month treatment with Daflon 500 mg (Day 180).*

Out of the 274 patients in the C5 or C6 classes, 115 presented an active venous ulcer which had either failed to heal over the past 6 months or had recurred. These recalcitrant venous ulcers healed completely in 13.1% of patients following a 6-month adjunctive treatment with Daflon 500 mg. (*Figure 2*).

DISCUSSION

Despite the open design of the trial, we can assume that treatment with Daflon 500 mg improves patients' quality of life, since venous symptoms have a very negative impact on the daily life of those suffering from PCVD.[10] Moreover, venous leg ulcers, the most severe manifestation of CVD, are usually painful and affect quality of life.[11] The impairment associated with CEAP classes C5 and C6 has been likened to the impairment associated with heart failure.[12]

The results of our trial adds weight to previous substantial evidence from randomized trials,[13] meta-analyses, and a large observational study,[14] in favor of the efficacy of Daflon 500 mg in relieving venous symptoms such as pain, sensations of heaviness and swelling, and cramps, and in reducing PCVD-related lower limb edema. However, there is little evidence indicating which CEAP clinical class benefits the most from treatment with Daflon 500 mg, since the majority of studies were carried out before the creation of the CEAP classification. Based on our results, it is reasonable to assume that patients at all stages of the disease, including the early CEAP stages, may benefit. Acceleration of venous leg ulcer healing (CEAP stage C6) was demonstrated in a double-blind study using Daflon 500 mg in combination with compression.[15] This was confirmed in 2005 by a meta-analysis of 5 trials with adjunctive MPFF in 723 patients with venous ulcers.[16] Since our trial focused on difficult-to-heal venous ulcers, it was deemed satisfactory to have achieved a 13% rate of healing.

The results of our trial are encouraging and larger randomized controlled trials should be performed to better specify which CEAP clinical class would benefit the most from such a treatment. This would give further strength to the current recommendation of Daflon 500 mg as an adjuvant to standard treatment in PCVD to relieve clinical symptoms and edema (grade 1B recommendation)[17] and heal ulcers.[18]

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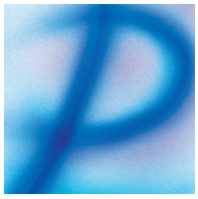

Pelvic vein incompetence: a review of diagnosis and treatment

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ABSTRACT

Pelvic vein incompetence is often associated with typical clinical signs of congestion as well as pelvic pain. This clinical entity is often underestimated and patients suffering from pain related to pelvic varicosities undergo a long and inconclusive diagnostic workup before the exact cause of symptoms is recognized. Besides the typical chronic pelvic pain, signs such as vulvar varicosities are not always present. Because of the wide variation of clinical and radiological presentations, there is a general consensus that diagnostic and therapeutic approaches should be patient-tailored.

To date, noninvasive diagnostic techniques including ultrasound, computed tomography, and magnetic resonance imaging have been used to identify patients who are candidates for treatment. Venous embolization is now accepted worldwide as the treatment of choice, because of its promising results in terms of clinical success and its limited invasiveness. This article reviews currently available diagnostic and therapeutic options.

INTRODUCTION

The important role of incompetent pelvic and ovarian veins in the etiology of pelvic congestion syndrome has emerged in recent decades thanks to the increasing number of reports dealing with this peculiar clinical condition.[1-4] Over the years, many investigators have suggested that pelvic varicosities may be responsible for the otherwise unexplained symptoms[5,6] that characterize pelvic congestion syndrome, and venographic studies in women following normal laparoscopy for chronic pelvic pain have revealed dilatation of the major pelvic veins and congestion in the ovarian plexuses and broad ligaments in more than 80% of cases.[7] Furthermore, ovarian vein dilatation has been observed in up to 10% of asymptomatic women and up to 60% of them can develop pelvic congestion syndrome.[1,8,9]

Most patients with pelvic vein incompetence (PVI) have undergone a wide range of diagnostic examinations, but despite this, few receive a correct diagnosis because of limited appreciation of this condition among practicing physicians. Patients who are likely to have PVI often present with atypical

Keywords:
diagnosis, endovascular treatment, pelvic congestion syndrome, pelvic veins, varicosity

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varicose veins arising at the buttocks or upper posteromedial thigh and extending to the vulvar and perivulvar regions. Many cases are found incidentally during lower limb venous duplex for recurrent varicose veins. Perrin reported a 17% incidence of PVI in female patients with recurrence after surgical treatment of varicose veins.[10]

In recent years, advances in technology have led to the use of noninvasive imaging methods such as ultrasound (US), computed tomography (CT), and magnetic resonance venography (MRV), which can differentiate cases of primary PVI from alternative causes of pelvic pain and at the same time provide a plan for minimally invasive treatment options for this not uncommon condition.

Due to its encouraging results,[4,11] percutaneous embolization is now accepted as first-choice treatment of symptomatic PVI.

This article reviews the imaging options for establishing diagnosis of PVI, and the emerging minimally invasive treatments.

ETIOLOGY

The precise etiology of PVI is poorly understood. The underlying mechanism is reflux of blood in the pelvic and/or ovarian veins. The primary defect is the absence of functioning valves, resulting in retrograde blood flow and eventual venous dilatation.[12] Valves are absent from the orifices of the gonadal veins in 15% of women, and, in those where valves are present, they are incompetent in 40% on the left and 35% on the right.[13]

Furthermore, during pregnancy, the vascular capacity of the ovarian veins may increase 60-fold and remain this way for months after delivery.[14] Moreover, dilated veins are more frequently observed with increased parity.[4,14,15] Dilatation of ovarian veins causes valvular incompetence and retrograde venous flow.

Some cases of pelvic varicosities have been associated with mechanical compressive causes, such as uterine malposition causing kinking of the ovarian veins,[16] and the nutcracker syndrome, where the left renal vein is compressed between the aorta and the superior mesenteric artery.[3]

The often associated worsening of congestion symptoms during intercourse, the higher prevalence in multiparous women, the positive therapeutic effects of hormonal substitution on symptoms[17] as well as the higher concentration of sexual hormones in blood refluxing to the groin[18] suggest that hormonal factors could play a crucial role in determining this peculiar clinical entity.

CLINICAL ASPECTS

Besides being a potential cause of symptomatic leg varicosities, PVI is often associated with a typical clinical pattern. Taylor[12] in 1949 identified a tetrad of symptoms consisting of pelvic pain, dysmenorrhea, dyspareunia, and pelvic varicosities. The important role of incompetent pelvic veins is underlined by the fact that the intensity of pain is higher in patients with lower limb varicosities and PVI compared with those with isolated lower limb varicosities.[19] The symptoms may be exacerbated by postural changes, walking, prolonged standing, or other activities that increase abdominal pressure, such as lifting. Urinary symptoms are also common.

PVI is also associated with a typical pattern of varicosities. Scultetus et al[20] described three different clinical presentations:

- vulvar varicosities without signs of pelvic congestion;
- varicose veins at the medial and posterior aspect of the thigh, usually caused by incompetent ovarian veins;
- gluteal as well as vulvar varicosities which are often caused by reflux in the internal iliac veins.

Besides clinically manifest varicosities, tenderness may be elicited by deep palpation of the ovarian point, which, if associated with dyspareunia, may be 94% sensitive and 77% specific for pelvic congestion.[21]

IMAGING

Typical pelvic symptoms in combination with the distinctive clinical pattern of varicosities help to identify patients who need to undergo a further diagnostic workup. Since anatomical venous variations in the pelvis are common,[22,23] it is important to know the anatomy of

these vessels for treatment planning. Imaging is critical in the evaluation of pelvic varices, both to differentiate them from other conditions and also because pelvic varices may be secondary to serious underlying pathologies, such as inferior vena cava obstruction, portal hypertension, and vascular malformations.

Furthermore, in a large number of cases, incompetence is present in more than one of the pelvic veins.[24] This underscores the importance of selectively examining the ovarian as well as the internal iliac venous system in every patient in order to identify adequately any existing reflux pattern.

Ultrasound

Transabdominal and transvaginal US is minimally invasive and as such is the tool most often used in gynecological practice. The presence of dilated pelvic veins and retrograde flow on color duplex Doppler examination is predictive of PVI. Besides its limited cost and high reproducibility, US allows dynamic examination of the blood flow through tortuous pelvic veins in patients with PVI. Furthermore, US is not associated with exposure to radiation or to iodinated contrast agents and can identify primary abdominal disorders that can cause pelvic varicosities.

Although several authors[2,14,15] consider that patients with clinical signs of PVI should first undergo transabdominal or transvaginal US, Park et al[8] could identify pelvic varicocele in only 53% of a group of 139 patients using US, which underlines the importance of further diagnostic workup.

An accurate duplex US examination of the groin may also provide evidence of PVI. A typical ultrasound finding is that of refluxing epigastric, pubic, and pudendal veins entering the groin with the reflux coming from above the inguinal ligament and not from the saphenofemoral junction. This reflux pattern in combination with typical clinical signs yielded a positive predictive value of 74% in a series of 101 patients.[25]

Computed tomography and magnetic resonance venography

CT and magnetic resonance venography (MRV) can be used as noninvasive methods to diagnose pelvic and ovarian varices. These appear as tortuous, dilated structures in the uterine adnexa or besides the ureter. The advantage of these techniques is their ability to provide information about any coexisting abdominal or pelvic disorder.

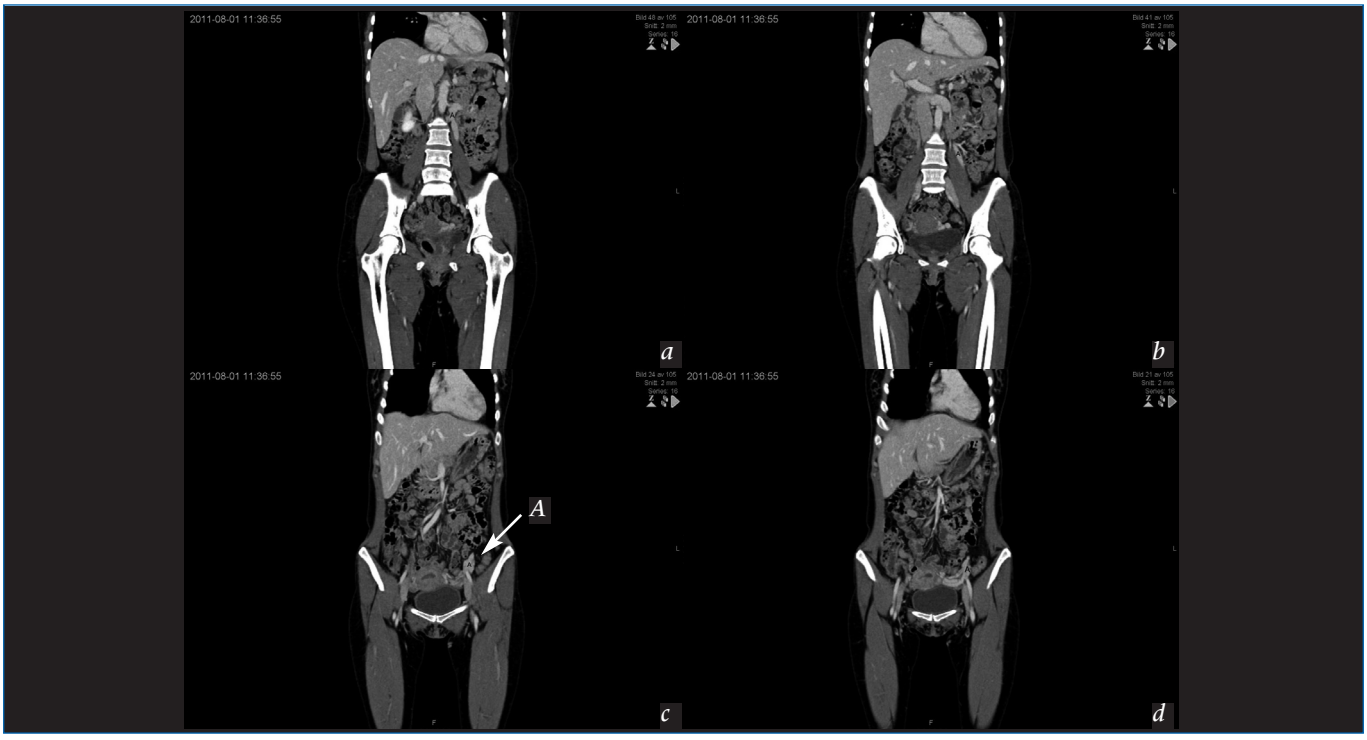

Figure 1. *Computed tomography (a,b,c) shows incompetent left ovarian vein (A) filling dilated ovarian plexus (d).*

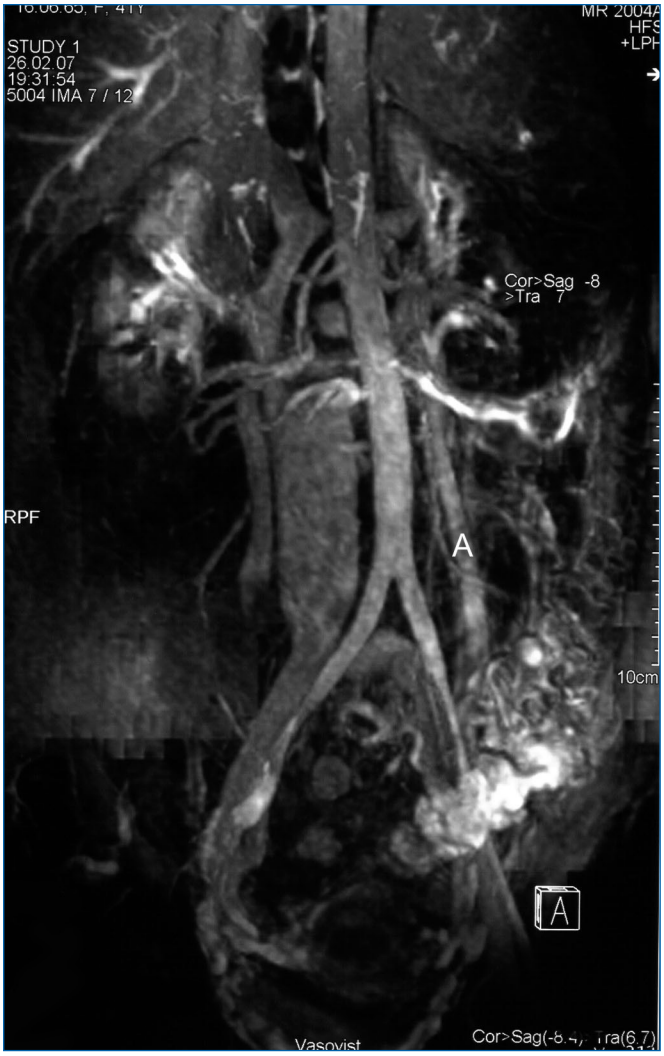

Figure 2. *Magnetic resonance imaging signs of pelvic reflux from the left renal vein to the left gonadal vein (A). Maximum intensity projection image demonstrates dilated parauterine varices filled due to passive reflux of contrast.*

On CT the varicosities are isodense to other abdominal veins on post-contrast imaging (*Figure 1*), while on MRV (*Figure 2*) they show no signal on T1-weighted sequences and are hyperintense on T2, but can also be hypointense or isointense, depending on the velocity of blood flow.[26] Gradient echo sequences show high signal intensity within the varices.

Contrast-enhanced MRV is likely to become the initial noninvasive investigation of choice in the diagnosis of PVI. It allows a complete examination of the pelvic anatomy because of its multiplanar imaging capability. Dynamic subtraction MR angiograms can provide an overview of the vessels and demonstrate abdominal vascular anatomy and vessel occlusions.[27-29]

Although the safety of MR procedures during pregnancy has not been definitively proven,[30,31] the risk of exposing the developing fetus to any radiological diagnostic imaging technique that uses ionizing radiation is probably greater than the theoretical risk of MRV.[32]

Furthermore, the isotonic nature of gadolinium eliminates the risk of thrombosis associated with conventional iodinated contrast agents.[33] The low risk of anaphylactic reactions inherent to extracellular paramagnetic agents is an additional factor contributing to the attractiveness of MRV. However, because of its low specificity MRV may underestimate venous disease.[34] This is because conventional cross-sectional imaging studies are generally performed in the supine position in which ovarian and pelvic varices may not be as prominent.

Catheter-directed venography

In recent decades, catheter-directed venography (*Figure 3a*) has become more a "therapeutic" than a diagnostic tool in the management of patients with PVI.

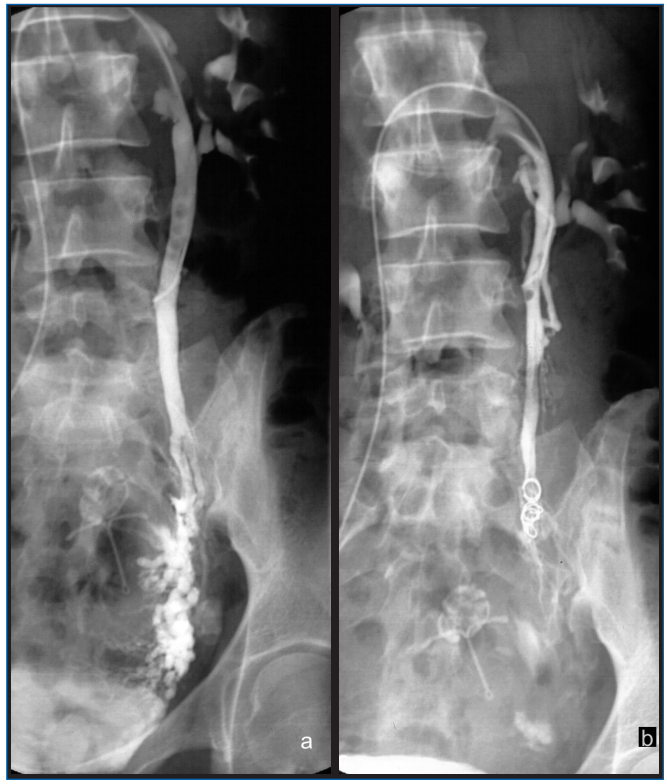

Figure 3. *(Same patient as seen in Figure 2) Anteroposterior view during left ovarian phlebography with patient in supine position shows significant stagnation of contrast material in the dilated vein (a). After embolization of the dilated left ovarian vein with 4 platinum coils (3 9x60 mm, 1 7x40 mm), no reflux was detected (b).*

Although related mortality and morbidity are low, patient discomfort and costs make this an unattractive method of diagnosis. Furthermore, though effective, this method is invasive and also exposes patients to ionizing radiation of the pelvis. The latter is a particular concern because many of these women are of childbearing age. In addition, complications associated with the use of iodinated contrast material are reported to occur in 2% to 5% of patients.[33]

Venographic diagnostic criteria for PVI are ovarian vein diameter >10 mm or dilatation throughout the course of the vessel, uterine venous enlargement, congestion of the ovarian plexus, retrograde filling of the main stem of the internal iliac vein and at least one side branch (gluteal, ischiatic, or obturator veins), filling of the pelvic veins across the midline and/or filling of vulvovaginal and thigh varicosities.[25,35] The advantage of selective catheter-directed venography, besides its excellent visualization of incompetent pelvic veins, is the option of performing interventional treatment if needed.

Future developments

As CT and MRV need the use of contrast agents and are still costly, researchers' attention has turned to alternative diagnostic methods that can guarantee high sensitivity and specificity as well as low costs. High sex hormone levels in venous blood sampled at lower leg varicosities have shown high sensitivity and specificity in identifying patients with phlebographic signs of PVI.[18] Tests on a larger number of patients are needed before routine use of blood sampling to identify patients with typical symptoms who can directly undergo interventional catheter-directed venography.

TREATMENT

Since venous valves are found in only about 10% of internal iliac veins and their tributaries,[36] there might be some degree of reflux in these veins even in healthy subjects. The clinical relevance of pelvic reflux not feeding varicose veins nor causing typical symptoms is still unclear.

Treatment failure is explained by the complex anatomy of the pelvic veins, which show a wide variation in terms of trunks, venous valves, duplications, and crossover connections.[22,36] This aspect combined with the fact that reflux often affects more than one pelvic vein makes it difficult to identify and treat all patterns of reflux and, on the other hand, facilitates the development of alternative reflux pathways once one incompetent vein has been successfully treated.

Medical suppression of ovarian function and hysterectomy with or without bilateral salpingo-oophorectomy have been described as potential alternatives[7,17,37] but are not widely used. Open surgical division of ovarian veins is infrequently performed due to the associated surgical trauma. Even laparoscopic division has been described.[38]

The continuous development of endovascular techniques offered a minimally invasive and very effective alternative to the above mentioned treatments. It was Edwards[39] who described the first case of successful embolization of an incompetent ovarian vein. Endovascular treatment can be carried out with coils (*Figure 3b*), glue, foam, or a combination thereof through a jugular or femoral approach, with local anesthesia and as a day-case procedure.

In the last two decades there has been wide variation in clinical success rates (40% to 93%) with short-term follow-up in relatively small patient cohorts.[1,4,11,40] This variation occurs because of the various definitions used for PVI and the use of different outcome measures. In particular, Creton[11] reported a high rate of technical success and a clinical improvement in 80% of cases 3 years after embolization in a group of 24 patients.

Similar results were achieved by Kim et al[4] in a larger cohort of patients (131) with a more aggressive approach consisting of embolization of all incompetent vessels throughout the ovarian and internal iliac venous system. In the eyes of Kim et al, this was necessary in order to eliminate all reflux pathways and to prevent recurrence.

Although endovascular treatment is minimally invasive, complications such as coil migration and local thrombophlebitis have been observed.

Due to the spread of endovascular techniques, the number of reports is constantly increasing and clinical trials have already been started in order to assess their long-term results using different sclerosing agents. Radiofrequency- and laser-based approaches have also been taken in consideration.

CONCLUSIONS

PVI is an often underestimated clinical entity that can be extremely debilitating. Its identification is based on the presence of typical symptoms and reflux patterns at dynamic diagnostic examinations. The diagnostic and therapeutic approach to PVI must be tailored to the individual patient's needs and must take into account the severity of symptoms. Recent experience shows encouraging technical and clinical success rates for selective embolization of incompetent veins. However, there is still a need for studies to address the long-term outcome and to clarify which patient populations benefit from which treatment approaches.

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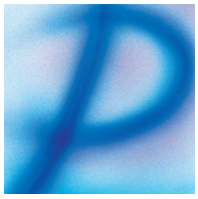

Randomized controlled trials in the treatment of varicose veins (2)

This is the second part of a review on randomized controlled trials of the treatment of varicose veins by open surgery or endovenous ablation. The first part of this review was published in *Phlebolymphology*. 2011;18:(4)196-207

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Randomized controlled trials (RCTs) remain the most reliable source of evidence.[1] We have therefore analyzed RCTs of treatment of varicose veins published since 1990 and have classified them by topic and added a brief comment. We may, nevertheless, have missed some and apologize to any authors who have been overlooked. We successively consider and comment upon:

Table X: Radiofrequency ablation versus endovenous laser ablation 92

Table XI: Endovenous laser ablation versus endovenous laser ablation 93

Table XII: Cryostripping versus endovenous laser ablation 94

Table XIII: Open surgery versus foam sclerotherapy 94

Table XIV: Variations in classic open surgery 96

Table XV: Open surgery versus endovenous laser ablation versus radiofrequency ablation versus foam sclerotherapy 97

Keywords:
chemical ablation, meta-analyses, randomized controlled trials, surgery, thermal ablation, varicose veins.

Phlebolymphology. 2012;19(2):91-99.

Table X: Radiofrequency ablation versus endovenous laser ablation

Operative procedure	Article	Conclusions
Radio-frequency ablation versus endovenous laser ablation	Almeida JI, et al. Radiofrequency endovenous closureFAST versus laser ablation for the Treatment of great saphenous reflux: A Multicenter, Single-blinded, Randomized Study (RECOVERY Study). *J Vasc Interv Radiol*. 2009;20:752-759.	69 patients Great saphenous vein RFA ClosureFAST™ vs EVLA Diode 980 nm bare fiber **Follow-up 2 weeks** *With RFA* All scores referable to pain, ecchymosis, and tenderness were statistically lower in the ClosureFAST™ group at 48 hours, 1 week, and 2 weeks. Minor complications were more prevalent in the EVL group *P*=0.0210 Venous clinical severity scores and quality of life scores were statistically lower in the ClosureFAST™ group No difference between RFA and EVLA in terms of postoperative vein occlusion or truncal elimination reflux
	Shepherd AC, Gohel MS, Brown LC, Metcalfe MJ, Hamish M, Davies AH. Randomized clinical trial of VNUS ClosureFAST radiofrequency ablation versus laser for varicose veins. *Br J Surg*. 2010;97;810-818.	131 patients Great saphenous vein RFA ClosureFAST™ vs EVLA Diode 980 nm bare fiber **Follow-up 6 weeks** *With RFA* Less postoperative pain (3-10 days. *P*=0.012-*P*=0.001) Less analgesic tablets (3-10 days. *P*=0.003–*P*=0.00) *RFA vs EVLA* QOL: Aberdeen varicose vein questionnaire and SF-12 No difference
	Gale SS, Lee JN, Walsh ME, Wojnarowski DL, Comerota AJ. A randomized, controlled trial of endovenous thermal ablation using the 810-nm wavelength laser and the ClosurePLUS radiofrequency ablation methods for superficial venous insufficiency of the great saphenous vein. *J Vasc Surg*. 2010;52:645-650.	141 lower extremities Great saphenous vein RF ClosurePlus™ vs EVLA Diode 810 nm bare fiber. 24 bilateral. 94 unilateral: 46 RFA,48 EVLA **Follow-up 1-4 weeks-1 year** *With RFA* Less bruising and discomfort Recanalization more frequent at 1 year *P*=0.002
	Goode SD, Chowdurry A, Crockett M, Beech A, Simpson R, Richards T, Braithwaite BD. Laser and Radiofrequency ablation Study): a randomized study comparing radiofrequency ablation and endovenous laser ablation (810 nm). *Eur J Vasc Endovasc Surg*. 2010;40:246-253.	87 lower extremities Great saphenous vein CELON RFiTT RFA vs EVLA Diode 810 nm bare fiber 17 bilateral. 36 unilateral:19 RFA,17 EVLA **Follow-up 6 weeks–6 months** *With RFA* Less postoperative pain and bruising in the bilateral group QOL and activity score no difference **Follow-up 9 months** Same occlusion rate 74% vs 78%
	Nordon IM, Loftus IM. EVVERT comparing laser and radiofrequency: An update on endovenous treatment options. In: Greenhalgh R, ed. BIBA publishing, UK. 2011:381-388.	Great saphenous vein 80 patients laser (Vari-Lase Bright tip 810 nm laser fiber); 79 patients RFA (ClosureFAST™). General anesthesia. **Follow-up** *1 week*: all great saphenous veins occluded. Pain and bruising significantly less after RFA *3 months*: 3/68 laser and 2/70 RFA reopened (*P*=?)

Abbreviations: EVLA = endovenous laser ablation; RFA = radiofrequency ablation

Five randomized clinical trials comparing radiofrequency ablation with endovenous laser ablation have been published.

Material used

For radiofrequency ablation: 4 closure catheters (3 ClosureFAST™, 1 ClosurePlus™) and one CELON RFITT.

For endovenous laser ablation: three 810-nm and two 980-nm bare fibers.

Less bruising and less pain with ClosureFAST™. New laser fibers are being developed, eg, radial or jacket-tip fibers. Kabnick has reported a pilot study comparing radiofrequency ablation (ClosureFAST™ in 50 patients) vs endovenous laser ablation (980-nm jacket-tipped fiber in 35 patients).[2]

At 72 hours, 100% closure was observed in both groups. At 1 week the pain and bruising scores were identical in the two groups. The results suggest that jacket-tipped laser fibers generate a uniform thermal reaction similar to that generated by ClosureFAST™. Kabnick's conclusion was that the most current radiofrequency ablation and jacket-tip laser methods and devices are indistinguishable in terms of efficacy and short-term side effects. With procedure time and tumescent anesthesia also equivalent, these procedures present no genuinely significant differences from the patient's point of view.

Table XI: Endovenous laser ablation versus endovenous laser ablation

Operative procedure	Article	Conclusions
HL+ EVLA versus EVLA without HL	Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser ablation of the great saphenous vein with and without ligation of the saphenofemoral junction: 2-year results. *Eur J Vasc Endovasc Surg*. 2008;36:713-718.	Great saphenous vein HL + EVLA (n=43) versus EVLA without HL (n=43) 810-nm diode laser continuous laser withdrawal **Follow-up 2 years** No difference between the 2 groups in terms of recurrence and venous clinical severity score
EVL bare tip versus EVLA radial fiber	Doganci S, Demirkilic U. Comparison of 980 nm laser and bare-tip fibre with1470 nm laser and radial fibre in the treatment of great saphenous vein varicosities: A prospective randomized controlled trial. *Eur. J Vasc Endovasc Surg*. 2010;40:254-259.	Great saphenous vein 106 limbs EVLA 980 nm bare-tip fiber vs EVLA 1470 nm radial fiber **Follow-up 1 month** With 1470 nm radial fiber Less postoperative pain and better venous clinical severity scores

Abbreviations: EVLA = endovenous laser ablation; HL = high ligation, VCSS

High ligation in association with endovenous laser ablation does not modify the 2-year outcome. Recommendation grade IB. Radial fiber 1470 nm is superior to bare-tip 980 nm in immediate postoperative course.

When comparing 1500 nm vs 980 nm bare fibers, immediate post operative course was better with 1500 nm, with less side effects including induration, pain, and better quality of life. At 6 months, the occlusion rate was similar in both groups.

Table XII: Cryostripping versus endovenous laser ablation

Operative procedure	Article	Conclusions
EVLA versus cryostripping	Disselhoff BC, der Kinderen DJ, Moll FL. Is there a risk for lymphatic complications after endovenous laser treatment versus cryostripping of the great saphenous vein? A prospective study. *Phlebology*. 2008;23:10-14.	Great saphenous vein EVLA 810-nm diode laser bare fiber, continuous laser withdrawal (n=17) versus high ligation + cryostripping (n=16) **Follow-up 6 months** One complication in cryostripping group: grade 1 lymphedema
	Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser with cryostripping for great saphenous varicose veins. *Br J Surg*. 2008;95:1232-1238.	120 patients Great saphenous vein EVLA 810-nm diode laser bare fiber, continuous laser withdrawal versus high ligation + cryostripping **Postoperative course** *Cryostripping* Procedure quicker *P*<0.001 *After EVLA* Less postoperative pain *P*=0.003 Return to normal activity quicker *P*<0.001 **Follow-up 2 years** No difference between the 2 groups in terms of recurrence and quality of life questionnaire (venous clinical severity score, Aberdeen varicose vein severity score)
	Disselhoff BCVM, Buskens E, Kelder JC, der Kinderen DJ, Moll FL. Randomized comparison of costs and cost-effectiveness of cryostripping and endovenous laser ablation for varicose veins: 2 –Year results. *Eur J Vasc Endovasc Surg*. 2009;37:357-363.	Great saphenous vein bilateral 120 patients EVLA 810-nm diode laser bare fiber, continuous laser withdrawal versus high ligation+ cryostripping **Follow-up 2 years** Cryostripping was less costly and more cost effective *P*=0.234; QALY(SF-6D) *P*=0.824 Cost effectiveness ratio *P*=0.788

Abbreviation: EVLA = endovenous laser ablation

This Dutch team initiated 3 randomized clinical trials comparing high ligation and cryostripping vs endovenous laser ablation: cryostripping was significantly quicker while endovenous laser ablation was associated with significantly less postoperative pain and a quicker return to normal activities. There was no significant difference in terms of recurrence, quality of life, or cost.

Table XIII: Open surgery versus foam sclerotherapy

Type of procedure	Article	Conclusions
CA + HL versus HL+S	Bountouroglou DG, Azzam M, Kakkos SK, et al. Ultrasound-guided foam sclerotherapy combined with sapheno-femoral ligation compared to surgical treatment of varicose veins: early results of a randomised controlled trial. *Eur J Vasc Endovasc Surg*. 2006;31:93-100.	Great saphenous vein Ultrasound-guided foam sclerotherapy + HL (n=30) versus HL+S (n=30) **Follow-up 3 months** Early recanalization in 13% after CA treated by complementary injection CA+HL less expansive, more rapid return to normal activities *P*<0.0001 No difference in terms of complications and occlusion
CA +HL versus HL+S	Abela R, Liamis A, Prionidis I, et al. Reverse foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard and invagination stripping: a prospective clinical series. *Eur J Vasc Endovasc Surg*. 2008;36:485-490.	Great saphenous vein HL+ reverse foam sclerotherapy (n=30) HL + invagination S (n=30) HL+ standard S (n=30) **Follow-up 2 weeks** HL+ reverse foam sclerotherapy less postoperative complication and greater patient satisfaction

Type of procedure	Article	Conclusions
CA versus HL+S	Figueiredo M, Araujo S, Barros N Jr, Miranda F Jr. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. *Eur J Vasc Endovasc Surg*. 2009;38:758-763.	Great saphenous vein Foam sclerotherapy (n=27) 1–3 sessions 10 mL/session vs HL+S (n=29) in C_5, Ep, As, Pr patients **Follow-up 6 months** Significant clinical improvement in both groups Vein obliteration CA 78%, HL+S 90%. *P*=ns, related to the small number of patients included
CA versus HL or HL+ S or Phlebectomy	Wright D, Gobin JP, Bradbury AW et al. Varisolve® polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. *Phlebology*. 2006;21:180-190.	Great saphenous vein and small saphenous vein 710 patients randomized to foam sclerotherapy (Varisolve polidocanol), surgery (HL 92%, stripping 88%, phlebectomies 53%) or conventional sclerotherapy (92% homemade foam) End point ultrasound determined occlusion of truncal veins and elimination of reflux; **Follow-up 12 months** Surgery superior to Varisolve foam (86 vs 63%) Varisolve foam superior to conventional sclerotherapy (90 vs 76%, *P*=0.001) Foam resulted in less pain and earlier returns to work than surgery.
HL+S versus HL+ CA	Kalodiki E, Lattimer CR, Azzam M, Shawish E, Bountouroglou DG, Geroulakos G. Long-term results of a randomized controlled trial on ultrasound-guided foam sclerotherapy combined with saphenofemoral ligation vs standard surgery for varicose veins. *J Vasc Surg*. 2011 Nov 18. [Epub ahead of print].	Great saphenous vein C_2-C_6 HL+ S+/- tributary phlebectomy (*n*= 39) group S HL+ ultrasound–guided foam sclerotherapy (*n*=41) group F Complementary foam sclerotherapy treatment Group S n=25 Group F n=33 **Follow-up 3-5 years** Venous clinical severity score no difference venous segmental disease score no difference Aberdeen Varicose Vein Questionnaire score better in Group S, *P*<0.0005 SF 36 Physical component no difference

Abbreviations: CA = chemical ablation; HL = high ligation; S = saphenous stripping

The first 5 randomized clinical trials comparing ultrasound-guided foam sclerotherapy with conventional surgery and in one case also with liquid sclerotherapy with short-term follow-up (max. 1 year) do not give any conclusive results. In 2007 in a meta-analysis on foam sclerotherapy, Jia et al suggested that, regarding complete occlusion, foam sclerotherapy was less effective than surgery, but more effective than liquid sclerotherapy.[3] They concluded that there is currently insufficient evidence to allow a meaningful comparison of the effectiveness of this treatment with that of other minimally invasive therapies or surgery.

Fortunately, the authors of a recently published and fully documented randomized clinical trial with 5-year follow-up concluded that the treatment was equally effective in the surgical and foam sclerotherapy groups, as demonstrated by improvements in the Venous Clinical Severity Score, Venous Segmental Disease Score, and the physical component of the SF-36 score. The Aberdeen Varicose Vein Questionnaire score was significantly better in the surgery group, but the margins were small and this may not have any clinical significance. Given that foam is less expensive, one can conclude that the cost effectiveness ratio is in favor of foam.

The only surprising point in this trial is the complementary high ligation in the foam procedure as it is generally admitted that high ligation enhances neovascularization at the groin.

Table XIV: Variations in classic open surgery

Type of procedure	Article	Conclusions
High ligation versus high ligation	Corder AP, Schache DJ, Farquharson SM, Tristram S. Wound infection following high saphenous ligation: a trial comparing two skin closure techniques:subcuticular polyglycolic acid and interrupted monofilament nylon mattress sutures. *J R Coll Surg Edinb*. 1991;36:100-102.	High ligation Skin closure with subcuticular polyglycolic acid (n=76) versus interrupted monofilament nylon matress sutures (n=86) **Follow-up 6 weeks** The higher infection rate found with subcuticular polyglycolic acid (*P*=0.05) appeared to be operator dependent
High ligation + stripping + tributary phlebectomy versus high ligation + stripping + tributary phlebectomy + subfascial endoscopic perforator surgery	Kianifard B, Holdstock J, Allen C, Smith C, Price B, Whiteley MS. 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.	Great saphenous vein Saphenous reflux+ perforator reflux (n=68), high ligation + stripping + tributary phlebectomy (n=34) versus high ligation + stripping + tributary phlebectomy + subfascial endoscopic perforator surgery (n=34) Excluded patients with isolated saphenofemoral junction reflux and/or deep reflux, C_6, and REVAS **Follow-up 1 week to 1 year** The addition of subfascial endoscopic perforator surgery was not associated with significant morbidity but did reduce number of incompetent perforator but had no effect on recurrence rate or quality of life
Open surgery General anesthesia + Local anesthesia: Lidocaine + Adrenaline versus saline solution	Nisar A, Shabbir J, Tubassam P, Shah AR, Khawajava N, Kavanagh EG, et al. Local anaesthetic flush reduces postoperative pain and haematoma formation after great saphenous vein stripping: a randomised controlled trial. *Eur J Vasc Endovasc Surg*. 2006:31:325-331.	Great saphenous vein General anesthesia + local lidocaine and adrenaline (*n*=50) versus saline solution (n=50) **Follow-up 1 day-6 weeks** *In group local lidocaine and adrenaline* Reduction of hematoma *P*=0.007 and postoperative pain. *P*<0.001
Saphenous stripping (Babcock) versus invaginated stripping	Scheltinga MR, Wijburg ER, Keulers BJ, De Kroon CE. Conventional versus invaginated stripping of the great saphenous vein: a randomized double–controlled clinical trial. *World J Surg*. 2007;31:2236-2242.	Great saphenous vein 92 patients Various anesthesia modality Conventional stripping, Babcock Group I (n=46) versus Invaginated stripping. Group II (n=46) Group II Less blood loss. *P*<0.001 **Follow-up 1-26 weeks** No difference in terms of postoperative pain and returned to work
Saphenous stripping (Babcock) versus pin stripping (Oesch stripper)	Butler CM, Scurr JH, Coleridge Smith PD. Prospective randomized trial comparing conventional (Babcock) Stripping with inverting (Pin) Stripping of the long saphenous vein. *Phlebology*. 2002;17:59-63.	Great saphenous vein 136 patients High ligation + stripping Under general anesthesia Conventional stripping (Babcock) Group I (n=68) versus Inverting stripping (Oesch stripper) Group II (n=68) Group II Shorter operative time and less blood loss **Follow-up 1 week** No difference in terms of hematoma, postoperative pain, mobility, or analgesia consumption

This table lists variations in classic open surgery including groin closure, local anesthesia, stripping modalities, and combination with subfascial endoscopic perforator surgery. The last two are the most valuable. Surprisingly, there is no difference between classic and inversion stripping in terms of postoperative complications. More interesting is Kianifard's randomized clinical trial showing that the addition of subfascial endoscopic perforator surgery made no difference in terms of recurrence and quality of life, but this study was selective

since it excluded open ulcer and REVAS patients, and the follow-up was short (1 year).

We still lack outcomes of a long-term randomized clinical trial with two arms—saphenous ablation with and without perforator ablation in primary disease.

Table XV: Open surgery versus endovenous laser ablation versus radiofrequency ablation versus foam sclerotherapy

Operative procedure	Article	Conclusions
Open surgery versus endovenous laser ablation versus radio-frequency ablation versus ultrasound-guided foam therapy	Rasmussen LA, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg*. 2011;98:1079-1087.	Great saphenous vein with saphenofemoral junction reflux 580 lower limbs Open surgery (group 1) versus endovenous laser ablation 980 and 1470 nm, bare fiber versus (group 2) radiofrequency ablation ClosureFAST™ (group 3) versus ultrasound-guided sclerotherapy, one or 2 sessions when needed (group 4) All procedures under local anesthesia and completed by phlebectomy **Follow-up** *3 days and 1 month* Better quality of life (SF 36) as well as lower pain score ($P<0.001$) and shorter time off work ($P<0.001$) in groups 3 and 4 *1 year* Duplex ultrasound examination: Great saphenous vein occlusion better in groups 1, 2, 3 compared with group 4 ($P<0.001$) Clinical recurrence: No significant difference

NB: Open surgery = saphenofemoral ligation + stripping, +/- perforator ligation +/- tributary phlebectomy

The final conclusions in the Society for Vascular Surgery/American Venous Forum guidelines for treatment of varicose veins published in *Journal of Vascular Surgery* in May 2011 are as follows:[4]

1. Because of the minimally invasive nature and similar or better early-term and equivalent midterm results, endovenous thermal ablation should be recommended over open surgery as the first line of treatment of varicose veins associated with axial reflux.

2. The committee also recognized that the results of foam sclerotherapy have improved but are not yet equivalent to those obtained after endovascular or open surgery.

3. The committee pointed to the urgent need for well-prepared, large randomized clinical trials comparing adverse effects and long-term saphenous occlusion rates of surgery, endovenous thermal ablation, and foam sclerotherapy.

4. This is the only randomized clinical trial comparing the four operative procedures for treating varices. The study has been well conducted and is fully documented. Results after one year showed that all treatments are efficacious, with a higher technical failure rate after foam sclerotherapy; radiofrequency ablation and foam sclerotherapy lead to faster recovery, less postoperative pain, and superior quality of life scores compared with endovenous laser ablation and open surgery. The conclusions are clear, however the follow-up is short and a bare laser fiber was used (See Table X comments). A 5-year follow-up is ongoing.

DISCUSSION

Three recently published meta-analyses on the treatment of varicose veins[2-5] refer to the need to conduct more RCTs to evaluate the efficacy of new procedures. In a 2008 meta-analysis of radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and foam sclerotherapy, Luebke and Brunkwall compared these procedures with conventional surgery and found that RFA was inferior to EVLA and foam sclerotherapy in saphenous occlusion rate, phlebitis, DVT, and paresthesia.[5] EVLA had the highest occlusion rate and least recurrence compared with RFA and foam sclerotherapy. Luebke and Brunkwall concluded that large, high-quality, prospective RCTs comparing endovenous techniques and endovenous techniques with surgery are needed.[5] In 2009, van den Bos et al performed a meta-analysis comparing EVLA, RFA, foam sclerotherapy, and surgery.[6] The estimated pooled success rate at 3 years was highest for EVLA (94%), followed by RFA (84%), surgery (78%), and foam sclerotherapy (77%). Van den Bos et al concluded that endovenous thermal ablation and foam sclerotherapy are at least as effective as surgery.[6] In a Society for Vascular Surgery/American Venous Forum–sponsored meta-analysis in 2011, Murad et al found that surgery was associated only with nonsignificant reduction in varicose vein recurrence compared with EVLA, RFA, or sclerotherapy.[7] They concluded that the evidence for the long-term safety and efficacy of surgery in the treatment of varicose veins is of low quality, and that short-term studies support the efficacy of less invasive treatments, which are associated with less early disability and pain.[7] This meta-analysis of 60 RCTs published in English since 1990 warrants several remarks: (i) Firstly, when long- or medium-term outcomes comparing new treatment techniques become available, the development is so rapid that the material or device employed in the RCT is no longer used. This point is particularly relevant for thermal ablation (see *Tables VIII-X*). (ii) Secondly, most new procedures are operator-dependent and when two or more are tested in RCTs it is important that the investigators are well trained in all of them.[8] (iii) Thirdly, a brief description of a procedure does not indicate precisely how it was performed. For example, the high ligation + stripping technique has evolved and is now less aggressive and invasive than it was in the past. (iv) Finally, RCTs are important in the evaluation of the outcome of new procedures. Skepticism about conventional RCTs in nonpharmacological interventions such as surgery remains and so-called expertise-based RCTs are suggested as an alternative where participants are randomized to clinicians with expertise in intervention A or clinicians with expertise in intervention B, and the clinicians perform only the procedure they are expert in. One advantage of the expertise-based RCT is that surgeons will perform only the procedure in which they have expertise, avoiding the problem of differential expertise bias. Accurate analysis of the presented RCTs is difficult as hidden bias can be hard to identify.

The conclusion based on the presented RCTs with the caveats mentioned above is that the differences between modern open surgery and the new endovenous procedures are insignificant and that no treatment modality can be recommended as superior to another.

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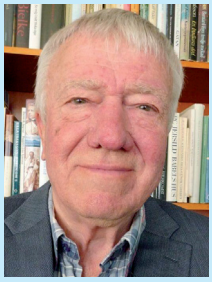

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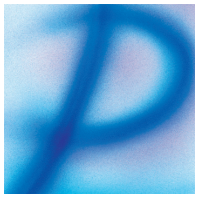

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