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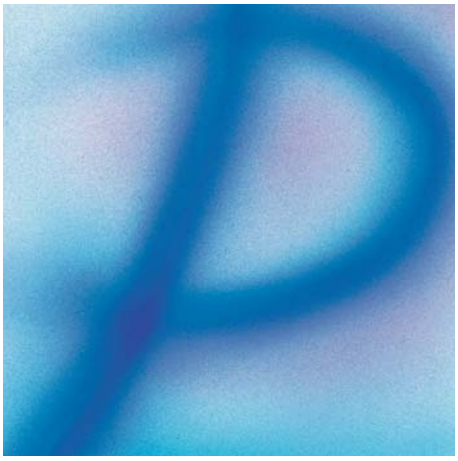

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AIMS AND SCOPE

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

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PHLEBOLYMPHOLOGY

Hugo Partsch
Editor in Chief

Dear Readers,

This issue of Phlebolymphology *offers an exciting insight into some actual and very relevant fields of phlebology.*

***Renate van den Bos** and **Marianne de Maeseneer**, both working at the Dermatological University clinic in Rotterdam and outstanding experts in the field, discuss the strengths and weaknesses of the endovenous thermal ablation of varicose veins. They point out that duplex-guided endovenous procedures have widely replaced classical stripping and that the newly developed steam ablation procedure has a promising future, being safer, faster, easier, and cheaper than endovenous laser and radiofrequency ablation (see also the article by René Milleret: Obliteration of Varicose Veins with Superheated Steam. Phlebolymphology. 2011;19:174-187).*

*In an extensive review article, Professor **Byung-Boong Lee**, George Washington University School of Medicine, shows that knowledge of embryology may be key to understanding vascular pathologies, for instance for the differentiation between truncular and extratruncular forms of vascular malformations. His article contains beautiful illustrations of clinical conditions: radiological, MRI, and nuclear medicine pictures and schematic drawings, which are helpful to understand this very complex topic.*

***Jean-Jérôme Guex** from Nice, together with a group of prominent coauthors working on the Vein Consult Program, a worldwide epidemiological survey (see the article by Francoise Pitsch in the last issue of Phlebolymphology; 2012;19:132-137), has analyzed a large group of symptomatic C0 patients, a cohort of patients that is well-known to every phlebologist. Out of a total of 91 545 subjects, 19.7% did not show any visible or palpable signs of venous disease—this is the definition of the C0 class according to the CEAP classification—but presented with subjective symptoms. Most of the 14% of patients who underwent a duplex scan examination had superficial reflux, and 18% had deep reflux. The authors suggest that an "inflammatory hypothesis" may be the cause of the symptoms, which include a reduced quality of life, and propose that venoactive drugs should be used for treatment.*

*Based on their extraordinary experience with sclerotherapy using Sigg's technique, **Francesco** and **Giovanni Ferrara** from Naples have showed, in a case series of 60 patients, that diabetes mellitus with good glycemic control (HbA1c<6.5%) is not a contraindication for this technique, but rather gives equally good results and no more complications than in nondiabetics.*

Have a great read!

Endovenous thermal ablation for varicose veins: strengths and weaknesses

Renate R. van den BOS,
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ABSTRACT

Endovenous ablation is a frequently used method for treating varicose veins. Endovenous laser ablation is the most frequently used technique, followed by radiofrequency ablation. Endovenous thermal treatments heat the vein, leading to thrombotic occlusion and finally fibrosis of the vein wall. Endovenous steam ablation is a new technique that has not yet been extensively studied. In this article, the procedures, strengths, and weaknesses of the currently available endovenous thermal ablation treatments are discussed.

INTRODUCTION

Endovenous treatment is currently one of the most frequently used methods for treating varicose veins. Varicose veins are manifestations of chronic venous disease (CVD), which may lead to serious complications. CVD is a common medical condition. The prevalence of varicose veins is estimated to range from 2%-40%.[1-4] The prevalence of venous leg ulcers, the end-stage of CVD, is much lower. It is very difficult, if not impossible, to predict which patients with varicose veins will develop a leg ulcer. Nevertheless, it has been estimated that about half of venous leg ulcers are the result of superficial venous insufficiency.[5] The cost of treating leg ulcers is very high; the treatment of varicose veins, which may reduce the incidence of leg ulcers by 50%, is therefore likely to be cost-effective.

Treatment for varicose veins can roughly be divided into four categories: compression therapy, surgical treatment, sclerotherapy, and endovenous thermal ablation. Surgical ligation of the junction with or without stripping has been the standard of care in the treatment of insufficient great and small saphenous veins for more than 100 years.

In the last decade, endovenous thermal ablation (EVTA) procedures have become the most frequently used therapy for saphenous varicose veins, especially in countries where reimbursement of the procedure has been introduced. Such minimally invasive techniques meet the demand for cosmetically superior, less invasive and more successful treatment modalities. Only introduced 10 years ago, these techniques have radically changed the

Keywords:
endovenous ablation treatments, saphenous insufficiency, thermal ablation, varicose veins

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treatment of varicose veins.[6] The EVTA techniques currently available are: endovenous laser ablation (EVLA), radiofrequency ablation (RFA), and endovenous steam ablation. The advantage of EVTA is that it is minimally invasive and can easily be performed under local tumescent anesthesia, without the need for spinal or general anesthesia. Moreover, according to a meta-analysis of the different treatment techniques for varicose veins, recurrence rates are lower after EVTA than after classic surgery.[7]

The first EVTA procedures were performed by RFA with the VNUS® Closure Plus system.[8] EVLA was developed soon after and soon became the most frequently used EVTA method around the world. In the last few years, two new RFA systems have been introduced: VNUS Closure Fast (segmental RFA) and radiofrequency induced thermotherapy (RFITT). The latest thermal ablation technique uses steam at a temperature of 120°C. In the following paragraphs, the different EVTA techniques will be described and their strengths and weaknesses explored.

ENDOVENOUS LASER ABLATION

Procedure

EVLA can be performed under local tumescent anesthesia in an outpatient setting. Venous access is obtained by puncturing with a 16F or 18F needle or cannula under ultrasound guidance. Most commonly, the insufficient great saphenous vein (GSV) is entered at knee level and the small saphenous vein (SSV) at mid-calf. After entrance to the vein has been established, a guide wire is passed through the needle into the vein up to the level of the junction with the deep venous system. If the vein is too tortuous, is small in diameter (due to spasm) and has large side branches, or contains thrombotic or sclerotic segments (after superficial vein thrombosis or prior treatment), advancing the wire can be difficult and caution is indicated because of the increased risk of perforation and embolic events. After checking the position of the guide wire with ultrasound, the needle is removed, and a small cutaneous incision of 3 mm is made. An introducer sheath is placed over the guide wire and is positioned a few centimeters below the junction. Subsequently, the laser fiber (diameter ranges from 200 to 600 µm) is introduced after removing the guide wire. In some laser sets, there is no guide wire and the sheath is directly introduced through a cannula. In other laser kits the laser fiber is already inside the sheath. A crucial step in the EVLA procedure is the positioning of the tip of the laser fiber 1 to 2 cm distally from the junction under ultrasound guidance, in longitudinal view (*Figure 1*). About 250 to 500 mL (depending on the length of vein treated) of tumescent anesthesia is administered into the perivenous space, again under ultrasound guidance using a syringe or mechanical infusion pump (*Figure 2*). Tumescent anesthesia is warranted because it reduces pain, cools perivenous tissue, and decreases the venous diameter. After activation, the protocol may use continuous laser pullback (usually at about 3-5 mm/s, depending on the power and wavelength; with the 1320-nm laser, a pullback speed of 1 mm/s is commonly used)[9] or a pulsed pullback, with the objective of administering

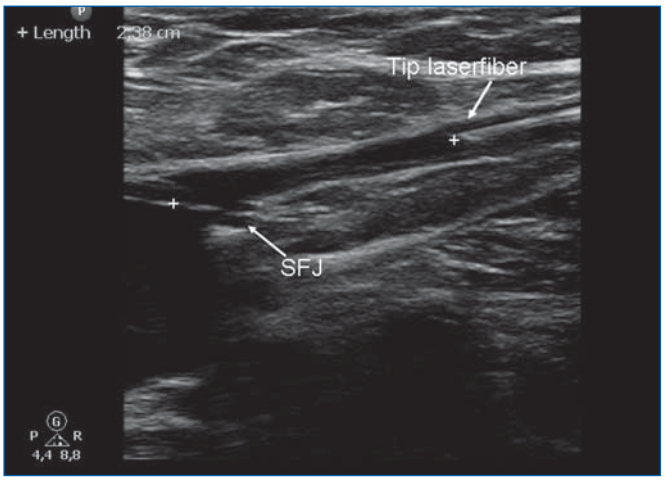

Figure 1. *The tip of the laser fiber is positioned 1-2 cm below the saphenofemoral junction (SFJ).*

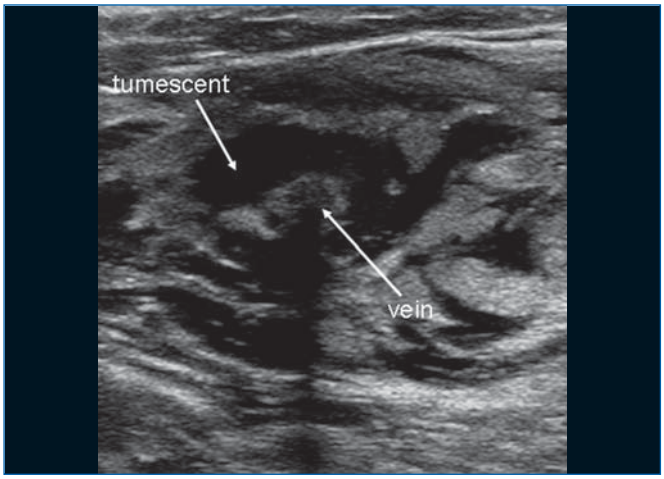

Figure 2. *Tumescent anesthesia is administered around the vein.*

about 30 to 60 J/cm. Compressive bandages or medical elastic stockings (20-30 mm Hg at the ankle) are indicated for 1 week after treatment.

Strengths

EVLA can be used for treating insufficient GSVs and SSVs. Due to the rigidity and size of the disposables, linear saphenous veins with a diameter of 5 mm or more are ideal for EVLA (*Figure 3*). EVLA can also be used for ablation of the anterior accessory saphenous vein or the

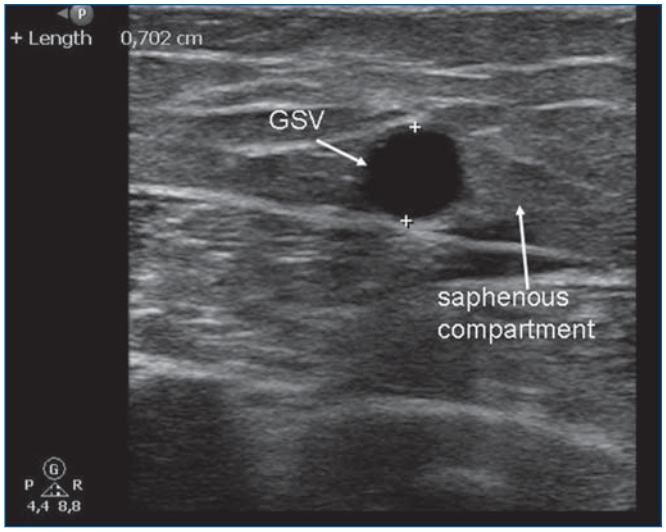

Figure 3. *The great saphenous vein (GSV) in the saphenous compartment.*

posterior accessory saphenous vein (often in conjunction with a Giacomini vein), and perforator veins.[10-11] EVLA is the least expensive endothermal treatment. In the Netherlands, the cheapest laser disposables cost approximately 120 Euros. Another advantage of EVLA is that the amount of delivered energy can be varied. By adjusting the pullback speed, the power, or both, the total amount of delivered energy per centimeter can be altered. For small veins, only 20 J/cm is used, whereas higher energy (ie, 60 J/cm) can be used when treating large veins. Of all the thermal ablation techniques, EVLA is the most extensively studied in the medical literature. The first large case series reported high success rates[12-13] and many series have followed with comparable results. In 2009, we published a meta-analysis on the different treatments for saphenous varicose veins and showed that EVLA had the highest success rate at 93% after 5 years of follow-up. EVLA did significantly better than stripping, RFA, and ultrasound-guided foam sclerotherapy.[7] A recent, large randomized clinical trial performed by Rasmussen et al[14] showed that EVLA, RFA, and stripping (under tumescent anesthesia) were all equally efficacious. RFA was associated with a faster recovery and less postoperative pain than EVLA and stripping.[14]

Weaknesses

Some technical difficulties may occur during an EVLA procedure, even in experienced hands. When treating recurrent varicose veins, caution is indicated because introducing the laser fiber may be difficult. In very tortuous veins, introducing the guide wire can be difficult and perforation of the vein is possible. Another disadvantage in some EVLA sets is that introduction is not a single step procedure, but requires several consecutive steps (introduction of the guide wire, the sheath, and then the laser fiber). Each additional step increases the risk of making errors. Some complications have been described that are disposable-dependant; for example, a guide wire remaining inside the body after finishing the EVLA procedure.[15] Such complications are usually serious and might be prevented if the procedure could be performed with only one disposable instead of three. The side effects of EVLA are usually mild. Systematically studying all publications on EVLA showed that the most common side effects were ecchymoses and pain, with or without induration (100%). Other less common side effects included: skin burns (<1%), dysesthesia (0-22%), superficial thrombophlebitis (0-25%), deep vein thrombosis (DVT) (0-6%), nerve injury (<1%), and hematoma. In our experience, postoperative pain may be slightly more pronounced after EVLA compared with RFA and steam ablation. Using a laser fiber with a modified tip (tulip or radial fiber) and avoiding a too high energy dose, may reduce postoperative pain;[16] however, there are no good comparative studies available.

RADIOFREQUENCY ABLATION

Several systems for radiofrequency ablation exist. The first RFA procedures were performed with the VNUS® Closure Plus system.[8] In the last few years two new RFA systems have been introduced: VNUS® Closure Fast (segmental RFA) and radiofrequency induced thermotherapy (RFITT). Segmental RFA is currently the most popular method.

Procedure

Access to the GSV is obtained with a 16-gauge needle under ultrasound guidance, typically at or below knee level or at the most distal point of reflux. The SSV is usually punctured at mid calf. The Closure catheter (VNUS Medical Technologies, Inc, Sunnyvale, California) is positioned 2 cm distally from the junction under longitudinal ultrasound visualization. With the Closure Plus system, a cuff or bandage can be used to express the blood from the vein. The small electrodes at the end of the "umbrella" catheter have direct contact with the venous wall and emit high radiofrequency energy (regulated by power, impedance, and time) that is generated by a radiofrequency generator (VNUS Medical Technologies, Inc). The radiofrequency heats local tissue up to 85°C to 90°C at the site of direct contact, with the heat conducted to deeper tissue planes, causing collagen shrinkage, denudation of endothelium, and obliteration of the venous lumen.[17] The catheter pullback speed is 3 cm/min (total pullback time is 20 min on average for the GSV between the saphenofemoral junction and knee level, but can be faster at higher temperatures).[18]

Segmental RFA (Closure Fast) has a 7 cm therapeutic distal segment that heats to 120°C.[19] This technique is much faster than the Closure Plus technique and can be performed under local tumescent anesthesia in an outpatient setting. Similar to EVLA, perivenous tumescent anesthesia is applied to optimize surface contact and to decrease pain and risk of dysesthesia.[20] According to the methodology described in the first report on segmental RFA, external compression provided by the ultrasound probe and manual compression is recommended during the treatment to enhance contact of the catheter with the vein wall.[21] The first 7 cm of vein is treated with two heat cycles (20 s each). The catheter is then repositioned to the adjacent segment guided by shaft markers in 6.5-cm steps to allow a 5 mm overlap of heated vein segments. Total treatment time is much shorter with segmental RFA than with the Closure Plus system and usually takes only 2 to 3 min. Compressive bandages or medical elastic compression stockings are indicated for 1 week after treatment.

Strengths

Since 2000, several published case series have shown that RFA can be successfully used to treat saphenous varicose veins.[8, 22-25] The first long-term, large, single-center case series reported that RFA was effective in about 90% of 140 limbs after 2 years.[20] A separate study reported success rates of 83%-88% after 5-year follow-up.[26] Our meta-analysis showed that RFA (using Closure Plus) had a success rate of 88%, which was lower than the success rate of EVLA.[6]

Segmental RFA was not included in the analysis, as at the time no studies were available. However, there are now a few publications on segmental RFA with promising results. The first case series of 252 treated GSVs reported an occlusion rate of 99.6%,[21] and two other trials demonstrated success rates >90%.[27,28] The main advantage of segmental RFA is probably that it results in less postoperative pain than EVLA. This is thought to be related to the lower maximal temperature that is reached during RFA, and the absence of vein wall perforations.[27] A further advantage of segmental RFA is that it is a standardized procedure and introduction of the catheter is performed in one step. This may lower the risk of disposable-related complications.

Weaknesses

On the one hand, standardization of a procedure is an advantage. On the other hand, it may not be possible to treat certain 'special' cases. With segmental RFA it is impossible to treat veins with a length smaller than 7 cm, although this may change with the recent introduction of a new catheter with a 3 cm heating segment. In certain cases (ie, patients with side branches, or small tortuous parts of varicose veins), it may also be desirable to change the energy delivery, but with segmental RFA it is not possible to treat veins at other than the preset temperature. As a result of the relatively low temperature that is reached during segmental RFA, the working mechanism is collagen denaturation and shrinkage of the vein wall.[17] This differs from EVLA in which carbonization and more rigorous destruction of the vein wall is also reported.[29] The long-term effectiveness of segmental RFA has not yet been studied and will only become clear after a randomized study comparing EVLA and segmental RFA with long-term follow-up has been conducted.

STEAM ABLATION

Procedure

Endovenous steam ablation (EVSA) is a new method of thermal vein ablation that works by heating the venous structure with steam to a maximum temperature of 120°C (*Figure 4*). The procedure is very similar to EVLA

Figure 4. Steam is ejected from two areas at the tip of the catheter.

and can be performed with the patient under local tumescent anesthesia in an outpatient setting. The vein is punctured with a 16-gauge needle or cannula under ultrasound guidance. The GSV is usually entered at the distal site of reflux, at or just above knee level because access is easy at this site and the risk of nerve injury is low. The SSV is usually punctured halfway or at a position in the distal third of the calf, depending on vein diameter and extent of reflux. After puncturing the vein, the steam catheter (1.2 mm diameter) is passed through the hollow needle into the vein and the echo-dense tip of the catheter is then carefully positioned 3 cm from the junction, under ultrasound guidance. This is again the most pivotal step in the procedure. About 250 to 500 mL (depending on the length of vein treated) of tumescent anesthesia is administered into the perivenous space under ultrasound guidance. Tumescent anesthesia is necessary to reduce pain, cool the perivenous tissue, and to decrease venous diameter. After activation, the catheter releases small "puffs" of steam and is pulled back in a stepwise fashion. At the first activation, 3 cm below the saphenofemoral or saphenopopliteal junction, four puffs of steam should be administered, while exerting gentle manual pressure on the junction. Further along the vein, two or three puffs of steam can be administered at 1 cm intervals depending on vein diameter. For the first 4 cm of treatment, manual compression of the junction should still be applied as the steam can reach several centimeters beyond the catheter tip. After the procedure, patients are advised to wear thigh-length medical elastic compression stockings (pressure range 25-35 mm Hg) for 1 week and to mobilize immediately after the treatment.

Strengths

Two features that might be advantageous (compared with EVLA) are that EVSA is performed with a very small volume of sterile water (approximately 2 mL per treated vein) and that the temperature is relatively constant, with a maximum of 120°C. The steam catheter is introduced directly through the puncturing needle, without the need for a guide wire or sheath, resulting in an easy and safe procedure. Only one case series on steam ablation has been published, which showed that patient-reported outcomes were favourable, the procedure was very well tolerated, pain scores were low, and patients were very satisfied with the treatment.[30] An advantage of the EVSA procedure is that the catheter is minute and very flexible (*Figure 5*); the diameter of the

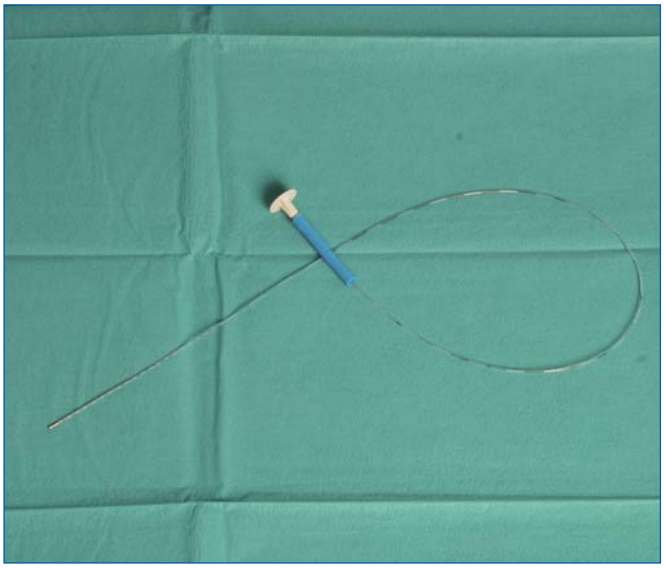

Figure 5. The flexible steam catheter has a small diameter.

SVS steam catheter (1.2 mm) is almost 50% smaller than the catheter used for segmental RFA (2.33 mm). The flexibility of the steam catheter may facilitate placement into more tortuous vessels and perforator veins, which are sometimes difficult to access with the more rigid catheters used for RFA and the stiff glass fibers used for EVLA. Even vein tributaries may, therefore, be treated with EVSA. The steam is released from two small areas at the tip of the catheter, allowing treatment of any length of vein. The steam is released under pressure and, therefore, disperses over a distance of at least 2 cm. This

may be of additional benefit in the treatment of short perforator veins and short segments of meandering tributaries.

Weaknesses

The main limitation of steam ablation is the lack of evidence; only three reports on steam ablation have been published to date.[30-32] The other problem is that steam ablation is not yet reimbursed, which will limit the number of procedures performed and thus make outcome measurements even more difficult to obtain. Larger comparative studies are needed to compare the long-term efficacy and the risk-benefit ratio of steam ablation with those of existing endovenous techniques.

DISCUSSION

The "gold standard" for the treatment of insufficient saphenous veins has been ligation plus stripping for the past 100 years. This situation has changed in the last decade with the introduction of endovenous thermal ablation techniques. EVTA techniques are always performed under duplex guidance and are proving to be very effective with high success rates at short-term follow-up. As the effectiveness of current EVTA treatments is excellent (>90%), side-effects are mild, and serious complications rare, any new EVTA procedure should at least perform equally or preferably have some advantages over existing techniques. The hypothesis is that EVSA will be at least as effective as EVLA or RFA. The advantages of steam over the other ablation procedures may be better patient tolerance; a safer, faster and easier procedure; lower costs; and ease of use for perforator veins and tributaries. Future studies should compare the different endovenous treatments in terms of effectiveness and patient-reported outcomes. Further work is also required to try to answer the remaining questions about the exact working mechanism of the different EVTA treatments. In an era of health technology assessment and cost-effectiveness analyses, treatment-related costs will become increasingly important and this will remain a crucial issue in the future.

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Venous embryology: the key to understanding anomalous venous conditions

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ABSTRACT

Venous embryology can explain many of the defects resulting in venous anomalies in later life, yet is often overlooked. Venous malformations are vascular malformations that only affect the venous system. They are classified into two different types depending on the embryological stage when the defective development occurs. Venous malformations originating during the early stage of embryogenesis are termed extratruncular, while those originating during the late stage of embryogenesis are classified as truncular. A defect at any point in the complex development stages of the evolution and involution of multiple paired embryonic veins can result in various conditions of defective venous trunkTherefore, truncular lesions in general are associated with more serious hemodynamic consequences than extratruncular lesions due to their direct involvement with the truncal venous system.

This review provides a detailed overview of venous embryology and a number of truncular venous malformations to illustrate how a thorough knowledge of this subject can aid in their diagnosis and treatment.

INTRODUCTION

A thorough understanding of vascular system anatomy is a prerequisite for all vascular specialists. However, a knowledge of venous embryology is seldom acquired even though all mature and named vessels originate from their precursor, embryonic vessels, and vascular anomalies are closely linked to them.

Vascular anomalies are relatively rare and difficult to understand and interpret. Yet, venous embryology is one of the most neglected areas of basic science in medicine despite its critical ability to explain the many obscure conditions related to anomalous anatomy (eg, membranous occlusion of suprahepatic inferior vena cava as a cause of primary Budd-Chiari Syndrome).[1,2]

Keywords:
chronic venous hypertension, embryology, extratruncular stenosis, truncular, venous malformation

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Such venous anomalies are a result of the defective development of embryonic veins during the vascular trunk formation period in the later stage of embryonic development.[3,4] A benign narrowing (stenosis) of the jugular-azygos vein system is a good example of how defective development can cause a unique condition, in this case chronic cerebrospinal venous insufficiency (CCSVI).[5,6]

A basic knowledge of vascular embryology and in particular, the evolutional and involutional development of the venous system involved in the maturation of the truncal vein, is essential for the recognition and interpretation of a number of venous anomalies.[7,8]

DEFINITION

When the embryo starts to grow at an exponential rate in the early stage of embryogenesis, rapid growth and expansion of the embryonic vessels must follow suit to fulfill their critical role as the channels to supply essential nutrient requirements. A defect at any point in the complex development stages of evolution and involution of multiple paired embryonic veins can result in congenital vascular malformations (CVM).[9,10] The prevalence of defective development in the vascular structure of the newborn is in the range of 1% to 3%.

As CVMs are birth defects that arise during the various stages of development of the vascular system,[11,12] they can involve one or more components: artery, vein, lymphatics, and/or capillary vessels. Venous malformations are vascular malformations that only affect the venous system.[13,14] They may exist alone as an independent lesion or combined with other CVMs as lymphatic malformations,[15,16] arteriovenous malformations,[17,18] and/or capillary malformations.[19,20] The clinical behavior of the malformation is solely dependent on the embryonic stage at which the developmental arrest/defect occurs.

When defective development occurs in the 'early' stage of embryogenesis, the embryonic vessels remain in the form of reticular networks and do not evolve into the vascular trunk formation. After birth these networks can remain as independent clusters of primitive venous tissue without direct involvement of the main venous trunk itself (eg, extratruncular venous malformation) (*Figure 1*). These primitive vascular structures maintain the mesenchymal cell properties and its evolutional ability to proliferate when stimulated by exogenous (eg, surgery, trauma) or endogenous factors (menarche, pregnancy, female hormones).[7,8,10,21,22]

When defective development occurs in the vascular trunk formation period in the 'later stage' of embryonic development, the defects involve 'named' vessels (eg, iliac, femoral, and popliteal vessels) and are limited to the vessel trunk itself. Examples of such truncular venous malformations include popliteal vein aneurysm, absence/aplasia of the femoral vein, jugular vein stenosis/webs, and hypoplastic iliac vein (*Figure 2*). These are 'embryologically mature' lesions, which no longer possess the evolutionary capacity to proliferate. However, truncular lesions present with more serious

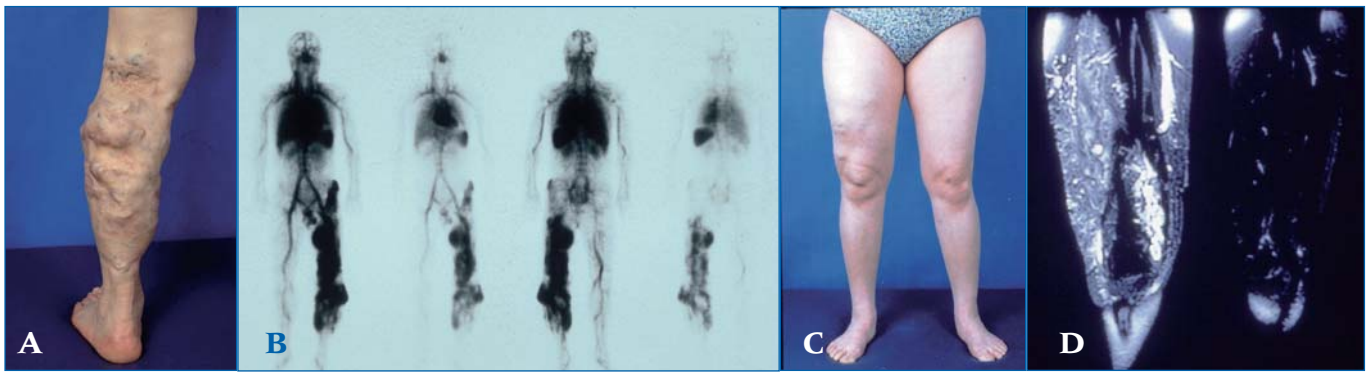


Figure 1 (A - D). *Extratruncular venous malformation (VM)*
1A depicts a clinical condition of extratruncular venous malformation (VM) lesions affecting the entire left lower leg, but mostly limited superficially to the soft tissue level. 1B (whole body blood pool scintigraphy) displays compatible findings to show the extent of the lesion on the same extremity. On the contrary, 1C shows a benign looking VM lesion in the right lateral upper thigh mimicking varicose veins. However, it is the tip of the iceberg of extensive lesions infiltrating into the surrounding soft tissue as well as the muscles, shown in MRI (1D).

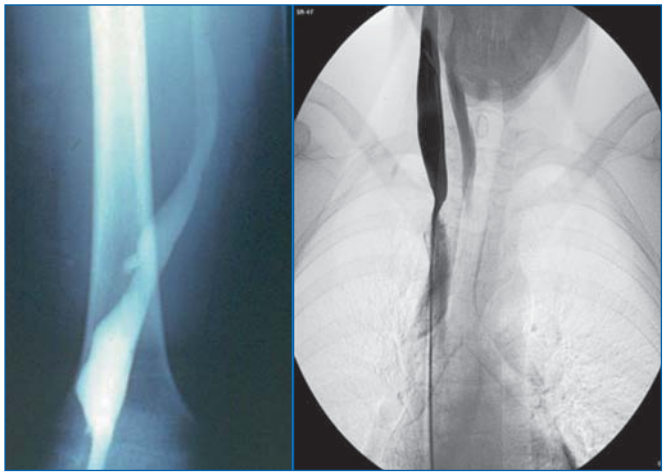


Figure 2 (A and B). *Truncular venous malformation (VM)*
2A demonstrates angiographic findings of a truncular VM lesion consisting of an aneurysmal dilatation of the right popliteal vein; this truncular lesion is the outcome of developmental arrest during the vascular trunk formation period in the 'later stage' of embryonic development.
2B also presents angiographic findings of another type of truncular VM lesion this time a stenotic condition involving the right internal jugular vein trunk along its junction with the superior vena cava (Courtesy of Professors P Zamboni and R.Galeotti for 2B).

hemodynamic consequences in general compared with extratruncular lesions due to their direct involvement with the truncal venous system (eg, avalvulosis, marginal veins, popliteal vein aneurysm, inferior vena cava stenosis/occlusion).[23,24]

Based on the above definitions, the modified Hamburg Classification separates venous malformations into two different types: extratruncular and truncular, depending on the embryological stage when the defective development occurred (*Table I*).[25,26] Venous malformations originating from the 'early' stage of embryogenesis are classified as extratruncular together with all other types of vascular malformation from the same 'early' stage (eg, lymphangioma). Venous malformations originating from the 'late' stage of embryogenesis are classified as truncular.

As all truncular lesions involve the already formed, established venous trunk to varying degrees, they present as either hypoplastic or hyperplastic vessels/lesions causing obstruction or dilatation (eg, internal jugular vein aneurysm, iliac vein stenosis), depending on the defect.[27,28] It should be noted that intraluminal defects within the vein (eg, vein webs or membrane) can result in similar conditions of stenosis or obstruction (*Figure 3*).[29,30]

Primary classification*
Arterial malformations
Venous malformations
Arteriovenous malformations
Lymphatic malformations
Capillary malformations
Combined vascular malformations
Anatomical/embryological subclassification**
Extratruncular forms • Diffuse, infiltrating • Limited, localized
Truncular forms • Obstruction or narrowing - Aplasia; Hypoplasia; Hyperplasia - Obstruction due to atresia or membranous occlusion - Stenosis due to coarctation, spur, or membrane • Dilatation - Localized (aneurysm) - Diffuse (ectasia)

Table I. *The modified Hamburg classification of congenital vascular malformations.*

** Based on the predominant vascular structure in the malformation.*
*** Based on anatomy and developmental arrest at the different stages of embryonic life: extratruncular form from earlier stages; truncular form from late stages.*

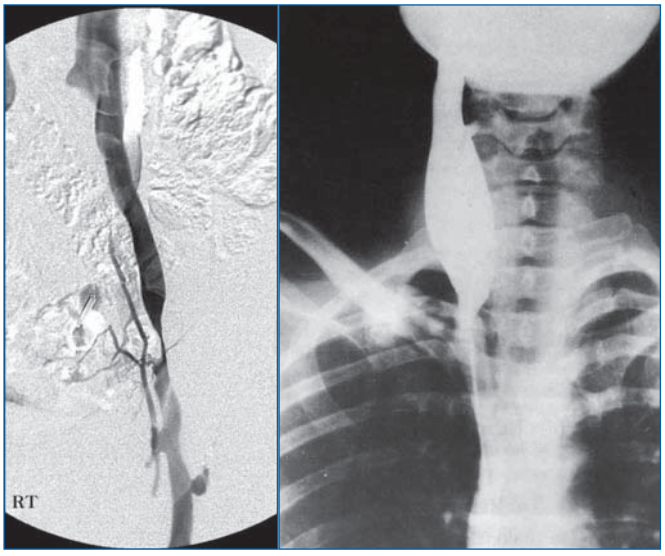


Figure 3 (A and B). *Truncular venous malformation (VM)*
3A shows angiographic findings for a truncular VM lesion involving a segmental stenosis of the left iliac vein. This benign looking condition precipitated a severe chronic venous insufficiency to the affected lower extremity.
3B shows another form of truncular VM involving an aneurysmal dilatation of the right internal jugular vein (Courtesy of Professors P. Zamboni and R. Galeotti for 3B).

Less frequently, truncular venous malformations may present as a persistent fetal remnant vein that has failed to involute or regress normally. This unique condition, which involves the lower extremity venous system, is known as «marginal/sciatic/lateral embryonic veins»[31,32] and represents the venous malformation component of Klippel-Trenaunay Syndrome (*Figure 4*).[3,4,21,22]

As a consequence of their direct involvement with the venous system, the chronic venous congestion and hypertension due to venous reflux or occlusion caused by truncular venous malformations result in more tissue and organ damage than extratruncal lesions. Membranous, focal, or segmental lesions can cause suprahepatic stenosis of the inferior vena cava along the proximal terminal segment, a condition known as primary Budd-Chiari syndrome. This has a profound hemodynamic impact, not only on the lower extremities where it causes chronic venous hypertension, but also on the liver where it results in severe portal hypertension due to hepatic venous outlet obstruction. This congenital/developmental anomaly most frequently involves Asian and African races (*Figure 5)*.[33,34]

The cerebrospinal venous circulation is not exempt from truncular venous malformations. Cerebrospinal venous malformations carry the potential risk of long-term chronic venous hypertension to the brain resulting in various clinical conditions/illnesses such as CCSVI.[35,36]

An example of CCSVI, internal jugular vein valve incompetence (IJVVI), has been postulated to be the cause of transient global amnesia.[37,38] IJVVI is diagnosed when retrograde jugular vein flow is detected by extracranial duplex ultrasound during Valsalva maneuver. It is believed that IJVVI may produce transient mesiotemporal ischemia by venous congestion. This mechanism requires a patent venous pathway from

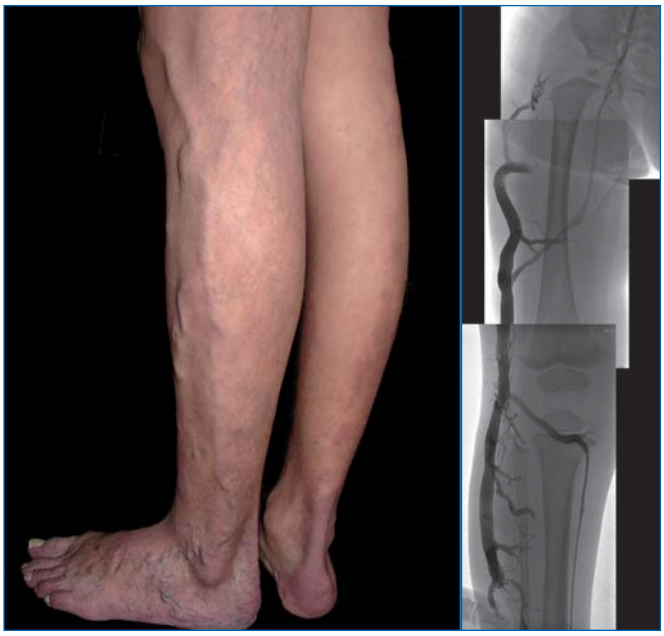


Figure 4 (A and B). *Truncular venous malformation: marginal/lateral embryonic vein*
4A depicts a clinical condition of the marginal/lateral embryonic vein along the lateral aspect of the left lower extremity. This unique vein structure is a persistent fetal remnant vessel following the failure of normal involution/regression and its 'avalvulosis' causes severe venous reflux. Marginal vein remains are a hallmark of Klippel-Trenaunay syndrome, representing its venous malformation component.
4B presents angiographic findings of this marginal vein, which is the only remaining major venous drainage route with a lack of normal development of the deep venous system. Surgical excision to control venous hypertension is therefore contraindicated.

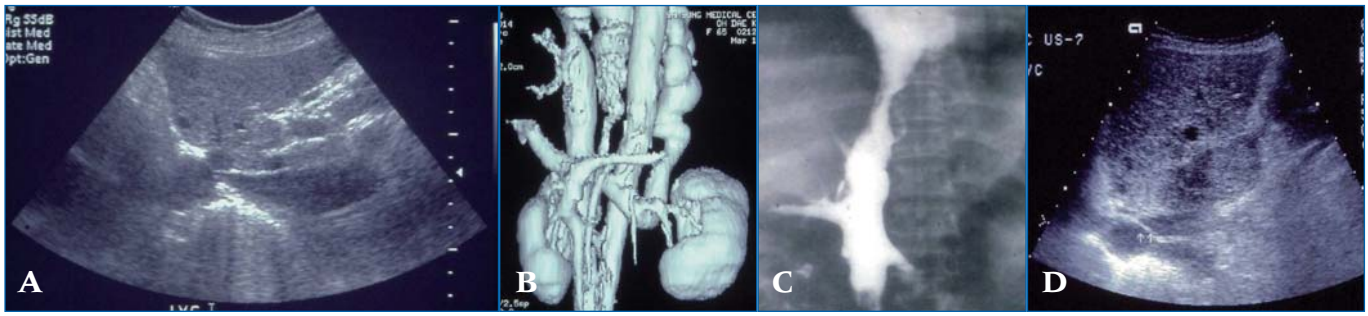


Figure 5 (A - D). *Suprahepatic inferior vena cava (IVC) occlusive lesion: primary Budd-Chiari syndrome*
A common cause of suprahepatic IVC occlusion is focal stenosis (shown in 5A and 5B) and segmental stenosis (5C), although membranous obstruction by the web is the most common cause among Asians (5D). These are relatively simple congenital VM, which develop during the late vessel trunk formation stage. However, they have a profound hemodynamic impact on the liver with portal hypertension due to hepatic venous outlet obstruction in addition to chronic venous insufficiency affecting the lower extremities.

the affected internal jugular vein through the transverse sinus, confluence, straight sinus, and vein of Galen into the basal vein of Rosenthal and into the internal cerebral veins.

There are now also data supporting a role for CCVI in the development of multiple sclerosis as reported in the International Union of Phlebology Consensus on Venous Malformations - 2009.[39] It is hypothesized that truncular venous malformations causing stenosis along the internal jugular, innominate, superior vena cava, and azygos vein system, may contribute to the development or exacerbation of multiple sclerosis.[40,41]

DEVELOPMENT OF THE PRIMITIVE VENOUS SYSTEM

The heart and blood vessels develop from the mesoderm as isolated masses and cords of mesenchymal cells as early as 15 to 16 days in order to rapidly deliver sufficient nutrients to the exponentially proliferating cells and dispose of waste products via connection with maternal blood vessels in the placenta.[42-44] By the beginning of the fourth week of gestation, an extensive network of blood vessels has formed from the mesenchyme as clusters of angiogenetic cells throughout the embryonic body to establish a communication with extra-embryonic vessels and to create a 'primitive vascular system': the Vitelline-Umbilical-Cardinal Vein System (*Figures 6 and 7*).[42-44]

The primitive vascular structure in complex capillary and reticular plexuses in the early embryonic stage is soon replaced by the newly developed paired cardinal veins as an axial, truncal venous system. In addition, the paired vitelline vessels from the yolk sac develop into the hepatic portal system, while the paired umbilical vessels from the chorion and body stalk form the ductus venosus. The anterior and posterior cardinal veins merge to become the 'common cardinal veins,' draining centrally into the sinus venosus (sinus horns) and also receiving the 'vitelline' and 'umbilical' veins (*Figure 6*). At 4 weeks, the paired umbilical veins return blood from the placenta to capillary networks in the liver. During the fifth week of development, the right umbilical vein degenerates, involutes together with the proximal portion of the left umbilical veins, leaving only the distal part of the left umbilical vein as a single vein to return blood from the placenta to the embryo.

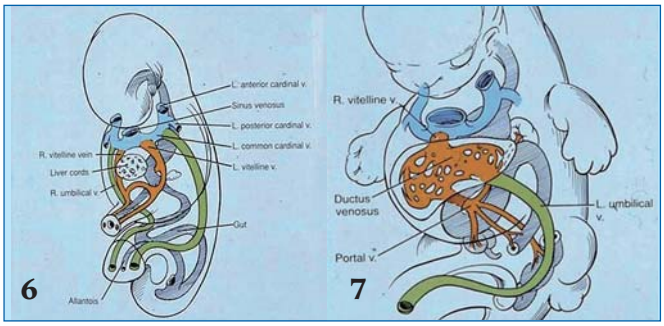


Figure 6. *Embryonic veins at the fifth week of gestation: anterior/posterior/common cardinal vein and vitelline/umbilical vein developmental process*
The embryo demonstrates the development of paired sets of 'vitelline' and 'umbilical' veins in its fifth week, which initially drain the yolk sac and allantois, but later drain the intestines and the placenta, respectively. Paired sets of anterior and posterior cardinal veins join to form the 'common cardinal veins', draining centrally into the sinus venosus. The common cardinal veins also receive 'vitelline' and 'umbilical' veins, as depicted.

Figure 7. *Embryonic veins at the seventh week of gestation: vitelline/umbilical vein developmental process*
At the seventh week of embryonic development, the entire right umbilical vein and proximal left umbilical vein regress. The distal left umbilical vein subsequently anastomoses with the hepatic sinuses to form the ductus venosus. The ductus venosus allows venous blood from the umbilical vein and the portal vein direct access to the inferior vena cava (IVC). The distal/upper-most segment of the right vitelline vein remains as the most proximal segment of the IVC reaching the heart via paired sinus venosus, while all other parts of the vitelline veins regress/involute completely.

At 8 weeks, the distal left umbilical vein anastomoses with the hepatic sinuses to form the ductus venosus. This newly formed structure allows venous blood from the umbilical vein and portal vein to bypass the liver and flow into the inferior vena cava and finally to reach the heart via the paired sinus venosus (*Figure 7*).

EVOLUTION OF THE EMBRYONIC VEIN FOR HEAD AND NECK: PRECARDINAL AND ANTERIOR CARDINAL VEINS

The part of the body distal to the developing heart (head, neck, upper torso, and upper limbs) drains through the 'bilateral anterior cardinal veins' also known as the precardinal veins, whereas, the caudal portion of the body (body and lower limbs) drains through the 'bilateral posterior cardinal veins' also known as the postcardinal veins.[45,46]

Numerous large tributary vessels develop from the anterior cardinal veins and converge as cerebral plexuses. Blood passes from the plexuses to the heart through the anterior cardinal and common cardinal veins. The anterior cardinal (precardinal) veins, common cardinal, and terminal/proximal posterior cardinal (postcardinal) veins go through a major evolutionary process to become the veins of the heart, the superior vena cava (SVC), and its tributaries.

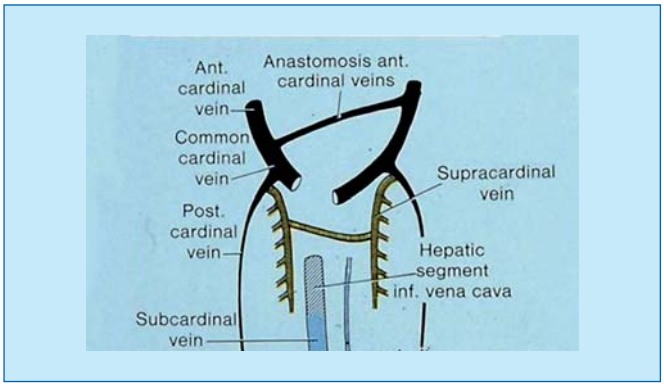
Paired anterior cardinal veins anastomose to allow blood to drain from the 'left anterior cardinal vein' into the 'right anterior cardinal vein'. This anastomosis grows from the left anterior cardinal vein to the right anterior cardinal vein to form the left brachiocephalic (innominate) vein.

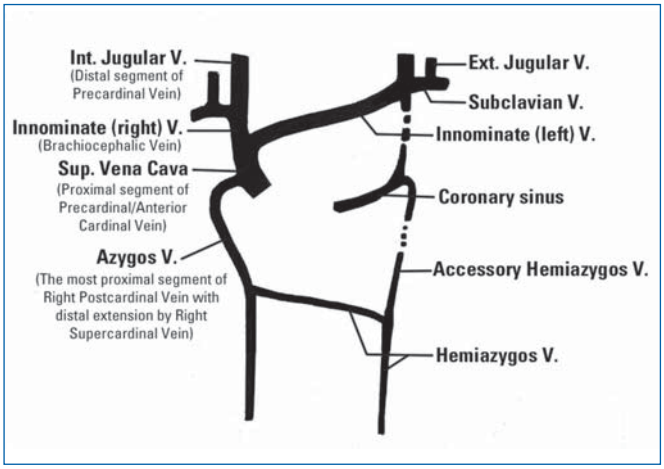
The portion of the left anterior cardinal vein distal to the anastomosis, becomes the 'left internal jugular vein' and joins the 'left subclavian vein' from the developing upper limb. The left anterior cardinal vein proximal to the brachiocephalic anastomosis regresses/atrophies with the terminal segment of the left posterior cardinal vein, ultimately becoming the Great Cardiac Vein. The 'oblique vein' of the left atrium (Vein of Marshall) at the back of the left atrium and the 'coronary sinus' of the heart comprise the Great Cardiac Vein. The distal portions of the bilateral anterior cardinal veins therefore become the bilateral internal jugular veins and the blood from the left internal jugular vein passes through the left brachiocephalic vein, draining directly into the SVC (*Figure 8*).[47,48]

On the right-hand side, the proximal part of the right anterior cardinal vein forms the SVC with the right common cardinal vein in conjunction with the right horn of the sinus venosus (*Figure 8*). The SVC therefore consists of three different segments:

1. Right anterior cardinal vein proximal to the brachiocephalic anastomosis
2. Right common cardinal vein
3. Right horn of the sinus venosus

These veins are further involved in the formation of the arch of azygos vein together with the proximal segment of the right posterior cardinal vein. The termination of the left posterior cardinal vein transforms into the Great Cardiac Vein, which drains into the left atrium. The azygos venous system is initially derived from the paired





Figures 8 (top) and 9 (bottom). *Precardinal/anterior cardinal vein developmental process*
Paired anterior cardinal veins form common cardinal veins with paired posterior cardinal veins, draining centrally into the sinus venosus (sinus horns) as depicted. Paired anterior cardinals soon form an anastomosis between them; the connection grows from the left to the right anterior cardinal vein to form the left brachiocephalic (innominate) vein. The left anterior cardinal vein distal (cranial) to the anastomosis becomes the 'left internal jugular vein,' while the left anterior cardinal vein proximal to the brachiocephalic anastomosis regresses/atrophies to become the base of the 'coronary sinus' of the heart as displayed. The right anterior cardinal (precardinal) vein proximal to the right brachiocephalic vein forms the superior vena cava (SVC) with the common cardinal, and terminal/proximal segment of the posterior cardinal (postcardinal) vein.

Three sets/pairs of cardinal veins: precardinal, postcardinal, and supracardinal, evolve to form the azygos venous system. The azygos venous system is initially derived from the paired supracardinal vein. The proximal segment of the right supracardinal vein forms the arch of azygos vein together with the cranial part of the right posterior cardinal vein, while the cranial part of the left supracardinal vein becomes the hemiazygos and also accessory azygos veins as displayed in 9. The hemiazygos vein on the left side drains into the azygos vein located in the right side before draining into the SVC. The 'accessory' hemiazygos vein runs along the course of the involuted left common cardinal vein and drains into the hemiazygos vein before it crosses over the midline to the azygos vein.

supracardinal venous systems, one of three cardinal veins that drain the caudal portion of the body together with the postcardinal (posterior cardinal) veins.[49,50]

The right supracardinal vein remains as the 'azygos vein' together with the distal portion of the right posterior cardinal vein to form the arch of azygos vein. The left supracardinal vein becomes the hemiazygos vein and accessory azygos vein. The hemiazygos vein on the left drains into the azygos vein located on the right side and subsequently into the SVC. The 'accessory' hemiazygos vein, which runs along the course of the involuted left common cardinal vein, drains into the hemiazygos vein before it crosses the midline to flow into the azygos vein (*Figure 9*).

ANOMALOUS DEVELOPMENT OF THE SUPERIOR VENA CAVA

Due to the complex nature of the various stages of evolution and involution of multiple paired embryonic veins, several anomalous conditions associated with the SVC can develop. These may affect the common cardinals, anterior and posterior cardinals, and primitive jugular veins. The likelihood of development anomalies associated with the SVC is relatively high due to the involvement of three different embryonic vein segments.

For example, a left-sided SVC may develop from 'persistent' left anterior and left common cardinal veins,[51,52] and is often associated with the absence of the right SVC.[53,54] In this condition, the right brachiocephalic vein crosses the midline to join a vertical left brachiocephalic vein, thus forming a left SVC. As a consequence of this developmental defect of the common cardinal vein, the persistent left SVC can be associated with the presence of two azygos veins. When a left SVC is present, the anatomy of the azygos veins may be reversed; the hemiazygos vein (the remnant of the proximal part of the left posterior cardinal vein) located on the left, will drain directly into the left-sided SVC, in the way that a normal azygos vein (the remnant of the proximal part of the right posterior cardinal vein) would drain into the SVC on the right side. This anomalous condition is the result of a developmental arrest/defect during the late stage of embryogenesis. The left SVC is grouped with other similar truncular venous malformations (eg, double SVC, internal jugular vein stenosis/aneurysm).

A double SVC is another well known vein anomaly that occurs as a result of failure of degeneration/involution of the left anterior cardinal vein proximal to the brachiocephalic anastomosis.[55,56] The double SVC is further subgrouped based on combined anomalous veins.

EVOLUTION OF EMBRYONIC VEINS OF THE TORSO: POSTCARDINAL, SUBCARDINAL AND SUPRACARDINAL VEINS

The posterior cardinal (postcardinal) veins are the first pair of embryonic veins to arise that drain the caudal body. They soon become integrated and taken over by the newly developing subcardinal and supracardinal veins.[57-59] The shift of the systemic venous return to the right atrium in early embryonic life initiates the radical remodeling of these cardinal (embryonic) venous systems. The postcardinal, subcardinal, and supracardinal veins go through extensive evolution as well as involution for complex remodeling to form the inferior vena cava (IVC), which drains the trunk and lower extremities (*Figure 10*).[60,61]

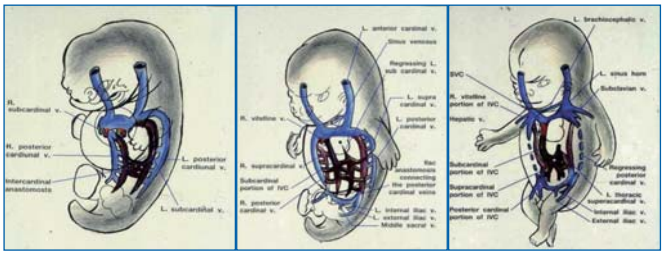


Figure 10 (A-C). *Developmental process for the inferior vena cava involving postcardinal, supracardinal, and subcardinal veins Three pairs of the post-/sub-/supracardinal veins go through extensive evolution and involution to form the inferior vena cava (IVC) as well as hepatic veins, together with the bilateral vitelline and umbilical veins. The role of postcardinal (posterior cardinal) veins, the first pair of embryological veins for venous drainage of the caudal body, is soon taken over by developing pairs of subcardinal and supracardinal veins, to form the IVC as shown.*

The IVC is formed in a complicated series of developmental stages from the following embryonic structures (*Figure 11*):

1. Suprahepatic - the most proximal segment of the IVC develops from the persistent proximal portion of the right vitelline vein, which is the precursor of the common hepatic vein.

2. A new hepatic segment develops from an anastomosis between the right vitelline vein and the right subcardinal vein distal/dorsal to the developing liver to connect this proximal-most (suprahepatic) segment to the distally located right subcardinal vein, while allowing drainage of the hepatic veins/liver.
3. The renal/mesenteric segment of the IVC is represented by a preserved segment of the right subcardinal vein.
4. The new junctional segment of the IVC is formed through an anastomosis between the right subcardinal vein and the more distally located right supracardinal vein.
5. The infrarenal segment is represented by the preserved segment of the right supracardinal vein.
6. The last segment of the IVC is formed as a new segment to connect the right supracardinal and most distal part of the bilateral posterior cardinal veins.

The IVC therefore undergoes a complicated fusion of multiple segments of different embryonic veins: vitelline, supracardinal, subcardinal, and posterior cardinal, anastomoses between these veins, as well as between sub- and supracardinal veins. As a result there is a high likelihood of developmental anomalies occurring during this complicated embryogenic process.

ANOMALOUS DEVELOPMENT OF THE INFERIOR VENA CAVA

The complex embryological development is such that variations and anomalies are common where embryological connections persist, either alone or in conjunction with aplasia or hypoplasia of normally developing channels.[62,63] There are therefore many different congenital anomalies of the IVC involving its length, location, duplication, abnormal connection and draining, and residual remnants of the embryonic tissue such as webs, membranes, etc.

'Double/duplicated' IVC occurs as a result of the bilateral persistence of the supracardinal veins,[64,65] while a 'left-sided' IVC is the result of caudal regression of the right supracardinal vein instead of the left supracardinal vein, which fails to involute/regress and persists (*Figure 11*).[66,67]

The absence of the suprarenal IVC arises from cava/iliac vein agenesis.[68,69] When the right subcardinal vein fails to anastomose with the liver, the IVC drains into the arch of the azygos vein and the hepatic veins drain independently through the diaphragm into the right atrium (*Figure 12*). A posterior/retroaortic left renal vein is another example of defective regression of the anterior portion of the renal ring (1%-2%).[70,71]

Membranous, focal, segmental, and obstructive lesions in the suprahepatic IVC belong to a group of intraluminal defects of the vein wall that cause varying degrees of stenosis and obstruction, and together with venectasia and aneurysm cause venous dilatation.[72,73]

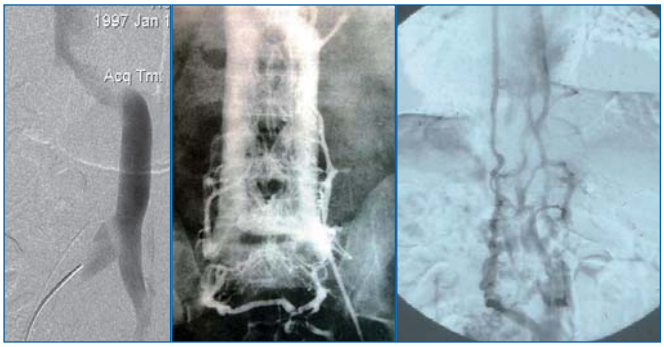


Figure 11 (A-C). *'Left-sided' IVC (11A) is one of the IVC anomalies that occurs as a result of failure of normal evolution and involution of the three pairs of cardinal veins. Other related anomalies are 'Double/ duplicated' IVC (11B) and absence of IVC development (11C).*

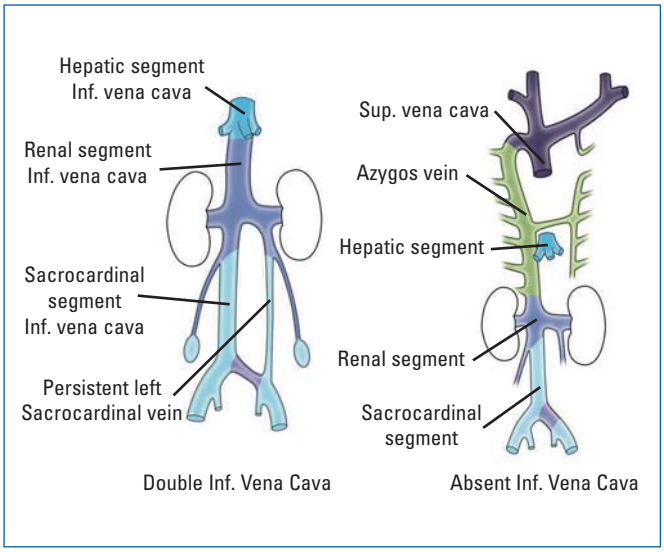


Figure 12. *Failure of subcardinal vein to anastomose with the liver*
When normal anastomosis of the right subcardinal vein with the liver fails due to abnormal development of the hepatic segment of the IVS, the distal part of the IVC drains directly into the arch of the azygos vein and the hepatic veins drain independently through the diaphragm into the right atrium.

EVOLUTION OF THE EMBRYONIC VEIN FOR THE LIMBS: THE LATERAL EMBRYONIC VEIN SYSTEM

Truncal venous development of the lower extremities occurs in three phases to form matured veins in the later stage of embryogenesis (*Figure 13*).[74,75]

First phase: primitive fibular (peroneal) vein

Early venous outflow from the primitive lower limb occurs through a lateral/posterior fibular (peroneal) vein into the posterior cardinal vein; this is the first embryonic vein of the limb.

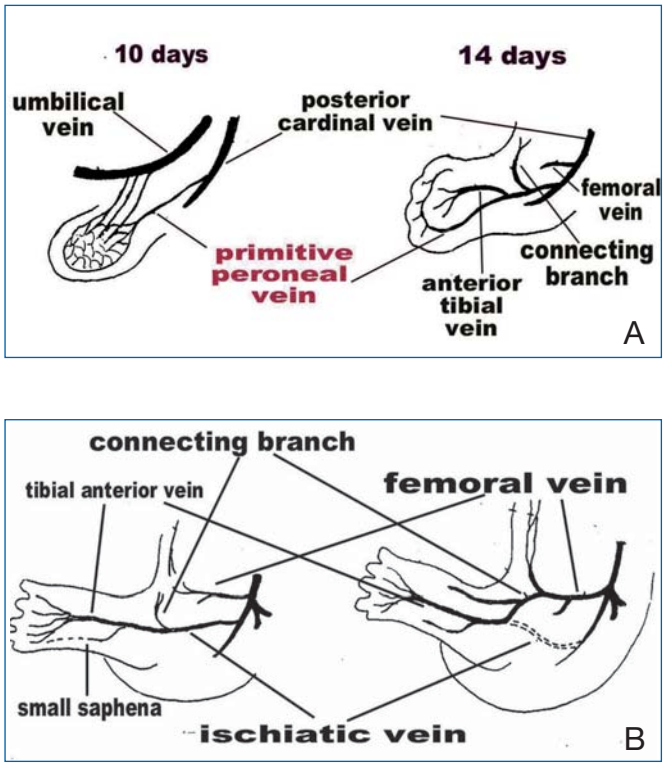


Figure 13 (A and B). *Truncal venous development of the lower extremities occurs in three phases.*
13A (left) depicts the first phase of truncal vein development involving evolution of the primitive fibular (peroneal) vein, which becomes the first embryonic vein of the lower limb. In the second phase (right), the 'primitive fibular vein' develops two branches: the 'anterior tibial vein' and 'connecting branch.' The anterior tibial vein and primitive fibular veins together now constitute the "sciatic vein", which is the second embryonic vein.
13B (left) illustrates the third phase in which the femoral vein is formed by 'a connecting branch' from the middle of the sciatic vein, to establish a new definitive deep venous system. The sciatic vein (right) regresses and the femoral vein is further evoluted, following anastomoses with sciatic veins, and passes down the leg as the 'posterior tibial' vein to complete the evolution of the veins along the lower limb.

Second phase: sciatic vein

The 'primitive fibular vein' develops two branches: the 'anterior tibial vein' and the 'connecting branch'. The anterior (medial) tibial vein becomes the main deep draining vein of the calf. The anterior tibial vein and primitive fibular veins together now constitute the "sciatic vein", which is the second embryonic vein. A part of the primitive fibular vein distal to the anterior tibial vein/branch evolutes to become the 'short/lesser saphenous vein.'

Third phase: femoral vein with persisting sciatic vein

'A connecting branch' growing medially from the middle of the sciatic vein connects with a new proximal medial vessel that will become the femoral vein and the definitive deep venous system, while the sciatic vein regresses. A third embryonic vein of the leg develops to become the femoral vein, which terminates in the posterior cardinal vein, anterior to the sciatic vein. This advances toward the connecting branch of the lateral fibular/sciatic vein. The femoral vein is further evoluted with anastomoses to sciatic veins and passes down the leg as the 'posterior tibial' vein, to finish the evolution of the veins along the lower extremity. This third embryonic vein is also known as the precursor of the long/greater saphenous vein.

With a defect in the second stage, the lateral fibular vein will persist and become the 'marginal vein.' However, if a defect occurs in the passage to the third stage, a 'sciatic vein' will remain as the main draining vein of the limb. As an embryonic vein, a persisting marginal vein is always 'valveless' and can cause a severe reflux resulting in chronic venous hypertension/stasis as well as a high risk of venous thrombosis and subsequent pulmonary embolism among Klippel-Trenaunay syndrome patients.[76,77]

The venous development of the upper extremities is almost identical to that of the lower extremities.[74,75] The ulnar portion of the border/marginal vein persists, forming the subclavian, axillary, and basilic veins at different levels. The subclavian vein eventually drains into the anterior cardinal vein, which subsequently evolutes to the internal jugular vein. The cephalic vein develops secondarily in relationship to the radial border vein, and it later anastomoses with the external jugular vein and finally opens into the axillary vein.

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The "$C0_S$" patient: worldwide results from the Vein Consult Program

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ABSTRACT

The Vein Consult Program is an international, observational, prospective survey that aims to collect global epidemiological data on chronic venous disorder (CVD)-related symptoms and signs based on the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification, assess the impact CVD may have on an individual's daily activities, and identify CVD management practices worldwide.

The survey was organized within the framework of ordinary consultations with general practitioners (GPs) trained in the use of the CEAP classification. Screening for CVD was performed by enrolling all consecutive outpatients over 18 years of age, whatever the reason for their consultation. Patients' data were recorded and patients were classified according to the CEAP, from stage $C0_S$ to C6. GPs were able to refer screened patients with CVD to a venous specialist for further ultrasound investigation.

A total of 6232 GPs participated in the program and 91545 subjects were analysed, of whom 15290 (19.7%) were assigned to category $C0_S$. The percentage of the global survey population eligible for a venous specialist consultation was 22.2%, but $C0_S$ subjects comprised only 4.1% (n=634). In the total survey population only 43% of eligible patients visited a specialist, but surprisingly most $C0_S$ patients eligible for referral did visit a specialist. Among the $C0_S$ patients a duplex scan investigation was performed in 14%. The majority were found to have reflux, which was mostly superficial, but an appreciable percentage (18%) had deep reflux.

$C0_S$ individuals were younger with a lower body mass index compared with the C1 to C6 subjects (48.6 versus 55.5 years; and 25.76 versus 27.24 kg/m^2, respectively), and had fewer CVD risk factors.

Of all screened women, 18.5% were at the $C0_S$ stage versus 22.4% of screened men. Whatever the age group, men were more likely to be assigned to the $C0_S$ class of the CEAP than women, except in the 18-34 age bracket.

Although the quality of life of $C0_S$ subjects was impaired, they were often not considered to have CVD by GPs (25.5% in $C0_S$ versus 71% in the total survey

population), and were poorly treated (13% received lifestyle advice).

It is not known whether $C0_S$ subjects deserve more investigation and treatment as longitudinal studies providing information on the possible progression of disease in such patients are lacking. Nevertheless, given the inflammatory nature of CVD, we can speculate that treatments able to hamper inflammation would at least relieve $C0_S$ symptoms.

INTRODUCTION

The grading of chronic venous disorders (CVD) was simplified and standardized by the introduction of the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification system.[1] The CEAP classification categorizes limbs into seven classes from C0 to C6. Each clinical class is further characterized by a subscript (S) if the categorized limb is symptomatic, or a subscript (A) if the limb is asymptomatic. $C0_S$ patients are defined as those presenting with one or more CVD-related symptoms, but showing no clinical signs of the disease during a physical examination, and generally no abnormalities on a duplex scan. In a revised CEAP classification published in 2004, the $C0_S$ patient profile was introduced.[2] Patients in this category are described as $C0_S$,En,An,Pn as no etiology, anatomical localisation or pathological cause can be found. Symptoms associated with CVD and with the $C0_S$ stage were further defined as "complaints related to venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg-tiredness and/or fatigue. Although not pathognomonic, these may be suggestive of chronic venous disease, particularly if they are exacerbated by heat or dependency in the day's course, and relieved with leg rest and/or elevation."[3]

Despite the acknowledgment that symptoms play an important part in CVD, little is known about their prevalence, particularly in the $C0_S$ patient. The aim of the present analysis was to determine the prevalence and clinical profile of $C0_S$ patients worldwide, how such patients are managed by general practitioners (GPs) in different geographical areas, the rate of spontaneous consultations due to $C0_S$, and finally the impact of symptoms alone on patients' quality of life. This was achieved through the Vein Consult Program (VCP), an international, observational, prospective survey carried out as an initiative of the *Union Internationale de Phlébologie* to raise awareness of CVD among patients, healthcare professionals, and health authorities.

MATERIALS AND METHODS

The VCP was conducted within the framework of ordinary GP consultations over a very short period of time (less than 2 weeks) to gather nationally representative data on the prevalence of CVD-related symptoms, signs, and CEAP classes. The design was a cross-sectional, two-part survey. In the first part of the survey, GPs recruited consecutive patients aged 18 years and over attending the practice for a routine consultation. Practices were distributed throughout the country and included both urban and rural locations. The only patients excluded were those attending for emergency visits. Informed consent was obtained from each participant.

The initial survey was conducted as a face-to-face interview. The 23-item questionnaire consisted of four sections and determined the individuals' demographics; CVD risk factors; any patient-reported symptoms suggestive of CVD such as leg pain, heat sensation, and itching; and any visible signs of CVD. Signs, including telangiectasies, varicose veins, edema, trophic changes, and/or ulcers, were reported by patients themselves, and confirmed by the physician during a physical examination. Patients were then assigned to an appropriate clinical category (C) according to the CEAP classification when any type of venous pathology (classification C1–C6) was seen in at least one leg. The results were recorded by physicians in a case report form. The grade was determined by considering only the highest single reported sign. Physicians were requested to report whether patients complained about their legs spontaneously. All patients with a physician diagnosis of CVD were invited to complete a 14-question form of the ChronIc Venous Insufficiency Questionnaire (CIVIQ-14).[4]

Physicians could refer any individuals with a diagnosis of CVD to a venous specialist, using their normal procedure. The aim of the second part of the survey was to confirm the initial physician diagnosis of CVD. The specialists completed an additional questionnaire to establish the patient's history of CVD and CVD risk factors. They also investigated the CVD status of the

patient using Doppler or duplex scanning and determined whether treatment was required. The specialists were unaware of the physicians' initial diagnosis.

STATISTICAL ANALYSES

Unless otherwise specified, qualitative and quantitative variables were respectively described as number (percentage) and mean ± standard deviation. Percentages were calculated out of the total number of valid answers, excluding missing values. In case of missing values, the number of valid answers was presented. For cross tables, statistical tests were performed to compare means for quantitative variables using the Student t-test or analysis of variance for one factor, and frequencies for qualitative variables using the Chi² test. An α level of 0.001 was used, and a *P*-value equal to or lower than 0.001 indicated a statistically significant difference.

For the venous specialist questionnaire, the prevalence of CVD was estimated as the number of patients with a Doppler abnormality (primary CVD with or without other symptoms) out of the total number of patients who received a Doppler examination.

For CIVIQ-14 (ChronIc Venous Insufficiency Questionnaire with 14 questions), a global index score (GIS) was calculated with values ranging from 0 to 100. In this analysis, we adopted the following scoring convention: GIS 0 equals worst score and GIS 100 equals best score.

RESULTS

The VCP was conducted between October 2009 and July 2011 in five geographical zones: Western Europe (France and Spain; 36 004 subjects), Central and Eastern Europe (Georgia, Hungary, Romania, Russia, Serbia, Slovak Republic, Slovenia, Ukraine; 32 225 subjects), Latin America (Brazil, Colombia, Mexico, Venezuela; 12 686 subjects), the Middle East (Pakistan, United Arab Emirates; 3518 subjects), and the Far East (Indonesia, Singapore, Thailand, Vietnam; 7112 subjects) totalling 20 countries.

Of the people who agreed to be screened, 91 545 had files suitable for analysis. The mean age of global participants was 50.6 ± 16.9 years, 68% were female, and the mean body mass index (BMI) was 26.17 ± 5.07. The profile of the global population of the survey has already been published elsewhere,[5] and the distribution of patients among the CEAP clinical classes was as follows: 16 901 (21.7%) in C1, 13 888 (17.9%) in C2, and 18 863 (24.3%) in C3 to C6 (chronic venous insufficiency patients), totalizing 46 451 patients. The number of subjects complaining solely of symptoms, the so-called $C0_S$ patients, was 15 290 (19.7%), indicating that almost 20% of the survey population had CEAP grade $C0_S$. Only 12 774 (16.4%) individuals had no symptoms or signs of CVD and thus were exempt from leg problems ($C0_a$).

Clinical profile of the $C0_S$ patient and comparison with the surveyed population presenting with clinical signs (C1 to C6 of the CEAP)

As shown in Table I, screened subjects were younger in the $C0_S$ than the C1 to C6 population: 48.3 ± 16.8 years versus 55.5 ± 15.3 years (*P<0.0001*), less often female (65.9% in $C0_S$ versus 77.4%; *P<0.0001*), with a lower BMI, although the latter did not reach statistical significance (25.76 ± 4.85 versus 27.24 ± 5.31; *P=NS*). Overall, the screened population was overweight (26.17 ± 5.07).

Frequency of CVD symptoms (Table I)

Participants described their symptoms in response to the questions set by the physician. The most frequent complaints in the C1-C6 population of the survey were 'heavy legs,' reported by 80%; 'pain in the legs,' reported by 74%; 'sensation of swelling,' reported by 63%, and 'night cramps,' reported by 48%. The average number of symptoms per patient was 3.1 ± 1.0. Symptom distribution and ranking was respected compared with the global population (not shown).[5] In the $C0_S$ population, despite symptoms being reported less frequently, the symptom distribution and ranking were similar to those of symptomatic subjects in the C1 to C6 population of the survey, except that night cramps ranked higher. The mean number of reported symptoms was lower in the $C0_S$ population compared with the C1-C6 population (2.1 versus 3.1; *P*<0.0001). Subjects were also asked what exacerbated their symptoms. The most frequent response, reported by 68.7% of symptomatic C1 to C6 participants, was that their complaints 'increase at the end of the day.' Subjects in C1 to C6 classes also reported that their complaints: 'increase with prolonged standing' (55.3%), 'increase during the night' (45.1%), 'increase in the summer' (39.0%), 'worsen during

	C1 to C6 (A or S) N= 46451	$C0_S$ patients N=15290	*P* value (Chi² test or Student t test)
Age (years)	**55.5 ± 15.3**	**48.6 ± 16.7**	***P* < 0.0001**
Mean BMI (kg/m²)	**27.24 ± 5.31**	**25.76 ± 4.85**	**NS**
Female (%)	**77.4**	**66.5**	***P* < 0.0001**
Spontaneous consultations for CVD (% patients)	**36.6**	**13.5**	***P* < 0.0001**
Prevalence of symptoms (% patients)	**N=46 451**	**N=15 290**	
Pain in the legs	**80.0**	**58.5**	***P* < 0.0001**
Sensation of swelling	**73.9**	**52.4**	***P* < 0.0001**
Night cramps	**62.7**	**29.1**	***P* < 0.0001**
Sensation of 'pins and needles' in legs	**48.2**	**32.6**	***P* < 0.0001**
Sensation of burning	**40.7**	**27.3**	***P* < 0.0001**
Itching	**34.6**	**15.5**	***P* < 0.0001**
	26.7	**15.1**	***P* < 0.0001**
Time when symptoms are most intense (% patients)	**N=46 451**	**N=14 819**	
End of day	**68.7**	**52.5**	***P* < 0.0001**
After prolonged standing	**55.3**	**35.4**	***P* < 0.0001**
During the night	**45.1**	**34.3**	***P* < 0.0001**
During the summer	**39.0**	**21.0**	***P* < 0.0001**
After prolonged sitting	**24.8**	**14.3**	***P* < 0.0001**
During walking	**20.1**	**11.6**	***P* < 0.0001**
After warm baths	**9.4**	**3.6**	***P* < 0.0001**
Mean number of symptoms	**3.1 ± 1.0**	**2.1 ± 1.1**	***P* < 0.0001**
Risk factors			
Positive family history of chronic venous disease (% patients)	**53.4**	**36.1**	***P* < 0.0001**
Positive personal history of thrombosis (% patients)	**14.8**	**3.7**	***P* < 0.0001**
Mean number of hours spent standing	**6.4 ± 3.1**	**6.5 ± 3.2**	**NS**
Mean number of hours spent sitting	**5.6 ± 2.8**	**5.6 ± 2.8**	**NS**
Absence of regular exercise (% patients)	**71.9**	**66.8**	***P* < 0.0001**
Present or past smoker (% patients)	**38.0**	**43.2**	***P* < 0.0001**
Women only	**33 520**	**8851**	
Mean number of births	**1.0 ± 0.7**	**0.8 ± 0.7**	**NS**
Women aged 18–49 years only	**12946**	**5440**	
Use of birth control pill at time of visit (% patients)	**28.9**	**31.4**	***P* < 0.0001**
Number of pregnant women (%)	**5.4**	**10.3**	***P* < 0.0001**
Duration of pregnancy at time of visit (months)	**4.8 ± 2.3**	**4.6 ± 2.3**	**NS**

Table I. *Comparison of the clinical profile of the C0s subjects of the VCP survey with that of C1 to C6 patients, either asymptomatic (A) or symptomatic (S).*

prolonged sitting' (24.8%), and 'worsen during walking' (20.1%).

Subjects in the $C0_S$ survey population reported significantly less often exacerbation of symptoms than the C1 to C6 population (*Table I*), but the ranking was identical, except for 'during night' and 'after prolonged standing,' which were reported by equal numbers of $C0_S$ subjects.

Risk factors

No significant difference in the mean BMI was found between the $C0_S$ and the C1 to C6 sub-groups of screened participants.

A family history of CVD was more often reported in C1 to C6 participants than in $C0_S$ subjects (53.4% versus 35.3%, respectively, $P<0.0001$). Similarly, C1 to C6 patients presented more frequently with a personal history of deep vein thrombosis compared with $C0_S$ subjects (15% versus 3.7% in $C0_S$, $P<0.0001$), and were more likely to lack regular exercise (72% versus 67% in $C0_S$; $P<0.0001$). On the other hand, $C0_S$ subjects were more frequently current or past smokers (43% in $C0_S$ versus 38% in C1-C6, $P<0.0001$). The average time spent standing and sitting was similar in both populations. The number of women on the birth control pill and the number of pregnant women were significantly higher in the $C0_S$ group.

$C0_S$ profile of VCP subjects by age and gender (*Table II*)

Men were more likely to be disease free ($C0_a$) than women (27.8% of VCP men versus 11.6% of VCP women), whatever their age ($P< 0.0001$). Men were also more likely to be assigned to the $C0_S$ class compared with women (22.4% of VCP men versus 18.5% of VCP women). This was true for all age groups with the exception of the ≤ 18 to 34-year age bracket. In this group, a significantly greater percentage of women than men were assigned to the $C0_S$ class, as most of the latter had no venous problems (54.4% of men aged ≤ 18 to 34 years were in $C0_a$ versus 28.4% of women of the same age). In terms of CVD signs, women were more often assigned to CEAP classes C1 to C6 than men whatever their age (69.9% women versus 49.8% men; $P< 0.0001$).

The $C0_S$ profile of VCP subjects by age, gender, and geographical area (*Table III*)

As reported above, men less than 34 years of age were less frequently encountered in $C0_S$ than women of the same age. This was true for Western Europe and Latin America only. After the age of 34 years, men assigned to the $C0_S$ class were more numerous than women whatever the geographical area, except in Western Europe and the Far East where the percentage of women in $C0_S$ was slightly higher than that of men in the 35-50-year age bracket.

The Middle East had the highest percentage of women and men in $C0_S$ whatever the age. In this geographical region, the ratio of women to men was almost equal, but men were more likely to consult than women after the age of 50 years. In general, however, women were far more likely to consult than men whatever the geographical region or age bracket.

GPs' behavior toward CVD patients, treatments prescribed and referral of patients to specialists (*Table IV*)

Spontaneous consultations for venous problems were less frequent among $C0_S$ subjects compared with the C1-

% subjects in clinical category of the CEAP classification:	All subjects N=77 716	*Women Total N=54 343*	*Men Total N=23 162*	Women ≥18-34 y N=10 160	Men ≥18-34 y N=3970	Women 35-50 y N=15 371	Men 35-50 y N=6200	Women 51-64 y N=15 518	Men 51-64 y N=6743	Women ≥65 y N=12 976	Men ≥65 y N=6135
$C0_a$	16.4	*11.6*	*27.8+++*	28.4	**54.4+++**	11.2	**31.9+++**	6.5	**20.0+++**	5.6	**16.2+++**
$C0_S$	**19.7**	***18.5***	***22.4+++***	**27.8**	**23.7+++**	**19.9**	**24.3+++**	**15.3**	**22.8+++**	**13.4**	**19.3+++**
C1 to C6	63.9	*69.9*	*49.8+++*	43.9	**21.9+++**	68.9	**43.9+++**	78.1	**56.2+++**	81.0	**64.6+++**

Table II. *C0s profile of screened subjects by age and gender.*

P difference between men and women: +++, P<0.0001

	C0s in the global population	Western Europe	Central and Eastern Europe	Latin America	Middle East	Far East
Mean age (years)	**50.6 + 16.9**	52.5 + 17.2	53.3 + 16.0	43.5 + 15.9	38.9 + 13.3	47.2 + 16.4
% women	**68.4**	66.1	70.8	73.2	51.3	69.2
% $C0_S$	**19.7**	18.1	19.2	19.2	43.4	19.6
% C1 to C6	**63.9**	59.8	67.9	68.6	41.8	67.4
Women-Global	**5433 (100%)**	20 498	**21 351 (100%)**	**7675 (100%)**	**1537 (100%)**	**3282 (100%)**
$C0_S$ (%)	**18.5**	18.1	17.6	17.7	40.5	18.8
Men-Global	**23 162 (100%)**	**9405 (100%)**	**8356 (100%)**	**2672 (100%)**	**1247 (100%)**	1482
$C0_S$ (%)	**22.4**	18.1	23.4	23.7	47.3	21.3
Women ≥18-34	**10 160 (100%)**	3325 (100%)	2929 (100%)	2437 (100%)	623 (100%)	846 (100%)
y $C0_S$ (%)	**27.8**	24.6	28.9	27.9	47.4	21.4
Men ≥18-34 y	**3970 (100%)**	1393 (100%)	1074 (100%)	880 (100%)	401 (100%)	222 (100%)
$C0_S$ (%)	**23.7**	11.1	30.7	20	56.1	25.2
Women 35-50 y	**15 371 (100%)**	5657 (100%)	5447 (100%)	2553 (100%)	651 (100%)	1063 (100%)
$C0_S$ (%)	**19.9**	20.5	20.0	14.8	37.6	17.7
Men 35-50 y	**6200 (100%)**	2373 (100%)	2032 (100%)	893 (100%)	519 (100%)	383 (100%)
$C0_S$ (%)	**24.3**	18.6	27.6	24.2	43.5	17
Women 51-64 y	**15 518 (100%)**	5486 (100%)	7216 (100%)	1753 (100%)	202 (100%)	901 (100%)
$C0_S$ (%)	**15.3**	17.0	14.1	11.7	30.7	18.2
Men 51-64 y	**6743 (100%)**	2658 (100%)	2862 (100%)	525 (100%)	247 (100%)	451 (100%)
$C0_S$ (%)	**22.8**	21.4	20.9	28.8	41.7	25.3
Women >65 y	**12 976 (100%)**	5978	5561 (100%)	940 (100%)	54 (100%)	443 (100%)
$C0_S$ (%)	**13.4**	13.2	13.6	9.8	35.2	17.6
Men >65 y	**6135 (100%)**	2955	2321	369 (100.0%)	73 (100%)	417 (100%)
$C0_S$ (%)	**19.3**	17.9	19.5	24.4	41.1	18.9

Table III. *C0s profile of the screened subjects by age, gender, and geographical area.*

	Global population of survey	$C0_S$ N=15 290	C2 N=13 888	C6 N=535
% of spontaneous consultations for chronic venous disease (N=64 942)	22.9	**13.5**	36.5	73.8
Considered as CVD patients by GPs (N=64 942)	71	**25.5**	89.2	93.8
Type of treatment % patients with (N= 91 545):				
Lifestyle advice	51.6	**13.1**	90.2	85.7
Venoactive drug	39.7	**7.9**	88.8	64.3
Compression therapy	24.4	**1.4**	44.9	35.7
Anticoagulant therapy	7.7	**0.2**	6.5	35.7
Sclerotherapy/endovenous ablation/open surgery	5.9	**0.0**	4.2	21.4

Table IV. *Treatment of $C0_S$ subjects in the Vein Consult Program. Comparison with the global population of the survey and with C2 and C6 patients.*

C6 population (13.5% versus 36.6%, respectively, *P*=0.0001, *Table I*), and with the global population of the survey (13.5% versus 22.9%, respectively, *Table IV*). The frequency of spontaneous consultation increased with CEAP class (36.5% of C2 and 73.8% of C6 subjects consulted spontaneously for venous leg problems).

GPs considered 71% of the total survey population to have CVD. Of the 15 290 patients in $C0_S$, only 3902 (25.5%), ie, one-quarter were considered to have CVD by GPs, which is far less than in the global survey population. In the C2 class, 89.2% were considered to have CVD by GPs, and in C6, 93.8% were considered to have CVD.

The percentage of $C0_S$ patients considered to have CVD was highest in Western Europe (almost 38%) and the Far East (56%). In contrast, C2 patients were less likely to be considered as having CVD in these two regions. Patients with ulcers were under-recognized in the Far East (69.8% were considered to have CVD by GPs, versus 93.8% for the global survey population).

$C0_S$ patients were poorly treated in general: only 13% received lifestyle advice and 8% were prescribed a venoactive drug. In contrast, lifestyle advice and drugs were administered to the majority of patients in the global population as well as those in C2 and C6. It is noteworthy that venoactive drugs were prescribed twice as frequently as compression therapy for C2 and C6 stages.

Quality of life score in $C0_S$ patients and relation to CEAP profile (*Table V*)

The GIS for the total survey population was 73.07. The GIS of $C0_S$ patients was lower (82.73) than that of healthy subjects (90.92), indicating that their quality of life was slightly worse. Quality of life decreased with increasing CEAP class (73.62 in C2 and 51.96 in C6), and drastically worsened with the mean number of presenting symptoms.

Characteristics of reflux according to CEAP profile – Population referred to specialists (*Table VI*)

GPs referred 22.2% of the global population to venous specialists. This included only 4.1% of $C0_S$ patients, 36.7% of C2 patients and 60.2% of C6 patients. It is interesting to note that a relatively low proportion of C2 and C6 patients eligible for referral actually visited a venous specialist (37% and 54%, respectively) compared with 89% of $C0_S$ patients.

Among the 565 $C0_S$ patients who visited a specialist, only 78 right legs and 69 left legs were investigated with either Doppler (45.4%) or duplex scan (54.6%). Most $C0_S$ legs had superficial reflux (72% and 67% in the right and left legs, respectively), 11% had perforator reflux, but an appreciable percentage had deep reflux

CEAP classification	N	Global Index Score
Survey population	34557	73.07 ± 20.18
Healthy subjects ($C0_a$)	2074	90.92 ± 14.32
$C0_S$	**2170**	**82.73 ± 16.43**
C2	7823	73.62 ± 18.37
C6	380	51.96 ± 26.39
P-value		<0.0001
Number of venous symptoms		
0	2074	90.92 ± 14.32
1	2929	85.74 ± 15.39
2	4807	80.18 ± 16.20
3	6073	75.24 ± 16.40
>3	14222	63.64 ± 19.97
P-value		<0.0001

Table V. *Quality of life score according to the CEAP profile and the number of venous symptoms.*

CEAP	Patients: Screened by GPs		Eligible for specialist visit		Having consulted a specialist		Having been investigated by specialist				
									Reflux in the most affected leg:		
									Superficial %	Deep %	Perforator %
	N	%	N	%	N	%	N	%			
Total	78 717	100	17 463	22.2	7 923	43	1 939	25	68	18	14
$C0_S$	**15 290**	**100**	**634**	**4.1**	**565**	**89**	**78**	**14**	**72**	**18**	**10**
C2	13 888	100	5 097	36.7	1 875	37	515	27	83	5	12
C6	535	100	322	60.2	174	54	91	52	44	44	12

Table VI. *Patient referral to venous specialists and characteristics of reflux in subjects referred to venous specialists. Comparison between $C0_S$, C2 and C6 patients.*

(18% and 20% in the right and left legs, respectively). This suggests that the $C0_S$ patients referred to a specialist were suspected of having a thrombotic problem that was detected by clinical examination at the GP level. It is noteworthy that 27% of C2 and 52% of C6 patients underwent investigation.

DISCUSSION

The VCP is one of the few surveys to have specifically screened for $C0_S$ subjects, which the CEAP identifies as patients with symptoms, but without visible clinical signs of CVD. However, despite the fact that the $C0_S$ profile is globally recognized, prevalence data on this category remain scarce. Although some studies have reported CVD symptoms (*Table VII*), prevalence data for the $C0_S$ class are usually missing. Results of previous surveys have allowed indirect calculations of $C0_S$ prevalence to be made: 3.8% in the VEINES study,[6] 3.9% in the Brazilian survey,[7] 13%-23 % in the Polish study,[8] and 15% in the San Diego Vein Study.[9] $C0_S$ prevalence was not reported in the Bonn Vein study.[10] In the present survey, almost 20% of individuals could be classified as $C0_S$,[5] which represents a significant proportion of the population. Interestingly, these $C0_S$ patients were equally distributed throughout the geographical zones, with the exception of the Middle East where the percentage of $C0_S$ patients was far higher (47.3% of men and 40.5 % of women). The young age of the screened patients together with the warm climate in this part of the world might be an explanation for such high numbers. The profile of the $C0_S$ patient could be distinguished from that of the global VCP population in that women were proportionally less represented, subjects were younger, with a lower BMI and fewer CVD risk factors. Symptoms in $C0_S$ subjects were evenly distributed compared with the global population, but had the same ranking; heaviness, pain and sensation of swelling being the most commonly encountered symptoms. The frequency of each symptom was lower in $C0_S$ subjects compared with individuals in the global survey population due to their younger age; the VCP has shown that the presence of CVD symptoms increases with age.[5] This is in line with former surveys.[10]

The frequency of a $C0_S$ classification was higher in men than women, with the exception of men aged 18-34 years who in general did not even have CVD symptoms. This would suggest that symptoms appear later in men than women. Fiebig reported a different timing of disease in the two sexes and concluded that women experienced an earlier disease onset, with the first symptoms of CVD observed at a mean of 30.8 years of age, compared with 36.8 years in men.[11] In the VCP survey, the Middle East was characterized by a particularly high level of $C0_S$ in both men and women compared with other regions, and by a higher percentage of men consulting for CVD. It is not known if this is due to cultural or social differences.

Study	1st Author Journal	Population (number)	Aim	Symptoms (Sy)	Signs (Si)	Investigation	QoL	Conclusions
VEINES	**Kahn** *J Vasc Surg* 2004.[6]	Patients with CVD (1531)	To evaluate relationships between CEAP class and QOL	YES 10 symptoms listed	**Basic CEAP**	**NO**	**SF-36 VEINES-QOL VEINES-SYM**	$C0_S$=3.8%, C1=13.3%, C2=24.1%, C3=12.8% C4=36.4%, C5=7.3%, C6=2.3%. Not to be considered as a prevalence rate. In univariate and multivariate analyses physical SF-36 score, VEINES-QOL and VEINES-SYM scores decreased significantly with increasing CEAP class
Brazil survey	**Scuderi** *Int Angiol* 2002.[7]	A randomized sample of a population consulting for any kind of trouble at the University hospital or health centers (2014)	To estimate prevalence of CVD To investigate complaints and to identify CVD risk factors	YES Any kind of venous related Sy	**Advanced CEAP**	**NO**	**NO**	**F age:14-22yr** $C0_a$=46.4% C0,1,2,3 s=12.29% Including $C0_S$ 3.9% **F age: 23-48 yr** (Average gestation 28.5%) $C0_a$=10.4% C1,2,3,4 s=37.53% C1,2,3,4,5 a=51.8% **F age: >48 yr** (Average gestation 61.8%) $C0_a$=4.7% C1,2,3,4,5,6 s= 62.8% C1,2,3,4, a=32.4% **M: all ages** $C0_a$= 65.5% C1,2,3,4,5,6 s=13.9%
Polish Study	**Jawien** *Phlebology* 2003.[8]	Polish adults rural (21%) and urban area (40,095) Cross-sectional population study	To study prevalence of CVD including Sy, Si and identify risks factors	YES 4 symptoms listed: pain, heaviness, swelling, and night cramps,	**Basic CEAP C0-C6**	**NO**	**NO**	$C0_a$, s 51.1%. In C0, Sy was present from 13.3% to 23.3% depending on the Sy considered. In C1-C6, Sy were present in 56.1–73.7% depending on the Sy and the highest C class considered. In VV, Sy were present in 78.9–61.1% depending on Sy considered.
San Diego	**Langer** *Arch Intern Med* 2005.[9]	University employees (2211) Cross-sectional study	To define relations between Sy, Si and DS anomaly	YES 7 symptoms listed	**Modified CEAP** Normal C0 C1 C2 C4-6	DS: 2 venous systems investigated: S and D 3 categories normal, S and D	**NO**	Sy more frequent **in F**. Sy more frequent if Si present or DS anomaly, but 18% C0s An, Pn. Sy more predictive of Si or DS anomaly = Swelling, pain, heaviness, itching, tired and cramping
Bonn Vein Study	**Rabe** *Phlebologie* 2003.[10]	Bonn and rural respondents (3072) Cross-sectional population study	To estimate prevalence of CVD To investigate complaints and type of therapy To identify CVD risk factors	YES	**Basic CEAP**	DS	**NO**	C0=9.6%, C1=59%, C2=14.3%, C3=13.4% C4=2.9%, C5=0.6%, C6=0.1%. To be considered a prevalence rate.

Table VII. *Review of the literature on epidemiological studies that have used the CEAP classification and have assessed symptoms.*

Abbreviations: CIVIQ = chronic venous insufficiency questionnaire; CVD = chronic venous disorder; CVI = chronic venous insufficiency (defined as chronic changes in the skin and subcutaneous tissues [C3 to C6]); C2 trunk = VV of the GSV and SSV trunks or their first or second generation branches; D = deep venous system; DS = duplex scanning; F = female gender; LL = left lower limb; M = male gender; N = number; QOL = quality of life; RL = right lower limb; RV = reticular vein; S = superficial venous system; S-F 36 = generic short-form health survey questionnaire; Si = signs; Sy = symptoms; T = telangiectasia; VV = varicose vein; VEINES-QOL = venous-disease specific questionnaire; VEINES-SYM = venous symptom severity questionnaire.

The present analysis showed a relationship between impaired quality of life and increasing CEAP class, as well as with increasing number of symptoms, a finding that has also been demonstrated in other studies.[6,12] Although they may be experiencing a poorer quality of life, $C0_S$ patients were hesitant to consult GPs, and even when they did so they received little treatment. Furthermore, only 13% received any lifestyle advice. It is important to note the lower-than-expected prescription of compression therapy in this survey, even at severe CVD stages, highlighting the need for patient and GP education.

The results of this survey suggest that $C0_S$ subjects are very frequently encountered in general practice, particularly in Western Europe and the Far East, the two regions where individuals were also more likely to be considered as to be suffering from CVD. However, only 4% of $C0_S$ subjects were referred to a specialist (referral was almost nonexistent in the Far East, and it is noteworthy that an appreciable proportion of $C0_S$ individuals who did consult a venous specialist were suffering with secondary venous disease.

The present analysis provides a snapshot of $C0_S$ subjects in ordinary consultation. A limitation is that this was not a longitudinal study and therefore the future of these $C0_S$ individuals and their CVD progression is not known. It remains to be determined whether such individuals deserve more in-depth investigation and care because of the possible progression of their symptoms to more severe stages of CVD. In the San Diego Vein Study, up to 15.5% subjects complaining of leg ache had no functional anomaly, and up to 14.2% of subjects with pain had no visible signs of CVD.[9] As a result, leg pain was considered a non-specific CVD symptom by the authors of this study, in which case the $C0_S$ subject would be denied a diagnosis of CVD.

Our understanding of the mechanisms at work in CVD-related pain is gaining momentum. A considerable body of evidence now shows that inflammatory reactions via the release of various mediators are involved in disease progression and might explain the origins of venous pain. Nerve structures known as C-nociceptors that are easily activated by inflammatory mediators have been found in the media of varicose veins[13] and are also located in perivenous connective tissue.[14] Such nociceptors are thought to be activated in the microcirculation, where contact between nerve endings, the arteriole, the vein, and the capillary is probably much closer than at a macrovascular level. Microcirculatory parameters have been studied and vary with increasing severity of CVD.[15,16] We are presently just able to assess macrocirculatory parameters, but these are not usually abnormal at the $C0_S$ stage, and there are currently no instrument sensitive enough at our disposal to assess the microcirculation at stages as early as $C0_S$. Without a means of assessment, we can only speculate that venous pain at the $C0_S$ stage might be the result of a disturbed microcirculation, but this remains to be documented.

Early work by Andreozzi brought attention to $C0_S$ subjects, who he referred to as hypotonic phlebopathic patients because of normal Duplex investigations, but disturbed parameters with photo- and strain-gauge plethysmography, leading him to suggest a hyperdistensibilty of the venous wall.[17] More recently, a study of casts from amputated legs has revealed that valvular incompetence can exist in the microvalves out to the third generation 'boundary'of tributaries from the great saphenous vein (GSV) from stages C0 and C1, even though no truncular reflux could be observed in the GSV.[18] Such findings lend support to a role for early degenerative processes in the microvasculature, long before the macrocirculation is targeted.

CONCLUSION

Little is known about the future of subjects with $C0_S$, a group that has until recently been poorly studied, but an inflammatory hypothesis to explain the nature of the reported symptoms is plausible. Given the high prevalence of such subjects in the population, whatever the geographical region, it would be beneficial to know which $C0_S$ patients deserve investigation and treatment. In the meantime, treatment that could delay and even hamper the inflammatory progression of the disease might prove useful. It has been shown that the symptoms of $C0_S$ individuals are greatly improved with conservative treatments, in particular, by venoactive drugs such as micronized purified flavonoid fraction (Daflon 500 mg*).[19]

**Also registered as: Alvenor®, Ardium®, Arvenum® 500, Capiven®, Detralex®, Elatec®, Flebotropin®, Variton®, Venitol®.*

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Sclerotherapy in the patient with diabetes: indications and results

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ABSTRACT

Goal: To assess the effects of combined compression and sclerotherapy treatment on varicose veins in patients with diabetes.

Materials and methods: We evaluated 60 lower limbs with varicose veins from people with diabetes who underwent one session of sclerotherapy according to Sigg's method. Varices were associated with reflux along the length of the great saphenous vein in 47 limbs, in the small saphenous vein in 8 limbs, and with nonsaphenous reflux in 5 limbs. Efficacy was determined by clinical and duplex scan examinations performed at 6, 8, and 12 months, and at 2, and 4 years.

Results: A total of 7 clinical failures (12%) and 14 duplex scan failures (23%) were observed. No major complications such as arterial injection, severe allergic reaction or deep vein thrombosis were reported.

Conclusions: Successful sclerotherapy for varicose veins can be performed independently of a history of diabetes, with a success rate similar to that observed in patients without diabetes, provided the patient has good glycemic control (HbA_{1c} <6.5%).

INTRODUCTION

Varicose veins of the legs are a common condition caused by venous insufficiency as a result of valve reflux.[1] Most varices are located in the great saphenous vein (GSV) and are associated with symptoms such as leg heaviness, fatigue, or throbbing pain.[2] People with diabetes may be particularly prone to varicose veins as they generally present with a number of common risk factors for chronic venous disease (CVD) including poor circulation, overweight, hypertension as well as a propensity for endothelial dysfunction. Indeed, a number of studies in the literature have shown that CVD and diabetes mellitus frequently coexist.[3-6] Furthermore, diabetes is associated with more severe signs in 50% of patients.[7] The medical rationale for treating varicose veins in patients with diabetes is the same as those

Keywords:
chronic venous disease, compression, diabetes, duplex scan, sclerotherapy, varicose veins.

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without diabetes: to reduce symptoms, improve quality of life, and prevent disease progression. Early intervention reduces the risk of ongoing vein- and skin-related damage secondary to chronic venous hypertension. These changes progressively worsen with time, and earlier treatment is preferable to a wait-and-see approach.

Traditionally, treatment of varicose veins involved an invasive procedure of groin to ankle stripping and ligation of the GSV. More recently, ultrasound-guided foam sclerotherapy has gained acceptance as an effective and safe alternative to surgery to treat varicose veins.[1] Sclerotherapy is defined as the targeted elimination of small vessels, varicose veins, and vascular anomalies by the injection of a sclerosant (chemical irritant) into the veins with a small needle.[8] The sclerosant causes inflammation, thrombosis, and finally fibrosis of the vein, which is transformed into a fibrous cord that cannot be recanalized. Sclerotherapy is a simple, cost-effective, efficacious, and esthetically acceptable modality for both therapeutic and esthetic purposes.

There are few studies in the literature discussing sclerotherapy for varicose veins in patients with diabetes and the few that do exist are contradictory with some stating that diabetes is a contraindication for sclerotherapy[8] and others stating that it is not.[9] Most contraindications and/or special precautions relating to sclerotherapy relate to factors that either directly increase the risk of deep vein thrombosis or indirectly interfere with posttreatment compression and mobilisation.[9]

Sclerotherapy should only be performed in people with chronic diseases if their condition is well controlled, and diabetes is no exception.[10] The standard measure of long-term glycemic control is glycosylated hemoglobin (HbA_{1C}). In a person without diabetes, normal HbA_{1C} levels fluctuate between 4% and 6%. A person with diabetes is considered to have good glycemic control if their HbA_{1C} level is below about 6.5%, although this may not always be achievable particularly in older patients or in those in whom hypoglycemia must be avoided.[11] When levels rise to above 7% the individual is not considered to have good control. However, in the absence of a true contraindication,[8] several precautions should be observed before performing sclerotherapy in an individual with diabetes.

Before the procedure

Before the procedure, a complete clinical examination and duplex scan investigation should be performed to detect any associated arterial disease. To avoid prolonging inflammation in the vein wall, any existing edema and soft tissue changes associated with CVD should first be reduced by the application of a short-stretch bandage.

Choice of sclerosing agent

Concerning the choice of sclerosing agent, foam is not contraindicated, but agents containing a hyperconcentration of glucose should be avoided. Foam has been shown to be superior to liquid sclerotherapy in the GSV in terms of clinical and hemodynamic outcomes, with several advantages over traditional liquid sclerotherapy.[12] When delivered as foam, detergent sclerosant is not diluted by blood, instead displacing it to allow direct contact of the sclerosant with the endothelium.[13] This allows for the use of a smaller dose of sclerosant, which is important as the vein walls of patients with diabetes are very sensitive to these agents. Second, should extravasation occur, foam is much better tolerated than extravasated liquid. Third, foam can be readily visualized by ultrasound, which increases the accuracy with which individual varicose veins can be treated.

Puncture procedure

Due to the impaired immune response in individuals with diabetes, they are particularly susceptible to infection. Care must therefore be taken to ensure that the materials and puncture site are sterile. When injecting the sclerosing agent, the bevel of the needle should be placed into the lumen of the vein as patients with diabetic neuropathy have reduced sensitivity to pain and if the needle is not properly positioned extravasation of sclerosant might go unnoticed.

Compression therapy

Prolonged compression therapy starting immediately after the procedure and lasting at least 30 days is imperative in all patients to achieve optimal results with sclerotherapy, but particularly in patients with diabetes because of their endothelial pathology.[14] Compression minimizes the blood reentering the injected area and thrombus formation, increases fibrinolytic activity and therefore reduces scar tissue formation, decreases the incidence of postsclerotherapy hyperpigmentation, and improves venous blood flow.

To be effective, compression hosiery must exert a high pressure at calf level during calf contraction and a low pressure at rest. Compression hosiery should be tightly applied on the lower limb starting from the foot. Short-stretch bandages (35%) in nylon and/or cotton are more effective than stockings or long-stretch bandages, either rubber or cotton band.

Few studies in the literature have documented the use of sclerotherapy in people with diabetes. The aim of our study was to evaluate the efficacy and safety of combined sclerotherapy and compression for varicose vein ablation in patients with well-controlled diabetes.

MATERIAL AND METHODS

Between 1982 and 2011 we performed a total of 47 000 sclerotherapy injections, of which 1400 (3%) were performed in 60 lower limbs from patients with diabetes presenting with class C2 to C6 CVD according to the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification.[15] CVD signs were associated with a reflux along the length of the GSV in 47 cases, in the small saphenous vein (SSV) in 8 cases, and with non-saphenous reflux in 5 cases.

Prior to the procedure

In 18 legs, edema associated with CVD was reduced by the use of a short-stretch bandage prior to the procedure. In 11 legs, symptomatic peripheral arterial disease (claudication) was identified, which was treated by surgery or an endovascular procedure.

Procedure technique

All legs were treated by puncture of the saphenous trunk at the level of the thigh with a large needle (18 G, 1.2 mm) according to Sigg's method (patient standing, open-needle technique). By allowing the blood to run it is immediately possible to determine if the needle is in an artery by the color of the blood and whether the flow is synchronous with the pulse (*Figure 1*). In this manner, paravenous injections can be avoided. With the patient in the Trendelenburg position (*Figure 2*), the saphenous trunk was then injected with a 1-2% iodate solution or polidocanol 2-3% (as a foam 0.5%). It is important to use a glass syringe that slides well and to determine its position immediately, especially when using a large needle. Resistance to injection is greater if the needle is outside a vein and the liquid spreading in tissues. Strong

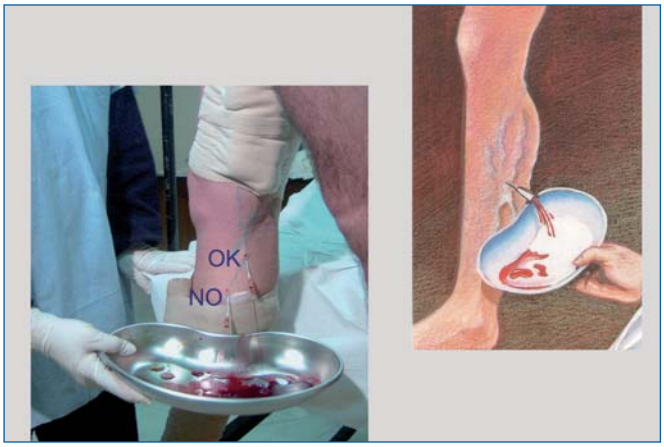

Figure 1. *Puncture of the vein with Sigg's technique « open needle »: patient standing, needle 18 G (short catheter) not connected to a syringe.*

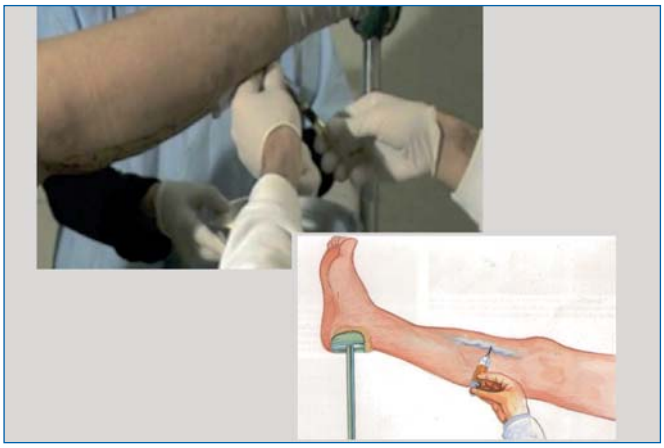

Figure 2. *: Injection of sclerosing agent according to Sigg's technique with the patient in the Trendelenburg position.*

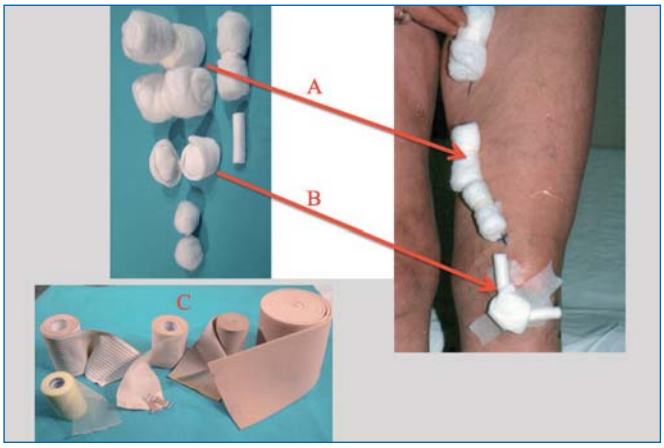

Figure 3. *Application of spot and concentric therapeutic compression after the sclerotherapy procedure: spot compression comprises balls or rolls of cotton wool applied over the treated veins; concentric compression uses a short-elastic bandage from foot to groin.*

compression is then applied (*Figure 3*).[10] This comprises immediate spot compression (to reduce the size of the vein sclerosis) with gauze pads applied over the treated varices for 2 days (*Figure 3A*) and 4-cm thick cotton wool balls with a hard center over the GSV injection sites for 7 days (*Figure 3B*). In addition, concentric compression with a removable short-stretch bandage (35%, removed at night and replaced in the morning) is applied for 30 days. Compression needs to be modified if there is evidence of significant peripheral arterial insufficiency and low-pressure compression stockings (class I) should be worn for 30 days by patients with chronic venous insufficiency or peripheral pulses.

Hemodynamic compression of the sapheno-femoral junction or sapheno-popliteal junction is applied for 3 days using Safeguard™ (Datascope) (*Figure 4A*). This device consists of an adhesive dressing and an inflatable balloon (achieved with the aid of a syringe) and is commonly used to achieve hemostasis after invasive vascular procedures. The balloon, which is transparent on Doppler ultrasound is inflated with gel (*Figure 4B*) until reflux at the saphenous junction is interrupted. The compressive effects of the balloon on the saphenous terminals can be verified echographically (*Figure 4C and 4D*). This method is used for the new sclerotherapy procedure (HCS method) that I proposed in 2010 and perform with selective suppression along the length of the GSV or SSV.[16]

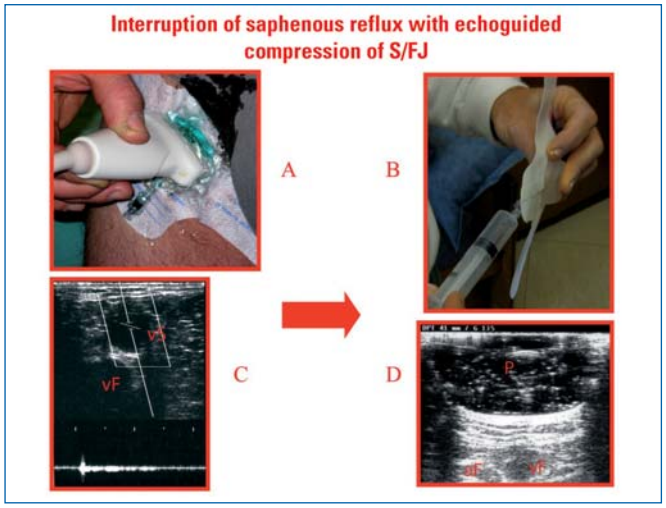

Figure 4. *Hemodynamic compression according to the HCS method. (A) The Safeguard™ device comprises an inflatable balloon and adhesive dressing. (B) Application of the Safeguard device at the terminal end of the GSV. (C) Echographic view of the terminal end of the GSV (vS) and the femoral vein (vF) before and (D) after inflation of the balloon (P) to interrupt saphenous reflux with the patient in a standing position.*

Study end points

Efficacy was determined by both clinical and echographic criteria at 6, 8, and 12 months and after 2, and 4 years of follow-up. Using clinical criteria, treatment failures were characterized by the presence of varices in quantities exceeding 50% of the original varices, and by the presence of symptoms of chronic venous insufficiency.

Echographic failures (using a 7.5-MHz probe) were characterized by the absence of the following signs: inability to compress the vein; morphological changes to the vessel wall such as endothelial thickening, disorganized collagen bundles and fragmentation of elastic fibers; luminal changes such as hyperechogenicity of the lumen and reduction of the vessel to a fibrous cord that cannot be recanalized.[17,18] On a hemodynamic level, the absence of flux, reflux or the persistence of reflux in the saphenous trunks, was determined if the reduction in size of the sapheno-femoral junction was greater than 30% of their initial diameter.[19]

RESULTS

Globally, after a 4-year follow-up, we documented seven clinical failures (12%) and 14 failures (23%) by Doppler ultrasound. Over time, the following recurrences occurred: 3 echographic failures at 6 months, 6 at 12 months, 4 at 2 years and 1 at 4 years; 3 clinical recurrences occurred at 12 months, and 4 at 2 years. These results are in line with those we have observed in nondiabetic patients in clinical practice.

We observed no major complications (necrosis, allergy or deep vein thrombosis). There were six cases of ascending vein wall inflammation (phlebitis) caused by a poorly applied bandage, and one case of a patient fainting (vasovagal reaction).

DISCUSSION

Few studies have examined changes to the vein wall in patients with diabetes. We demonstrate that sclerotherapy is an effective and well-tolerated procedure for varicose veins in patients with well-controlled diabetes mellitus. The proportion of clinical and Duplex scan treatment failures was similar to that reported in another study from our group, which documented clinical and echographic treatment failure

Sclero sensitization	Hepatitis C, hepatitis B Estrogen-plus-progesterone pills Sclerosing agents
Sclero sensitivity	Endocrine diseases and diabetes Collagen and rhumatological disorders Metabolic syndrome Pregnancy and menopause Obesity and low body weight (anorexia) Thrombophilia
Sclero resistance	Embryologic factors Constitutional factors Genetic factors

Table I. *Sclerotherapy in patients with arteriopathy – a decisional tree.*

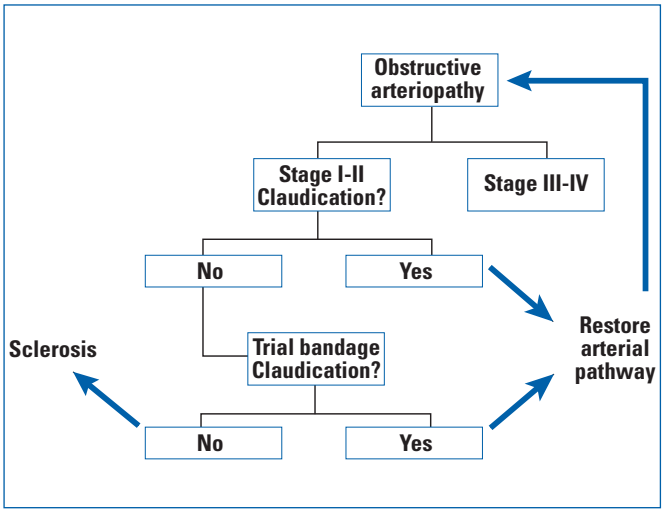

Table II. *Three different treatment responses for varicose veins in patients with general pathophysiological conditions.*

rates of 12% and 23%, respectively, in 1500 cases of GSV reflux treated with the Sigg method over the course of 15 years.[18,19]

We have previously evaluated the results of sclerotherapy in different pathophysiological contexts (*Table I*).[20] Diabetes is associated with vascular sensitivity, as proposed by Lanza et al who suggested the existence of a "diabetic phlebosclerosis".[21] Endothelial dysfunction in patients with diabetes, as a result of chronically elevated blood glucose levels, may influence several mediators secreted by the endothelium. For example, there is an augmentation of levels of von Willebrand factor (vWF), a glycoprotein synthesized and stored in the vascular endothelium, increased levels of which may contribute to an increased risk of thrombosis, and a decrease in production of prostacyclin, which is associated with platelet hyperaggregability. For this reason, when performing sclerotherapy in people with diabetes, concentrations of sclerosing agent must be reduced by half (whether using foam or liquid) and suitable compression must be applied.

In our center, compression is provided by a short-stretch bandage (35%), which only prevents arterial perfusion in the presence of a significant arterial obstruction, with a systolic pressure of less than 70 mm Hg at the ankle. However, the latter is a hypothetical patient and we would not propose sclerotherapy or surgical treatment in a person with significant symptoms of peripheral arterial disease. In reality, it is the patient with claudication and varices that occasionally presents for phlebological consultation (*Table II*). This patient is a candidate for sclerotherapy when the claudication has been resolved. We should highlight that in these patients, the re-establishment of the arterial pathway by catheter or surgery should be attempted. However, sclerotherapy may then pose a problem, as it demands compression associated with ambulation. A test bandage worn during the day for 1 week, without injections should be conducted as a feasibility assessment. A similar approach should be followed in case of suspected arterial disease. A nonelastic bandage may be tolerated in patients with a suspected subclinical arteriopathy.[10] In these patients, a compression stocking delivering compression greater than 20 mm Hg should be avoided, especially in the absence of good systolic blood pressure.

Sclerotherapy, when performed appropriately, is an efficacious and safe technique, but complications can occur. The most severe include cutaneous necrosis, as a result of extravasation of sclerosant into perivascular tissues or direct injection into an arteriole, allergic reactions to sclerosants, and deep vein thrombosis. None of these adverse events were observed in our study. The persistence of significant reflux into a vein that has been treated with a sclerosing agent can lead to phlebitis and this was documented in six cases as a result of poorly applied compression. We observed one vasovagal reaction, which resolved spontaneously.

Sclerotherapy is an important tool for preventing the progression of CVD to more severe stages. 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.[22] 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. This may be particularly the case in patients with diabetes who are at greater risk of more severe CVD because of their already impaired endothelial function.

CONCLUSIONS

The results of our study show that sclerotherapy is not contraindicated in the presence of well-controlled diabetes ($HbA_{1c} < 6.5\%$). On the contrary, this may be one of the best indications for sclerotherapy for a number of reasons. First, the long-term prognosis of chronic venous insufficiency can be severe with subcutaneous tissue involvement and ulcer formation. Safe and effective measures to delay or prevent this scenario are therefore beneficial, particularly in patients with diabetes. Second, excess scar tissue and aggravation of diabetic neuropathy via nerve damage are common complications following surgery, limiting the benefits of invasive procedures for removing varicose veins in patients with diabetes. Finally, there was no significant difference in sclerotherapy results between our patients with diabetes and our global population of patients undergoing sclerotherapy by the same method.

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Instructions for authors

AIM AND SCOPE

Phlebolymphology is a quarterly peer-reviewed publication that aims to provide clinicians with updated information on every aspect of the venous and lymphatic disorders: epidemiology, pathophysiology, diagnosis, management, and basic science. Articles are usually in the form of review articles on timely topics with a broad update of recent developments and their clinical applications.

GENERAL INSTRUCTIONS

Articles should discuss a topic of current interest, outline current knowledge of the subject treated, give personal views and also analyze the different opinions regarding the topic discussed, and be up to date on the latest literature data.

The text should be 3000-5000 words, not including references, tables, figures. Illustrations are strongly encouraged. All texts should be submitted in English.

Submission: Manuscripts may be submitted by e-mail[1], double-spaced, 8 to 16 typed. All pages should be numbered. All corresponding authors should supply a portrait photograph for inclusion at the end of the article. This may be sent by e-mail, provided the resolution of the file is at least 300 dpi.

Title page: The title page should include a title, the full names of all the authors, the highest academic degrees of all authors (in country-of-origin language), affiliations (names of department[s] and institution[s] at the time the work was done), a short running title (no more than 50 letters and spaces), 5 to 10 keywords, the corresponding author's complete mailing address, telephone, fax, and e-mail., and acknowledgments.

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Article in a supplement: Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al. Chronic venous insufficiency: dysregulation of collagen synthesis. *Angiology.* 2003;(suppl 1):S13-S18.

Chapter in a book: Coleridge Smith PD. The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum.* 2nd ed. London, UK: Arnold; 2001:309-321.

Web-based material: Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. American Heart Association, 2000. Available at: http://www.circulationaha.org. Accessed October 17, 2005.

Presentation at a conference: Jantet G. Epidemiological results of the RELIEF study across different continents. Paper presented at: 15th World Congress of the Union Internationale de Phlébologie; October 2-7, 2005; Rio de Janeiro, Brazil.

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7-9 December 2012	3RD LISBON INTERNATIONAL FORUM ON VASCULAR DISEASES	Portugal	Lisbon
8 December 2012	ANNUAL MEETING OF THE AUSTRIAN SOCIETY OF PHLEBOLOGY	Austria	Vienna
17-19 Januay 2013	CONTROVERSIES AND UPDATES IN VASCULAR SURGERY	France	Paris
24-26 January 2013	ANNUAL CONFERENCE OF VENOUS ASSOCIATION OF INDIA VAICON 2013	India	Goa
2-3 February 2013	3E CONTROVERSIAS EN CIRURGIA VASCULAR E ENDOVASCULAR	Brazil	São Paulo
19-22 February 2013	XXI SLOVAK ANGIOLOGY CONGRESS WITH INTERNATIONAL PARTICIPATION	Slovakia	Tatranska Lomnica, High Tatras
28 February - 2 March 2013	XXXVIII. ANGIOLOGICAL DAYS 2013 WITH INTERNATIONAL PARTICIPATION	Czech Republic	Prague
Mid March 2013	XXXIII VENOUS MEETING OF PORTUGUESE SURGICAL SOCIETY	Portugal	Lisbon
14-16 March 2013	46ÈME CONGRES DU COLLEGE FRANÇAIS DE PATHOLOGIE VASCULAIRE	France	Paris
18-19 April 2013	UKRAINIAN NATIONAL CONGRESS "ANGIOLOGY AND VASCULAR SURGERY"	Ukraine	Kiev

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DATES	CONGRESS	COUNTRY	CITY
25-27 April 2013	CONGRESO DEL CAPÍTULO ESPAÑOL DE FLEBOLOGÍA	Spain	Málaga
May 2013	XX CONGRESO ARGENTINO E INTERNACIONAL DE FLEBOLOGÍA Y LINFOLOGÍA	Argentina	Buenos Aires
May 2013	NATIONAL ANNUAL CONGRESS OF GEORGIAN ASSOCIATION OF ANGIOLOGISTS AND VASCULAR SURGEONS GAAVS	Georgia	Tbilisi
Mid June 2013	XIII ANNUAL CONGRESS OF THE PORTUGUESE SOCIETY OF ANGIOLOGY AND VASCULAR SURGERY	Portugal	-
September 2013	CHINA VASCULAR SURGREY 12TH	China	TBD
18-21 September 2013	20TH ANNUAL CONFERENCE OF VASCULAR SOCIETY OF INDIA	India	Kodaikanal

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