PHLEBO LYMPHOLOGY

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 the EMBASE and Elsevier BIOBASE databases.

Phlebolymphology is made up of several sections: editorial, articles on phlebology and lymphology, review, news, and congress calendar.

CORRESPONDENCE

Phlebolymphology

CONTENTS

EDITORIAL

*Several exciting phlebological problems will be discussed in this issue of **Phlebolymphology**.*

Up to now, our understanding of how venous valves work was mainly based on theoretical concepts. Modern ultrasound technology enables the observer to record simultaneously the motions of valve leaflets, and changes in size and shape of the venous sinus and blood flow through the valve during the respiratory cycle and during exercise in different body positions.

***Fedor Lurie, together with Robert Kistner and coworkers** from the University of Hawaii provide us with a meticulous analysis of the exact mechanisms of a valve cycle between the opening and closing of a valve. A spontaneous rhythm can be observed in the supine position, which is obviously influenced by respiratory and cardiac cycles. Valve closure does not need reversed flow!*

***Michel Perrin and coworkers** provide a report of a survey conducted among 198 French angiologists who tested different severity scores in 1900 patients with chronic venous disease. In addition to the venous disability score from the CEAP-classification, the French team also used the venous clinical severity score (VCSS) and the venous segmental disease score (VSDS). This is a very interesting article, since for the first time the usefulness of the rather theoretical constructs have been tested in daily clinical practice by experienced clinicians.*

*A survey on the benefits of daflon 500 mg in venous edema is reported on by **Françoise Pitsch.***

According to the large epidemiological study by Eberhard Rabe in Germany, 14.3% of the adult population has some degree of leg swelling. Despite this enormous clinical importance the average interest in diagnosis and treatment of this common condition is rather poor. For many doctors it is a kind of therapeutic reflex to prescribe diuretics, forgetting that prolonged use may induce a disturbance in the rennin-angiotensin mechanism that will even exacerbate the edema.

***Jean-François Uhl and coworkers** discuss the vicinity of the sural nerve to the junction of the small saphenous vein and its clinical consequences. The reason for this vein-nerve association can be found in embryological development. Recently Stefano Ricci from Rome surprised us with Duplex pictures, showing that a trained eye is able to see the nerve in the popliteal fossa nearly in every case.*

*Last but not least, **Giuseppe Andreozzi and colleagues** from the University of Padova discuss the frequent and practically important clinical group of patients presenting with subjective leg symptoms without visible signs of a venous disorder. According to the CEAP classification they describe such cases as C0s, En, An, Pn. However, they were able to find some objective abnormalities in the venous tone by plethysmographic investigations and also by measuring the difference between the venous diameters in the supine and in the upright position using Duplex. The scoring "Pn" for "no pathophysiology detectable" may therefore be disputed. It would be interesting to see such tests established as routine methods, which could be carried out with multicenter cooperation between different vascular labs.*

Enjoy reading,

Hugo Partsch, MD

A new concept of the mechanism of venous valve closure and role of valves in circulation

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One can not overestimate the importance of venous valves in the vascular system. They are relatively simple membranous structures, and yet, their malfunction causes almost all known venous disorders. In primary venous insufficiency malfunction of the valves leads to broad spectrum of pathological changes, from spider varicose veins to lypodermatosclerosis to venous ulcers. Venous thrombi originate from the valve sinus. As the thrombus resolves, additional damage to venous valves occurs, leading to secondary (post-thrombotic) chronic venous disorder.

The fascinating history of venous valve discovery and re-discovery shows that, even before Harvey, their role was seen as ensuring unidirectional flow in veins.[1] *Excercitarto Anatomicae de Motu Cordis et Sangunis in Animalibus* laid the basis for modern understanding of the cardiovascular system by introducing the concept of circulation.[2] Demonstration of unidirectional venous flow was an essential part of this concept. Since that time the venous valve has been viewed as a simple passive structure reacting to reversed flow by closing the vein's lumen.

In 1926, E.B. Carrier first described an intricate blood flow pattern around the venous valve leaflets in his direct observation of red blood cell movement in the bat's wing.[3] This was exactly the same pattern as predicted by Leonardo da Vinci, and later confirmed by K.D. Kele for a geometrically similar aortic valve.[4] In vitro experimentation with saphenous valves confirmed that they do not open all the way out to touch the sinus wall.[5] These findings have opened up new aspects of the physiology of venous valves. They demonstrated the complexity of hemodynamics around the valve far exceeding the simple sequence of forward and backward flow, and challenged the simplicity of current concept of physics behind closing of the venous valve.

In 1980s, E. Strandness's group in Seattle developed modern ultrasound techniques for detecting valvular incompetence.[6] At that time, ultrasound equipment did not allow reliable visualization of the valve itself. Instead, Doppler-based registration of reversed blood flow in the venous segment in response to Valsalva or rapid compression-decompression, maneuvers were used to define valvular insufficiency. This approach advanced venous diagnosis by providing a reliable tool for reflux detection that is used to this day. Unfortunately, the indirect approach also created confusion between the presence of reversed flow in the vein and function of the valve itself. The terms "reflux time" and "valve closure time" were falsely used interchangeably. As a consequence, the view that reversed flow through the valve is necessary for valve closure was promulgated.[7]

A new generation of ultrasound equipment, particularly the introduction of ß-flow modality, has made it possible to observe venous valve and blood flow in the area of the valve in undisturbed physiologic conditions. Artificial maneuvers to force the blood backward to check the competency of the valve are no longer needed for normal valve observations. One can simultaneously observe the motions of valve leaflets, changes in venous sinus shape and size, and blood flow through the valve during normal respiratory cycle, in different positions of the body and during exercises such as dorsal and plantar flexion of the foot.

THE VALVE CYCLE

By observing valves in femoral and great saphenous veins of healthy volunteers, we identified a consistent pattern of flow events as the blood passes through a valve station during rhythmic opening and closing of the valve
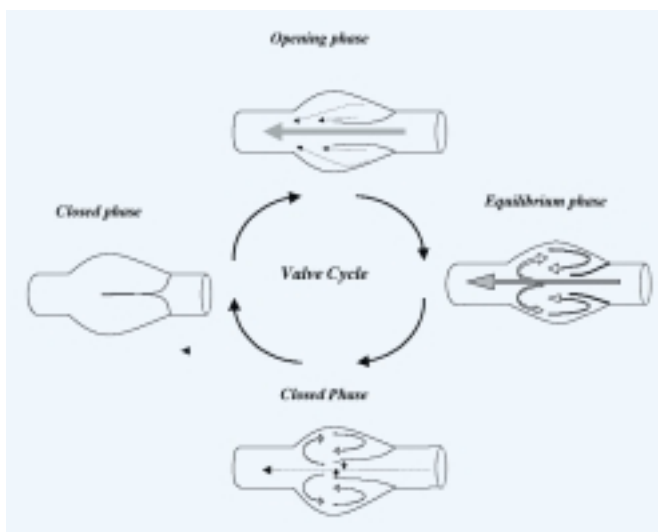
Figure 1. The valve cycle.
*During the **Opening phase** the cusps move from the closed position toward the sinus wall. After reaching a certain point, the valves cease opening and enter the **equilibrium phase**. The valve is maximally open during this phase. Still cusps maintain their position at some distance from the wall, creating a funnel-like narrowing of lumen. The flow accelerates in this stenotic area resulting in a proximally directed flow jet. The smaller part of the flow turns into the sinus pocket behind the valve cusp. This part of the stream forms a vortex along the sinus wall and the mural side of valve cusp before re-emerging in the main stream in the vein. Rising pressures on the mural side and falling pressures on the luminal side of the cusps initiate their movements toward the center of the vein, ie the **closing phase**. The cusps of the valve assume a symmetrical position at an equal distance from the walls on both sides of the sinus remaining in this position during the **closed phase**.*

cusps. The flow events and the movements of the valve leaflets appear to be two parts of the same physiologic process of the "valve cycle" - the time period between two consecutive closures of the valve, which we arbitrarily divided into the four phases (*Figure 1*).

Opening phase: During this phase, the cusps move from the closed position toward the sinus wall. This phase lasts on average 0.27 +/-0.05 seconds when the patient is in the horizontal position. After reaching a certain point in this phase, the valves cease opening and enter the ***equilibrium phase***. During this phase, the leading edges remain suspended in the flowing stream and undergo oscillations that resemble the flutter of flags in the wind. The valve is maximally open during this phase. Still cusps maintain their position at some distance from the wall, creating a funnel-like narrowing of lumen. The cross-sectional area between the leaflets is about two thirds of the cross-sectional area of the vein distal to the valve. The flow accelerates in this stenotic area resulting in a proximally directed flow jet. Upon impact of the jet against a layer of much slower-moving blood proximal to the valve, reflection of flow occurs in the mural parts of the stream. While the larger stream located in the center of the vessel is directed proximally along the axis of the vein, the smaller part of the flow turns into the sinus pocket behind the valve cusp. This part of the stream forms a vortex along the sinus wall and the mural side of valve cusp before re-emerging in the main stream in the vein.

As vortical flow persists, it applies pressure upon the mural surface of the valve cusps. When the pressure on the mural side of the cusp and the pressure on the luminal side of the cusp are in equilibrium, the valve remains open and the cusps float in the stream. This dynamic equilibrium is sustained by equilibrium in velocities of the two streams – vortex on the mural side, and axial flow on the luminal side of the valve cusps. Changes in any of these streams can lead to the closure of the valve. Self-excited oscillations of the leading edges of the leaflets that occur during this e*quilibrium phase* make this balance unstable and very sensitive to small changes in flow.

When the venous flow rate increases distal to the valve, as occurs during foot movements, the velocity of the flow between the valve cusps rapidly increases. This causes a fall in the pressure on the luminal side of the cusp, and the cusps start moving toward the axis of the vessel, further constricting the lumen (*Figure 2*). With rising pressures on the mural side and falling pressures on the luminal side of the cusps, valve closure is favored.

Figure 2. Mechanism of valve closure.
When the venous flow rate increases distal to the valve, as occurs during foot movements, the velocity of the flow between the valve cusps (V_{axial}) rapidly increases. This causes a fall in the pressure on the luminal side of the cusp (P_o) while slower velocity of vortex applies higher pressure on the mural side of cusp (P_i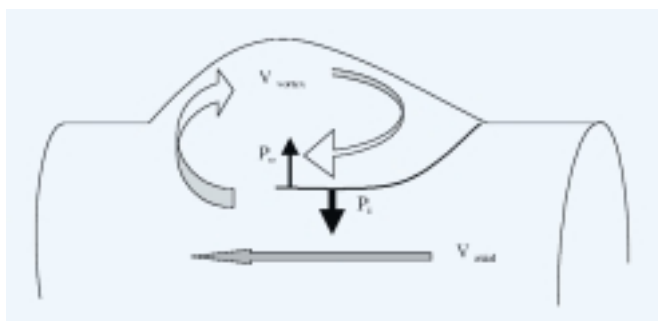), and the cusps start moving toward the axis of the vessel, further constricting the lumen maintaining or even increasing the pressure gradient between the two sides of the cusp.

The **closing phase** ensues. The leaflets move synchronously toward the center. The cusps of the valve assume a symmetrical position at an equal distance from the walls on both sides of the sinus. This phase lasts 0.41 +/- 0.07 sec when the patient is at rest and is much shorter when foot movements are performed. The last phase is the **closed phase**, during which the cusps remain closed.

The duration of the valve cycle and of each of its four phases depends upon the position of the body. In the standing position, the duration of the cycle is from 2.9 sec to 3.2 sec (95% confidence interval), which corresponds to frequency of 18.8 to 20.4 per minute (similar to respirations). In a horizontal position, the duration of the cycle was from 1.7 to 1.8 sec (95% CI). This rhythm (34.2 to 36.1 per minute) is most likely influenced by both respiratory and cardiac cycles. Muscle activity (dorsal and plantar flexions of the foot) causes shortening of the closing phase. As we observed, every single foot movement causes significant increase of velocities and closure of the valve.

Based on our observations, we proposed a new concept of the mechanism of venous valve closure and role of valve in circulation. In the absence of forced reversed flow, the valve cusps consistently undergo the four phases constituting the valve cycle. The local hemodynamic events such as vortical flow in the sinus pocket play important roles in the valve operation. These hemodynamic events are predetermined by the shape and mechanical properties of the sinus and the valve cusps, and they constitute a self-sustained mechanism for competent valve operation.

In addition to prevention of retrograde flow, the valve acts as a venous flow modulator. The vortical stream forms behind the valve cusp, and axial jet forms at the center of the vein. The vortex participates in the operation of the valve, and prevents stasis inside the valve pocket. The central jet possibly facilitates outflow.

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Evaluation of the new severity scoring system in chronic venous disease of the lower limbs: an observational study conducted by French angiologists

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SUMMARY

In 2000, Rutherford proposed a new tool to measure the severity of venous disease. Its aim was to quantify the progression and treatment of chronic venous disease. It consists of three scores comprising clinical aspects, anatomic and pathophysiologic abnormalities (venous segmental disease score), and disability.

French angiologists, in order to evaluate the relevance and usefulness of such scores in their daily practice, conducted an observational study.

The scores were tested on 1900 patients by 398 angiologists, who completed an opinion questionnaire.

In any class of the CEAP classification, the three scores were low, specifically the segmental score. Although considered as easy to grade and relevant by the majority of respondents, only a minority of angiologists, stated their intention to use these scoring parameters in everyday practice for C4-C5-C6 patients (71.8% of the 1900 patients): 42.0% for the clinical severity score, 32.9% for the segmental score, and 38.7% for the disability score. These figures were even lower for C1-C2 and C3 patients: 21.6%, 19.6%, and 26.9% respectively.

The new severity scores to assess chronic venous disease seem difficult to use in daily practice, in particular the venous segmental score. They seem more appropriate to evaluate the evolution and efficacy of therapy in severe chronic venous disease.

INTRODUCTION

Chronic venous disease (CVD) covers many aspects, requiring adoption of a common international language: this is the objective fulfilled by the CEAP classification.[1] The CEAP classification describes CVD in its clinical (C), etio-

logical (E), anatomical (A), and pathophysiological (P) aspects. Published in 1995, and updated in 2004,[2] the CEAP is now internationally recognized and has been widely disseminated to physicians specializing in vascular disease. However, this classification is only of descriptive value and does not allow quantification of severity of CVD. Concomitant with this classification, a committee of experts had developed scores to determine the severity of CVD based on three items (clinical, anatomo-pathophysiological, and disability). These scores had never been validated nor tested, and therefore were not used by physicians. A few years later, in 2000, the original authors of the CEAP system and other experts proposed new scores to grade the severity of CVD and to evaluate the efficacy of different therapies.[3] These scores were mainly developed for severe forms of CVD according to the CEAP clinical classification (grades C4, C5, and C6), ie, for cases designated traditionally in terms of chronic venous insufficiency (CVI).[4,5] These severity scores for CVD grade clinical severity, anatomo-pathophysiologic severity and disability. Without a doubt, these severity scores deserve to be tested and evaluated by their potential users, ie, French angiologists, in this specific case.

AIMS OF STUDY

The objective of this observational, opinion survey conducted on a representative sample of French phlebologists was to test and evaluate the interest and usefulness in daily practice of three new severity scores for CVD:
- The venous clinical severity score (VCSS),
- The venous segmental disease score (VSDS),
- The venous disability score (VDS).

METHODS

Description of populations

This survey was conducted with 398 angiologists, distributed throughout France (mainland). Each angiologist had to evaluate the three severity scores for CVD in five consecutive patients who met the inclusion criteria. Then the physician had to fill out an opinion questionnaire.

The inclusion criteria for patients were based on the previous CEAP clinical classification.[1] This classification system describes CVD in all of its aspects using a coding system with four subject headings:[1]

- the heading C describes 7 clinical classes, ranging from C0 to C6, defined as follows:

- C0: No visible or palpable sign of venous disease
- C1: Telangiectasias or reticular veins
- C2: Varicose veins
- C3: Edema
- C4: Skin changes ascribed to venous disease: pigmentation, venous eczema, hypodermic inflammation
- C5: Skin changes as defined in C4 with healed ulceration
- C6: Skin changes as defined in C4 with active, unhealed ulceration

In this survey the basic CEAP was used; this means that only the highest clinical class was quoted.

In addition, this clinical classification is supplemented by addition of a letter: (A) stands for asymptomatic, and (S) symptomatic if the patient presents with "venous" symptoms: pain, sensation of lower-limb heaviness, paresthesias, etc.

The etiology heading differentiates three types of causes of CVD (Ec for congenital, Ep for primary, Es for secondary).

The anatomical heading codifies CVD according to the anatomic distribution of venous disease (As stands for superficial venous network; Ad for deep venous network, and Ap for perforator veins) and specifies the venous segment involved by addition of a number corresponding to 18 predefined segments.

Lastly, the pathophysiological heading differentiates CVD associated with reflux (Pr), obstruction (Po), or a combination of the two mechanisms (Pr + o).

To be eligible for inclusion, patients had to present with CVD and signs corresponding to classes C4, C5, or C6 of the CEAP clinical classification, be 18 years of age or older and not have peripheral arterial disease.

Description of severity scores for CVD

Severity scores were compiled for patients presenting with CVD. They quantify the degree of severity of venous disease according to three criteria: clinical, anatomo-pathophysiological, and functional.[3]

The VCSS takes ten items into account represented by the following:

- Symptoms and signs of CVD: pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, and ulceration. Regarding ulceration, different items were chosen: number of active venous ulcers, their size, and duration.

- Compliance with compression therapy.

Each item was scored separately in terms of severity on a 3-point rating scale ranging from 0 (absent) to 3 (severe).

Scores obtained for each item were added up to comprise the overall VCCS, which ranges from 0 to 30 (*Table I*).[3]

- The VSDS takes into account both the pathophysiological mechanisms involved, ie, reflux and obstruction, and the anatomic distribution of the diseased veins. It contains two different and independent components: the "reflux" score and the "obstruction" score. Depending on location of the diseased veins, and since pathophysiological effects do not have the same severity, a specific coefficient ranging from 0.5 to 2 was assigned to each segment of a vein. Each of the two scores comprising the segmental score was calculated independently by adding up the coefficients assigned to the diseased segments of the vein. They ranged from 0 to 10 (*Table II*).[3]

- Lastly, the VDS provides a quantitative evaluation of the functional impact of CVD on a 4-point scale, from 0 (asymptomatic) to 3 (unable to carry out usual activities even with compression therapy and/or limbs elevated) (*Table III*).[3]

The scores could be calculated only when information was provided for all items (no missing data).

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting activity *or* requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities *or* requiring regular use of analgesics
Varicose veins*	None	Few, scattered: branch VV's	Multiple: GS varicose veins confined to calf *or* thigh	Extensive: thigh *and* calf *or* GS *and* SS distribution
Venous edema†	None	Evening ankle edema only	Afternoon edema, above ankle	Morning edema above ankle *and* requiring activity change, elevation
Skin pigmentation‡	None *or* focal, low intensity (tan)	Diffuse, *but* limited in area, *and* old (brown)	Diffuse over most of gaiter distribution (lower 1/3) *or* recent pigmentation (purple)	Wider distribution (above lower 1/3) *and* recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Severe cellulitis (lower 1/3 and above) *or* significant venous eczema
Induration	None	Focal, circummalleolar (< 5 cm)	Medial *or* lateral, less than lower third of leg	Entire lower third of leg *or* more
No. of active ulcers	0	1	2	> 2
Active ulceration, duration	None	< 3 mo	> 3 mo < 1 y	Not healed > 1 y
Active ulcer, size§	None	< 2-cm diameter	2- to 6-cm diameter	> 6-cm diameter
Compressive therapy‖	Not used *or* not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance: stockings + elevation

Table I. Venous clinical severity score (VCSS).

* "Varicose" veins must be > 4-mm diameter to qualify so that differentiation is ensured between C1 and C2 venous pathology.
† Presumes venous origin by characteristics (e.g., Brawny [not pitting or spongy] edema), with significant effect of standing/limb elevation and/or other clinical evidence of venous etiology (ie, varicose veins, history of DVT).
   Edema must be regular finding (eg, daily occurrence).
   Occasional or mild edema does not qualify.
‡ Focal pigmentation over varicose veins does not qualify.
§ Largest dimension/diameter of largest ulcer.
‖ Sliding scale to adjust for background differences in use of compressive therapy.
VV, Varicose vein; GS, Great saphenous; SS, Small saphenous.

	Reflux		Obstruction†
1/2	Small saphenous vein		‡
1	Great saphenous vein	1	Great saphenous vein (only if thrombosed from groin to below knee)‡
1/2	Perforators, thigh		‡
1	Perforators, calf		‡
2	Calf veins, multiple (PT alone = 1)	1	Calf veins, multiple
2	Popliteal vein	2	Popliteal vein
1	Femoral vein	1	Femoral vein
1	Profunda femoris vein	1	Profunda femoris vein
1	Common femoral vein and above‡	2	Common femoral vein
		1	Iliac vein
		1	IVC
10	Maximum reflux score §	10	Maximum obstruction score §

Table II. Venous segmental disease score (VSDS, based on venous segmental involvement with reflux or obstruction*).

Note: Reflux means that all the valves in that segment are incompetent. Obstruction means there is total occlusion at some point in the segment or >50% narrowing of at least half of the segment. Most segments are assigned one point, but some segments have been weighted more or less to fit with their perceived significance (eg, increasing points for common femoral or popliteal obstruction and for popliteal and multiple calf vein reflux and decreasing points for small saphenous or thigh perforator reflux). Points can be assigned for both obstruction and reflux in the same segment. This will be uncommon but can occur in some postthrombotic states, potentially giving secondary venous insufficiency higher severity scores than primary disease.
* As determined by appropriate venous imaging (phlebography or duplex scan). Although some segments may not be routinely studied in some laboratories (eg, profunda femoris and tibial veins), points cannot be awarded on the basis of presumption, without interrogating the segments for obstruction or reflux.
† The excision, ligation, or traumatic obstruction of deep venous segments counts toward obstruction points just as much as their thrombosis.
‡ Normally there are no valves above the common femoral vein, so no reflux points are assigned to them. In addition, perforator interruption and saphenous ligation/excision do not count in the obstruction score, but as a reduction of the reflux score.
§ Not all of the 11 segments can be involved in reflux or obstruction. Ten is the maximum score that can be assigned, and this might be achieved by complete reflux at all segmental levels.
IVC, Inferior vena cava; PT, Posterior tibial.

0 = asymptomatic 1 = symptomatic but able to carry out usual activities* without compressive therapy 2 = can carry out usual activities* only with compression and/or limb elevation	3 = unable to carry out usual activities* even with compression and/or limb elevation *Usual activities = patients activities *before* onset of disability from venous disease.

Table III. Venous disability score (VDS).

Scores Angiologist opinion

After including five patients, the angiologist had to evaluate the ease of use, value, and usefulness for managing patients in daily medical practice, of each of the three CVD severity scores, using a six-item questionnaire. Each item was evaluated on a verbal scale according to four levels: "not at all in agreement," "do not agree," "agree," "agree entirely."

In addition, these four reply modalities were combined into two classes: "not favorable," by adding up the modalities "not at all in agreement," and "do not agree," on the one hand, and "agree," and "agree entirely," on the other hand.

Lastly, verbatim comments were collected.

Statistical analyses

The survey was designed to target solely patients in clinical class C4, C5, or C6 of the CEAP classification. But an analysis of case reports revealed that a certain number of patients recruited presented with class C1, C2, or C3 CVD. Therefore, two groups were formed based on the CEAP clinical classification, the [C4-C5-C6] group and the [C1-C2-C3] group. It appeared relevant to perform all the statistical analyses, both on all patients enrolled and also on each of the two groups thus formed. Intergroup comparison of quantitative variables was performed with a nonparametric Mann-Whitney-Wilcoxon test when two groups were compared, and with a Kruskal-Wallis test for comparisons on more than two

groups. The analysis was descriptive. In terms of test results, a value of 0.05 was considered as significant.

RESULTS

Surveyed population

A total of 398 angiologists (49.8% men, 48.7% women) distributed throughout France participated in the survey between March 10 and September 4, 2001. These physicians practiced primarily in urban areas.

They recruited 1900 patients, 1365 of who were in the [C4-C5-C6] group, ie, 71.8% of all patients, and 484 patients in the [C1-C2-C3] group.

Patients, mainly women, were 61 years of age on average, but those in the [C1-C2-C3] group were significantly younger than the [C4-C5-C6] patients and the percentage of men was higher in the latter group (*Table IV*). Mean body mass index (BMI) was higher and significantly different between the [C1-C2-C3] and [C4-C5-C6] groups. In addition, the especially high percentage of patients who were overweight and obese in the [C4-C5-C6] group compared with the [C1-C2-C3] group should be noted (*Table IV*).

Regarding clinical classes, based on the "C" heading of the CEAP system, the ones most often represented were classes C4, C6, and C2 (*Table V*).

The majority of patients were symptomatic and this was enhanced even more in the [C4-C5-C6] patients compared with those in the [C1-C2-C3] group (*Table V*).

The etiology of CVD was mainly primary, but more frequently secondary in the [C4-C5-C6] group than in the [C1-C2-C3] group (*Table V*).

Although venous reflux was the cause of CVD in the majority of cases, the combination of reflux and obstruction appeared more commonly in [C4-C5-C6] patients than in the [C1-C2-C3] group (*Table V*).

Furthermore, in the total population as well as in the [C4-C5-C6] group, the venous segments most commonly involved were the calf perforator veins, (38.2% and 44.1% respectively) the great saphenous vein (GSV) above the knee (34.6% and 38.6%), and below the knee (18.6% and 19.9%). On the contrary, in the [C1-C2-C3] group, GSV above the knee (26.2% of cases), the reticular veins (26.0%), and the calf perforator veins (25.4%) were involved.

Variable											CEAP Clinical classification	
	Total (n = 1900)		MD (n = 49)		C0 (n = 2)		C1-C2-C3 (n = 484)		C4-C5-C6 (n = 1365)		Test* P value	
Sex	n	%	n	%	n	%	n	%	n	%		
Men	481	25.3	5	10.2	0	0.0	88	18.2	388	28.4	chi-square test	
Women	1,344	70.7	41	83.7	2	100.0	379	78.3	922	67.6	P < 0.0001	
MD	75	4.0	3	6.1	0	0.0	17	3.5	55	4.0		
Age (y)												
Mean	61.0		43.2		38.5		51.4		65.0		Mann-Whitney	
SD	15.1		12.7		5.0		13.6		13.6		Wilcoxon test	
MD	11		0		0		2		9		P < 0.0001	
BMI (kg/m^2)												
Mean	26.3		22.7		20.8		24.0		27.2		Mann-Whitney	
SD	5.0		4.3		1.4		3.8		5.1		Wilcoxon test	
MD	36		1		0		10		25		P < 0.0001	
BMI (kg/m^2)	n	%	n	%	n	%	n	%	n	%		
MD	36	1.9	1	2.0	0	0.0	10	2.1	25	1.8		
< 19 kg/m^2	55	2.9	6	12.2	0	0.0	29	6.0	20	1.5		
[19; 25 - normal]	775	40.8	32	65.3	2	100.0	286	59.1	455	33.3		
[25; 30 - overweight]	681	35.8	9	18.4	0	0.0	114	23.6	558	40.9		
> 30 kg/m^2 (obesity)	353	18.6	1	2.0	0	0.0	45	9.3	307	22.5		

Table IV. Demographic characteristics of patients.

Abbreviations:
N: frequency
%: percentage
MD: missing data
SD: standard deviation
BMI: body mass index
*: intergroup test of comparison [C1-C2-C3] and [C4-C5-C6]

Variable		CEAP Clinical classification									Test*
	Total (n = 1900)		MD (n = 49)		C0 (n = 2)		C1-C2-C3 (n = 484)		C4-C5-C6 (n = 1365)		*P* value
	n		%		n		%		n		%
Clinical classification: [3] C											
MD	49	2.6	49	100.0	0	0.0	0	0.0	0	0.0	
C0	2	0.1	0	0.0	2	100.0	0	0.0	0	0.0	
C2	315	16.6	0	0.0	0	0.0	315	65.1	0	0.0	
C3	169	8.9	0	0.0	0	0.0	169	34.9	0	0.0	
C4	777	40.9	0	0.0	0	0,0	0	0.0	777	56.9	
C5	20	1.1	0	0.0	0	0.0	0	0.0	20	1.5	
C6	568	29.9	0	0.0	0	0.0	0	0.0	568	41.6	
Clinical classification according to presence of symptoms: [3]											
MD	127	6.7	6	12.2	0	0.0	41	8.5	80	5.9	chi-square test
A	282	14.8	9	18.4	2	100.0	98	20.3	173	12.7	*P* < 0.0001
S	1,491	78.5	34	69.4	0	0.0	345	71.3	1,112	81.5	
Etiological classification: [4] E											
MD	136	7.2	7	14.3	1	50.0	41	8.5	87	6.4	
Ec	369	19.4	12	24.5	1	50.0	127	26.2	229	16.8	
Ep	876	46.1	25	51.0	0	0.0	259	53.5	592	43.4	
Es	519	27.3	5	10.2	0	0.0	57	11.8	457	33.5	
Pathophysiological classification: [5] P											
MD	339	17.8	31	63.3	1	50.0	142	29.3	165	12.1	
Po	42	2.2	7	14.3	1	50.0	14	2.9	20	1.5	
Pr	1,292	68.0	11	22.5	0	0.0	311	64.3	970	71.1	
Pr, o	227	12.0	0	0.0	0	0.0	17	3.5	210	15.4	

Table V. Clinical, etiological, and pathophysiological characteristics of patients according to the CEAP classification.

Abbreviations:
N: frequency
%: percentage
MD: missing data
(1): intergroup test of comparison [C1-C2-C3] and [C4-C5-C6]
(2): C0: no visible or palpable sign of venous disease; C2: varicose veins; C3: edema; C4: skin changes of venous origin; C5: skin changes as defined in C4 with healed ulcer; C6: skin changes as defined in C4 with active ulcer.
(3): addition of letter A: asymptomatic; S: symptomatic
(4) Ec: congenital; Ep: primary; Es: secondary.
(5) Po: obstruction; Pr: reflux; Pr, O: reflux and obstruction

Lastly, 87.7% of the 1900 patients underwent Duplex scanning (DS) and 94.1% underwent DS and/or Doppler examination.

Severity scores for CVD

The analysis revealed a markedly lower clinical severity score in the [C1-C2-C3] group compared with the [C4-C5-C6] group (*Figure 1*).

Furthermore, regarding the two components of the VSDS:

- The mean "reflux" score obtained on all 1900 patients was low; it was slightly higher in the [C4-C5-C6] group compared with the [C1-C2-C3] group,
- The mean "obstruction" score obtained was even lower, whatever the group of patients involved (*Figure 2*),
- The VDS most commonly was of level 1 (38.6% of 1900 patients), and 2 (44.6% of them), with a majority of score 1 in the [C1-C2-C3] group (60.1% of
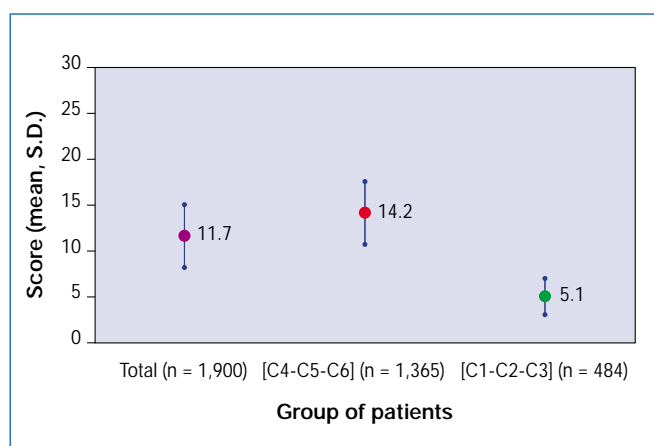
Figure 1. VCCS.
score: 0 – 30

patients), and score 2 in the [C4-C5-C6] group (53.0%) (*Figure 3*).
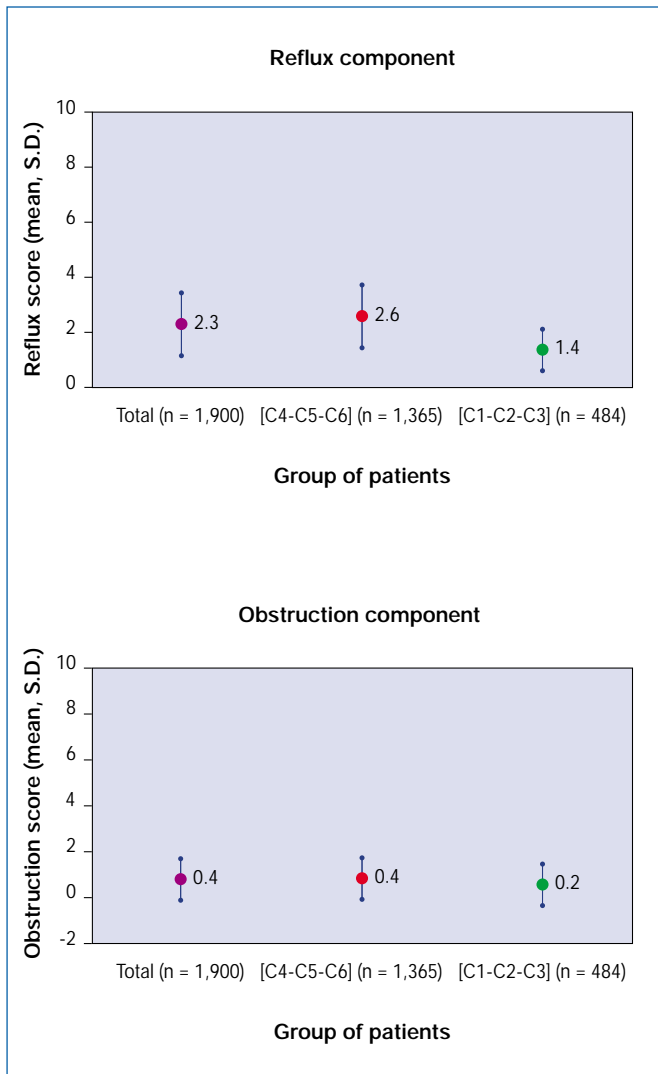
Figure 2. VSDS.
score: 0 – 10
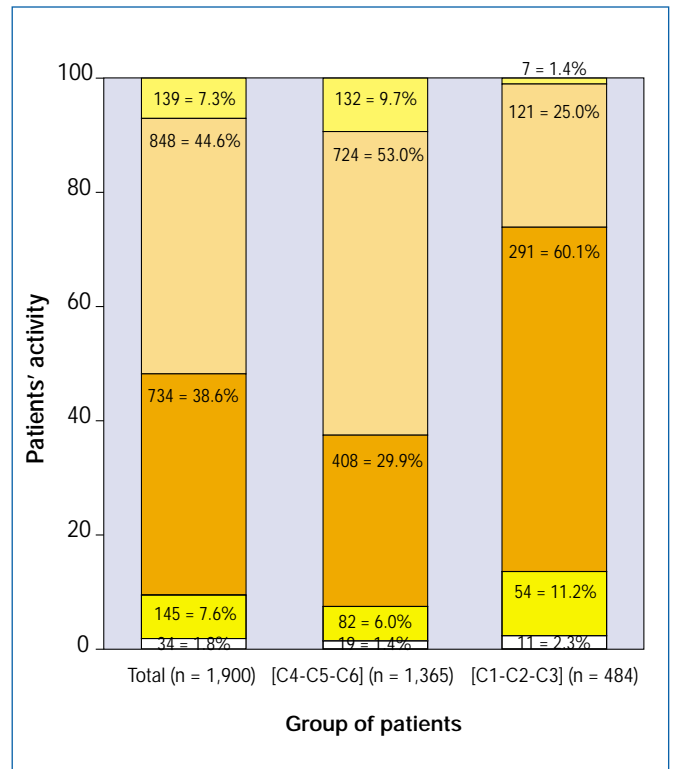
Figure 3. VDS.
☐ *No information given,*
🟨 *Symptomatic, but able to carry out usual activities conducted without compression therapy,*
🟧 *Unable to carry out usual activities even with compression therapy and/or limb elevation,*
🟨 *Asymptomatic,*
🟨 *Can carry out usual activities only with compression therapy and/or limb elevation.*
* *Usual activities = patient activities before onset of disability from venous disease*

MD: missing data
"Favorable" opinion corresponds to addition of opinions "agree" and "totally agree"
"Unfavorable" opinion corresponds to addition of opinions "do not agree at all" and "do not agree"
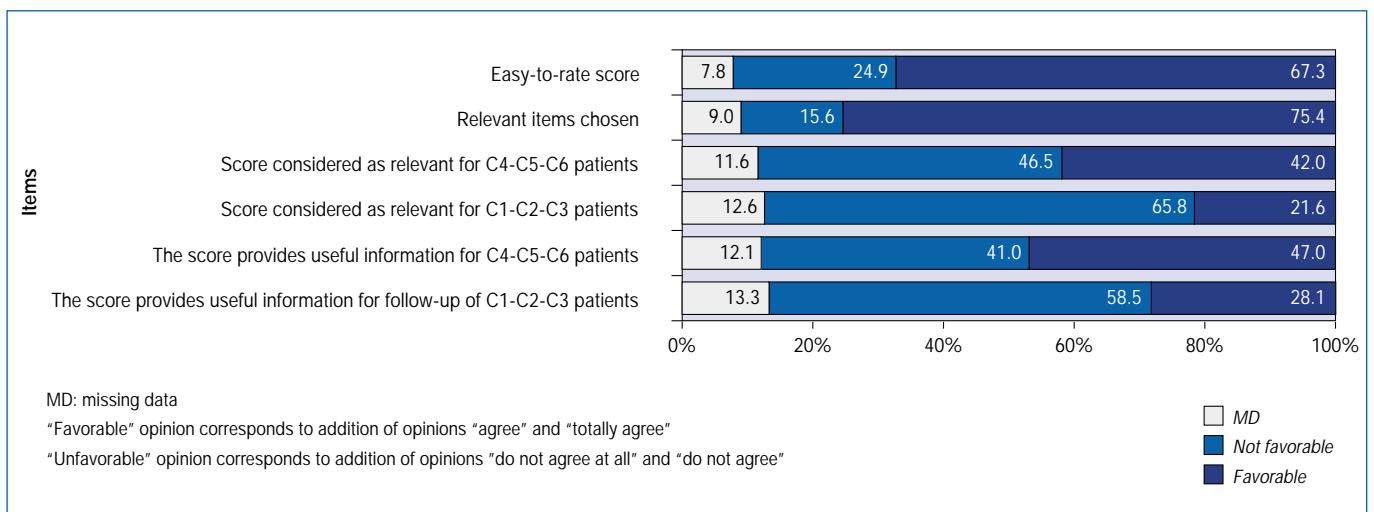
Figure 4. Evaluation of VCCS by angiologists.

Angiologists' opinion

The majority of angiologists considered the three scores as easy to grade, and the items comprising them appeared relevant, especially for the VCCS (*Figure 4*) and VDS (*Figure 5*).

Far fewer angiologists planned to use them in daily practice and to expect an advantage from using them in therapeutic monitoring of their patients. In their opinion, the usefulness of these scores seemed lower for C1-C2-C3 patients compared with C4-C5-C6 patients (*Figures 4, 5, 6*).

In terms of all criteria evaluated, the percentage of physi-cians favourable to VSDS was lower than for the other two scores (*Figure 6*).

Furthermore, 34.2% of the angiologists commented on this new measurement instrument for angiologists who provided verbatim comments, 56.6% of them considered that it was not suited to their daily practice, and 16.9% said it should be reserved for clinical studies.

In addition, they reported that severity scores for CVD did not take into account all the diseased veins nor con-comitant disease in both lower limbs. Lastly, in the physi-cians' opinion, the VCCS was not precise enough with regard to skin changes such as dermatitis or hypodermic inflammation.

Figure 5. Evaluation of VDS by phlebologists.

Figure 6. Evaluation of VSDS by angiologists.

DISCUSSION

The 398 angiologists who participated in this survey, ie, about one fourth of all angiologists in France, comprised a representative sample.
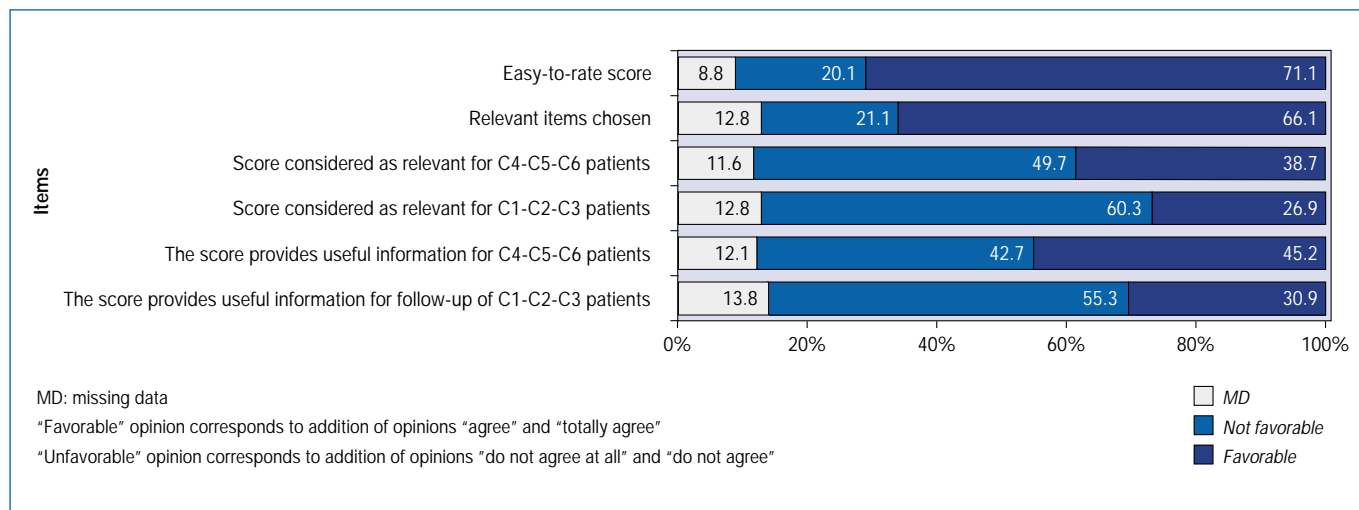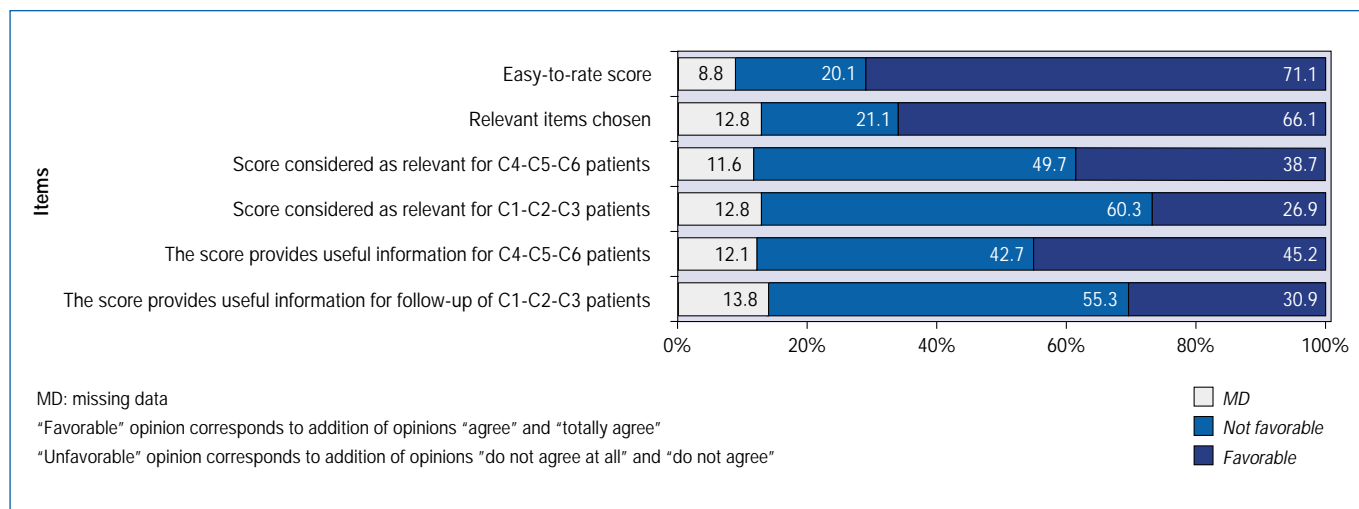
Regarding patients' demographic characteristics, traditionally the [C1-C2-C3] patient population was younger and less commonly overweight than that of the [C4-C5-C6] group. However, these characteristics cannot be compared with those of epidemiological surveys generally conducted on CVD because the study population was selected in a manner so as to recruit patients in class C4, C5, and C6, according to the CEAP classification, ie, patients presenting with CVI.

It should be kept in mind that at this time in France CVD was not differentiated from CVI, unlike the definitions of these terms used in the United Kingdom.[4,5]

Out of 1900 patients enrolled, 71.8% were classified C4, C5, or C6, and thus met planned inclusion criteria, which is important since the three severity scores for CVD are designed for these clinical classes of the CEAP. However, the C4 class was dominant (40.9% of the total sample size). However, it should be noted that this class combines sufficiently different signs some of which (eczema, etc) are not of a severity such that the patient can be considered as presenting with severe CVI. The updated CEAP has divided C4 into 2 subgroups C4a and C4b to improve the identification of the clinical class.

Furthermore, interobserver reproducibility of the CEAP clinical classification was not very good for some items.[6] Therefore, even though patients belonged to all grades of the CEAP classification, we considered it relevant to analyse both the overall patient population as well as the two groups of patients [C1-C2-C3] and [C4-C5-C6].

Severity scores

It emerged from this study that severity scores for CVD were not distributed over all of the proposed scales: 0 to 30 for VCCS, 0 to 10 for VDS (separately both for reflux, and obstruction), and 0 to 3 for VDS, and that the mean values obtained for each of the three scores were not very high.

It is important to note that the authors of the severity scores for CVD specify that these scores were designed to evaluate the most severe forms of CVD. And yet, patients in classes C1, C2, and C3 were also analyzed in this study.

However, it is no less true that scores for patients in classes C4, C5, and C6 were also low, which can be explained in particular by the fact that the C4 class included relatively heterogeneous cases, involving patients whom it is difficult to define as presenting with CVI. These results confirm the fact that severity scores are not adapted to grade non severe CVD.

In addition, it is necessary to differentiate the results of VCCS and VDS from those of the VSDS. Indeed, in the first place, the VSDS obtained was lower than the other two scores. Second, the percentage of "reflux" and "obstruction" scores that were invaluable (due to missing data) was higher than for VCCS and VDS (about 30% of cases for VSDS versus less than 10% for the other 2 scores).

Therefore, the VCCS and VDS seem easier to grade than the VSDS.

Furthermore, it should be noted that no complementary investigation was required during this study. However, Doppler and duplex scanning examinations were performed in the majority of cases. But these methods cannot evaluate with sufficient quality all the venous segments inventoried for the VSDS,[7] whether in terms of reflux or obstruction.

Logically, the VSDS posed technical problems for angiologists.

Furthermore, as could be expected, the clinical severity score increased with the CEAP clinical classification (*Figure 1*). It was also noted that patients classified as C4-C5-C6 had a more severe VDS (*Figure 2*). Thus, only 29.9% of symptomatic patients in the C4-C5-C6 group had normal activity without compression therapy, while this figure was 60.1% of patients in the C1-C2-C3 group. Therefore, the VDS was a good indicator of disease severity.

Lastly, no parallel can be drawn between VSDS and CEAP clinical class for the following reasons:

- First, the scores for reflux and obstruction were very low, and consequently, the differences between the scores were very low, many data were missing, and the number of cases of obstruction in this survey was low (less than 15%): therefore, an analysis would have little relevance;

- Second, hemodynamic data evaluated by the VSDS were hard to interpret because it is difficult to correlate the number or degree of involvement of venous segments producing a reflux or obstruction and its clinical impact.

The opinion of angiologists

In this context, a review of the angiologists' opinion is of considerable interest.

Clinical severity and disability scores were considered easy-to-rate and relevant according to about two-thirds of angiologists (*Figures 4 and 5*). They were good indicators of the severity of CVD. However, even though for almost half of the angiologists these two scores provided more precise monitoring of therapy of [C4-C5-C6] patients, the percentages fell when the question of using them arose.

On the contrary, evaluation of the VSDS was less favourable. Even for patients in the [C4-C5-C6] group, less than 40% of angiologists considered that the score provides an advantage, and only one third of them plan to use it in their daily practice (*Figure 6*).

Furthermore, the coefficients assigned to the different venous segments comprising the "reflux" and "obstruction" scores were subject to criticism. They seem to take more into account the number of segments involved rather than the degree of involvement, even though different figures were assigned to different segments. Furthermore, in addition to the overall evaluation of the VSDS and the technical difficulties in providing information on it, the difficulty in interpreting it also is an issue. Besides, some angiologists propose incorporating the following items in the VCCS for CVD: previous venous surgery, the recurring nature of CVD, and possible involvement of both lower limbs. Furthermore, they consider that these items do not take into account all the skin changes observed in patients classified as C4.

All these suggestions do not necessarily appear suited to the objective of severity scores insofar as their purpose is to evaluate a patient at a given time, in a reproducible manner and to follow disease progression, above all in the setting of evaluation of therapeutic management. On the other hand, although clinical and VSDS involve only one lower limb, involvement of both lower limbs logically has an impact on VDS. Furthermore, more precise evaluation of skin changes, in terms that they signify a level of severity, may favourably have a place in these scores, specifically for class 4 in the CEAP clinical classification.

CONCLUSION

In conclusion, 398 French angiologists, evaluated 1900 patients, the majority of whom had class C4, C5, and C6

venous disease based on the CEAP classification, and they evaluated the new severity scores for CVD developed by Rutherford et al.[3]

They determined that these scores do not seem very well suited to their daily practice. Nevertheless, VCCS and VDS, easy-to-rate and relevant, comprise an instrument whose measurement varies with the severity of venous disease, but above all they were intended to evaluate the efficacy of treatment of CVI.

Lastly, the VSDS is especially hard to score and interpret. In particular, it requires complementary investigations, which cannot be performed in angiologist's office. This score clearly seems to be reserved for clinical studies. However, to facilitate its interpretation, it can be useful to study its correlation with the VCCS.

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Benefit of daflon 500 mg in chronic venous disease-related edema

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INTRODUCTION

Lower-extremity edema is often encountered in clinical practice, and represents a manifestation of a variety of possible disease processes. Edema results from fluid accumulation in the interstitial compartment of the extravascular space.[1] This fluid retention clinically is shown by the "pitting" test.

The underlying cause should be actively investigated to optimize treatment. The etiology is multifactorial, revolving around the intricate balance of capillary blood and oncotic pressures, tissue pressures, lymphatic flow, and capillary permeability. Changes in any of these factors can offset the extravascular fluid balance. Hormonal impregnation, plasma and interstitial protein concentration, as well as leukocyte activation, play a role in edema formation. There is increasing evidence that the leukocyte is a key cell in the chronic inflammation which leads to valve damage. This might subsequently increase venous hypertension, which has direct consequences on increased capillary permeability and edema formation.

PREVALENCE OF CHRONIC VENOUS DISEASE-RELATED EDEMA

The edema associated with chronic venous disease (CVD) is the most common type of edema (90%) and is the first sign of microangiopathy.[2] The place of edema in the natural course of CVD has not been clearly elucidated.[3] CVD-related edema is assigned to class 3 in the CEAP clinical classification (*Table I*), which is made up of 7 clinical classes.[4,5] Venous edema is considered in the Venous Clinical Severity Score (VCSS) which extents the descriptive clinical CEAP classification and allows scoring of the disease (*Table II*).[6]

> *Edema:* a perceptible increase in volume of fluid in subcutaneous tissue characterized by indentation under pressure (Only for edema attributable to venous disease, occurring usually in the ankle region).

Table I. Description of chronic venous disease-related edema according to the CEAP classification (Adapted from ref 4).

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Venous edema	None	Evening ankle edema only	Afternoon edema, above ankle	Morning edema, above ankle and requiring activity change, elevation

Table II. Scoring of chronic venous disease-related edema according to the Venous Clinical Severity Score (VCSS) (Adapted from ref 6).

PATHOPHYSIOGENESIS OF EDEMA

Four major mechanisms may be responsible for edema formation:[3]
- blood pressure increase in the venous system (chronic venous disease or chronic venous insufficiency, and heart failure),
- capillary hyperpermeability with high molecular weight protein and water leakage (endocrine abnormalities, inflammation, and anaphylaxis),
- decrease in lymphatic drainage,
- diminution of plasma protein concentration (in particular hypoalbuminemia) due to proteinuria.

THE DIFFERENT TYPES OF EDEMA[1]

Lower-limb edema may be unilateral or bilateral. Physical examination and diagnostic evaluation are mandatory to differentiate between different types of lower-extremity edema.

Unilateral lower-extremity edema may be due to

- **Lymphedema:** the development of lymphedema is a slow, insidious process. Primary lymphedema which may occur as a hereditary (eg, Milroy's disease) or a sporadic disease starts frequently in the distal part of the extremity. The causes for secondary lymphedema are related to traumatic or surgical disruption of the lymphatic system, or lymphatic obstruction (eg, filaria invasion).
- **Other causes:**
- Venous abnormalities: acute DVT, post-thrombotic syndrome. The thrombosis often damages the valves with subsequent development of chronic venous disease. The incompetent valves result in transmission to capillaries of high venous pressure, promoting both fluid and protein loss into the interstitial tissues.
- Arterial abnormalities: popliteal artery aneurysms often are associated with lower-extremity edema and congen-

ital or acquired vascular anomalies with arteriovenous fistulas may be first noted as lower-extremity swelling.
- Infection: cellulitis (erysipelas) is frequently associated with some swelling of the affected extremity.
- Trauma: fractures, skin and soft-tissue disruptions, and muscular injuries associated with trauma frequently result in edema of the affected limb.
- Tumors: popliteal cysts, otherwise known as Baker's cysts, may produce localized and distal swelling of the extremity. The cyst compresses the popliteal vein and subsequently the venous return, which can result in an acute DVT.

Bilateral or unilateral lower-extremity edema may be due to

- **Chronic venous disease (CVD):** Edema related to CVD generally occurs after prolonged standing, at the end of the day, and is diminished in the morning, by supine position, or with the legs elevated. Also this type of edema may form due to warmth, the summertime season, hot baths, and floor-based heating systems, and improve in winter and with cold temperatures. The CVD-related edema is characterized by its diurnal variation, mainly worsened at the end of the day and relieved in the morning, after rest or elevation of the legs. The venous, lymphatic, and capillary networks are often intricate and involved in the appearance of such an edema. A classification has been proposed depending on which system is at the origin of edema formation[7] (*Table III*).
- **Other causes:**
- Congestive heart failure: bilateral edema can be the early manifestation of right-sided congestive heart failure, which is common with myocardial infarctions.
- Systemic and metabolic abnormalities: bilateral edema may result from secondary liver failure, and in protein deficiency states such as protein-losing gastroenteropathy and severe malnutrition. Acute glomerulonephritis,

	Venous edema	Lymphatic edema	Microcirculatory edema
Clinical criteria	Enhanced by heat, prolonged standing or prolonged sitting position. Relieved after rest or elevation of the legs Ankle and foot involvement "Pitting" edema	Enhanced by physical efforts May involve the entire lower leg and often forms a dorsal hump on the foot Sensitive to the "Stemmer test"	Enhanced by hormonal imbalance Involves the entire lower limb
Diagnostic evaluation	Increased venous pressure (photoplethysmography or Duplex Scan)	Isotopic lymphography	Isotopic Landis test

Table III. The different types of nonsystemic edema (Adapted from ref 7).

due to damage to the renal glomerulus, results in altered renal function. The kidney becomes unable to excrete sodium, leading to salt and water retention.

- Endocrine abnormalities: Cushing's syndrome often results in edema formation.

- Lipedema: predominantly affects women, producing a bilateral deposition of fat in the lower limbs. The feet are typically excluded. The edema is non-pitting and not relieved by leg elevation, contrary to chronic venous disease-related edema.

- Iatrogenic edema: many drugs can cause edema in lower limbs. These include corticosteroids, contraceptive pills, nonsteroidal anti-inflammatory drugs, certain antibiotics, etc.

CLINICAL EVALUATION AND DIAGNOSIS OF EDEMA

The time of onset is an important factor in determining the cause of edema. Sudden onset suggests an acute process such as deep vein thrombosis (DVT), trauma, or infection. Whereas the gradual appearance of edema over weeks or months suggests chronic causes such as chronic venous disease, medications, or a progressive systemic process. Intermittent episodes of edema often occur with recurring erysipelas (cellulitis) or lymphangitis. Systemic disease must be excluded as a cause of peripheral edema. The history and investigations should focus especially on the cardiac, hepatic, and renal functions.

Edema, especially when it is related to chronic venous disease, worsens after prolonged standing and improves after rest. Redistribution of the extracellular fluid occurs after rest or sleeping in a horizontal position. This diurnal variation is typical of the chronic venous disease-related edema.

ASSESSMENT OF CHRONIC VENOUS DISEASE-RELATED EDEMA

- *Methods based on volumetry:*
  • Volumetry by water displacement[8] (*Figure 1*): Archimedes' principle is applied in this method which postulates that the leg volume is equal to the volume of water displaced. The patient stands up and is requested to place her (his) lower limb in a plexiglas container filled in with water. Usually the dimension of the container, around 50 cm in height, allows the measurement of a volume of 2500 to 4000 mL includ-
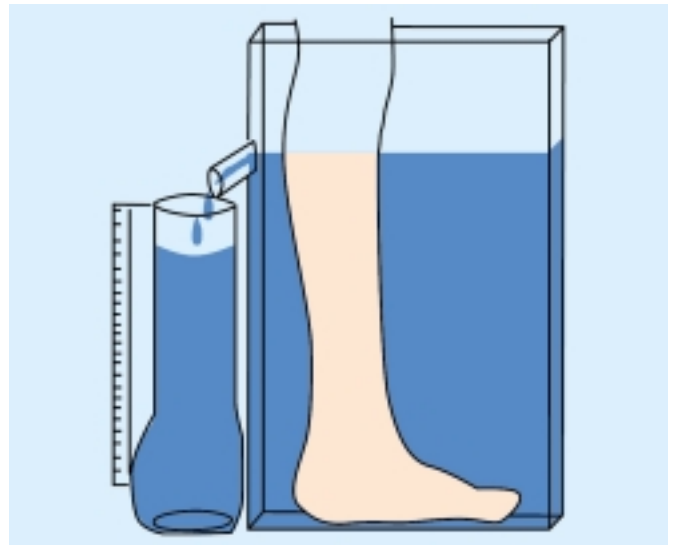
Figure 1. Schematic presentation of the volumeter by water displacement.

ing foot, ankle, and calf. All sorts of lower-limb edema including those related to CVD and lymphedema can be assessed using this method.

• Optoelectronic volumetry[9] (*Figure 2*): this is the most sophisticated method for assessing edema. The leg passes through a four-sided rigid frame which can be moved along a rail in the long axis of the limb. The frame is equipped with infrared-detecting diodes emitting an infrared beam which allows precise measurement of the lower limb volume. Markers placed on the leg allow the identification of the upper and the lower reference point.
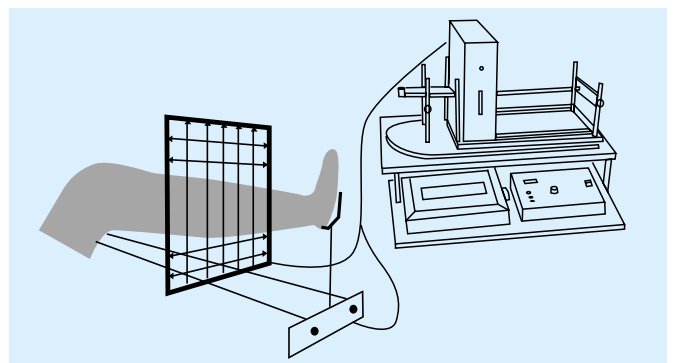
Figure 2. Schematic presentation of the optoelectronic volumeter.

- *Methods based on circumference measurement:*
  The most used methods are the following:
  • Spring tape[10] consists of a conventional tape-measure locked in a small box. The tape is pulled out of the box, put around the limb to measure and the end of the tape hooked to the box. The tape is automatically tightened by a spring mechanism, guaranteeing that the tightening force is similar with all measurements.
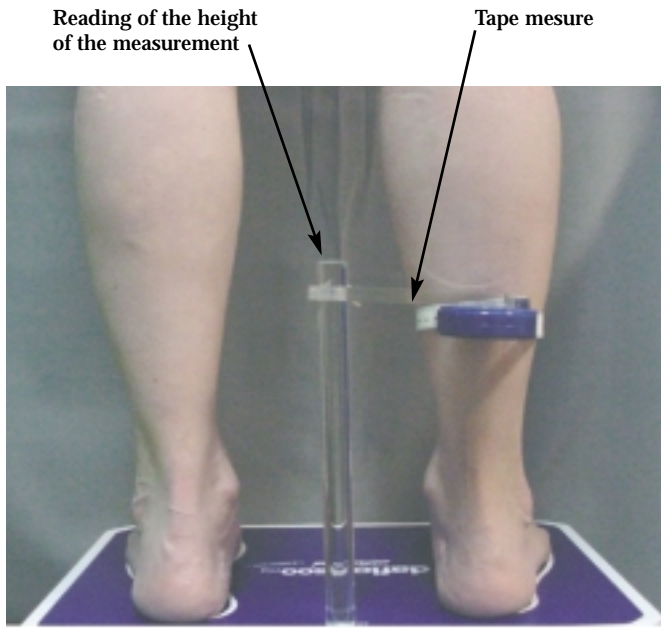
Figure 3. Assessment of ankle circumference with a Leg-O-Meter®.

• Leg-O-Meter®[11] (*Figure 3*) is derived from the spring tape. This device takes into account the height at which the measurement is taken, which greatly increases the precision and the reproducibility of the measurement.
• Assessment of lymphatic drainage.
• Indirect lymphography and lymphoscintigraphy are currently used to confirm the involvement of the lymphatic system in the edema formation.

THE BENEFIT OF DAFLON 500 MG IN CHRONIC VENOUS DISEASE-RELATED EDEMA

Evaluation of the edema associated with chronic venous disease and the expected benefit of therapy with daflon® 500 mg has been evidenced in randomized, controlled studies as well as in open prospective trials.

- *Placebo-controlled studies*
Ankle and calf circumference measurement was used in the two double-blind, randomized, placebo-controlled studies with daflon® 500 mg. In the study by Chassignolle et al,[12] a significant decrease in ankle and calf circumferences was observed ($P<0.001$ for both levels of measurement and for both legs). The protocol used by Gilly et al[13] included the measurements of the calf (maximum circumferences) and ankle (minimum supramalleolar circumference) on each affected leg using a spring tape measure. The changes in these parameters were significantly greater in the daflon® 500 mg group (-7.15 mm)

compared with placebo (-1.15 mm) after 8 weeks of treatment (*Figure 4*). The decrease in supramalleolar circumference correlated well with the improvement in the sensation of swelling ($r=0.56$; $P<0.001$).
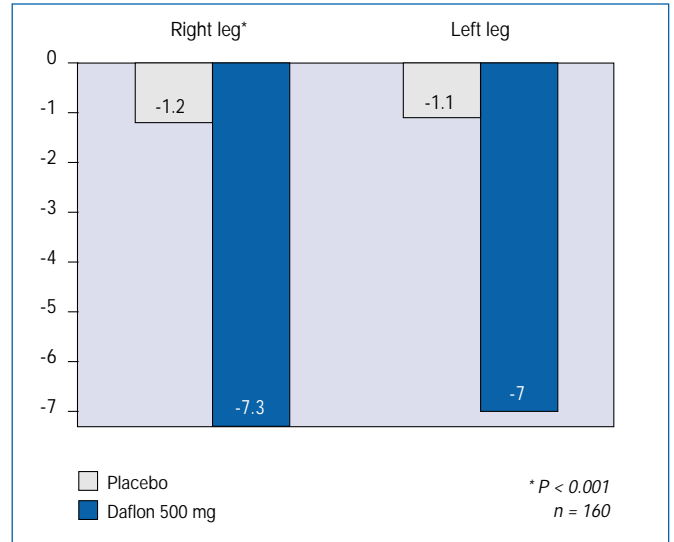
Figure 4. Ankle circumference of affected legs. Mean decrease (in mm) after 2 months of treatment with daflon 500 mg (in blue) or placebo (in grey), 2 tablets/day (Adapted from ref 13).

- *Open trials*
In the multicenter RELIEF study[14] in which 5052 patients assigned C0s to C4 according to the clinical CEAP classification, edema was assessed by the Leg-O-Meter®. A significant improvement ($P<0.0001$) was observed in patients with and without venous reflux (*Figure 5*).
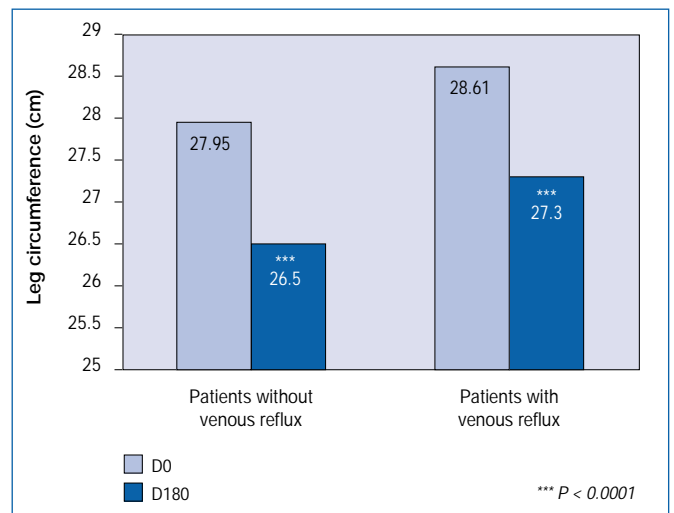
Figure 5. Leg circumference measured with Leg-O-Meter® in the Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids (RELIEF) study. Comparison between patients with a reflux and patients without reflux (Adapted from ref 14).

In 20 patients with CVD stage I-II of the Widmer's classification, the optoelectronic method was used for assessing edema.[15] Nine patients had post-thrombotic syndrome and 11 had varicose veins. Patients with varicose veins showed a significant decrease in the volume of the leg that was more affected (-392 mL; *P*<0.001). For all patients and for the more affected leg, the decrease was of 263 mL (*P*<0.05).

- *Comparative study*

Cospite compared daflon® 500 mg with diosmin and evaluated edema with a simple tape measure.[16] The measurements of ankle and calf circumferences revealed significantly better efficacy in the daflon® 500 mg group (*P*<0.001) (*Figure 6*). This difference was also found for several parameters of strain-gauge plethysmography (with *P* ranging from *P*=0.05 to *P*<0.001).

DAFLON® 500 MG: THE REFERENCE TREATMENT QUOTED IN GUIDELINES

In recent guidelines[17,18] or extensive reviews[19] on the treatment of chronic venous disease, daflon® 500 mg has been quoted as a better-established and well-tolerated anti-edema drug. Daflon® 500 mg is indicated as the first-line treatment of edema and the associated chronic venous disease-related symptoms (eg, edema, fatigue, nocturnal cramps, and heaviness) at any stage of the disease.
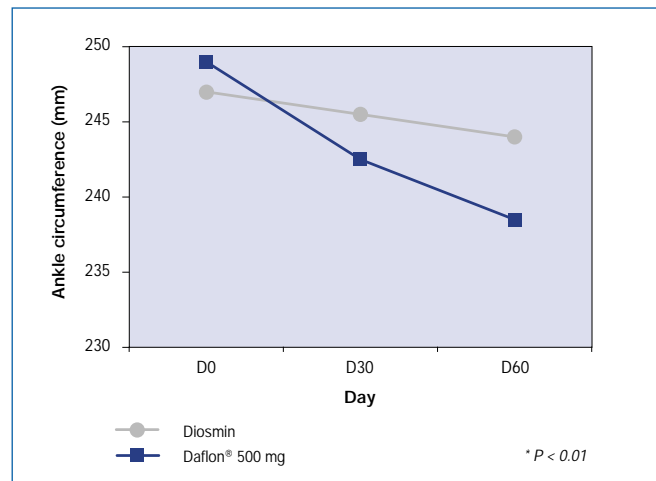

Figure 6. Decrease in ankle circumference (in mm: comparison between two treatment groups daflon® 500 mg and diosmin at the daily dose of 2 tablets (Adapted from ref 16).

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Relationship between the small saphenous vein and nerves: implications for the management of chronic venous disease

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SUMMARY

The aim of this study was to describe the anatomical relations of the short saphenous vein in the lower limb as an aid in locating important anatomical landmarks in the surgical treatment of chronic venous disease. The small saphenous vein (SSV) runs in a compartment demarcated by muscular fascia and a membranous layer of subcutaneous tissue. Muscular contraction can affect the diameter and hemodynamics of the SSV. In light of the close proximity to associated nerves, the clinician should be well aware of the anatomical pitfalls in order to avoid injury to adjacent structures. Providing complete anatomical information facilitates surgical intervention involving SSV procedures for treatment of venous disease.

INTRODUCTION

The saphenous venous compartments

The venous system of the lower limb consists of two major sets of veins. The deep venous system is comprised mainly of the femoral vein and its tributaries which lie beneath the muscles of the leg and carry most of the blood from the leg. The second set of veins is the superficial venous system, ie, the great saphenous vein and the small saphenous vein. The small saphenous vein arises from the outer aspect of the ankle, passes up the posterior aspect of the calf and leg and empties into the popliteal vein. The great saphenous vein starts anterior to the medial malleolus, ascends vertically along the inner aspect of the thigh and leg and empties into the femoral vein.[1] These superficial veins are commonly subject to chronic abnormal dilation and development of varicose veins.

OBJECTIVE

To identify potentially hazardous areas in the treatment of venous disease with surgery and other methods based on anatomical, venographic and ultrasound imaging studies of the saphenous venous compartment.

METHODS

The subcutaneous tissues of the lower limb are arranged in two connective fasciae in the thigh and the leg: superficially below the skin in a membranous layer (formerly called the fascia superficialis), and a deeper layer, the muscular fascia, covering the muscles. These two layers are in close relation with the saphenous venous system. The superficial layer covers the saphenous trunks, while the tributaries are located subcutaneously.

Bailly[2] and then, Lesmasle et al[3], described the great saphenous vein (LSV) as forming the "Egyptian eye" describing the configuration of the LSV between the muscular fascia and saphenous fascia. With duplex scanning, these fasciae appear as two white lines surrounding a black dot; thus, forming an "eye." The other more superficial veins are tributaries.

Ultrasonographic imaging shows that the saphenous veins are interfascial veins, demarcated by two connective fasciae, the saphenous fascia and the muscular fascia, and thus are contained in a "saphenous compartment" (*Figure 1*).[4,5]
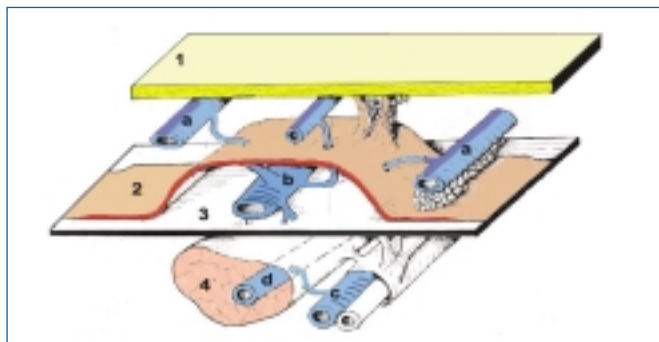
Figure 1. (Adapted from A. Caggiati) The three compartments of the venous system of the lower limb:
1. the skin
2. the saphenous fascia
3. the muscular fascia
The deep venous system is located in the deep layer, beneath the muscular fascia: deep trunks (c) and muscular veins (d) inside the muscles (4). The saphenous trunks (b) are located between the two layers of fascia in the saphenous compartment (saphenous "eye"). Tributaries (a) of the saphenous trunks are found under the skin.

Caggiati and Ricci[6] have proposed the term "saphenous fascia." For this reason, the saphenous veins do not fit the classical description of "superficial" veins.

This is easily recognized by ultrasound, forming the so-called "Egyptian eye" sign (*Figure 2*). This concept was validated at a consensus meeting organized at the UIP congress in Rome.[7]
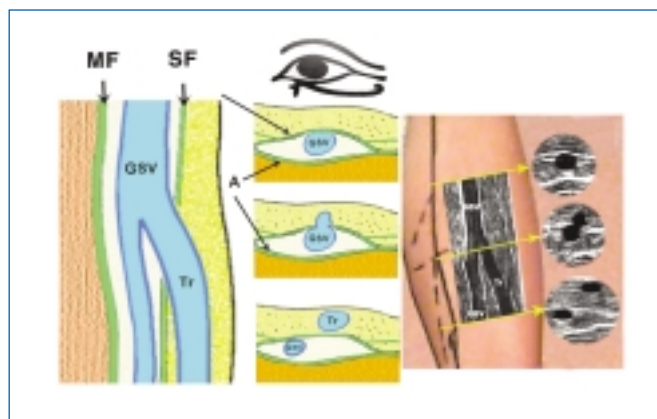
Figure 2. The "Egyptian eye."
MF = muscular fascia / SF = saphenous fascia / GSV = great saphenous vein / Tr = Tributary of GSV.

Functional anatomy

The fascial relations of the saphenous trunks suggest that muscular contraction affects their diameter and hemodynamics. In addition, the saphenous fascia acts as a type of mechanical barrier that can counteract pathologic vasodilatation in varicose veins.

The saphenous tributaries and collateral vessels emerge from this space and are devoid of any fascial sheath. In fact, they are unprotected and thus subject to varicose dilatation before the large saphenous trunks are affected.[6]

Particularities of the small saphenous system

The small saphenous vein (SSV) starts at the lateral malleolus. Running up the calf and back of the leg (*Figure 3,*
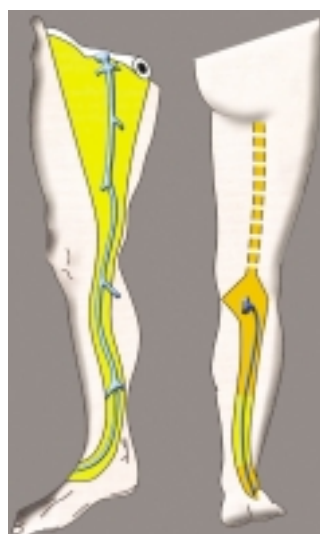
Figure 3. The saphenous compartments for the GSV and the SSV.

shown in orange), the SSV and the great saphenous vein (LSV) (shown in yellow) are located in the "saphenous compartment."[8] But in these areas, the membranous layer (saphenous fascia) is different. It is thick and resistant, appearing more like an aponeurosis (*Figure 4*). Therefore, the SSV is an interfascial vein.

Figure 4. Photograph by C. Gillot: the thick membranous layer (open) of the SSV (1) at the upper calf level, showing the sural nerve (2) and a medial gastrocnemius perforating vein (3).

Figure 5. Drawing by C. Gillot: embryogenesis with the three angio-guided nerves:
1. the axial nerve (sciatic nerve)
2. the preaxial nerve (femoral nerve)
3. the postaxial nerve
4. the preaxial venous plexus (femoral vein)
5. postaxial plexus (dorsal extension of the SSV)
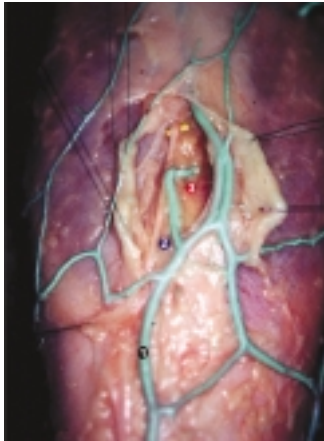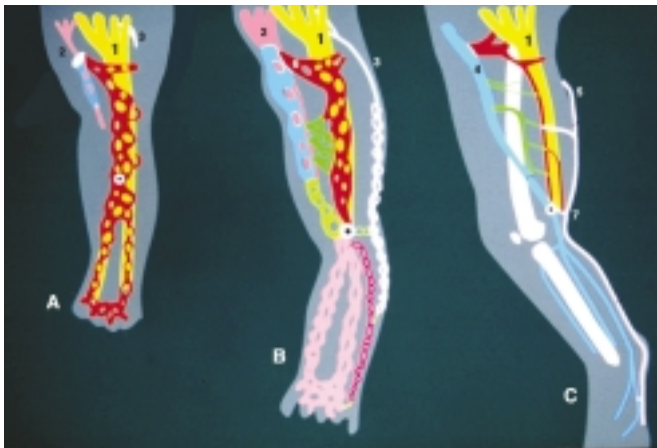*6. axio-preaxial anastomosis (deep femoral vein)*
7. axio-postaxial anatomosis (arch of SSV)
A: Embryo / B: Foetus / C: Adult

Embryology: theory of "angio-guiding" nerves
(*Figure 5*)

Angiogenesis and neurogenesis are closely interrelated during prenatal development and continue to play a physiological part in postnatal life.[9] Evidence indicates that nerves and blood vessels exert reciprocal control over their own growth. For example, "guidance factors,"

including vascular endothelial growth factor A (VEGF-A), should play a pivotal part in the three-dimensional growth patterns of arteries and nerves.

Three "angio-guiding" nerves in the embryo induce angiogenesis of lower limb veins[9,10] along the limb axis:
1. The axial nerve or sciatic nerve (No 1, in yellow). One of its branches, the sural nerve directs development of the SSV.
2. The preaxial nerve becomes the femoral nerve (No 2, in pink).
3. The postaxial nerve (No 3, in white) becomes the posterior femoral cutaneous nerve.

The axial venous plexus (shown in red) participates in formation of the saphenous system. Ventrally, the preaxial venous plexus (shown in blue) becomes the femoral vein and the great saphenous vein. Dorsally, the postaxial venous plexus (shown in purple) becomes the postaxial or dorsal extension of the small saphenous vein.

Thus, capillary blood vessels differentiate along vascular-guided nerves and produce several anastomoses, determining the final configuration of the venous system.

The axio-preaxial anastomosis in the thigh forms the emergence pathway for the deep femoral vein. It connects the axial plexus and its popliteal anastomosis dorsally with the postaxial venous plexus. This is the small saphenous vein arch. Ventrally, it connects with the preaxial venous plexus. It is the origin of the popliteal vein. Lastly, Giacomini's vein represents the posterior anastomosis of the SSV at the root of the thigh.

The SSV and related nerves

The sural nerve (*Figure 6*) is formed by sensory branches of the tibial and peroneal nerves. It is an axial nerve
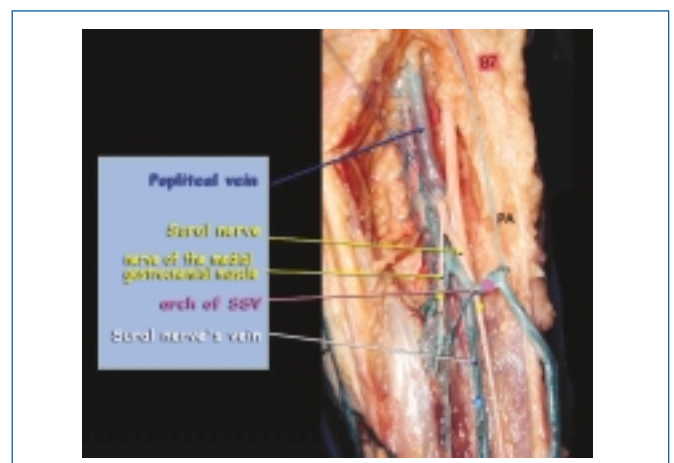

Figure 6. Photograph by C. Gillot: the SSV arch and the nerves. (PA: dorsal or postaxial extension of SSV).

located below the muscular fascia. It is distant from the SSV in the upper part of the calf, joining the SSV at the apex of the calf.

The sural accessory nerve emerges from the fibular nerve, oblique and anterior to the lateral head of the gastrocnemius muscle, below the muscular fascia.

At the apex of the calf, the sural nerve and its accessory branch join in a common trunk (*Figure 7*). This nerve can be called the "SSV nerve" because it accompanies the vein down to the ankle.

Figure 7. Photograph by C. Gillot: the sural nerve (1) with its companion vein (2, in blue), and artery (3, in orange). The SSV (4, in light purple) joins the sural nerve to form a common trunk in the medial aspect of the popliteal vein (5). Laterally, note the accessory nerve (6) joining the sural nerve at the lower part of the diagram (apex of the calf).

RELEVANCE OF THESE ANATOMICAL FEATURES

The close proximity of these nerves to the SSV accounts for possible injury to the nerve during certain surgical procedures (invagination, phlebectomies, and endovenous procedures), particularly at the popliteal level and the apex of the calf.

Anatomy of the SSV[10]

Origin: (*Figure 8*)
- The SSV arises posterior to the lateral malleolus as a continuation of the lateral marginal vein of the foot, close to its companion (sural) nerve. It rises along the lateral border of the tendocalcaneus and then, crosses to reach the middle of the posterior aspect of the leg. Running upwards, it perforates the deep fascia in the lower part of the popliteal fossa between the heads of the gastrocnemius muscle. It ends in the popliteal vein. The lateral malleolar plexus: the origin of the SSV is often a plexus.

The junction at the apex of the calf provides an exchange for blood flow.
- With its inferior leg tributaries (medial and lateral)
- The distribution pathways of the SSV are:

Figure 8. Photograph by C. Gillot: the SSV and the sural nerve (yellow dot) at the ankle. Note the thickness of the fascia layer covering the structures peeled back (on the left).

- The great saphenous trunk or a posterior tributary
- The medial gastrocnemius vein: this is the "vein of the sural nerve"
- The muscular perforator veins in the calf:
  - Posterior and superior perforating veins (Gillot) of the medial head of the gastrocnemius
  - Apical perforating vein of the lateral head of the gastrocnemius
  - Trans-gastrocnemius: soleus perforating veins (lateral)
  - Lateral perforating veins of the soleus muscle

Termination of the SSV

In the popliteal fossa, the small saphenous vein runs a few cm above the popliteal fold to form an anterior arch before terminating in the posterior or posterolateral surface of the popliteal vein.

However, many variations exist, and several types of termination of the small saphenous vein have been proposed based on surgical and echographic findings.

According to a practical and surgical point of view, we described **5 termination types of the SSV**[11] (*Figure 9*) according to the presence (A and B) or the absence (C, D, and E) of SPJ:

Type A: Normal SPJ located less than 5 cm above the crease (83%)
- Type A1: without a common trunk with the medial gastrocnemial veins (62%)
- Type A2: with a common trunk with the medial gastrocnemial veins (21%)

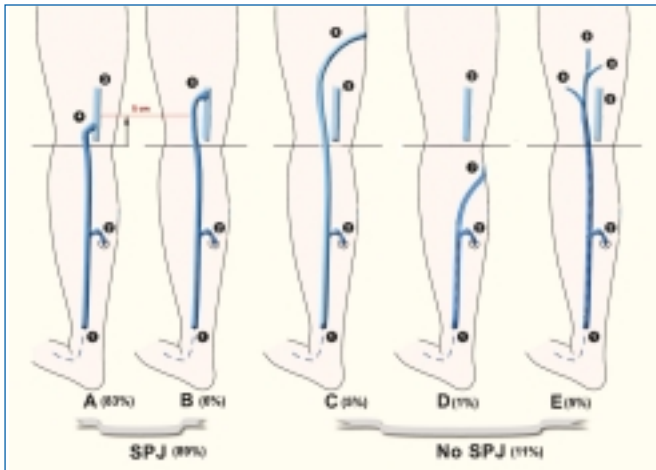Type B: High SPJ, egal or more than 5 cm above the crease (6%)

Figure 9. The 5 different types of SSV termination. A, B with SPJ; C, D, and E with no SPJ.
SSV (1); Calf gastrocnemial perforator (2); Popliteal vein (3); Normal SSV termination with a low arch (4); High termination (5); Giacomini vein (6); Short type of SSV ending with a communicating vein into the GSV (7); Muscular perforators of the thigh (8); Dorsal or cranial extension of SSV (9).

Type C: No SPJ SSV prolongated by Giacomini vein (5%)
Type D: No SPJ Plexiform deep termination in the thigh muscles (5%)
Type E: No SPJ Short termination at the leg level (1%)

Venous arch

The existence of a venous arch (french "crosse") is not a constant finding in normal subjects (70%). It is more common in patients with varicose veins because it is often responsible for a pathological reflux in this area.[12] Such a reflux from higher points, the popliteal or deep femoral vein, feeds the superficial network little.

1/ ARCH of the SSV
The SSV terminates in the popliteal vein; the arch of the SSV usually crosses the lateral aspect of the tibial nerve, close to the nerve (*Figure 10*). The saphenopopliteal junction is located just above the femoral condyle.
The arch of the SSV must be differentiated from the saphenopopliteal junction, the only site of implantation of the SSV in the popliteal vein.
Sometimes (30% of cases) the SSV terminates at a lower level in the popliteal vein, near the femoral condyle. In this case:
- The arch crosses the medial aspect of the tibial nerve.
- The SSV often shares a common trunk with the gastrocnemius veins.
However, the SSV scarcely has a common course with the sural nerve (*Figure 7*).

Figure 10. Photograph by C. Gillot: the arch of the SSV (purple dot) crossing the medial aspect of the tibial nerve. The nerve of the medial head of the gastrocnemius muscle (yellow dot) crosses over the termination of the SSV in the medial aspect of the popliteal vein. The gastrocnemius trunk (blue dot).

2/ "DEEP" EXTENSION of the SSV[10,13]
It is known as an axial extension because it is located dorsally, near the tibial nerve (axial nerve in the embryo). It can join an axial arch (or sciatic nerve arch) which is located ventrally to the sciatic nerve (*Figure 11*).
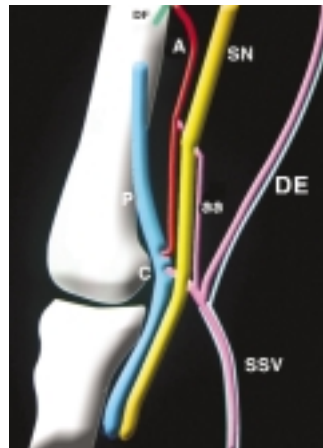
Figure 11. Drawing by C. Gillot: the dorsal or postaxial extension of the SSV (PA). A preaxial vein (A) along the sciatic nerve (SN), axial nerve of the embryo and the axial arch (aa) joining the deep femoral vein (DF).
P = popliteal vein; SSV = small saphenous vein; C = arch of SSV.

3/ "DORSAL" EXTENSION of the SSV
Known as the postaxial or cranial extension of the SSV[14,15] (postaxial nerve of the embryo), it is located more superficially, but below the muscular fascia. It accompanies the femoral posterior cutaneous nerve (*Figure 11*).
It perforates the fascia at various levels, and with Giacomini's vein[16,17] (intersaphenous anastomosis) joins the LSV.

CONCLUSION

The clinician needs to be aware of potentially hazardous areas in treatment of venous disease with SSV approach and procedures. These findings emphasize the usefulness of ultrasonographic mapping prior to an invasive procedure for treatment of chronic venous disease.[18,19]

1/ At the ankle, the origin of the SSV is often plexiform, located deep below the fascia. The nerve is located very close to the vein, surrounded by fat tissue, often dense and associated with sclerosis, which makes approach to it rather difficult.

2/ In the apex of the calf: this is an area of very high risk and the most hazardous:

- It is the junction of several veins, with risk of perforations or of entering the wrong vein during catheterization.

- Possible existence of a "short saphenous artery" which poses a high risk for injection of a sclerosing agent, due to a highly variable surrounding disposition of this artery. For this reason, ultrasonographically-guided procedures in this area are mandatory.[20,21]

- The confluence of nerves which perforate the aponeurosis.

- The perforating veins join the gastrocnemius muscles.

3/ In the popliteal fossa, the veins are very close to the nerves:

- The short saphenous arch is close to the tibial nerve, or sometimes the nerve of the medial head of the gastrocnemius muscle.

- The existence of a common SSV trunk with the gastrocnemius veins is always associated with a medial arch of the tibial nerve.

- The axial extension of the SSV is along the tibial nerve and the sciatic nerve.

- The postaxial or dorsal extension is along the posterior cutaneous femoral nerve.

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Prevalence of patients with chronic venous disease-related symptoms but without visible signs (described as C0s in the CEAP classification): the Italian experience

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SUMMARY

The [$C_{[0S]}$] item of the CEAP classification is one of the emerging topics in venous disease epidemiology. It has been referred to by several studies, but until today it has not been clearly assessed by any specific study. In Italy, the topic has interested several groups of researchers since the 1980s. The author carried out several pilot studies with infrared photoplethysmography (PPG), strain-gauge plethysmography, laser-Doppler and echo-duplex. The results suggested that one of the pathophysiological causes of venous disease-related subjective symptoms without varicose veins could be caused by the reduction of the venous wall tone, and the term hypotonic phlebopathy (HP) to describe these patients with chronic venous-disease related symptoms without varicose veins has been proposed. The diagnosis criteria are focused on symptoms (heavy legs in upright position, restless leg syndrome, subedema and/or evening edema) and signs detected by photoplethysmography (PPG), strain-gauge plethysmography and duplex scanning (reduction of the muscle-venous calf pump and increase of the venous wall compliance).

The prevalence of HP has been assessed between 1989 and 1992 by the Acireale Project, and it showed a 15.90% morbidity, with higher prevalence in females. The most important risk factors for HP are family history and pregnancy. However HP is not rare in males; the principal risk factor for this gender is long periods in a standing position at work.

These observations have been independently confirmed by two studies carried out in France in 1992, which showed a 15% prevalence in a similar group of subjects with functional venous insufficiency.

The author suggests the introduction of the functional phlebopathy term into clinical practice; the diseases characterised by subjective symptoms without anatomic damage, and in their context identify several different frameworks such as the constitutional phlebostasis, HP, and probably many more.

INTRODUCTION

The C_{0S} class of the clinical CEAP classification[1] indicates a particular kind of subject with venous disease-related symptoms, such as heavy legs in the upright position, restless leg, subedema, and/or evening swelling, but without visible signs of venous diseases.

All these subjective symptoms immediately evoke the picture of chronic venous insufficiency, at least when they are associated with clear signs of varicose veins or previous venous disease. Despite the condition is often encountered in daily practice, the so-called phlebopathic symptoms have never been specified in any of the published literature, not even when this aspect was among the main objectives of the study.[2,3] Conversely, it is harder to interpret the meaning of these symptoms when the clinical picture is not clearly defined, and when there are no objective signs of reference of venous disease.

In the past, different definitions have been proposed, such as *phlebopathic diathesis*, *prevaricose syndrome*, and *functional phlebopathy*. The last one, proposed by Bassi in the 1970s,[4] is the most correct, in our opinion, because it stresses the presence of an incorrect functioning in the absence of anatomic alterations.

In 1982, our group indicated that the prevalence of these subjects with varicose symptoms without varicose veins was about the 20% of all people who visited our vascular lab because of suspected venous disease.[5]

In 1986, we investigated 35 symptomatic subjects, using reflection light photoplethysmography (PPG) and we found a ΔR of 200 ± 30 mV, significantly ($P<0.005$) lower than normal values for our laboratory.[6,7] The ΔR indicates the difference between the reflexion light of subcutaneous venous plexus measured after 10 flexion-extension movements of the foot and the same measurement at rest. The measurement's unit of the PPG investigation utilised in the 1980 was the milli volt (mV). This reduction in muscle-venous calf pump effectiveness, according to the pathophysiological behaviors of the varicose syndrome, suggested that the varicose symptoms without varices could be caused by a reduction of the venous wall tone. In fact, by artificially increasing the venous tone with elastic bandages, we observed a normalization of ΔR of PPG.[8]

Believing that these subjects have a reduction of the venous tone without any organic damage, we proposed the term of hypotonic phlebopathy, and we set up an epidemiological study to confirm our hypothesis and to assess the morbidity of this venous dysfunction.

METHODS FOR THE "ACIREALE PROJECT"

One thousand five hundred people were enrolled from the electoral list of Acireale, small town of western Sicily with 50 000 inhabitants, stratifying subjects for age, sex, social level, and residency (sample groups of farmers, fishermen, service industry workers, and students).

One thousand thirty-one people replied positively to the invitation by mail to join the study. All participants received a detailed questionnaire on venous disease history, and underwent an angiological clinical examination to assess the evidence of subcutaneous veins, and several vascular investigations, such as continuous wave (CW) Doppler, strain-gauge (SG) plethysmography, PPG, Echo-Duplex scanning, and laser-Doppler.

Epidemiology

The questionnaire enquired about subjective symptoms, family history, obesity, number of pregnancies, and use of oral contraceptives. The prevalence of hypotonic phlebopathy was assessed according with the following criteria based on subjective symptoms and objective signs assessed by the clinical examination.

Hypotonic phlebopathy
- Subjective symptoms always present;
- Continuous wave Doppler or echo-duplex scanning showing venous patency and absence of valve dysfunction or reflux;
- PPG with $\Delta R < 250$ mV;
- Strain-gauge plethysmography: MVIV >3.0 mL %, with DV <1.7 mL %.

The *maximal venous incremental volume* (MVIV) is the maximal volume reached by the calf during the venous occlusion at the rest, in supine position with the strain gauge placed around the maximal circumference of the calf.

The ΔV indicates the difference between the calf volume measured after 10 flexion-extension movements of the foot and the same measurement at rest. In this dynamic measurement the subject was in the seating position with the strain gauge placed around the maximal circumference of the calf.

Latent hypotonic phlebopathy
- Subjective symptoms referred to in intermittent fashion (spring, summer, pregnancy, standing work, etc);
- Continuous wave Doppler or echo-duplex scanning

showing venous patency and absence of valve dysfunction or reflux;
- PPG with ΔR <250 mV;
- Strain-gauge plethysmography: MVIV >3.0 mL %, with ΔV <1.7 mL %.

Enhanced hypotonic phlebopathy
- Subjective symptoms referred to as continuously present during the examination period, but occasionally in the past, and related to an identifiable cause (ie, people with occasional subjective symptoms in the past and stable symptoms in the last 4 years, after pregnancy).
- Continuous wave Doppler or echo-duplex scanning showing venous patency and absence of valve dysfunction or reflux;
- PPG with ΔR <250 mV;
- Strain-gauge plethysmography: MVIV >3.0 mL %, with ΔV <1.7 mL %.

Senile hypotonic phlebopathy
- Subjective symptoms referred to by aged people as continuously present since the 6th decade, and never or occasionally in the past;
- Continuous wave Doppler or echo-duplex scanning showing venous patency and absence of valve dysfunction or reflux;
- PPG with ΔR < 250 mV;
- Strain-gauge plethysmography: MVIV >3.0 mL %, with ΔV <1.7 mL %.

Varicose disease
- Evidence of subcutaneous dilated veins with reflux, with or without subjective symptoms.

Venous valve incompetence without varicose veins
- People showing a small reflux (less than 0,5 sec) in one or more parts of some superficial veins, without dilatation.

This last unusual diagnosis was needed because more people showed small anatomical and functioning alterations, so small that it was impossible to assign to the varicose vein a diagnosis, but nevertheless it was impossible to consider it normal from an anatomical point of view because of the reflux.

Instrumental measurement and pathophysiology

Continuous-wave Doppler was performed in the standing position, focusing on the most important veins of the lower limb (femoral vein, saphenous cross, great saphenous vein above and below the knee, popliteal vein, small saphenous vein, tibial veins) assessing the venous patency and the reflux.

Echo-Duplex scanning was used in people who showed any evidence or suspicion of venous reflux at continuous-wave Doppler, and in a small group of thirty subjects to assess the venous compliance. This parameter was reported by measuring the difference between the venous diameters in the supine position and in the upright position.

PPG (reflection light photoplethysmography) was performed the standardized way, that is, in the sitting position, to assess the ΔR between the baseline and top values of the curve after 10 flexion-extension movements of the foot; the refilling time was also measured in the ankle.

Strain-gauge plethysmography was performed to assess the venous wall compliance during venous occlusion, measuring in the supine position the maximum incremental venous volume at the calf level (MVIV). In the sitting position the drop of volume (ΔV) was measured after 10 flexion-extension movements.

Laser Doppler parameters (resting and standing flux and venous-arteriolar reflex VAR) were used in a small group of twenty subjects to assess the microcirculatory features. Fifty healthy subjects, without symptoms and/or signs of venous disease were utilized as a normal control group.

RESULTS

The results shown in this paper come from those published in the original paper in 2000,[9] and have been revised and classified following the CEAP criteria,[1] including the recent revisions and refinements.[10-18] The most important suggestion of these recent revisions was to add the letter N in the items E, A, and P of the CEAP classification. The item A_N indicates the condition of patients without any anatomical alteration of the venous system; this suggestion is very appropriate for Hypotonic Phlebopathy [HP] patients and we used it in our results. The item P_N indicates the absence of reflux, obstruction, and reflux plus obstruction (frequently observed in several veins of patients with chronic venous disease). We agree also with this suggestion. Nevertheless, because we hypothesized and identified the reduction of venous tone as pathophysiological alteration in HP patients presenting without reflux and without obstruction, and because the reduction of venous tone is not a physiological status, instead of P_N we prefer to indicate HP as $P_{//(N)}$.

Concerning the item E_N, which would indicate an unidentified aetiology, we disagree with this suggestion

because in the universal semiology of medical definition, until today, a disease with unidentified aetiology is defined as PRIMARY DISEASE. Because HP cannot be defined as CONGENITAL DISEASE, and it is not SECONDARY to other pathophysiological conditions, we considered HP as a primary disease. For these reasons in the following pages the Hypotonic Phlebopathy (HP), is indicated as $C_{(0S)}$ $E_{(P)}$ $A_{(N)}$ $P_{(//N)}$.

Epidemiology

Prevalence of the different conditions:

The 1031 participants of the survey were divided up as follows:
- 330 (32.00%) were healthy;
- 140 (13.57%) were affected by "other vascular diseases";
- 234 (22.69%) had varicose veins (VV [$C_{[2\text{-}3\text{-}4]S}$ – E_P – A_S – P_R]);
- 163 (15.80%) were symptomatic and had small reflux (valve incompetence) without varicose vein dilatation (reflux without varicose veins (RWVV [$C_{[0S]}$ – E_P – A_N - P_R]);
- 164 (15.90%) were symptomatic but did not present varicose veins (hypotonic phlebopathy, HP [C_{0S} – E_P – A_N - $P_{//[N]}$]). Among the 164 HP patients one can distinguish:
  • 44 (26.83%) with hypotonic phlebopathy (HP)
  • 45 (27.43%) with latent HP
  • 49 (29.89%) with enhanced HP
  • 26 (15.85%) senile HP

The prevalence of HP in females was twice as many this in males whatever the age group.
Latent, enhanced, and senile HP showed a uniform distribution for sex.
Males showed a higher prevalence in latent HP than females in the groups aged 30 to 39, and 40 to 49; in the 40-to-49 year age group, males had a higher prevalence in the enhanced HP too.

These findings are probably due to the greater attention paid to health problems in the 4th and 5th decades of age, with a greater response to the invitation to participate.

Prevalence of venous symptoms in hypotonic phlebopathy

About the most characteristic symptoms of these 164 patients with HP, we found:
- *heavy legs*: 122 (74.39%: 26.21% males, and 48.17% females);
- *evening edema*: 58 (35.36% : 10.36% males, and 25.0% females); edema, never reached the clinical characteristics of C3 classification;
- *night resting cramps and restless leg syndrome*: 48 (29.26%: 9.14% males, and 20.12% females).

Leg heaviness is the most frequent symptom. Women, especially, report it (48.17%), in agreement with usual clinical observations.
Men report it less (26.21%). Evening edema and restless leg syndrome have a lower prevalence than heavy legs.

Prevalence of risk factors in hypotonic phlebopathy

The risk factors considered by our questionnaire were family history for venous disease, obesity, constipation, pregnancy, and use of oral contraceptives. The prevalence of the risk factors in the different sub-groups of HP is summarized in *Table I*.

Out of the 89 women identified as HP (all categories), 45 had one or more pregnancies, and 11 used oral contraceptives, either at time of examination or in the past. The prevalence of risk factors in the women of our study is summarized in *Table II*.

Vascular Investigations

PPG - The average of ΔR was 275±40 mV in healthy people, and 200±15 mV in HP [C_{0S} – E_P – A_N - $P_{//[N]}$] (*P*<0.005), showing a small yet significant reduction of the effectiveness of muscle-venous calf pump. In VV

	Total (men and women) n = 164	Hypotonic phlebopathy (HP) n = 44	Latent HP n = 45	Enhanced HP n = 49	Senile HP n = 26
Family history n (%)*	69 (42.1)	19 (43.2)	20 (44.4)	27 (51.1)	10 (38.5)
Obesity n (%)*	61 (37.2)	8 (18.2)	13 (28.9)	28 (57.1)	12 (46.1)
Constipation n (%)*	48 (29.3)	12 (27.3)	10 (22.2)	15 (30.6)	11 (46.3)

*The percentage (%) is related to the number of patients n in each sub-group of HP.

Table I. Prevalence of risk factors in male and female patients with hypotonic phlebopathies (Acireale study).

	Total (women)	Hypotonic phlebopathy (HP)	Latent HP	Enhanced HP	Senile HP
	n = 89	n = 30	n = 21	n = 24	n = 14
Family history n (%)*	46 (51.7)	15 (50.0)	13 (61.9)	16 (66.6)	2 (14.3)
Obesity n (%)*	31 (34.8)	7 (23.3)	4 (19)	13 (54.2)	7 (50.0)
Constipation n (%)*	26 (29.2)	10 (33.3)	7 (33.3)	4 (16.7)	5 (35.7)
Pregnancy n (%)*	45 (50.6)	15 (50.0)	6 (28.6)	20 (80.5)	4 (28.6)
Use of oral contraceptive n (%)*	11 (12.3)	4 (13.3)	2 (9.5)	5 (20.8)	-

*The percentage (%) is related to the number of patients n in each sub-group of HP.

Table II. Prevalence of risk factors in the women with hypotonic phlebopathies (Acireale study).

$[C_{[2-3-4]S} - E_P - A_S - P_R]$ ΔR showed the lowest values, with very high ($P<0.0005$) statistical significance versus HP and healthy people (*Figure 1*). The refilling time of PPG showed similar behavior, with a small reduction in the HP and very important reduction in VV (*Figure 2*). *Strain-gauge plethysmography* - The average of MVIV was 4.5±0.4 mL % in HP and 2.9±0.3 mL % in healthy people ($P<0.005$). ΔV was 2.7±0.5 mL % in HP and 1.5±0.4 mL % in the controls.

Echo-Duplex-scanning – We did not find reflux or obstruction in subjects with HP. Out of 20 subjects with HP and 10 healthy subjects, received an Echo-Duplex scanning examination, to assess the venous wall compliance, measuring the difference between the vein diameter in supine and upright position. The diameter was measured
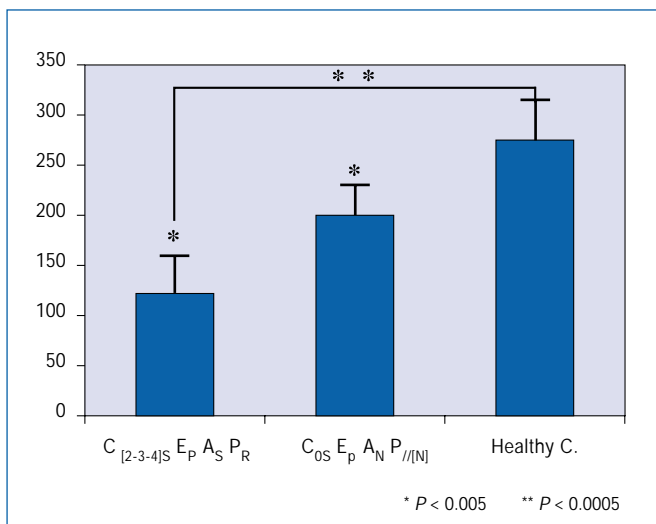

Figure 1. Photoplethysmography (PPG) investigation of the Acireale patients. Values on the Y-axis represent the difference between the reflexion light (ΔR) of subcutaneous venous plexus measured after 10 flexion-extension movements of the foot and the same measurement at rest. ΔR is expressed in mill volts (mV). Comparison of ΔR between healthy subjects and patients with varicose veins, and hypotonic phlebopathy is shown on this graph.
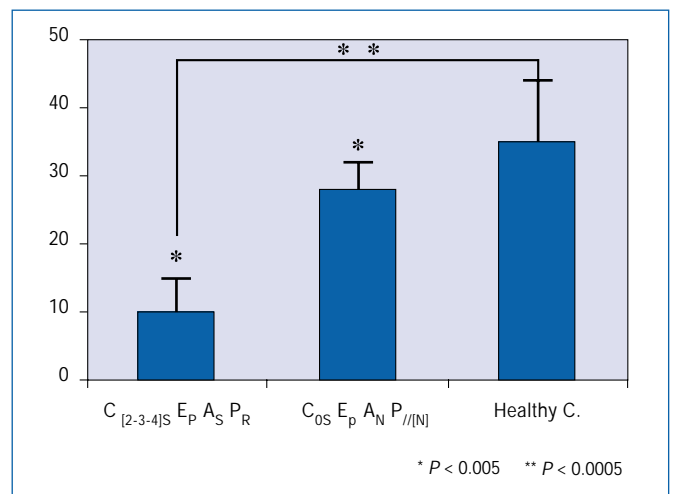

Figure 2. Photoplethysmography (PPG) investigation of the Acireale patients. Values on the Y-axis represent the refilling time in seconds (sec). Comparison of refilling time between healthy subjects and patients with varicose veins, and hypotonic phlebopathy is shown on this graph.

at the popliteal vein, tibio-peroneal trunk, and gastrocnemial veins. The venous diameter was always higher in the upright position. The difference between diameters in the two positions was:
- HP $[C_{0S} - E_P - A_N - P_{//[N]}]$: popliteal v. 3.40±1.10 mm; tibio-peroneal trunk 2.70±0.80 mm, gastrocnemial v. 3.50±1.30;
- healthy people: popliteal v. 1.50±0.53 mm, tibio-peroneal trunk 1.10±0.57 mm, gastrocnemial v. 1.30±0.48 mm.
The statistical analysis showed that the difference was relevant ($P<0.0001$)[19] (*Figure 3*).
People with RWVV $[C_{[0S]} - E_P - A_N - P_R]$ mostly showed a localized valve dysfunction, with flaps or prolapse.

Laser-Doppler - 10 HP $[C_{0S} - E_P - A_N - P_{//[N]}]$ subjects and 10 healthy people received a laser-Doppler examination (with the probe placed 10 cm above the internal malleo-
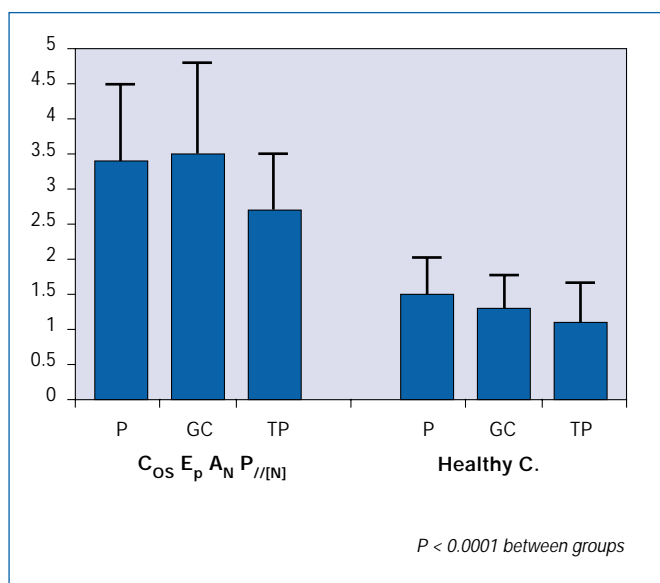
Figure 3. Echo-Duplex scanner examination of the Acireale patients. Values on the Y-axis represent the difference in venous diameter (in mm) in the measurement between the upright and the supine position. Abbreviations: P = popliteal vein, GC = gastrocnemial vein and TP = peroneal tibial vein.

lus) to complete the functional venous assessment. This study showed a significant ($P<0.0001$) increase of resting and standing flux in HP (RF 10.4 ± 1.9 perfusion unit, SF 7.28 ± 1.2) than in healthy people (RF 8.0 ± 0.9, SF 3.6 ± 0.6). The venous-arteriolar reflex was reduced (30% in HP, 55% in controls).[20]

COMMENTS

In our opinion, the increased MVIV and the decreased ΔV of strain-gauge plethysmography, and the decrease in PPG ΔR without reflux or venous obstruction, demonstrate that the symptoms in HP [$C_{0S} – E_P – A_N - P_{//[N]}$] could be sustained by the increase of the venous wall compliance.

The reduction of PPG refilling time without valve dysfunction could be explained as a faster refilling caused by a decrease of filling resistance sustained by the reduction of the venous and venular tone, showed also by the changes of the parameters of the laser Doppler.

On the other hand, the reduction of venous tone in these symptomatic subjects is confirmed by the behavior of venous diameter difference in the supine and upright positions.

These results confirm our hypothesis of the reduction of venous tone with the increase of venous wall compliance

are the pathophysiological substrate of the varicose symptoms without varicose veins HP [$C_{0S} – E_P – A_N - P_{//[N]}$].

Our findings, collected since 1982, have been independently confirmed by two French studies. One was carried out on military recruits,[21] the second on a vast survey in the Paris region.[22] The authors found a 15% prevalence of functional venous insufficiency in the 20-to 30-year age group. They remark that the clinical disturbances are only functional (heavy legs, paresthesia, nocturnal cramps in the calves, restless legs) without clinical and anatomical abnormalities of the veins. The disturbances often reflect a hyperdistensibility of venous wall, which can be detected by venous occlusion plethysmography, but it is fairly common to see varicosities and telangiectasias.[23]

This occasional concurrency of experimental data and the similar conclusions reached by two different groups in different times are a very good unexpected confirmation that our hypothesis was true.

The venous wall hypotonia could be sustained by the structural alterations of connective,[24,25] cellular,[26,27] matrix, and smooth muscle cells dysfunction[28] of the venous wall, like those recently described in the varicose veins.

Leg heaviness is the most frequent symptom, especially referred to by women in agreement with usual clinical observations. Men report this symptom fewer times (26.21%). Evening edema and restless leg phenomena have a lower prevalence than heavy legs, as underlined also by the Edinburgh study.

The family history of venous disease is the risk factor with the highest prevalence (42.07%). It seems to be important in determining the appearance of all types of HP and it occurs especially in the female gender, except in senile HP.

Obesity is the second risk factor of HP (37.19%); nevertheless its importance is modest in constitutional HP, and only for women (15.90%). In latent HP its role remains low, though more important for males (20.00%). In senile HP it is important for both sexes, appearing in 46.15% of senile population. But its highest importance is as an enhancing factor in enhanced HP (57.14%), especially for men (30.61%).

Constipation has a general prevalence of 29.26%. It is an important risk factor especially for women, and in senile HP for both gender. Like obesity, it plays a very important role as an enhancing factor for males.

Pregnancy is a very high risk factor for HP. In our study we found 89 women with HP and 45 of them (50.56%)

had had one or more pregnancies. It has a very important role as an enhancing factor; 80.53% of the women with enhanced HP had had one or more pregnancies. However, we think that in senile HP the enhancing role of previous pregnancy is less important than obesity and constipation.

Conversely, the use of oral contraceptives is not a risk factor for HP; its general prevalence is below 20%, reaching this prevalence value only as an enhancing factor, but the significance is very low.

About the 163 patients of the study population (15.80%) with valve incompetence and reflux in different levels of the superficial venous system, without varicose veins (RWVV $[C_{[0S]} - E_P - A_N - P_R]$), we underline the relevance of this anatomic and functional condition in males, being related to stress caused by work in a prolonged standing position. From the pathophysiological point of view, it is never a healthy state. Its clinical evidence could be modest or absent for a long time but its progression in varicose veins is always possible.

CONCLUDING REMARKS

The C0s CEAP patients' condition as described in the CEAP classification is a true problem in the clinical practice. Few papers have been published about this topic but recently the interest of the researchers has been growing. Beyond our opinion, we remind the constitutional phlebostasis with endocrine peculiarities described by Allegra,[29,30] the papers by the group of Cloarec, and the recent report by Jawien. In his epidemiological study,[31] the majority of the people classified as C_0 (20% of general population) was symptomatic[32] (C_{0-S}).

According to Bassi, we suggest including in the classification of venous diseases the *functional phlebopathies* characterised by subjective symptoms without anatomic damage, and in their context identify several frameworks such as the constitutional phlebostasis, hypotonic phlebopathy, and probably many more.

The identification of these clinical pictures is important not only from the nosographic and academic point of view, but also in clinical practice. In fact, especially severe symptoms of HP are improved by regular use of phlebotonic drugs, (spring and summer times).

The hypothesis that the functional phlebopathies, and particularly hypotonic phlebopathy, could be a pro-

dromic phase of varicose disease (prevaricose syndrome) is rather improbable. Our uncontrolled follow-up carried out for over 10 years has shown varicose evolution only in the group RWVV in which a structural anatomic damage in the form of the valve dysfunction is still present.

The diagnosis of HP must be supported by the assessment of venous wall hypotonia by instrumental examination; the $[C_{0S} - E_P - A_N - P_{//[N]}]$ alone, until today does not authorize the conclusive diagnosis of HP. As remarked by H. Partsch in his kind comment to the Acireale Project,[9] our paper is probably the first attempt to correlate the subjective venous disease-related symptoms with the functional parameters from vascular lab.

The strength of the relationship does not emerge because this goal was not included in the study design. The relationship between subjective symptoms and functional parameters from vascular lab is one of the main goals of another study recently approved by the Ethic Committee of Padua, and that we hope it will start as soon as possible.

From the epidemiological point of view, we confirm the importance of family history and pregnancy as the main risk factors of dilative phlebopathies. Conversely, the often-suggested role of oral contraceptives as a risk factor for venous wall dysfunction (varicose veins and HP) has not been confirmed.

Therefore, concerning these kinds of phlebopathies, the use of oral contraceptives is not harmful; on the contrary, since they reduce the number of pregnancies, which are directly related to varicose veins, they could be paradoxically considered preventive. Nevertheless, we need to remember that using oral contraceptives enhance the risk of venous thrombosis because they interfere with the coagulative system.

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Congress and conference calendar

■ XIXth ANNUAL CONGRESS OF THE AMERICAN COLLEGE OF PHLEBOLOGY

This congress will be held in San Francisco (USA) from November 10-13, 2005.

• *For further information, please contact:*

President: Neil S. Sadick

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■ XIIth ANNUAL NATIONAL CONFERENCE OF THE VASCULAR SOCIETY OF INDIA (VSICON 2005)

This congress will be held in Kerala (India) from November 10 to 13, 2005.

• *For further information, please contact:*

Dr M. Unnikrishnan
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Sciences & Technology, Medical College
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■ IXth CONGRESSO NAZIONALE COLLEGIO ITALIANO DI FLEBOLOGIA - CIF

This congress will be held in Fermo (Italy) from November 10 to 13, 2005.

• *For further information, please contact:*

Congress President: Prof G. Genovese

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■ IXth CONGRESSO NAZIONALE CIF

This congress will be held in Fermo (Italy) from November 11 to 13, 2005.

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GC Congressi - Roma

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Web site: www.flebologia.unisi.it

■ **XXVIIth CONGRESSO NAZIONALE DELLA SOCIETA' ITALIANA DI ANGIOLOGIA E PATOLOGIA VASCOLARE (SIAPAV)**

This congress will be held in Rome (Italy) from November 16 to 19, 2005.

• *For further information, please contact:*

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■ **ANNUAL SYMPOSIUM OF THE BELGIAN WORKING GROUP OF ANGIOLOGY / SYMPOSIUM ANGIOLOGY, VASCULAR DISEASE AND THE KIDNEY**

This congress will be held in Brussels (Belgium) on November 19, 2005.

• *For further information, please contact:*

Congress President: Prof S. Motte
Secretariat: Dr K. Von Kemp

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■ **VIth ASIAN CHAPTER CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY "UPDATE MANAGEMENT OF VASCULAR DISEASE"**

This congress will be held in Bangkok (Thailand) from November 18 to 20, 2005.

• *For further information, please contact:*

Congress President: Prof Novo S.

Chairman organizing committee: Sopon Jirasiritham, MD

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      +662 20 11 527
Fax: +662 20 11 316

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■ **JIFA (JOURNEES INTERNATIONALES FRANÇAISES D'ANGEIOLOGIE)**

This congress will be held in Paris (France) from January 13 to 14, 2006.

• *For further information, please contact:*

President: Prof F. A. Allaert
Scientific Secretariat: Dr Michèle Cazaubon
Secretariat: Dr Isabelle Koskas

Tel: +33 1 47 27 10 63
Fax: +33 1 47 27 21 47

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Web site: www.sfa-online.com

■ XXXIst TRADITIONAL ANGIOLOGICAL DAYS 2006

This congress will be held in Prague (Czech Republic) from February 24 to 26, 2006.

• For further information, please contact:

President: Dr Roztočil Karel
Secretariat: Eva Uhrova

Clinic of Cardiology, IKEM
800 Vídeňská
140 00 Praha 4, Czech Republic

Tel: +420 261 362 238
Fax: +420 261 362 216

E-mail: karel.roztocil@medicon.cz
Web site: www.angiologie.cz

■ CFPV (COLLEGE FRANÇAIS DE PATHOLOGIE VASCULAIRE)

This congress will be held in Paris (France) from March 15 to 18, 2006.

• For further information, please contact:

President: Prof M. Vayssairat
Secretariat: Mrs F. Staud

18, rue de l'Université
75007 Paris, France

Tel: +33 1 55 04 82 13
Fax: +33 1 55 04 82 17

E-mail: cfpv-jmv@wanadoo.fr
Web site: www.cfpv.imag.fr

■ NATIONAL SURGERY CONGRESS

This congress will be held in Ankara (Turkey) from May 24 to 28, 2006.

• For further information, please contact:

President: Prof Altan Tuzuner
Secretariat: Prof Semih Baskan

Turk Cerrahi Dernegi Merkez Binasi
Koru Mah. Ihlamur Cad. No :26
06810 Cayyolu Ankara, Turkey

Tel: +90 312 241 99 90
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E-mail: turkcer@turkcer.org.tr

■ XIXth EDUCATIONAL CONFERENCE OF POLISH PHLEBOLOGICAL SOCIETY - Vth POLISH-ITALIAN PHLEBOLOGICAL SYMPOSIUM

This congress will be held in Bydgoszcz (Poland) from June 01 to 03, 2006.

• For further information, please contact:

President: Prof Arkadiusz Jawień

Klinika Chirurgii Ogólnej
Szpital im. J. Biziela SP ZOZ
ul. Ujejskiego 75
85-168 Bydgoszcz, Poland

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E-mail: ajawien@ceti.com.pl

■ XXIInd WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY

This congress will be held in Lisbon (Portugal) from June 24 to 28, 2006.

• *For further information, please contact:*

Congress President:
Prof José Fernandes e Fernandes

Organizing secretariat:
AISC & MGR – AIM Group
Via Adelaide Ristori, 38
00197 Rome, Italy

Tel: +39 06 809681
Fax: +39 06 8088491

E-mail: iua2006@aimgroup.it

■ VIIth ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM

This congress will be held in London (UK) from June 30 to July 2, 2006.

• *For further information, please contact:*

President: Prof Alun H. Davies

Anne Taft, Executive Secretary
EVF, Beaumont Associates
PO Box 172
Greenford, Middx, UB6 9ZN, UK

Tel: +44 20 8575 7044
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E-mail: evenousforum@aol.com

■ INTERNATIONAL SOCIETY OF COLO-RECTAL SURGEONS CONGRESS

This congress will be held in Istanbul (Turkey) from June 25 to 28, 2006.

• *For further information, please contact:*

President: Prof Kemal Alemdaroglu
Secretariat: Prof Ergun Erdogan

Istanbul University
Cerrahpasa Medical Faculty
Department of Surgery
34303 Cerrahpasa Istanbul, Turkey

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Fax: +90 212 633 48 41

■ TURKISH NATIONAL CARDIOVASCULAR SURGERY CONGRESS

This congress will be held in Istanbul (Turkey) from September 01 to 05, 2006.

• *For further information, please contact:*

President: Prof Isa Durmaz
Secretariat: Prof Serap Aykut Aka

Turkish Cardio Vascular Surgery Association

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