CONTENTS

PHLEBOLYMPHOLOGY

EDITORIAL

Dear Readers,

*In their article entitled "Interaction between ageing, inflammation process, and the occurence of varicose veins", **Julia Buján** and coworkers from Spain report interesting immunohistochemical findings on leg veins in normal subjects and varicose veins in chronic venous disease patients. Specimens were obtained from aortocoronary bypass and varicose vein surgery and were differentiated according to age: patients under and over 50. This approach showed that inflammatory cells play an important role in both the aging process and the development of varicose veins.*

***Oscar Maleti and Marzia Lugli** from Modena, Italy, give an overview of their experiences with the revolutionary surgical technique they have developed in which a neovalve is created in patients with postthrombotic syndrome and massive, deep axial reflux. The essential idea of this method is to perform a vein wall dissection and to create an intimal flap that may act like a venous valve. The method was applied in carefully preselected patients only, some of them suffering from congenital venous valvular aplasia. Valvular competence assessed by duplex ultrasound and air plethysmography was regained in 86% of cases, and 90% of leg ulcers healed. This new procedure is certainly an ingenious technique in the hands of extremely skilled and well-trained vascular surgeons.*

*A very useful collection of different instruments for describing patient-reported outcome can be found in the survey presented by **Françoise Pitsch**, Servier, Paris. Such tools are of increasing interest not only to assess the efficacy of phlebotonic drugs, but should also for use in longitudinal studies and after endovenous procedures. Good doctors do not base their judgment only on objective tests, but will always consider patient satisfaction as well.*

***Olle Nelzen** from Sweden, who is a pioneer of modern epidemiological studies, specifically in the field of leg ulceration, gives us some important hints concerning data collection. It is very encouraging to read in his article how systematic improvements in health care reduced the point prevalence of venous leg ulcers by 46% within a 14-year period in his region. This was mainly achieved by venous surgery based on Doppler/duplex investigations, which should be done in every leg ulcer patient.*

*The three-dimensional computer reconstructions of blood vessels presented by **Jean-François Uhl** and co-workers from Paris at the end of this issue of Phlebolymphology are fascinating and their implications for our understanding of vascular anatomy are self-explanatory. What a bright future for our students and young surgeons!*

Happy reading.

Hugo Partsch, MD

Interaction between ageing, inflammation process, and the occurence of varicose veins

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SUMMARY

Failure of the vein wall continues to be a subject of intense research, the aim of which is to establish a cause that will allow us to prevent or at least slow down this undesirable process. We have investigated the role played by inflammatory cells, especially leukocytes, in the etiology of varicose veins. We hypothesize that venous insufficiency could result from the interaction between two processes: tissue aging and abnormalities in the leukocyte/endothelial cell interaction. These two processes, the individual contribution of which depends on the context, are believed to compound each other resulting in venous insufficiency. Thus, in young individuals, venous insufficiency might be induced by accelerated tissue aging, whereas in older subjects, it could be due to an interaction between the aging process, which is slower and prolonged, and abnormalities in the interaction between leukocytes and endothelial cells.

Selected abbreviations and acronyms

CVI	chronic venous insufficiency
IL	interleukin
iNOS	inducible nitric oxide synthase
MMP	matrix metalloproteinase
TGF-β	transforming growth factor β
WBC	white blood cell

Keywords:
varicose veins, white blood cells, leukocytes, chronic venous insufficiency

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The venous circulation is today perhaps among the most well-understood systems of the human body. However, the insidious and often prolonged nature of venous insufficiency hinders investigation into the factors that could trigger this disease, the progression of which is intimately linked to the natural process of tissue aging. Hence, in this area of medicine, as in many others grouped under the term "chronic," the clear conscience of the clinician occurs at the expense of the despair of the specialist. We believe that through analyzing some aspects of our understanding of this "silent" disease, patients, doctors, and health care managers will soon act together in combating venous disease.

Chronic venous insufficiency (CVI) as a clinical definition indicates a loss in efficiency of normal vein function. Its symptoms, however, are a product of effects secondary to the inefficiency of the system, and thus the origin of this disease is not yet clearly established.

The vein wall is a highly dynamic structure with 2 well-differentiated sides that guarantee its correct functioning: the luminal and adventitial sides. The luminal side of the vein wall, where the presence of valves indicates that the complex interaction between blood and wall takes on a particularly dynamic and metabolic dimension, is lined with an endothelium whose characteristics differ from the well-known properties of the arterial or microvascular endothelium. The adventitial side, the site of mechanical support and nutrient intake for the entire wall, also plays an active role in fighting against the forces of gravity. This complex role of the vein wall is, nevertheless, discrete and any decrease in its efficiency runs a slow course; hence its ambiguous assigning to the group of "chronic diseases."

Our interest lies in the role that certain endogenous or environmental factors have in the development of CVI. Among the intrinsic factors, aging is being ascribed an ever more relevant role. Some of the genetic features of the aging process, such as the loss of function of telomerases and their involvement in maintaining the cell population or changes in the expression (dysregulation) of other genes, lead to qualitative and quantitative changes in cellular and extracellular proteomics that enter into the realm of consequences more than cause.

The participation of white blood cells where they release in the development of venous disease is well established,[1-3] and aggregated when they are known to be the most common cause of venous stasis. Stasis of blood flow, whether at the luminal level due to valve failure or at the adventitial microvascularization level, triggers the activation of leukocytes as part of an inflammatory process aimed at functional recovery and tissue repair. Hence, what in principle is a protective mechanism can turn hostile to the detriment of the blood vessels.

Little is known about how CVI leads to the local tissue destruction seen so commonly in clinical practice.[1] Increased evidence points to a central role for abnormal leukocyte–endothelial cell interactions in the pathogenesis of this condition.[4-6] Some theories have suggested that leukocytes are sequestered in the legs of patients with CVI. This sequestering leads to the activation of white cells, which results in the generation of free radicals, proteases, histamine, neutrophil chemoattractants, and complement.[7-10] The actions of these substances destroy the endothelial layer of the vessel and their basement membranes, increasing vascular permeability and disturbing microcirculatory flow.[11,12] Other authors propose other factors that might activate leukocytes and cause them to act inappropriately in the venous system. Some factors present in the plasma of patients can activate unstimulated leukocytes.[13] Such a factor could be any of a variety of stimuli, including bacteria, fungi, and their products. Endothelial cells also need to be activated so that leukocytes can migrate into the tissue through the endothelium. Scarce cytokine expression has been observed in some investigations, even though a considerable number of monocytes have been noted to adhere to the endothelium and migrate into tissue, suggesting that factors other than inflammatory mediators (high pressure, low shear stress) may activate the endothelium.[14]

Little is known about the role of inflammatory cells in the biochemical and histological changes observed in varicose disease. Increased numbers of macrophages/monocytes and mast cells have been observed in varicose veins,[15,16] suggesting that vein damage in refluxing saphenous veins is associated with a leukocyte infiltrate.[15] Mononuclear cells such as neutrophils normally circulate in a quiescent state, but when activated are capable of adhering to the endothelium and entering tissues a variety of noxious substances known for their ability to cause tissue damage.[1] Active proteases can either be secreted directly by inflammatory cells, including elastase and cathepsin G produced by polymorphonuclear leukocytes, chymase and try ptase by mast cells, and granzymes by lymphocytes, or can be generated from circulating zymogens by activation in close contact with the cells.[17]

The aim of the present study was to establish the influence of age on the changes that occur in the vein wall and to characterize leukocyte infiltration in the wall, exploring its association with the varicose condition.

PATIENTS AND METHODS

Forty vein specimens were obtained during surgery from patients undergoing bypass surgery (controls) or surgery for varicose veins. All 40 subjects gave their informed consent to participate in this study. The vein specimens were first visually checked for the presence of damaged areas and then divided according to subject age to establish the following study groups:

Group I control (n=20)

This group comprised 10 vein specimens harvested from patients under 50 years of age (mean 38±8.8; range 36-45 years) and a further 10 specimens from patients aged 50 years or over (mean 71.5±10.6; range 57-89 years). These segments of saphenous vein were obtained from patients with no history of venous insufficiency or proven reflux during aortocoronary bypass surgery.

Group II varicose veins (n=20)

This group comprised 10 vein specimens harvested from patients under 50 years of age (mean 39.4±6.8; range 26-46 years) and a further 10 specimens from patients aged 50 years or over (mean 60.7±9.4; range 52-70 years). This time, the portions of saphenous vein were obtained during vein stripping from patients with primary venous insufficiency and clinically confirmed reflux.

Inflammatory cells

The detection and quantification of inflammatory cells was undertaken using immunohistochemical techniques. For the identification of CD4/CD8 and CD68 cells, tissue samples were fixed in 10% formaldehyde, embedded in paraffin, and cut into 5-mm slices using a microtome (Microm, Barcelona, Spain). The sections were then deparaffinated, hydrated, and equilibrated in phosphate-buffered saline (PBS) buffer (pH 7.4). Pretreatment of tissue by heat-induced epitope retrieval was required. This involved immersing the tissue in 10 mM citrate buffer pH 6.0 and microwave boiling for 2 minutes. Acetone-fixed frozen sections were used to identify CD19-positive cells and neutrophil collagenase (matrix metalloproteinase [MMP] 8).

We used as primary antibodies a mouse monoclonal anti-human CD68 (1:50) (DakoCytomation, Glostrup, Denmark) to identify macrophages/monocytes, mouse monoclonal anti-human CD4 (1:10) (Neomarkers, Fremont, Calif) and CD8 antibodies (1:50) (DakoCytomation, Glostrup, Denmark) to identify T cells, a mouse monoclonal anti-human CD19 antibody (1:100) (Neomarkers, Fremont, Calif) to identify B cells, and a mouse monoclonal anti-human MMP8 (1:200) (Chemicon, Temecula, Calif) to identify neutrophils. The antigen-antibody reaction was detected by the alkaline phosphatase- labeled avidin-biotin procedure. The chromogenic substrate contained alpha-naphthol and fast red. Nuclei were counterstained with Carazzi hematoxylin. After the immunohistochemical procedure, the tissue sections were examined under a light microscope (Zeiss, Jena, Germany). Infiltrated cells were counted under the microscope (× 200) in 4 areas of 0.5 mm^2 per patient (40 high-power fields per group). All values were expressed as means±SE. Data were compared using the Student *t* test. The level of significance was set at $P<0.05$.

RESULTS

Inflammatory cells

In general, we observed increased numbers of CD4$^+$ cells, B cells (CD19$^+$), and monocytes/macrophages (CD68$^+$) in the varicose veins with respect to the normal patients. No differences were observed in CD8 and neutrophils compared with control veins. In addition, we examined the distribution of these cells as an indication of the inflammatory environment in aging and CVI.

In the control vein specimens, CD4$^+$ cells were scarce, appearing mainly in the adventitial layer in segments obtained from the young subjects *(Figure 1a)* and more toward the media and infiltrating the valves in control

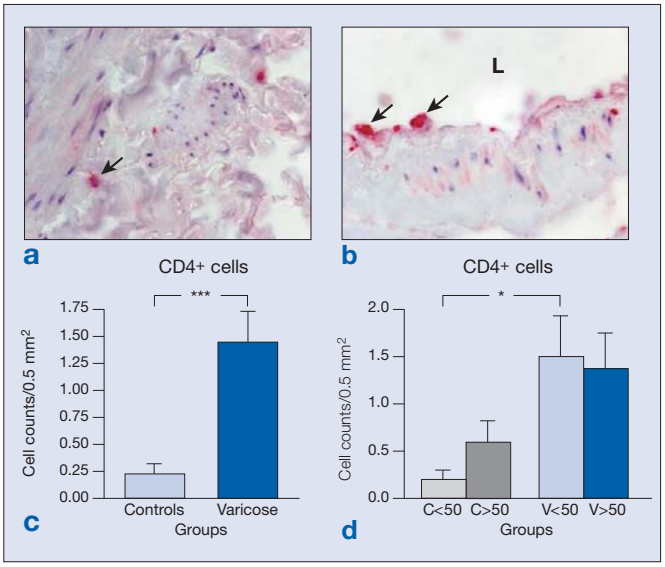


*Figure 1. Immunohistochemical detection of CD4$^+$ cells (➔) in the control veins (a) and varicose veins of an older patient (b). Quantification of the stained cells in the different groups excluding the age factor (c) showing significant differences (***P<0.005) between varicose and normal veins due to the disease process. Quantification and statistical analysis including the age of the patients (d). Note that this factor did not affect the number of CD4$^+$ cells (*P<0.05).*

Abbreviation: C, control; L, lumen; V, varicose vein.

specimens from older subjects. Varicose veins showed significantly increased numbers of CD4+ cells compared with controls *(Figure 1c)* ($P<0.005$). In specimens from the older subject group, CD4+ became infiltrated in the subendothelium and valves *(Figure 1b)*, while in the varicose vein/young specimens these cells were mainly observed in the adventitial and medial layers. Varicose veins showed significantly increased CD4+ cells compared with normal veins, in the younger population *(Figure 1d)*. These results appear to indicate that the presence of CD4+ cells is related to the varicose condition.

Immunolabeling for CD8 cells was scarce both in the vein wall of healthy and varicose specimens and appeared in the adventitial and medial layers *(Figure 2a and b)*. Differences between the groups were not found *(Figure 2c and d)*. Only vein specimens from one subject, in which areas of hemorrhage and inflammation were observed, showed significantly higher numbers of CD8+ cells. This subject was therefore excluded from the study. B cells were identified by the CD19 antibody. The distribution of CD19+ cells was conditioned by age. In the wall of specimens from young subjects, B cells mostly appeared in the endothelium *(Figure 3a)*, whereas in vein specimens from the older subjects *(Figure 3b)*, CD19+ cells were mainly confined to the adventitial layer, regardless of the varicose or healthy condition. B-cell numbers were significantly higher in varicose veins compared with healthy veins *(Figure 3c)* ($P<0.005$). When stratified by age, this difference was only maintained for the group of older subjects *(Figure 3d)* ($P<0.01$).

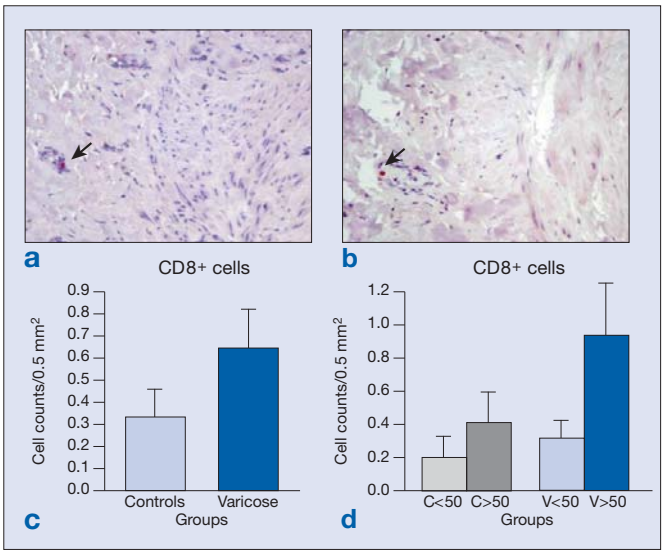


Figure 2. Image of the immunohistochemical detection of the number of CD8+ cells (➔) in the vein walls of healthy specimens (a) and varicose specimens (b). Quantification of CD8-labeled cells in the different groups excluding the age factor (c) showing no significant differences between the varicose and normal veins. Differences were also not significant when the different age-groups were compared (d).

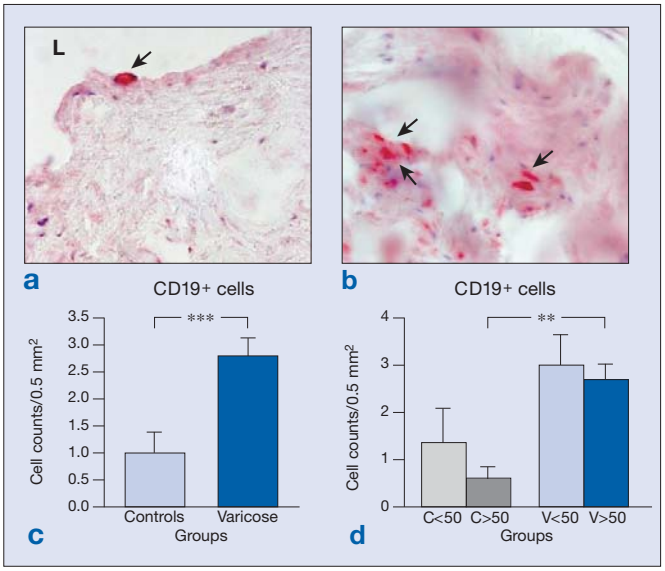


*Figure 3: Immunohistochemical detection of CD19+ cells (➔) in control (a) and varicose veins (b). Quantification of positive cells in both groups excluding the age factor (c) showing significant differences (***P<0.005) attributed to the disease process. When stratified by age (d), differences between control and varicose veins were only maintained in the older study population (**P<0.01).*

Abbreviations: C, control; L, lumen; V, varicose vein.

In control specimens, CD68+ cells were observed in the lower layers of the tunica media *(Figure 4a)*, while in the varicose vein specimens, these cells infiltrated the upper areas of the media.

Higher numbers of CD68+ cells (macrophages/monocytes) were recorded in the varicose group *(Figure 4c)* ($*P<0.05$). In specimens from young persons, the odd CD68+ cell appeared throughout the vessel wall with the exception of the intimal layer of the vein. In the specimens from elderly subjects, these cells were observed in the upper media layer, endothelium, and valves.

The most notable changes in the distribution of CD68+ cells in varicose vein specimens were the presence of monocytes/macrophages at the valves and nearby

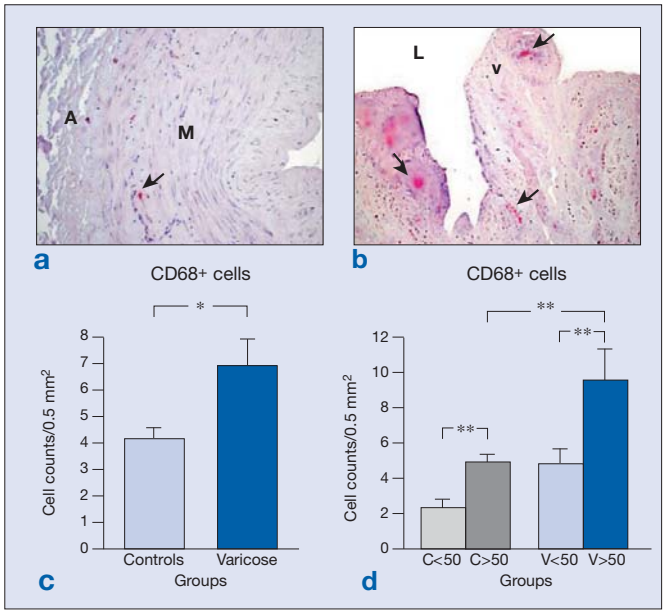


*Figure 4. Images showing the immunohistochemical detection of CD68+ cells (➔) in control (a) and varicose veins (b). Regardless of age (c), the varicose state was related to a significantly increased infiltration of CD68+ cells in the vein wall (*P<0.05). Quantification and statistical analysis including the age of the patients (d) indicated that this factor significantly increased the number of labeled cells in the two groups of patients (**P<0.01).*

Abbreviations: A, adventitia; L, lumen; M, media; v, valve.

endothelium *(Figure 4b)*. In addition, significantly higher numbers of these cells were detected in the older varicose veins ($P<0.05$).

When stratified by age, higher numbers of CD68+ cells were detected in both healthy and varicose specimens from the older subject group *(Figure 4d)*. Among the specimens from older subjects, significantly more CD68+ cells were detected in the varicose veins than in the controls ($P<0.01$) *(Figure 4d)*. Hence, overall there were clear differences attributable to age and the varicose condition in the distribution patterns and the numbers of CD68+ cells. These cells were also found to be associated with valve failure.

MMP8 is a type II collagenase secreted by neutrophils. The expression of this enzyme was not observed in the control vein specimens from the younger group *(Figure 5a)*. In healthy specimens from the older subjects, MMP8 labeling appeared in areas of the tunica media and adventitia corresponding to degranulated neutrophils *(Figure 5b)*. In specimens from young subjects with varicose veins, small numbers of nondegranulated cells could be seen, in all the layers of the vein wall. In the varicose vein specimens from older subjects, MMP8+ cells were found in the valves *(Figure 5d)*, intima, adventitia *(Figure 5c)*, and vasa vasorum of the vein wall, many of which were already degranulated. Hence, the most outstanding finding related to this enzyme was neutrophilic degranulation related to age regardless of the healthy or varicose condition of the veins.

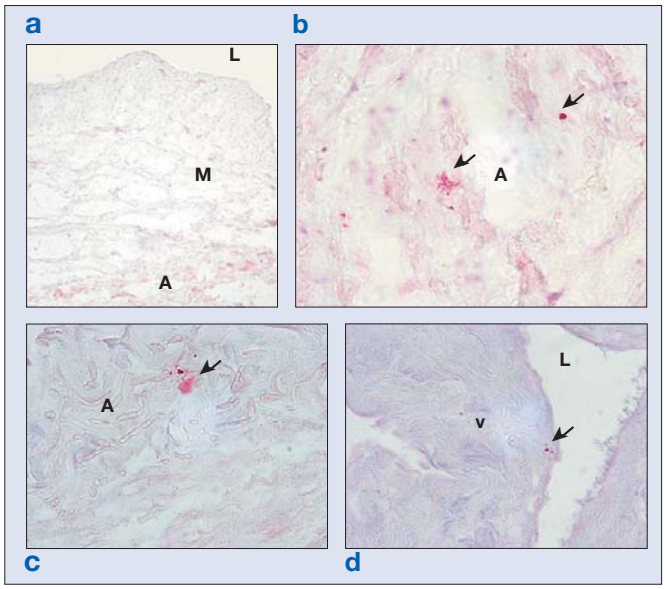


Figure 5. Immunohistochemical matrix metalloproteinase (MMP) 8 study showing staining for neutrophils (➔). In the control group of patients younger than 50 years (a), we observed no neutrophils in the vein wall.
In control (b) and varicose (c) specimens from the older subjects, some preserved cells were observed in the adventitial layer and other neutrophils appeared degranulated. In the older control specimens, some neutrophils could also be observed on the valves (d).

Abbreviations: A, adventitia; L, lumen; M, media; v, valve.

DISCUSSION

In previous papers,[18] aging was established as an important factor responsible for changes in the vein wall, and these changes were similar to those produced at the different stages of CVI. In this study, we tried to separate the effects of these 2 overlapping processes particularly those related to the inflammation process contributing to the general mechanism of aging (physiological) or the inflammatory response to disease (venous insufficiency).

The basal state of vein wall is characterized by a special property of microcirculation venules, where the wall shear stress is low and endothelial cells can recruit inflammatory cells. In young people, white blood cells are rarely seen in the adventitial microvessels. During aging, we observed the movement of white blood cells from the adventitia to the medial layer and the upper part of the vein wall, along with the presence of white blood cells at the level of the valves, especially CD4+ and CD68+. These types of inflammatory macrophages/monocytes play a key role in tissue remodeling due to their ability to release MMPs, growth factors, and proinflammatory cytokines. In addition, some authors advocate that macrophages/monocytes can enhance cell adhesion molecule expression by the vascular endothelium[19] and induce changes in the smooth muscle phenotype.[20] It would be interesting to determine whether the presence of these cells was a consequence or cause of vein wall remodeling during aging. Whichever the case, the discrete presence of these cells from the microvessels toward the vein interior would be consistent with the immunohistochemical changes in collagen and MMPs in the aging vein wall[21] and with the reduction in elastin components and increased elastase activity previously described by us.[22] The presence of these inflammatory cells in the medial layer of the wall could be the triggering factor for remodeling of the wall, perhaps as the consequence of a discrete but sustained chronic inflammatory process.

When we evaluated the appearance of white blood cells in varicose processes, we found a general significant increase in all the cells examined (except CD8 and neutrophils) with respect to control, healthy veins, once again supporting the participation of inflammatory cells in the changes that affect the insufficient vein wall. Nevertheless, the distribution of these cells in the vein wall and the effects of age also need to be established.

In young CVI patients, CD4+ T lymphocytes were detected mainly in the adventitial area as occurred in the control group, only these appeared in significantly greater numbers. In the vein specimens from older subjects, a change was observed in the distribution of these cells, which accumulated at the level of the valves and in adjacent endothelial and subendothelial areas. Our findings differ in part from those of other authors,[16] who described no significant increase in the number of T lymphocytes in varicose veins. The increased number and more importantly the distribution of CD4+ cells confirm the changes that occur at the valve and luminal surface of the insufficient vein in older patients.

CD4+ lymphocytes, depending on the types of cytokine they produce, can be of the T helper (Th) 1 or Th2 type.[23] Th1 lymphocytes secrete interleukin (IL) 2 and interferon gamma, which induce the inflammatory response through 2 mechanisms: facilitating the cell immune reaction and stimulating B cells. Th2 lymphocytes produce IL-4, IL-5, IL-9, IL-10, and IL-13. This array of cytokines is, in part, responsible for activating B cells. The increased numbers of the CD19+ population in the varicose condition could be correlated with the change from an inflammatory status provoked by the CD4+ cells. Other authors[24] find no changes in B lymphocytes (CD20+,CD30+), although we observed the expression of the CD19+ epitope in all B cells except plasma cells, indicating the wide distribution range of this cell type.

It is well known that macrophages/monocytes accumulate at varicose vein valves, and they are more commonly observed adhering to the valve and to the vein wall above the valve complex,[24] suggesting a role in the genesis of primary vein dysfunction.[15] These findings confirm those of other studies[16] in which macrophages/monocytes and mast cells were differently distributed throughout the vessel wall, showing a significant increase in the varicose vein wall, compared with controls. Takase et al[14] observed CD68+ macrophages on the endothelium, subendothelium, and all other areas of the insufficient vein wall. We propose that the presence of these cells on the luminal surface and in particular on the valves is a good indication of valve dysfunction, a rationale supported by its significant increase with age. The set of varicose vein specimens from the older subjects showed a greater accumulation of macrophages both in the areas of the vein wall and along the valves. The disease thus enhances this difference.

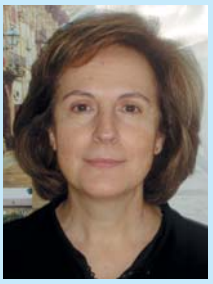
The increase in CD68+ cells has been correlated with the overexpression of transforming growth factor β (TGF-β) and that of inducible nitric oxide synthase (iNOS)[24] with the extent of damage. These findings are in agreement with previous results from our laboratory. Thus, we detected increased TGF-β levels in the veins of CVI patients,[22] which, added to the augmented CD68+ cells detected here, would support Jacob's findings.

The deposition of these cells in the valve area in CVI allows us to establish an infiltration gradient during the aging and disease process, which is probably related to the changes in pressure and shear stress at the level of the valves proposed by Takase et al.[14]

Finally, we examined the part played by neutrophils in these processes. In the literature regarding the genesis of CVI, authors such as Sayer[16] report no difference in the behavior of these cells in the vein wall, although others have described differences in the peripheral circulation. According to some authors, in the disease state, neutrophils in the blood are activated through the mediation of enzymes secreted upon the degranulation of neutrophils.[25,26] Our findings are not completely in line with this theory concerning neutrophil activation (as measured by their degranulation), since we observed neutrophil degranulation in both control and varicose vein specimens from older subjects, suggesting an indirect measure of vein wall ischemia. This factor would support the chronicity of the process.

In summary, the findings of our study indicate a clear increase in the inflammatory environment provoked by aging, which starts with the vasa vasorum and goes on to markedly affect the valves in the vein wall. In our young patients with CVI, most damage appears in the luminal area and this damage then becomes more generalized in older patients with CVI, particularly at the level of the valves.

It may therefore be concluded that inflammatory cells play a pivotal role both in the aging process and the varicose process. The distribution of these cells is a good indicator of the state of the vein wall and also allows us to infer that dysfunction of the microvascular endothelium is the primary effect related to age, while valve dysfunction is most marked in venous insufficiency. Although the disease and aging processes run a parallel, overlapping course, the aging process may be accelerated in CVI coinciding with the remodeling of the vein wall affecting both its cellular component[18,21,22] and its extracellular component, as observed in our previous work.



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Neovalve reconstruction in postthrombotic syndrome. Technique, indications, and results

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ABSTRACT

Patients with leg venous ulcer (C6 patients according to the CEAP classification) affected by deep venous reflux often fail to respond to conservative therapies, and the presence of non-healing or recurrent ulcers may lead one to consider surgery. However, even if surgery is properly indicated, traditional techniques such as femoral transposition and valve transplantation are not always suitable, and in these cases a de novo valve reconstruction represents a surgical opportunity. Our neovalve reconstruction technique consists in creating an intimal flap by performing a wall dissection. The purpose is to create an antireflux mechanism that reduces venous hypertension. This technique was applied from December 2000 in 39 selected patients (43 operations) affected by postthrombotic syndrome or valve agenesis with grade IV according to Kistner's classification.

The results are extremely encouraging and would seem to suggest that deep venous surgery may be appropriate in cases where conservative therapies fail, and where treatment of superficial and perforator insufficiency disappoints.

INTRODUCTION

A significant section of the population suffers from chronic venous disorders, which are often the cause of severe and permanent invalidity. When associated with superficial venous insufficiency without compromise of the deep venous system, chronic venous insufficiency can be more easily controlled and healing achieved in almost all cases.[1,2] By contrast, when the deep venous system is itself directly affected, healing can only be achieved in a limited number of cases. In most cases, we have to settle for a kind of "peace with honor", a delicate balancing act. By this is meant a scenario in which discomfort, edema, and trophic lesions are controlled with conservative therapies. The most common treatment is the application of an elastic stocking,[3] however, the more severe deep venous system disorders demand compression levels that are not well tolerated. It should also be mentioned that even where an elastic stocking is worn, the treated limb can

Keywords:
neovalve, deep venous surgery, deep venous insufficiency, postthrombotic syndrome.

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deteriorate due to episodes of lymphangitis or dermatitis, particularly in warm climates. Wearing an elastic stocking can also create psychological problems for young patients, who tend to regard themselves as invalids. The result can be a drastic reduction in their quality of life. Requests for corrective surgery or definitive treatment are now common, and they come from patients who have heard media reports that describe varicose surgery as the rapid and lasting solution to their problems. When they seek medical advice, they often meet with caution, and their disappointment is all the more intense. To understand why so many colleagues are skeptical, it needs to be borne in mind that surgical tradition has always defined postthrombotic patients as inoperable.

The reasons for this are threefold.[4] The first is doubtless the fear of significant complications following surgery, for instance pulmonary embolism. A complication of such gravity, possibly fatal, might not be tolerated in the context of a disease that is certainly invalidating, but with a negligible risk of death. The second reason is that venous pathophysiology presents far more complicated hemodynamic mechanisms than arterial pathophysiology. Furthermore, our experience in the field is comparatively scant and still in its initial stages. The third and not least significant reason is that the surgery is by no means simple. As such, it requires prolonged training in centers of excellence, but since these centers are few and far between, there is still widespread ignorance of the specific surgical techniques involved.

Besides these three factors, a controversial note needs to be sounded about the efficacy of such surgery. Many critics remain skeptical because at 5 years of follow-up the results show a deterioration. Our reply to such reservations, which we throw down as a provocative gauntlet, is simply this: if the exact, same criteria were used to point the finger at other branches of surgery, many operations would not be performed.

It was Kistner[5] who first provided definitive evidence that the effective relief of symptoms could be achieved after neutralizing deep venous reflux. Kistner's pioneering operation was the first surgical approach to restoring the femoral valve to its original, functional condition.

Controversial at the time, the case involved reflux in a pathophysiological configuration that today we know as primary valve insufficiency (PVI). Unlike postthrombotic syndrome, where the valves are completely destroyed, in primary valvular incompetence the valves are present but malfunctioning. Despite this difference, the pathophysiological scenario is similar. Kistner was able to restore hemodynamic equilibrium to the leg by reconstructing only one femoral valve.

A few years later, Kistner[6] pioneered another operation, valve transposition, whose objective was to create a mechanism which achieved valvular continence in a leg affected by postthrombotic reflux; in other words where the valves were destroyed. Taheri[7] and Raju[8] followed a similar route, performing an arm-to-leg venous valve transplant.

It should be mentioned that deep venous insufficiency, which generates hypertension at deep venous system level, almost invariably entails varicose veins and perforator insufficiency. Treating superficial reflux is required, since such cases often present severe clinical symptoms and ulcers, even if in isolation. Correcting the superficial venous system without correction of the deep venous system achieves a significant improvement, but results are less lasting.

Attempts to create a neovalve in a devalvulated axis have also involved experiments with homograft and allograft implants in animals. However, such operations have not yielded satisfactory results in humans.[9,10]
Other surgical attempts at creating an antireflux mechanism have been reported,[11,12] and the operation we are proposing can be situated in this research field. In a nutshell, neovalve reconstruction aims at creating an antireflux mechanism by fashioning one or two flaps constructed by dissecting thickened vein wall tissue. These neovalves perform a similar function to a physiological venous valve as we reported in previous papers.[13,14]

TECHNIQUE

The anatomical structure of the human valve is so complex that we are not at present able to attempt a precise reproduction. It is for this reason that our objective is to create a mechanism that has the same function as nature's valve, though not necessarily the same morphology. The neovalve is based on the creation of a flap that allows the blood to flow in one direction only, preventing its return in the opposite direction. The

idea came to us when we observed that in cases of postthrombotic syndrome the vein wall is thickened by a process of fibrosis. This thickened tissue, it occurred to us, might be used to obtain a flap that could be fashioned so as to imitate the action of the valve (*Figure 1*). To create a neovalve it is first necessary to perform a phlebotomy, a perpendicular parietal incision and dissection so as to obtain a leaflet or flap. If the vein wall were always of an even thickness, the procedure would be based on a few simple guidelines: the length of the parietal incision and the depth of the dissection (*Figure 2*). The bicuspid valve, in which two pockets are fashioned, would require less depth of incision than in the monocuspid, where just one deeper pocket is fashioned. However, in postthrombotic disorders the fibrosis is so uneven and anarchic that in the patients we have operated on we have never found two cases similar in terms of anatomy and lesions. This means that each neovalve construction varies from case to case. In the absence of standard scenarios, the only common denominator in our series of patients was that of actual flap creation. Preoperative assessments and intraoperative manual palpation can partly help in determining the construction site, but in the majority of cases it is only possible to decide on how to proceed after the phlebotomy has been performed and the precise nature of the lesions ascertained. The fibrosis is often so thick that it creates a double channel inside the vein and this particular anatomical feature can be exploited to create the neovalve. Once the pocket has been created and its efficiency tested, experience shows that there is a risk of recurrent adhesion. To prevent this from happening it is enough to fix the flap in the semi-open position.

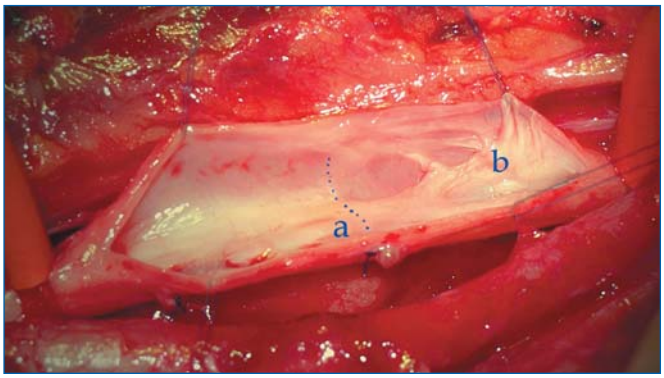

Figure 1: Postthrombotic wall damage
a) line of parietal dissection
b) fibrotic native valve

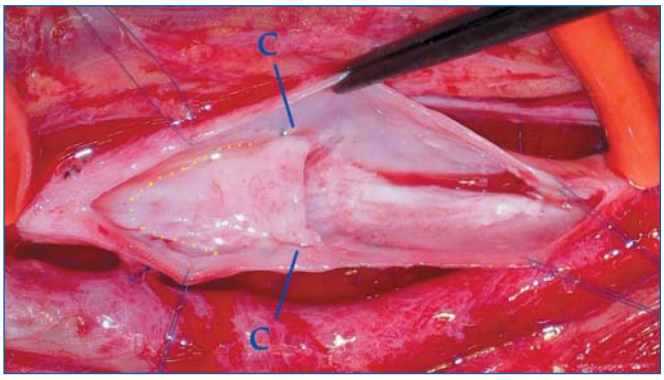

Figure 2: Neovalve and endophlebectomy
c) stitch fixing the flap in semi-open position dotted line: depth of dissection

The ideal site for the neovalve would be the popliteal vein, since an antireflux mechanism here would obviate a reflux in several axes, femoral and profunda veins flowing together in this area. However, this rarely proves practicable for technical reasons, hence the preferred site is the femoral vein. The valve's efficiency is tested during the operation by applying a suture on the proximal side of the phlebotomy and inspecting the pocket's continence (bulge in valve) on the distal side while the phlebotomy is still open. This is most important and allows us to make minor adjustments before concluding the operation. It is not always possible to create a flap, but given that our series has an intention-to-treat rate of 3/43, failure is infrequent.

MATERIAL AND METHODS

From December 2000 to December 2007 we performed 43 neovalve construction operations in 39 patients (20 males, 19 females, median age 57, range 29 - 82) affected by severe chronic venous insufficiency. All patients presented an ulcer resistant to conservative therapy, and treatments on the superficial venous system and perforators did not prove feasible. The ulcer had been present or recurrent for over 5 years and caused the patient major discomfort. Thirty-five patients were affected by postthrombotic syndrome and presented deep venous thrombosis almost 10 years previously; 4 patients were affected by valve agenesis. All patients underwent descending venography that showed a reflux grade IV according to Kistner. Two patients presented thrombophilia: one patient presented a Leiden-factor alteration and the other a congenital defect of antithrombin III. No patient had a contraindication to anticoagulant therapy. This group of patients had been

excluded from conventional antireflux surgery, such as femoral transposition or valve transplant. All patients underwent duplex scanning and air plethysmography detecting venous filling index (VFI) and ejection fraction (EF). Associated comorbidities were not sufficient to dissuade us from operating. All patients were adequately informed about the innovative nature of this technique and received a detailed informed consent form.

Apart from 4 operations under general anesthesia, the others were performed under epidural anesthesia. The position of the patients on the operating table was supine with the leg rotated externally and the knee slightly flexed. The operation is performed through an incision of 10 cm in length in most cases at the intermediate third of the thigh, but could also be performed at the proximal or distal third. We proceed with careful dissection of the femoral vein, taking care not to damage the lymphatic vessels so as to avoid loss of lymph in the postoperative period. Particular refluxes in the deep collateral circle, the result of postthrombotic syndrome, should be tied, as should reflux in the doubled femoral vein.

A foot-thigh elastic stocking (35 mm Hg) was applied in the postoperative period. Movement of the leg was encouraged and certain patients underwent physiotherapy and distal 30° bed-elevation. On the second postoperative day movement was resumed and anticoagulant therapy was replaced by oral anticoagulation therapy to obtain an international normalized ratio of 2.5–3 for a six-month period. In other cases subcutaneous heparin was administered for one month. Patients were advised to use a Class I elastic stocking for at least one month after the healing of the ulcer. Ulcer healing was finally achieved with a short-stretch bandage.

RESULTS

During follow-up, all lower extremities were screened with duplex scanning at 1 and 6 months after the operation and thereafter at one-year intervals. Air plethysmography was performed one month after surgery to assess VFI and EF variations, and thereafter annually. The average follow-up was 33 months (range 1-84) at December 2007.

The operative and postoperative mortality rate was 0% and no cases were complicated by pulmonary embolism. The median hospital stay was 6 days.

Minor postoperative complications occurred in 7 patients (17.5%): 3 wound hematomas, 3 seromas, and 1 wound infection.

Early deep vein thrombosis located below the neovalve site was detected in two patients (5%). One patient stopped anticoagulant therapy for reasons unknown. No early thrombosis at the operative site was detected. Early deep vein thrombosis below the neovalve site occurred in 2 cases (4.7%). Late deep vein thrombosis occurred in one patient (2.3%), 8 months after the operation when she resumed oral contraception. Ulcer healing was observed in 39 cases (90.7%), while ulcer recurrence was observed in 3 cases (7%).

Neoalve competence was established in 37 cases (86%). There were 6 cases of valve failure during the follow-up period, making for 14% overall neovalve incontinence. Postoperative instrumental assessment shows statistically significant improvement in VFI and EF. Postoperative venography was performed in 27 patients before discharge.

DISCUSSION

In the majority of patients classified CEAP C6 or C5, conservative therapies are selected. Various types of bandage are applied to achieve ulcer healing when, as happens periodically, the ulcers reappear. Elastic stockings are also used as reinforcement, but the high levels of compression required usually cause discomfort that meets with reluctance on the patient's part. Requests from patients seeking a more radical solution also meet with reluctance on the part of doctors, who manifest misgivings about saphenous vein stripping in patients with a history of deep venous thrombosis. It is easy to imagine that treatment of the deep venous system is still regarded with particular suspicion and diffidence. Aging goes hand in hand with the increase in problems related both to deterioration of muscle compliance and to the presentation of diseases affecting joints and arteries. This all aggravates problems to do with compression stockings. Young patients, by contrast, in an attempt to strike a balance between their health and a normal social life, are often inconstant in their use of containment stockings, and this can lead to a rapid deterioration in their condition, complicated further by problems of self-image and, in some patients, depression. In terms of hemodynamics the health of these patients is compromised on various levels: deep, superficial, and

perforator. Correcting a superficial-system reflux can restore equilibrium to the system, and it should be observed that deep venous system reflux is not necessarily synonymous with serious symptoms or cutaneous ulcers. Not infrequently, we come across young patients with a deep reflux which is well compensated by physical exercise and an efficient muscular pump, provided, of course, that there is careful monitoring of the superficial system.[15] When the problem is related to perforator insufficiency, results can be achieved by treating this alone, but the presence of deep venous reflux often highlights the long-term inadequacy of such treatment and the risk of recurrence is high. Sclerotherapy also helps in maintaining homeostasis, and the various systems work in synergy to achieve acceptable clinical conditions, provided compression is not excessive. Should such therapies fail, and in the absence of contraindications of a general and local nature, serious consideration should be given to an operation on the deep venous system. Treating postthrombotic syndrome is not easy since we still lack a means of gauging thoroughly the full extent of an occlusion or the significance of a stenosis and reflux.[16] Clinical observation reveals that reflux is often less tolerated than occlusions, but this distinction is often not valid since the two processes, reflux and stenosis-occlusion, are frequent bedfellows. Raju points out the key role of stenosis-occlusion of the proximal iliocaval system rather than subinguinal reflux pathology.[17]
The availability of endoluminal corrective surgery has revolutionized the treatment of postthrombotic syndrome in this area. However, our personal experience is that a persistent, Grade IV subinguinal reflux provokes a state of hypertension both in patients with a serious primary iliocaval disease as well as in those where iliocaval flow has been restored. This hypertension is quite capable of maintaining the clinical situation under discussion. One can quite readily understand how in hybrid diseases reopening the iliocaval axis can result in a limb's improvement. However, if this were all that is needed, the logical conclusion would be that the subinguinal tract can manage quite happily, free of symptoms, in the absence of a valve. This flies in the face of daily clinical evidence.

The association of refluxing segments with occluded segments—anarchic and refluxing subfascial collateral pathways, the presence of postthrombotic pseudo-valves, obstructing and hence antiphysiological reflux—all contribute to making postthrombotic syndrome a multifaceted scenario which is difficult to assess.

In straightforward primary venous insufficiency, we are restoring valves that don't work to functionality. As Kistner has shown, significant physiological results can be achieved, even though not all valve structures have been restored to continence.[18] In postthrombotic syndrome, valves cannot be repaired, and even if repair were not possible in one segment, it would have scant hemodynamic significance. Preventing reflux in a principal axis does not mean resolving the patient's problem since he or she may also be affected by a more significant reflux in the deep femoral axis.[19] Before undertaking any therapy on the deep venous system, it is thus necessary to carry out a close study in which, unlike in studies of the superficial venous system, phlebography is still the benchmark. From screening of a selection of patients, a percentage will emerge who can benefit from surgery to correct deep venous reflux.

Kistner's transposition technique resolves the problem ingeniously by transposing the femoral vein to a position above a continent valve in the deep femoral vein or the saphenous vein. It should be observed, however, that only a small percentage of cases present the anatomical situation that makes this operation feasible.

Valve transplantation is another operation worthy of note: it entails the removal of a segment containing a valve from the brachial vein and inserting it at popliteal level.

This operation also has its limits, principally where the donor vein has a noncontinent valve or where the popliteal vein is not anatomically suitable for the procedure.

Various surgeons have begun experimental work: valve-cusp transplants; invagination of a saphenous vein segment to create an antireflux mechanism; the implant of a heterologous valve inserted into stents. Some attempts have failed and other techniques are still in the research stage.

Our contribution resulted from constant observation in the course of operations such as femoral transposition. We were struck by the frequent thickening of the vein wall, which was sometimes uniform in texture and distributed around the vein's circumference, at other

times patchy. This thickening suggested the idea of creating a parietal flap by dissection in order to obtain an antireflux mechanism entirely similar to a venous valve. Not infrequently, it is necessary to combine with endophlebectomy,[20] or to ablate a pseudovalve against the flow. The flap is tailored to individual requirements, but based on general principles. It is still unclear exactly how the flap works, but it probably differs from the delicate action of the natural human valve,[21] even if the antireflux mechanism proves effective. By contrast, other procedures, such as perforator ligation, yield results that are not lasting. Several techniques combined will probably produce a definitive solution to invalidating diseases with a high social cost.

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Assessment of treatment efficacy on venous symptoms: the example of Daflon 500 mg

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INTRODUCTION

Leg symptoms are the most frequent reason why patients with chronic venous disease seek medical help. The patient hopes to get rid of them. This may explain the high consumption of venoactive drugs (VADs) in 10 countries (mostly European) in a recent survey: 17 million people per year are treated with VADs,* while 140 million among the adult population in these countries complain of leg symptoms.** The relationship between venous symptoms and venous signs is tenuous, as it is between venous symptoms and venous reflux. Therefore the medical literature concludes that these venous symptoms are nonspecific. This raises the question of the value of the available diagnostic tools and their specificity for venous symptoms.

The present review considers tools currently used to assess efficacy in symptom management, some of which were used in efficacy studies of Daflon 500 mg.

DEFINITION OF SYMPTOMS

A transatlantic interdisciplinary faculty of experts under the auspices of the American Venous Forum (AVF), the European Venous Forum (EVF), the International Union of Phlebology (IUP), and the International Union of Angiology (IUA) provided recommendations for venous clinical terminology in the Vein-TERM consensus document with the purpose of enhancing the use of a common scientific language in chronic venous disease (CVD) management and research.[1] Venous symptoms are defined as: "aching or pain, burning, muscle cramps, swelling/throbbing sensation, heaviness,

Keywords:
assessment, tools, symptoms, varicose veins.

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* *Source SERVIER and IMS 2007: yearly evaluation of patients with 3-month VAD treatment in 10 countries (Austria, Czech Republic, France, Greece, Italy, Poland, Romania, Russia, Spain, Turkey)*

** *Deduced from the percentage of symptomatic patients among adults (>18 years) in recent epidemiological trials in the 10 countries above*

itching, restless legs, leg tiredness/fatigue. Although not pathognomonic, these may be suggestive of CVD if exacerbated with dependency on the day's course, and heat, and relieved with leg rest and/or elevation, particularly in light of supportive clinical and/or laboratory evidence".

PREVALENCE OF VENOUS SYMPTOMS

Venous symptoms are seldom reported in epidemiological studies. However, data in the general population from four countries show a high prevalence of venous symptoms ranging from 29% to 61%,[2,3] with a clear predominance in women (*Table 1*), while data in populations seeking medical help[4-6] show up to 75% prevalence of pain related to venous problems (*Table 2*).

Assessment of therapeutic effect on venous symptoms

Characterizing venous symptoms is the first goal when ensuring that symptoms are of venous origin. With CVD, treatment efficacy can basically be assessed in two ways: the patient's quality of life assessment and the physician's evaluation of clinical symptoms and signs.

First author, year, country	Sample	Type of symptoms	Prevalence in %
Widmer, 1981, Switzerland	Chemical workers	Any kind	29
Preziosi, 1999, France	SUVIMAX cohort	Any kind	30
Pannier-Fisher, 2003, Germany	General population (population register)	Any kind	56
Carpentier, 2004, France	General population (phone list)	Any kind	41
Langer, 2005, USA	Employees of the University of California	Aching Others	18 14

Table I: Prevalence of venous symptoms in population-based surveys

Instrument, developer, year	Specific for CVD	Number of items Tested indications	Languages validated
Aberdeen Varicose Veins Questionnaire (AVVQ), Garratt, 1993	Yes	13 C2 (varices)	1
ChronIc Venous disease quality of llfe Questionnaire (CIVIQ), Launois, 1996	Yes	20 C4 (skin changes), surgical procedures (venous stenting, stripping vs Closure®)	13
Charing CROSS Venous Ulceration Questionnaire (CXVUQ), Smith, 2000	Yes	- C6 (venous ulcer)	1
Veines-Qol/Sym, Lamping, 2003	Yes	35 C0s to C6 DVT	4
36-item Short Form health survey (SF-36)	No	In conjunction with CIVIQ, VEINES, CXVUQ, and AVVQ	-

Table 2. Patient-reported outcomes in chronic venous disease

Ascribing symptoms to chronic venous disease

The Phleboscore® by Blanchemaison[7] is an 11-item self-administered questionnaire which helps predict the risk of developing CVD. It includes questions about risk factors (gender, age, sedentary life, weight excess, number of pregnancies, working conditions, family history, sporting activities), as well as questions about the frequency of symptoms (heavy legs, sensation of swelling) and the circumstances in which symptoms worsen (heat, birth pill, long-haul travel). The score ranges from 0 to 31. A score >12 identifies patients at risk of CVD, while a score >23 pinpoints a need for venous exploration.

The VEINES-Sym by Lamping[8] is a 10-item self-report questionnaire which includes questions on the frequency of 9 CVD-related symptoms (heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling sensation), and the intensity of leg pain. The scores range from 0 to 10, with high values indicating better outcomes.

The more recent scoring system by Carpentier[9] is a diagnostic tool administered to patients which aims to ascribe leg symptoms to CVD. This system "might also help predict the usefulness of treatment in patients with CVD seeking medical help for their symptoms". It consists of a combination of 4 criteria: sensation of heavy or swollen legs, associated with itching, restless legs, or phlebalgia, worsened by a hot environment or improved by a cold environment, and not worsened by walking. Scores range from 0 to 4. With a threshold level of >3, there was a high specificity (0.95) and fair sensitivity (0.75) for CVD.

None of these 3 scales has been extensively studied, or validated except within a select research group during its development.

Patient-reported outcomes, and the use of generic and disease-specific quality of life scales[10]

The 13-item Aberdeen Varicose Veins Questionnaire addresses all features of varicose vein disease. Physical symptoms and social issues, including pain, ankle edema, ulcers, compression therapy use, and the effect of varicose veins on daily activities are examined, in addition to the effect of varicose veins from a cosmetic standpoint.

The 20-item ChronIc Venous disease quality of lIfe Questionnaire (CIVIQ) gives a global score, plus a score for each of the 4 areas in which quality of life is likely to be affected: physical, psychological, social, and pain. CIVIQ has been used in studies including a range of patients: Launois initially developed CIVIQ in a clinical trial of 934 patients and an epidemiologic survey of 26 681 patients, Neglén used it along with the CEAP classification in an 8-year study on venous outflow stenting, Lurie used it to compare two surgical procedures (stripping vs Closure®), and Jantet tested it in 3948 C0s to C4 patients. CIVIQ has been extensively used and is validated in 13 languages including Canadian English, English for Singapore, British English, American English, French Canadian, French for France, German for Austria, Greek, Italian, Polish, Portuguese for Portugal, and Spanish for Spain and for the USA.

The Charing Cross Venous Ulceration Questionnaire was developed to provide a valid quality of life measure for patients with venous ulcers and to assess the effects of the many treatments available for venous ulcers.

The VEINES instrument consists of 35 items in 2 categories to generate 2 summary scores. The VEINES quality of life questionnaire (VEINES-QOL) comprises 25 items that estimate the effect of disease on quality of life, and the VEINES symptom questionnaire (VEINES-Sym) has 10 items that measure symptoms. The focus of this instrument is on physical symptoms as opposed to psychological and social aspects. Coupled with the division of summary scores into symptoms and disease effect, this makes the VEINES instrument applicable to a range of clinical arenas. VEINES-QOL is validated in 4 languages: English, French (for Belgium and France), Italian, and French Canadian.

These four specific assessment tools were used in conjunction with the 36-item Short Form Health Survey (SF-36), which is the most widely used and validated generic quality of life instrument, whatever the medical field. The SF-36 has been developed over time with questions in the following two categories: physical health (assessed as the patient's level of functioning) and mental health (assessed as an indication of well-being). These two groups have been broken down into 8 areas that include evaluation of physical and social functioning, role limitations due to physical or emotional problems, mental health, pain, vitality, and health perception. When complete, the survey generates a score

ranging from 0 to 100, with higher scores indicating better general health perception. The SF-36 has proven to be a good fit for generic quality of life assessment in the population with CVD.

Disease-specific reporting tools for physicians

The Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification has become a universal method of classification of venous disease.[11] It can be used by the clinician in keeping office records of diagnostic information. Adoption of this single classification worldwide based on correct diagnosis has facilitated meaningful communication about the disease and served as a basis for a more scientific analysis of management alternatives.

The CEAP classification is descriptive, but cannot be used for venous severity scoring because many of its components are static and do not change in response to treatment. Therefore, a venous severity scoring system (VSSS) was proposed.[12] It consists of 2 scores: 1) *Venous Clinical Severity Score* (VCSS). The VCSS includes 10 hallmarks of venous disease that are likely to show the greatest change in response to therapy and are scored on a scale of severity ranging from 0 to 3; 2) *Venous Segmental Disease Score* (VSDS). The VSDS uses the anatomic and pathophysiologic classifications in the CEAP system to generate a grade based on venous reflux or obstruction.

Of the various recommendations by the San Diego Consensus meeting regarding these tools, we can focus on the following:

- The CEAP classification is a descriptive instrument to categorize patients into different groups of severity of CVD;
- The VSSS, as presented by the AVF ad hoc committee on outcomes, is a useful complement to the CEAP classification, and should be used for research;
- Use of all CEAP components should be encouraged. However, use of only the clinical component (C) at the time of the initial evaluation is appropriate, and the E, A, and P components can be added as the diagnostic evaluation progresses.

Although reportedly easy to use, in the view of angiologists the VSSS is more likely to be of value in more severe cases of CVD.[13] The descriptive CEAP and the VSSS, particularly the VCSS, are valid but imperfect instruments for evaluation of the early stages of CVD and treatment outcome. It seems that the time has come to revise the VCSS to allow proper reporting of common patient symptoms.

Nonspecific reporting tools for physicians

Analgesic consumption has proved a reliable indicator, if not reported solely by patients but also by physicians. Pain intensity can be reproducibly rated using a visual analog scale or numerical scale. Far more complex scales have been devised to rate the overall impact of pain. One of the most widely referenced is the McGill Pain Questionnaire. This questionnaire is duly validated, but is impractical in routine use and poorly adapted to CVD pain. The Brief Pain Inventory and the Multidimensional Pain Inventory explore the various dimensions of pain and its impact on activities of daily living, social repercussions, and psychological distress, thus making them very similar to quality of life questionnaires such as those specifically developed and validated for CVD.[14]

ASSESSMENT OF THERAPEUTIC EFFECT ON VENOUS SYMPTOMS: THE EXAMPLE OF DAFLON 500 MG

Using analgesic consumption

In a multicenter study from the Czech Republic, Veverkova and co-workers compared the outcome of varicose vein surgery in two groups of patients. The treatment group (n= 92) received Daflon 500 mg, 2 tablets/day, starting two weeks before surgery and continuing for up to 14 days after the procedure. The control group (n=89) did not receive Daflon 500 mg in the pre- and postoperative periods. It was shown that

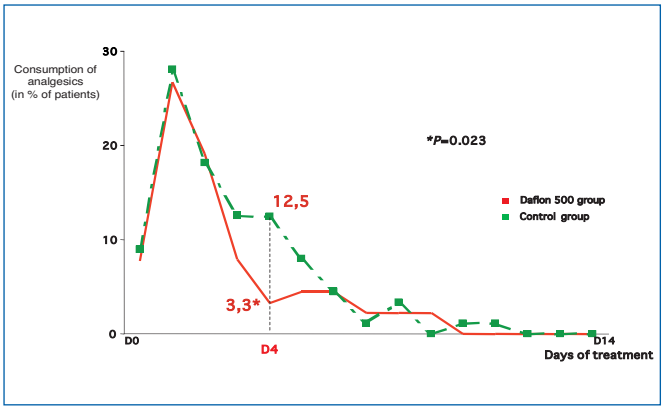

Figure 1. Evaluation of analgesic consumption to assess the efficacy of Daflon 500 mg treatment of postsurgical pain.

the drug significantly reduced analgesic consumption within 2 weeks after surgery.[15] (*Figure 1*)

Using the 10-cm visual analog scale

In the large, prospective, multicenter RELIEF trial, 3132 patients assigned CEAP classes C0s to C4 were assessed for pain. Patients with or without venous reflux showed significant reduction in pain as assessed by visual analog scale scores (GIS) after 2, 4, and 6 months of treatment (P=0.0001).[16]

Using the CIVIQ

Improvements in the clinical signs and symptoms of CVD with 2 tablets of Daflon 500 mg twice daily were associated with significant improvements in CIVIQ (health-related quality of life) scores in the RELIEF trial. The C0s to C4 patients showed significant improvement in CIVIQ global index scores (GIS) after 2, 4, and 6 months of treatment (P=0.0001). GIS increased throughout the study period with the largest improvement occurring during the first 2 months of treatment.[16] (*Figure 2*)

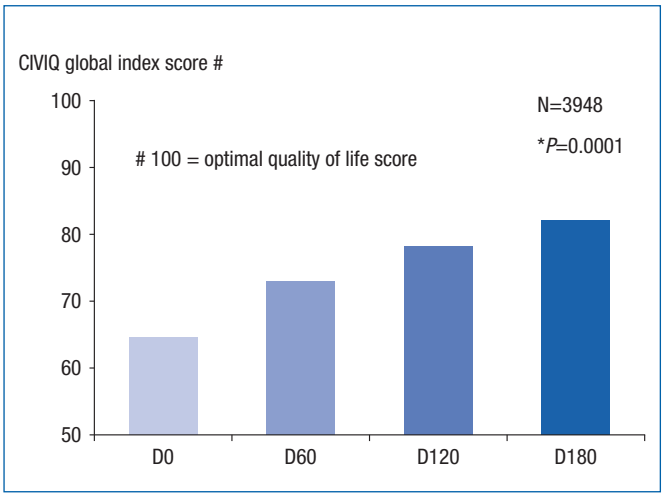

Figure 2. Use of CIVIQ to assess improvement in the quality of life of C0s to C4 patients with Daflon 500 mg treatment.

Using both the 10-cm visual analog scale and the CIVIQ

In a double-blind study vs placebo, 592 C3 to C4A patients with superficial (mean 34%), deep, or perforator reflux (mean 66%) and severe pain over 4 cm on the visual analog scale were analyzed. Patients in the treatment group received Daflon 500 mg, 2 tablets a day, while those in the placebo group received 2 tablets of placebo/day. A pain decrease of at least –3 cm on the visual analog scale and a significant quality of life improvement of at least 20 on the CIVIQ scale were the end points. The results were significantly in favor of the Daflon 500 mg group (RR=1.67) (unpublished data).

Using the 5-point numerical scale

Daflon 500 mg, two tablets daily, maintained its efficacy in the long-term treatment of patients with symptoms of CVD in a nonblinded, multicenter trial of 12 months' duration. In 170 evaluable patients, a significant reduction from baseline values in physician-assessed clinical symptoms (using a numerical scale of 0 to 5) was demonstrated at each 2-month evaluation (P<0.001). The rapid reductions observed during the first 2 months of treatment represented approximately 50% of the total improvement ultimately observed after 1 year of treatment. Continuing improvements in all parameters, albeit less rapid, were reported at each timepoint from month 2 to month 12.[17]

Percentage of patients without symptoms after therapy

A simple way to assess the effect of therapy on symptoms uses statistical analysis of the percentage of patients who no longer present with the symptoms.

The efficacy of Daflon 500 mg in decreasing symptoms associated with venous ulcers was evaluated in a meta-analysis of 5 randomized trials including 459 patients. Two tablets of Daflon 500 mg daily plus standard venous ulcer management was compared with standard venous ulcer management (compression therapy plus local treatment). Patients were included in the trials if they had a venous leg ulcer for a duration of at least 3 months. Significant symptom reduction in favor of the Daflon 500 mg group was seen after 4 and 6 months of treatment (P<0.001).[18]

INDICATIONS OF DAFLON 500 MG AND RECOMMENDATIONS IN GUIDELINES

Daflon 500 mg is a well-established treatment option and is strongly recommended in the recent guidelines for patients with CVD.[19,20] Daflon 500 mg is indicated as a first-line treatment of edema and the symptoms of CVD in patients at any stage of the disease. At more advanced disease stages, Daflon 500 mg may be used in conjunction with sclerotherapy, surgery, and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible.[21] The healing of venous ulcers is accelerated by the addition of

Daflon 500 mg to standard venous ulcer management (compression therapy and local treatment).[22]

CONCLUSION

There is no universal consensus as to which outcome tool should be used to assess CVD-related symptoms. Quality of life questionnaires are valuable indicators, but some are still cumbersome and need to be simplified. Venous scoring systems like the VCSS should be more adapted to the early stages of CVD. The few existing scoring systems that can ascribe symptoms to venous disease are still poorly used. The tools used to quantify and qualify venous symptoms, either through patients' self-report questionnaires or by physician reporting, have been widely validated. These tools have also been used to assess the efficacy of treatments of venous symptoms, as in the case of Daflon 500 mg.

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Prevalence of venous leg ulcer: the importance of the data collection method

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ABSTRACT

Many epidemiological studies have been performed to assess leg ulcer prevalence, but not all have given reliable results due to weaknesses in the methodology. A proper prevalence assessment is not easily done and requires time and effort. Most studies have just focused on prevalence of leg ulcers of all causes and only a few have really validated the leg ulcer diagnosis objectively by use of hand-held Doppler, color Doppler ultrasound, or plethysmography. There are many pitfalls in performing a prevalence study of venous leg ulcers which introduce a risk of misinterpretation of the true prevalence. Some of these pitfalls and their likely effects are presented. Based on the available and most qualitative studies the overall prevalence of venous ulcers (healed + open) is, astonishingly stable between different countries and over time, around 1% in most populations. The point prevalence of open ulcers is more variable and is likely to be in the region of 0.1-0.3% depending on whether or not people who self-treat are included.

INTRODUCTION

Leg ulcers have plagued mankind since ancient times and still pose a considerable burden for both patients and carers in most countries of the world. With more elderly in the populations this problem is likely to increase unless effective actions are taken to treat the various diseases that cause leg ulcerations. Venous disease is the most common causative factor for leg ulcers, but has to be properly diagnosed in order to establish a reliable diagnosis. This has been overlooked in several epidemiological studies attempting to establish the prevalence of leg ulcers and venous ulcers in particular. There are different assessments of prevalence, which is a measurement of the occurrence of a disease or disorder within a certain population, namely point prevalence and period prevalence estimates. The latter is most often used for a lifetime period and gives an overall prevalence, as opposed to point prevalence, which measures the number of patients with open ulcers during a narrow time period, usually one to three months. One can quite often see misuse of prevalence data in reviews by mixing overall

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venous ulcer, epidemiology, data collection, leg ulcer, cross-sectional study, point prevalence, prevalence, review.

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prevalence figures with point prevalence data, causing an inaccurate wide range that leads to incorrect interpretations of prevalence data between countries and studies. To analyze the methods used in various studies is therefore of utmost importance in order to generate accurate comparisons and to provide the most reliable data in order to assess the magnitude of the problem. The aim of this article is to point out the variations in methodology in previous epidemiological studies and how these differences can affect the result, and to present available data on venous leg ulcer prevalence. In reality very few studies can really be used to give reliable data on venous ulcer prevalence.

WHAT IS A VENOUS LEG ULCER?

What may be obvious to some is not clear to others, even within the medical profession. It is even more difficult for patients or relatives, who frequently misidentify erosions caused by venous eczema as an ulcer.[1] A definition of a leg ulcer or a venous leg ulcer is frequently missing in many prevalence studies.[2] A venous ulcer is usually considered as a "chronic" disorder, although we now know that it does not have to be, and therefore a venous ulcer has to have been present for 4-6 weeks in order to distinguish it from an "acute" ulcer. A reliable diagnosis is mandatory, especially if you attempt to sort out venous ulcers from all other causes of leg ulceration. We have previously shown that simple reliance on clinical examination, and signs and symptoms of probable venous disease, without the support of noninvasive diagnostics (Doppler), will result in misdiagnosis every fourth ulcer.[3] Today it is reasonable to require objective data proving venous dysfunction and excluding other major diseases, such as arterial insufficiency, before diagnosing a venous ulcer. The most used diagnostic tool today is color Doppler ultrasound (CDU), which is the gold standard in diagnosing venous dysfunction. Alternative techniques sometimes used are plethysmography and hand-held Doppler assessments both of which give more limited and less detailed information. That this is a reasonable requirement is perhaps more easily understood if you realize that the diagnostic spectrum regarding leg ulcers is much diversified, with a number of diagnoses apart from venous and arterial ulcers.[4,5] Not least it is important to realize that mixed arterial and venous ulcers and multifactorial ulcers are becoming more and more common, probably because of aging populations. Today it is no longer valid to diagnose a venous ulcer based on signs and symptoms, without the aid of noninvasive diagnostics.

WHY ARE PREVALENCE DATA IMPORTANT?

Epidemiological studies are used to assess the prevalence (occurrence) of diseases or disorders within populations in order to establish the magnitude of a certain problem. Usually cross-sectional studies have been used to assess the number of patients with a certain disease within the health care system. Large random samples have been used to assess populations and have the advantage of including people who self-treat. Prevalence data from such studies will serve as a valuable basis for the planning of appropriate actions to deal with the problem, in this case venous leg ulcers. By repeating a prevalence study within a defined geographical area, we have a unique opportunity to assess the effect of treatment changes.[6]

A matter often creating some confusion is that there are various prevalence estimates and that the difference between incidence and prevalence is not always understood. The definitions of these terms are found in *Table I*. When venous ulcers are concerned we often speak of either point prevalence or overall prevalence, the first meaning the proportion with open ulcers over a certain short period of time and the second meaning the proportion of people who have ever had a venous leg ulcer, thus including both open and healed ulcers. The incidence of venous leg ulcers is estimated to be one tenth of the current point prevalence, meaning that only one out of ten venous ulcers is newly developed.[5]

In Skaraborg we used data from our first epidemiological studies (1988-1992)[1,3,4,7-9] to improve leg ulcer management in general and venous ulcer treatment in particular. By a repeat study in 2002 we found that the prevalence of venous ulcers had been decreased by 46% within the health care system, giving a strong indication that our changed management strategy was successful.[6] In short, the management strategy was based on multidisciplinary cooperation, training of carers in the community, improved proper use of bandaging and compression stockings and, maybe most important, increased use of varicose vein surgery. Without the repeat study in 2002 it would have been much more difficult to detect the result of this change of management strategy.

Incidence	*Number of new cases per time unit and population - usually one year*
Point prevalence	*Proportion with a certain disease at any point of time – time period usually shorter than three months*
Period prevalence	*Proportion with a certain disease within a longer period of time – usually one year or more*
Overall prevalence	*Proportion that have ever had a certain disease – lifetime period = lifetime prevalence*

Table I. Definitions of incidence and the various form of prevalence estimates.

METHODOLOGICAL PITFALLS

To perform an epidemiological study properly takes time and effort in order to get a reliable result. Prevalence is easily underestimated if the study is inadequately prepared. Overestimation is also possible, but generally for other reasons, which will be discussed later. Methodology is crucial and should be studied first when reading an article dealing with prevalence data, in order to be able to evaluate the results presented. Even in a meticulously performed study one should be aware that the results are often based on assumptions and that the result is not always representative of the general population in, for example, the whole country. Cautious generalization may be appropriate.

Prevalence data are often harvested from cross-sectional studies or large population samples. The former investigate a defined cohort, generally all patients receiving treatment from health care professionals within a relatively short time frame, usually 1-3 months. The latter usually consist of randomly selected people of a certain age range, not necessarily previously in contact with the health care system. The benefit of population samples is that people who self-treat are included, unlike in cross-sectional studies. The drawback of a population sample is that usually not all age groups are represented.

What are the pitfalls of a cross-sectional study? As mentioned above it is necessary to contact all potential carers within the health care system in an area where leg ulcer patients are likely to be treated and persuade them to participate and to contribute patient data. A lot of time is needed to ensure that most carers are providing accurate responses. Failing this, underestimation is likely. As an example, we found in the Skaraborg study in 2002[6] that only 361 individual patients were initially reported from 79 units. Following several reminders this figure rose to 802 patients reported from 250 units, so reminders are necessary to get a reliable result. To facilitate recruitment it is important to avoid approaching carers and patients with lengthy questionnaires. Such forms take time to fill in and introduce a risk of dropout because of lack of time for the carer or patient or both. Make the primary recruitment form as simple as possible, including only age, gender, identification number, and address. More detailed information can be gathered later. To avoid erroneous inclusions, the carer may mark the location of the ulcer on a drawing of a leg. There are examples of very low point prevalence reported from studies using extensive questionnaires,[10] which raises doubts about the reliability of such estimates.

For prevalence data to be reliable, the study has to be large enough. By calculating the 95% confidence interval, certainty is possible when examining a smaller population. Validation of all or a randomly selected sample of the reported patients is mandatory to determine the number of false positives and to establish the diagnosis, which is usually done nowadays by performing CDU in combination with clinical

examination. It is not appropriate to rely on a venous ulcer diagnosis by the carer without verification from a previous objective noninvasive assessment. Without objective validation there is a high risk of overestimating venous leg ulcer prevalence. One example is a study from Ireland[11] that only assessed ankle pressures to diagnose arterial ulcers and most other ulcers were considered as being venous, clearly resulting in an overestimation of venous ulcer point prevalence. Leg ulcer diagnosis is more complicated than that.[4,5]

A cross-sectional study involves selection bias since only patients treated within the health care system will be included. Such a study will give the workload for health care professionals, but there are in addition people caring for their ulcers on their own. A population sample will overcome this by including all people within the selected sample. What are the problems of population sample study? The biggest problem is that they need to be fairly large (~10 000 people or even more) in order to detect enough patients with ulcers so that a reliable prevalence estimate can be made. These studies are expensive, time-consuming, and difficult to perform. To overcome this we selected patients using a very simple questionnaire to identify those who really had a history of leg ulcer.[1] Other studies have examined all patients, but then the main object was to look at venous disease in general and not specifically venous ulcers and the samples were therefore smaller.[12,13] resulting in more uncertain estimates of venous ulcer prevalence. The youngest and oldest age groups are usually excluded in such surveys, because ulcers are seldom found below the age of 30 and the eldest are likely to have difficulty in attending. However, most elderly people are treated by health care professionals and the prevalence can be adjusted by using information from previous cross-sectional studies. Furthermore, it is important to use random selection when the sample is defined to avoid introducing unnecessary selection bias. Samples based on cohorts attending outpatient departments are often heavily selected and can not generally be used to assess the magnitude of the problem within the population, but merely show the workload for that specific department. The need for validation is high and usually all or a randomly selected sample of patients reporting ulcers are invited for more detailed examination with the aid of objective noninvasive techniques, usually Doppler and CDU and sometimes also plethysmographic methods.[2] Getting people to attend for the detailed examination can be a problem, which is generally bigger in population sample studies where many are likely to be quite healthy. In fact, all studies have shown attendance rates lower than 60%.[12,13] In our own, slightly differently designed, study the attendance rate among those who claimed a history of leg ulceration was even lower (46%), but we were able to validate a random sample of the dropouts and to verify leg ulcer history in a percentage similar to that among those examined.[1] We learned that people in general have difficulty in discriminating an ulcer from erosions due to venous eczema. The false-positive response rate was high (43%), mostly due to venous eczema. This underlines the

Pitfalls	*Effect*
Extensive primary questionnaire	May affect patient recruitment negatively – underestimation of actual prevalence
Lack of validation of leg ulcer	Risk of overestimations of prevalence
Lack of validation of venous leg ulcer diagnosis	Risk of overestimation of venous ulcer prevalence
Insufficient reminders and direct contacts with carers	Risk of underestimation of prevalence
Sample too small	Uncertain prevalence estimate
Selection bias	Prevalence not representative for the general population
Low response rate	Risk of underestimation of prevalence
Validation of dropouts not performed	Uncertain prevalence estimate

Table II. Pitfalls in performing prevalence studies and their effects on the results.

importance of validating studies of patients claiming a history of ulceration to avoid overestimation of prevalence of venous ulceration. *Table II* summarizes the most common pitfalls in prevalence studies.

VENOUS ULCER PREVALENCE

Numerous studies have assessed leg ulcers regardless of etiology, but very few give details of venous ulcer prevalence, since not many have validated the diagnoses.[2,5] One of the most uniform prevalence estimations regards overall prevalence of venous ulcers. Around 1% of the adult population has a history of healed or open venous leg ulcers,[14,15] an estimate that seems astonishingly stable over the years and in many different countries (*Table III*). Based on data from Skaraborg in Sweden, we found that a roughly equal proportion had chronic lower limb ulceration of causes other than venous (*Table IV*).

There are few published point prevalence estimates of venous ulcers (*Table III*). In six studies the diagnosis of a venous ulcer was validated with noninvasive methods.[1,3,6,8,10,17] Four studies of cross-sectional design assessed prevalence among venous ulcer patients receiving professional treatment,[3,6,10,17] and the other two were based on a random population sample[1] and a selected population sample,[8] respectively. The lowest point prevalence, 0.024%, was found in the latest published study from the UK.[10] That prevalence was, however, based on a study with a questionable methodology using an extensive questionnaire, which is likely to bias recruitment of patients negatively, and therefore probably underestimates the true point prevalence. The highest prevalence was not surprisingly found in the two studies that were based on large random population samples and thus also included people who self-treat. Both in Germany[16] and Sweden[1] the point prevalence was 0.29%, but in the German study no objective diagnostics were used. The recently performed population studies in Edinburgh[12] and Bonn[13] found very few actual ulcer cases and therefore have not generated any reliable data regarding point prevalence. The observed overall prevalences from these studies were, however, in line with the expected 1%, albeit slightly lower due to the chosen age ranges (*Table III*). Reported prevalences for patients receiving professional care range from 0.06% to 0.20%.[3,6,8,17] It seems reasonable to expect the point prevalence in the total population to be somewhere in the region of 0.1% to 0.3% in most Western populations, although local variations are likely to exist. The highest point prevalences were found in population studies including people who self-treat.[1,16] As a result of our previous three epidemiological studies in Skaraborg County (population 270 800), we have been able to weigh the separate results in a more detailed estimate shown in *Table IV.*

CAN VENOUS ULCER PREVALENCE BE REDUCED?

The conditions and evidence have never been better than they are today provided that the right actions are taken. In Skaraborg we have been able to reduce the point prevalence of venous ulcer from 0.16% to 0.09% within the health care system, representing a reduction of 46% within a 14-year period.[6] This is the first, but surely not the last, study that will show that a change of management will result in a detectable reduction in leg ulcer point prevalence. In 2005 we repeated a large population sample study (10 000 people aged 30-89 years) and a preliminary analysis has shown no more ulcer patients in that study, a result that points in the same positive direction. Overall prevalence is likely to be lowered over the long term, but at a slightly slower speed. Why were we able to reach this result? We feel that the creation of organized care pathways has been important in the multidisciplinary cooperation and teamwork around these patients. A very important step has been to point out the value of a proper early diagnosis by offering patients with presumed venous ulcers a diagnostic CDU. In this way we detect early patients with superficial venous insufficiency and incompetent perforators that may be correctable surgically. Our policy has been to offer patients this kind of surgery early and to follow up healing by proper bandaging and later with custom fit compression stockings in case of any persisting deep or superficial venous insufficiency. That this was a wise policy has been supported by results from the ESCHAR study in the UK where surgery significantly reduced the risk of leg ulcer recurrence compared with conservative compression treatment alone.[18,19] It is likely that the early surgical intervention was the most important component in reducing the number of patients with open venous ulcers in our population. This is validated by the good long-term healing and recurrence results

					Prevalence %	
Authors (publ.year)	**Country**	**Method**	**All known to health care**	**Objective noninvasive diagnosis**	**Overall**	**Point**
Bobek et al. (1966)[14]	Czechoslovakia	Pop. study n=15 060 adults >15 y	No	No	1.0 adult pop.	-
Widmer (1978)[15]	Switzerland	Selected sample n=4 529 industrial workers 25-74 y	No	No	1.0 adult pop.	-
Fischer (1981)[16]	West Germany	Random pop. sample n=4 260 adults 20-74 y	No	No	2.7 in sample 2.3 based on examined	0.44 in sample 0.29 based on examined
Nelzén et al. (1994)[3]	Sweden	Cross-sectional study Pop. 270 800 n=387/827 ulcer pat. validated (randomly selected)	Yes	Yes. Two-dimensional Doppler arterial and venous	n.a.	0.16 total pop. 0.22 adult pop.
Baker et al. (1991)[17]	Australia	Cross-sectional study Pop. 238 000 n=246/259 ulcer pat. validated	Yes	Yes. Doppler + photoplethysmography	n.a.	0.06 total pop.
Nelzén et al. (1996)[1]	Sweden	Random pop. sample n=12 000 people 50-89 y	No	Yes. Two-dimensional Doppler arterial and venous	0.8 total pop. 1.0 adult pop.	0.29 total pop.
Nelzén et al. (1996)[8]	Sweden	Selected sample n=2785 industrial workers 30-65 y	No	Yes. Two-dimensional Doppler arterial and venous	0.8 in sample	0.2 in sample
Moffatt et al. (2004)[10]	UK	Cross-sectional study in health care Pop. 252 000 n=113 ulcer pat. validated	Yes	Yes. Doppler + photoplethysmography	n.a.	0.024 total pop.
Evans et al. (1999)[12]	UK	Random pop. Sample n=1566 (54% of invited) 18-64 y	No	Yes. Doppler+color Doppler ultrasound	0.6 in sample	n.a.
Rabe et al. (2003)[13]	Germany	Random pop. Sample n=3072 (59% of invited) 18-79 y	No	Yes. Color Doppler ultrasound	0.7 in sample	*(0.1 in sample) Very few cases*
Forssgren et al. (2008)[6]	Sweden	Cross-sectional study Pop. 254 111. n=291/621ulcer pat. validated (randomly selected)	Yes	Yes. Doppler + color Doppler ultrasound	n.a.	0.09 total pop.

Adult pop. = population above the age of 15;n.a. = not assessed

Table III. Estimates of venous leg ulcer prevalence.

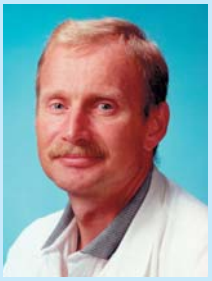
A. Point prevalence open ulcers	*(Figures given as percentages)*			
	Known to health care		*Self-care included*	
	all causes	***venous***	***all causes***	***venous***
Total population	0.30	0.16	0.6	0.3
Adult population (>15 years)	0.40	0.22	0.8	0.4
Retired population (>65 years)	1.40	0.76	1.9	1.0
B. Overall prevalence healed and open ulcers				
	Known to health care		*Self-care included*	
	all causes	***venous***	***all causes***	***venous***
Total population	0.9	0.5	1.9	1.0
Adult population (>15 years)	1.2	0.6	2.4	1.3
Retired population (>65 years)	4.2	2.3	5.6	3.0

Table IV. Combined prevalence estimates, from Skaraborg county, of leg ulcers of all causes and of venous ulcers.[5]

from a prospective study on subfascial endoscopic perforator surgery performed for venous ulcers in Skaraborg during the same period.[20] However, it is important to point out that surgery would probably not have been so successful without all the other improved more conservative components of leg ulcer management. Together all of the actions raised leg ulcer management to a higher level to the benefit of both patients and carers. For society the result indicates yearly cost savings of around 1.7 to 2.3 million Euros in Skaraborg alone.[6] This emphasizes the enormous yearly spending mainly on providing dressings and bandaging for venous ulcer patients.[21] One varicose vein operation equals the cost of approximately three to four months of dressing changes and is money well spent when considering the savings involved.

CONCLUSION

Reliable epidemiological data regarding point prevalence and overall prevalence of venous ulcers are hard to come by and there are few representative studies where objective methods have been used. It is important to be aware of the pitfalls in methodology so as to judge the reliability of results and to compare them with findings from other studies. If certain pitfalls are not avoided, overestimation or underestimation is likely. The most reliable studies suggest that both point prevalence and overall prevalence of venous ulcers are still quite high and there appears to be room for management improvements in reducing the size of the problem of venous leg ulcers. That this is possible has been shown from Skaraborg in Sweden where leg ulcer point prevalence has been reduced by 46% within a 14-year period. If this can be achieved in Sweden, it ought also to be possible elsewhere. The future for leg ulcer patients has never been brighter.



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New computer tools for virtual dissection to study the anatomy of the vascular system

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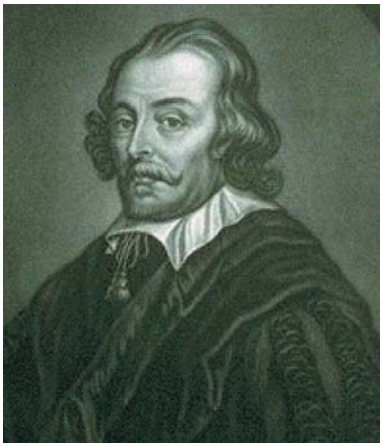
SUMMARY

The aim of this paper is to demonstrate the major role played by the new computerized imaging tools available today in the fields of morphology and vascular anatomy. For anatomical studies or educational purposes, they enhance classic techniques.

Three-dimensional reconstruction, which is already used in daily clinical practice, will be the basis for computation of validated volumetric protocols enhancing our diagnostic, prognostic, and therapeutic methods. It is also a fantastic educational tool: interactivity and virtual dissection make it simple, efficient, attractive, and easily understandable, particularly in the field of venous anatomy.

BACKGROUND TO VASCULAR ANATOMY

Although the existence of blood vessels was discovered in ancient times, probably in prehistoric Egypt, their precise description can be attributed to the Arab physician Ibn al-Nafis (1250). Subsequently, further progress did not come until the Renaissance period, with Andreas Vesalius and his famous 1543 work De humani corporis fabrica. The first person to make an anatomical and functional description of the venous valves was William Harvey in 1628 in his work "Exercitatio anatomica de motu cordis et sanguinis in animalibus" ("On the motion of the heart and blood") (*Figure 1*).



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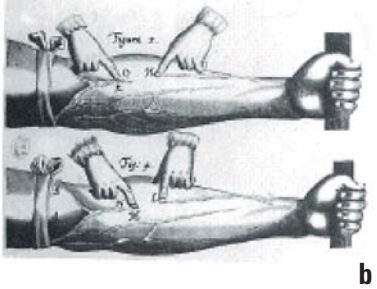

b

Figure 1a: Sir William Harvey (1578-1657)

Figure 1b: Demonstration of the presence of the valves against reflux in the venous system.

Keywords:
angioscanner, three-dimensional imaging, anatomy, computer simulation

Phlebolymphology. 2008;15(4):151-155.

TOOLS FOR THE STUDY OF VASCULAR ANATOMY

Classic techniques are dominated by the following:

Anatomical dissection of cadavers. This is the basic technique for learning about anatomy.[1] Claude Gillot developed a method adapted to the study of the venous system using color segmentation of the veins of the lower limbs: after injection of green latex, followed by meticulous anatomical dissection and identification, the veins are colored according to different color codes.[2] Anatomical sections and diagrams supplement photographs and anatomical drawings made during dissection.

Plastination is an anatomical technique used to preserve biological tissues by replacing the different organic fluids with silicone, a method created in 1977 by the anatomist Gunther von Hagens.[3] A famous example of an earlier and similar technique, as applied to a horseback rider and his mount, can be seen in the museum of the veterinary school in Maisons-Alfort, near Paris, by Fragonard.

Corrosion casting is a technique in which an organ or body system (vascular, bronchial, liver, digestive, etc.) is injected with latex and then put in a solution of concentrated acid, causing the gradual destruction of all the surrounding tissues.

New tools of digital anatomy using virtual reality.[4-6]

The use of virtual reality in medical imaging allows true virtual dissection, in the living subject, of anatomical structures in the human body: bone, muscle, and blood vessels.

Using these techniques, data acquisition with venous spiral CT scan, with or without[7] injection of diluted contrast medium, can produce a 3D reconstruction of the anatomy of the venous system.[8-10]

Dedicated computer software (Vitrea" [Vital Images], Voxar" from Barco.com and VolViz" on a Windows operating system and OsiriX"[11] on an Os X operating system (Apple) can be used for interactive 3D modeling of anatomical structures, which can be differentiated from each other by their density.

Computer software, in particular QuickTime Virtual Reality from Apple",[12] can be used to vary tissue transparency and angle of view (zoom, rotation), thus enabling a true virtual dissection of the lower limb. This is very much an anatomical study of the living leg and foot that visualizes their bone and muscle structures. Although such methods do not provide hemodynamic information, it is easy to see how useful they are for detailed anatomical study.

METHODS OF 3D MODEL RECONSTRUCTION

3D vector reconstruction or surface rendering requires manual segmentation, generally by image digitization. It uses specific software (Mimics, Analyse, OsiriX).
The result of this type of modeling is a point cloud, a vector configuration which describes the shape of anatomical structures and which enables 3D mapping of the anatomical structure studied.

Direct volumetric 3D reconstruction or the volume rendering technique (VRT)[13] uses ray tracing of voxel data (*Figure 2*).

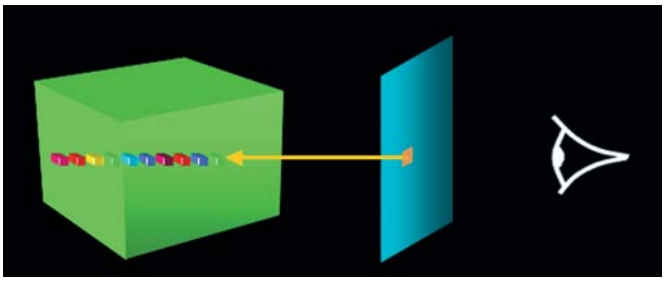

Figure 2: Ray tracing of voxel data*
In the eyes of the observer looking at the screen, each point is the result (color, transparency) of projections of all voxels crossed by the light ray.*
**Voxel: (volume element): small elementary cube which comprises the acquisition volume.*

Many types of VRT software are available (GE, Siemens, Philips, Toshiba ...), almost all of which are intended for radiologists. They automate the segmentation process, have the advantages of rapidity and simplicity, and also allow more complete utilization of data acquisition.

Digitization can be used to handle tissues and vary their transparency, by creating a correspondence between the different tissue densities and a color, a transparency, and a luminosity for each voxel in the reconstructed 3D model.

Consider a histogram of density distribution in Hounsfield units (HU) of a CT scan with injection of contrast medium (*Figure 3, upper right*). We observe 2 density peaks: one on the left, that of air, at around +1000 HU, and one the right, that of soft tissue, at 0-200 HU.

The densest tissues, 400-1000 HU, correspond to bone and injected contrast medium.

Example 1 shows the result of the model without black and white shading, without transparencies (similar to a chest film presentation).

Example 2 shows the result of the yield by rendering the skin transparent yellow, eliminating the intermediate soft tissue and leaving bone white.

Lastly, example 3 shows only dense tissues (colored yellow) and injected blood vessels (colored orange).

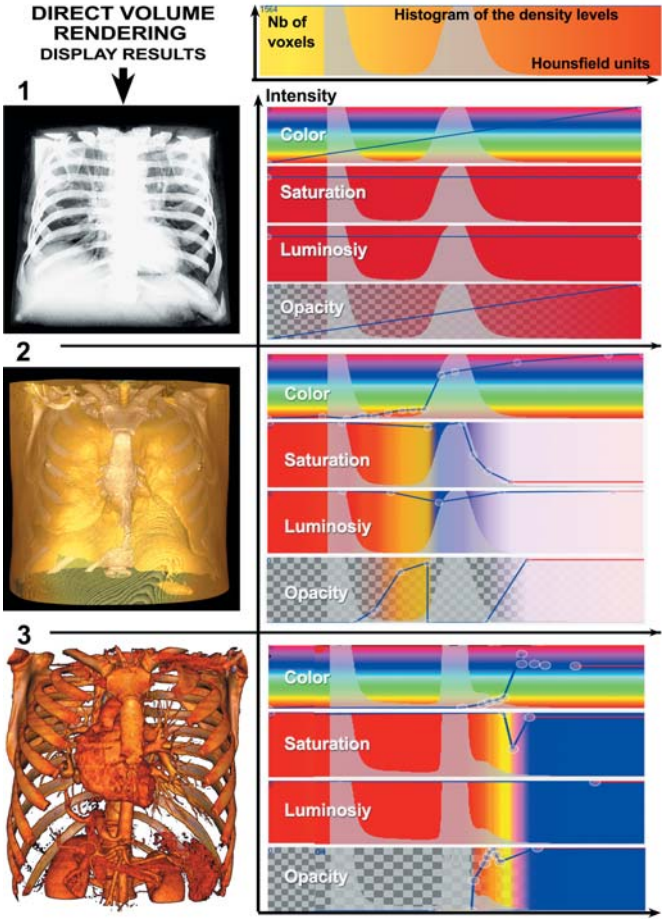

Figure 3: Thresholding technique for the 3D modeling of tissues by direct volume rendering.

Visualization and utilization of the 3D model

Whatever the method of reconstruction, the result obtained by this 3D modeling, after surface texturing and lighting, provides a highly realistic visualization of anatomical structures: rotation of the model, a zoom-in view, various angles and changes in transparency of tissues, producing a true virtual anatomical dissection
An example is shown in Figure 4, with the venous CT scan of the lower limbs.

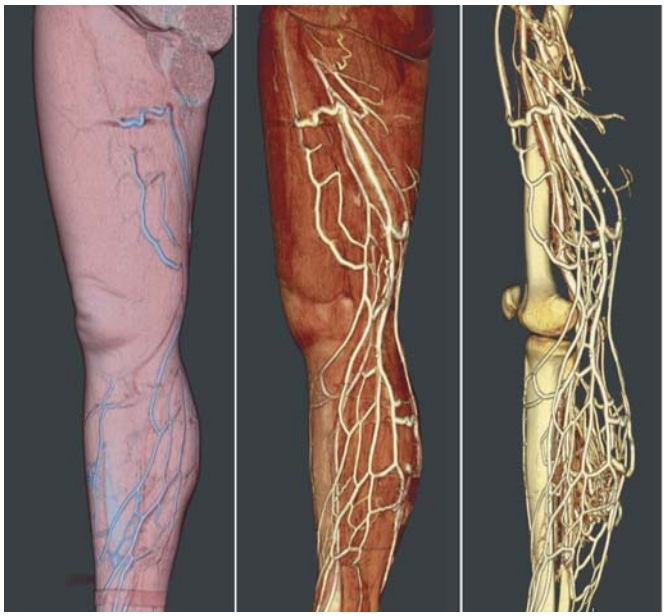

*Figure 4: Result of a venous CT scan of the lower limbs with injection of contrast medium.
Display of three levels of transparency: skin, muscles, bones and veins.*

New tools of virtual dissection

The new imaging methods using 3D modeling of anatomical structures are a considerable advance in angiology: Based on data acquisition with a spiral CT scan and injection of contrast medium, specific software allows very precise 3D reconstruction of vascular anatomy. This method can be used in the study of both arteries and veins.

THE MAIN FIELDS FOR USE OF THESE NEW TOOLS:

- ***Investigation of patients***

For arterial disease (a check-up before and after surgery), for chronic venous disease (complex recurrent varicose veins, assessment of congenital vascular malformations). Here, it is mandatory to add a hemodynamic evaluation with color duplex.

- ***Educational purposes***. These are fine tools for learning anatomy, particularly of the venous system, the most complex of the human body. Here, the virtual dissection of anatomical structures is a precious aid, using interactive movies and animation.

- ***Research*** to enhance our anatomical knowledge.

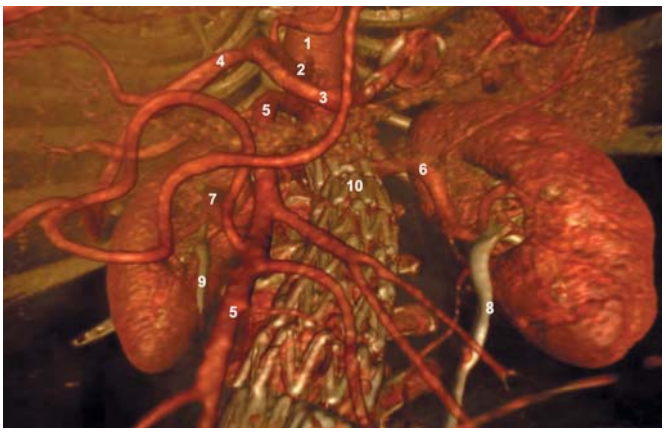

Figure 5: Postoperative check-up of an aorto-bi-iliac bypass. Anterior view of the celiac trunk with the superior mesenteric artery.

1 = Celiac aorta
2 = Celiac trunk
3 = Gastro-duodenal artery
4 = Common hepatic artery
5 = Superior mesenteric artery
6 = Left renal artery
7 = Right renal artery
8 = Left ureter and kidney
9 = Right ureter and kidney
10 = Wire mesh of aortic stent

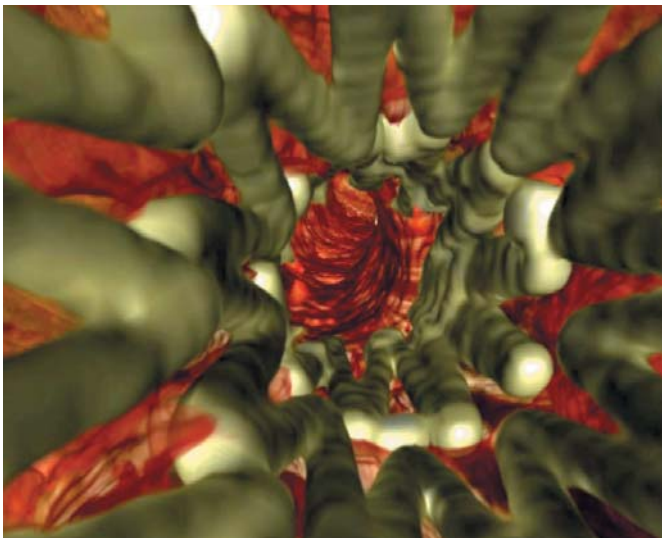

Figure 6: Endoluminal view of the stent.

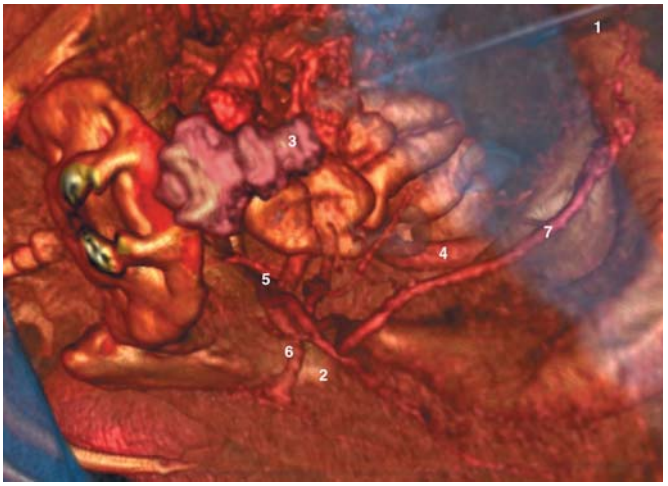

Figure 7: Investigation of an arteriopathy of the lower limbs with impotence: inferior view of the pelvic arteries and stenosis of the left pudendal artery

1 = Iliac bone
2 = Greater sciatic notch
3 = Coccyx
4 = External iliac artery
5 = Hypogastric artery (dividing into tributaries)
6 = Ischiatic artery
7 = Pudendal artery

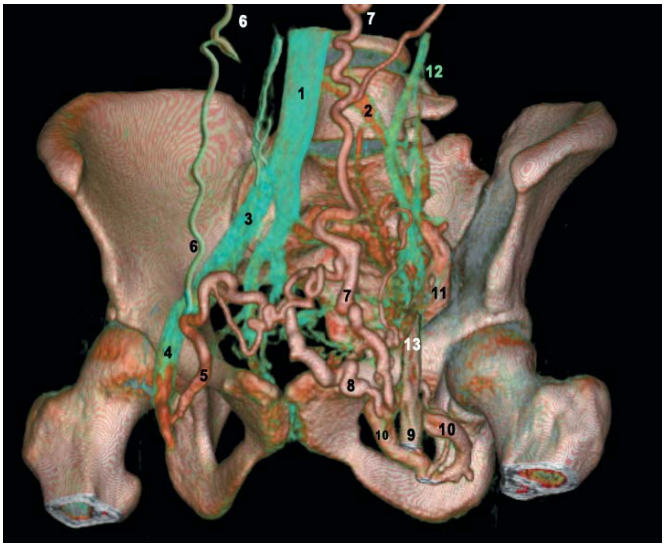

Figure 8: Shunt routes of postthrombotic syndrome of the left external iliac vein (related to May-Thurner syndrome).

1 = Inferior vena cava
2 = Residual channel of the left common iliac vein
3 = Right common iliac vein
4 = Right common femoral vein
5 = Dilated right pudendal vein draining the left femoral vein
6 = Right epigastric vein (shunting)
7 = Left epigastric vein (shunting)
8 = Dilated left pudendal vein
9 = Left common femoral vein
10 = Obturator vein (shunting)
11 = Internal iliac vein (hypogastric)
12 = Ilio-lumbar vein
13= Stump of the external iliac vein (occluded)

Three clinical examples are shown, using the VolViz® volume visualization software:

An aorto-bi-iliac bypass check-up showing an anterior view of the celiac trunk and superior mesenteric artery (*Figure 5*), an endovascular view of the stent (*Figure 6*), an assessment of the pelvic arteries for functional disability (*Figure 7*), and a venous CT scan to investigate a postthrombotic syndrome of the left external iliac vein (*Figure 8*).

CONCLUSION

Advances in computer technology have led to new tools for 3D modeling of anatomical structures in the human body, in particular vascular anatomy. By means of interactive virtual dissection and dissemination on the Internet, these methods are an educational tool of unparalleled value.[14] With 3D vector modeling, they will improve imaging data analysis and so represent a major advance in determining prognosis and therapeutic strategy. In the very near future, these tools will open the way to treatment simulations and assisted surgery[15] or pre-operative training, which, for young surgeons, will be comparable to the use of flight simulators to train airplane pilots.

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About new articles

Kearon C, Kahn S R, Agnelli G, Goldhaber S, Raskob G E, and Comerota A J. Antithrombotic Therapy for Venous Thromboembolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133:454S-545S

A Review by Grégoire LE GAL

The 8th edition of a "bedtime reading" work for physicians involved in the management of Venous Thromboembolic Disease (VTED) ("Antithrombotic and Thrombolytic Therapy, American College of Chest Physicians Evidence-Based Practice Guidelines", 8th edition) has just been published. This new volume, which is almost 1000 pages long, presents a state of the art description of antithrombotic agents (platelet anti-aggregants, anticoagulants, thrombolytics), their indications (VTED, atrial fibrillation, valvular heart disease, coronary artery disease, peripheral arterial disease or cerebrovascular disease), and also their complications (hemorrhagic events, heparin-induced thrombocytopenia (HIT) and the management of these disorders in a certain number of specific cases (perioperative period, children, pregnant women).

Before reading and using these recommendations, the reader needs to understand the important changes made in the methodology and how they were developed. The strength of the recommendation (1 : "We recommend", or 2 : "We suggest") no longer is based, as only a few years ago, solely on the type and quality of available studies. It is a true judgement on the overall value of the balance between the benefits and risks incurred by following this recommendation, a judgement based on the expected benefits in terms of health, treatment-related risks, patients' values and preferences, but also on economic considerations and the allocation of resources.

What's new in the treatment of VTED ?

Regarding acute deep vein thrombosis (DVT) and pulmonary embolism (PE), the novel aspect is the introduction of fondaparinux (a fixed-dose pentasaccharide administered as one subcutaneous injection a day), recommended in the same capacity as unfractionated heparin (UFH) or low molecular weight heparin (LMWH) (grade 1A). This treatment should be continued for at least five days and up until therapy with a vitamin K antagonist (VKA) started on day 1 of management becomes effective (INR>2 of at least 24 hours' duration) (grade 1C). For DVT, ambulatory treatment is possible (1C).

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The indications for aggressive management of DVT have been expanded. While in the previous edition, catheter-guided systemic thrombolysis or surgical thrombectomy were reserved for extreme cases (limb salvage, venous gangrene), they are now suggested interventions, with priority given to catheter-guided thrombolysis, for the prophylaxis of post-thrombotic disease in selected patients with acute symptomatic extensive proximal DVT, a low risk of bleeding, good functional status, and a life expectancy of more than one year. But caution is necessary. This is a grade 2B or 2C recommendation, and it is specifically mentioned that these procedures should be performed only if the appropriate expertise and resources are available.

One of the most striking changes is the duration of treatment. The recommended duration of treatment continues to be three months for thromboembolic events provoked by a major reversible risk factor (surgery, immobilisation, etc.). On the contrary, in patients who have had an event not provoked by such a factor, whereas the previous edition recommended initial therapy for 6 to 12 months followed by consideration of possible extended therapy, long-term therapy is now recommended (grade 1A) for all patients in the absence of a high risk of bleeding, and if good control of anticoagulation is feasible. Periodic reevaluation of the benefit to risk ratio is recommended. An exception is made for cases of isolated distal DVT where three months of anticoagulation is adequate treatment, even in cases of un-provoked events (grade 2B).

A major result of this stratification based on the provoked feature of the event or not and the recommendation of long-term therapy in the majority of patients with unprovoked VTED is that biological thrombophilias (factor V Leiden, etc.) have completely disappeared from these recommendations, while previously they were used to modulate the duration of treatment of patients with unprovoked VTED. This is probably justified, for example, regarding factor V Leiden, whose impact on the risk of recurrence is not clearly established. It is more debatable for antiphospholipids, which should always be screened for in patients in whom discontinuation of anticoagulant therapy is being considered.

Lastly, apart from antithrombotic therapy, the management of post-thrombotic disease (PTD) is discussed more thoroughly than in previous editions. The prophylaxis and treatment of PTD without an associated venous ulcer involves the wearing of compression stockings. If a venous ulcer exists, regarding physical measures to be taken, intermittent pneumatic compression therapy is suggested (Grade 2B). In terms of pharmacological therapy, the administration of local care and compression therapy is suggested in combination with pentoxifyllin, micronized purified flavonoid fraction or sulodexide (Grade 2B).

Congress and conference calendar

DATES	CONGRESS	COUNTRY	CITY
9 - 11 January 2009	9th NATIONAL PHLEBOLOGY CONGRESS	Turkey	Izmir
24 - 25 January 2009	II ANNUAL CONGRESS OF THE VENOUS ASSOCIATION OF INDIA	India	Hyderabad
30 January 2009	CORSO DI FLEBECTOMIA AMBULATORIALE	Italy	Bologna
31 January - 2 February 2009	CORSO DI SCLEROTERAPIA ECOGUIDATA	Italy	Bologna
26 - 28 February 2009	13th EUROPEAN VASCULAR COURSE	Netherlands	Maastricht
4 - 7 April 2009	VASCULAR & ENDOVASCULAR CONTROVERSIES UPDATE (Incorporating the Global Endovascular Forum)	UK	London
30 April - 2 May 2009	MAYO CLINIC INTERNATIONAL VASCULAR SYMPOSIUM	Hungary	Budapest

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Peter Gloviczki, PhD Haraldur Bjarnason, MD Raymond C. Shields, MD *Mayo Clinic Course Directors*		www.mayo.edu/cme/apr2009.html

DATES	CONGRESS	COUNTRY	CITY
14 - 16 May 2009	18th CONGRESO ARGENTINO E INTERNACIONAL DE FLEBOLOGIA Y LINFOLOGIA	Argentina	Buenos Aires
28 - 30 May 2009	VI CONGRESS OF POLISH PHLEBOLOGICAL SOCIETY	Poland	Warsaw
5 - 7 June 2009	10th ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM	Denmark	Copenhagen
31 August - 4 September 2009	XVI WORLD MEETING OF THE UNION INTERNATIONALE DE PHLEBOLOGIE (UIP)	Principality of Monaco	Monaco
19 - 22 September 2009	18th CONGRESS OF THE EUROPEAN CHAPTER OF THE INTERNATIONAL UNION OF ANGIOLOGY	Italy	Palermo
21 - 25 September 2009	22nd INTERNATIONAL CONGRESS OF LYMPHOLOGY	Australia	Sydney
5 - 8 November 2009	ACP - 23rd ANNUAL CONGRESS	USA	Palm Springs
21 - 25 April 2010	XXIV WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY (IUA)	Argentina	Buenos Aires

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