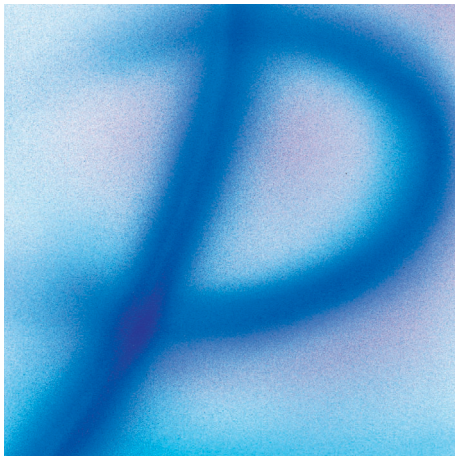
PHLEBOLYMPHOLOGY N°47

ISSN 1286-0107



2004 • N°47 • p.298-336

AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous disease.

The aim of *Phlebolymphology* is to provide doctors with updated and interesting information on phlebology and lymphology written by well-known specialists from different countries worldwide.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, was included in the EMBASE database in 1998.

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

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PHLEBOLYMPHOLOGY

This issue of Phlebolymphology *contains many interesting articles, which will stimulate discussion.*

Everyone dealing with practical phlebology will be convinced that, in patients with chronic venous disease, the insufficiency of the venous pump is caused not only by valvular damage and hindrances to venous backflow, but also by muscular dysfunction. However, it is not easy to differentiate these components by clinical testing. There are published data showing that a restriction of ankle movement, which is a frequent sequel of painful leg ulcers, leads to a reduction of the venous pumping capacity. Muscles that are not trained will become atrophic and therefore the motor of the venous pump will fail.

In his article, ***Dr Simka*** *from Poland, discusses a plethysmographic method to evaluate whether measurements in the supine and standing position could determine the motor component of the venous pump. In this short paper, no methodological details are given and the results are only reported in terms of "percentage insufficiency" and not in absolute terms characterizing the efficiency of the venous pump. Therefore, it seems unlikely that his method will solve the problem.*

Dr Corcos *from Florence shows us the close relationship between morphological and hemodynamic changes in varicose veins, pointing to the unresolved question: which came first, the chicken or the egg? As we know, correction of the venous hemodynamics will improve morphological changes.*

A real treasure is the article from ***Drs Humbert*** *and* ***Meaume*** *from France, which gives a broad overview of the various technologies available for the assessment of leg ulcers. This will be a very useful aid for all investigators involved in ulcer trials.*

Finally, ***Prof Lee*** *from Korea gives us an insight into the difficult world of lymphedema-angiodysplasia syndromes and their management. His vast experience, especially in this field, is amazing.*

Dr Hugo Partsch

Calf muscle pump dysfunction in the patients with severe chronic venous insufficiency

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ABSTRACT

Severe chronic venous insufficiency is often caused by calf muscle pump failure. Proper outflow of venous blood from the lower extremities depends on three factors: vein patency, competence of valves, and proper calf muscle function. All disturbances in these three components result in venous hypertension and chronic venous insufficiency. Failure of the muscle pump seems to be the most under-estimated pathophysiological factor, as Doppler sonography and phlebography cannot assess its function. To assess calf muscle pump function in patients with venous leg ulcers, 59 legs were examined by means of air plethysmography. The examination was performed in the supine and standing position. Insufficiency of the muscle pump in the supine position was revealed in 49% of cases, and in the standing position in 38%. In 24.5% of legs, an impaired muscle pump was found both in the supine and standing position. It was also found that in 73% of legs the venous outflow was compromised, and in 34% there was pathological reflux. However, in 18% of examined legs, the calf muscle pump impairment was the only abnormality. Patients with an insufficient calf muscle pump were older compared with those without this abnormality, and there were more longstanding ulcers in this group. Moreover, it was found that ulcers in legs with an insufficient muscle pump were larger, and their healing time was longer. It could be concluded that calf muscle pump failure is common in patients with venous leg ulcers, and this pathology can result in delay of healing of the ulceration.

INTRODUCTION

Venous return from the leg depends primarily on the emptying of the venous plexus in the muscles of the calf during the plantar flexion of the ankle in the presence of competent valvular system and the absence of obstruction of main veins. If these three parameters of proper functioning are intact, the blood is propelled inward (from superficial veins via perforators to the deep venous system) and toward the heart. Lack of physiological emptying of veins results in ambulatory venous hypertension, which finally can even lead to development of ulceration. Nowadays, most therapeutic decisions in phlebology are based on clinical and anatomic data. The role of functional tests remains underestimated.[1] Furthermore, most patients with severe forms of chronic venous insufficiency have incompetence in many systems.

Keywords:
calf muscle pump, chronic venous insufficiency, leg ulcer, plethysmography

The aim of this study was to evaluate functional disturbances revealed in air-plethysmographic examination, as well as to estimate the clinical relevance of these abnormalities.

PATIENTS

Fifty-nine legs with open ulcerations in 48 patients, were examined. Patients were aged 33 to 87 years, mean 67 years. There were 35 female and 13 male patients (73% versus 27%). All ulcerations were regarded as "venous" due to their typical localization and other signs of chronic venous insufficiency: edema, varicosities, corona phlectatica, hyperpigmentation, etc. However, in some patients, ulcers were of mixed origin, eg, also related to arterial occlusive disease, diabetes mellitus, or rheumatoid arthritis.

METHODS

To assess function of venous system in these patients, air-plethysmographic method has been chosen, as this examination could be performed even in patients with profound skin changes, and several functional tests – assessing different components of venous physiology - could be done. As it was found (details are discussed further) that as far as proper healing of the ulcer was concerned, calf muscle pump function was of major clinical importance, this paper is focused on this part of plethysmographic examination.

Routinely – air-plethysmographic examination consists of some independent tests. Each of them serves purpose of assessment of different part of the proper venous blood flow. Changes of volume of veins are measured calculating the changes of pressure in the cuffs placed on the examined leg. Cuffs are filled with air under the pressure 6-8 mmHg (pressure in cuffs should not be higher to prevent compression of the veins). After the calibration, changes of pressure can be transferred to changes of volume. As veins are the only system in the leg, which can significantly and quickly change its volume, every change of pressure in cuffs is correlated with dilation or collapse of the veins.

To assess the presence and volume of venous reflux, the examined leg is elevated, and then – lowered. If there is venous reflux, pressure in cuffs increases; volume of reflux can be also calculated. Patency of venous system is checked by inflation and deflation of the additional cuff placed over patient's thigh. During this examination, volume of distal part of leg increases (while the femoral cuff is inflated), and should rapidly decrease to the baseline after the femoral cuff is deflated. Prolonged return of leg's volume to the baseline indicates venous occlusion (there are some additional tests to distinguish superficial from deep obstructions). To assess the calf muscle pump function, after the calibration of the set, patient is asked to perform some plantar flexion of the foot (tip-toe maneuvers in the upright position). In our protocol, this examination is performed in supine and upright position. During flexions of calf muscles, the blood is ejected from deep veins of the calf, thus resulting in decrease of volume of the examined leg. As the volume of leg decreases, the pressure of air in the plethysmographic cuff also goes down. These changes are recorded as a curve, and so can be measured and evaluated. The calf muscle pump was regarded as abnormal if the drop of pressure in cuffs was lower than 1 mmHg, which corresponded to approximately 20 ml of ejected blood *(fig. 1-3)*. This value has been found to be physiological in examinations performed in healthy subjects. Presence of venous reflux does not interfere with the assessment of muscle pump. But it should be underlined, that volumes of lower leg decrease during described maneuvers only on condition that blood is expelled proximally. In some cases however, though the blood is ejected from deep veins of lower leg, it is not propelled proximally. This is due - either to profound varicosities (in these cases blood is ejected mainly to the dilated superficial veins – so, the overall volume of the extremity does not change), or to obstruction of main venous trunks (in these cases the volume of the leg can even increase). All these additional pathologies which compromise the function of muscle pump can be easier found if the examination is performed in supine position. But it seems reasonable to perform the examination in both positions (supine and upright), as the function is assessed in two different conditions, corresponding to the daily activity of the patient – when the veins are not dilated and the rest pressure is low (supine), and when veins are dilated and the rest pressure is high (upright). Therefore the method of evaluation of calf muscle pump described in this paper does not assess "pure" function of the pump (as it is done in foot volumetry), irrespective of other components of the system, but rather it helps answering the question – if the volume and pressure in venous system of lower leg decrease during the active contractions of calf muscles, and movements in the ankle joint. This, from pathophysiological point of view seems to be even more important than intact anatomical structures of muscles and skeleton. In this study Smartdop-20EX detector (Hadeco, Japan) with air-plethysmographic probe PV-20 was used. It should be emphasized that examination protocol of our

plethysmographic set differs from most often described in medical papers air-plethysmography performed by means of American set (APG-1000C; ACI Medical Inc, USA).[1,2]

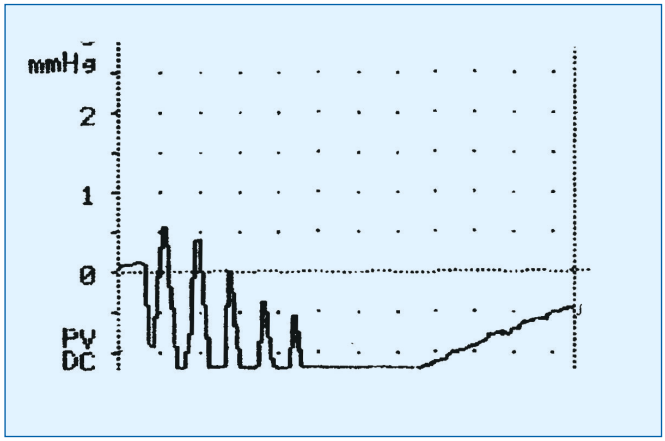

Figure 1. Normal function of calf muscle pump: drop of pressure below the baseline.

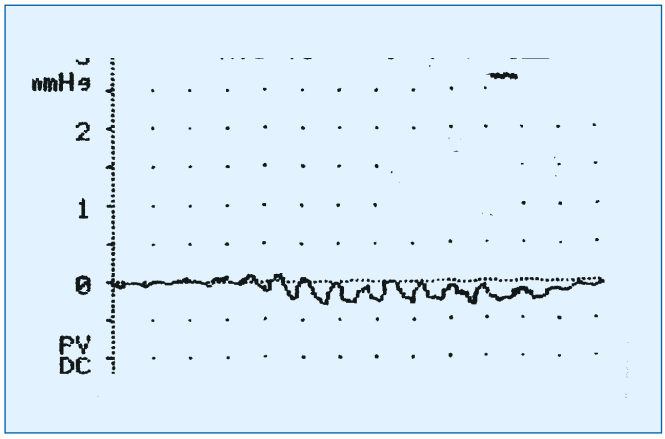

Figure 2. Failure of muscle pump: virtually no blood is expelled during plantar flexion of the foot.

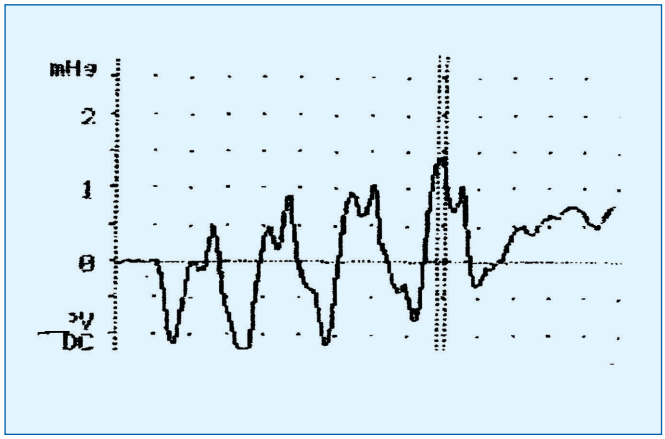

Figure 3. Volume of the leg increases during plantar flexions of the foot due to coexisting obstruction of popliteal vein.

RESULTS

Insufficiency of the calf muscle pump in the supine position was found in 49% of legs, and in 38% of legs in the standing position. In 24.5% of legs, there was impaired muscle pump in both the supine and the standing position. Moreover, there was pathological outflow in the occlusion test in 73% of extremities, and pathological reflux was revealed in 63% of cases. Insufficiency of all three components (patency, lack of reflux, and normal pumping) was found in 34% of extremities. An insufficient calf muscle pump was the only significant venous abnormality in 18% of cases. It was also found that failure of the calf muscle pump was present more often in older patients *(Figure 4)*; ulcerations in legs with a compromised pump were larger *(Figure 5)*. Presence of an abnormal pump correlated with poorer results of treatment of venous ulcers. Failure of the pump was found more often in patients who began the specialized care after a long period of unsuccessful home

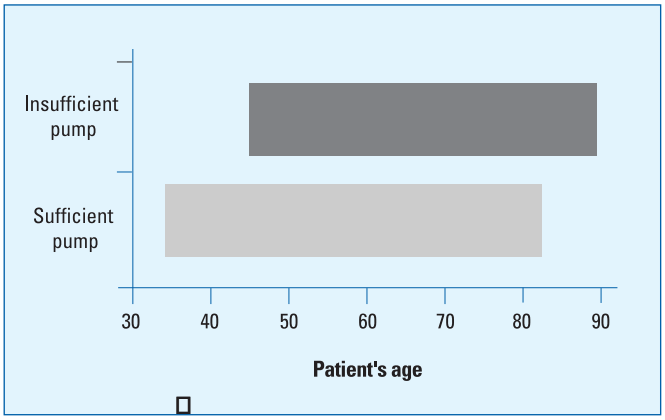

Figure 4. Patients' age and calf muscle pump.

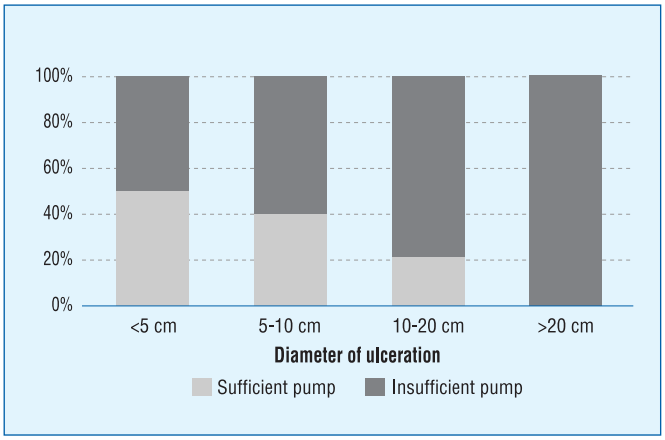

Figure 5. Percentage of patients with sufficient and insufficient calf muscle pump in terms of ulcer diameter.

treatment *(Figure 6)*, and the healing time in specialized leg ulcer clinic was prolonged in the legs with insufficient pumps *(Figure 7)*.

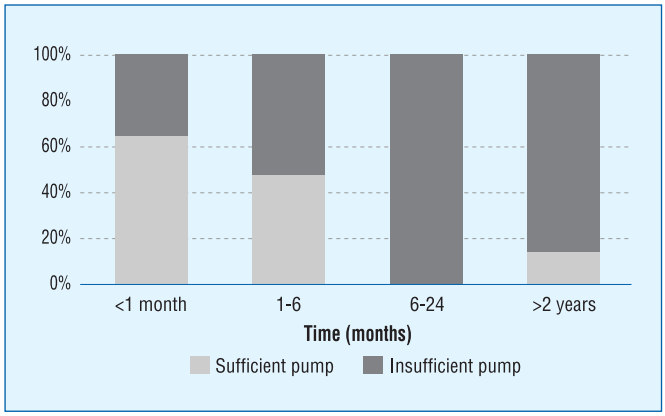

Figure 6. Percentage of patients with sufficient or insufficient calf muscle pump in terms of time from the opening of the ulcer to the beginning of specialized care.

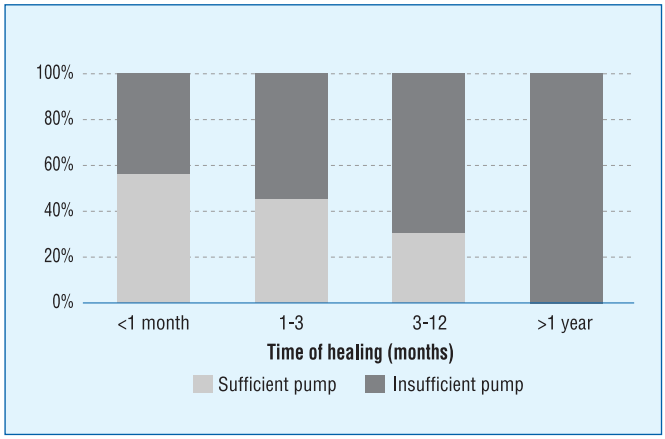

Figure 7. Percentage of patients with sufficient and insufficient calf muscle pump in terms of time of healing of the ulceration in the specialized leg ulcer clinic.

DISCUSSION

A thorough evaluation of the patient with chronic venous insufficiency should include clinical (physical examination and history), anatomic (phlebography, color Doppler sonography), and functional (eg, plethysmography) assessment. Though the majority of patients do not require full evaluation, complicated cases with profound disability often require extensive assessment of the abnormality, also by means of functional testing. There are some functional tests of the venous system of the leg: photoplethysmography, air plethysmography, and assessment of valve closure time. Photoplethysmography is widely used; however, its clinical relevance has been shown to be limited. This examination cannot be performed in the presence of ulceration or profound skin induration and hyperpigmentation. Photoplethysmography only measures blood stasis in dermal vessels, and can only assess main veins indirectly. Doppler sonographic valve closure time measurement can only be done locally, and the assessment of the global venous function is not possible. Air or strain-gauge plethysmography can assess this function; however, this examination is not widely used, and the procedure is not yet standardized. Air plethysmography seems to be the most promising procedure. In this examination obstruction, reflux, and calf muscle pump can be quantified.[3-5]

It was reported in several papers that failure of the calf muscle pump interferes with healing of venous ulcers. Araki[6] found that patients with active leg ulcer revealed more profound dysfunction of the calf muscle pump (investigated by means of air plethysmography) in comparison with patients with healed ulcers or with signs of severe chronic venous insufficiency, but without ulceration (CEAP-4). As it is rather improbable for the muscle pump to improve significantly after the ulcer has been healed, he hypothesized that it was associated with the fact that patients with more compromised calf muscle pump have a lower possibility of healing of the ulcer. In our patients, it was also revealed that insufficiency of the calf muscle pump was associated with prolonged time to healing, and the failure of muscle pump was more often seen in patients who began specialized treatment (probably those with correct functioning of muscle pump could heal their ulcers using home treatment only).

Failure of the calf muscle pump in some patients is related to decreased mobility of the ankle joint due to painful ulceration in this area. In these patients, the failure can be reversible. Moreover, insufficiency of the calf muscle pump mainly in the supine position can be related not only to muscular and articular disorders, but also to other problems, eg, stiffness of venous wall or even obstruction associated with previous venous thrombosis. Probably, the higher incidence of muscle pump insufficiency in the supine position in our patients could be explained by this phenomenon.

However, in longstanding ulcers, the patient's walking pattern changes from the light standing on toes to hard, "duck-like" standing on heels. This results in permanent slight flexion of knees and ankle joints leading to focal overloading of joint cartilages and ligaments, finally resulting in ankle joint stiffness and varus deformation of the knee joint. After the contraction of the ankle joint,

leading to a nonfunctioning calf muscle pump, so-called arthrogenic congestive syndrome develops.[7] In these cases venous ambulatory hypertension cannot be managed with routine compression therapy only. If the chronic abnormality has led to stiffening of ankle joint, muscular atrophy of the lower leg, and atrophic changes in the articular capsule, qualified (and costly) physiotherapeutic care seems to be unavoidable. Therefore, it seems reasonable to institute exercise programs as well as appropriate compression therapy early in patients with insufficiency of the calf muscle pump.[8] These however can be done only if failure of the calf muscle pump is diagnosed on plethysmographic examination.

CONCLUSIONS

Insufficiency of the calf muscle pump is the common cause of profound chronic venous insufficiency. Results of treatment of venous leg ulcers in patients with calf muscle pump failure revealed in the air-plethysmography are worse if compared with those with sufficient pump. Perhaps, routine plethysmographic assessment could predict patients with poor prognosis for proper healing of the ulceration.

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Histopathology of great saphenous vein valves in primary venous insufficiency

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Keywords:
venous valves, venous insufficiency, saphenous vein, varicose veins

ABSTRACT

Objective: To verify some of the previous findings of venous valves described in the literature, their pathophysiological significance, and the clinical implications.
Materials and methods: The elementary components of 65 proximal valves of the great saphenous vein and their interrelationships were subjected to histopathological examination. Valves were taken from patients subjected to great saphenous vein surgical removal for varicose veins of the lower limbs. Measurements and morphological evaluations were performed by optical microscopy.
Results: The valvular sinus, leaflet insertion segment, and proximal portion of the cusp undergo parallel variations of thickness. The thickening of the proximal portion of cusp is related to the smooth muscle cells increasing in the leaflet insertion segment, and the elastic layer dissociation. The thickening of the distal portion of cusp depends on the collagen component, and it may shorten, crumple, and lead to the formation of a thickened border. The vein wall in a commissural aneurysm is usually thinner than in the valvular sinus.
Alterations in the intima, in the elastic membrane, and in the media were found in the 98% of the valvular anulus. Ectasia and asymmetry of the venous wall are mainly related to the muscular hypoplasia of the media.
Conclusions: The development of primary venous insufficiency seems to be due to the following tissue alterations: dilatation of the valvular anulus and hypotrophy of the cusp. The hemodynamic mechanical injury increases the tissue damage of both anulus and cusps. This pathophysiological interpretation of venous insufficiency leads to the need a detailed diagnostic procedure before reparative surgery of valves.

INTRODUCTION

Starting from the beginning of the century and up until about 10 years ago, several authors have developed the theory of "primary vein wall dilatation and late cusp degeneration" in order to explain the development of primary venous insufficiency. On these bases, various techniques for surgical valve repair in

deep and superficial veins were developed and performed with satisfactory results. However, some discrepancies with the basic pathophysiological concept were observed, and the theory of "primary valve degeneration" gave no satisfactory explanation for either the onset or the development of the disease.

A recent retrospective study performed on 72 cases affected with saphenofemoral junction insufficiency subjected to external valvuloplasty demonstrated that the best results can be obtained in cases with early disease, that in 18% of the early cases the valvular cusps were already damaged, and that in 50% of the late cases the cusps still had normal structure and function.

Different parts and surfaces of cusps were taken into consideration in the previous studies: the leaflet insertion segment and the parietal and luminal parts of the leaflet, as well as the proximal and distal portions and border. The main tissue alterations observed were the following: increase in smooth muscle and connective tissue cells in the leaflet insertion segment; intimal plaques below the leaflet insertion segment (endophlebohypertrophy); leaflet irregular thinning or thickening with elastic membrane fragmentation and dissociation and fibroblast proliferation; segmentary irregular thickness of leaflet parietal surface (crypts); and cyst-like structures containing erythrocytes beneath the leaflet endothelium in some cases, and thickening of the free borders. Postthrombotic-like alterations in subterminal valves of long saphenous varicose veins led several authors to develop the theory of postthrombotic valvular destruction. Inflammatory cells were found in cases with inflammatory general diseases.

Some normal cusps were observed in dilated or aneurysmatic veins and, in some others, pathological cusps were found in undilated valvular anulus. The same finding emerged on a first verification performed in our departments by clinical, echographic, angioscopic and histopathological studies on 42 saphenofemoral valves. However, the conclusion of the study was that in the majority of the cases primary anulus dilatation and some early hypotrophic cusp damage can develop simultaneously.

OBJECTIVES

To detect the relationships between the elementary alterations of the venous wall and the cusps, to define the concept of cusp hypotrophy, and its clinical significance, and to clarify the pathophysiology of primary venous insufficiency in order to perform a more detailed diagnostic assessment of venous valves before reconstructive surgery.

MATERIALS AND METHODS

The valvular sinus, commissure, leaflet insertion segment, and leaflet thickness were evaluated and measured (microns) *(Figure 1)*.

The clinical and anatomical characteristics of the patients and histological techniques employed are summarized in *Table I*. Seventeen longitudinal and 48 cross-sections (two

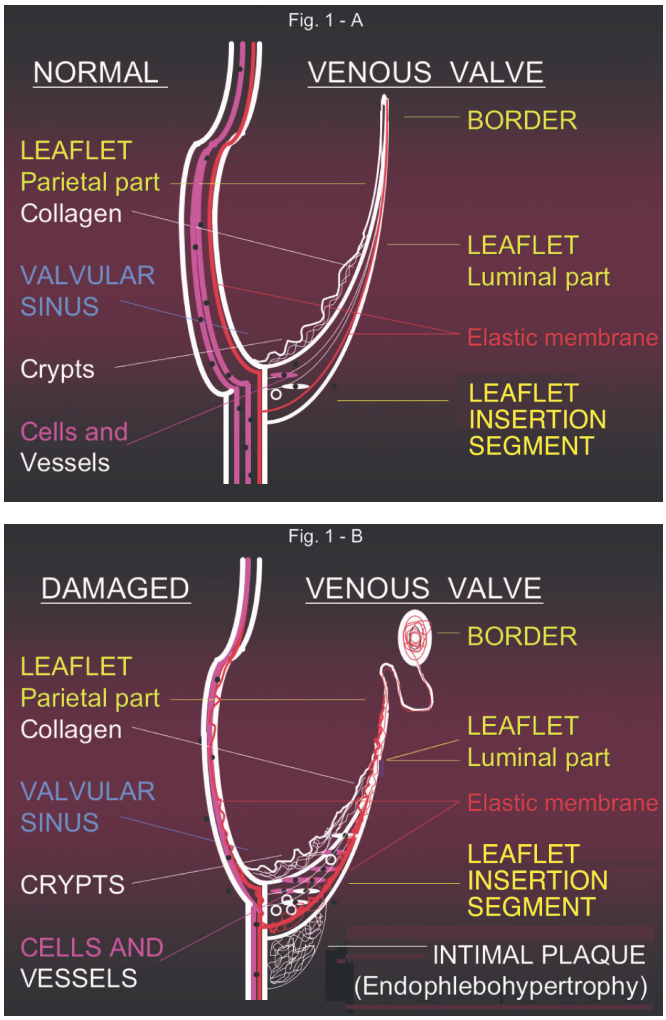

Figure 1. A - Schematic example of a great saphenous vein proximal valve in a longitudinal section. The valvular apparatus appears to be free from elementary tissue alterations, as it should be in normal conditions. The different valvular parts and the anatomical and histological components studied are shown.
B - In this example of a damaged valve we summarize the main alterations observed: thinning of the venous wall and distal portion of the leaflet, where the border is often crumpled and thickened; thickened leaflet insertion segment with an increased number of cells and vessels; elastic membrane fragmentation and dissociation; flattened crypts; and endophlebohypertrophy below the valve leaflet insertion segment. The more frequent and significant combinations of these elementary tissue alterations are described and analyzed in the text.

were oblique) of proximal saphenous valves were studied. The protocol of the microscopic evaluation is summarized in *Table II*. The anatomical and histological details subjected to microscopic evaluation are schematically described in *Figure 1*.

Correlations between thickness, morphology, and elementary tissue alterations of the valvular apparatus were investigated, evaluated, and underwent statistical analysis.

Pathology	Varicose veins of the lower leg 65 cases
Sex	Males 18, females 47
Age of patients	Min 33, Max 84, Mean 56.7 sc 1.66
Age of disease	Min 3, Max 40, Mean 20.0 sc 1.17
Valves	Terminal 9, Subterminal 45, Indeterminate 11
Stain	Hematoxilin-eosin, Weigert, Van Gieson
Sections	Cross 46, Longitudinal 17, Oblique 2

Table I. Histopathological examination of 65 proximal great saphenous vein valves. Clinical and anatomical characteristics and histological techniques.

@ANATOMICAL PART		COMPONENTS	MEASURES AND GRADING
CUSP	LEAFLET INSERTION SEGMENT	Thickness: max min	Microns
		Smooth muscle cells	0 = none; 1 = some isolated cells; 2 = spaces between cells; 3 = full
		Fibroblasts	0 = none; 1 = some isolated cells; 2 = spaces between cells; 3 = full
		Vessels	0 = none; 1 = one; 2 = some; 3 = numerous
	LEAFLET (proximal distal)	Thickness: max min	Microns
		Thickened, thinned, normal	Morphologic evaluation
		Smooth muscle cells	0 = none; 1 = some isolated cells; 2 = spaces between cells; 3 = full
		Elastic membrane fragmentation-dissociation	0 = normal; 1 = rare duplications; 2 = extensive dissociation; 3 = dissolvement
		Collagen parietal part, collagen luminal part	0 = absent; 1 = elastic membrane thickness; 2 = elastic membrane thickness x 2; 3 = elastic membrane thickness > x 2
		Crypts: normal, deeper, flatter	Morphologic evaluation
	BORDER	Normal, thickened, thinned	Morphologic evaluation
ANULUS	SINUS WALL	Thickness	Microns
		Ectasia-asymmetry	Yes - No
		Muscular hyperplasia	Yes - No
		Muscular hypoplasia	Yes - No
		Sclerosis of the media	Yes - No
		Elastic membrane fragment	Yes - No
		Intimal plaques below V	0 = none; 1 = 1/3 vein wall; 2 = 1/2 vein wall; 3 = vein wall
SPECIAL FINDINGS		Thrombosis Thrombotic sequelae Tributary veins with valves Endothelial cysts	Description
COMMISSURE	1 - 2	Aneurysm or dilatation	Yes - No
		Thickness (max min mean)	Microns
		Elastic membrane fragment	0 = normal; 1 = rare duplications; 2 = extensive dissociation; 3 = dissolution
		Intimal plaques (endophlebohypertrophy)	0 = none; 1 = 1/3 vein wall; 2 = 1/2 vein wall; 3 = vein wall

Table II. Histopathological examination of 65 proximal great saphenous vein valves: parameters examined and study protocol.

RESULTS

Nonsignifiant correlations are summarized in *Table III*. Flattened or absent crypts were mainly observed in the distal portion of thinned leaflets (*P*=0.075). Thickening of the border was detected in 71.8% of the samples. Endophlebohypertrophy in the anulus below the valve was observed in 21.4% of cases, and dilatation or aneurysm of one or both commissures in 74.4%. Some inflammatory cells were detected in the valve tissues of only six cases with thrombotic occlusion. No inflammatory cells or microthrombi were observed in any of the other cases.

Significant correlations are summarized in *Table IV*. The main results are the following. The mean thickness values of the valve leaflet insertion segment, valvular sinus, and proximal part of the leaflet undergo parallel variations *(Figures 1 and 2)*. The thickening of the whole leaflet appeared to be mainly related to the collagen thickness in the parietal part *(Figure 3)*. The number of smooth muscle cells in the leaflet insertion segment increases in the thickened proximal part of the leaflet *(Figure 4)*. The fragmentation-dissociation of the elastic membrane and the increase in elastic fibrils are prevalent in the thickened leaflets *(Figure 5)*. A thickened border may represent the result of retraction and crumpling of the thinned hypotrophic distal

ELEMENTARY ALTERATIONS AND ANATOMICAL COMPONENTS OBSERVED	Statistical significance
Thickness of leaflet (microns) / cells, vessels, collagen of the luminal part (morphology)	ns
Thickness of hypotrophic leaflet distal part (microns) / flattened crypts (morphology)	ns
Commissural aneurysm or dilatation / thickened border / intimal plaques (morphology)	ns
Commissural wall elemetary alterations (morphology) / anulus dilatation (morphology)	ns
Inflammatory cells – none	Not analyzed

Table III. Histopathological examination of 65 proximal great saphenous vein valves: no significant correlations.

MEASUREMENTS AND ANATOMICAL COMPONENTS COMPARED	Statistical significance
Thickness of valvular sinus (microns) / leaflet insertion segment (microns) / proximal portion of cusp (microns)	*P*<0.001
Thickened distal portion of cusp (microns) > thinned (microns)	*P*<0.05
" (microns) / thickened border (morphology)	*P*<0.05
" (microns) / collagen increased (morphology	*P*<0.001
Thickened proximal portion of cusp (microns) / smooth muscle cells in the leaflet insertion segment (morphology)	*P*<0.05
" (microns) / elastic layer dissociation (morphology)	*P*<0.05
Commissural aneurysm mean thickness (microns) < valvular sinus mean thickness (microns)	*P*<0.001
Intimal plaques, elastic dissociation, sclerosis of the media in >98% valvular anulus (morphology)	*P*<0.001
Ectasis-asymmetry of the valvular anulus / muscular hypoplasia (morphology)	*P*<0.001

Table IV. Histopathological examination of 65 proximal great saphenous vein valves: significant correlations.

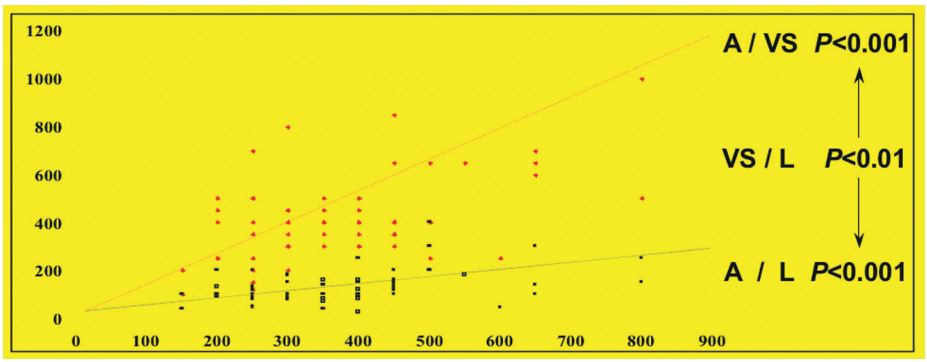

Figure 2. Cusp leaflet insertion segment, leaflet proximal part, and valvular sinus thickness evaluation and comparison. Comparison between cusp leaflet insertion segment (A)and valvular sinus (VS) thickness: P<*0.001.Comparison between cusp leaflet insertion segment (A) and leaflet proximal part (L) thickness:* P<*0.001.Comparison between leaflet proximal part (L)and valvular sinus (VS) thickness:* P<*0.01. The thickness of the three structures seem to overlap and undergo parallel variations.*

part of the leaflet *(Figures 6 and 7)*. The ectasis-asymmetry of the vein wall in the valvular sinus and commissure are mainly due to muscular hypoplasia. Sclerosis of the media, elastic membrane fragmentation-dissociation, and intimal fibromuscular hypertrophy with plaques were found in 97% of the vein walls examined *(Figure 8)*.

DISCUSSION

The valvular sinus, valve leaflet insertion segment, and proximal part of the leaflet are of similar thickness in the same subject, and this confirms the overlapping of the two main pathophysiological theories of primary venous disease: the first based on the primary vein wall dilatation and the second on primary cusp degeneration. Cusp hypotrophic thinning (hypotrophy) was observed in the

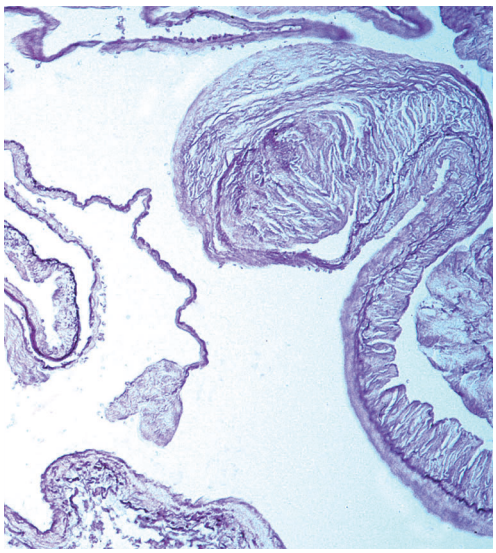

Figure 3. Low cross-section of a proximal valve. Two opposite cusps are visible: one is thickened and the opposite is thinned. The main difference is represented by the collagen thickness in the parietal part of the leaflet. The two borders are thickened. A whirled architecture is visible in the larger one. Weigert 150 x.

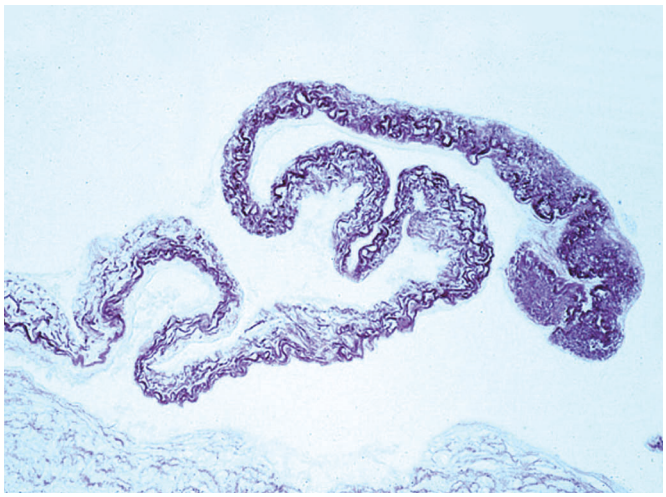

Figure 5. Cross-section of a proximal valve. A 3-degree elastic membrane fragmentation and dissociation in the whole leaflet and in the border are present with the elastic fibrils spreading throughout the thickness of the leaflet. Weigert 300 x.

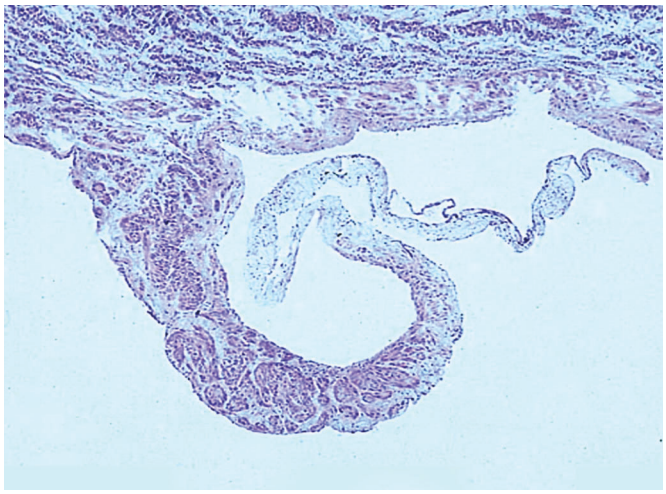

Figure 4. Longitudinal section of a prolapsed proximal valve. The leaflet insertion segment and the proximal part of the leaflet are thickened by the presence of smooth muscular cell bundles. Hematoxilin-eosin 125 x.

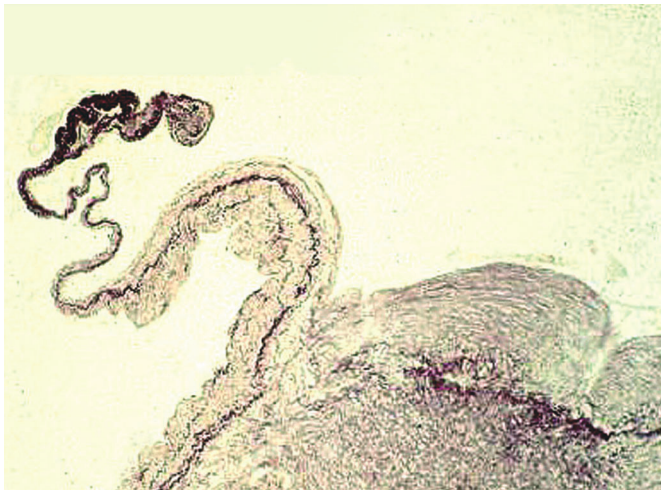

Figure 6. Longitudinal section of a terminal valve. The proximal part of the leaflet is thickened by increased collagen in the parietal side. The distal part is thinned and the elastic membrane appears to be crumpled close to the end of the leaflet and in the border. A thick fibromuscular plaque below the leaflet insertion segment is visible. Weigert 125 x.

majority of the degenerated cusps in the distal part of the leaflet, and was usually represented by the reduction of the collagen and striking thinning to a minimum of 3 microns.
The increase in the vasa vasorum, connective tissue cells, smooth muscle cells, and elastic fiber in the leaflet insertion segment and leaflet of degenerated cusps seem to represent mainly a structural variation rather than the expression of the valvular pathology, except for the smooth muscle cells and the elastic membrane alterations.
The absence of inflammatory cells and microthrombi do not confirm the pathogenetic theory based on postthrombotic alterations.
The thickened borders seem to be composed of crumpled distal hypotrophic leaflets caused by some mechanical factors as the turbulence and cusp abnormal mobility due to the valvular reflux.
The intimal fibromuscular plaques (endophlebohypertrophy) below the valve were not frequent, nor they can be considered as one of the specific expressions of primary valvular alterations. It can be supposed that these findings may be due to a combination of biochemical and mechanical factors depending on the venous stasis caused by the reflux and its turbulence.
Muscular hypoplasia was found to be prevalent in the ectasic and asymmetric valvular anulus and mainly in the commissure aneurysm. The symmetric dilatation or aneurysm of both commissures in the valvular anulus seems to prevail in the pathological saphenofemoral valves of varicose subjects. In one third of cases the commissures were not dilated. In these subjects the valvular incompetence was probably due to primary hypotrophic cusp degeneration.

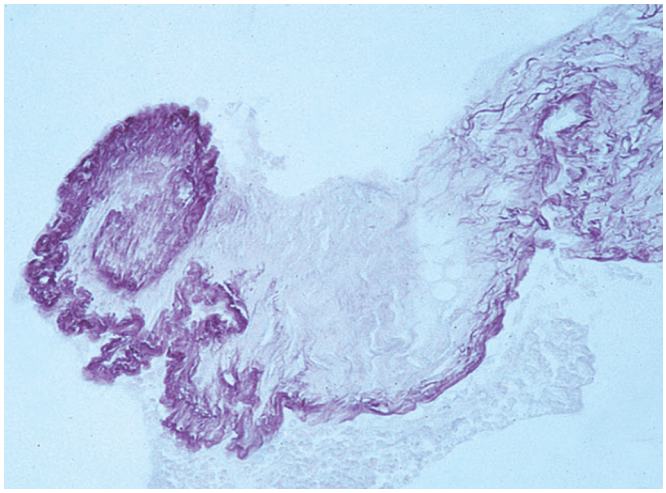

Figure 7. Cross-section of a proximal valve. The elastic membrane in the thickened border is crumpled in a spiral. The thickened border is the latest result of the crumpling of the distal part of the leaflet. Weigert 150 x.

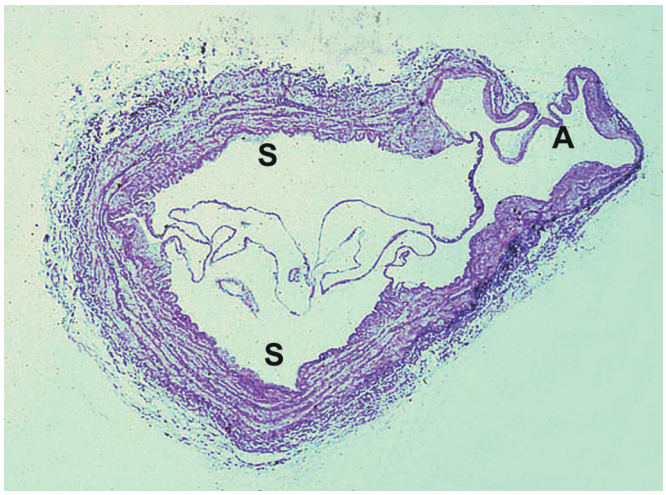

Figure 8. Cross-section of a proximal valve. Sclerosis of the media, ectasis and asymmetry of the wall, fibromuscular hypertrophy of the intimal layer. The minimum thickness in the commissural aneurysm (A) is less than in the valvular sinus (S). Weigert 15 x.

CONCLUSIONS

The concept of valvular hypotrophy seems to emerge from the prevalence of the structural thinning at the distal part of the leaflet, the valvular sinus, and the commissural aneurysm. Hypotrophy of these structures is mainly due to reduction in the collagen component in the leaflet and to the media smooth muscle tissue hypoplasia of the valvular anulus.
The histological study of saphenofemoral valves was able to detect the tissue changes due to three pathophysiological factors: primary wall dilatation, cusp tissue alterations, and the structural consequences of the hemodynamic disorder such as the thickening of the border and the endophlebohypertrophy below the valve. It can be now supposed that hemodynamic disorders may play an additional role in the already incompetent valves and lead to further injuries to the anulus and cusps. A modern combined theory for the explanation of primary venous insufficiency can be summarized in the concept of a vicious circle *(Figure 9)* basically due to the interaction between hypotrophic structural degeneration and hemodynamic mechanical injury due to reflux.
These new aspects of venous valve pathophysiology seem to lead to a plausible explanation for the controversial results obtained by reconstructive valve surgery. Their clinical implications are mainly represented by the need for a more careful instrumental assessment of venous valve conditions by ultrasound and/or angioscopic detailed examination before and during reconstructive surgical procedures in order to make the best technical choice.

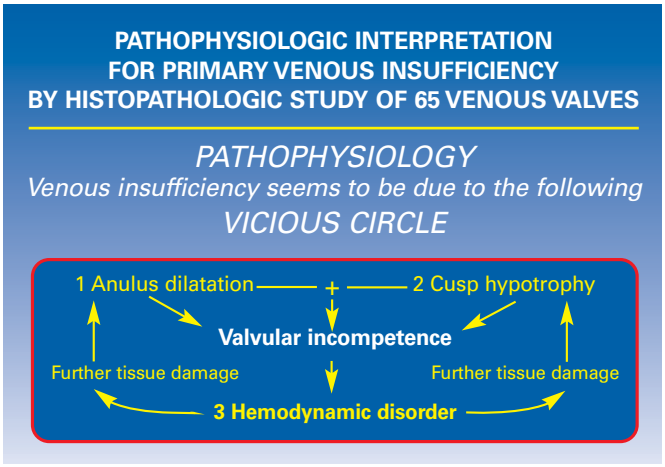

Figure 9. Three factors seem to concur in the onset and development of primary venous insufficiency: (1) anulus dilatation with hypotrophic parts, (2) cusp hypotrophy, and (3) hemodynamic disorder which leads to a mechanical injury of both anulus and cusps. One of the three factors can represent the beginning of the vicious circle which leads to venous insufficiency. In the majority of the cases studied they seem to overlap.

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COMMENT BY THE AUTHOR

At the time of the study, our interest was focalized on the main anatomical causes of valvular incompetence, and our conclusions made possible a better selection of patients to be subjected to the external banding of the proximal great saphenous vein.[1] The characteristics of the proximal valves were carefully observed and measured by echography, and the cases affected with early and evident hypotrophy of the valve cusps were excluded. The number of the interventions decreased, but the quality of the clinical and hemodynamic outcome increased.[2] At the present, these criteria are still taken into consideration before performing the procedure.

In the meantime, we were also interested in deep venous repair in cases affected with primary and secondary chronic venous insufficiency, and the topic was presented and discussed during several meetings in Rome (1998), Bremen, and Florence (1999).[3-7] Some atypical intravenous valvuloplasties of the femoral or the popliteal veins were successfully performed in cases with unusual anatomical alterations by primary disease, such as venous aneurysms and a monocuspid valve, and in postthrombotic veins where the cusps appeared to be severely damaged. While performing such interventions, the histological knowledge of the valvular elementary alterations was of great help in the choice of the surgical strategy: single residual cusps were found suitable to be transposed in the vein lumen in order to create monocuspid valves. Others were divided into two cusps and tricuspid valves were obtained. The results of the new procedures were satisfactory at a mean follow-up of 5 years.[7,8]

By the interpretation of the histological findings, and on the basis of the recent results, the creation of autologous intimal

flaps for monocuspid valvular reconstruction in cases with primary and secondary valveless syndromes was taken into consideration.[9,10] The preliminary results are satisfactory and the follow-up of new cases is still in progress.

More recently, Crotty published an impressive article on a pathogenetic hypothesis for the explanation of valvular incompetence in primary chronic venous insufficiency.[11] The study indicates that noradrenaline can regulate the tone of the vein as a venoconstrictor and can also act as a venodilator when it diffuses from the vein lumen into the media through the vasa venarum located in the valvular sinus. A malfunction of this feedback leads to the progressive dilatation of the vein wall by physiological reflux and turbulence. When the elastic sphincter of the valvular leaflet insertion segment is finally damaged, reflux and turbulence become stable and pathological. This vicious circle seems to confirm our histological hypothesis *(Figure 9)* and gives a satisfactory explanation for the progressive annulus dilatation. The simultaneous development of cusp hypotrophy and the significance of the intimal fibromuscular plaques below the valve are still to be better clarified.

The knowledge of vein valve pathophysiology, histology, and histopathology seems to represent the basis for the future of the pharmacological and surgical treatment of chronic venous insufficiency.

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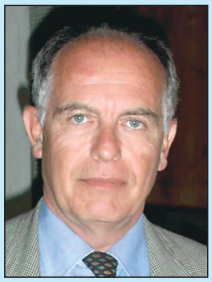

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Wound healing assessment

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ABSTRACT

Evaluation of healing requires the qualitative and quantitative analysis of chronic ulcers and wounds. The assessment of ulcers has been commonly based on the measurement of the perimeter or the surface of the wound. Nevertheless, the measurement of the volume and the color of a chronic wound is also an important step in its follow-up over time. Quantitative methods which permit the wound healing rate assessment are essential for checking the response to treatments. Numerous techniques are available, ranging from the simple use of tracings to more sophisticated methods requiring the use of cameras, videos, and computers. The parameters most frequently used to measure a wound are the length of the principal axes (length and width of the wound), the projected surface area, and the perimeter. Various mathematical calculations have made it possible to establish a relationship between the surface area of a wound, and its perimeter, length, and width. The most commonly employed technique uses an acetate film to obtain a tracing of the wound perimeter. Computer-assisted planimetry is a wound measurement method often used in clinical studies. The most simple method to assess the depth of a wound consists in using a sterile blunt-tipped rod which enables an assessment of the maximum depth of the wound. The use of an alginate mould enables the measurement of wound volume by weighing or water displacement. Stereophotogrammetry allows the measurement of the contours, surface area, and volume of a wound. It is based on determining the depth of the wound by viewing from two different angles. Ultrasound takes advantage of the difference in pathlength of an ultrasound wave reflecting at the bottom of the wound compared with the adjacent normal skin. This high-precision and simple method (because of the ability of silicone rubber to harden and be stored) uses profilometric analysis followed by computerized volume assessment. The first stage consists in making a negative imprint of the wound using silicone rubber. In vivo measurement using interferometry and fringe projection is a new method to measure in vivo the volume of ulcers. The three-dimensional reconstruction of profiles of the wound is based on a Fourier-transform method of fringe-pattern analysis. The system is made up of a Charged-Coupled Device (CCD) camera and a projection module. The resolution of the system depends on the fringe width and on the angle between the optical axis of the camera and the optical axis of the projector. The deformation of the fringes over the reference plan is proportional to the height separating the object and the reference plan. Thus, an appropriate

Keywords:
wound, wound healing, assessment, biometrology, fringe projection

algorithm allows the reconstruction of the three-dimensional profile from the projected fringes on the object, in this case the wound. Colorimetry or thered-yellow-black concept for this method consists in taking into account the color characteristics of an ulcer, which are a function of its clinical stage. Necrotic lesions are black, a fibrinous surface looks yellow, and granulation tissue is red. Nowadays, wound measurements or follow-up of healing require the use of quantitative methods, which are available and allow comparison of different treatments.

INTRODUCTION

The measurement of the surface area, volume, and color of a chronic wound is an important step in its follow-up over time. Numerous techniques are available, ranging from the simple use of tracings to more sophisticated methods requiring the use of cameras, videos, and computers. When they exist, the techniques usually employed in outpatient care units to record the woundstate over various time points are often inaccurate. Furthermore, studies of wound healing are often complicated by the few objective measurement methods which can be used in a noninvasive and ethical manner in man.[1] However, quantitative methods that permit the wound healing rate assessment are essential for checking the response to treatments, either drug-containing dressings or systemic therapies.

Briefly, wound measurements are of value for three main reasons *(Table I)*. The degree of precision required is related to the purpose of the measurement, and also the technique used.

To monitor the time course of the wound (this is a part of patient assessment)
To assess the efficacy of topical and/or systemic therapies
To attempt to forecast the time required for healing

Table I. Objectives of wound measurements.

Wound assessment meets three main difficulties:

- The definition of wound perimeter. This is an entirely subjective estimate that depends on the observer, who decides what forms part of a wound or not. The most frequent source of error comes from the difficult delineation of the epidermis edge, owing to its thinness and translucency.
- The variable aspect of large, deep wounds, which depends on the position of the patient. Such wounds are capable of marked changes in appearance, which render measurements nonreproducible if the patient is not placed in exactly the same position each time the wound is measured.
- The convex shape of human limbs. Measurements frequently do not keep in view possible errors due to this factor.

Despite such problems, several measurement techniques may be employed to assess the surface or volume of wounds. *Table II* lists the principal ones.

In contact with the wound	Tracing: dimensions, surface area, and contours Measurement of depth Volume: liquid or molding
Without contact with the wound	Photography Video film Stereophotogrammetry Analysis of structured light

Table II. Wound measurement techniques.

WOUND PARAMETERS: PERIMETER AND SURFACE AREA

The parameters most frequently used to measure a wound are the length of the principal axes (length and width of the wound), the projected surface area, and the perimeter. Different mathematical calculations have made it possible to establish a relationship between the surface area of a wound, its perimeter, length, and width.

Direct measurement of wound dimensions with a ruler

Historically, the first parameters used were the outer dimensions of the wound: length (along the longest axis = L) and width (smaller axis perpendicular to L = W). These parameters are measured directly on the wound using a graduated instrument. The same instrument must always be used if the aim is to compare dimensions, and strict conditions of asepsis must prevail to prevent the transmission of microorganisms between patients. Although imprecise, this technique is the first objective approach to a wound *(Figure 1a,b,c)*. It allows the calculation of the surface area (A), which of course is subject to some error, but this can be partly circumvented through the application of formulae for correcting surface area.[2,3] Thus, according to Mayrovitz,[3] $A = 0.73 \times L \times W$,[4] in the case of a rectangular wound. The area of an elliptic wound may be calculated as follows: $A = 0.763 \times L \times W$[4] or $A = 0.785 \times L \times W$.[5] This technique is principally applicable when wounds are

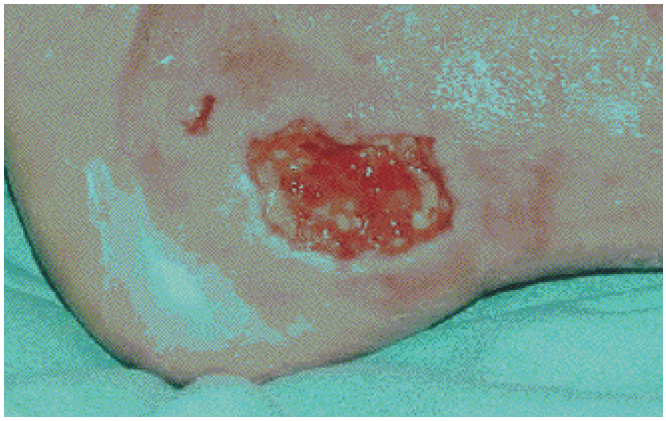

Figure 1a. The ulcer.

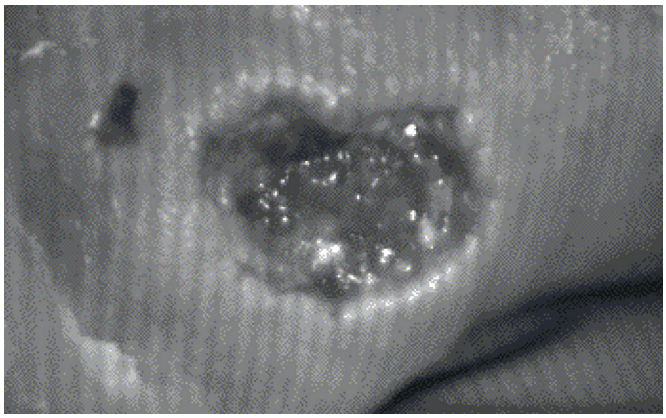

Figure 1b. Fringe projection on ulcer.

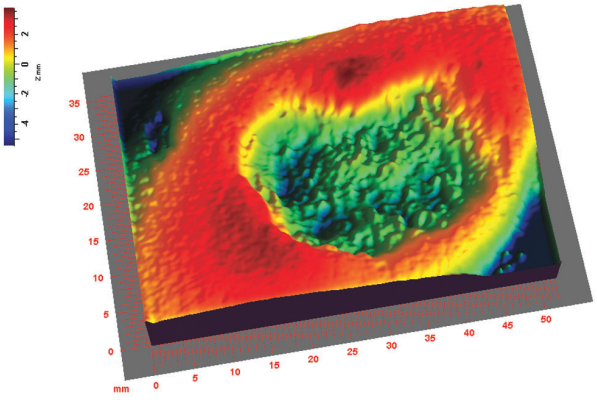

Figure 1c. 3-D reconstruction of ulcer.

rather shallow and regularly shaped. Good training in such measurements improves their sensitivity.

Transparent tracings

The most commonly employed technique, delineation of perimeter on transparent material, uses an acetate film to obtain a tracing of the wound perimeter, drawn using a fine marker pen. The paper may be a plain transparent film or may already be calibrated in millimetres. As a general rule, it is better to use a double sheet of transparent material; the tracing is drawn on the upper sheet and the lower sheet, which is in direct contact with the wound and may be soiled by exudate, can be discarded. Flexigrid® opsite (Smith and Nephew) is an adhesive, polyurethane film, which is protective and cross-ruled and can serve as a tracing to follow up the treatment of superficial wounds. The principal limitation to this technique is the difficulty encountered by the observer in determining the perimeter of the wound with enough precision.[6] A too thick line is also a source of error.

This is a rapid method (less than a minute is required to complete the tracing of a wound), which is inexpensive and requires minimal training.

Use of scale paper

The next stage consists in analyzing the tracing. As above, the two main diameters, the perimeter and the surface area, can be measured. To measure the surface area the simplest way consists in placing the tracing on a sheet of graph paper and counting the number of 1-mm squares within the area.[7,8] This is a tiresome and lengthy method (10 minutes for a 70 cm^2 wound). When the wound outline does not perfectly meet the cross-ruling, the area can be deduced using the formula: [N + Nc/2] x surface area of a square, where N is the number of squares fully contained and Nc the number crossing the outline. A more rapid method consists in cutting out the tracing or copying it on a card with a regular thickness, then weighing it on a high-precision scale.[6] Additional errors are possible when the drawing is reproduced and the card or film cut out. The use of a scanner that copies the shape of the tracing and enters the data into a computer, or the use of a flat or camera scanner, obviates such drawbacks. A program then allows a rapid and accurate analysis of the tracings, especially calculating its area, and can also measure the area of islands of newly formed epidermis that might have been recognized within the wound and traced.[9] This technique is the most widely employed in clinical studies aimed at validating products for wound treatment.

Computer-assisted planimetric measurement

Computer-assisted planimetry is a wound measurement method often used in clinical studies. The perimeter of the wound is delineated by the clinician using a pen linked to a computer. There is a close correlation between the

surface area of a wound measured by planimetry and the following parameters: length, width, perimeter, and the product of length by width.[10,11] However, this correlation diminishes in the case of very large wounds. In addition, these parameters would be predictive of the healing after 24 weeks. They may be taken either directly on the wound or indirectly from a tracing made on a transparent substrate (tracing paper, plastic film, or mylar),[12] or from a photograph taken in a standardized way.

All such measurements enable a calculation of the healing rate, and more particularly of the epithelialization. The latter appeared to be constant in certain studies,[13] reaching about 1 to 2 mm per week. Furthermore, this rate would be independent of the size of the wound.

Standardized photography

It is possible to measure wound parameters from a standardized photograph. The method has been compared with the conventional tracing method, and the results obtained do not differ significantly.[14] This procedure avoids an important disadvantage of the above methods, direct contact with the wound, which may be painful and a source of contamination. However, as an indirect procedure, it has a number of drawbacks. In order to know the scale of the image, a graduated ruler must be placed alongside the wound. It is often difficult to compensate for the concave or convex nature of the wound. The photograph must be taken exactly perpendicular to the wound. A deviation of only 20° from the perpendicular axis will cause a reduction in the wound surface area of about 10%.[15] Indeed, photography must take place under clearly defined conditions in terms of disposition and lighting, and these conditions must be reproducible.[16]

Various options are available when analyzing a photograph: computer-assisted image analysis is highly preferable to the old-fashioned projection of the photo onto paper and the secondary tracing of wound contours. Interestingly, the information obtained from photographs permits the assessment of wound parameters other than dimensional ones: aspect of the wound bed; changes in color; presence of necrosis, fibrin, or granulation tissue; and epithelialization. Standardization of the technique is essential: choice of focal distance, adjustment of speed and diaphragm, lighting, distance from the wound, angle of shot. One group of authors[17] used a Polaroid camera with accessories that allowed them to take photos at a constant angle and distance from the wound, thus enabling comparisons between photos. New Polaroid® systems are particularly well suited to the measurement of wounds. Health Cam System® allows the alignment of two lights, so that photographs are taken in a reproducible and comparable manner. Gridfilm® allows for the superimposition over the wound of a grid, which enables its direct measurement. In most cases, a graduated scale is placed alongside the wound and later enables an easy measurement of its dimensions whatever the magnification of the photo. In the semimanual recording technique the contour of the wound is followed by a digital pen. The signal thus emitted, whose motion has previously been calibrated, is processed by microcomputer. Another technique consists in superimposing the contour traced by the operative using a mouse, over the digital image of the wound, this being visualized directly on the computer screen (image patterning process).[18]

In practice, a direct data recording from a photograph is difficult to obtain, except in the case of a wound with a simple, geometric shape and a well-defined perimeter. The use of calibrated photographs may be of value when studies are made in a single center, because the reproducibility required with respect to the conditions of photography at different stages of a treatment can be satisfactory. The current need for multicenter studies to assess wounds limits this method of evaluation, and tracings should be preferred. Techniques involving photographs appear to benefit from a certain degree of reliability and reproducibility, only if strict rules are respected.[14,19]

Video image analysis

This method employs a video camera to film the wound.[20] The recording of the image is then analyzed by a computer using a special software program, which permits correction of the figures obtained for wound dimensions to compensate for the concave or convex nature of the wound. The technique is more accurate than the analysis of photographs, and is simple, rapid, and inexpensive.

A comparison of measurements using rulers, tracings or photographs is shown in *Table III*.[21]

WOUND VOLUME

Graduated ruler

The depth of a wound is not accessible to the measurement systems we have described above, because most wounds are three-dimensional (3D). It is necessary to employ specific techniques. The most simple consists in using a sterile blunt-tipped rod, which enables an assessment of the maximum depth of the wound.[22,23] The technique

involving the use of a cotton tip is easier in practice. However, such measurements are often inaccurate, and determination of the deepest point of the wound is subjective.

Kundin[5-24] developed a mathematical formula to assess the volume V of a wound through its surface area A, using the two largest diameters (length L and width W) and the depth (D): V = A x D x 0.327, where A = L x W x 0.785. Thomas and Wysocki[23] showed that these measurements were comparable to those obtained with tracings and photographs in the case of small wounds, and were consistently underestimated in the event of large or irregular wounds (particularly those with a sinuous shape). Variation in the measurement of the same wound, with the patient in the same position, nevertheless demonstrated standard deviations of 40% regarding wound volume when using these methods.[25]

Wound molds using silicone rubber

This high-precision and simple method, because of the ability of silicone rubber to harden and be stored, uses profilometric analysis followed by computerized volume assessment.[26,27] The first stage consists in making a negative imprint of the wound using silicone rubber of a type frequently used in dentistry for its safety. Two products are commonly used: Silflo® and xanthoprene. The mixture obtained by mixing the silicone rubber with its catalyst has a viscous consistency and is applied into the wound using a spatula. It will shape all the wound contours to a very fine extent, penetrating into the smallest crevices. After 2 to 3 minutes' polymerization, and thus hardening, it is easy to remove as a single piece corresponding to the negative shape of the wound. It is possible to store and archive this mold, as it will be unaffected by time. It is then scanned by a laser beam, which recognizes the location of each point using a positional detector. The vertical position of the laser spot (about 30 µm in diameter) can be deduced using double triangulation (Stil, Marseille, and Digital Surf, Besançon) or after refocalization of the beam (Optilas, Evry, France). Parallel linear scanning of the mold surface creates a certain number of profiles, the sum of which enables the calculation of wound volume. When assessing the volume of a leg ulcer, it is recommended to perform laser scanning along the axis of the leg, so as to cancel out the usual concave shape of the wound in this site. This method also permits in some cases a precise definition of wound contours by automatic detection, which is achieved by comparing altitude at each point with that of adjacent healthy skin.

The time course of a wound or its healing is a dynamic process. Monitoring thus requires repeated measurements over time. This method makes such measurements possible, particularly because of the safety of the silicone rubber used and the painless and nontraumatic nature of its application.

Weighing alginate molds

The use of an alginate mould enables the measurement of wound volume by weighing or water displacement.[28] However, this method has certain limitations, particularly because of possible alterations in the alginate mold depending on its water content, conditions of storage, and of wound volume.

Stereophotogrammetry

Stereophotogrammetry[29] allows the measurement of contours, surface area, and volume of a wound. It is based on determining the depth of the wound by is viewing from two different angles. The first models of this device were difficult to manipulate[30], but new, simpler models are now available.[29] The accuracy ensured by this method is about

Table III. Comparison of three techniques to measure the surface area of a wound.[21]

	Ruler (length,width)	Tracing of wound	Photograph
Ease of use	Easy	Easy	Moderately easy
Time required for recording	1 minute	A few minutes	A few minutes
Cost	Very low	Low	Moderate
Use	Common	Common	Common
Type of record	Numbers	Tracing and numbers	Image and numbers
Contact with wound	Yes	Yes	No
Learning	Little	Moderate	Moderate
Percentage error*	20% to 25%	8% to 10%	10% to 12%

** The lowest percentage corresponds to large wounds and the highest percentage to small wounds.*

3.5% regarding measurement of the surface area and 5% regarding volume. This method, developed by Bulstrode in 1986,[29] is not widely used. The time necessary for each evaluation is a further limitation to its everyday use.

Direct measurement of volume using physiological saline and a polyurethane film

Berg[31] recalled the value of this simple method which consists in placing a transparent adhesive film over a wound, and then injecting physiological saline below the film. The quantity of saline corresponds to the wound volume.

In practice, the wound is covered with a sterile polyurethane film and then filled up with physiological saline injected using a needle that pierces the film. Evaluation of this method has shown that accuracy of more than 20% is rarely possible,[25] principally because some amount of liquid is absorbed by the wound, and losses by leakage occur around the adhesive, through detachment of the film from the wound perimeter. Furthermore, it is sometimes impossible to place the patient in a satisfactory position to fill the wound with a liquid. The existence of tissue detachment also constitutes a limitation to this technique, as does the potential risk of infection, discomfort for the patient, and the risk of trauma to the wound which is inherent to any technique involving direct contact.

Analysis of structured light

This method enables the measurement of the surface area and volume of a wound without direct physical contact. Parallel lines of colored light are projected onto the wound surface area.[4] A video camera connected to a computer, records any distortion to the light beams. The dimensions of the wound are then calculated by triangulation. The accuracy of this method is similar to the previous one, but its implementation is simpler.[32]

Ultrasound

This technique takes advantage of the difference path length of an ultrasound wave reflecting at the bottom of the wound as compared with the adjacent normal skin. Healing may be assessed using this technique,[33] as was demonstrated in a clinical study of wounds caused by punch biopsies in volunteer subjects. In this study, the depth and internal diameter of the wound were assessed by ultrasound at intervals, while its outer surface area was measured by planimetry after first taking a tracing. This technique appears to be of value only if the wound is of a small size, because it is necessary for the wound edges to lie within the field of the ultrasound beam, as they serve as a reference to measure wound depth. Application of the probe must not flatten these edges, and appropriate precautions must be taken to avoid this. Several ultrasound scans should be taken (usually three), from which mean values of the parameters are determined. Ultrasound may also be useful to monitor wound dimensions following cryosurgery, or to better assess the quality of perilesional tissue.[34,35]

In vivo measurement using interferometry and fringe projection

A new technology based on interferometry principle has been developed in the Laboratory of Engineering of Besançon-France (Humbert P, unpublished data) in order to quantify the volume of ulcers in vivo. The 3D reconstruction of profiles of the wound is based on Fourier-transform method of fringe-pattern analysis *(Figure 1)*.

The system is composed of a CCD camera and a projection module. The resolution of the system depends on the fringe width and on the angle between the optical axis of the camera and the optical axis of the projector. The deformation of the fringes over the reference plan is proportional to the height separating the object and the reference plan. Thus, an appropriate algorithm allows the reconstruction of the 3D profile from the projected fringes on the object, in this case the wound.

This system has a resolution of 10 µm for a 5 x 5 cm^2 area. The search for the perimeter and the volume of the wound is based on the method previously described by Zahouani et al.[26]

A comparison between the above quoted measurement techniques is shown in *Table IV.*[25]

COLORIMETRY OR THE RED-YELLOW-BLACK CONCEPT

The technology for this concept was developed by Hellgren and Vincent[36,37] and consists in taking account of the color characteristics of an ulcer, which are a function of its clinical stage. Necrotic lesions are black, a fibrinous surface looks yellow, and granulation tissue is red. This clinical description has been accepted worldwide as an indication of the stage and prognosis of an ulceration.[38,39] Thus computerized colormetry analysis (CWA: computerized

wound analysis) was developed to ensure more objective measurements.[40] A photograph of the wound is taken, together with a gray scale placed alongside the lesion to control the quality of the photograph. Photographic data are transmitted to a computer. The image is digitalized and reconstituted in the form of colored pixels. The color of each pixel is expressed in red, blue, and green values of intensity (each from 0 to 255). This method has been the subject of validation studies. In practice, the clinician takes the photographs using a camera recommended by the CWA Institute in Sweden, the promoter of the technique. Images are then sent to this center where they are processed blind. The results are returned within 6 weeks. A detailed guide is provided regarding the best way for taking the photo, as the reliability of the results depends upon its quality.

CONCLUSION

The clinical follow-up of wound healing requires data on the geometry of the lesion. This quantification is necessary to ensure an objective assessment. The techniques most widely employed in clinical studies involve the tracing of wound contours using transparent film. Only a rigorous training in this technique made it possible to lend credence to the results obtained. More sophisticated techniques that increase the accuracy of wound volume measurements are currently available, but are at present only employed in a research setting.

	Ruler and cotton tip	Mold	Saline	Stereophoto-grammetry	Structured light
Ease of use	Easy	Moderately easy	Moderately easy	Difficult	Difficult
Time required for recording	1 minute	A few minutes	A few minutes	20-30 minutes	4-5 minutes
Cost	Very low	Low	Low	Very high	High
Use	Common	Common	Common	Research	Prototype
Type of record	Numbers	Mold and numbers	Numbers	3D reconstitution and numbers	Image and numbers
Contact with wound	Yes	Yes	Yes	No	No
Training	A few hours	Less than 1 h	1 hour	A few hours	A few hours
Percentage error*	10% to 40%	5% to 15%	8% to 25%	0% to 3%	3% to 5%

** The lowest percentage corresponds to large wounds and the highest percentage to small wounds.*

Table IV. Comparison of five methods to measure wound volume.[25]

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The role of Daflon 500 mg in the treatment of symptomatic patients with varicose veins

One of several theories put forward as a possible cause of varicose veins (VV) is primary valve dysfunction, which can be congenital or acquired. The role of inflammation in acquired valve dysfunction is predominant and could possibly explain varicose vein etiology.[1]

THE ROLE OF VARICOSE VEINS IN THE EVOLUTION OF CHRONIC VENOUS DISEASE

Varicose disease represents the C2 class in the CEAP classification.[2] Varicose disease is not the cause of severe morbidity per se (indeed some have seen VV as a simple cosmetic problem). Nevertheless, the complications varicose veins may cause are mainly inflammatory. This may lead to superficial thrombophlebitis and venous ulcers.[1]

Varicose veins: the first visible sign of chronic venous disease

Varicose veins are one of the commonest manifestations of chronic venous disease (CVD), occurring in 26% to 38% of women and to 10% to 20% of men.[3] The condition starts early in life, as 10% of the schoolchildren in the Bochum study, aged between 10 and 12 years, had slight varicose veins.[4]

The venous valves play a key role in the genesis of VV, and the detection of reflux usually precedes the clinical appearance of the varicose disease as shown in the children of Bochum. At 10 years, reflux was present in 12%, and there were no VV in these children. At age 30, incidence of reflux increased to 26%, and VV appeared in 12% of the sample,[5] while telangiectases appeared later (0% at 10 and 50% at 30).

Varicose veins: leading to further complications

Varicose veins are likely to increase with age. The prevalence of VV was 10% in 10-year-old Bochum schoolchildren (studies I to IV), and this further increased to 75% at the age of 30. It has now been demonstrated that VV lead to further complications, including leg ulceration. *(Figure 1)*

In the 11-year follow-up of the chemical workers in the Basle study, the prevalence of venous ulcers was related to the severity of varicose veins. Twenty percent of subjects with severe varicose veins developed ulceration compared with only 0.8% of those with mild varicose veins.[6]

Superficial thrombophlebitis is thought to be one of the possible complications of VV.[7] *(Figure 1)*

The cause of superficial thrombophlebitis in patients with varicose veins has been postulated as being inflammatory cell infiltration secondary to denudation of the endothelium.[1,8]

Varicose veins: often associated with symptoms

Despite the fact that the mechanisms causing symptoms have not been fully elucidated, it is widely reported that symptoms appear at the onset of venous insufficiency, and most of time, long before reflux and the appearance of varicose veins. The CEAP classification contains a C0S clinical class to include those patients with venous symptoms but without obvious signs of venous insufficiency. It is thought that pain related to CVD might mirror the endothelial activation with the cascade of inflammatory mediators released early in the disease process.

A recent cross-sectional study in patients with CVD (C0s to C6) showed that the percentage of patients presenting with any venous symptom significantly increased with CEAP C class.[9] In this study, the prevalence of symptoms was 84.6% in patients with varicose veins.

Varicose veins: the cause of quality of life impairment

Varicose veins affect the quality of life (QoL) not only by the real cosmetic problem they cause but also by the influence they may have on physical disability. In the San Diego study,[10] spider veins and varicose veins were found to have

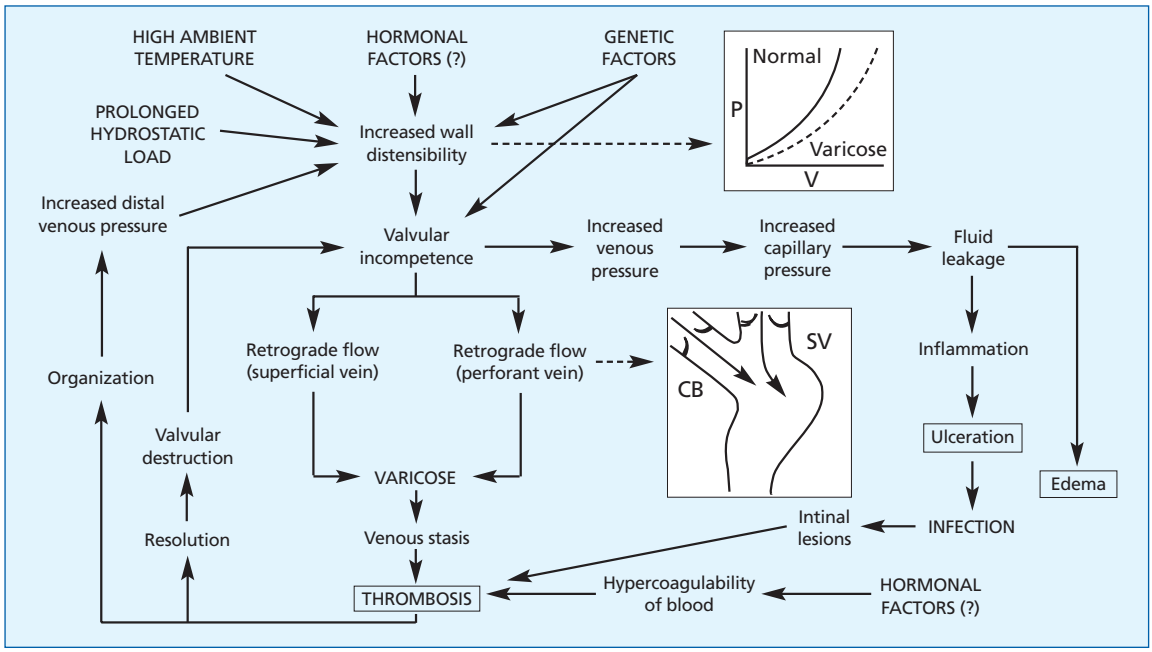

Figure 1. Complications of varicose veins (adapted from reference 7)

a significant effect on the physical component scores of the generic QoL scale SF 36.

In a study of the relationship between signs, symptoms, and quality of life in patients with chronic venous disease, it was demonstrated that symptoms usually attributed to CVD are the factors with the most negative influence on the patient's QoL.[11] In the VEINES study,[12] QoL scores decreased in C2 patients but were close to these in C1or C0s. This was attributable to the presence of symptoms that are most often associated with VV.

These previous studies showed the negative impact VV may have on the QoL of patients, most probably related to the presence of the associated symptoms. This has important consequences on the daily life of patients with CVD, even right from the onset of the disease, and long before the occurrence of reflux and VV.

OBJECTIVE OF TREATMENT OF CVD

Bearing in mind that varicose disease is most often painful and that it is likely to progressively lead to severe complications, there is a twin goal to be achieved by any treatment of VV:

– first of all, to rapidly and powerfully relieve patients from symptoms and pain in order to help them recover a better quality of life.

– secondly, to protect VV patients from further complications. For this reason, the biochemical processes involved in the CVD development are the main target of pharmacological treatment, since they are theoretically modifiable by systemic therapy.

How does Daflon 500 mg act in the prevention of CVD development?

Daflon 500 mg: an ability to inhibit leukocyte activation

It has been observed that firm leukocyte attachment to the endothelial wall and subsequent migration of leukocytes into the interstitium is a mechanism of tissue damage during inflammation, and that attenuation of this phenomenon during ischemia-reperfusion could explain the positive effects of Daflon 500 mg on clinical edema.[13, 14] In an ischemia-reperfusion model by Korthuis,[15] Daflon 500 mg significantly inhibited leukocyte adhesion and migration through the venous endothelium as well as the protein leakage observed in this model. During restoration of venous blood flow, the number of rolling, adherent, and migrating leukocytes as well as cells exhibiting apoptosis in the parenchyma significantly decreased in animals pretreated with Daflon 500 mg compared with control subjects.

The molecular mechanisms in leukocyte adhesion and activation in CVD patients involve the increased expression of several types of cell adhesion molecules at the leukocyte surface, particularly L-selectins (CD62L) and integrins (CD11b). The expression of these leukocyte adhesion molecules were substantially decreased on monocytes and neutrophils after a 60-day treatment with Daflon 500 mg in patients with CVD (C2 to C4).[16] *(Figure 2)* This implies that Daflon 500 mg would prevent the inflammatory process in CVD.

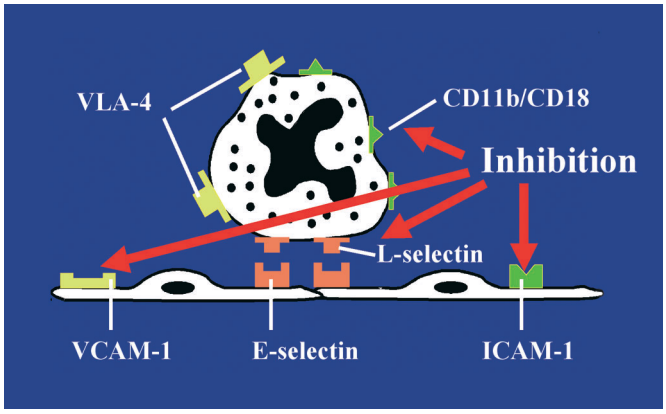

Figure 2. Inhibition of the leukocyte activation by Daflon 500 mg (adapted from reference 16)

Daflon 500 mg: an action at the core of the disease, ie, the leukocyte-endothelium interaction.

In patients with CVI as well as after prolonged standing, plasma concentrations of endothelial adhesion molecules, vascular cell adhesion molecule (VCAM) and interstitial cell adhesion molecule (ICAM) are increased. In the study by Shoab,[16] plasma level of VCAM-1 and ICAM-1 significantly decreased in C2 to C4 patients pretreated with Daflon 500 mg. This reflects the ability of Daflon 500 mg to prevent the interaction between the endothelium and the leukocytes which is at the core of the CVD progression.

Daflon 500 mg: a protective effect against valve damage

Acquired valve dysfunction can occur due to inflammation, as evidenced by monocyte infiltration.[17] It seems possible that activated leukocytes can migrate into the endothelium of proximal surfaces of the vein valves as well as proximal vein walls and promote destruction of supporting structures and remodeling of the valves with consequent valvular insufficiency. Immunohistochemical studies have demonstrated monocyte/macrophage infiltration into the valve leaflets and venous wall of patients with varicose veins.[17]

In a recent study by Schmid Schönbein et al, performed on a pharmacological model of hypertension,[18] Daflon 500 mg was shown to limit the leukocyte infiltration into the vein valve and to inhibit the expression of leukocyte adhesion molecules.

As a result, Daflon 500 mg attenuated the vein and valve destruction and significantly reduced the reflux rate in a dose-dependent manner.

By acting at the core of the disease, ie, the leukocyte-endothelium interaction, Daflon 500 mg is the only phlebotropic drug with a protective effect on the valve endothelium. Daflon 500 mg delays the reflux appearance and is thus likely to prevent the evolution of the CVD towards complications.

Daflon 500 mg: a therapeutic efficacy right from the first symptoms and in the longterm:

Effects of Daflon 500 mg on symptoms of CVD

In the Reflux assEssment and quality of lIfe improvEment, with micronized Flavonoids (RELIEF) study (n=4527, intention-to-treat population), patients receiving 2 tablets of Daflon 500 mg daily showed progressive improvement in the symptoms of CVI.[19] After 6 months, patients in the per-protocol population showed significant improvement from baseline in the study outcome measures (ankle circumference, pain, leg heaviness, cramps, sensation of swelling; $P<0.012$). In the 1-year trial of 2 tablets of Daflon 500 mg daily in 170 patients,[20] a significant reduction from baseline values in physician-assessed clinical symptoms (functional discomfort, cramps, and evening edema), ankle and calf circumference, and patient overall assessment of symptom severity 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 improvement in all parameters, albeit less rapid, was reported at each time point from month 2 to month 12.

Effects of Daflon 500 mg on leg edema

The reduction in leg edema with Daflon 500 mg, 2 tablets daily, was demonstrated in the Blume study in which the reduction was assessed by volumetric measurements after 6 weeks of treatment.[21] In this study, the reduction in the mean volume was 263 mL (8%) in all patients, and was 392 mL (12%) in patients with leg edema associated with varicose veins. In both trials, the reduction in leg volume was highly significant ($P<0.001$).

Edema, measured by leg circumference, significantly decreased compared with baseline in patients in the RELIEF study.[19]

Daflon 500 mg: improves QoL by reducing symptoms

During the course of a 6-month period of treatment with Daflon 500 mg, changes in the QoL scores were comparable across the different CEAP subgroups.[22] Only patients

with symptoms had greater improvement in QoL than patients without symptoms. These changes in QoL scores resulted mainly from the alleviation of symptoms: improvement between D180 vs D0 in pain, heaviness, swelling and cramps was significant (P <0.001 for all symptoms).[11] However, the associated signs (telangiectases, varices, edema, or skin changes) did not show such a direct impact on QoL.[19]

In this study, the dramatic improvement of QoL observed in patients treated with Daflon 500 mg can be interpreted as a result of symptom alleviation.

Daflon 500 mg: its therapeutic value in leg ulcer healing

The preliminary results of a meta-analysis of five comparable, prospective, randomized, controlled studies identified from medical literature databases and from the files of the manufacturer in which 723 patients were pooled[23] confirm that venous ulcer healing is accelerated by adding Daflon 500 mg, 2 tablets daily, to conventional treatments: the rate of complete ulcer healing at 6 months was in favor of the Daflon 500 mg group (61.3% vs 47.7%; OR =2.02; CI =1.05-3.89; P =0.035).

CONCLUSION

Pharmacological attenuation of leukocyte activation and leukocyte-endothelium interactions by Daflon 500 mg at the level of the venous valve, venous wall, and the microcirculation is an explanation of facilitation it brings to ulcer healing as well as the improvement in symptoms it allows. Daflon 500 mg also shows promise in preventing the continuing deterioration of venous function produced by valve insufficiency.[13]

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Lymphedema-angiodysplasia syndrome: a prodigal form of lymphatic malformation

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Keywords:
primary lymphedema, lymphatic malformation, congenital vascular malformation, extratruncular form, truncular form, complex decongestive physiotherapy, compression therapy, compliance, sclerotherapy

ABSTRACT

Primary lymphedema is a clinical outcome of lymphatic malformation (LM) following developmental arrest in the latter stage of embryogenesis, and known as the truncular (T) form. LM caused by developmental arrest in the earlier stage of lymphangiogenesis, often termed cystic/cavernous lymphangioma, is referred to as the extratruncular (ET) form. Primary lymphedema has been managed as a chronic lymphedema together with secondary lymphedema, although its etiopathophysiology is entirely different from that of secondary lymphedema. However, lately primary lymphedema has been recognized as being related to the ET form of LM, and new the classification of congenital vascular malformation (CVM) has finally included the ET and T forms of LM as types of CVM. The ET form of LM, known as cavernous and/or cystic lymphangioma, and the T form, known as primary lymphedema, are now considered as members of the LM family, which develop at different stages of lymphangiogenesis. A retrospective review of the clinical data of a total 254 patients with LM (186 T form and 68 ET form) has therefore been done, aiming to provide a proper basis for advanced management of the T and ET forms as aspects of LM, based on newly developed concepts.

Patients and methods: The diagnosis of LM was made using various combinations of different noninvasive diagnostic tests: MRI and/or CT, Tc-99m RBC whole-body blood pool scintigraphy, Tc-99m antimony sulfide colloid lymphoscintigraphy, and duplex ultrasonography. For the 186 T form LMs, diagnosed following proper clinical/laboratory staging, treatment was instituted using various combinations of MLD (manual lymphatic drainage)-based CDP (complex decongestive therapy) and SIPC (sequential intermittent pneumatic compression)-based compression therapy depending upon the clinical stage of the chronic lymphedema. Various surgical therapies, either reconstructive or ablative, were also implemented as adjunct therapies for primary lymphedema to improve the efficiency of CDP-based therapy in the earlier clinical stage, and compression therapy in the later stage. For the 68 ET LMs, the best treatment option was selected per indication, from the various combinations of sclerotherapy and/or surgical therapy; OK-432 sclerotherapy as the option of choice as a primary therapy and absolute ethanol sclerotherapy and/or a surgical excision as the second option, preferably after the first option had failed. The T form was evaluated using clinical and laboratory assessments of chronic lymphedema status every 6 months including treatment response, either medical (physical) only or surgical combined. The evaluation of the ET form was

made by duplex sonography and MRI where feasible, and by clinical assessment.

Results: Of 68 ET form patients, 51 pediatric patients, treated with OK-432 sclerotherapy for a total of 108 sessions, showed satisfactory lesion control in the majority of cases (84.3%): a complete to marked shrinkage in 88.9% of the limited cystic type. Seventeen ET forms of the total 68 underwent preoperative embolo/sclerotherapy and subsequent surgical excision, which gave clinically good to excellent results for 14 of the 17. One hundred and eighty-six T form patients, treated for chronic lymphedema, showed an excellent to good response in the majority in clinical stages I and II, and a good to fair response in stages III and IV. Long-term results of additional surgical therapy, either reconstructive or ablative, on 8 patients were totally dependent on patent compliance to maintain postoperative CDP/compression therapy-based maintenance care.

Conclusion: Conventional management of the T form of LM as for primary lymphedema is limited even with supplemental surgical therapy. The treatment of the ET form of LM, especially of the infiltrating cavernous type, is also limited by conventional sclerotherapy. Therefore, the overall management of LMs should be further improved by adopting an innovative genetic approach to the correction of (lymph) angiogenesis and/or vasculogenesis defects.

INTRODUCTION

Primary lymphedema is a form of lymphatic malformation (LM), and shares the background of other congenital vascular malformations (CVMs), as a birth defect that affects only the lymphatic circulation system of the three (peripheral) vascular systems, ie, arterial, venous, and lymphatic systems.[1,2]

Primary lymphedema[3] is a clinical outcome of LM following developmental arrest in the latter stage of embryogenesis, the so-called truncular (T) LM form.[1,2,4] LM caused by developmental arrest in the earlier stage of lymphangiogenesis, often termed cystic/cavernous lymphangioma, is referred to as the extratruncular (ET) LM form, to delineate its mesenchymal embryologic characteristics.[1,2,5]

Primary lymphedema has been unintentionally ignored by the majority of CVM specialists, and has been managed as a chronic lymphedema by lymphologists[3,6,7] for decades together with secondary lymphedema, although its etiopathophysiology is entirely different from that of secondary lymphedema. However, lately, primary lymphedema has been recognized as being related to the ET form of LM, although the relation between it and secondary lymphedema should be retained, especially from the management point of view.[5]

The concept of CVMs based on new classification, new diagnostic technologies, and the novel multidisciplinary team approach have provided solid clues that explain many of the perplexities associated with CVMs, also known as angiodysplasia.[8] The modified Hamburg classification, based on the original Hamburg consensus of 1988, finally included the ET and T forms of LM as types of CVM. The ET form of LM, known as cavernous and/or cystic lymphangioma, and the T form, known as primary lymphedema, are now be considered as members of the LM family, that develop at different stages of lymphangiogenesis.[1,2] This new concept of LM as a vascular malformation enables patients to benefit from the conceptual advances made in CVM treatment, and facilitates the restructuring of old perceptions to accommodate the style of management required to address its causative (lymph)angiogenic and vasculogenic abnormalities at the biomolecular level.[9,10]

AIM

A retrospective review of the clinical data of a total 254 patients with predominant LMs (186 T form and 68 ET form), registered at the CVM Clinic and the Lymphedema Clinic of Samsung Medical Center & Sungkyunkwan University School of Medicine, Seoul, Korea, during the period September 1994 to December 2000, was conducted. Our aim was to provide proper basis for approaching the management of the T and ET forms as aspects of LM, and subsequently for their advanced management based on newly developed concepts concerning the genetic defects responsible for developmental arrest at different stages of embryonic life.

PATIENTS AND METHODS

Diagnosis

One hundred and eighty-six T form LMs, registered at the Lymphedema Clinic as primary lymphedema, underwent clinical and laboratory evaluation for the proper clinical and laboratory staging of clinical lymphedema in order to later assign pertinent therapy. The T form was also re-evaluated as a vascular malformation through separated registration at the CVM Clinic, together with the ET form of LM as well as various other CVMs. This T form of LM was further investigated for differential diagnosis,

especially with the combined form of CVM, which exists mainly as the hemolymphatic malformation (HLM). HLM represents a mixed condition of venous malformation (VM) and LM in ET form as the major component.[11,12]

A total of 68 ET LM cases, registered at the CVM Clinic, also underwent a laboratory evaluation specifically designed for LM, in addition to the basic tests required for all the CVMs to differentiate CVMs from each other and obtain crucial information of the LM status either as a "pure" form or a "mixed" form with other CVM (eg, HLM).

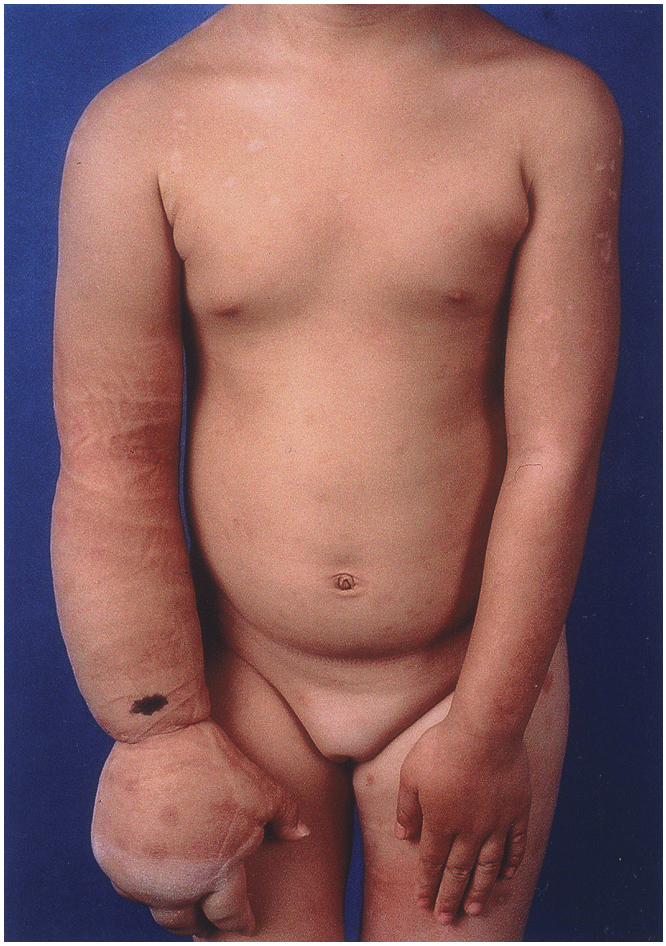
The diagnosis of LM, either of the T or ET form, was made using various combinations of different noninvasive diagnostic tests[8,11,13]: MRI and/or CT, Tc-99m RBC whole-body blood pool scintigraphy, Tc-99m antimony sulfide colloid lymphoscintigraphy,[14,15] and duplex ultrasonography, and occasionally with added optional MR and/or ultrasound lymphangiography *(Figures 1 and 2)*. However, diagnosis seldom required an invasive study for the differential diagnosis of CVM type by direct puncture lymphangiography or conventional angiography. The simultaneous assessment of venous function status during the LM diagnostic procedure was included as a mandatory requirement.

Treatment

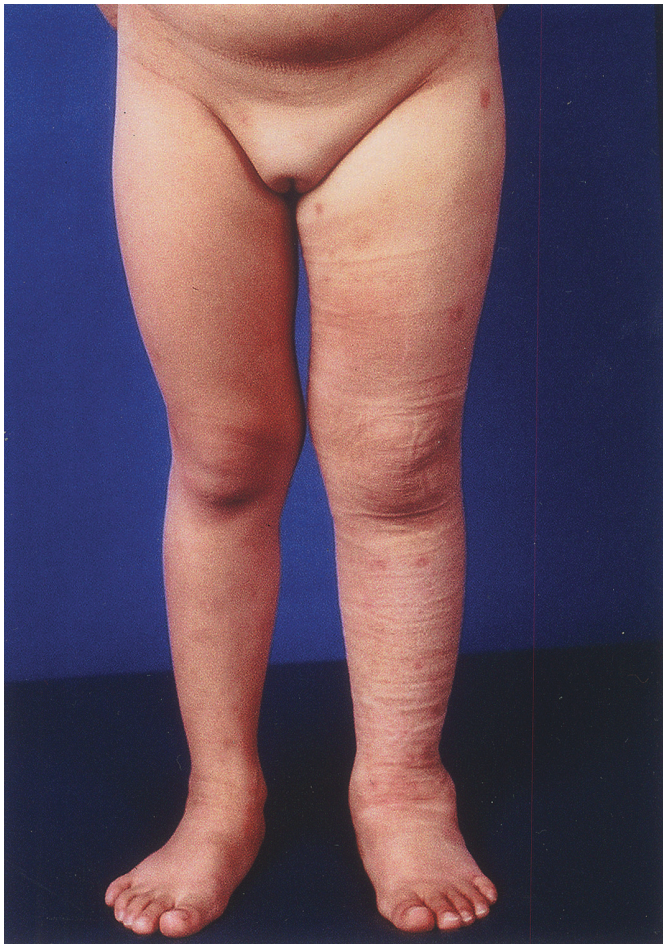
For the 186 T form LMs, diagnosed following proper clinical/laboratory staging, treatment was instituted using various combinations of MLD (manual lymphatic drainage)-based CDP (complex decongestive therapy) and SIPC (sequential intermittent pneumatic compression)-based compression therapy depending upon the clinical stage of the chronic lymphedema.[7,16]

Various surgical therapies,[5,17,18] either reconstructive or ablative, originally designed for secondary lymphedema, were also implemented as adjunctive therapies for primary lymphedema to improve the efficiency of CDP-based

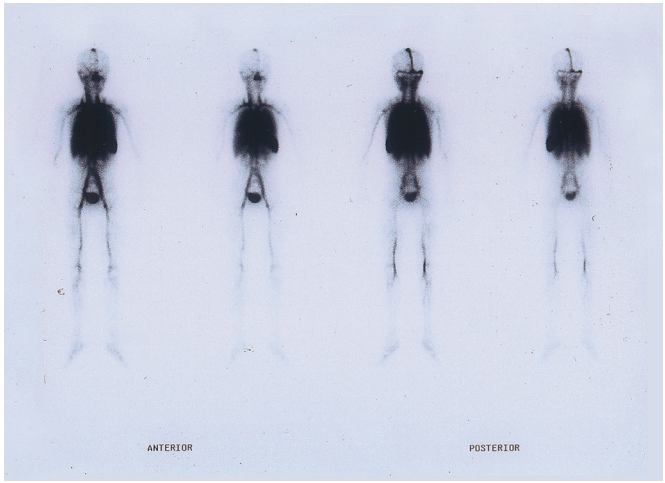
Figure 1. A to E. Truncular (T) form of lymphatic malformation (LM) with multiple involvement throughout the body.



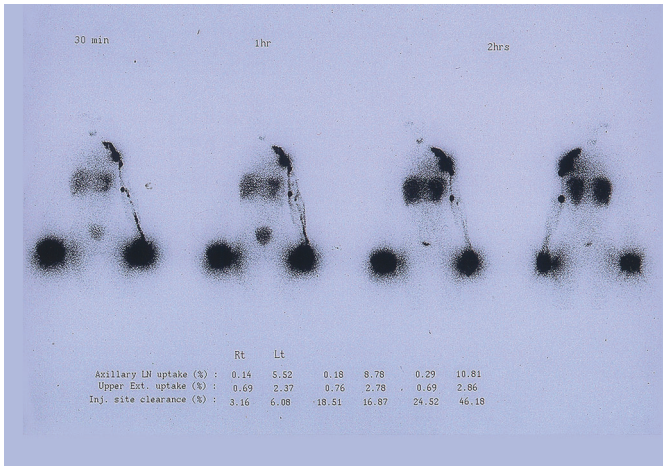
A. Clinical appearance of primary lymphedema along the right upper extremity (forearm and hand) due to a T form LM.



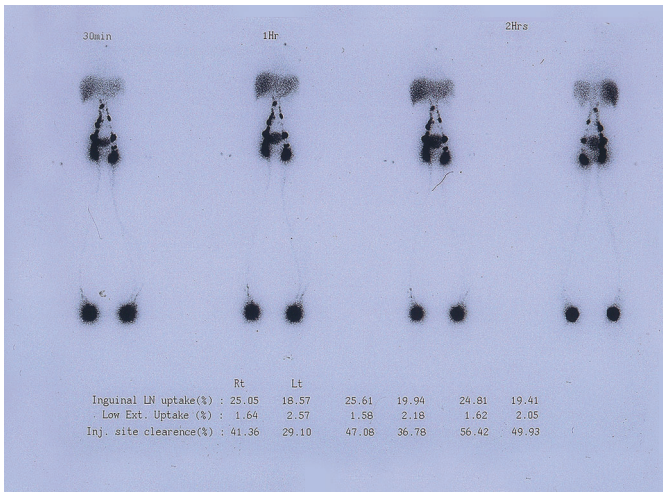
B. Clinical appearance of primary lymphedema along the left lower extremity due to a T form LM, with simultaneous involvement of the upper extremity.



C. WBBPS finding of no abnormal blood pool over the LM-affected limbs, ruling out combined VM*.*

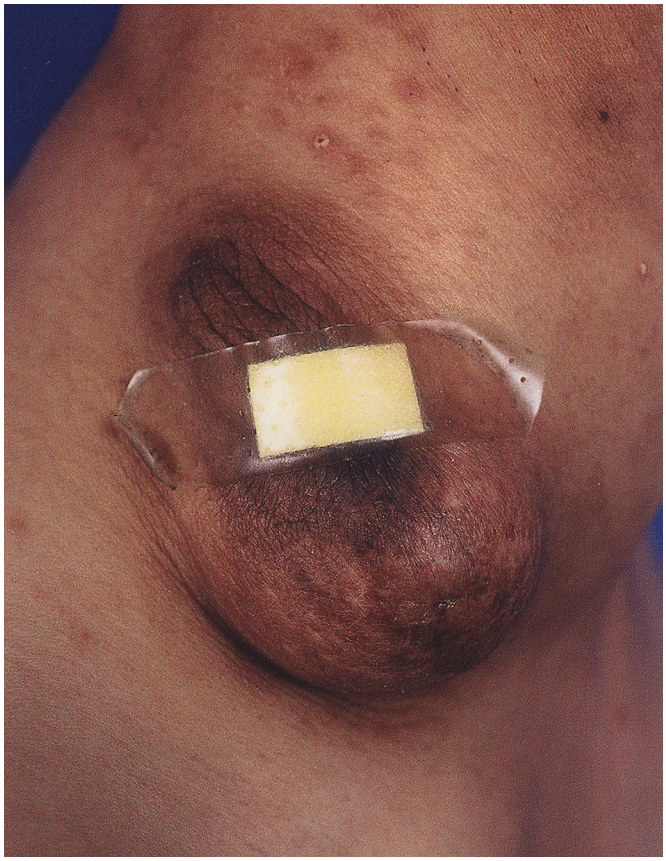


D. Lymphoscintigraphic findings of a lack of normal lymphatic system development, due to T form VM, affecting the right upper extremity.

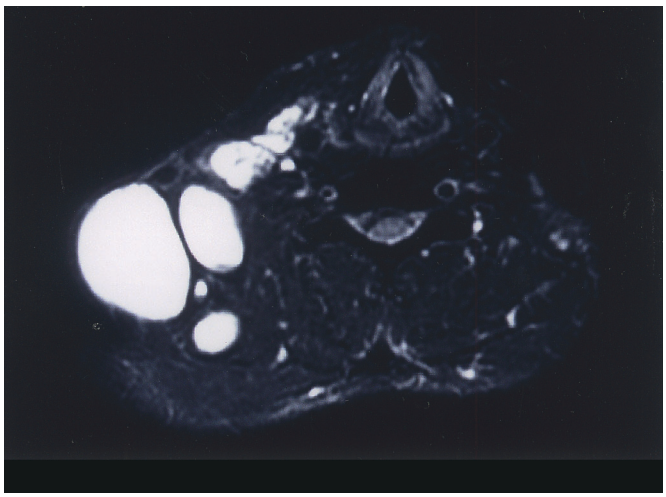


E. Lymphoscintigraphic finding of reduced lymphatic function along the left lower extremity due to incomplete development of the normal lymph node-collecting lymph vessel system.

Figure 2. A, B. Extratruncular form (ET) form of a multiple cystic lymphatic malformation (LM).



A. Clinical appearance of a superficially located ET LM with recurrent leakage and infection.



B. MRI finding of an ET form of multiple cystic LM affecting the right neck, shoulder, and anterior chest wall.

therapy at the earlier clinical stage, and compression therapy in the later stage, when physical therapy failed to provide an adequate response, despite maximum available treatment, or the disease progressed. However, the decision to select a candidate for further surgery was made upon consensus by the multidisciplinary team, based on strict result assessment; in particular, patient compliance was the most critical factor. Good compliance was a mandatory prerequisite for all surgical candidates, since postoperative maintenance relies heavily on a self-initiated home-based maintenance program under periodic supervision.

For the 68 ET LMs, the best treatment option was selected per indication, once a proper diagnosis had been made, from the various combinations of sclerotherapy and/or surgical therapy when indicated.[5,11,18] However, OK-432 sclerotherapy was implemented as the option of choice as a primary therapy whenever and wherever possible. Absolute ethanol sclerotherapy and/or a surgical excision were selected as the second option, preferably after the first option had failed. Recurrent and/or deeply seated lesions, preferably of the cystic type, were generally treated with ethanol, while de novo and/or superficially seated lesions were treated by OK-432 sclerotherapy. Multisession sclerotherapy either with OK-432 or high concentration ethanol (>75%) were performed either as independent therapies, mainly for the cystic type, or as adjunctive therapy, mainly for the cavernous type of ET form perioperatively.

Treatment of the 68 ET LMs was usually indicated by a cosmetically severe deformity (eg, face) and/or functional disability (eg, hand, foot, wrist, ankle, etc).[5,11] Urgent treatment was also indicated for 9 lesions located near vital structures or organs (eg, airway), threatening critical functions like breathing, vision, hearing, and eating, or to lesions accompanied by complications (eg, bleeding by the mixed venous component, lymph leaking, and recurrent erysipelas/cellulitis, etc).

Assessment

The T form was evaluated using clinical and laboratory assessments of chronic lymphedema status every 6 months by a multidisciplinary care team to ensure proper disease progress staging. Treatment response, either medical (physical) only or surgical combined, was also assessed every 6 months during follow-up. Additional tests were added to the schedule for episodes of local and/or systemic sepsis with cellulitis. The preoperative assessment of surgical candidates with the T form included duplex scan study for venous assessment, lymphoscintigraphic study for lymphatic function assessment, and an infrared volumetric study of the extremities to provide a baseline assessment for the clinical results of treatment. The postoperative assessment included volumetry of the extremities on each visit and lymphoscintigraphy after 6 months postoperatively, and subsequently at each postoperative anniversary. A venous duplex scan was also added at the end of follow-up when indicated. All follow-up assessments of the various surgical therapies were made at a postoperative 1, 2, 3, 6, 12, 18, and 24 months, with an additional evaluation at each episode of local and/or systemic sepsis. This follow-up assessment was extended when possible from the first end point at 24 months to 48 months after surgery as the second and final end point of assessment.

The evaluation of the ET form was made separately every 6 months by the CVM clinic team, by duplex sonography and MRI where feasible, and by clinical assessment. Supplemental reviews were given by the consultants annually.[8,12,13]

RESULTS

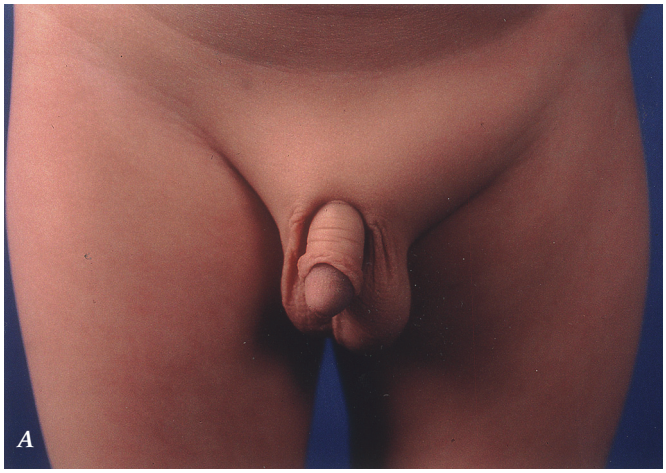
ET form

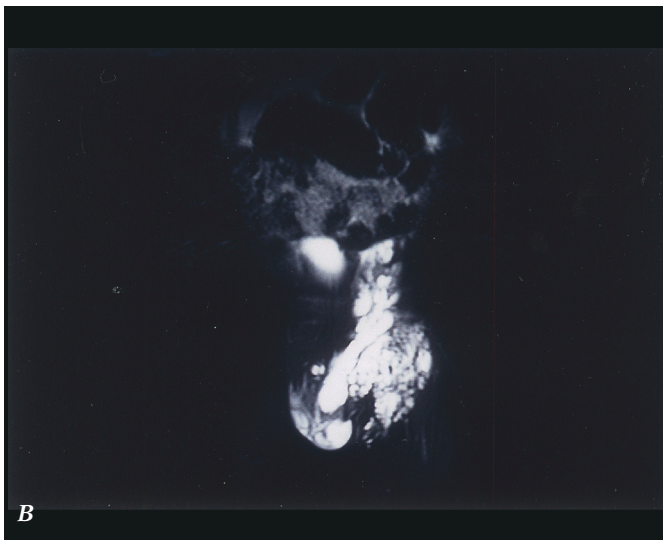
Of 68 patients confirmed for the pure ET form of LM with no other vascular malformation combined, 51 pediatric patients were selected for treatment with OK-432 sclerotherapy and underwent a total of 108 sessions. Its long-term results with an average follow-up period of over 24 months showed satisfactory lesion control in the majority (84.3%): excellent response showing a complete to marked shrinkage in 88.9% of the limited cystic type (40/45), and in 50% (3/6) of the diffuse infiltrating cavernous type *(Figure 3)*.

Seventeen ET form (9 infiltrating type; 8 limited type) of total 68 underwent preoperative OK-432, ethanol and/or *N*-butylcyanoacrylate embolo/sclerotherapy and subsequent surgical excision, which gave clinically good to excellent results for 14 of the 17 *(Figure 4)*. No evidence of recurrence for all 17 LM lesions has emerged over a minimum follow-up of 24 months.

T form

One hundred and eighty-six T form (mostly clinical stage II of primary lymphedema) were treated for chronic lymphedema using various combinations of CDP and/or compression therapy depending upon the clinical/laboratory stage. They cases have shown an excellent to good response in the majority in clinical stages I and II (115/130) and a lower level of improvement with a good to fair





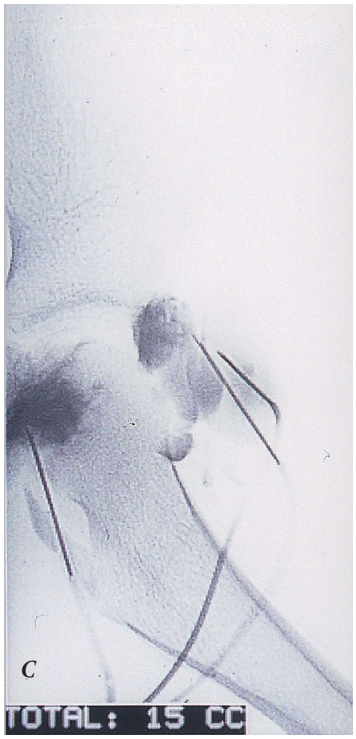


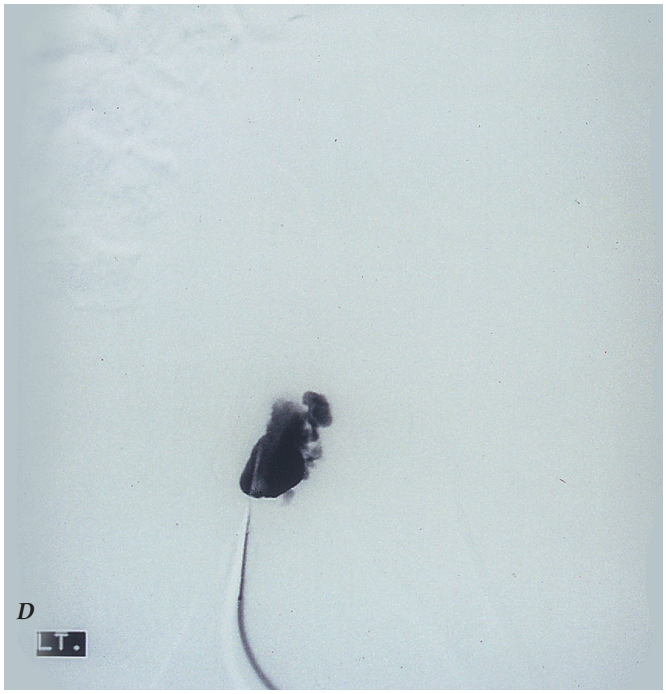
Figure 3. Ethanol and OK-432 sclerotherapy of extratruncular (ET) lesions.

A. Clinical appearance of an ET lymphatic malformation (LM) affecting the left groin with recurrent infection.

B. MRI finding (sagittal view) of the infiltrating ET form of a mixed cystic and cavernous type LM.

C. Angiographic finding by ethanol sclerotherapy of a deeply seated cystic lesion.

D and E. Angiographic findings of OK-432 sclerotherapy of a superficially locating cystic lesion (D) and its subsequent satisfactory control (E).



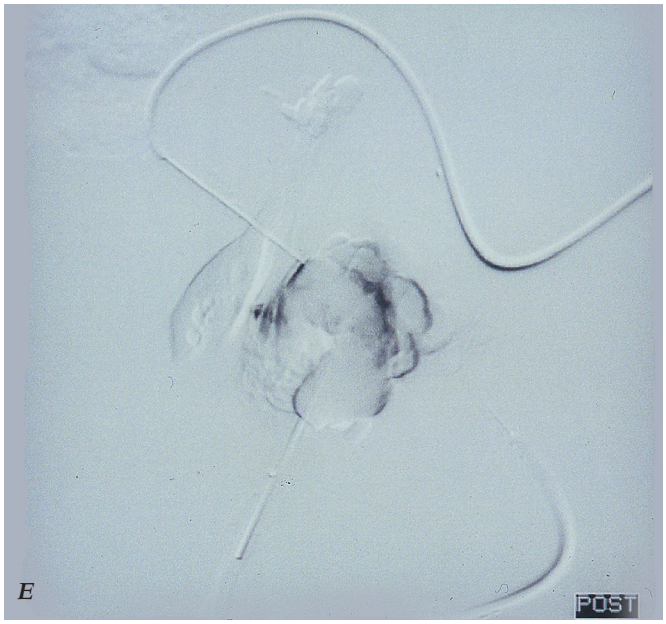


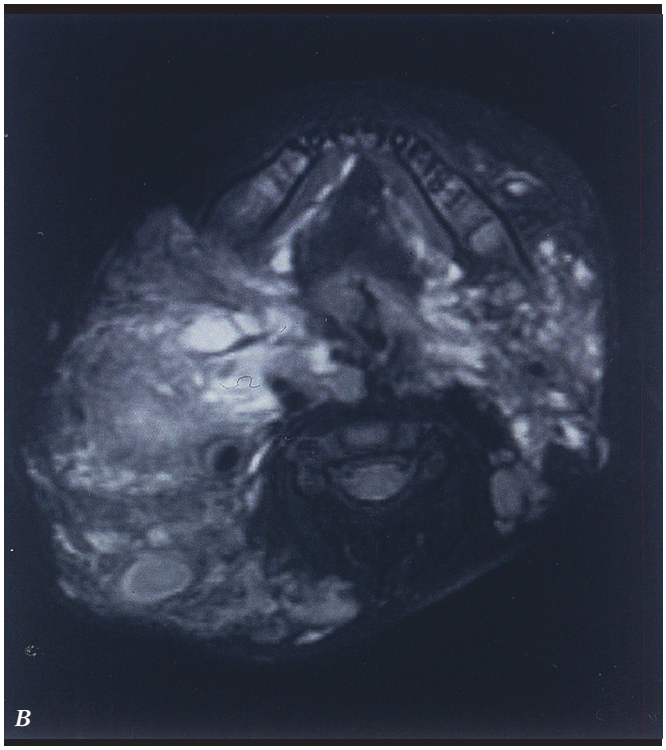
Figure 4. Surgical therapy combined with preoperative sclerotherapy using OK-432 for a recurrent extratruncular (ET) lymphatic malformation (LM) lesion following a poor surgical strategy.

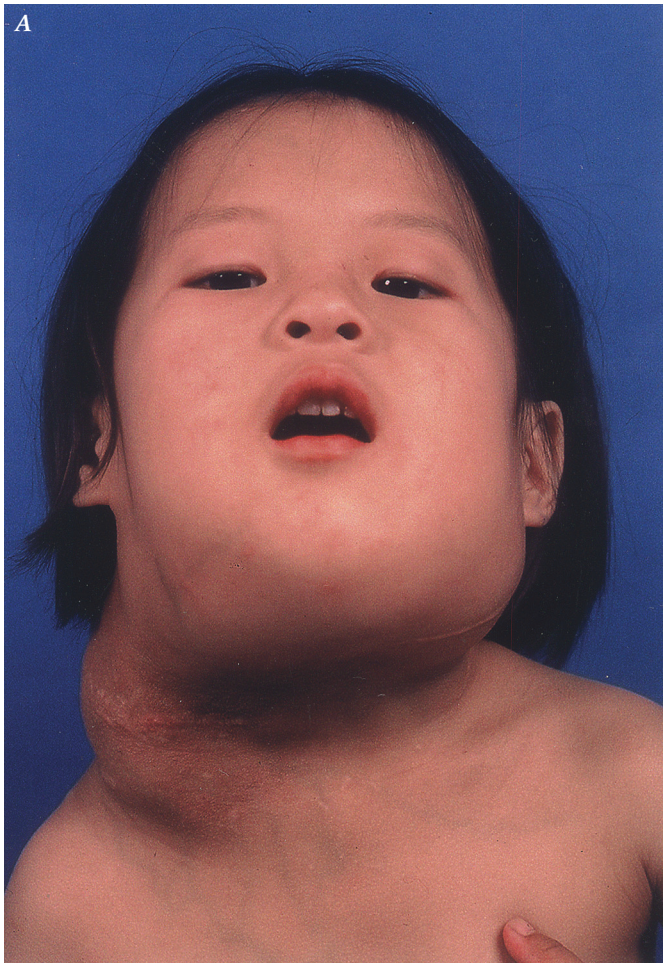
A. Clinical appearance of a recurrent lesion over the right neck as a diffuse swelling along the incision scar.

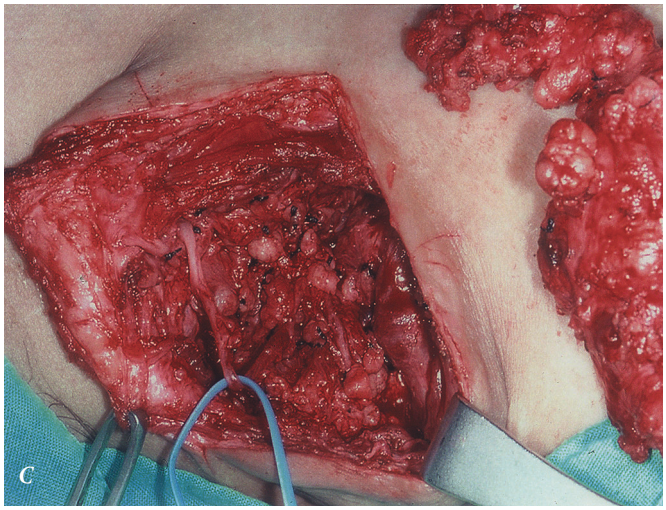
B. MRI finding of the extensive nature of an ET LM, involving the entire soft tissue of the right neck and extending to the retropharyngeal and left submandibular regions.

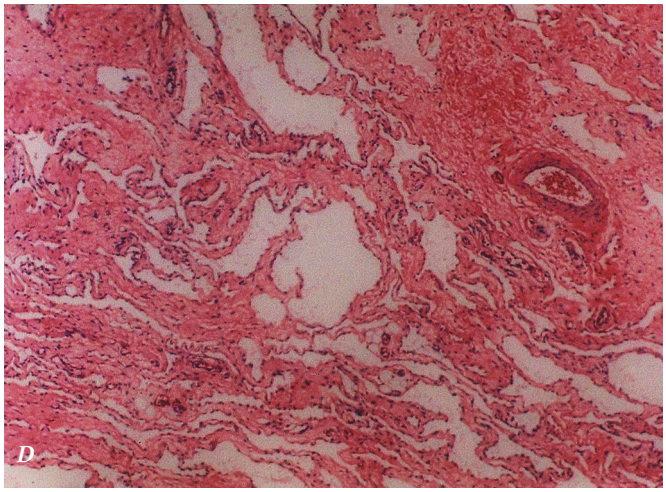
C. Operative finding of the lesion together with the surgical specimen, which was excised safely following preoperative multisession OK-432 sclerotherapy.

D. Histopathological finding of the ET form of an LM.









response in stages III and IV (21/56), following initial in-hospital care. Long-term maintenance of the initial treatment results through a self-initiated home-maintenance care program up to an average of 48 months of follow-up period has been excellent for 46, good to fair for 85, and poor for 38, with slow progress from the initial clinical stage when CDP was started; rapid progression with recurrent sepsis was observed in 17 of the 186 patients with a loss to follow-up for 17 patients.

Long-term results of additional surgical therapy, either reconstructive or ablative (4 venolymphatic anastomotic reconstruction, and 8 excisional surgery on 4 patients) on 8 patients to the end point of the follow-up (48 months) were found to be totally dependent on patent compliance to maintain postoperative CDP/compression therapy-based maintenance care: only good to fair results for 4 patients, and good compliance in 8 patients.

DISCUSSION

Diagnosis

The ET form of LM is due to an embryonicl remnant,[2,4] which is believed to be involuted when organogenesis moves into the T stage of embryonal life, but which remains at birth. This ET form of LM is therefore the final outcome of developmental arrest during earlier embryonic life at the plexular and/or reticular stages, and retains its evolutive potential (omnipotential evolutibility), a characteristic of mesenchymal cells of mesodermal origin (eg, angioblasts). Moreover, whenever triggered by conditions like trauma, pregnancy, surgery, or hormonal therapy, they regrow uncontrollably. Therefore, like the ET form of all other CVMs, the ET form of LM also presents this clinically serious issue of the risk of continuous growth or recurrence after treatment.

The T form of LM, often known as primary lymphedema, however, does not have the evolutive potential of the ET form, because it is the result of developmental arrest at a later stage of embryonic life, during the T stage following the reticular stage. It is the consequence of a failure to develop a normal lymphnodolymphatic vessel system at the T stage, and therefore, it often manifests as aplasia, hypoplasia, hyperplasia, obstruction, and/or dilatation of the lymphatic vessels, with/without combined lymphnodo-dysplasia.

Lymphatic malformations may exist alone as independent vascular defects or may exist with various other vascular defects, which produce addition hemodynamic effects due to their interactions, ie, in addition to their individual functions.[1] For example, the ET and T forms of LM are often colocalized and affect each other markedly in terms of lymphatic function, especially in combined forms of vascular malformations, like HLM, which is often known as Klippel-Trenaunay syndrome. Both ET and T form LMs and have a close hemodynamic relationship with the venous system, especially combined with VM when they can profoundly affect each other functionally. Increasing evidence indicates a negative impact of VM on LM, especially following the aggressive treatment of the VM component of HLM (eg, marginal vein resection), but of a positive impact on LM when it is combined with micro-AV-shunting AVM lesions that are properly managed.

Therefore, the ET form of LM, often called cystic or cavernous lymphangioma, has to be carefully evaluated for possible combinations with the T form of LM and with other types of CVM, ie, venous, AV shunting, capillary, and hemolymphatic malformations, for optimal clinical management, since there is a reasonable chance of it being accompanied by other kinds of VMs.

Treatment

The ET form of LM is not a life- or limb-threatening condition in general. Therefore, treatment modalities with a high risk of complications and/or morbidity (eg, absolute ethanol sclerotherapy) should *not* be considered for initial treatment, even if long-term results (eg, recurrence) might be improved.[26] Safer, less risky methods (eg, OK-432) are preferred for initial treatment, even given the higher risk of recurrence versus the stronger agent.

However, sclerotherapy, either with ethanol or OK-432, has not been uniformly successful in the treatment of the cavernous ET form in contrast to the cystic type, and attempts to improve therapeutic results in this group by using combined surgical/sclerotherapy have produced promising results, although further study is warranted to prove the accuracy of this clinical impression.[11] The ET form of LM also carries the inherent problem of recurrence with significant morbidity regardless of the treatment modality, especially in cases of infiltrating cavernous ET form.

Our experiences with the T form of LM with CDP and/or compression therapy as a basic form of lymphedema clinical management have not been uniformly successful, especially in advanced clinical stage cases, mainly due to reduced patient compliance to a lifetime commitment to this incurable disease, and due to the ignorance of medical personnel who fail to encourage patients to maintain compliance. Additional surgical therapy to supplement this physiotherapy-based treatment of the T form has also not

been uniformly successful, due to a failure to maintain proper postoperative physiotherapy, although it should be added that our experiences with primary lymphedema are limited.

Therefore, the need for a modality capable of dealing with both the T and ET forms of LM at the genetic level is urgently required. Rapid advances in genetic engineering will hopefully open up a new chapter in the treatment of these conditions through proper gene manipulation in the near future.

CONCLUSION

Conventional management of the T form of LM by CDP/compression therapy, as for primary lymphedema, is limited, even with supplemental surgical therapy. The treatment of the ET form of LM, especially of the localized infiltrating cavernous type, is also limited by conventional sclerotherapy with or without combined preoperative sclerotherapy.

Therefore, the overall management of LMs should be further improved by adopted an innovative genetic approach to the correction of (lymph) angiogenesis and/or vasculogenesis defects. The proper identification and characterization of those genes responsible for vascular malformations (CVM) is warranted as a first step toward a gene therapy for the T and ET forms of LM.

Acknowledgments

The author expresses the gratitude to each member of the multidisciplinary team of the Congenital Vascular Malformation Clinic and the Lymphedema Clinic, Vascular Center of Samsung Medical Center, and to EunKyung Cho, administrative manager for her devotion to the manuscript preparation, EunSook Kim, nurse coordinator, JiYoung Moon, research coordinator, and to MiAe Han, clinical nurse, for their assistance.

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Congress and conference calendar

XXVIth CONGRESO NAZIONALE DELLA SOCIETA ITALIANA DI ANGIOLOGIA E PATOLOGIA VASCOLARE (SIAPAV)

This congress will be held in Messina (Italy) from November 18 to 21, 2004.

• *For further information, please contact:*

President: Prof N. Longo, Prof C. Allegra

GC Congressi
Via Borsieri, 12
00195 Rome, Italy

Tel: +39 (06) 37.00.541
Fax: +39 (06) 373.52.337

Email: md2535@mclink.it

EUROPEAN SOCIETY OF SURGERY – VIIIth ANNUAL MEETING

This congress will be held in St Julian's (Malta) in November 2004.

• *For further information, please contact:*

President: Prof L. Cutajar

Chairman, Organizing Committee, ESS Meeting
Department of Surgery, The Medical School
G'Mangia, Malta

XIIth INTERNATIONAL CONGRESS OF ANGIOLOGY AND VASCULAR SURGERY

This congress will be held in Lisbon (Portugal) from December 10 to 11, 2004.

• *For further information, please contact:*

President: Prof Fernandes e Fernandes

Instituto Cardiovascular de Lisboa
Complexo Hospitalar das Torres de Lisboa
R. Tomás da Fonseca – Torre F – Piso 2
1600-209 Lisbon, Portugal

Tel: +21 722 13 90
Fax: +21 722 13 92

ALL-INDIA CONGRESS OF OBSTETRICS AND GYNAECOLOGY (AICOG) 2005

This congress will be held in Aurangabad (India) from January 6 to 9, 2005.

• *For further information, please contact:*

President: Dr Kanan Yelikar

Ashwini hospital
12, Samarth Nagar
Aurangabad 431 001
Maharashtra, India

The Federation of Obstetric and Gynaecological Societies of India
Cama and Albless Hospital, New Building,
6th floor
Mahapalika Marg
Mumbai 400 001, India

Tel: +91 22 226 72044
Fax: +91 22 226 706405

Email: aicog2005@indiatimes.com

LVIIèmes JOURNEES INTERNATIONALES FRANCOPHONES D'ANGEIOLOGIE

This congress will be held in Paris (France) from January 14 to 15, 2005.

• *For further information, please contact:*

President: Prof Jean-Pierre Laissy,
Dr Michel Perrin

General secretary: Dr Michèle Cazaubon

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

Email: micazang@noos.fr
Website: sfa-online.com

CONTROVERSIES AND UPDATE IN VASCULAR AND CARDIAC SURGERY

This congress will be held in Paris (France) from January 21 to 22, 2005.

• *For further information, please contact:*

President: Dr Jean-Pierre Becquemin

Atelier Phenix
C/o Nathalie Fontant
41, rue du Dr Morucci
13006 Marseille, France

Tel: +33 4 91 37 50 83
Fax: +33 4 91 57 15 28

Email: nfontant@aphenix.com
Website: aphenix.com
cacvs.org

SOCIETE FRANCAISE D'ANGEIOLOGIE (SFA)

This congress will be held in France (Paris) from March 18 to 19, 2005.

• *For further information, please contact:*

Presidents: M. Vayssairat, J-J. Guex

Fax: +33 1 5504 8217/+33 1 4250 7518

AMERICAN COLLEGE OF PHLEBOLOGY 21st SPECIAL REGIONAL SYMPOSIUM

This congress will be held in New Orleans (USA) on April 2, 2005.

• *For further information, please contact:*

American College of Phlebology
100 Webster Street, Suite 100
Oakland, Ca 94607-3724, USA

Tel: + 1 510 834 6500

SOCIETY FOR VASCULAR SURGERY

This congress will be held in Chicago (USA) from June 16 to 19, 2005.

• *For further information, please contact:*

SVS
633 N. Saint Clair Street
Chicago, Il 60611, USA

Fax: +1 312 202 5007

Website: www.vascularweb.org

VIth ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM

This congress will be held in Heraklion, Crete (Greece) from June 24 to 26, 2005.

• *For further information, please contact:*

President: Prof Asterios Katsamouris

Vascular Surgery Department
University of Crete Medical School
Heraklion, Crete, Greece

Tel: +30 2810 392 379
Fax: +30 2810 392 379

Email: asterios@med.uoc.gr
Website: europeanvenousforum.org

XVth WORLD CONGRESS OF THE UNION INTERNATIONALE DE PHLEBOLOGIE

This congress will be held in Rio de Janeiro (Brazil) from October 2 to 7, 2005.

• *For further information, please contact:*

Chairman: Angelo Scuderi

RIO UIP 2005 Secretary
Rua Santa Clara, 494
Sorocaba
18030-421- SP, Brazil

Tel: +55 15 231 6619
Fax: +55 15 221 4074 / 232 9241

Email: inspecmoc@dglnet.com.br
angelo.scuderilebologiabrasil.com.br
Website: www.flebologiabrasil.com.br

XIVth CONGRESS OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY (EADV)

Skin and sexual health: the challenge for Europe

This congress will be held in London (UK) from October 12 to 16, 2005.

• *For further information, please contact:*

Congress President: Prof Martin Black

EADV Congress Secretariat
4 Fitzroy Square
London W1T 5HQ, UK

Fax: + 44 20 7383 0266

e-mail: eadv@bad.org.uk

XIXTH ANNUAL CONGRESS OF THE AMERICAN COLLEGE OF PHLEBOLOGY

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

• *For further information, please contact:*

President: Neil S. Sadick

ACP Headquarters
100 Webster Street, Suite 101
Oakland, California 94607-3724, USA

Tel: +1 510 834 6500
Fax: +1 510 832 7300

Email: acp@amsinc.org

VIIth ANNUAL MEETING OF THE EUROPEAN VENOUS FORUM

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

• *For further information, please contact:*

President: Prof Alun H. Davies

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

Tel: +33 44 20 8575 7044
Fax: +33 44 20 8575 7044

Email: evenousforum@aol.com

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Submission deadline:
30 April 2005

The competition is open to young candidates who have a specific interest in the field of phlebolymphology and are a member of a national society in this field. The projects must consist of **original clinical or basic science research** in an area of phlebolymphology, such as anatomy, physiology, pathophysiology, diagnostic methods, or clinical research. The fellowship will be made available from 1 November 2005 and end in October 2007.

The review of the submitted projects and the selection of the best candidate will be made by a committee of **recognized worldwide specialists** in the field of phlebolymphology.

Send us your project at the following address:

Jean-Jérôme GUEX, MD
Fonds de Recherche de l'UIP
32, boulevard Dubouchage
06000 Nice, France

Next winner awarded at the UIP World Congress in Rio de Janeiro (October 2005)

The latest research fellowship winner, Dr Maria Gemma PASCUAL GONZALEZ (Vascular Biology, Spain) was awarded the grant at the 2003 UIP Chapter in San Diego for her project "Elastin dysregulation in varicose veins."

Invitation to the 2007 UIP Chapter to present the project's results

Candidates must submit a synopsis of 8 to 10 pages, double-spaced, typewritten in English, in the form of 5 original printed copies. The synopsis should clearly present the objectives, methodology, planning, and references of the projected work. Candidates must also submit a curriculum vitae and a letter from a referee supporting the project and confirming its backup, together with details of how the fellowship money will be spent. After the first year of work, the award-winner must submit to the committee a synopsis of progress so far. The project's results will have to appear in a form suitable for publication in an international journal.

For further information or subscription online:
www.servier.com / www.uip-phlebologyonline.org

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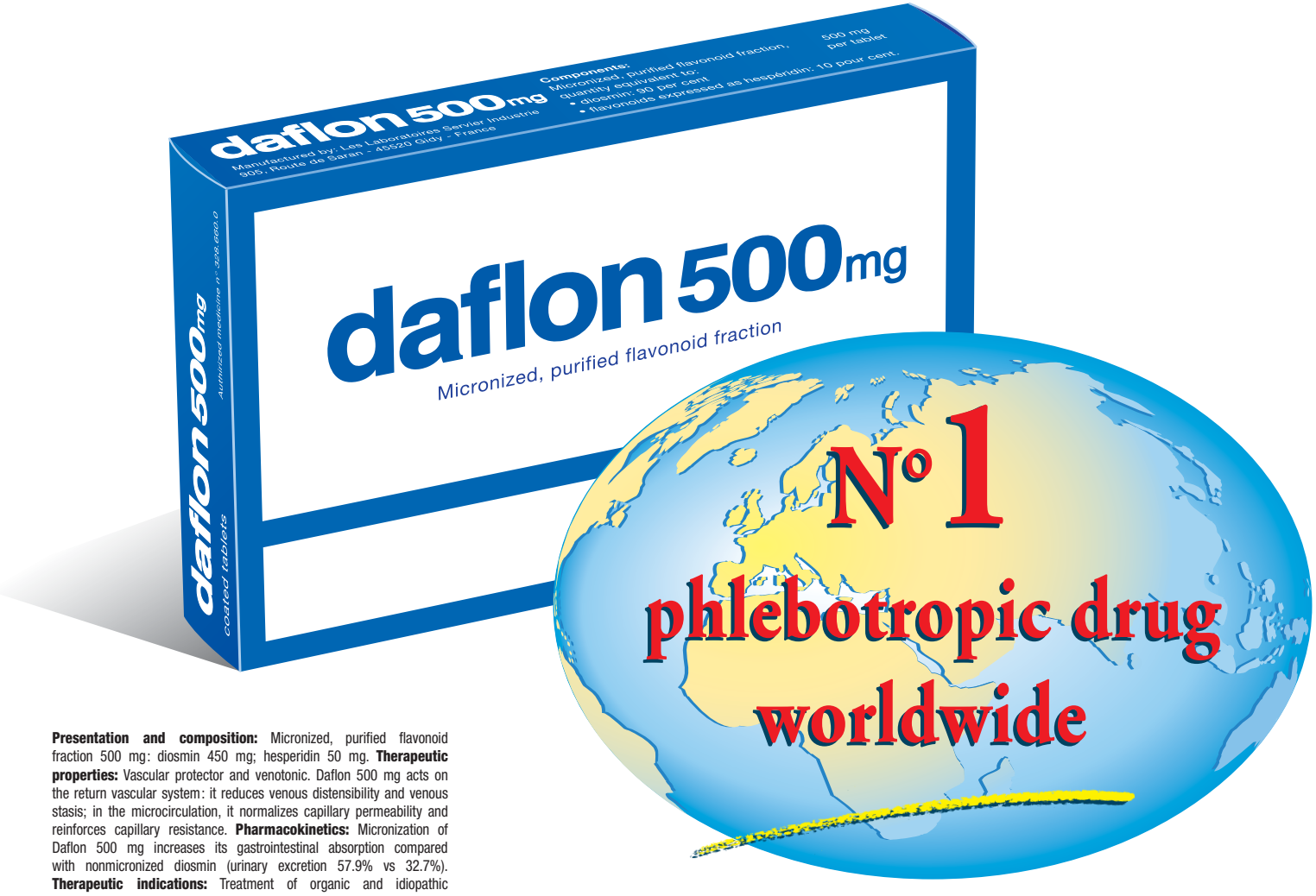

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Hemorrhoidal disease

up to 6 tablets daily

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