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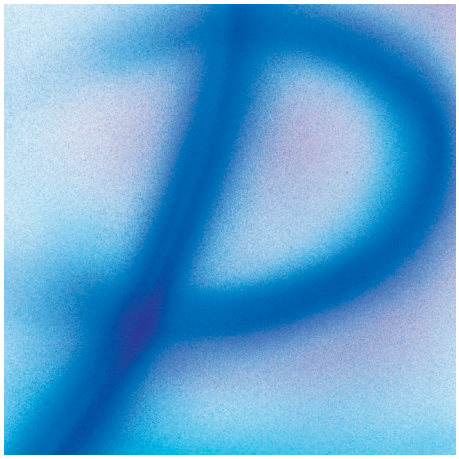

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AIMS AND SCOPE

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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CONTENTS

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PHLEBOLYMPHOLOGY

Phlebolymphology is a fascinating field encompassing important clinical entities, which often are widely ignored or neglected in general medicine.

The contributions in this issue of our journal, all written by top experts in their field, provide some very impressive examples.

Together with lymphatic malformations, venous angiodysplasias are the most common form of congenital vascular malformations. B. B. Lee from Seoul, Korea, one of the world's most experienced authorities in this field, presents his data on diagnosis and management of these congenital venous anomalies. The indication for active treatment depends on complications such as hemorrhage, pain, functional disability, or chronic venous hypertension; on a critical location, which threatens vital functions or carries a high risk of complication; and on the severity of the cosmetic deformity. The author has wide experience with ethanol sclerotherapy. Extratruncular malformations are treated by embolo-sclerotherapy using acrylate before surgical excision.

Peter Neglen from Raju's department in Jackson, Mississippi, reports on his experiences with stents for the treatment of venous iliofemoral obstructions, which date back 6 years, and which certainly comprise one of the largest series ever published. The intravascular procedure is less invasive and safer than open surgery, which has broadened the indication for an aggressive approach in pelvic venous obstructions. The indication for this procedure should not only be based on morphological criteria but should also take into account hemodynamic parameters. Some important technical hints for the procedure are given.

Tomohiro Ogawa and Shunichi Hoshino, two leading specialists in the field of venous diseases from Fukushima, Japan, present an interesting review on the epidemiology of pulmonary embolism in Japan, it has been demonstrated that the frequency of this entity is approaching the Western level, while some years ago it was only between one third to one tenth as common as in the West. The incidence of deep venous thrombosis after surgery is presently in the same range as reported in Europe or in the US. The reason for this development is obviously associated with the westernization of the Japanese lifestyle, and with the growing life expectancy.

Corradino Campisi and his group from the famous school of Tosatti in Genova, Italy, not only report on their own vast experience with microsurgical techniques in over 600 patients with lymphedema, but also give us an informative overview on the historical development of surgical techniques in this indication. The authors underline the importance of prevention of lymphedema, for instance after surgery for breast cancer, and advocate an interdisciplinary concept, in which conservative therapy plays a major role.

I hope you will all enjoy the extraordinary quality of the articles.

Prof Dr Hugo Partsch

Current concepts of venous malformation (VM)

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SUMMARY

Introduction. Venous malformation (VM) is one of the most common forms of congenital vascular malformations (CVM). The VM is further classified into extratruncular (ET) forms and truncular (T) forms, depending on the embryonic stage when the developmental arrest occurrs. This new classification provides critical information on clinico-anatomo-pathophysiology.

Methods. Proper combination of the various noninvasive to minimally invasive diagnostic tests provided a precise diagnosis of the VM. Invasive studies were reserved mostly for differential diagnosis and/or for a treatment "road map." Once the treatment was indicated, the crucial decision of the selection of proper treatment modalities and the time to begin was made through a multidisciplinary approach. Treatment was indicated in the case of hemorrhage, pain, functional disability, chronic venous hypertension, critical location which threatens vital functions or carries a high risk of complication, and severe cosmetic deformity. Various surgical and nonsurgical therapies were implemented: sclerotherapy, mostly for the surgically inaccessible or difficult lesions, and surgical (excisional) therapy of the surgically accessible lesion with or without preoperative embolo/sclerotherapy.

Results. Among a total of 294 VM, 99 surgically inaccessible ET forms received a total of 419 multisession ethanol sclerotherapy sessions, with an immediate success rate of 98.8% and excellent interim results (average 18.2 months). Most of the 25 surgically amenable ET forms received 36 sessions of preoperative embolo/sclerotherapy with *N*-butyl cyanoacrylate (16/25) and subsequent surgical excision, with excellent results with minimum morbidity (average 21.2 months).

Discussion. Absolute ethanol, accepted as the primary choice of the sclerotherapy for VM, can have various major and/or minor acute complications, even when used with extreme precaution. Chronic morbidity with or without sequelae still remains to be assessed.

Conclusion. A multidisciplinary approach based on a new classification will allow the best combination of treatment. Careful assessment and proper control of the potential risk involved with each treatment can deliver much-improved results.

Keywords:
Venous malformation, Hamburg classification, extratruncular, truncular, embolo/sclerotherapy, multidisciplinary

INTRODUCTION

Venous malformations (VM) are one of the most common forms of congenital vascular malformations (CVM), after lymphatic malformations (LM). CVM are one of the vascular anomalies which can occur together with (infantile) hemangioma. The hemangioma is a true vascular tumor which develops after birth. It has a rapid growth course through its proliferative phase, but has self-limiting evolution (growth) followed by natural involution (regression).[1] CVM are, in contrast, true vascular defects originating from defective embryogenesis of unknown etiology, and continue to grow proportionally to general body growth. The CVM are now classified into five groups, depending on their predominant component: arterial, venous, arteriovenous (AV) shunting, lymphatic, and combined (mostly hemolymphatic) defects, based on the modified Hamburg classification *(Table I)*.[2,3]

The VM itself is further classified into two groups, like any other form of CVM; extratruncular forms and truncular forms, depending on the stage of embryonic life when the developmental arrest has occurred. The extratratruncular (ET) form is relatively common among VM. It is an embryonic tissue remnant following developmental arrest at the earlier stage of embryonic life. Any embryonic tissue remnants from the earlier stage (eg, reticular stage) of organogenesis can retain the characteristics of the mesodermal cell origin. Therefore, this ET form maintains its potential evolutive power like any other tissue originating from the mesenchymal cells.[4] It can often grow explosively when the condition (eg, trauma, surgery, hormone therapy, pregnancy) adequately stimulates it. This, in turn, has serious consequences for clinicians in terms of "recurrence." The truncular (T) form, in contrast, lacks this evolubility since it is a growth defect developed in the latter stages of embryonic life to grow as the normal (axial) venous system after it loses the mesenchymal cell characteristics.

Species	Anatomical Form	
Predominantly Arterial defects	Truncular forms	Aplasia or obstruction Dilatation
	Extratruncular forms	Infiltrating Limited
Predominantly Venous defects	Truncular forms	Aplasia or obstruction Dilatation
	Extratruncular forms	Infiltrating Limited
Predominantly AV *shunting defects * Arteriovenous	Truncular forms	Deep AV fistula Superficial AV fistula
	Extratruncular forms	Infiltrating Limited
Combined Vascular defects	Truncular forms	Arterial and venous hemolymphatic
	Extratruncular forms	Infiltrating hemolymphatic Limited hemolymphatic
Predominantly Lymphatic defects	Truncular forms	Aplasia or obstruction Dilatation
	Extratruncular forms	Infiltrating Limited

Table I. Hamburg Classification of Congenital Vascular Malformation - 1988 with modification.[2,3]

Though classical (traditional) name-based nomenclature (eg, Klippel-Trenaunay syndrome, Parkes-Weber syndrome) is still popular among the clinicians, its fundamental liability is that it can not provide crucial information of the clinico-anatomo-pathophysiology of these complicated birth defects.[5] The new modified Hamburg classification is finally able to provide this critical information and clear up confusion regarding the proper definition of the VM for the right diagnosis and management.[6]

METHODS – DIAGNOSIS

Proper combination of the various noninvasive to minimally invasive diagnostic tests were implemented in all the CVM patients registered at our Clinic, to provide accurate diagnosis of the VM.[7]

These newly introduced tests, mostly of a noninvasive to minimally invasive nature, based on advanced diagnostic technology, were able to provide the crucial hemodynamic and anatomophysiologic information for the diagnosis of the VM; duplex sonography (color Doppler image and spectral waveform analysis), whole-body blood pool scintigraphy (WBBPS) utilizing radioisotope-tagged erythrocytes, standard T1 and T2 MRI image study, transarterial lung perfusion scintigraphy (TLPS) utilizing radioisotope microalbumin, aeroplethysmography (APG) and/or lymphoscintigraphy.

Various invasive studies (eg, ascending, descending, and percutaneous phlebography and standard, selective, and superselective arteriography) were seldom needed for the diagnosis of the malformation per se. They were often reserved only for the differential diagnosis and/or for a treatment "road map."[7]

Differential diagnosis with other CVMs were further included when indicated for the possible combined lymphatic malformation (LM) and/or AV shunting malformation

(AVM). This is often critical for the proper management of the VM since there is potential risk of negative impact on VM management. Precise assessment of the deep vein system was mandatorily required when the T form of VM is involved the marginal (lateral embryonal) vein as a venous component of the hemolymphatic malformation (HLM).[8]

METHODS – MULTIDISCIPLINARY APPROACH

Once the accurate diagnosis of the VM was established, further decisions were referred to the multidisciplinary board of the CVM Clinic. The summed-up results and opinions of each member were reviewed together by the team, involving 15 related specialists *(Table II)*. The first crucial decision as to whether the lesion was indicated for treatment was made on the basis of a consensus among the multidisciplinary team members.

Vascular Surgery, Pediatric Surgery, Interventional and Diagnostic Radiology, Anesthesiology, Vascular Medicine, Pathology, Plastic and Reconstructive Surgery, Nuclear Medicine, Orthopedic Surgery, Head and Neck Surgery, Oral-maxillary Surgery, Physical Medicine and Rehabilitation, Psychiatry, Dermatology, Social Services

*Table II. Multidisciplinary team**

** The Congenital Vascular Malformation Clinic, Vascular Center, Samsung Medical Center & Sungkyunkwan University, Seoul, Korea*

Once the VM lesion was confirmed as needing treatment with various indications, the next decision for the selection of proper treatment modalities, as well as the time to begin, was made per-protocol.[7] Unless the VM lesion is a life-, if not limb-threatening, condition, or seriously affecting functioning, the treatment is generally delayed until the child grows old enough to tolerate various treatment strategies (eg, age 6 to 9). Though with VM in general it is relatively safe to wait, buying enough time to observe its behavior for proper planning, VM in the lower extremity accompanying the vascular-bone syndrome was selected for earlier treatment, before abnormal long bone growth caused significant functional disability by the discrepancy between long bone length and pelvic tilt.[9,10]

The principle of the treatment strategy aimed at the primary lesion of the VM was first to control its hemodynamic impact. The treatment for secondary morbidity of the primary lesion (eg, Achilles tendon shortening) was deferred until the primary lesion was under adequate control.[8]

METHOD – INDICATIONS AND TREATMENT MODALITIES

Various indications[7] were implemented to select VM patients for treatment; hemorrhage, pain with or without functional disability, chronic venous hypertension with secondary morbidity, critical location (eg, proximity to the airway) threatening vital function, vulnerable location with increased risk of complication (eg, knee, ankle, and foot), severe cosmetic deformity decreasing quality of life, and vascular-bone syndrome.

Various surgical and nonsurgical therapies were implemented independently, or combined with other modalities of treatment depending on the indication. Sclerotherapy with various agents (eg, absolute ethanol) was given mostly to surgically inaccessible or difficult lesions. Surgical (excisional) therapy with or without preoperative supplemental embolo/sclerotherapy was selected for the surgically accessible lesion. A multidisciplinary approach to integrate the surgical therapy and embolo/sclerotherapy was strictly implemented in every possible case to reduce morbidity and/or complications, and also the recurrence rate.[8]

The treatment strategy was repeatedly reviewed by the multidisciplinary team to weigh the benefit over the risk of morbidity following the therapy before commitment to continuous treatment.

RESULTS

We performed retrospective analysis of a total of 294 patients with VM in order to assess the results of contemporary management of VM based on the new concepts.

Among a total of 797 patients with various CVMs, 294 patients (male-138, female-156, mean age 18.6 years, 3 months – 59 years) were confirmed as VM mostly located in the extremities (128/294: upper – 30 and lower – 98), and often as multiple lesions (73/294). They all were diagnosed based on the noninvasive tests only. One hundred and twenty four of a total of 294 VM were selected for treatment with various indications. Ninety-nine infiltrating types of the ET form indicated for the treatment but not for surgical therapy, received a total of 419 multisession ethanol sclerotherapy treatments. Twenty-five limited types of ET forms which were surgically amenable were excised surgically but mostly combined with preoperative embolo/sclerotherapy (16/25) with N-butyl cyanoacrylate (NBCA). Thirty-six sessions of NBCA embolotherapy were given independently or in conjunction with ethanol sclero-

therapy as preoperative adjunct therapy for the subsequent surgical excision of 16 ET forms. Nine T forms of VM (eg, venectasia, venous aneurysm) were indicated for treatment hemodynamically, and underwent various surgical treatments as independent therapy successfully. Follow-up assessment of treatment results was made with the duplex scan, WBBPS, and/or MRI at regular intervals by the multidisciplinary team.

Ninety-nine ET forms, treated with ethanol sclerotherapy as independent therapy through a total of 419 sessions, showed an immediate success rate of 98.8% (414 sessions out of 419 sessions). The interim results were also excellent, with no evidence of recurrence of the treated lesions during the limited follow-up period of average 18.2 months after the completion of multisession therapy – average 3.2 sessions per patient – *(Figures 1A and 1B)*. Sixteen ET forms which underwent various combinations of preoperative embolo/sclerotherapy (eg, ethanol, N-butyl cyanoacrylate) and subsequent surgical excision showed excellent results with minimum morbidity and no recurrence during the

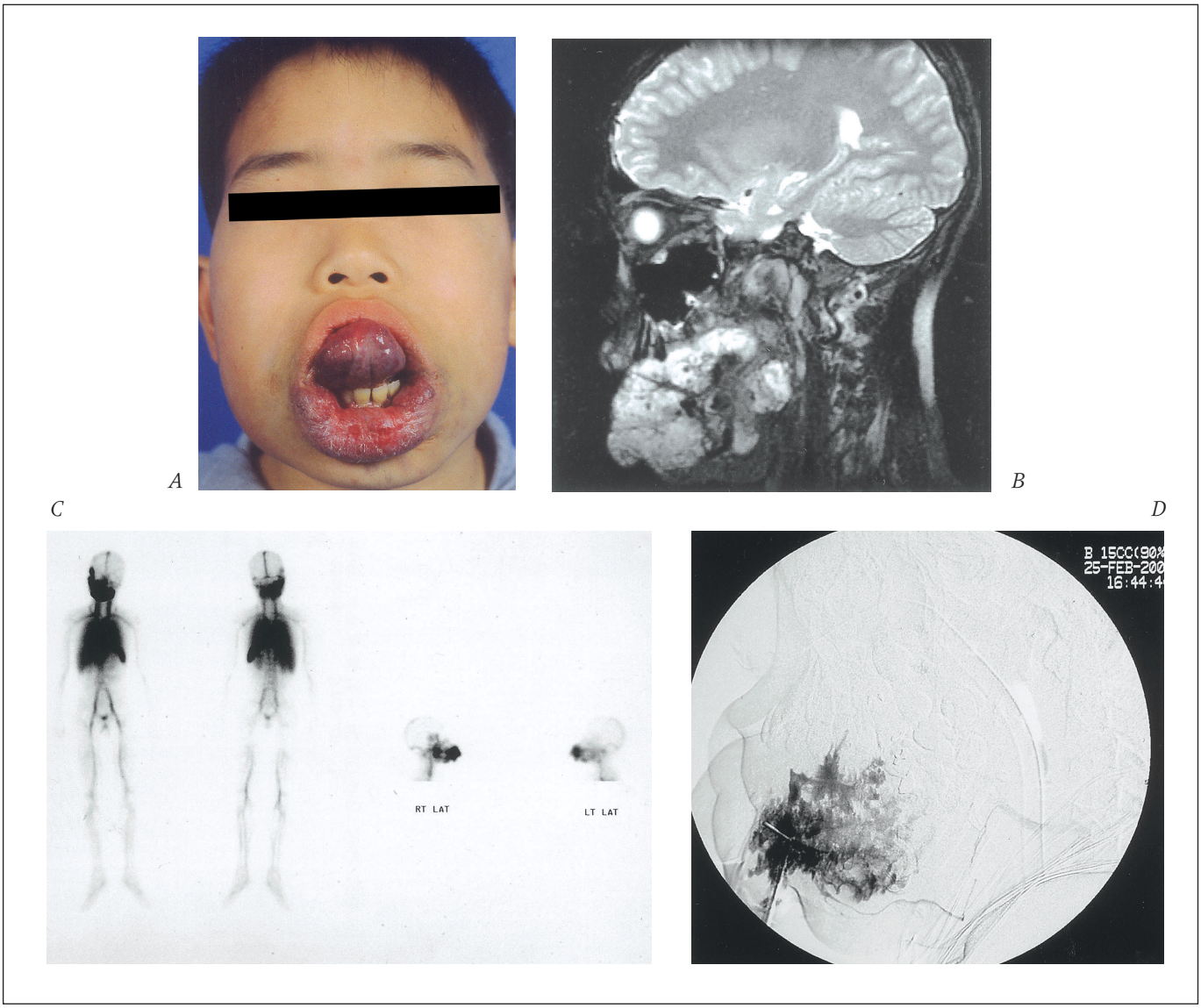
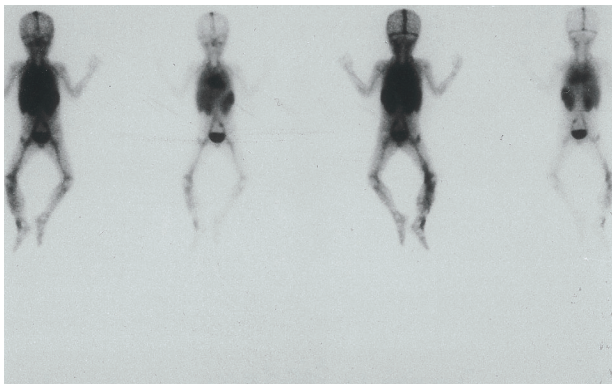


Figure 1-A. Management of the diffuse infiltrating ET form of the VM with ethanol sclerotherapy as independent therapy.
A. Clinical appearance of the extensive lesion affecting the tongue, cheek, lips, and mouth floor, etc. with severe functional disability.
B. MRI image of the lesions through whole mouth cavity involving multiple perioral structures - infiltrating type.
C. WBBPS image of extensive abnormal blood pooling along the lesions.*
D. Angiographic image of multisession ethanol sclerotherapy by percutaneous direct puncture technique with excellent response.

** WBBPS: whole body blood pool scan*



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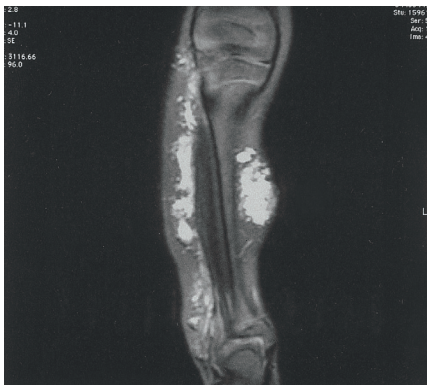

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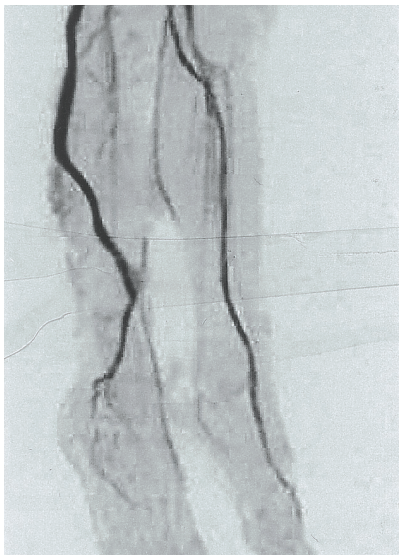

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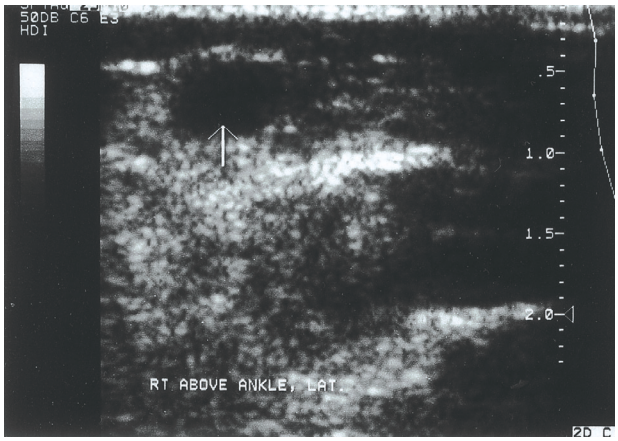

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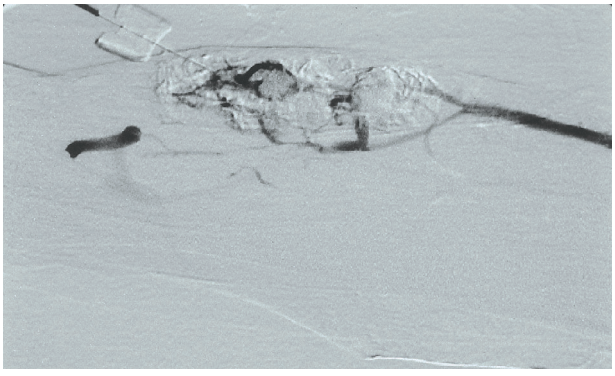

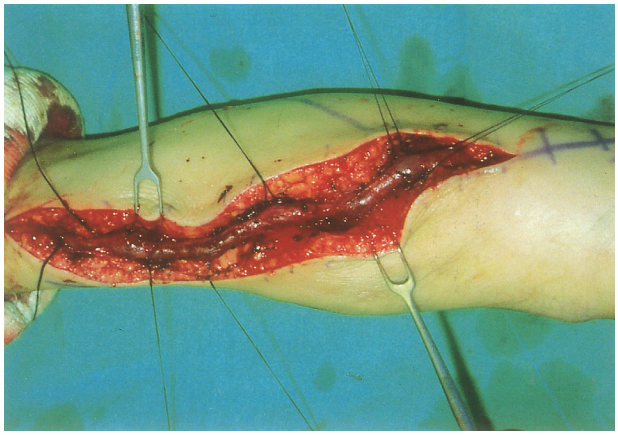

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Figure 1-B. Management of the ET form of the VM with ethanol sclerotherapy and the T form with surgical therapy as independent therapy.
A. WBBPS image of extensive abnormal blood pool along right lower extremity by VM lesions.*
B. MRI images of multiple infiltrating type of ET lesions, along upper thigh.
C. MR venography image of the marginal vein as one of T forms along right lower leg.
D. Ultrasonographic image of the superficially located marginal vein.
E. Angiographic image of the ethanol sclerotherapy to the infiltrating ET lesion with excellent response.
F. Operative image of the surgically isolated marginal (lateral embryonal) vein for the resection.

** WBBPS: whole body blood pool scan*

limited follow-up period (average 21.2 months) *(Figure 2)*. Nine T forms underwent various surgical therapy (eg, venorrhaphy) as independent therapy, and showed excellent results.

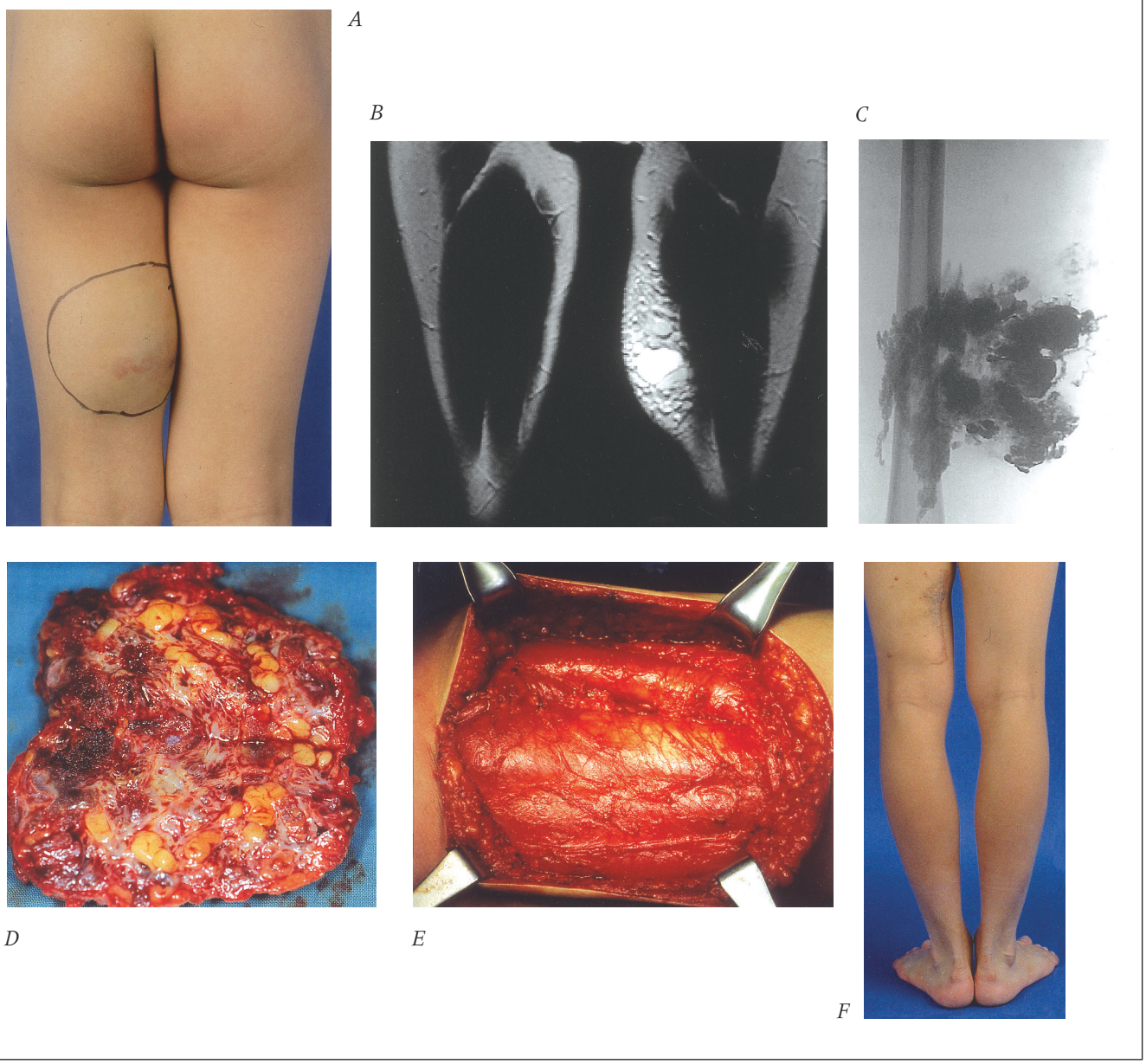

Figure 2. Management of the localized ET form of the VM with preoperative NBCA glue embolotherapy and subsequent surgical excision.*
A. Clinical appearance of rapidly growing lesion at the posterior aspect of left thigh with recurrent bleeding following minor body-contact sport and progressive ache.
B. MRI image of the infiltrating type of the ET lesion as localized form.
C. Angiographic image of the lesion, filled with NBCA glue preoperatively for the subsequent excision.
D. Surgical specimen of the glue-filled ET lesion.
E. Surgical field following complete removal of the lesion.
F. Clinical appearance of the satisfactory result with no evidence of recurrence on the follow-up (2 years).

** NBCA: N-butyl cyanoacrylate*

DISCUSSION

The critical value of close communication, not only among the multidisciplinary team members, but also with the patient and family before the acceptance of the risk involved in the treatment cannot be overemphasized. Though the "cure" can be achieved theoretically by the proper treatment, this is not always possible with minimum morbidity. It is wiser to choose "adequate control" of VM lesions with minimum adverse effects to improve the quality of life, if the morbidity for the curative treatment seems to be prohibitively high (eg, Malan operation I).

As we recently reported,[7] we controlled most of the surgically inaccessible VM lesions with absolute ethanol quite successfully. Now, absolute ethanol has been accepted as the primary choice for sclerotherapy of VM at our Clinic. However, the price to pay for the satisfactory results with the promising long-term outcome with minimum recurrence was much higher than we wished. There were various major and/or minor acute complications, though mostly manageable skin complications, in spite of extreme precautions taken. The chemical toxicity of absolute ethanol is also an imminent threat during each session of the therapy, with potential risk of serious morbidity and/or mortality. All the procedures therefore should be done under general anesthesia, and close cardiovascular and pulmonary monitoring is essential for the immediate control of this acute morbidity. This potentially lethal pulmonary hypertension by the spillover ethanol reaching the pulmonary bed has to be aborted, if not minimized, by prompt control with adequate measurement. In addition to these acute complications and morbidity, the long-term results and chronic morbidity with or without sequelae following the sclerotherapy still remain to be assessed.[11]

CONCLUSION

New classifications can properly verify each component as well as characteristics of VM properly to become the basis of contemporary management of VM. A multidisciplinary approach with full integration of various modalities of surgical and/or nonsurgical treatment will allow the best combination of the treatment to be safely implemented for each different component of the VM. Through the careful assessment and control of the potential risk involved with each treatment, substantial improvement of the overall treatment results can be achieved. Complex forms of extensive VM which have been inaccessible to conventional treatment can now also obtain benefit from this contemporary strategy.

REFERENCES

1. **Mulliken JB.** Cutaneous vascular anomalies. *Semin Vasc Surg*. 1993;6:204-218.
2. **Belov S.** Classification of congenital vascular defects. *Int Angiol*. 1990;9:141-146.
3. **Belov S.** Anatomopathological classification of congenital vascular defects. *Semin Vasc Surg*. 1993;6:219-224..
4. **Woolard HH.** The development of the principle arterial stems in the forelimb of the pig. *Contrib Embryol*. 1922;14:139-54.
5. **Malan E.** *Vascular Malformations (Angiodysplasias)*. Milan: Carlo Erba Foundation;1974:17.
6. **Lee BB.** Advanced management of congenital vascular malformation (CVM). *Int Angiol*. 2002;21:209-213.
7. **Lee BB, Kim DI, Huh S, et al.** New experiences with absolute ethanol sclerotherapy in the management of a complex form of congenital venous malformation. *J Vasc Surg*. 2001;33:764-772.
8. **Lee BB, Bergan JJ.** Advanced management of congenital vascular malformations: a multidisciplinary approach. *J Cardiovasc Surg*. 2002;10:523-533.
9. **Mattassi R.** Differential diagnosis in congenital vascular-bone syndromes. *Semin Vasc Surg*. 1993;6:233-244.
10. **Belov S.** Correction of lower limb length discrepancy in congenital vascular-bone disease by vascular surgery performed during childhood. *Semin Vasc Surg*. 1993;6:245-251.
11. **Lee BB, Do YS, Byun HS, et al.** Advanced management of venous malformation with ethanol sclerotherapy: mid-term results. *J Vasc Surg*. 2003. In press.

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Endovascular treatment of chronic Iliofemoral venous obstruction – A review

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SUMMARY

The importance of venous outflow obstruction is increasingly recognized as an important contributing factor in chronic venous disease. Obstruction of the iliofemoral venous outflow appears particularly important, and results in more severe symptoms than does lower segmental blockage. Selection of patients for treatment is hampered by the lack of accurate noninvasive or invasive tests for evaluation of obstruction. In fact, it is not known precisely what degree of venous stenosis should be considered hemodynamically critical. It is presently impossible to detect potentially hemodynamically important borderline obstructions. The diagnosis must be made on clinical signs and symptoms having a high index of suspicion, and treatment must be based on morphologic investigations, eg, transfemoral phlebography or, preferably, intravascular ultrasound (IVUS). Percutaneous iliac venous balloon venoplasty and stenting is a safe, minimally invasive method with minimal complication rate, no mortality, a 4-year acceptable patency, and substantial sustained clinical improvement. It is a less invasive alternative, and relatively safer than open surgery, and can therefore be offered to a larger group of patients. In case of immediate or late failure venous stenting does not preclude subsequent bypass surgery or surgical correction of reflux when necessary. Although venous stenting is presently the preferred treatment for iliofemoral obstruction, more research is necessary to define accurate hemodynamic criteria for assessment and treatment and to study the long-term effects of stents in the venous system.

Keywords:
Iliac vein, femoral vein, obstruction, balloon dilation, stent, postthrombotic, May-Thurner syndrome

INTRODUCTION

Following successful arterial endovascular surgery, balloon venoplasty and stenting of chronic venous obstructions were introduced in the late 1980s and early 1990s. Most studies of venous stents have reported results of stent treatment of residual obstruction following removal of acute iliac or subclavian vein thrombosis,[1,2] or in the venous outflow tract of arteriovenous fistulae used for hemodialysis.[3,4]

The behavior of venous stents varies greatly depending on indication and anatomic placement of the stents. Assessment of the results of 707 throm-

bolyzed and stented iliofemoral veins in 24 reports shows primary and assisted primary patency rates varying from 50% to 100% and 63% to 100%, respectively, during a follow-up time of 1 to 46 months. Few of these patients had late follow-up with imaging and no actuarial curves were constructed.[5] The primary patency rate following balloon angioplasty without stent and decompression surgery in the subclavian vein after thrombolysis is very poor, as low as 6% at 2 years.[6] Owing to its anatomic location, the subclavian vein is prone to flexion during movement, and the vessel may be compressed by external structures, most often between the first rib and clavicle. Stents have been reported to be deformed or even fractured by the forceful compression in the thoracic outlet, resulting in secondary thrombosis.[7,8] Although no larger long-term study exists, probably balloon angioplasty and stenting of the subclavian vein should always be combined with decompression surgery.[9] The result following angioplasty and stenting of the catheter-induced central vein stenoses and the dialysis access outflow tract of the upper or lower extremities is dismal. The neointimal hyperplasia at the venous anastomosis is very resistant to balloon angioplasty; the primary patency rates at 24 months after angioplasty and stenting for central veins and peripheral veins are only 9% and 17%, respectively.[3] The best results have been obtained with treatment of the iliofemoral vein with chronic nonmalignant obstruction. This review will focus mainly upon the symptoms, diagnostic dilemma, technique, and clinical and morphological results (patency and in-stent restenosis rates) after iliofemoral stenting of chronic obstructions.

SYMPTOMS

Symptoms of chronic venous disease may vary greatly, ranging from moderate swelling and pain to discoloration and stasis ulcers. The main emphasis has been on treatment of severe skin changes and stasis ulcer, chiefly by controlling reflux. It is our experience that a substantial number of patients with CVI, however, complain of disabling limb pain and swelling without skin changes.[10] These symptoms are not always improved by wearing compression stockings or performing venous valve repair. The dominant pathophysiologic component in these patients may be obstruction rather than reflux, and it is possible that these symptoms are mainly attributable to the outflow blockage. "Venous claudication" is described as an exercise-induced "tense" pain, which requires several minutes of rest and leg elevation to subside. Certainly patients with significant outflow obstruction may have less dramatic symptoms, with less distinct lower extremity pain and discomfort, with decreased quality of life and moderate disability. Previous estimations that obstruction is a major contributor in only 10% to 20% of patients with severe chronic venous disease are probably markedly low.

DIAGNOSIS

Often when algorithms are constructed for workup of patients with chronic venous insufficiency, investigations for reflux are emphasized, and testing for outflow obstruction is completely omitted. This is probably owing in part to a lack of accurate objective noninvasive or invasive tests for evaluation of hemodynamically significant chronic venous obstruction, and in part to the lack of practical treatment alternatives prior to the introduction of venous stenting. There are many tests for delineating focal and global reflux but this is not so for outflow obstruction. Ultrasound investigation and outflow fraction determinations by plethysmographic methods have been shown to be unreliable and play only a limited role. Although abnormal plethysmography findings may indicate obstruction to the venous outflow, significant blockage may be present with normal findings.[11-13] Even the invasive pressures, ie, hand/foot pressure differential and reactive hyperemia pressure increase, and indirect resistance calculations appear insensitive and do not define the level of obstruction.[11] Only a small pressure gradient over a venous stenosis or pressure increase below an obstruction on exercise or hyperemia may indicate significant obstruction. These pressure differences are certainly much lower than in the arterial system, often as low as 2 to 3 mm Hg, which may be difficult to measure accurately.[14-16] Thus, although a positive hemodynamic test may indicate hemodynamic significance, a normal test does not exclude it. Unfortunately, it is presently impossible to detect borderline obstructions, which may potentially be of hemodynamic importance.

Since accurate hemodynamic tests are unavailable, diagnosis and treatment must be based on morphological findings. Single-plane transfemoral phlebogram is the standard investigation, and may show obstruction and development of collaterals. Increased accuracy may be achieved with multiple angled projections *(Figures 1a-c)*.[17] Although the degree of stenosis may be obtained, the hemodynamic impact of this stenosis is not known from morphologic studies. In fact, it is not known what degree of

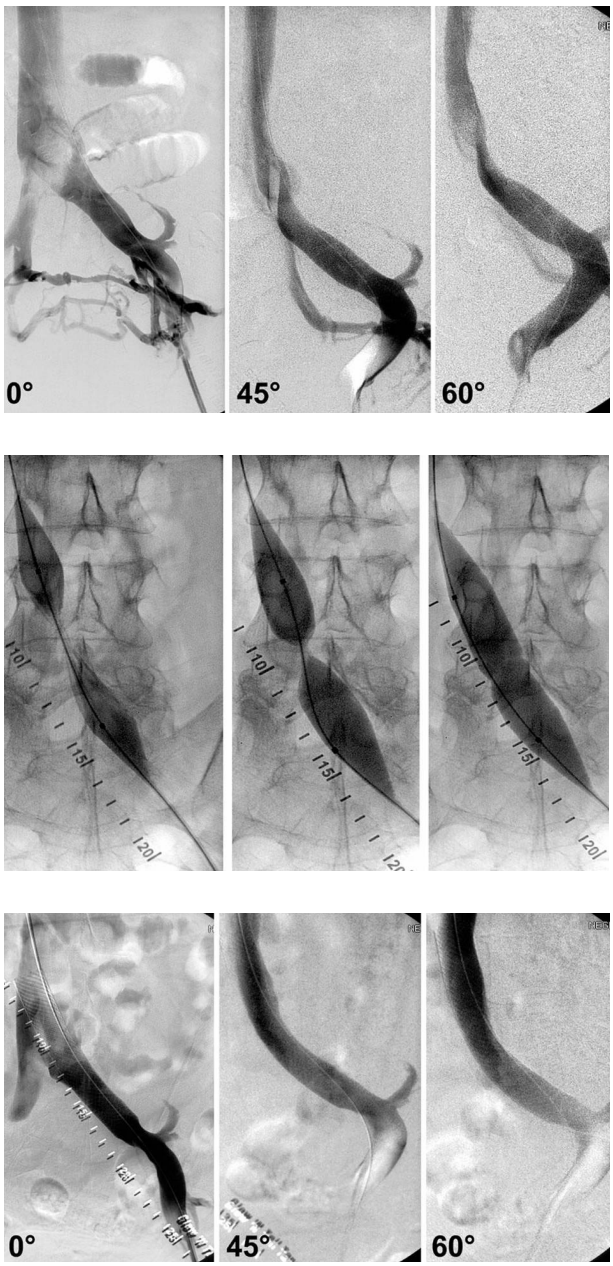

Figure. 1. Transfemoral phlebogram showing a May-Thurner syndrome in multiple projections: a) before venous stenting, showing absence of stenosis but presence of collaterals in the AP view. The stenosis is detected by rotation; b) waisting of balloon during inflation by the stenosis; and c) post-stent phlebogram revealing no stenosis.

venous stenosis should be considered hemodynamically "critical."[18] Although the formation of collaterals is classically looked upon as a compensatory mechanism to bypass and thus neutralize the effects of an obstruction, the mechanism and inducement of collateral formation are, however, unknown. It is doubtful if that blood flow through this meandering vessel may replace that through the straighter main vein. The collaterals observed prestent often disappear promptly following stenting of a significant stenosis *(Figure 2)*. The flow through the stent is obviously favored. It may be that the development of collaterals should be considered an indicator of obstruction and a

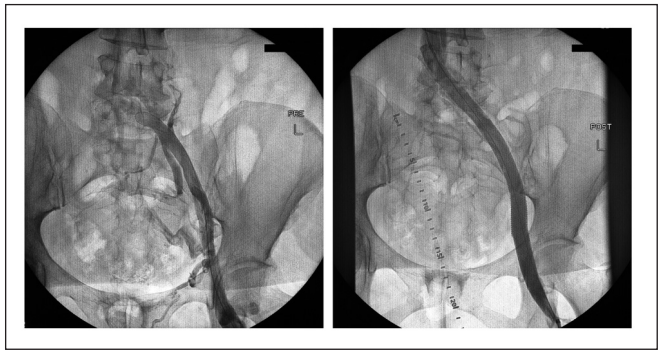

Figure 2. Chronic iliofemoral thrombotic stenosis before and after stenting. Note the disappearance of collaterals after disobliteration.

failed compensatory feature if the patient is symptomatic. Intravascular ultrasound (IVUS) can detect only axial collaterals running close to the original vessel. Transpelvic collaterals will escape detection. Several studies have shown, however, that IVUS is superior in detection of the extent and morphologic degree of stenosis as compared to the single-plane phlebography.[19-21] IVUS shows intraluminal details, eg, trabeculations and webs, which may be hidden in the contrast dye *(Figure 3)*. An external compres-

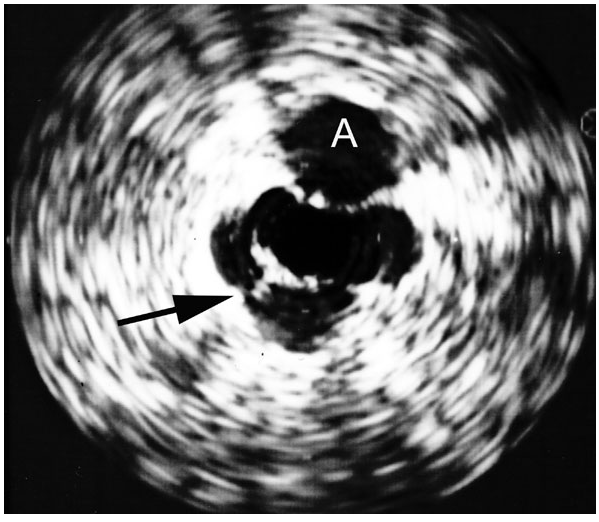

Figure 3. Intravascular ultrasound (IVUS) showing trabeculation (arrow) not visualized by phlebogram. The adjacent artery is marked with an A.

sion with the resulting deformity of the venous lumen can be directly visualized, and wall thickness and movement can be seen. Most importantly, IVUS appears superior to standard single-plane venography for estimating the morphological degree of iliac vein stenosis. On average the transfemoral venogram significantly underestimated the degree of stenosis by 30%. The phlebogram was actually considered "normal" in one fourth of limbs despite the fact that IVUS showed >50% obstruction.[22] IVUS is clearly superior to single-plane venography in providing adequate morphological information, and is presently the best available method for diagnosing clinically significant chronic iliac vein obstruction. Owing to the lack of hemodynamic tests, the diagnosis and treatment must presently be based on invasive morphological investigations of the iliac venous outflow (preferably IVUS). Limiting workup of patients with chronic venous disease to only duplex ultrasound will not suffice. In order to identify patients with potentially important venous outflow obstruction, transfemoral phlebography (multiplane) or IVUS should be utilized more generously in patients with significant signs and symptoms of CVI.

We consider the following as indicators of obstruction warranting further investigations: 1) phlebographic stenosis >30%; 2) presence of pelvic collaterals; and 3) positive invasive pressure test.

The patient is taken to the OR, and IVUS is performed when one or several of these indicators are present and the patient is symptomatic. The symptoms may range from painful swelling, pain in excess of clinical findings to severe stages with lipodermatosclerosis or ulcer. We have arbitrarily chosen to stent only venous stenosis of >50% as seen on IVUS and clinical results have been good. With this policy10 to 15% of iliofemoral veins are found to be normal.

TECHNICAL HINTS

Venous stenting is a minimally invasive procedure and may appear to be simple. To achieve good results, however, attention to detail is important. Venous balloon angioplasty and stenting is a different procedure from that employed in the arterial system. Some important aspects are emphasized:[19,23]

1. Balloon angioplasty is insufficient in the venous system. Stent insertion is mandatory. Severe recoil of the vein is already observed intraoperatively in the majority of limbs and simple balloon dilation leads to early restenosis.
2. Always use ultrasound to guide cannulation of the femoral vein, especially when low thigh cannulation is necessary to enter below iliofemoral occlusions. Ultrasound guidance has largely eliminated access complications.
3. IVUS is invaluable, both as a diagnostic tool and as an intraoperative aid in direct placement of the stent.[20,21]
4. Stenting of a stenosis adjacent to the confluence of the common iliac veins requires that the stent be placed well into the IVC to avoid early restenosis.[19] This is especially important when a Wallstent® is used. Owing to its inherent property this stent may be "squeezed" distally and a proximal restenosis may develop. This placement of the stent into the IVC does not appear to significantly impair the flow from the contralateral limb resulting in thrombosis. A few cases of contralateral limb thrombosis have been observed and raised concern. These clots, however, appear to be caused by recurrent attacks of thrombosis rather than stent occlusion.
5. The "kissing" balloon technique utilized at the aortic bifurcation is unnecessary at the confluence of the common iliac veins and bilateral stents are not inserted at this location.
6. Insertion of a large-diameter stent (14 to 16 mm wide) is recommended. Unlike the artery, the vein accepts extensive dilation without clinical rupture. No such rupture has been reported, even when a total occlusion is recanalized and dilated up to a width of 14 to 16 mm.
7. It is important to redilate the stent after insertion to avoid its possible movement. A good wall apposition should be achieved as evaluated by IVUS.
8. The diseased vein segment is more extensive in reality than seen on phlebography. To avoid early restenosis and occlusion it is vital to cover the entire obstruction as outlined by the IVUS investigation. Short (<5 cm) skip areas in between two stents should be avoided. The occlusion rate does not appear to be related to the length of stent or metal load per se. Probably the most common cause of early restenosis is inadequate stenting of the entire lesion.

COMPLICATIONS

The nonthrombotic complication rate related to the endovascular intervention is minimal and comprises mostly cannulation site hematoma, although a few cases of retroperitoneal hematoma requiring blood transfusions have been described.[24,25] The utilization of ultrasound-guided cannulation and closure with collagen plugs has largely abolished these problems, reducing the nonthrombotic complication rate from 3% to <1%. After introduc-

tion of these modifications, we had no procedure-related complications. The mortality has been zero.

Data regarding early rethrombosis rate (<30 days) after iliofemoral stenting are sparse. The rate was found to be 11% in the Creighton University experience following stenting after thrombolysis of an acute DVT[26] and 15% in the National Registry study.[27] The early thrombosis rate was found to be lower (4%) when stenting was performed for chronic iliofemoral venous obstruction without earlier thrombolysis.[22] All early occlusion occurred in patients with thrombotic disease (8% thrombosis rate), while none occurred in nonthrombotic limbs. Early failures appear more common with long stents extending below the inguinal ligament, stents placed across complete occlusions rather than across stenoses, and in patients with thrombophilia.[28] (Neglen P, Raju S, 2003, unpublished data) The occlusions appeared to be related to limbs with incomplete dilation owing to nonyielding obstruction leaving residual stenosis after stenting. Thrombolysis of the newly formed clot may be attempted in initially technically successful limbs to reveal and treat unknown additional obstructions.

PATENCY RATES

There are many small case reports in the literature, but only a few larger series with acceptable follow-up. The majority of these mix obstructions of different etiologies. O'Sullivan et al have reported a 1-year patency of 79% in a retrospective analysis of 39 patients.[29] Only half of the patients presented with chronic symptoms. When initial technical failures are removed, the stented patients had a 1-year patency of 94%. The clinical results were excellent in the stented limbs.

A similar group of 18 patients were reported by Hurst et al.[13] Six limbs were treated after disobliteration of an acute deep vein thrombosis. The primary patency rates at 12 and 18 months were 79% and 79%, respectively. Most patients (13/18) had resolution or substantial improvement of leg swelling and pain. However, five patients (28%) continued to have pain despite resolved swelling and widely patent stents on venogram. Similarly, Binkert et al reported a 100% patency at an average follow-up time of 3 years in 8 patients (in 4 limbs following surgical thrombectomy) with resolution or substantial improvement of symptoms in most patients.[30] Nazarian et al reported a 1-year primary assisted patency rate of 66% of 29 iliac obstructions.[28] The lower patency rate may be explained by the selection of patients (13/29 had complete occlusion and 16/19 were caused by malignancy). Interestingly, few occlusions occurred after 6 months and the patency rate remained the same at 1- and 4-year follow-up. The same group has also reported overall 1-year primary and secondary patency rates of 50% and 81%, respectively, in a mixed population including 56 patients with iliac obstruction caused by malignancy, trauma, pregnancy, and postoperative stenosis.[31] Lamont et al[32] have reported an 87% patency rate at median follow-up of 16 months in 15 patients stented for common iliac vein compression following clearance of acute thrombus by thrombolysis.

We have followed 455 limbs which underwent iliac vein stenting between 1997 and 2001.[25] Transfemoral venogram was performed in 324 of these limbs. The obstructive lesion was considered thrombotic if the patient had a known occurrence of deep vein thrombosis diagnosed with duplex ultrasound or ascending venogram and subsequently treated by anticoagulation; or findings on venogram (occlusion, stenosis, or collaterals) and/or duplex ultrasound indicating previous deep vein thrombosis below the inguinal ligament (direct visualization of thrombus or indirect indication by partial or total inability to compress the vein [54%]). The remaining limbs were considered nonthrombotic. Cumulative primary, assisted-primary, and secondary patency rates at 4 years were 57%, 92%, and 93%, respectively *(Figure 4)*. The stented limbs with non-

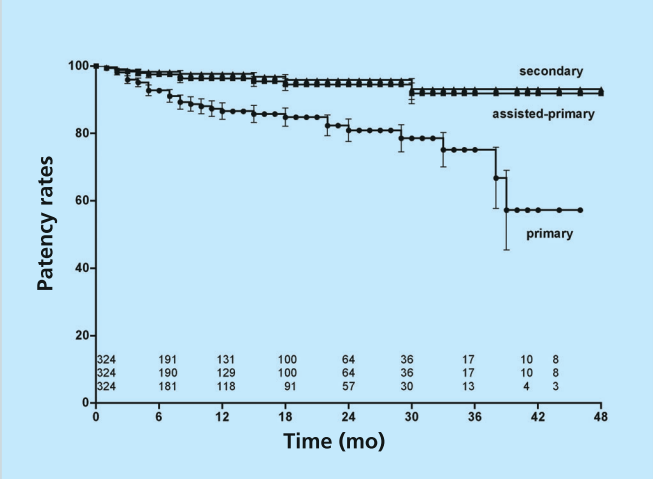

Figure 4. Cumulative primary, assisted-primary, and secondary patency rates of 324 limbs after iliofemoral stenting.
The lower numbers represent limbs at risk for each time interval (all SEM <10%).

thrombotic disease appeared to fare significantly better than did those with thrombotic disease (primary, assisted-primary and secondary cumulative patency rates of 89%, 100% and 100%, and 65%, 85%, and 88% at 36 months, respectively) *(Figure 5)*. Thus, it appears that balloon

venoplasty and stenting of an iliac vein obstruction for a chronic obstruction is a safe, minimally invasive method with minimal complication rate, no mortality and a 4-year acceptable patency. A smaller number of patients have been followed for 5 years or more without precipitous deterioration of clinical efficacy and stent patency.

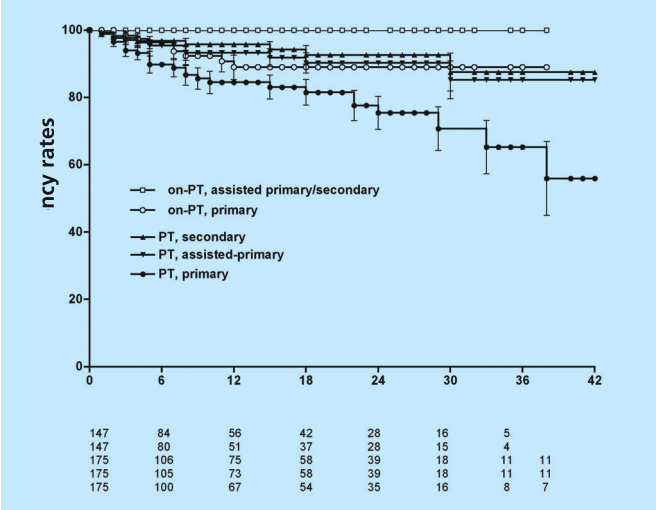

Figure 5. Cumulative primary, assisted-primary and secondary patency rates for stented limbs with thrombotic (PT) and non-thrombotic (non-PT) obstruction. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

IN-STENT RESTENOSIS RATE

To assess the development of in-stent restenosis (IRS), any narrowing of the stent on transfemoral phlebography was measured in the same group of patients described above using a caliper and expressed as percentage diameter reduction of patent lumen. (Neglen P, Raju S, 2003, unpublished data) At 42 months only 23% of limbs remained with no in-stent restenosis at all, but only the minority of limbs had severe (>50%) obstruction. Most had only minimal narrowing. The cumulative IRS-free rates of limbs with >20% and >50% in-stent restenosis were 39% and 85%, respectively *(Figure 6)*. The gender of the patient or sidedness of treated extremity did not affect the outcome. At 36 months, limbs with thrombotic disease had lower IRS-free rates than did nonthrombotic (37% and 59% of >20% narrowing, and 77% and 96% of >50% narrowing, respectively (P<0.01)*(Figure 7)*. Similarly, IRS-free rates were found in patients with thrombophilia and long stents extending below the inguinal ligament. The three major risk factors appear to be presence of thrombotic disease, positive thrombophilia test, and stent placement below the

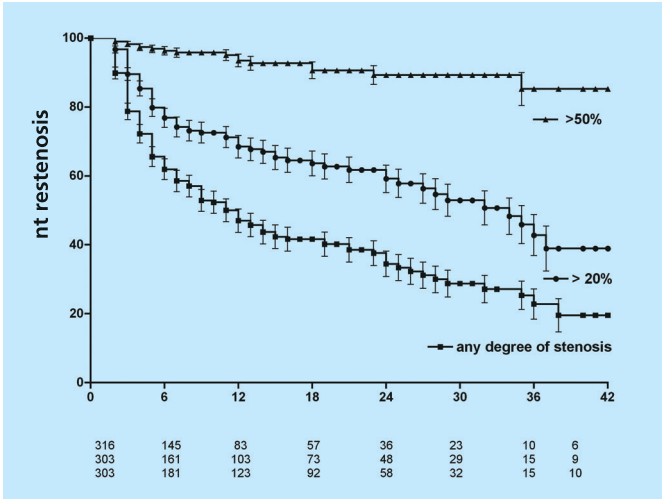

Figure 6. Cumulative in-stent restenosis-free rates for all limbs with any degree of stenosis, >20% and severe (>50%) narrowing. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

inguinal ligament (long stents). Although the cumulative patency rate and in-stent restenosis-free rate curves have a similar course in both nonthrombotic and thrombotic limbs, the hyperplasia-free curve drops more rapidly than do the patency curves. The development of in-stent restenosis appears to precede the development of obstruction *(Figure 7)*. These findings may suggest a cause-effect

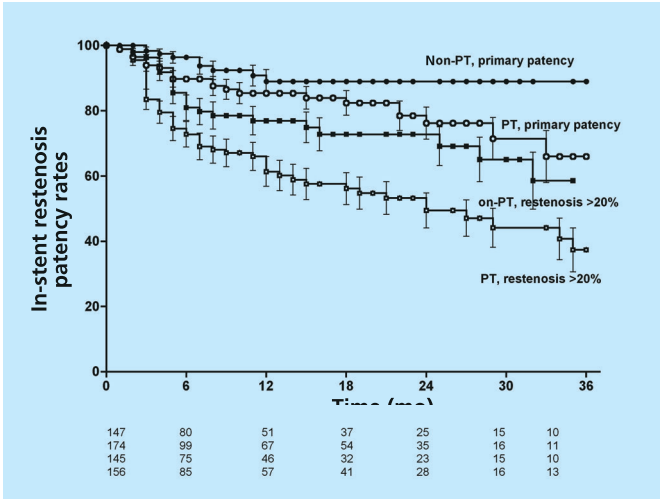

Figure 7. Cumulative in-stent restenosis-free rates (>20% in-stent restenosis) and cumulative primary rates for stented limbs with thrombotic (PT) and nonthrombotic (non-PT) obstruction. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

relationship. Also, the stented limbs that eventually occluded during this study had similar risk factors. However, no conclusion regarding cause-effect relation-

ship between in-stent restenosis and occlusion can be drawn from the data presented. Whether the late occlusions occur owing to acute thrombosis or to gradual development of true intimal hyperplasia needs further study.

CLINICAL RESULTS

As alluded to above, the reports describing patency rates indicate clinical improvement in most patients (>90%).[29, 30] Hurst et al showed resolution or substantial improvement in 72% of limbs.[13] In addition to ulcer healing and ulcer recurrence rate, we have followed the patient's clinical result by quality-of-life questionnaires,[33] degree of swelling assessed by physical examination (Grade 0: none; Grade 1: pitting, not obvious; Grade 2: ankle edema; and Grade 3: obvious swelling involving the limb), and level of pain measured by the visual analogue scale method.[19, 22, 25, 34] The incidence of ulcer healing after iliac vein balloon dilation and stent placement in 41 limbs with active ulcer was 68% and the cumulative ulcer recurrence-free rate at 2 years was 62%.[25] Frequently these limbs had remaining reflux, which was untreated during the observation period. Despite the presence of reflux the stasis ulcers stayed healed. Median swelling and pain severity scores decreased significantly (grade 2 to 1 and 4 to 0, respectively). The rates of limbs with any objective swelling or pain decreased significantly by approximately 55% (from 88 % to 33% and from 83 % to 29 %, respectively). Using a quality-of-life questionnaire assessing subjective pain, sleep disturbance, morale, and social activities, and routine and strenuous physical activities, the patients indicated significant improvement in all major categories after venoplasty and stenting.

The presence of ulcer may influence the degree of pain and swelling apart from that caused by iliac obstruction. However, the reduction in pain and swelling was significant in both limbs with and without stasis ulcer. The prestenting level of pain was similar in both groups, suggesting the important contribution by iliac vein obstruction to pain and swelling in these patients. Interestingly, patients with recurrence of obstruction also had recurrence of symptoms after a symptom-free period.

These results clearly indicate a significant symptom relief after balloon venoplasty and stenting of iliofemoral vein obstruction, even in the presence of remaining reflux. The results also suggest that outflow obstruction is a more important and frequent component of chronic venous disease than previously realized.

CONCLUSIONS

Patients have now been followed for more than 6 years after stenting of the iliofemoral venous outflow. Ongoing evaluation indicates that venous balloon angioplasty and stenting is a safe, relatively simple, and efficient method for the treatment of iliofemoro-caval vein obstruction. It is now the preferred treatment over open surgery for this condition and may be offered to a larger group of patients. An immediate or late failure of the procedure does not preclude later open surgery to correct the obstruction. Additional interventions to correct any associated reflux may be performed subsequently when necessary.

Although a promising technique, some caveats must be stated. Selection of patients for treatment based on morphologic investigations is not satisfactory. Hemodynamic criteria are preferred. Further research should be encouraged to achieve better understanding of the nature of venous obstruction and to develop reliable methods to test hemodynamic significance. Monitoring of these patients should continue to acquire knowledge of the long-term effects of stents in the venous system and potential development of threatening in-stent restenosis.

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REFERENCES

1. **AbuRahma AF, Perkins SE, Wulu JT, Ng HK.** Iliofemoral deep vein thrombosis: Conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. *Ann Surg*. 2001;233:752-760.
2. **Kreienberg PB, Chang BB, Darling RC 3rd, et al.** Long-term results in patients treated with thrombolysis, thoracic inlet decompression, and subclavian vein stenting for Paget-Schroetter syndrome. *J Vasc Surg*. 2001;33(2 Suppl):S100-105.
3. **Oderich GS, Treiman GS, Schneider P, Bhirangi K.** Stent placement for treatment of central and peripheral venous obstruction: A long-term multi-institutional experience. *J Vasc Surg*. 2000;34:760-769.
4. **Funaki B, Szymski GX, Leef JA, Funaki AN, Lorenz J, Farrell T, et al.** Treatment of venous outflow stenoses in thigh grafts with Wallstents. *Am J Roentgenol.* 1999;172:1591-1596.
5. **Thorpe PE, Osse FJ, Dang HP.** Endovascular reconstruction for chronic iliac vein and inferior vena cava obstruction. In Gloviczki P, Yao SJT, eds. *The Handbook of Venous Disorders, Guideline of The American Venous Forum. 2nd* ed. London: Arnold; 2001:347-361.
6. **Glanz S, Gordon DH, Lipkowitz GS, Butt KMH, Hong J, Sclafani SJ.** Axillary and subclavian vein stenosis: Percutaneous angioplasty. *Radiology*. 1988;168:371-373.
7. **Phipp LH, Scott DJ, Kessel D, Robertson I.** Subclavian stents and stent-grafts: Cause of concern? *J Endovasc Surg.* 1999;6:223-226.
8. **Maintz D, Landwehr P, Gawenda M, Lackner K.** Failure of Wallstents in the subclavian vein due to stent damage. *Clin Imaging*. 2001;25:133-137.
9. **AbuRahma AF, Robinson PA.** Effort subclavian vein thrombosis: Evolution of management. *J Endovasc Ther*. 2000;7:302-308.
10. **Raju S, Neglén P, Carr-White PA, et al.** Ambulatory venous hypertension: Component analysis in 373 limbs. *Vasc Surg*. 1999;33:257-267.
11. **Neglén P, Raju S.** Detection of outflow obstruction in chronic venous insufficiency. *J Vasc Surg*. 1993;17:583-589.
12. **Labropoulos N, Volteas N, Leon M, et al.** The role of venous outflow obstruction in patients with chronic venous dysfunction. *Arch Surg*. 1997;132:46-51.
13. **Hurst DR, Forauer AR, Bloom JR,** et al. Diagnosis and endovascular treatment of iliocaval compression syndrome. *J Vasc Surg*. 2001;34:106-113.
14. **Negus D, Cockett FB.** Femoral vein pressures in post-phlebitic iliac vein obstruction. *Br J Surg*. 1967;54:522-525.
15. **Rigas A, Vomvoyannis A, Giannoulis K, et al.** Measurement of the femoral vein pressure in edema of the lower extremity. *J Cardiovasc Surg.* 1971;12:411-416.
16. **Albrechtsson U, Einarsson E, Eklöf B.** Femoral vein pressure measurements for evaluation of venous function in patients with postthrombotic iliac veins. *Cardiovasc Intervent Radiol*. 1981;4:43-50.
17. **Juhan C, Hartung O, Alimi Y, Barthélemy P, Valerio N, Portier F.** Treatment of nonmalignant obstructive lesions by stent placement: mid-term results. *Ann Vasc Surg*. 2001;15:227-232.
18. **Neglén P, Raju S.** Proximal lower extremity chronic venous outflow obstruction: Recognition and treatment. *Semin Vasc Surg.* 2002;15:57-64.
19. **Neglén P, Raju S.** Balloon dilation and stenting of chronic iliac vein obstruction: technical aspects and early clinical outcome. *J Endovasc Ther.* 2000;7:79-91.
20. **Neglén P, Raju, S.** Intravascular ultrasound scan evaluation of the obstructed vein. *J Vasc Surg.* 2002;35:694-700.
21. **Forauer AR, Gemmete JJ, Dasika NL, Cho KJ, Williams DM.** Intravascular ultrasound in the diagnosis and treatment of iliac vein compression (May-Thurner) Syndrome. *J Vasc Interv Radiol.* 2002;13:523-527.
22. **Neglén P, Berry MA. Raju S.** Endovascular surgery in the treatment of chronic primary and post-thrombotic iliac vein obstruction. *Eur J Vasc Endovasc Surg.* 2000;20:560-571.
23. **Raju S, McAllister S, Neglén P.** Recanalization of totally occluded iliac and adjacent venous segments. *J Vasc Surg.* 2002;36:903-911.
24. **Ouriel K, Kandarpa K, Schuerr DM, Hultquist M, Hodkinson G, Wallin B.** Prourokinase vs. urokinase for recanalization of peripheral occlusions, safety and efficacy: the PURPOSE Trial. *J Vasc Intervent Radiol.* 1999; 10:1083-1091.
25. **Raju S, Owen S Jr, Neglén P.** The clinical impact of iliac venous stents in the management of chronic venous insufficiency. *J Vasc Surg.* 2002; 35:8-15.
26 **Thorpe PE.** Endovascular therapy for chronic venous obstruction. In: Ballard JL, Bergan JJ, eds. *Chronic Venous Insufficiency.* New York: Springer;1999:179-219.
27. **Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH.** Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology*. 1999;211:39-49.
28. **Nazarian GK, Austin WR, Wegryn SA, et al.** Venous recanalization by metallic stents after failure of balloon angioplasty or surgery: four-year experience. *Cardiovasc Intervent Radiol.* 1996;19:227-233.
29. **O'Sullivan GJ, Semba CP, Bittner CA, et al.** Endovascular management of iliac vein compression (May-Thurner) syndrome. *JVIR*. 2000;11:823-836.
30. **Binkert CA, Schoch E, Stuckmann G, et al.** Treatment of pelvic venous spur (May-Thurner syndrome) with self-expanding metallic endoprostheses. *Cardiovasc Intervent Radiol.* 1998;21:22-26.
31. **Nazarian GK, Bjarnason H, Dietz CA Jr, et al.** Iliofemoral venous stenosis: Effectiveness of treatment with metallic endovascular stents. *Radiology*. 1996;200:193-199.
32. **Lamont JP, Pearl GJ, Patetsios P, Warner MT, et al.** Prospective evaluation of endoluminal venous stents in the treatment of the May-Thurner syndrome. *Ann Vasc Surg.* 2002;16:61-64.
33. **Launois R, Reboul-Marty J, Henry B.** Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). *Qual Life Res.* 1996;5:539-554.
34. **Scott J, Huskisson EC.** Graphic presentation of pain. *Pain*. 1976;2:175-184.

The pharmacological treatment at the UIP, San Diego: the American recognition

UIP World Congress CHAPTER MEETING SAN DIEGO03

UIP SAN DIEGO, USA
August 27-31, 2003

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INTRODUCTION

For the first time ever, the organization of the world congress of the Union Internationale de Phlebology (UIP) in conjunction with the American College of Phlebology took place in the USA: San Diego, California, from August 27th to August 31st, 2003. This congress is the major event in this medical field and demonstrates the evolving approach of American specialists to venous disease.

Chronic venous insufficiency* (CVI), at onset, classically presents with the symptoms of leg heaviness, pain, cramps, itchiness, sensation of swelling, and the sign of edema. A recent Polish epidemiological survey put the prevalence of these symptoms at 80% to 90% and signs, such as edema, at about 70% in CVI patients.[1] These symptoms are known to be due to venous hypertension caused by venous abnormalities (functional or structural) and can exist at any stage of the disease. However, new data acknowledged in San Diego has also linked these symptoms and signs to the inflammatory cascade following initial leukocyte adhesion to the endothelium of the vein wall in early CVI.

A number of drugs are put forward as effective treatment for the symptoms and signs of CVI. However, over the past few years international experts have reviewed the evidence for the use of such drugs and produced guidelines for the treatment of CVI. In 1996, initial guidelines from American physicians gave little scope to pharmacological treatment, whereas, by 2001, in the second edition of guidelines by American experts and also in San Diego, an entire chapter was devoted to pharmacological treatment, and within that, a major role assigned to the treatment by daflon 500 mg.

They recognized that, of all the phlebotropic drugs, daflon 500 mg, or micronized purified flavonoid fraction (MPFF), consisting of 90% micronized diosmin and 10 % flavonoids expressed as hesperidin, is the only phlebotropic drug effective at any stage of CVI. This efficacy is due to its comprehensive mode of action which acts at the heart of the disease, namely the inhibition of leukocyte adhesion. Coupled with this mode of action daflon 500 mg is unique in that it is micronized. The process of micronization has been demonstrated through several clinical studies to accelerate daflon 500 mg's onset of action and to improve its efficacy in reducing inflammation and treating clinical symptoms and signs (such as edema).

Indeed, this clinical efficacy has recently been given recognition by the guidelines of the American Venous Forum in the treatment of CVI, and has been one of the highlights of the UIP congress.

** In this paper, CVI includes symptoms usually attributable to the disease and signs (C1 to C6) described in the clinical CEAP classification.*

A unique mode of action at the very heart of the disease reported at the UIP international congress, San Diego

The pathophysiology of CVI and its complications are well-documented. In fact, from the initial symptoms and signs of leg heaviness, cramps, pain, swelling, and edema, to the most severe stage of CVI, venous leg ulcers, the cause remains the same throughout. For a long while now researchers have known that, at the level of the microcirculation, the leukocyte-endothelial interaction is an integral step in the development of venous leg ulcers. However, at the recent International Congress of the "Union Internationale de Phlébologie" (UIP), San Diego, USA, Prof Nicolaides presented results showing that leukocyte adhesion to the endothelium and subsequent damage not only plays a central role in venous leg ulcer development but also occurs at the level of the venous wall in early CVI patients. Therefore, the CVI symptoms and signs (including leg edema) that patients often complain of in early disease, through to advanced disease (venous leg ulcers), can all be attributed to the inflammatory cascade that occurs as a result of leukocyte adhesion to the endothelium.

For optimal efficacy in treating the symptoms and signs at any stage of CVI and its most severe complication, venous leg ulcers, a drug has to act at the very heart of the disease (ie, the leukocyte-endothelium interaction). The only phlebotrope to have demonstrated a comprehensive action at the heart of the disease is daflon 500 mg. This evidence comes from several studies that clearly show daflon 500 mg inhibits leukocyte adhesion and subsequent activation, decreases capillary hyperpermeability, and reduces the indices of inflammation.[2] Daflon 500 mg also increases venous tone and improves lymphatic drainage, thereby offering comprehensive protection of the microcirculation and treating all the other aspects of chronic venous insufficiency.

Daflon 500 mg's clinical efficacy in venous leg ulcers has been comprehensively demonstrated by several randomized controlled studies.[3,4,5] Moreover, the results from 5 individual studies have recently been analysed in collective form as the "meta-analysis of the venous leg ulcer healing in prospective randomized studies using Micronized Purified Flavonoid Fraction and presented in San Diego"for the first time by Prof P. Gloviczki[6] (USA). In 723 patients with venous leg ulcers, the addition of daflon 500 mg to conventional therapy increases the number of complete healed venous leg ulcers after 6 months. This occurs with a significantly faster ulcer healing rate (P =0.003) and an larger decrease in ulcer area ($P \leq 0.01$).

Micronization offers improved efficacy in CVI

By acting at the heart of CVI, daflon 500 mg is effective at all stages of disease. However, flavonoids have a poor gastrointestinal absorption. This is overcome, in daflon 500 mg's case, by the process of micronization: a high-tech process which reduces daflon 500 mg's mean active particle size by 35 µm with a subsequent faster and better absorption in humans

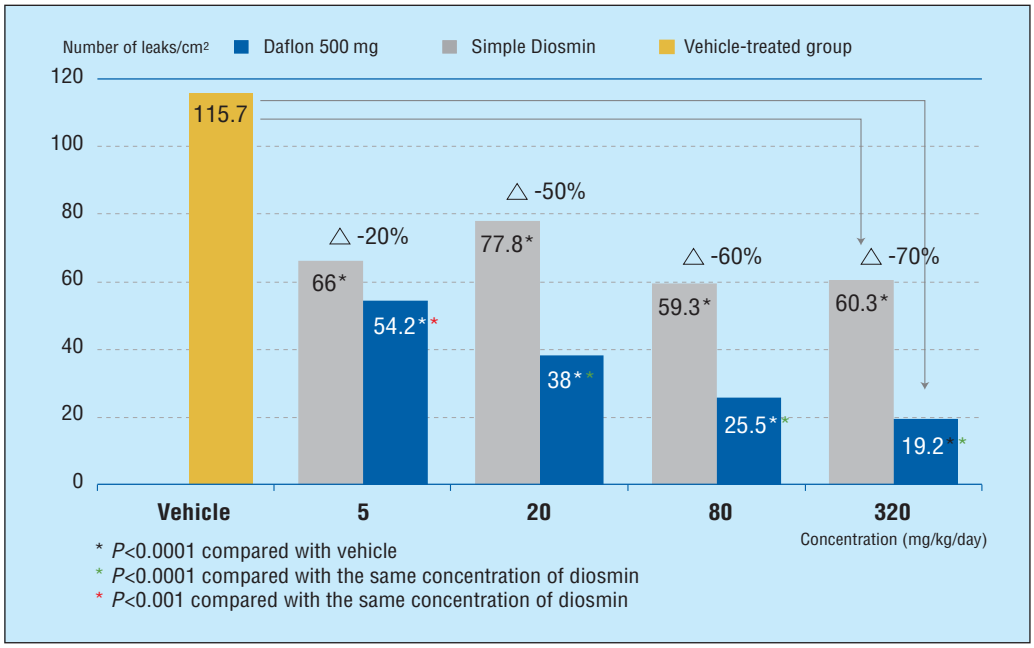

Figure 1. Daflon 500 mg significantly improves capillary hyperpermeability more than simple diosmin in the damaged microcirculation (adapted from ref 8).

with improved bioavailability. This has been conclusively demonstrated in a single-center, randomized, double-blind, crossover study in 12 healthy male volunteers. Immediately from 24 hours postingestion, daflon 500 mg's absorption (measured by urinary radioactivity) is almost twice that of simple diosmins (P<0.0001). This improved absorption of daflon 500 mg over simple diosmins is maintained after 2 weeks of treatment (57.9% vs 32.7%; P<0.0004).[7] Therefore, evidence that, thanks to micronization, daflon 500 mg's absorption is almost doubled, leading to significantly improved clinical efficacy.

Further proof of the benefit that micronization gives daflon 500 mg comes from a study performed by Prof Bouskela and her team.[8] Over a 10-day period, they looked at the influence of daflon 500 mg and simple diosmin, at 4 different doses, on capillary permeability in an inflammatory model (induced by ischemia/reperfusion) in the hamster cheek pouch. In addition, one group of hamsters was treated with vehicle (10 % lactose solution) as the control group. Capillary hyperpermeability was assessed by counting the number of leakage sites at a microscopic level in the cheek pouch after 30 minutes of local ischemia. At each concentration daflon 500 mg inhibited hypermeability significantly better than simple diosmin and in a dose-dependent fashion. Simple diosmin inhibited hyperpermeability but not in a dose-dependent fashion *(Figure 1)*.

As a consequence: daflon 500 mg's unique efficacy in edema at any stage of the disease

Micronization therefore provides daflon 500 mg with this comprehensive mode of action and a unique efficacy in CVI at the level of the microcirculation. However, a phlebotrope must be demonstrated to be clinically effective in CVI patients for it to be of any use. Patients with CVI are seeking relief of their debilitating symptoms and signs. In fact, recent guidelines have recommended the use of phlebotropic agents in the treatment of edema and CVI symptoms at any stage of the disease and, in this regard, daflon 500 mg's efficacy is unique.[9] Indeed, daflon 500 mg is the only phlebotropic drug to have demonstrated its effectiveness in the most severe stage of the disease: leg ulcer (see page 213).

In addition, recent recognition of daflon's efficacy in the treatment of edema and its associated symptoms has come from the world-renowned journal, *Drugs*.[1] No less than 14 world experts in the field of phlebology reviewed the use of daflon 500 mg in CVI, venous leg ulcers, and hemorrhoidal disease. In their opinion the recommendations for daflon 500 mg's use in CVI in symptoms and edema is supported by its extensive clinical trials:

In the "Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids (RELIEF)" study, 5052 symptomatic patients, with CVI (CEAP stages C0s to C4), underwent a 6-month study with 2-monthly assessments which included CVI symptoms and edema (leg circumference measured by leg-o-meter), and venous reflux.[10] Each patient took daflon 500 mg, 2 tablets daily, and was grouped into either "with venous reflux" or "without venous reflux". At the end of 6 months there was a significant reduction in edema in both groups from baseline (P=0.0001) *(Figure 2)* and symptoms (including pain) were improved also (P=0.0001).

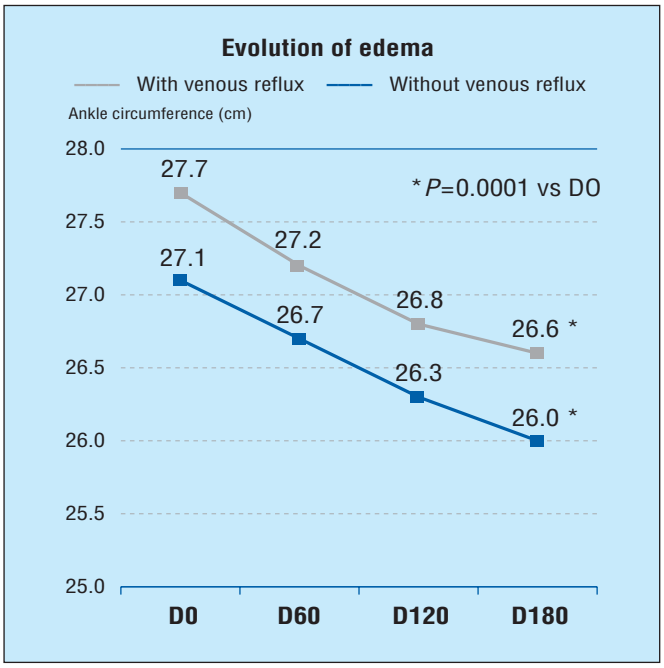

Figure 2. Evolution of edema in RELIEF study after 6 months of daflon 500 mg treatment (adapted from ref 10).

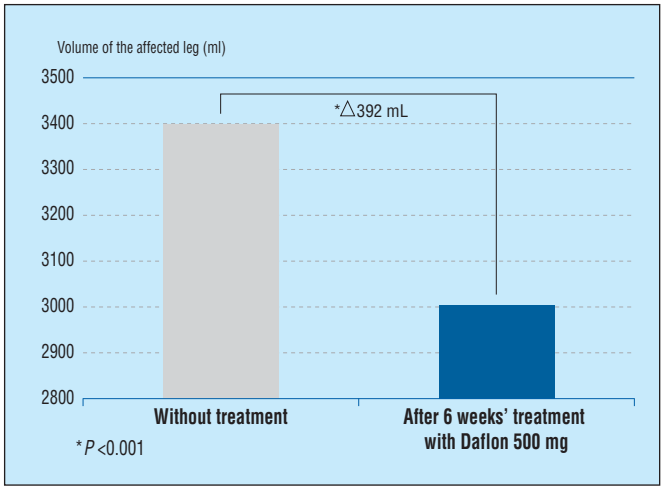

Figure 3. Daflon 500 mg significantly reduces leg edema associated with varicose veins (adapted from ref 11).

Another study looked specifically at the reduction of edema associated with varicose veins. Over 6 weeks, patients took daflon 500 mg, 2 tablets/daily, and were assessed 2-weekly for symptoms and edema (by optoelectronic volumetry). At the end of 6 weeks treatment with daflon 500 mg, there was a significant decrease in edema by 392mL ($P<0.001$) *(Figure 3)*. In addition, patient symptoms of pain, sensation of swelling, and cramps were significantly improved (P<0.001).[7]

In addition, daflon 500 mg has also demonstrated an early onset and prolongation of efficacy in the reduction of edema: in a multicenter, randomized, double-blind placebo-controlled study over 8 weeks, 160 patients were randomized to either receive daflon 500 mg (2 tablets/daily) or placebo.[2] Assessment of symptoms and edema (by calf and ankle measurement) took place at inclusion, 4, and 8 weeks. From as early as 4 weeks daflon 500 mg had improved leg edema ($P<0.001$) and sensation of leg swelling ($P<0.001$). Both of these factors were further improved after 8 weeks ($P<0.001$) there by demonstrating daflon 500 mg's prolonged efficacy in the reduction of leg edema *(Figure 4)*.

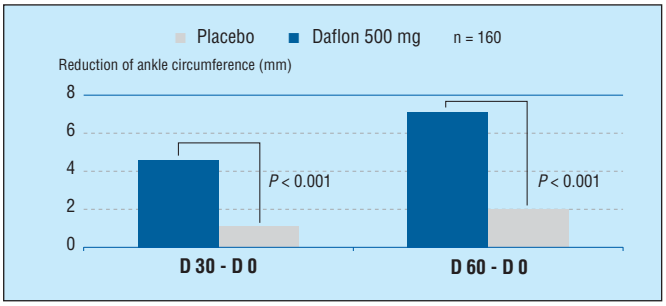

Figure 4. Daflon 500 mg's early onset of efficacy and prolonged benefits in edema (adapted from ref 12).

CONCLUSION

Through its rigorous clinical studies daflon 500 mg is now recognized, by International Guidelines in CVI, which were confirmed by the Americans, in San Diego as the most effective phlebotropic drug. This is due to its action at the very heart of the disease, namely its unique inhibition of leukocyte adhesion, which has now been shown to be at the cause of all symptoms and signs (including edema) from the early to the most severe stages of the disease. A consequence of leukocyte adhesion is the inflammatory cascade (including capillary hyperpermeability). Daflon 500 mg's unique micronized form has demonstrated a significantly better inhibition of capillary hyperpermeability compared to simple diosmin. Therefore, in any CVI patient complaining of symptoms and signs (including venous leg edema) from the disease onset to the most severe stage, daflon 500 mg, 2 tablets daily, is the reference treatment for immediate and sustained reduction of edema.

REFERENCES

1. **Jawien A.** Prevalence of chronic venous insufficiency (CVI) in men and women of Poland: multicenter cross-sectional study of 40 095 patients. *Angiology.* 2003;54(suppl1): 519-532.
2. **Lyseng-Williamson KA, Perry CM.** Micronised purifed flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs.* 2003;61:71-100.
3. **Glinski W, Chodynicka B, Roszkiewicz J, et al.** The beneficial augmentative effect of micronized purified flavonoid fraction (MPFF) on the healing of leg ulcers: a multicenter controlled study. *Phlebology.* 1999;14:151-157.
4. **Roztočil K, Štvrtinová V, Strejček J.** Efficacy of a 6-month treatment with daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. *Int Angiol.* 2003;22:24-31.
5. **Guilhou JJ, Dereure O, Marzin L, et al.** Efficacy of daflon 500 mg in venous leg ulcer healing : a double-blind randomized, controlled versus placebo trial in 107 patients. *Angiology.* 1997;48:77-85.
6. **Ramelet AA, Coleridge-Smith PD, Gloviczki P.** A meta-analysis of venous leg ulcer healing in prospective randomized studies using micronised purified flavonoid fraction. *Abstract presented at the International Congress of the UIP, San Diego, USA.* August 27-31, 2003.
7. **Garner RC, Garner JV, Gregory S, Whattam M, Calam A, Leong D.** Comparison of the absorption of micronized (daflon 500 mg) and non-micronized ^{14}C-diosmin tablets after oral administration to healthy volunteers by accelerator mass spectrometry and liquid scintillation counting. *J Pharm Sci.* 2002;91:32-40.
8. **Bouskela E, Cyrino FZGA, Lerond L.** Micronization enhances the protective effect of purified flavonoid fraction on postischemic microvascular injury in the hamster cheek pouch. *Int Angiol.* 2001;20(suppl 1):19
9. **Coleridge-Smith P.** The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders. Guidelines of the American Venous Forum.* 2 ed. London: Arnold; 2001:309-321.
10. **Jantet G, and the RELIEF Study Group.** Chronic venous insufficiency: worldwide results of the RELIEF study. *Angiology.* 2002; 53:245-256.
11. **Blume J, Langenbahn H, de Champvallins M.** Quantification of edema using the volometer technique: therapeutic application of daflon 500 mg in chronic venous insufficiency.*Phlebology.* 1992; 7(suppl 2):37-40.
12. **Gilly R, Pillion G, Frileux C.** Evaluation of a new venoactive micronized flavonoid fraction (S 5682) in symptomatic disturbances of the venolymphatic circulation of the lower limb: a double-blind, placebo-controlled study. *Phlebology.* 1994;9:67-70.

Epidemiology of pulmonary embolism in Japan

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INTRODUCTION

Pulmonary thromboembolism (PTE) is a well-known fatal disease. It is estimated that the annual incidence of pulmonary embolism ranges from 20.8 to 210 per 100 000.[1-3] In the USA, approximately 10 % of patients die within 1 hour after a PTE.[3] In Japan, it is thought that the incidence of PTE is much lower than that of the USA and Europe.[4] However, several studies show that the incidence of PTE in Japan is increasing.[5-7] The increased incidence of PTE is thought to be due to not only the progress of diagnostic techniques, but also westernization of the Japanese lifestyle and greater life expectancy.[8] As the importance of PTE in Japan has been recognized, air travel-related thrombosis (also called "economy class syndrome") has come to the attention of physicians and lay people in Japan.

PTE research in Japan is increasing. This study was undertaken using Japanese data to determine the current epidemiology of PTE in Japan.

Incidence of acute PTE

The rate of PTE detected from autopsy data ranges from 1.38 to 24%. [5,6,9,10]*(Table I)* These studies showed that the incidence rate increased gradually, 2.3 times from 1958 to 1978, and 3.0 times from 1965 to 1985.[5,6] Compared with Western autopsy studies, the frequency of PTE in Japan is 1/3 to 1/10 of that in western countries.[11-14] Also, Mieno's study showed that massive PTE, which made up 25.4 % of all PTE over 22 years, had a rate which increased over the years.[6]

Table I.
The Incidence of PTE at autopsy.

Study	Duration	Number of Autopsy	The rate of PTE
Nakano et al[9]	1980	225	24%
Hasegawa et al[15]	1958-78	403 533	1.38%
Mieno et al[6]	1965-1986	559 826	1.52%
Yutani et al[10]	1977-1984	1 700	11%

According to death certificates, the number of deaths due to PTE increased remarkably from less than 100 in the 1960s to about 1700 patients in 2000.[15]

In Japan, there are few reports about the incidence of PTE. *(Table II)*. Kumasaka

Study	Duration	Number of cases	Major information source
Kumasaka et al[4]	2 months in 1996	237	Touhoku area
Nakamura et al[16]	1994-1997	533	JASPER
Ohgi et al[19]	1999	123	The Japanese Society of Phlebology

Table II. Registry of PTE in Japan.

estimated that there are 3492 patients with PTE (95% confidence interval 3280-3703) per year (2.91 per 100000) according to the questionnaire from 2341 hospitals in Touhoku area.[4] The estimation of PTE incidence in Japan from clinical diagnosis is at least 10 times less than that in the USA.

In the multicenter registry of PTE in Japan,[16,17] 18% of patients had chronic PTE. However, in the USA only, 0.1% to 1% of patients progressed from acute pulmonary embolic events to chronic PTE.[18] Nakamura estimated that the difference of incidence in acute and chronic PTE between Japan and the USA may come from the characteristics of Japanese PTE, or an underestimate of the number of acute pulmonary embolism.[17]

Deep vein thrombosis (DVT) is the major cause of PTE – causing 8.2% to 24% of cases.[16,19] Hoshino reported that 54% of DVT with PTE was asymptomatic.[20] This may mean that a large number of PTE cases are not diagnosed in Japan. There are few reports of the frequency of DVT in Japan; however, the incidence of DVT after general surgery, gynecologic surgery, and orthopedic surgery was as high as the incidence of DVT in Western reports.[21]

In acute PTE, the female rate tends to be higher than the male rate. The rate of chronic PTE is higher than that of acute PTE. *(Table III)* In distribution of PTE by age, the peak incidence of both acute and chronic PTE was 60 years. On the other hand, *(Figure 1)* the incidence of acute PTE increases with age in the USA.[22] In Japan, quite a few patients over 70 with PTE may not be diagnosed.

Study	F/M ratio of acute PTE	F/M ratio of chronic PTE
Kumasaka et al[4]	145/92 (1.58)	
Mieno et al[6]	1142/1018 (1.12)	
Nakamura et al[16]	187/122 (1.5)	46/22
Ohgi et al[19]	57/63 (0.9)	8/5
Kunieda et al[24]	76/56 (1.36)	37/26
Total	1607/1351(1.19)	91/53 (1.72)

Table III. Male / female ratio of PTE in Japan. Studies by Kumasaka and Mieno may be included the cases of chronic PTE.

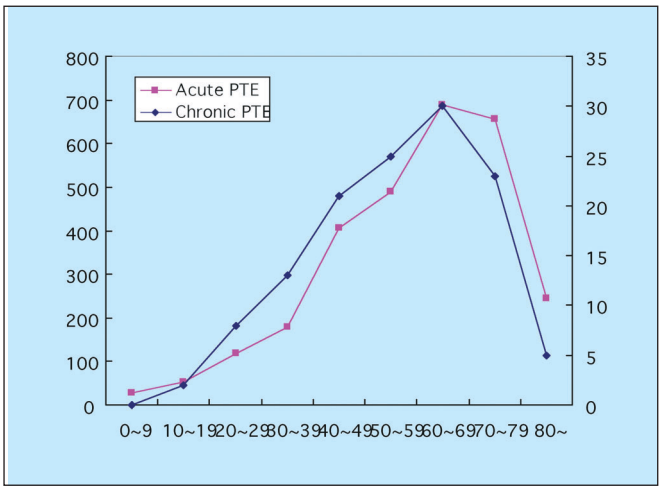

Figure 1. The incidence of acute and chronic PTE with age. Data from Nakamura et al[16] Ohgi et al[19] and Kunieda et al.[24]

PTE positions: 70% of PTE were detected in the right lung, especially in the right lower lobe (33%).[9]

Symptoms of PTE

The most frequent symptoms of PTE is dyspnea, chest pain, palpitation, cardiogenic shock, and syncope *(Table IV)*. Comparing to the report from the USA,[3] the rate of the critical symptoms of Japanese PTE such as syncope and cardiogenic shock is high. This result may show many mild PTE is not diagnosed. Concerning the place of onset of PTE, it is a frequent in inpatients as in outpatients. Due to sudden death, it may be difficult to diagnose PTE in outpatients.

Symptom	Acute PTE (%)	Chronic PTE (%)
Dyspnea	65.1	82.7
Chest pain	45.0	23.5
Palpitation	19.6	33.3
Syncope	19.6	7.7
Cardiogenic shock	33.8	15.4

Table IV. Symptoms of PTE. Data from Nakamura et al[16] and Ohgi et al.[19]

Risk factors of PTE and detection of the origin of embolus

The major risk factors in acute PTE are recent major operations, recent major trauma, malignant tumor, and prolonged immobilization. Thrombophilia was found in only 6%. The most frequent thrombophilia parallels a positive lupus anticoagulant. On the other hand, the major risk factor of chronic PTE is thrombophilia *(Table V)*. The DVT

registry showed that 9.2% of all DVTs are associated with thrombophilia. The major thrombophilia is protein C, S deficiency and positive lupus anticoagulant.[20]

The detection rate of the origin of embolus (DVT) in PTE patients is from 33% to 71%.[16,19] This difference of detection rate of DVT may depend on whether cardiovascular physicians or internists do the research. The origin of DVT was the femoral vein in 40% of PTE, iliac vein in 5%, and calf vein in 40%.[19] The cause of the low rate of embolus from the iliac vein may be that the embolus has already moved to the pulmonary artery. It is remarkable that in Japan, one of the major embolus origins of PTE is a calf vein thrombus.

Risk factor	Acute PTE (%)	Chronic PTE (%)
Recent major operation	34.1	6.2
Recent major trauma	8.1	0
Malignant tumor	22.6	7.4
Prolonged immobilization	22.9	4.9
Thrombophilia	5.7	17.3

Table V. Risk factors for PTE.
Data from Nakamura et al[16] and Ohgi et al.[19]

PTE diagnostic strategy

The detection of PTE from symptoms and risk factors is important in the diagnosis PTE. Generally, the first tests performed is blood gas sampling, chest X ray, electrocardiogram, and echocardiogram.

The major diagnostic method is lung scan in acute PTE and pulmonary angiography in chronic PTE. The lung scan is used to screen for PTE. Pulmonary angiography is performed to confirm the PTE diagnosis because of the low specificity of PTE diagnosis by the lung scan. Contrast-assisted computed tomography (CT) was used to diagnose PTE together

Diagnostic method	Acute PTE (%)	Chronic PTE (%)
Lung scan	73.3	59.2
Pulmonary angiography	46.9	63.0
Contrast computed tomography	20.2	30.9
Magnetic resonance imaging	2.0	8.6
Autopsy	4.2	4.9

Table VI. Diagnostic workup.
Data from Nakamura et al,[16] Nakamura,[25] and Ohgi et al.[19]

with lung scan and pulmonary angiography. The frequency of using CT for PTE diagnosis is increasing remarkably.[25] *(Table VI)* One reason is that there are quite a few hospitals without lung scan or cine angiography equipment that can confirm a diagnosis of PTE. The another reason is that the remarkable advance of CT and magnetic resonance imaging assure more accurate diagnosis of PTE.[23] Clearly, the progress of diagnostic equipment plays a role in the increase of PTE in Japan.

The treatment of PTE

The treatment of PTE is to save lives, improve symptoms, and prevent further PTE. According to Japanese guidelines for acute PTE, the severity of acute PTE has been classified into 3 grades.[26] Anticoagulation therapy is recommended for all grades of PTE. Thrombolysis, interventional therapy, and surgical thrombectomy are recommended for more severe PTE. The indication of surgical thrombectomy is the unimproved PTE with medication or severe PTE where medication is contraindicated. A temporary or permanent IVC filter is used to prevent PTE from recurring. As interventional therapy, aspiration thrombectomy, fragmentation thrombectomy, and rheolytic thrombectomy are performed. The one advantage of interventional therapy is that it can be performed immediately. The temporary and permanent IVC filter is used for prevention of recurrent PTE. A

Treatment	Acute PTE (%)	Chronic PTE (%)
Anticoaglant therapy	74.7	77.8
Thrombolysis	57.3	40.7
Catheter interventional therapy	6.6	3.7
Surgical thrombectomy	2.9	14.8
Inferior vena caval filter	22.3	32.1

Table VII. the treatment of acute and chronic PTE
Data from Nakamura et al,[16] Nakamura,[25] and Ohgi et al.[19]

combination of anticoagulant and thrombolytic therapy was used on 74.7% of all acute PTE patients. Of acute PTE, 6.6% was treated by catheter interventional therapy; surgical thrombectomy was performed on only 2.9% of acute cases. The temporary and permanent IVC filter is used for prevention of recurrent PTE. An IVC filter was put in for 22.3% of acute embolic patients. Thromboendoarterectomy is used for severe chronic PTE (Table VII). Therefore, the rate of surgical therapy in the chronic PTE group is higher than in acute PTE. Chronic PTE cases with recurrent PTE underwent thrombolytic therapy.

Mortality of PTE

The overall hospital inpatient mortality rate of acute PTE was 14%. The mortality of PTE patients with cardiogenic shock is high compared with that of PTE patients without cardiogenic shock.[16] The mortality rate of PTE patients getting thrombolytic therapy was 20%, and the mortality

rate using only anticoagulation was 50 %, a significantly higher mortality.[16] In chronic PTE with massive embolus, this average life expectancy is 6.6 years.[24] The average life expectancy of patients with chronic PTE and cardiac index less than 2.2 is 4.6 years.[24]

CONCLUSION:

Clearly, from the analysis of PTE incidence from previous reports, further detailed research is needed. The incidence rate is increasing. Accurate diagnosis contributes to accurate knowledge and treatment of PTE.

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REFERENCES

1. **Dalen JE, Alpert JS**. Natural history of pulmonary embolism. *Prog Cardiovasc Dis*. 1975;17:257-270.
2. **Gillum RF**. Pulmonary embolism and thrombophlebitis in the United States, 1970-1985. *Am Heart J*. 1987;114:1262-1264.
3. **Anderson FA Jr, Wheeler HB, Goldberg RJ, et al**. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study. *Arch Intern Med*.1991;151:933-938.
4. **Kumasaka N, Sakuma M, Shirato K**. Incidence of pulmonary thromboembolism in Japan. *Japn Circ J*. 1999;63:439-441.
5. **Hasegawa H, Nagata H, Yamaguchi M**. Statistical Status of Pulmonary Embolism in Japan (II). *Jpn J Thorac Cardiovasc Surg*. 1980;8:677-681.
6. **Mieno T, Kitamura S**. Incidence of pulmonary thromboembolism in Japan. *Jpn J Thorac Dis*. 1989;37:323-327.
7. **Sakuma M, Shirato K**. Epidemiology of pulmonary embolism. *Jpn J Cardiol*. 2001;49:372-377.
8. **Nakano T, Nakamura M, Fujioka H**. Venous thrombus and pulmonary thromboembolism. *Jpn J Phlebol*. 1997;8:211-228.
9. **Nakano T, Itou S, Takezawa H**. The epidemiology of pulmonary embolism. *Nippon Iji Sinpou*. 1980;2949:43-447.
10. **Yutani C, Imakita M, Ueda H, et al**. Pulmonary embolism. *Jpn Angiol*. 1993;33:339-406.
11. **Freiman DG, Suyemoto J, Wessler S**. Frequence of pulmonary thromboembolism in man. *N Engl J Med*. 1965;272:1278.
12. **Bergqvist P, Lindblad B**. A 30-years survey of pulmonary embolism verified at autopsy: an analysis of 1274 surgical patients. *Br J Surg*. 1985;72:105-108.
13. **Makelvei PA**. Autopsy evidence of pulmonary thromboembolism. *Med J Aust*. 1994;160:127-128.
14. **Stein PD, Henry JW**. Prevalence of acute pulmonary embolism among patients in a general hospital at autopsy. *Chest*. 1995;108:978-981.
15. **Sakuma S, Takahashi T, Kitamuki T**. Mortality from pulmonary embolism in Japan. *Jpn Angiol*. 2001;41:225-229.
16. **Nakamura M, Fujioka H, Yamada N et al**. Clinical Characteristics of Acute Pulmonary Thromboembolism in Japan: Results of Multicenter Registry in the Japanese Society of Pulmonary Embolism Research. *Clin Cardiol*. 20014;24:132-138.
17. **Nakamura M, Okada O, Sakuma M, et al**. Incidence and clinical characteristics of Chronic Pulmonary Thromboembolism in Japan Compared with acute Pulmonary Thromboembolism – Results of a Multicenter Registry of the Japanese Society of Pulmonary Embolism Research -. *Circ J*. 2002;66:257-260.
18. **Moser KM, Auger WR, Fedullo PF**. Chronic major-vessel thromboembolic pulmonary hypertension. *Circulation*. 1990;81:1735-1743.
19. **Ohgi S, Hirai M,Ohta T et al**. Pulmonary embolism. *Jpn J Phlebol*. 2000;11:341-346.
20. **Hoshino S, Satokawa H**. Deep vein thrombosis. *Jpn J Phlebol*. 1997;8:307-311.
21. **Matumoto K, Hirose H, Hayashi M**. Clinical studies on postoperative deep venous thrombosis. *Jpn J Phlebol*. 1994;5:163-70.
22. **Silverstein MD, Heit JA, Mohr DN et al**. Trends in the incidence of deep vein thrombosis and pulmonary embolism. *Arch Intern Med*. 1998;158:585-593.
23. **Indik JH, Alpert JS**. Detection of pulmonary embolism by D-dimer assay, spiral computed tomography, and magnetic resonance imaging. Prog. *Cardiovasc Dis*. 2000;42:261-272.
24. **Kunieda T**. Pulmonary Arterial Thromboembolism: present status of epdemiology in Japan. *Jpn J Thorac Dis*. 1997;45:325-332.
25. **Nakamura M**. The status of diagnosis and treatment of acute and chronic pulmonary thromboembolism. *Jpn Therapeutic research*. 1998;9:119-122.
26. **Nakano T et al**. The guideline of treatment for pulmonary hypertension. *Jpn Circ J*. 2001;65:1077-119.

Current use of microsurgery in lymphedema

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SUMMARY

The authors, after a short introduction on historical role of surgery and microsurgery in lymphatic vessel pathology, report their own 25-year experience in lymphatic microsurgery and lymphatic-venous-lymphatic anastomoses.

In particular, the authors describe the derivative and reconstructive microsurgical techniques, pointing out the preoperative diagnostic, the indications and the obtained results concerning 798 patients affected by primary and secondary limb lymphedema.

Keywords:
Lymph - Lymphology - Lymphedema - Microsurgery - Lymphatic-Venous Anastomoses - Lymphatic-venous - Lymphatic Anastomoses - Lymph Vessels - Lymphoscintigraphy.

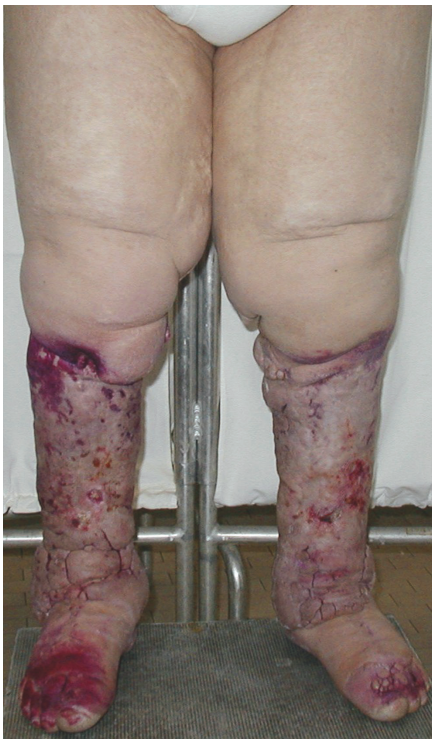


Figure 1. Long-term-results (30 years), after radical Charles's excisional operation.

INTRODUCTION

Lymphedema, refractory to nonoperative methods, may be managed by surgical treatment. Indications[1] include insufficient lymphedema reduction by well-performed medical and physical therapy[2-4] (less than 50%), recurrent episodes of lymphangitis,[5] intractable pain, worsening limb function, and patients dissatisfied with the results obtained by nonoperative methods and willing to proceed with surgical options.

In 1908, Handley described his technique of "lymphangioplasty," running silk threads subcutaneously to provide a conduit for lymphatic drainage.[6] The procedure was abandoned, as postoperative infection and spontaneous extrusion of the implanted foreign material commonly occurred.

Excisional operations, such as Charles' *(Figure 1)* total resection of subcutaneous tissue,[7] Thompson's subfascial drainage of a scarified skin flap,[8] and Servelle's total surface lymphangectomy,[9] aimed at removing excess tissue to decrease the volume of the extremity. However, prolonged hospitalization, poor wound healing, long surgical scars, sensory nerve loss, residual edema of the foot and ankle, and poor cosmetic results can be important problems to use these highly debulking operations only in the most severe and advanced cases of elephantiasis, not responding to conservative measures.

In 1962, Cockett and Goodwin[10] described the anastomosis of a dilated lumbar lymphatic to the spermatic vein to treat a case of chyluria.

Subsequent development of microsurgical techniques has enabled lymphatic-venous anastomosis to emerge as a potential treatment of lymphedema.

EXPERIMENTAL AND CLINICAL STUDIES

In 1977, O'Brien and coworkers[11] described microlymphatic surgery in the treatment of secondary obstructive lymphedema. They preferred three or more lymphaticovenous anastomoses at, or above, the elbow. They observed that the incidence of postoperative cellulitis was significantly less. The microlymphatic techniques were applicable to both upper and lower limbs, and perhaps could be extended to localized cases of obstructive lymphedema following trauma and congenital constriction bands. They underlined that considerable experience in microvascular surgery is required for doing this type of work. The results of microlymphatic surgery in obstructive secondary lymphedema were encouraging, even though the authors remarked that a long-term evaluation of the clinical outcome was required before judging the potential of those techniques.

In 1981, Degni[12] introduced an original technique of lymphatic-venous anastomosis in cases of lymphedema of the limbs. The procedure was easy and could be indicated for both the upper and lower limbs, and also for thoracic duct or any blocked lymphatic vessels of the abdomen. He used this technique to treat lymphedemas due to surgical resection of benign tumours (lipomas of the thigh) or plastic surgery (pendulous abdomen, plastic surgery of the thigh), orthopedic operations on the knee, and after stripping of varicose veins. The purpose of the procedure was to divert the lymph to the vein in cases of blocked lymphatic vessels, particularly when lymphographic findings demonstrate good function and permeability of lymphatic vessels. A longitudinally divided needle was used to introduce the lymphatic trunk into the vein, pulling the lymphatic into the venous lumen and fixing the lymphatic to the upper venous wall with one suture.

Clodius,[13] in 1982, observed that microsurgery for primary and secondary lymphedema, consisting of shunts between lymphatic vessels and veins, was a well-established surgical technique. The problems consisted of the irreversible changes in the peripheral lymphatic system and in the connective tissues, as well as the obliteration of the deep lymphatics, best suited for lymphaticovenous anastomoses. Therefore, lymphaticovenous shunts should be performed precociously before fibrotic tissural changes appear.

Huang and coworkers,[14] in 1985, described their experience of 91 cases of lymphedema treated by microlymphaticovenous anastomosis, with very satisfactory immediate and long-term results in 79.1 percent. The data they obtained suggested that the quality of results is proportional to the number of anastomoses.

In 1987, Krylov and coworkers[15] reported an experience of 510 cases of primary and secondary lymphedema in upper and lower extremities with two thirds of primary lymphedema cases among them. Most favorable results were obtained in secondary obstructive lymphedema cases (total 81.2%) due to a condition of hypertension in lymphatic vessels that contributes to better functioning of the lymphaticovenous anastomoses.

In 1987, Zhu and coworkers[16] reported a clinical experience of 185 limbs with lymphedema treated by lymphaticovenous anastomosis with excellent results achieved in 72.9% of the cases.

Al Assal, Cordeiro and coworkers,[17] in 1988, reported experimental studies in dogs using a new technique of microlymphovenous anastomosis to improve long-term patency rates and clinical results in lymphedema therapy. Technical points, such as an oval window on the wall of the vein and a few sutures piercing only two lymphatic layers, adventitia and media, outside the lumen for successful results were emphasized. Three methods for assessment of patency of anastomoses were used: (1) observation with operating microscope of dye transit across the anastomotic site; (2) lymphography, and (3) histopathologic examination. Based on the encouraging results obtained with this technique, the authors suggested that end-to-side anastomosis might be the technique of choice.

In 1988, Ho and coworkers[18] described the use of microlymphatic bypass for the treatment of obstructive secondary lymphedema in the lower and upper limbs. They underlined the importance of preoperative assessment by lymphangiography and lymphoscintigraphy to assess suitability for the procedure. Postoperatively, patent lymph collectors were demonstrated by lymphoscintigraphy. Moreover, they were convinced of the fact that microlymphatic bypass should be carried out before the peripheral lymph collectors had been destroyed or permanently damaged by increasing back pressure and recurrent infection.

Olszewski[19] published in 1988 his personal 20-year clinical experience in diagnosis and treatment of various types of lymphedema of the lower limbs with microsurgical lymph node-vein and lymph vessel-vein anasto-

moses. He limited indications for surgical therapy of lymphedema to a carefully selected group of patients with the local, segmental obstruction of proximal lymphatics. Peripheral lymphatic should be patent and have their contractility at least partly preserved. He underlined that long-term penicillin therapy was indispensable prior to surgery in cases with a history of lymphangitis.

A critical review of microsurgical lymphovenous anastomois for the treatment of lymphedema was published by Gloviczki and coworkers[20] in 1988. They performed lymphovenous anastomoses (LVA) to treat chronic lymphedema. Mean follow-up was 36.6 months. They reported that LVA offered ideal physiologic treatment, above all of secondary lymphedemas. Lymphoscintigraphy appeared to be a suitable method for both identifying patent lymph channels before surgery and determining function of LVA after operation.

Another experience in the treatment of lymphedemas by microsurgical lymphatic grafting was presented by Baumeister and Siuda[21] in 1990. Lymphatic grafts were anastomosed to peripheral lymphatics distal to and central lymphatics proximal to the regional blockade. In the case of unilateral blockade at the groin or pelvis, the grafts connected the lymphatics of the thigh of the affected leg with lymphatics in the contralateral healthy groin.

In 1990, O'Brien and coworkers[22] reported their clinical experience in the treatment of obstructive lymphedema by microlymphaticovenous anastomoses. They described a subjective improvement in 73 percent of patients and, objectively, volume changes showed a significant improvement in 42 percent of cases, with an average reduction of 44 percent of the excess volume. Authors also underlined the significant reduction in the incidence of cellulitis following surgery. Their long-term results (average follow-up of 4 years) indicated that microlymphaticovenous anastomoses had a valuable place in the treatment of obstructive lymphedema and should have been the treatment of choice in patients with obstructive lymphedema. Again, authors pointed out that improved results could be expected with earlier operations because patients referred earlier usually have less lymphatic disruption.

Despite advances in microsurgery, the most suitable operation for primary lymphedema remained unclear. A variety of tissue transplants and artificial substances had been used to facilitate drainage of peripheral lymph. The greater omentum was used experimentally in the treatment of canine obstructive lymphedema (O'Brien and co-workers,[23] Abalmasov and coworkers,[24]). The findings indicated that experimental obstructive lymphedema in the dog could be reduced significantly by insertion of a vascularised omental graft. However, because there is no natural lymph nodal-venous (L-V) shunt within the greater omentum, the addition of a L-V shunt in dogs to omental transplantation seemed to increased effectiveness of the omentum for draining hind-limb lymph after its autotransplantation.

AUTHORS' CLINICAL EXPERIENCE AND LONG-TERM RESULTS

Lymphatic-venous (LV) derivative microsurgery

Clinical indications for **lymphatic-venous (LV) derivative microsurgery** include the following conditions:

- Appropriate lymph nodes and lymphatic collectors;
- No venous dysfunctions;
- Normal or increased lymphatic-venous pressure gradient.

It is recommended to treat patients with lymphedema as earlier as possible.[25]

Different techniques of LV anastomoses have been developed, end-to-end *(Figure 2)* or end-to-side, performed with different technical "tricks" and refined both through experimental studies and through extensive clinical practice.[26]

Over the last 25 years, 665 patients affected by peripheral primary or secondary lymphedema have been submitted to derivative microsurgical LV anastomoses.[27] A total of 446 patients are available for long-term follow-up study, extending over more than 15 years in 11% of the cases. The age of the patients (whose female-to-male ratio was 1.5) ranged from 2 to 67 years (average 27 years). There were 231 patients with lymphedema of the upper limbs (37 primary and 194 secondary) and 434 patients with lymphedema of the lower limbs (230 primary and 204 secondary).

Primary lymphedemas *(Figure 3)* mainly included lymphnodal dysplasias (LAD II, according to Papendieck's classification), consisting of hyperplastic lymph nodes with sinus histiocytosis, thick and fibrous capsule with microlymphangioadenomyomatosis.[28] In these cases, lymph flow obstruction is revealed by alterations of the afferent lymphatics, which appear dilated and swollen with thickened walls; smooth muscle cells are reduced in number and appear fragmented by prevailing fibrous elements.

Figure 2. End-to-end multiple lymphatic-venous anastomoses (25-30x). After passing the needle inside the vein, lymphatic collectors are anchored by their adventitial and periadventitial tissue. At the end of lymphatic–venous anastomoses, blue dye passing inside the vein demonstrates the patency of microanastomoses.

In our experience, secondary lymphedemas *(Figures 4, 5, and 6)* were mostly due to lymphadenectomy and radiotherapy performed for oncological reasons (because of carcinoma of the breast, uterus, penis, bladder, prostatic gland, rectum, and seminoma of didymus), as well as to minor operations for varicose veins, crural and inguinal hernias, lipomas, tendinous cysts, or axillary and inguinal lymph node biopsies.

Most of the lymphedemas treated by microsurgery were at stages II (39%) and III (52%), while 3% of the patients were stage Ib and 6% were stages IV and V.

Derivative microsurgical LV anastomoses were performed both end-to-end and end-to-side. The end-to-end procedure was performed by a telescopic method with a single U-shaped stitch, anastomosing lymphatic collectors to a continent venous secondary branch. End-to-side LV anastomoses were performed by using the outlet of the vein as entry hole for lymphatic vessels, so that the risk of stenosis of the anastomoses is reduced to a minimum.

Particularly at pediatric ages, lymphatic-capsular-venous anastomosis was performed. The technique consists in anastomosing the lymph nodal capsular segment (which includes afferent lymphatics) directly to the vein, like a patch.

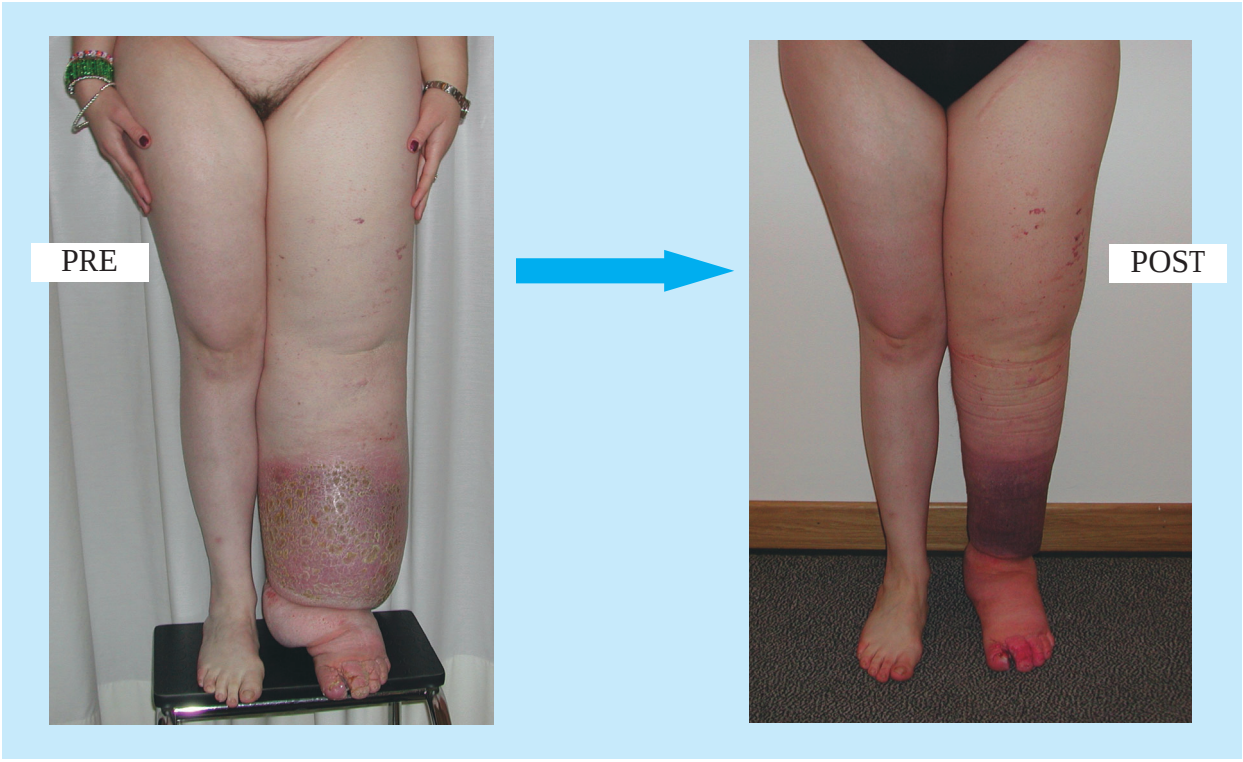


Figure 3. Primary left lower-limb lymphedema (V stage), before and 2 years after lymphatic-venous microanastomoses at the left groin.

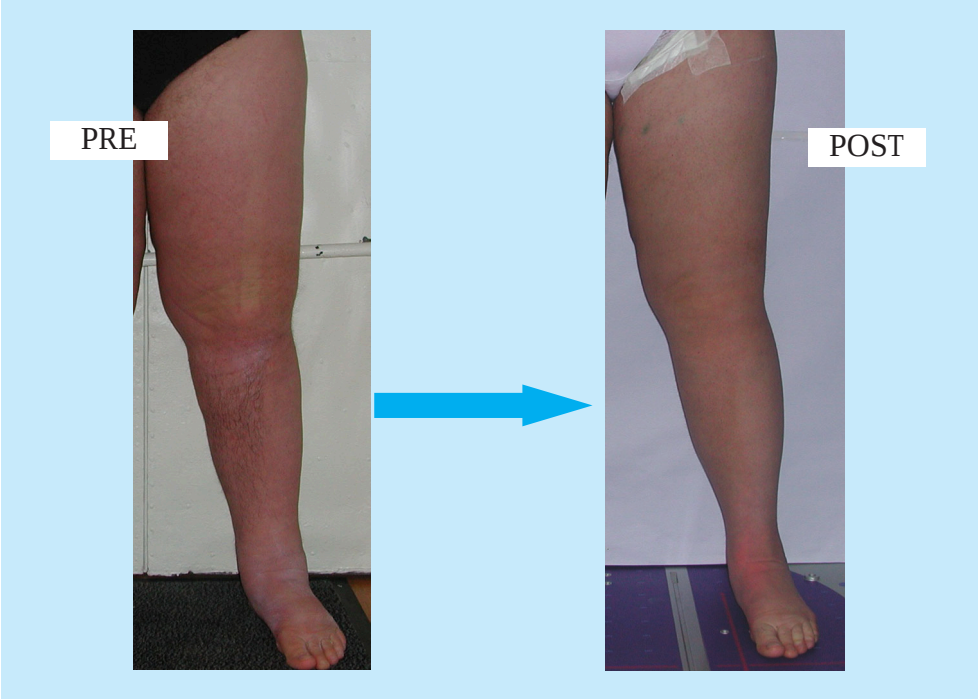


Figure 4. Secondary left lower-limb lymphedema (IV stage), before and immediately after lymphatic-venous microanastomoses at the left groin.

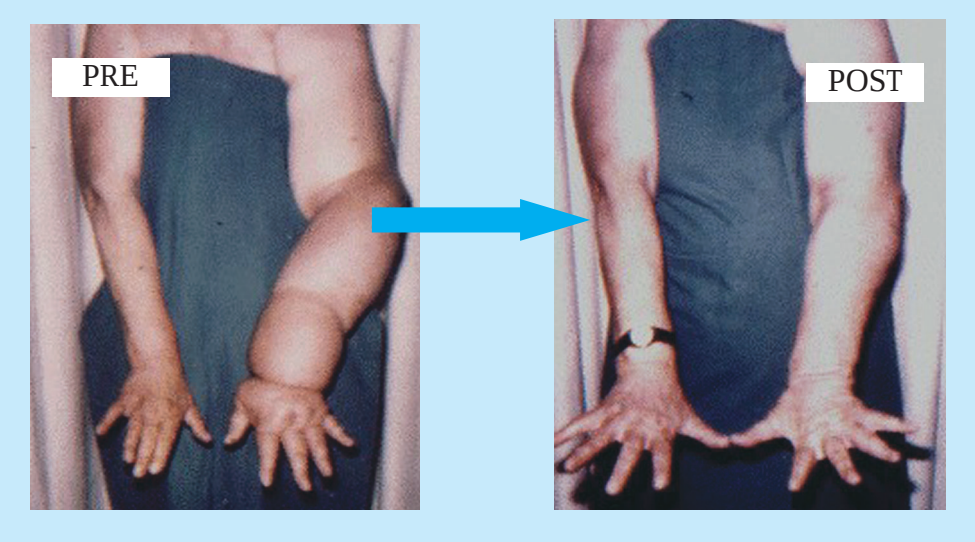


Figure 5. Left upper-limb lymphedema (V stage) following breast cancer treatment, before and after microsurgical lymphatic-venous anastomoses at the left arm.

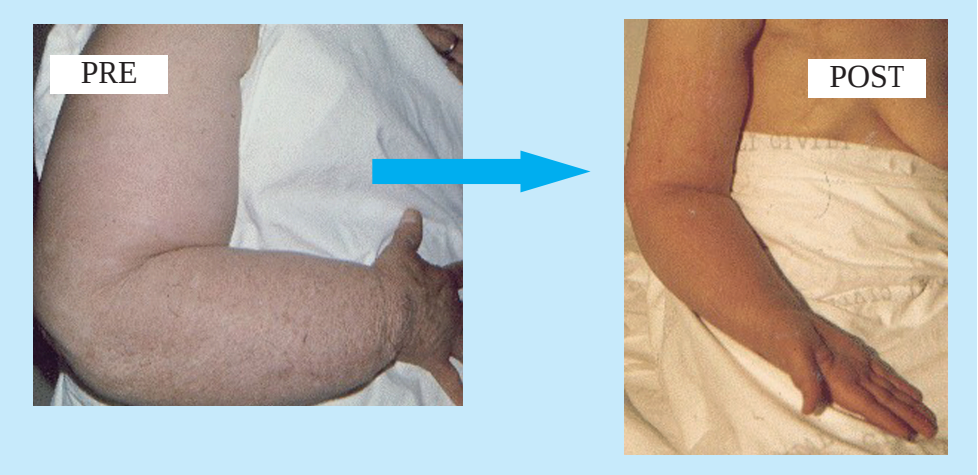


Figure 6. Right upper-limb lymphedema (V stage) following breast cancer treatment, before and after microsurgical lymphatic-venous anastomoses in the right arm (long-term result).

Lymphoscintigraphy[29] *(Figure 7)*, performed with either ^{99m}Tc-labeled antimony sulfur colloid or ^{99m}Tc-nanocolloid human serum albumin (90% of the particles > 80 nm in size), was employed in the diagnostic workup of patients with lymphedema and as a test for selecting patients for derivative microsurgical operations. Lymphoscintigraphy clearly discriminated whether or not edema was of lymphatic origin, and also supplied important data upon the etiologic and pathophysiologic aspects of lymphedemas.

Echo-Doppler was employed in all patients to identify any venous disorders possibly associated with lymphedema. In most patients, venous dysfunctions were corrected at the same time as microlymphatico-venous anastomoses (ie, valvuloplasty in case of vein insufficiency). In other cases, finding venous dysfunctions contraindicated derivative lymphovenous shunts, but it allowed to refer the patient to reconstructive microsurgical operations.

Conventional oil contrast lymphangiography was employed only in selected patients with lymphedema due to gravitational reflux, in order to better define the extension of the pathology and sites of lymphatic and chylous leakage.

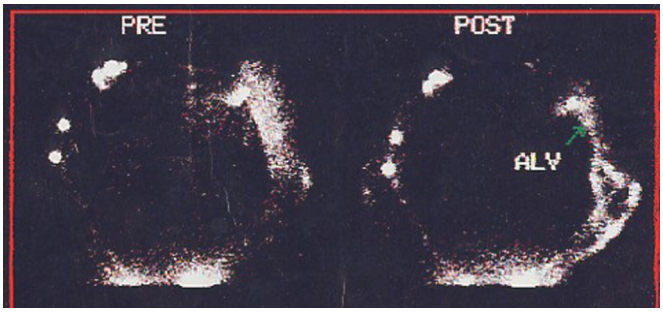


Figure 7. Lymphoscintigraphic demonstration of patency of lymphatic-venous anastomoses. Marked reduction of dermal backflow, appearance of preferential lymphatic pathways, disappearance of the tracer at the site of microanastomoses (Lymphoscintigraphy performed by Nuclear Medicine Unit, University of Genoa).

Results have been evaluated in the short-medium-and long-term (over 15 years) after operation. Subjective improvement occurred in 578/665 patients (87%). Objectively, volume changes showed a significant improvement in 552 patients (83%), with an average 67% reduction of the excess volume. Out of the 446 patients included in the follow-up, 379 patients (85%) have been able to discontinue the use of conservative measures, with an average follow-up of over 7 years and an average 69% reduction in excess volume. There was an 87% reduction in the incidence of cellulitis following microsurgery. In those patients who improved their clinical condition, the restored lymphatic drainage resulted in increased softness of the limbs. Peripheral edema (hand and foot) diminished considerably in most patients.

Efficacy of microlymphatico-venous anastomoses was confirmed by the following lymphoscintigraphic patterns *(Figure 7)*: 1) reduced dermal backflow; 2) rapid clearance in the bloodstream of the tracer at the site of microanastomoses, and 3) earlier tracer uptake by the liver indicative of more rapid entry into the bloodstream.

In particular, postoperative lymphoscintigraphy was performed in 119 patients (18%) with an average follow-up of over 7 years after surgery (maximum of 15 years in 7 patients). This procedure demonstrated patency of the microanastomoses in almost all patients (93%). In 9 patients, despite the absence of specific lymphoscintigraphic patterns positively proving the efficacy of microanastomoses, volume changes were clinically relevant anyway.

Reconstructive lymphatic microsurgery

Clinical indications for ***reconstructive lymphatic microsurgery*** *(Figure 8)* included patients with peripheral lymphedema (mostly of the lower limbs) under the following conditions:

- adequate lymphatic collectors;
- associated venous disorders that contraindicate derivative lymphovenous techniques;
- in whom the possible treatment of venous dysfunction can not ensure, anyway, a valid lymphatic-venous pressure gradient.

We used the technique of lymphatic-venous-lymphatic (LVL) plasty.[30] It consisted of the interposition of autologous vein grafts between lymphatic vessels below and above the site of lymph blockage. This reconstructive method of interpositional LVL shunt transports a great volume of lymph because of the high number of lymph collectors which can be anastomosed to the venous graft. The technique (LVL), moreover, is easily feasible, esthetically satisfactory, and without risk of causing a secondary lymphedema in the uninvolved contralateral limb.

Over the last 21 years, 133 patients with obstructive lower-limb lymphedema have been treated with interposition of autologous LVL shunts. There were 79 women and 54 male patients, with an average age of 43 ± 5 y.

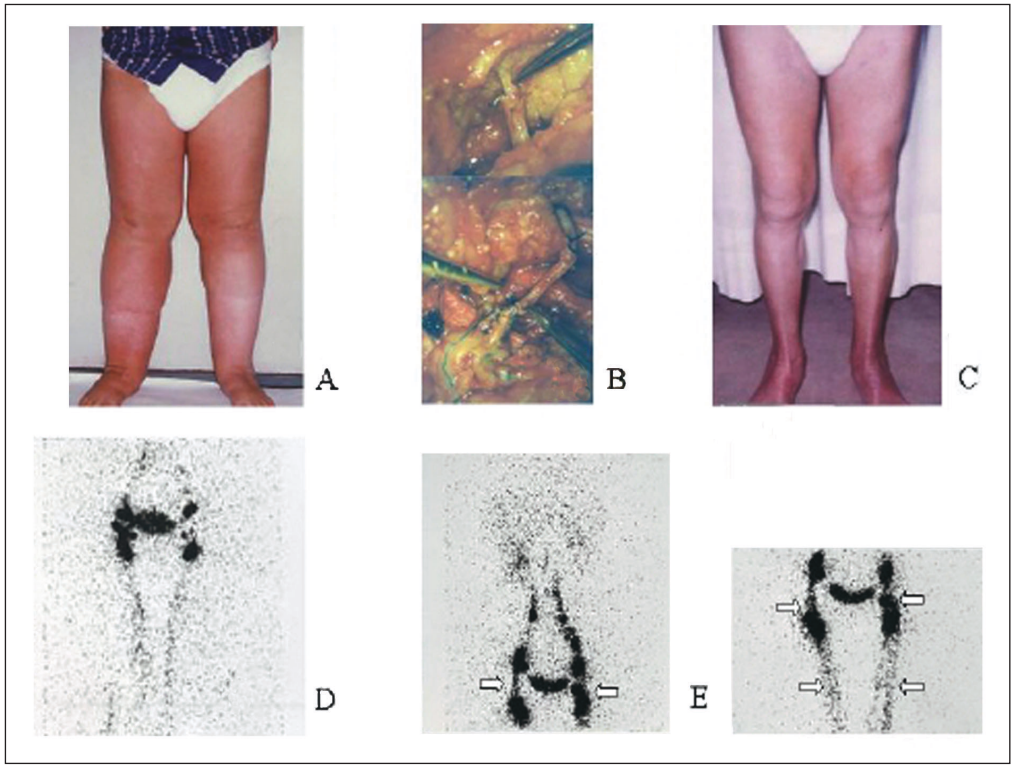


Figure 8. Primary lower-limb lymphedema (A), treated by LVLA (B), with 10-year follow-up after microsurgery (C). Lymphoscintigraphy - pre-op (D) and post-op (E) – shows preferential lymphatic pathways and interposed vein grafts (arrows).

(age ranged from 27 to 68 yrs). Thirty-nine patients (27 women and 12 men) presented with bilateral lymphedema. From the etiopathogenetic point of view, 87 were primary lymphedemas and 46 secondary. Primary lymphedemas were due to lymphnodal fibrosclerosis (lymphadenodysplasia - LADII, according to Papendieck's classification) with good, dilated, and hyperplastic lymphatic collectors.[31] Secondary lymphedemas were caused by surgery and/or radiotherapy for oncological reasons (seminomas, penis cancer, lymphomas, bladder cancer, prostatic cancer, cancers of the female genitalia, melanoma). Ninety-seven patients had stage III lymphedema, 21 had stage II, and 15 had stages IV-V, based upon a clinical instrumental staging of lymphedemas of five stages. In both clinical settings (primary and secondary lymphedemas), there was the coexistence of venous disorders that could not be corrected during the same operation, thus precluding the possibility of using derivative lymphatico-venous shunt operations. All patients were studied by lymphoscintigraphy and echo-Doppler.

The microsurgical method used in these patients was interposition of autologous vein grafts between lymphatic collectors below and above the lymph obstruction (lymphatico-venous-lymphatic anastomoses — LVLA).[32] The site of operation was at the groin. The lymphatics were colored blue by injection of blue dye (Patent Blue V) just below and above the site of operation. The lymphatic vessels afferent and efferent from the inguinal region were prepared for anastomoses, and the gap between them was bridged by interposing a venous graft, harvested from the same operative site (collateral branches of the great saphenous vein) or from the forearm. The anastomoses were performed by microsurgical technique, using 8/0 nonabsorbable suture material, microsurgical tools an the operative microscope with magnification variable from 25x to 35x. We employed the telescopic end-to-end lymphatico-venous technique, anastomosing several lymphatics altogether, at the same time, inside the proximal and distal cut-ends of the venous graft. Valved vein grafts were chosen to avoid possible lymphatic gravitational back flow, and the collateral branches of the vein were preserved for further lymphatico-venous anastomoses. Moreover, the number of lymphatics anastomosed to the distal vein cut-end was higher than that of the proximal end, in order to keep the vein graft filled with lymph and avoid vein graft fibrosis or ischemia. The patency and good closure of anastomoses was directly checked perioperatively at the microscope. A light functional bandage was applied to the leg for the first 2 to 3 postoperative days. The patients were discharged from the hospital after 5 to 7 days wearing

proper elastic garments, which had the aim of maintaining an adequate lymph flow through the vein segment. As a consequence of the operation, lymphatic flow inside the vein graft quickly tended to reduce, owing to the fast reduction in lymphedema volume. For this reason, just for the significant decrease of limb volume immediately after microsurgical operation, the patient needed to wear stockings from 1 to 5 years after microsurgery (according to the stage of the disease before the treatment and to the entity of fibrose tissue) to maintain and improve the results with time.[33]

The only medical therapy these patients needed was antibiotics peroperatively, and long-acting penicillin if there were signs of recurrent episodes of erysipeloid lymphangitis.

Follow-up of the patients *(Table I)* included, besides pre- and postoperative photographs, water volumetry and lymphoscintigraphy. Ninety-five patients were available for the long-term follow-up study.

The excess volume percent reduction was higher in patients treated at the early stages (II-III) than at later stages (IV-V). The average reduction of the excess volume was over 75% in 63 patients (47%), between 50% and 75% in 45 patients (34%), between 25% and 50% in 20 cases (15%), and less than 25% in 5 patients (4%).

The average incidence of lymphangitic episodes decreased significantly, from 3 to 4 per year to 0 to 1 per year.

The reduction in edema volume obtained by microsurgery was seen immediately after operation (already at the 1st, 2nd, and 3rd postoperative day), and a further decrease in lymphedema was observed also in the mid- and long-term after microsurgery, particularly between the first and the fifth year after operation. From the 5th year on, the clinical conditions of the limb remained stable with time, even at over 10 to 15 (in seven patients) years after operation.

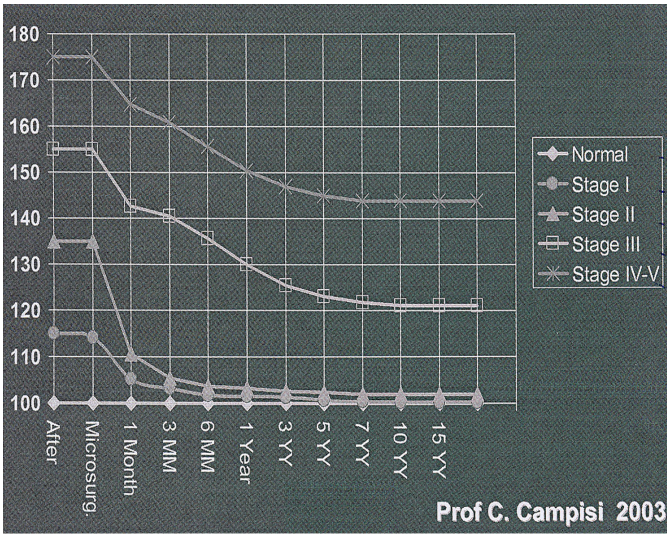


Table I. Table of long-term results (water volumetry).

Lymphoscintigraphy visualized lymph flow through the venous grafts, even over 10 and 15 years after operation, thus mirroring clinical improvement. The lymphoscintigraphic patterns consistent with efficacy of the microsurgical lymphatic reconstruction operations were as follows:

- reduced dermal backflow;
- appearance of preferential ways of lymph drainage;
- visualization of the intralymphatic interposition autologous venous grafts.

DISCUSSION AND CONCLUSIONS

Nowadays, primary and secondary peripheral lymphedemas are a quite well understood and curable problem. Present nonoperative measures are aimed at minimizing morbidity without removing the cause of the pathology. Microsurgical derivative and reconstructive operations can restore lymphatic drainage, both in the short and long term, and the best results are obtained when these surgical procedures are combined with physical rehabilitative methods.

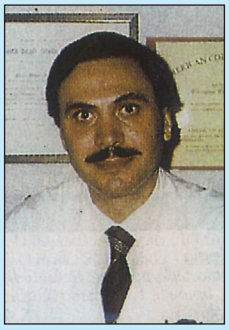
Emphasis should be placed on prevention above all of secondary limb lymphedemas based on a proper understanding of the multifactorial etiology of the pathology. Presently, it is possible to identify preoperative factors that distinguish women at greatest risk of developing lymphedema, and alter the proposed management of the axilla without compromising the principles of cancer treatment. It is also possible to detect postoperative changes in the latent phase before the development of swelling, thus identifying those in whom lymphedema is most likely to occur. Early prophylactic initiation of nonoperative methods prove more effective than their institution when swelling has become established.

The authors'clinical experience in the prevention of secondary peripheral lymphedemas regards the use of a personal and original diagnostic and therapeutic protocol for lymphedema prevention which includes, apart from the clinical evaluation of the patient, also lymphangioscintigraphy. Lymphoscintigraphy may demonstrate the presence of pre-existing anatomical conditions of lymphatic circulation predisposing to specific lymphatic

circulatory disorders, or prove the presence of impaired lymph drainage before the clinical evidence of the edema.

A proper therapeutic preventive protocol, including nonoperative measures and microsurgical operations, helps in avoiding the appearance of lymphedema or in treating it very early allowing to recover from the pathology completely and definitively.[34]

Finally, studies to investigate phenotype-genotype correlation are under way. In families where linkage or mutations are identified, testing of young clinically unaffected members permits early diagnosis and preventive management of congenital lymphedemas. Gene therapy aimed at stimulating new lymphatic growth in affected limbs is a possibility. Animal models exist to test gene therapy. New large families with primary lymphedema are required for further molecular genetic studies.



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REFERENCES

1. **Campisi C, Boccardo F**. Role of microsurgery in the management of lymphedema. *Int Angiol*. 1999;18:47-51.
2. **Földi E, Földi M**. *Physiothérapie complexe décongestive*. Paris: Editions Frison-Roche; 1993.
3. **Leduc A**. *Le drainage lymphatique. Théorie et pratique*. Paris: Masson; 1980.
4. **Vodder E**. *La méthode Vodder – Le drainage lymphatique manuel*. Institute. For Lymph Drainage; DK-2880, Bagsvaer; 1969.
5. **Olszewski W**. Recurrent bacterial dermatolymphangioadenitis (DLA) is responsible for progression of lymphoedema. *Lymphology*. 1996;29(Suppl):331.
6. **Handley WS**. Lymphangioplasty: a new method for the relief of the brawny arm of breast-cancer and for similar conditions of lymphatic oedema. *Lancet*. 1908;i:783-785.
7. **Charles RH**. A system of treatment. In: Latham A, English TC, eds. Churchill, London, 1912;3:504.
8. **Thompson N**. The surgical treatment of chronic lymphoedema of the extremities. *Surg Clin North Am*. 1967;47:2.
9. **Servelle M**. La lymphangiectomie superficielle totale. Traitement chirurgical de l'éléphantiasis. *Rev Chir*. 1947;294.
10. **Cockett ATK, Goodwin WE**. Chyluria: attempted surgical treatment by lymphatic venous anastomosis. *J Urol*. 1962;88:566-568.
11. **O'Brien BM, Sykes P, Threlfall GN, Browning FS**. Microlymphaticovenous anastomoses for obstructive lymphedema. *Plast Reconstr Surg*. 1977;60:197-211.
12. **Degni M**. New microsurgical technique of lymphatico-venous anastomosis for the treatment of lymphedema. *Lymphology*. 1981;14:61-63.
13. **Clodius L**. Problems of microsurgery in lymphedema. Handchir Mikrochir Plast Chir 1982; 14: 79-82.
14. **Huang GK, Hu RQ, Liu ZZ, Shen YL, Lan TD, Pan GP**. Microlymphaticovenous anastomosis in the treatment of lower limb obstructive lymphedema: analysis of 91 cases. *Plast Reconstr Surg*. 1985;76: 671-685.
15. **Krylov Vs, Milanov NO, Abalmasov KG, Sandrikov VA, Sadovnikov VI**. Reconstructive microsurgery in treatment of lymphoedema in extremities. *Int Angiol*. 1985;4:171-175.
16. **Zhu JK, Yu GZ, Liu JX, Pang SF, Lao ZG, Tang HY**. Recent advances in microlymphatic surgery in China. *Clin Orthop*. 1987;215:32-39.
17. **Al Assal F, Cordeiro AK, De Souza e Castro I**. A new technique of microlympho-venous anastomoses. Experimental study. *J Cardiovasc Surg*. 1988;29:552-555.
18. **Ho LC, Lai MF, Yeates M, Fernandez V**. Microlymphatic bypass in obstructive lymphoedema. *Br J Plast Sug*. 1988;41:475-84.
19. **Olszewski WL**. The treatment of lymphedema of the extremities with microsurgical lympho-venous anastomoses. *Int Angiol*. 1988;7:312-321.
20. **Gloviczki P, Fisher J, Hollier LH, Pairolero PC, Schirger A, Wahn HW**. Microsurgical lymphovenous anastomosis for the treatment of lymphedema: a critical review. *J Vasc Surg*. 1988;7:647-652.
21. **Baumeister RG, Siuda S**. Treatment of lymphedemas by microsurgical lymphatic grafting: what is proved? *Plast Reconstr Surg*. 1990;85:64-74.
22. **O'Brien BM, Mellow CG, Khazanchi RK, Dvir E, Kumar V, Pederson WC**. Long-term results after microlymphaticovenous anastomoses for the treatment of obstructive lymphedema. *Plast Reconstr Surg*. 1990;85:562-572.
23. **O'Brien BM, Hickey MJ, Hurley JV, Dvir E, Khazanchi RK, Pederson WC, Pribaz JJ**. Microsurgical transfer of the freater omentum in the treatment of canine obstructive lymphoedema. *Br J Plast Surg*. 1990;43:440-446.
24. **Abalmasov KG, Egorov YS, Abramov YA, Chatterjee SS, Uvarov DL, Neiman VA**. Evaluation of the greater omentum in the treatment of experimental lymphedema. *Lymphology*. 1994;27:129-136.
25. **Campisi C**. Rational approach in the management of lymphedema. *Lymphology*. 1991;24:48-53.
26. **Campisi C**. Lymphoedema: modern diagnostic and therapeutic aspects. *Int Angiol*. 1999;18:14-24.
27. **Campisi C, Boccardo F, Zilli A, Macciò A, Napoli F**. Long-term results after lymphatic-venous anastomoses for the treatment of obstructive lymphedema. *Microsurgery*. 2001;21:135-139.
28. **Badini A, Fulcheri E, Campisi C, Boccardo F**. A New Approach in Histopathological diagnosis of Lymphedema: pathophysiological and therapeutic implications. *Lymphology*. 1996;29:190-198.
29. **Mariani G, Campisi C, Taddei G, Boccardo F**. The current role of lymphoscintigraphy in the diagnostic evaluation of patients with peripheral lymphedema. *Lymphology*. 1998;31:316-319.
30. **Campisi C, Boccardo F, Tacchella M**. Reconstructive microsurgery of lymph vessels: the personal method of lymphatic-venous-lymphatic (LVL) interpositioned frafted shunt. *Microsurgery*. 1995;16:161-166.
31. **Dellachà A, Fulcheri E, Boccardo F, Campisi C**. Post-surgical lymphedema: Iatrogenic or pre-existing disease? *Lymphology*. 1998;31:562-565.
32. **Campisi C, Boccardo F, Zilli A, Macciò A, Napoli F**. The use of vein grafts in the treatment of peripheral lymphedemas: long-term results. Microsurgery. 2001;21:143-147.
33. **Campisi C, Boccardo F**. Frontiers in lymphatic microsurgery. *Microsurgery*. 1988;18:462-471.
34. **Boccardo F, Campisi C et al**. A pilot study on prevention of secondary lymphedema. *Lymphology*. 2000;33:222-225.

Congress and conference calendar

APICON 2004 – 59th JOINT ANNUAL CONFERENCE OF ASSOCIATION OF PHYSICIANS OF INDIA

This congress will be held in Hyderabad (India) from January 18 to 22, 2004.

• *For further information, please contact:*

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XXIIth WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY

This congress will be held in Rome (Italy) from May 22 to 26, 2004.

• *For further information, please contact:*

Scientific Secretariat
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Vth MEETING OF EUROPEAN VENOUS FORUM

This congress will be held in Warsaw (Poland) from June 25 to 27, 2004.

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XIIth UNITED EUROPEAN GASTROENTEROLOGY FEDERATION (UEGF)

This congress will be held in Madrid (Spain) from Septembre 25 to 30, 2004

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:*

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Chairman, Organising Committee, ESS Meeting
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This congress will be held in Brazil (Rio de Janeiro) from October 2nd to 7th, 2005.

• *For further information, please contact:*

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