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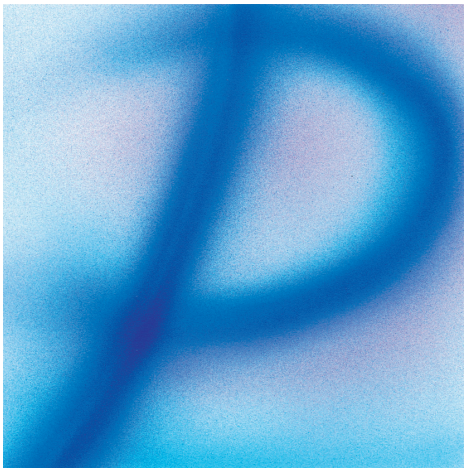

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AIMS AND SCOPE

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, news, and a congress calendar.

CORRESPONDENCE

Editorial Manager
Françoise PITSCH
Servier International
50, rue Carnot
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 68 96
Fax: +33 (1) 55 72 56 86
E-mail: francoise.pitsch@fr.netgrs.com

Publication Director
Laurence ALLIOT
Suresnes, France

Publisher
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 60 00
Fax: +33 (1) 55 72 68 88

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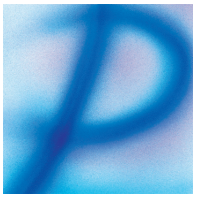

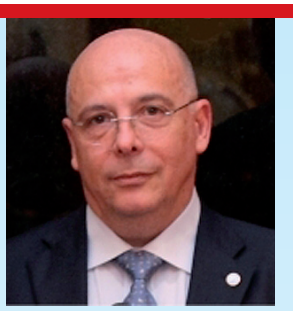

Pier-Luigi Antignani

Dear Readers,

This issue of Phlebolymphology *once again brings topics of immediate interest to the fore.*

A high number of chronic venous ulcers will have a prolonged healing, despite the best medical practices. This could be due to their malignant transformation into squamous cell carcinomas that are referred as "Marjolin's ulcers." ***P. Senet*** *analyzes the connection between cancer and chronic venous ulcers in this issue. She points out that one of the key clues for Marjolin's ulcer diagnosis is the prolonged duration of the preexisting wound.*

The review of the foam sclerotherapy trials for the treatment of varicose veins as written by ***M. Perrin****, highlights that foam sclerotherapy is a safe procedure with a low rate of adverse reactions. In terms of cost effectiveness yet, foam sclerotherapy is no doubt the "winner" but is credited with more frequent recurrences when compared with other operative procedures for treating varices.*

The role of the venous component in both HD pathogenesis and the occurrence of postsurgery symptoms should not be ignored.. In their paper regarding the benefits of micronized purified flavonoid fraction (MPFF) in the reduction of symptoms after HD operation, the authors ***V. Astashov*** *and* ***D. Timchenko*** *recommend the use of MPFF in association with HD surgery because the drug has a positive impact on the local hemodynamic component due to a normalization of venous tone in hemorrhoidal plexuses, a reduction in excessive capillary permeability and capillary walls fragility, an improvement of lymphatic drainage, and an inhibition of local inflammatory processes.*

M. Boisseau *points out in his review that many hereditary factors influence the quality of the venous wall in venous disease, and the always feared occurrence of an ulcer. Genetic screening include family studies, gene expression analysis (Single candidate gene expression, DNA microarrays), or genotyping methods (single nucleotide polymorphisms, mutation).*

Other interesting aspects of the pathophysiology of chronic venous disease has been reported by ***S. Nees****. He emphasizes that the goal of treatment must be to normalize venous pressure and the function of the "vasa venarum," and all measures aimed at improving venous return such as compression, surgical interventions, and pharmacological therapies including flavonoids must be considered.*

Enjoy reading this issue!
Pier-Luigi Antignani

Cutaneous cancers and chronic leg ulcers

Patricia SENET

Hôpital Tenon (Paris 20ème),
Service de Dermatologie,
UF de Médecine Vasculaire, France

ABSTRACT

The association between malignancies and chronic venous ulcer is not rare and include 2 distinct entities: malignant transformations of long lasting venous ulcers and primary ulcerating skin carcinomas misdiagnosed as venous ulcers. Malignant transformation of chronic venous ulcers into squamous cell carcinomas (SCCs), referred to as Marjolin's ulcer, is characterized by a median duration of 25 years. Malignant transformation of leg ulcers into basal cell carcinomas (BCCs) is still under debate. Skin cancers may also arise de novo, become ulcerated, and mimic chronic venous ulcers in appearance. In such cases, the most frequent cutaneous malignancies are BCCs, SCCs, and melanomas that arise mainly on sun exposed areas. The exact mechanism of a malignant transformation of leg ulcers remains unknown, but may be related to overexpression of factors favoring cell proliferation, susceptibility to malignancy, and also external factors (eg, ultraviolet radiation). In a recent prospective study, abnormal excessive tissue granulation at wound edges and abnormal bleeding in a leg ulcer that fails to heal within 3 months of treatment appeared to be highly associated with positive diagnosis of chronic venous ulcer–associated malignancies. Recent guidelines recommend performing a biopsy after 6 weeks to 3 months on nonhealing wounds to confirm diagnosis.

INTRODUCTION

Chronic leg ulcers (CLU) affect 0.5% to 1% of the general population, and results of several studies indicated that a high number of CLUs will have a prolonged healing, despite the best medical practices.[1] CLU-associated malignancies include 2 distinct entities: malignant transformations of long lasting CLU and primary ulcerating skin carcinomas misdiagnosed as CLU.

Malignant transformation of CLU into a squamous cell carcinoma (SCC) (*Figures 1 and 2*) has been well known for more than a century, although it is often under recognized. In the literature, SCCs that arise from CLUs or scars are referred to as Marjolin's ulcers, after the first description by the French physician named Jean-Nicolas Marjolin in 1827. One of the key clues for the diagnosis of Marjolin's ulcer is the prolonged duration (≥10 to 15 years) of a preexisting wound in well documented cases.[2] Skin cancers may also arise de novo and mimic the appearance of CLU in appearance (*Figures 3 and 4*). In the absence of previous negative histology, to diagnose a malignant CLU transformation and to exclude the possibility that a primary cutaneous

Keywords:
biopsy; cancer; healing; leg ulcer; malignancy; wound

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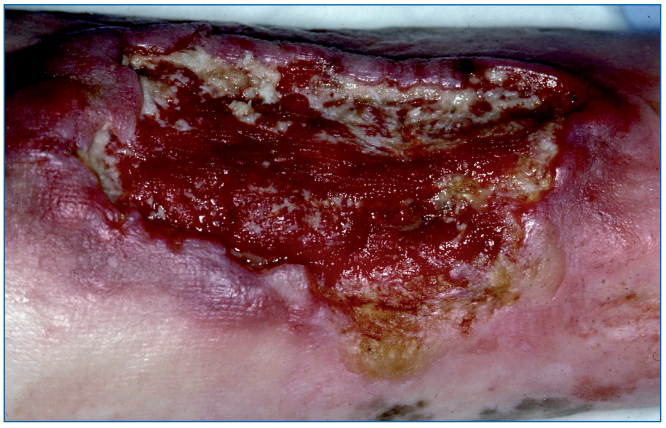

Figure 1. Marjolin's ulcer: transformation of a long lasting chronic leg ulcer in squamous cell carcinoma. Abnormal excessive granulation tissue at the wound edges, with induration.

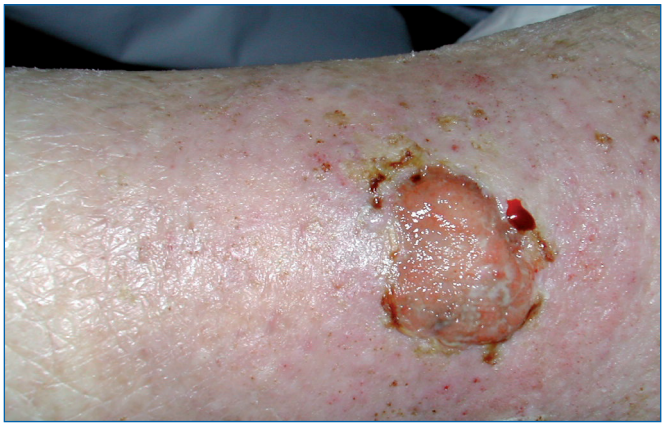

Figure 3. Basal cell carcinoma mimicking a chronic leg ulcer. Note the excessive granulation tissue in the center of the wound.

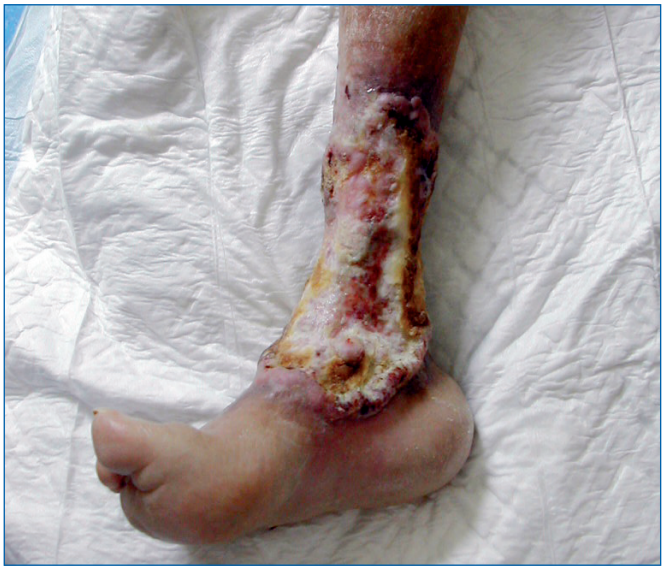

Figure 2. Marjolin's ulcer: transformation of a long lasting chronic leg ulcer in verrucous squamous cell carcinoma with a warty appearance.

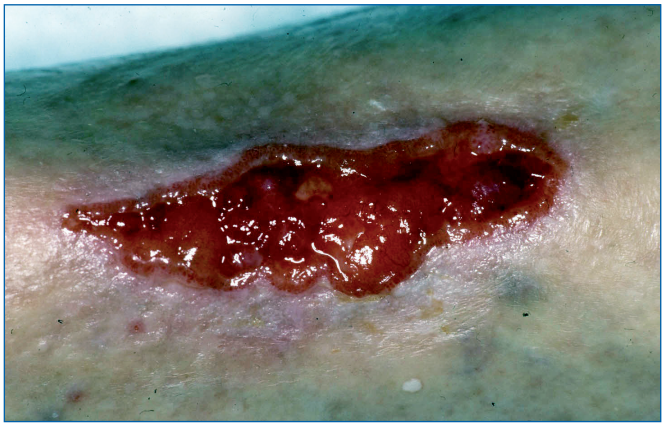

Figure 4. Ulcerated squamous cell carcinoma on leg, treated as a chronic venous leg ulcer.

carcinoma is mimicking a CLU, the CLU must be present for at least 3 years.[2] However, very few studies distinguish between these two possibilities.

Primary cutaneous malignancies, when located on the leg, may ulcerate and be misdiagnosed as CLU. The most frequent cutaneous malignancies are basal cell carcinomas (BCCs), SCCs, and melanomas and arise mainly on areas exposed to the sun. Moreover, BCCs and SCCs mostly affect people over the age of 60 when venous insufficiency and/or peripheral arterial disease are also frequent.[3] The average incidence of skin carcinomas is increasing around the world and is estimated to be between 75 and 100/100 000 person-years for BCC, 23 to 33/100 000 person-years for SCC, and 5 to 20/100 000 person-years for melanoma in Europe.[4]

Other skin malignancies, although less frequent, may arise on legs and then rapidly ulcerate. Classic Kaposi's sarcoma (*Figure 5*) follows an indolent course, and patients present with plaques and nodules on the lower extremities, which frequently ulcerate. Primary cutaneous B-cell lymphoma, leg type, belongs to a distinct group of B-cell lymphoproliferative disorders defined by its clinical presentation as red to bluish nodules or tumors, and location, on one or both lower legs. Some primary cutaneous T-cell lymphoma may have an aggressive behavior and become early necrotic and ulcerated *(Figure 6)*.

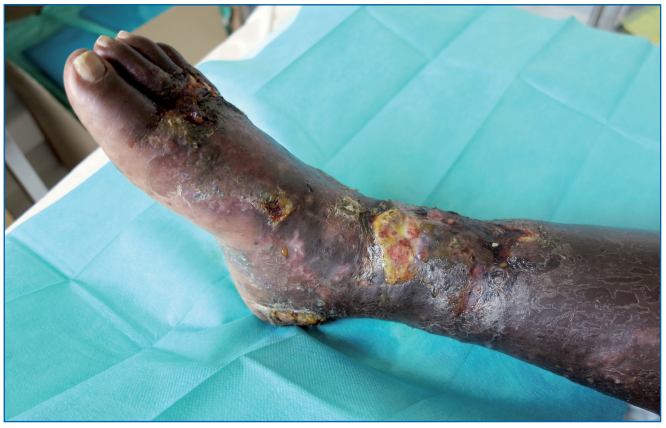

Figure 5. Ulcerated Kaposi sarcoma on the leg of an immunosuppressed patient (renal transplantation). Note the leg lymphedema related to the extension of the Kaposi sarcoma.

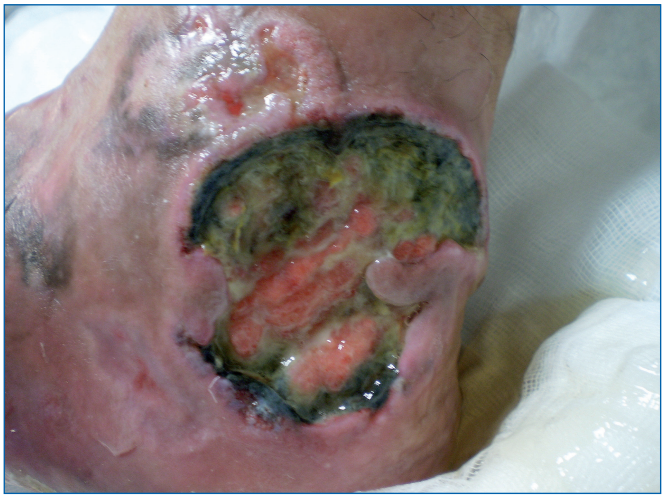

Figure 6. Ulcerated cutaneous T-cell lymphoma (CD8+, cytotoxic).

Clinical appearances of CLU-associated skin cancers (including primary ulcerating carcinomas misdiagnosed as CLU and malignant CLU transformations) range from innocuous lesions to overtly exophytic growths. Thus, guidelines recommend taking a biopsy of any atypical CLU for differential diagnoses,[5] or in the case of an atypical clinical progression.[6]

EPIDEMIOLOGY

The relative risk of SCC in CLU, as compared with the risk of developing SCC on the lower limbs for a normal population, has been estimated to be 5.8 based on two epidemiological studies from Sweden.[7,8] In an important study, 10 913 patients with venous leg ulcers, identified from the Swedish Inpatient Registry, were matched with registrations of lower limb SCC recorded by the Swedish Cancer Registry whereby. 17 SCC cases were considered to have occurred secondarily to venous leg ulcers. The median duration of the ulcer before the diagnosis of cancer was 25.4 years, which is very concordant with cases reported in the literature. Ulcers with duration shorter than 3 years were not considered. A retrospective study of all the CLU biopsies performed in a specialist wound clinic located in Great Britain identified 4 carcinomas out of 17 biopsies (24%) that were performed for suspicious clinical features (exophytic growth, irregular base or margin), 9 carcinomas out of 24 biopsies (37.5%) performed because of nonhealing ulcer without carcinoma features, and 0 carcinomas out of 35 biopsies performed for inflammatory features.[9]

In an Australian study, the frequency of carcinomas associated with CLU was 2.2% for leg ulcers. Biopsies were systematically performed in cases of nonhealing CLUs despite appropriate treatments or in cases where suspicious features suggested a possible malignancy.[10] This prevalence of malignancies was very high because, in contrast with the Swedish studies, primary ulcerated skin cancers misdiagnosed as CLU were considered. Therefore, it is not surprising that this study found more BCCs than SCCs (75% versus 25%), which is the same proportion of whole body surface BCCs and SCCs in Australia, where the skin cancer rate is the highest in the world.

In a recent prospective study, we prospectively determined the frequency of skin cancers associated with CLU, presumed to be of vascular origin and failing to heal despite ≥3 months of appropriate therapy. The overall skin-cancer frequency among 154 CLUs was 10.4%: 9 SCC, 5 BCC, 1 melanoma, and 1 leiomyosarcoma. Taking into account the wound duration, 43% of the cancers were long lasting (>5 years) and were highly suspected of being malignant transformation of CLUs, and 19% had lasted for <5 years and were highly suspected of being ulcerated cancers misdiagnosed as CLUs. In 38%, it was not possible to definitively decide between CLU malignant transformation and ulcerated cancer misdiagnosed as CLU.[11]

HISTOLOGICAL DATA

Malignant transformations of CLU occurs mainly toward SCCs (>75% of the cases), usually in a well-differentiated form or in verrucous type, which may be difficult to distinguish from benign pseudoepitheliomatous

hyperplasia (PEH).[12-14] Verrucous carcinoma is a low-grade SCC variant that is locally invasive, well-differentiated, and has a low metastatic potential. Tumors have a warty appearance and are locally aggressive. A superficial biopsy is usually not sufficient to distinguish these tumors from verruca vulgaris or PEH. PEH is a reactive epithelial proliferation characterized by a prominent and irregular hyperplasia of the epithelium, which closely simulates a SCC. PEH may be present in a number of conditions characterized by prolonged inflammation and/or chronic infection, as well as in association with many cutaneous neoplasms. Therefore, repeated biopsies or histological examination on the complete excision of the wound may be necessary to distinguish between PEH and a well-differentiated SCC, in the case of high clinical suspicion of malignancy. Nevertheless, histology may also find poorly or moderately differentiated SCC that are probably more aggressive.[15]

Malignant CLU transformation into a BCC is still debated. In most cases, the time between CLU onset and the diagnosis of BCC is less than 3 years,[2] making differential diagnosis between CLU transformation into BCC and primary ulcerated BCC difficult. Transformation of a long lasting CLU into a BCC has been described, although it is rare.[13]

Few cases of sarcomas, lymphomas, or melanomas have been documented in CLU biopsies, despite arising quickly after onset of CLUs. In these cases, the tumors were the cause of the ulceration being misdiagnosed as a CLU, rather than a complication of a chronic CLU.

MECHANISMS OF TRANSFORMATION

The exact mechanism of malignant transformation of CLU to SCC remains unknown. Elevated expressions of proto-oncogenes, known to be involved in cellular proliferation and transformation, were observed in chronic wounds as compared with normal skin or acute wounds, and may increase the susceptibility to malignant transformation.[16] More recently, overexpression of p53 and p21WAF/CIP1 was observed within the tumors.[17] Human papilloma virus infection was not found in malignant transformation of CLU.[18] Extrinsic factors (eg, ultraviolet radiation) may be implicated in the malignant transformation as Marjolin's ulcers are located on areas exposed to the sun. Chronic inflammation and infection with repeated tissue stress may also lead to malignancy, as in other skin chronic conditions, like dystrophic epidermolysis bullosa.[19]

CLINICAL ASPECTS

In a recent prospective study[11] of CLUs that failed to improve despite 3 months of adequate treatment, abnormal excessive tissue granulation at the wound edges appeared to be highly sensitive parameters for positive diagnosis of CLU-associated malignancies. However, high clinical suspicion of CLU transformation, high clinical suspicion of ulcerated skin cancer, and abnormal bleeding were highly specific parameters.

In a retrospective study of 85 malignancies arising in CLUs, 76% of them were biopsied because of abnormal granulation or overt tumor growth of the wounds, and 20% because of a protracted course or spreading of the CLU despite appropriate treatment. Only 5% were biopsied because of abnormal pain or bleeding.[13] For malignant transformation of CLU, mean age of the patients was around 75 years, with a logical female predominance, related to the age of the population and venous disease. Mean ulcer duration was identical in all retrospective studies, around 25 years, with a range between 7 and 51 years.[7,12,13,15,20] Carcinomas may arise in open wounds, but also at the site of remitting/relapsing ulcers. Ninety percent of the ulcers were from venous origin or from mixed origin with a venous predominance.[13] Exophytic irregular growth of the wound edges and/or bed, excess tissue granulation that extends beyond the margins, increase in pain or bleeding, absence of healing despite adequate treatment, and unusual extension have been reported as clinical features of malignant transformation.[12,13] Several biopsies of both the margins and the wound bed may be required to obtain a definitive diagnosis, and may be repeated if clinical suspicion is high.[11] The poor prognosis of malignant transformation of CLU is, at least, partly related to the delay in diagnosis, which is made at the metastatic stage in 30% to 34% of cases.[7,12] Magnetic resonance imaging seems to be the most valuable study in these patients to evaluate the bone and surrounding tissue extension.[20] More recently, 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (18F-FDG PET/CT) seems to be useful in differentiating Marjolin's ulcers from benign inflammatory conditions and in the evaluation of the invasion depth; however, these preliminary results remain to be confirmed.[21]

Primary skin carcinomas mimicking a CLU, usually presents clinically as a single ulceration with indurated or pigmented edges. For BCC, the ulceration frequently has well-defined borders, with a "pearly" appearance of the edges (*Figure 4*). For melanoma, dark pigmentation may be present on the edges and spreads to the perilesional skin. In the case of Kaposi's sarcoma, several dark blue macules are present on the same leg, or more frequently, on both legs that progress to plaques and tumors with lesions of different ages (*Figure 5*).

PROGNOSIS AND TREATMENT

SCCs arising in CLUs have been shown to be more aggressive and metastasize more frequently than those arising on the limbs de novo, probably because of a delay in diagnosis. A median survival of 1 year has been reported in the Baldursson's study.[15] In a French retrospective study,[13] the death rate increased from 25% to 70 % in the case of lymph node involvement and to 83% if visceral metastasis was present, with an overall death rate of 37.2%; leg amputation was performed in 57% of the cases.

All SCCs arising in CLUs may benefit from a multidisciplinary approach for treatment.[22] Surgery is the treatment of choice and leg amputation is often considered. Although, in cases of a well-differentiated tumor without bone involvement, excision with a large margin for high risk SCCs (at least 6 to 10 mm) seems to be an appropriate treatment.[12-14,20] Radiation treatment should probably not be considered, even as a palliative treatment, as it inhibits wound healing without curing the tumor.[13,14] Lymph node dissection is not performed in absence of nodal involvement.[22]

For BCCs and melanomas, surgical excision is the first line of treatment. BCCs have a potential of local invasion, but metastasize exceptionally. Excision margins are usually between 5 and 10 mm in this localization.[23] Melanomas have the presence of an ulceration the results in upstaging by one substage compared with a nonulcerative melanoma. The excision margins, adjuvant treatment, and sentinel lymph node staging are decided according to Breslow thickness within a multidisciplinary team including surgeons, oncologists, dermatologists, and histologists because of a high risk of recurrence and metastases;.[3]

CONCLUSION

Taking into account the frequency of cutaneous malignancies associated with CLU; CLU presumed to be of vascular origin should be biopsied after 3 months of adequate treatment, as it seems to be a reasonable threshold in our practice and in the literature, to evaluate the response to treatment. Some authors recommend performing biopsies for all ulcers without evidence of healing after 2 weeks of standard treatment, although recent guidelines recommend taking a biopsy after 6 weeks to 3 months of nonhealing wounds. One of the limitations to performing a biopsies may be related to the clinician's fear of making the wound worse. However, it was recently shown that wound biopsies are a safe procedure, do not worsen the CLU healing process, and that the biopsy sites healed within a few weeks.[24]

Corresponding author
Patricia SENET
Hôpital Tenon (Paris 20ème),
Service de Dermatologie,
UF de Médecine Vasculaire,
4 rue de la Chine,
75970 Paris Cedex 20

E-mail: patricia.senet@tnn.aphp.fr

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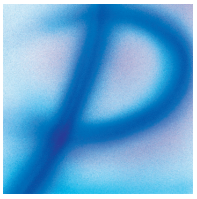

Randomized control trials on sclerotherapy for varicose veins

Michel PERRIN

Vascular Surgery, Unite de Pathologie Vasculaire Jean Kulin, Lyon, France

ABSTRACT

Ultrasound-guided foam sclerotherapy (UGFS) is presently challenging other operative varices treatment. Randomized controlled trials are considered to be solid, evidence-based studies. In varices management, many randomized trials have been published in order to try to determine what the best treatment option is, and they are discussed in this review. Other randomized controlled trials dealing with varices sclerotherapy are analyzed including: (i) sclerosing agent versus placebo; (ii) liquid versus foam; (iii) the type, dose, and concentration of sclerosing agent; (iv) sclerotherapy in patients with or without thrombophilia; and (v) postsclerotherapy compression. The conclusions are that UGFS is both efficient and safe. Ideal sclerosing agent and dose as well as postsclerotherapy compression are still under discussion. Compared with other treatments, ultrasound-guided foam sclerotherapy is credited with more frequent recurrences, but they are easy to treat by redoing the injection with good success. Presently, in terms of cost effectiveness, UGFS is in a perfect position.

ABBREVIATIONS

VV = varicose veins
SFJ = saphenofemoral junction
UGFS = ultrasound-guided foam sclerotherapy
RCT = randomized controled trial
GSV = great saphenous vein
HL = high ligation
AVP = ambulatory venous pressure
VFS = visual foam sclerotherapy
RT = refill time
VCSS = venous clinical severity score
VSDS = venous segmental disease score
AVVQ = Aberdeen Varicose Vein Questionnaire
PE = pulmonary embolism

Keywords:
chronic venous disease; randomized controled trial; ultrasound-guided foam sclerotherapy; varicose veins

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INTRODUCTION

In the last decade operative treatments for varices have been enriched with new methods. Presently, procedures for varicose vein (VV) treatment can be

classified into 2 groups:[1] (i) open surgery; and (ii) endoluminal procedures.

1. Open surgery with techniques to distinguish between sparing the saphenous trunk or not

The first subgroup encompasses incompetent tributary phlebectomy, (French acronym ASVAL), ambulatory Conservative HemodynamIc management of Varicose Veins, (French acronym CHIVA), saphenofemoral junction (SFJ) valvuloplasty, ligation, or cuffing + incompetent tributary phlebectomy.

The second one groups classical open surgery together with SFJ preservation or not, +/- perforator ligation, +/- incompetent tributary phlebectomy.

2. Endoluminal procedures including thermal ablation (laser, radiofrequency, steam, and cryostripping) and chemical ablation (glue and sclerotherapy)

The latter, although used for several centuries, has been drastically improved by ultrasound guidance and by delivering the sclerosing agent combined with gas to form foam. (*Figures 1-6*). Ultrasound-guided foam sclerotherapy (UGFS) is gaining favor among phlebologists. Many articles on UGFS including consensus analyses, meta-analyses, observational studies, and randomized controlled trials (RCT's) have been published. The American College of Chest Physicians has established recommendation grades that are adopted and used worldwide (*Table I*).[2-5]

Grade of recommendation/ description	Benefits vs risks and burdens	Methodological quality of supporting evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh the risks and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits, risk, and burdens may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Table I. *Grading recommendations (Chest, 2006;129:174-181)*

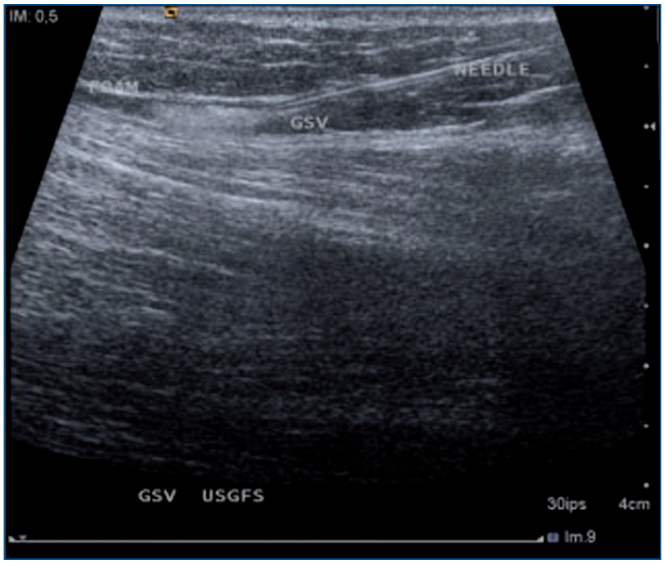

Figure 1. The needle and the foam injected in the great saphenous vein are clearly identified.
(Courtesy C. Hamel-Denos MD)

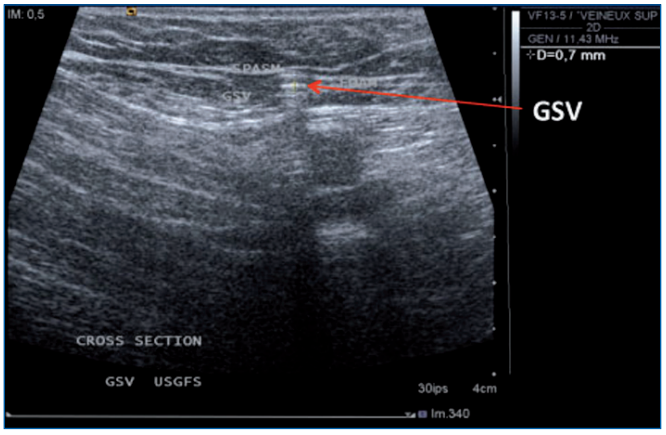

Figure 2. . Spasm following foam injection into the great saphenous vein.
(Courtesy C. Hamel-Denos MD)

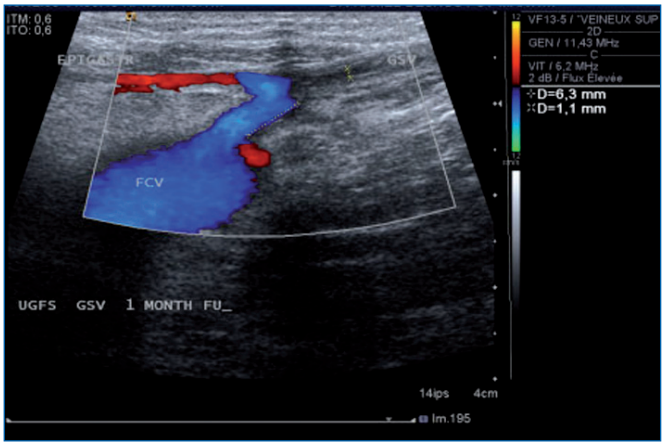

Figure 3. One month follow-up after UGFS. GSV, great saphenous vein; EPIG; epigastric vein; FCV common femoral vein.
(Courtesy C. Hamel-Denos MD)

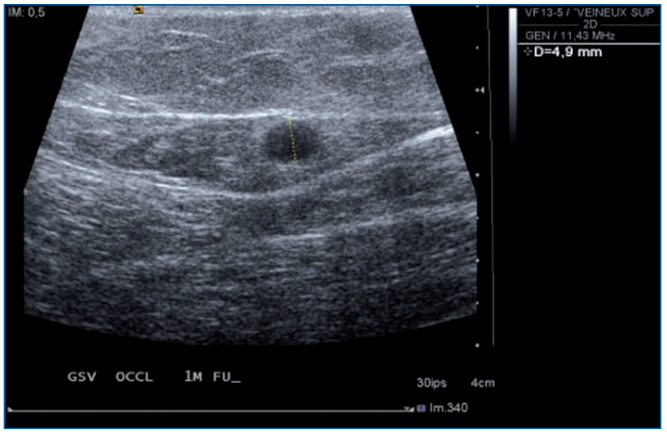

Figure 4. One month follow-up after UGFS. GSV, great saphenous vein; EPIG; epigastric vein; FCV common femoral vein.
(Courtesy C. Hamel-Denos MD)

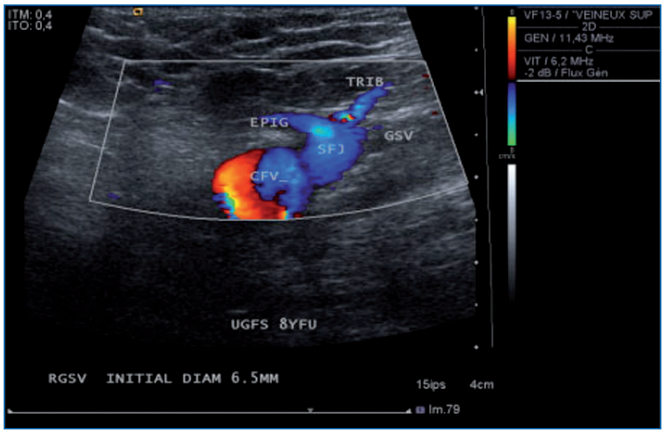

Figure 5. Eight year follow-up after ultrasound-guided foam sclerotherapy. GSV, great saphenous vein; EPIG, epigastric vein; TRIB, tributary; CFV, common femoral vein; SFJ, saphenofemoral junction.
(Courtesy C. Hamel-Denos MD)

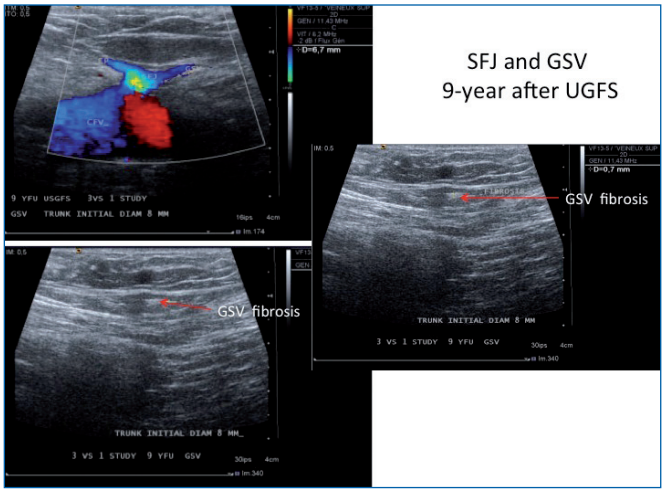

Figure 6. Nine years follow-up after ultrasound-guided foam sclerotherapy. GSV, great saphenous vein; CFV, common femoral vein; SFJ, saphenofemoral junction.
(Courtesy C. Hamel-Denos MD)

AIM

To report and review RCT's on sclerotherapy for treating VV.

MATERIAL AND METHODS

A PubMed search was conducted in English and French for the years 2000 to 2012 with the keywords sclerotherapy, foam, ultrasound-guided foam sclerotherapy, and their counterparts in French. Only articles, but not meeting abstracts, dealing with lower limb VV were selected. RTC's identified were classified into distinct groups: (i) sclerosing agent versus placebo; (ii) liquid versus foam; (iii) sclerosing agent usages (type, dose, and concentration); (iv) sclerotherapy in patients with thrombophilia; (v) postsclerotherapy compression; and (vi) outcome after sclerotherapy versus other treatment procedures.

RESULTS

1. RCTs of diverse sclerotherapy modalities

Sclerosing agent vs normal saline injection[6] (*Table II*)

Comment. The trial has demonstrated that polidocanol is efficient at closing the vein and modifying hemodynamics by measuring the venoarterial flow index by using ultrasound investigation.

Liquid versus foam[7-11] (*Table III*)

Comment. German, Japanese, and French articles related to Varices (C2-C6) come to the same conclusions; foam is more efficient than liquid in terms of vein occlusion with polidocanol as the sclerosing agent by using the EASY-FOAM-kit with a 2-year follow-up or Tessari method after 1 year. Unfortunately, the 4 RCT's did not provide clinical data except for a quality of life survey in the German article. The Catalan RCT is difficult to interpret, as the group is heterogeneous and the methodology questionable, but the outcome seems to be in favor of foam, although at 1 year there is no difference in terms of patient satisfaction. In conclusion, if sclerotherapy is considered for treating varices, the use of UGFS deserves a strong grade 1B recommendation.

Sclerosing agent: type, dose, and concentration[12-15] (*Table IV*).

Comment. Four articles (3 RCTs), without major bias, provided the same conclusion. Results obtained by using either 1% or 3% Polidocanol are equivalent, although the German study shows a trend that favors the 3% concentration in terms of cosmetic results at 1-year follow-up (P=0.569). Presently, there is no RCT comparing the most commonly used sclerosing agents, ie, polidocanol and tetradecyl sodium sulphate. In conclusion, if Polidocanol is used for treating varices by UGFS at a concentration of 1%, then it deserves a strong grade 1B recommendation.

Compression after sclerotherapy[16-18] (*Table V*)

Comment. The 3 available RCTs assessed have different elements. The first trial perfectly documented recommending a short-term compression after classical surgery.[16] Nevertheless, the type of compression prescribed in this trial is questionable: bandages followed

Treatment	Article	Results
Polidocanol vs saline solution	Kahle B, Leng K. Efficacy of sclerotherapy in varicose veins: A prospective, blinded, placebo-controlled study. *Dermatol Surg*. 2004;30:723-728.	25 patients C_2-C_4; Competent SFJ et SPJ but varices Polidocanol versus saline solution: Group 1, UGFS, 2% or 3% polidocanol (n=14); Group 2, saline solution (n=11) **Follow-up 4 to 12 weeks** *Venous occlusion:* Group 1, 1/14 (76, 8%); Group 2, 0/11; P<0.0001 *VAFI:* Group 1, all veins occluded, VAFI decreased from 1.5 to 0.98; Group 2, no VAFI modification; P<0.05

Table II. Sclerosing agent vs normal saline injection

Abbreviations: SFJ, saphenofemoral junction; SPJ, saphenopopliteal junction; UGFS, ultrasound-guided foam sclerotherapy; VAFI, venoarterial flow index

Article	Results
Hamel-Desnos C, Desnos P, Wollmann JC, Ouvry P, Mako S, Allaert FA. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. *Dermatol Surg.* 2003;29:1170-1175.	83 patients; Incompetent GSV; Multicenter study 3% polidocanol; 2 to 2.5 mL UGFS Turbofoam® (n=45) vs UGLS (n=43) Direct puncture technique. Injection at upper or middle-third of the thigh. Complementary UGFS or UGLS when presence of persistent reflux was identified. **Follow-up: 3 weeks to 12 months** At 3 weeks *Reflux suppression:* UGFS, 84%; UGLS, 40%; *P*<0.01 At 6 to 12 months *Recanalization:* UGFS, 6; UGLS, 2
Yamaki T, Nozaki M, Iwasaki S. Comparative study of duplex-guided foam sclerotherapy and duplex-guided liquid sclerotherapy for the treatment of superficial venous insufficiency. *Dermatol Surg.* 2004;30:718-722.	77 patients; Incompetent GSV 3% polidocanol, 1 mL or 1% polidocanol, 2 mL UGFS Tessari method (n=37) vs UGLS (n=40) **Follow-up: 3 to12 months** *Treated vein occlusion:* UGLS, 17.5%; UGFS, 67.6%; *P*<0.0001 *Recurrent varicose vein:* UGLS, 8.1%; UGFS, 25%; *P*=0.048 *Venous filling index (APG):* Significant difference in favor of UGLS, *P*<0.0005
Alòs J, Carreño P, López JA, Estadella B, Serra-Prat M, Marinel-Lo J. Efficacy and safety of sclerotherapy polidocanol foam: a controlled clinical trial. *Eur J Vasc Endovasc Surg.* 2006;31:101-107.	75 Symptomatic patients; Reticular varices and REVAS; Monocenter study 0.5% to 2.5% polidocanol, 0.5 to 2 mL; according to vein size UGFS according to Tessari method (n=75) vs UGLS (n=75) Injection only in one varicose vein; 150 procedures; In the same patient for identical lesions **Follow-up: 2 to 4 weeks** *Pain:* UGFS, less painful; *P*<0.001 **Follow-up: 3 months** *Treated vein occlusion:* UGLS, 53 %; UGFS, 94.4 %; *P*<0.001 *Occlusion length:* UGLS, 7.2 cm; UGFS, 10.1 cm; *P*<0.001 **Follow-up: 1 year** *Patient satisfaction. Numerical scale 0 to 10*: UGLS, 7.2; UGFS, 7.4; NS *Pigmentation*: Less with UGFS *P*<0.0001
Ouvry P, Allaert FA, Desnos P, Hamel-Desnos C. Efficacy of polidocanol foam versus liquid in sclerotherapy of the great saphenous vein: a multicentre randomised controlled trial with a 2 year follow-up. *Eur J Vasc Endovasc Surg.* 2008;36:366-370.	95 patients C_2-C_6; Incompetent GSV; Multicenter study 3% polidocanol, 2 to 2.5 mL UGFS Turbofoam® (n=47) vs UGLS (n=48) Direct puncture technique, injection at upper- or middle-third of the thigh. Complementary UGFS or UGLS when presence of persistent reflux was identified. **Follow-up: 3 weeks to 24 months** At 3 weeks *Reflux suppression*: UGFS, 85%; UGLS, 35%; *P*<0.01 At 24 months *GSV occlusion*: UGFS, 53%; UGLS, 12%
Rabe E, Otto J, Schliephake D, Pannier F. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. *Eur J Vasc Endovasc Surg.* 2008;35:238-245.	108 patients C_2-C_8; Incompetent GSV; Multicenter study 3% polidocanol, 3.3 to 3.8 mL UGFS Turbofoam® (n=55) vs UGLS (n=53) Catheter technique. Injection at middle-third of the thigh with Turbofoam®. **Follow-up: 3months** *Reflux suppression:* UGFS, 69%, UGLS, 27%; *P*<0.001 *Occlusion GVS:* UGLS, 17%; UGFS, 54%; *P*=0.0001 *Total number of sessions:* UGLS, 1.6; UGFS, 1.3 *Refilling time:* UGLS, 13.6 seconds; UGFS, 19.5 seconds; *P*=0.0017 *Patient Satisfaction CIVIQ:* Better in UGFS group. *P*<0.0001

Table III. *Liquid sclerotherapy vs foam sclerotherapy*

Abbreviations: APG, air plethysmography; GSV, great saphenous vein; IV, injected volume; REVAS, REcurrent VArices after Surgery; UGLS, ultrasound-guided liquid sclerotherapy; UGFS, ultrasound-guided foam sclerotherapy

Article	Results
Hamel-Desnos C, Allaert FA, Benigni JP, et al. Etude 3/1. Mousse de polidocanol 3% versus 1% dans la grande veine saphène: premiers résultats. *Phlébologie.* 2005;58:165-173.	158 patients; Incompetent GSV; Mean diameter, 6.1 mm 1% polidocanol 3.1 mL (Group 1, n=79) or 3% polidocanol 3.1 ml (Group 2, n=79) UGFS with Turbofoam® **Follow-up: 3 weeks to 6 months** *RA: (3 weeks)* Group 1, 91.1%; Group 2, 91.1%; *(6 months)* 14 patients lost to follow-up; Global evaluation, 80%
Ceulen RP, Bullens-Goessens YI, Pi-VAN DE Venne SJ, Nelemans PJ, Veraart JC, Sommer A. Outcomes and side effects of duplex-guided sclerotherapy in the treatment of great saphenous veins with 1% versus 3% polidocanol foam: results of a randomized controlled trial with 1-Year follow-up. *Dermatol Surg.* 2007;33:276-281.	80 patients, Incompetent GSV including SFJ; Mean diameter, 5.4 mm 1% polidocanol, 4.6 ml (Group 1, n=40); 3% polidocanol, 4.4 ml (Group 2, n=40) UGFS single injection with catheter **Follow-up: 1 week to 1 year** *GSV occlusion: (1 week)* Group 1, 86.7%; Group 2, 91.5%; NS; *(1 year)* Group1, 69.5%; Group 2, 80.1%; NS *Cosmetic improvement:* Group 1, 67.5%; Group 2, 77.5%; NS *Venous symptomatology:* Group 1, 29.7%; Group 2, 25.0%; NS
Hamel-Desnos C, Ouvry P, Benigni JP, et al. Comparison of 1% and 3% polidocanol foam in ultrasound-guided sclerotherapy of the great saphenous vein: a randomized, double-blind trial with 2 year-follow-up. "The 3/1 study." *Eur J Vasc Endovasc Surg.* 2007;34:723-729.	148 patients; Incompetent GSV; Mean diameter, 4 to 8 mm; Multicenter study 1% polidocanol, 4.6 ml (Group 1, n=74); 3% polidocanol, 4.4 ml (Group 2, n=74) UGFS with Turbofoam®; 1 injection **Follow-up: 3 weeks to 2 years** *RA: (3 weeks)* Group 1, 96%; Group 2, 88%; NS; *(2 years):* (14 patients lost to follow-up): Group 1, 69%; Group 2, 68%; NS *GSV occlusion length (3 weeks):* Group 1, 38 cm; Group 2, 34 cm; NS
Blaise S, Bosson JL, Diamand JM. Ultrasound-guided sclerotherapy of the great saphenous vein with 1% vs. 3% polidocanol foam: a multicentre double-blind randomised trial with 3-year follow-up. *Eur J Vasc Endovasc Surg.* 2010;39:779-786.	143 patients C_2-C_5, Incompetent GSV, Multicenter study 1% polidocanol, 6.1 ml (Group 1, n=73); 3% polidocanol, 6.3 ml (Group 2, n=70) UGFS with Turbofoam® Complementary UGFS; when persistent reflux is present at 3 weeks, 3 months, and 6 months; Group 1, 49%; Group 2, 33%; *P*=0.04 **Follow-up: 3 weeks to 3 years** *Severity venous score, CIVIQ Score: (3 years)* no difference *RA: (6 months)* Group 1, 69%; Group 2, 85%; *(3 years)* Group 1, 79%; Group 2 78%

Table IV. *Sclerosing agent: dose and concentration*

Abbreviations: GSV, great saphenous vein; RA, Reflux abolition; UGFS, ultrasound-guided foam sclerotherapy

by use of antithrombotic stockings. In conclusion, if compression is considered after UGFS treatment, short term compression is recommended, but related to above remarks, the grade of recommendation is weak, we suggest grade 2B.

The second trial questions compression usefulness after UGFS.[17] Although many parameters are assessed, the cohort studied is disparate both in terms of clinical class (C) as well as veins treated. The third trial compared biological changes in inflammation and coagulation between 2 post UGFS groups, one treated with compression and the other treated without compression therapy. No significant biological changes were observed between the 2 groups.[18] Several observational studies argue for compression after sclerotherapy, but all of them used a liquid sclerosing agent.[19-21] In conclusion, these trials received only a weak grade 2B recommendation, suggesting no compression is needed after UGFS.

Visual foam sclerotherapy alone, or in combination with, UGFS[22] (*Table VI*)

Comment. In two well-matched groups, 1% polidocanol was used for treating patients that were prospectively randomized to receive either visual foam sclerotherapy (VFS) alone or VFS combined with UGFS of the great saphenous vein (GSV). The results show that UGFS + VFS and VFS alone are equally effective for the treatment of GSV reflux, despite the lower volume of foam used for VFS alone. However, as the authors

Compression after UGFS	Article	Results
Compression Duration	O'Hare JL, Stephens J, Parkin D, Earnshaw JJ. Randomized clinical trial of different bandage regimens after foam sclerotherapy for varicose veins. *Br J Surg.* 2010;97:650-656.	124 patients C_2 (lower extremity) UGFS treatment Group 1 (n 61); Compression by bandages first 24 hours, then compression with antithrombosis stockings for 14 days Group 2 (n 63); Compression by bandages first 5 days, then compression with antithrombosis stockings for 14 days **Follow-up: 1 day to 6 weeks** *Pain and AVVSS: (1 day to 2 weeks)* No difference *Superficial thrombophlebitis: (2 weeks)* No difference *SF-36, AVVSS: (1 day to 6 weeks)* No difference *Vein obliteration: (6 weeks)* Group 1, 90%; Group 2, 89%; NS
Compression by stocking vs no compression	Hamel-Desnos CM, Guias BJ, Desnos PR, Mesgard A. Foam sclerotherapy of the saphenous veins: randomized controlled trial with or without compression. *Eur J Vasc Endovasc Surg.* 2010;39:500-507.	64 patients C_{2s}-C_6; GSV or SSV incompetence UGFS treated then stocking compression (15 to 20 mm Hg) for 3 weeks vs no compression **Follow-up: 14 to 28 days** *Venous obliteration, Length of obliterated vein, Reflux suppression, Side effects, Pain, Edema, Paraesthesia, Patient satisfaction QoL:* No difference
	Hamel-Desnos CM, Desnos PR, Ferre B, Le Querrec A. In vivo biological effects of foam sclerotherapy. *Eur J Vasc Endovasc Surg.* 2011;42:238-245.	40 patients C_{2s}-C_6,E_p,A_s,P_{r2-4}; GSV or SSV incompetence; UGFS treated then stocking compression (15 to 20 mm Hg) for 3 weeks (n=20) vs no compression (n=20) **Follow-up: 1, 7, 14, and 28 days** *Biological markers of inflammation:* fibrinogen, factor VIII, thrombomodulin, thrombin-antithrombin complex, D-dimers, platelet factor 4 and troponin; NS **Follow-up: 28 days** *Venous obliteration:* 100% in both groups

Table V. Compression after sclerotherapy

Abbreviations: AVVSS, Aberdeen varicose vein severity score; SF-36, generic quality of life questionnaire; QoL, quality of life; UGFS, ultrasound-guided foam sclerotherapy

Treatment	Article	Results
VFS alone vs VFS+UGFS	Yamaki T, Hamahata A, Soejima K, Kono T, Nozaki M, Sakurai H. Prospective randomized comparative study of visual foam sclerotherapy alone or in combination with ultrasound-guided foam sclerotherapy for treatment of superficial venous insufficiency: preliminary report. *Eur J Vasc Endovasc Surg.* 2012;43:343-347.	103 lower limb patients C_2-C_4; Incompetent GSV including SFJ 1% polidocanol; 10 mL maximum; Tessari method Group 1 (n 51), UGFS in GSV+VFS in tributary; Group 2 (n 52), VFS in tributary Only one complementary session during follow-up **Follow-up: 2 weeks and 1, 3, and 6 months** *US control. 4 types: occlusion, partial recanalization with and without reflux, total recanalization with reflux:* No difference in terms of US findings and VCSS between the groups, despite the lower volume of foam used in group 2; *P*=0.017

Table VI. Visual foam sclerotherapy alone or in combination with UGFS

Abbreviations: US, ultrasound investigation; GSV, great saphenous vein; SFJ, saphenofemoral junction; UGFS, ultrasound-guided foam sclerotherapy; VFS, injection of foam under visual control; VCSS, venous clinical severity scores

Treatment	Article	Results
Anticoagulation (LMWH vs Warfarin) in patients with documented thrombophilia and treated by UGFS for varices	Hamel-Desnos CM, Gillet JL, Desnos PR, Allaert FA. Sclerotherapy of varicose veins in patients with documented thrombophilia: a prospective controlled randomized study of 105 cases. *Phlebology*. 2009;24:176-182.	105 patients presenting with thrombophilia; Factor V mutation (heterozygous and homozygous); Factor II mutation; High factor VIII; and combination of 2 factors Group H; nadoparin at 4000 UI at the same time as UGFS treatment; Group W; warfarin at 1 mg per day for 4 weeks after UGFS treatment In both group compression was used at 15 to 20 mm Hg for 4 weeks **Follow-up:** No episodes of symptomatic DVT or PE occurred; no instances of DVT were revealed by US monitoring

Table VII. *Sclerotherapy of varicose veins in patients with documented thrombophilia*

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; US, ultrasound; UGFS, ultrasound-guided foam sclerotherapy

stated some parameters were not taken into account including optimal foam volume, injection techniques, vein diameter, and gas fabrication. In conclusion, no recommendation can be drawn from this trial.

Sclerotherapy of varicose veins in patients with documented thrombophilia[23]

Comment. This study suggests that in the three most common forms of thrombophilia; sclerotherapy in combination with thromboprophylaxis, can be performed safely. Prophylaxis with low molecular weight heparin is easier to use than warfarin. In conclusion, this RCT can be graded 1B.

2. Sclerotherapy versus other operative treatments

Sclerotherapy versus open surgery[24-31] (*Table VIII*)

Comment. The main interest of Belcaro's article is the 10-year follow-up duration, but its design is deceptive for various reasons. First, patients are distributed in 6 groups where procedures are either obsolete (in group 3, the technique used was isolated high ligation [HL]) or poorly described (in group 6, the sclerosing agent was tetradecyl sodium sulphate combined with the tensoactive agent J&J-93FA). In the follow-up, ultrasound examination and ambulatory venous pressure was routinely performed for measuring refill time, which is unusual and invasive; consequently, it is surprising that patients accepted this investigation. Furthermore, only noncomplicated varices (C2) were enrolled and we know that C2 refill time is usually not strongly modified. Additionally, the number of patients assessed at year 10 is not documented. To conclude, it looks difficult to draw valid conclusions from Belcaro's article.[24]

The second article (Wright) compared Varisolve® with either open surgery or sclerotherapy.[25] Unfortunately, open surgery involves various procedures including isolated HL, HL+stripping, and phlebectomy rendering the outcome difficult to assess. Nevertheless, the authors concluded that surgery was more efficacious. Varisolve® versus sclerotherapy was conclusive in favor of Varisolve®, but the sclerotherapy group was not homogenous as both liquid and handmade foam as well as polidocanol or sodium tetradecyl sulphate were used.[25]

Three other articles combining HL+UGFS and comparing the combination with conventional open surgery concluded more or less in favor of HL+UGFS, but follow-up was only a 6-month maximum duration.[26-28]

Conversely, Kalodiki's article is a fully documented 5-year follow-up RCT, which concluded that treatment was equally effective between the surgical and foam groups, as demonstrated with the venous clinical severity score (VCSS), venous segmental disease score (VSDS), and the physical component of the SF-36 score improvements. The Aberdeen Varicose Vein Questionnaire (AVVQ) was significantly better in the surgery group, but the margins were small and this may not have any clinical significance.[29] In addition, foam is less expensive; therefore, the cost effectiveness ratio is in favor of foam. It is important to keep in mind that in the above mentioned articles, UGFS was combined with HL.[26-29]

Operative procedure	Article	Results
Open surgery vs open surgery+UGFS vs UGLS	Belcaro G, Cesarone MR, Di Renzo A, et al. Foam-sclerotherapy, surgery, sclerotherapy, and combined treatment for varicose veins: a 10-year, prospective, randomized, controlled, trial (VEDICO trial). *Angiology.* 2003;54:307-315.	887 patients, 1371 lower extremity C_2; Incompetent GSV including SFJ; Multicenter study Patients randomized into 6 groups Sclerosing agent TSD: Group 1, UGLS low dose; Group 2, UGLS high dose; Group 3, UGLS+SFJ ligation+SS; Group 4, phlebectomy; Group 5, OS+UGFS high dose; and Group 6, UGFS OS **Follow-up: 10 years** 117 lost to follow-up; No difference in terms of results taking into account PREVAIT: 37% to 56%; NSD between the 6 groups AVP and RT improved compared to preoperative data; NSD between the 6 groups
Liquid or foam sclerotherapy vs SFJ ligation or SFJ ligation +S, or phlebectomy	Wright D, Gobin JP, Bradbury AW, et al; Varisolve® European Phase III Investigators Group. Varisolve® polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. *Phlebology*. 2006;21:180-190.	710 patients; C_{2s-6}; GSV and SSV; surgery: no information on anesthesia Randomized into 3 groups foam sclerotherapy (Varisolve polidocanol), surgery (HL 92%, stripping 88%, phlebectomies 53%), or conventional sclerotherapy (92% homemade foam) Endpoint ultrasound determined occlusion of truncal veins and elimination of reflux; **Follow-up: 12 months** Surgery superior to Varisolve foam (86% vs 63%) Varisolve foam superior to conventional sclerotherapy (90% vs 76%, *P*=0.001) Foam resulted in less pain and earlier returns to work than surgery.
UGFS+SFJ ligation vs open surgery	Bountouroglou DG, Azzam M, Kakkos SK, Pathmarajah M, Young P, Geroulakos G. Ultrasound-guided foam sclerotherapy combined with sapheno-femoral ligation compared to surgical treatment of varicose veins: early results of a randomised controlled trial. *Eur J Vasc Endovasc Surg*. 2006;31:93-100.	GSV; General anesthesia for all procedures UGFS+HL (n=30) versus HL+S (n=30) **Follow-up: 3 months** *UGFS+HL:* Early recanalization (13%) by complementary injection; less expansive, more rapid return to normal activities (*P*<0.0001) No difference in terms of complication and occlusion
	Abela R, Liamis A, Prionidis I, et al. Reverse foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard and invagination stripping: a prospective clinical series. *Eur J Vasc Endovasc Surg*. 2008;36:485-490.	GSV; General anesthesia for all procedures HL+reverse foam sclerotherapy (n=30); HL+invagination S (n=30); HL+ standard S (n=30) **Follow-up: 2 weeks** *HL+reverse foam sclerotherapy*: less postoperative complications and better patient satisfaction
	Liu X, Jia X, Guo W, et al. Ultrasound-guided sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard stripping. *Int Angiol.* 2011;30:321-326.	GSV C_{2-6}; General anesthesia for all procedures HL+S+/-TP (Group S, n=30); HL+USFGS (Group F, n=30) Complementary foam sclerotherapy treatment (Group F n=5) **Follow-up: 6 months** *Group F:* Shorter operation time, return-to work time and less analgesia treatment (*P*<0.01) *Obliteration:* Group F, 80%; Group S, 89.5%
	Kalodiki E, Lattimer CR, Azzam M, Shawish E, Bountouroglou D, Geroulakos G. Long term results of a randomized controlled trial on ultrasound-guided foam sclerotherapy combined with sapheno-femoral ligation vs standard surgery for varicose veins. *J Vasc Surg*. 2012;55:451-457.	GSV C_{2-6}; classical surgery with general anesthesia HL+USFGS local anesthesia: Group S, HL+S+/-TP (n=39); Group F, HL+USFGS (n=41) Complementary foam sclerotherapy treatment; Group S, n=25; Group F, n=33 **Follow-up: 3 to 5 years** *VCSS:* no difference; *VSDS*: no difference; *AVVQ*: better in Group S (*P*<0.0005); *SF 36*, physical component no difference

Open Surgery vs UGFS	Figueiredo M, Araújo S, Barros N Jr, Miranda F Jr. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. *Eur J Vasc Endovasc Surg.* 2009;38:758-763.	GSV $C_{5,}E_{p,}A_{s,}P_{r}$; surgery under local anesthesia UGFS (n=27) 1 to 3 sessions, 10 mL/session vs. HL+S (n=29) **Follow-up: 6 months** Significant clinical improvement in both groups *GSV obliteration:* UGFS=90% and HL+S=78% (*P*=ns related to the small number of patients included)
	Shadid N, Ceulen R, Nelemans P, et al. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. *Br J Surg.* 2012;99:1062-70.	Incompetent SFJ +GSV incompetence at least 20 cm at the thigh UGFS (n=230); 3% polidocanol 1 mL vs HL+S (n=200); Partial GSV stripping+/- tributary phlebectomy under general anesthesia **Follow-up: 2 years** *PREVAIT Symptoms+QoL:* HL+S, 9% (16/177); UGFS, 11.3% (24/213) (*P*=0.407) *Reflux:* More than 2 cm in the length of the GSV treated; HL+S, 21%; UGFS, 35% (*P*=0.003) *Cost:* HL+S, €1824; UGFS, €774

Table VIII. Sclerotherapy vs open surgery

Abbreviations: AVP, ambulatory venous pressure; AVVQ, Aberdeen Varicose Vein Questionnaire; CA, chemical ablation; GSV, great saphenous vein; HL, high ligation; NDS, no significant difference; OS, open surgery; PREVAIT, presence of varices after operative treatment; RT, refill time; S, saphenous stripping; SFJ, saphenofemoral junction; SSV, small saphenous vein; TP, tributary phlebectomy; TSD, tetradecyl sodium sulfate; UGFS, ultrasound-guided foam sclerotherapy; UGLS, ultrasound-guided liquid sclerotherapy; VCSS, venous clinical severity score; VSDS, venous segmental disease score

Treatment	Article	Conclusions
EVLA+phlebectomy vs UGFS	Lattimer CR, Kalodiki E, Azzam M, Geroulakos G. Validation of a new duplex derived haemodynamic effectiveness score, the saphenous treatment score, in quantifying varicose vein treatments. *Eur J Vasc Endovasc Surg.* 2012;43:348-354.	66 patients C_2-C_6; GSV incompetence with refluxing SFJ UGFS vs EVLA+phlebectomy under local anesthesia **Follow-up: 3 weeks to 3 months** *DUS and APG to build a STS: (3 months)* no difference in AK in terms of STS improvement between the 2 procedures
	Lattimer CR, Azzam M, Kalodiki E, Shawish E, Trueman P, Geroulakos G. Cost and effectiveness of laser with phlebectomies compared with foam sclerotherapy in superficial venous insufficiency. Early results of a randomised controlled trial. *Eur J Vasc Endovasc Surg.* 2012;43:594-600.	100 patients C_2-C_6; GSV incompetence with refluxing SFJ Randomized UGFS vs EVLA+phlebectomy under local anesthesia **Follow-up: 3 weeks-3 months** *AK GSV obliteration rate, AVVQ, VCSS, VFI: (3 months)* NS, UGFS significantly outperformed EVLA in cost, treatment duration, pain, analgesia requirements and recovery

Table IX. Endovenous laser ablation vs UGFS

Abbreviations: AK, above knee; APG, air plethysmography; AVVQ, Aberdeen Varicose Vein Questionaire; DUS, duplex ultrasound; EVLA, endovenous laser ablation; GSV, great saphenous vein; SFJ, saphenofemoral junction; STS, saphenous treatment score; UGFS, ultrasound-guided sclerotherapy; VCSS, venous clinical severity score; VFI, venous filling index

Does UGFS without HL provide the same results or, more importantly, are pulmonary embolisms (PE) more frequent. Two RCT's without HL do not mention immediate postoperative PE.[30-31] Shadid's article provides a middle term outcome.[31] There is no difference in terms of clinical results, but presence of reflux is significantly more frequent after UGFS, but conversely total cost is in favor of UGFS.

In conclusion, UGFS is credited as with having a better postoperative course, but recurrence of varices seems more frequent. The Society for Vascular Surgery and the

Operative procedure	Article	Conclusions
Open surgery versus EVLA vs RFA vs UGFS	Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg.* 2011;98:1079-1087.	580 lower limbs; CEAP, $C_{2-4}E_pA_sP_r$; GSV with SFJ reflux All procedures under local anesthesia and by phlebectomy OS (group 1) vs EVLA 980 and 1470 nm bare fiber (group 2) vs RFA Closure Fast™ (group 3) vs UGFS, 1 or 2 sessions (group 4) **Follow-Up:** *3 days and 1 month* Better QoL (SF 36) as well as less pain ($P<0.001$) and shorter time off work ($P<0.001$) in groups 3 and 4 *1 year* *DS examination:* GSV occlusion better in group 1, 2, and 3 compared with group 4 ($P<0.001$) *Clinical recurrence:* No significant difference
	Rasmussen LA, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins with 3 years follow-up. *J Vasc Surg Venous Lymphat Disord.* 2013;1:349-356.	580 lower limbs; CEAP, $C_{2-4}E_pA_sP_r$; GSV with SFJ reflux All procedures under local anesthesia and completed by phlebectomy OS (group 1) vs EVLA 980 and 1470 nm, bare fiber (group 2) vs RFA Closure Fast™ (group 3) vs UGFS, 1 or 2 sessions (group 4) **Follow-Up: 3 years** *DS examination*: better GSV occlusion in groups 1, 2, and 3 compared with group 4 ($P<0.001$) *Clinical recurrence*: NSD ($P=0.6596$) *Reoperations:* more frequent in group 4 ($P<0.001$), but were mainly treated by UGFS in all groups *VCSS* improved in both groups, NSD between groups. *AVVSS* improved significantly in both groups from 3 days onwards ($P<0.0001$), NSD between the groups at any point in time *SF-36 scores* improved in all domains and all groups

Table X. *EVLA vs radiofrequency ablation vs UGFS vs surgical stripping*

Abbreviations: AVVSS, Aberdeen varicose vein severity score; DS, duplex ultrasound; EVLA, endovenous laser ablation; GSV, great saphenous vein; NSD, no significant difference; OS, open surgery: saphenofemoral ligation +stripping, +/-perforator ligation, +/-tributary phlebectomy; QoL, quality of life; RFA, radiofrequency ablation; SFJ, saphenofemoral junction; UGFS, ultrasound-guided sclerotherapy; VCSS, venous clinical severity score

American Venous Forum recommendations are not fully conclusive. They provided a grade 1B recommendation for UGFS in the treatment of varices, but there are no recommendations available to differentiate between open surgery and UGFS for the treatment of incompetent saphenous vein.[32]

Endovenous laser ablation (EVLA) versus UGFS[33,34]

(*Table IX*)

Comment. This trial, based on 2 articles, favors UGFS, but the follow-up was short (3 months), besides the EVLA fiber was a bare one, and we know from various studies that jacket-tipped, radial fiber, or tulip–assisted EVLA improve the immediate postoperative course.[35-38] Lattimer's RCT conclusion contradicts the grade 1B recommendation from the Society for Vascular Surgery and the American Venous Forum. For treatment of the incompetent saphenous vein, they recommend endovenous thermal ablation over chemical ablation with foam.

EVLA vs radiofrequency ablation vs UGFS vs surgical stripping[39,40]

These two RCTs are for a five-year ongoing trial. Results after one year showed that all treatments are efficacious with a higher technical failure rate after foam sclerotherapy.[39] Laser and foam sclerotherapy leads to faster recovery, less postoperative pain, and superior quality of life scores compared with laser and surgery.[39]

A 3-year follow-up duplex scan confirms that the GSV occlusion rate is lower in the UGFS group ($P<0.001$),[40]

but there was no difference in terms of clinical recurrence; VCSS, AAVVQ, and SF-36 scores. Reoperations were more frequent in UGFS group ($P<0.001$), but interestingly, recurrence were mainly treated by UGFS in all groups.[40]

Sclerotherapy versus other procedures for ablation of varices

There are no RCTs comparing sclerotherapy with open surgery preserving the saphenous trunk, other thermal ablation techniques (radiofrequency, foam), or a new technique such as Clarivein®[41] or Sapheon®[42]

DISCUSSION

Although RCTs remain the best tool for comparing clinical effectiveness, as mentioned in Grade system, nevertheless, RCTs must be evaluated carefully. Skepticism about conventional RCTs in nonpharmacological interventions (eg, sclerotherapy) remains, and expertise-based RCTs are suggested as an alternative where participants are randomized to clinicians with expertise in intervention A or clinicians with expertise in intervention B, and the clinicians perform only the procedure for which they are the expert.[43]

Accurate analysis of the presented RCTs is difficult as hidden bias can be hard to identify. For example, in some RCTs, surgery was performed either under local tumescent anesthesia or general anesthesia that may influence short-term evaluation.

CONCLUSION

Twenty-two RCTs (27 articles) and an analysis of observational studies were evaluated, which provided some conclusions regarding sclerotherapy. Sclerotherapy is a safe procedure with a low rate of adverse reactions. UGFS is more efficient in terms of obliteration than liquid sclerotherapy, where 1% and 3% polidocanol foam demonstrated equivalent efficacy in GSV treatment when the trunk was less than 8 mm in diameter. Benefits from optimal compression are still being debated. UGFS can be performed safely in combination with thromboprophylaxis in patients with thrombophilia. Compared with other operative treatments, UGFS is credited with more frequent recurrences, but they are easily treated by reinjection with satisfactory results. Presently, UGFS is cost effective when compared with other operative procedures for treating varices.

Corresponding author
Michel PERRIN, MD
Vascular Surgery, Unite de Pathologie Vasculaire Jean Kunlin,
26 Chemin de Decines,
F-69680, Chassieu, France

E-mail: m.perrin.chir.vasc@wanadoo.fr

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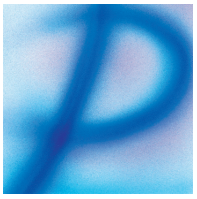

Benefits of micronized purified flavonoid fraction in the reduction of symptoms after operation for hemorrhoidal disease

Vladimir ASTASHOV,
Dmitry TIMCHENKO

N.N. Burdenko Main Military Clinical Hospital of the Ministry of Defense of the RF, Moscow, Russia

ABSTRACT

Analysis of the treatment of patients with chronic hemorrhoids was carried out in the department of abdominal surgery at the N.N. Burdenko Main Military Clinical Hospital. The use of micronized purified flavonoid fraction (contained in Detralex) in 56 patients with stage II to IV hemorrhoidal disease in the pre- and postoperative period resulted in improved treatment outcomes.

The term "hemorrhoids" comes from the Greek words "haema" (blood) and "rhoos" (flowing). This term was first used by Hippocrates to describe bleeding from veins of the anus.[1] The term "hemorrhoids" in English-language literature stands for both pathological and normal anatomical structures of the anal canal, which can be found in persons of any age. In developed countries, hemorrhoidal disease (HD) is the most prevalent disease of the rectum.[2] The estimated population of people with hemorrhoids at any given time in Russia reaches 35% to 47% of all coloproctology disorders and the number of new cases of hemorrhoids diagnosed each year is 140 to 160 cases per 1000 in the adult population.[3] Prevalence in Austria was estimated to be 39% of the adult population,[4] and a high body mass index (BMI) was found to be an independent risk factor for developing HD. According to estimates from the United States up to 50% of the adult population will develop hemorrhoids, usually after the age of 30.[5]

The term "hemorrhoids," commonly encompasses two different vascular structures: (i) internal hemorrhoidal plexus, which is submucosal; and (ii) external hemorrhoidal plexus, which is subcutaneous.

Histological analysis of the hemorrhoidal plexus shows clear predominance of a venous (cavernous) component. Veins have thick walls composed of an endothelium lined with collagen fibers. This fibrous layer comprises a frame

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bleeding; flavonoids; hemorrhoid diseases; MPFF; surgery; symptoms

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made of elastic fibers and is not associated with the mucosa. The veins form vascular "lakes" representing fusiform, sacciform, or serpiginous extensions with a structure resembling the structure of veins in cavernous bodies. There are also thin-walled capillaries consisting of simple endothelium surrounded by sparse collagen fibers, and they are hardly distinguishable from the surrounding connective tissue membrane, which has no elastic frame. These capillaries run between the mucous membrane and the cavernous bodies. Obviously, these tissues have independent vascularization. Another feature of hemorrhoidal plexuses is arteriovenous anastomoses (shunts).[6] Their presence helps to explain arterialization of the venous blood contained in the cavernous bodies. It is also supposed that anastomoses allow for a more rapid filling of cavernous bodies during arterial blood inflow, observed immediately after defecation.

Therefore, the presence of hemorrhoidal tissue with dilated venous structures (caverns) in the anal canal is a normal situation. These veins are characterized by a particular structure and have no valves.

The available evidence strongly suggests that the function of the internal sphincter itself is not sufficient to ensure complete closure of the anal canal. Internal hemorrhoids play an important role to keep intestinal contents in the rectum. At rest, vascular "lakes" (caverns) are filled with blood and are in contact with each other; as a result, the pressure in the anal canal is only 15% of the pressure in hemorrhoids.[7] During defecation, longitudinal anal muscles woven with the submucousal layer contracts, which squeezes and moves the internal hemorrhoidal structures toward the internal sphincter, which then relaxes.[8] The contraction of the longitudinal anal muscle leads to a shortening of the anal canal, devastation of the hemorrhoidal plexus, and inversion of the anal margin. After defecation, hemorrhoids are not under pressure anymore and gradually begin to fill with blood. This process is facilitated by the opening of precapillary sphincters, which enable blood flow through arteriovenous shunts. The volume of hemorrhoidal plexuses rise causing the anal canal to close and the pressure in the sphincter to increase.

What factors lead to the transformation of this normal physiological process into a pathological one? The generally accepted pathological mechanism of the development of clinical symptoms of HD is that hemorrhoids increase in size and become displaced with time. As a result, lesions occur in the mucous membrane that lines the hemorrhoidal plexuses, which causes bleeding from the rectum.

Research from many authors have demonstrated that hemodynamic and degenerative factors are the main causes of hemorrhoid development.[3] Hemodynamic factors are represented by vessel dysfunction, which provides blood inflow and outflow in cavernous formations, and results in their overflow, thereby contributing to the abnormal increase of hemorrhoids. The development of dystrophic processes in the common longitudinal muscle of the submucosal layer of the rectum and the Parks ligament, which holds the cavernous bodies in the anal canal, results in a progressive and irreversible hemorrhoid displacement (prolapse).

Current concepts on the HD pathogenesis unalterably include venous components of hemorrhoids as one of the major substrates of the disease. Increase in the pressure in hemorrhoidal plexuses and their venous structures (corpora cavernosa) leads to lesion formation in the vascular wall, which accounts for the occurrence of consequences such as: (i) inflammation processes; (ii) swelling of the perivascular connective tissue; (iii) hemorrhoid thrombosis; and (iv) local arterial bleeding.

Doctors should direct their efforts, if possible, toward the above mentioned pathological mechanisms to more effectively relieve these manifestations. Therefore, we paid considerable attention to the drug containing micronized purified flavonoid fraction (MPFF)*. This oral venoactive drug, which consists of 90% micronized diosmin and 10% flavonoids expressed as hesperidin, diosmetin, linarin, and isorhoifolin, has been shown to effectively reduce symptoms of HD. Several randomized double-blind placebo-controlled trials have evaluated the efficacy of oral MPFF in the management of acute internal hemorrhoids.[9-12] It is acknowledged that MPFF counteracts pathological mechanisms of HD at an early stage of clinical manifestation and has a positive impact on the local hemodynamic component due to normalization of venous tone in

** Registered as Ardium®, Alvenor®, Arvenum® 500, Capiven®, Daflon® 500 mg, Detralex®, Elatec®, Flebotropin®, Variton®, and Venitol®.*

hemorrhoidal plexuses,[13,14] a reduction in excessive capillary permeability and capillary walls fragility,[14,15] an improvement in lymphatic drainage,[16] and an inhibition of local inflammation processes.[14,17,18]

Patients who continue to have symptoms of acute internal hemorrhoids while receiving medical treatment may require instrumental or surgical treatment.[14] Surgical treatment is required in a small fraction of patients (5% to 10%) with chronic external or internal hemorrhoids.[19] The addition of MPFF to surgical procedures appears to be cost effective. MPFF may reduce the duration and/or intensity of post-hemorrhoidectomy symptoms[20-23] and reduce patient recovery time. Hemorrhoid grade was not known in the previous trials.

The aim of the present trial is to know whether the association of MPFF with surgery for hemorrhoid stages II to IV may be more effective at reducing post-hemorrhoidectomy symptoms.

MATERIALS AND METHODS

For patients who came in for outpatient consultation, MPFF was prescribed at 2 tablets daily for 30 days before the surgery in the treatment group (MPFF treatment group). In the postoperative period, all these patients received 2 MPFF tablets twice daily for 4 days, and then 2 MPFF tablets twice daily for 3 days. The control group was comprised of 24 patients who were not treated with MPFF before surgery.

Patients with stage II HD underwent hemorrhoid dearterialization using the A.M.I. HAL-Doppler device. Patients with stage III to IV HD underwent Milligan-Morgan hemorrhoidectomy in the 2nd modification by the Institute of Coloproctology.

Statistical analysis. Comparison was made between the results of the 2 groups (MPFF-treated group and control group) using a Student t test. The results were considered significant at $P<0.05$

RESULTS

A total of 56 patients underwent surgery for stage II to stage IV chronic HD in the Department of abdominal surgery at the N.N. Burdenko Main Military Clinical Hospital during 2008 to 2011; 35 were males and 21 were females. The age of the patients ranged from 26 to 65 years. Median age was 58.5 years. Fifteen patients were diagnosed with stage II HD, 32 patients with stage III HD, and 9 patients with stage IV HD. The most frequent reason for seeking medical advice was rectal bleeding, and then, prolapse of internal hemorrhoids. All patients in either group presented with rectal bleeding, pain, and prolapse.

Reduction of postoperative symptoms at day 2 following the procedure was more pronounced in the MPFF-treatment group compared with the control group (*Table I*). Compared with the control group, the stage II HD patients of the MPFF treatment group no longer had postsurgery symptoms at day 2. This was significant for both bleeding and prolapse (P=0.01), but not pain (P=NS). Symptoms were present in stage III HD patients at day 2 after surgery, which was significantly less in the MPFF-treatment group compared with the control group ($P<0.02$). Reduction of symptoms in stage IV HD patients was slightly better in the MPFF-treatment group compared with the control group, but the difference between groups was not significant except for bleeding (P = 0.008) (*Table I*). No allergic reactions were observed.

Symptoms	Stage II			Stage III			Stage IV		
	Treatment group n=9	Control group n=6	*P*-value	Treatment group n=18	Control group n=14	*P*-value	Treatment group n=5	Control group n=4	*P*-value
Bleeding, n (%)	0 (0)	4 (66.7)	0.002	2 (11.1)	10 (71.4)	<0.001	1 (20)	4 (0)	0.008
Pain, n (%)	0 (0)	1 (16.7)	NS	5 (27.8)	9 (64.3)	0.021	2 (40)	3 (75)	NS
Prolapse, n (%)	0 (0)	2 (33.3)	0.031	13 (72.2)	14 (100)	0.012	4 (80)	4 (0)	NS

Table I. *Post-surgery symptoms in each group at day 2 after intervention.*

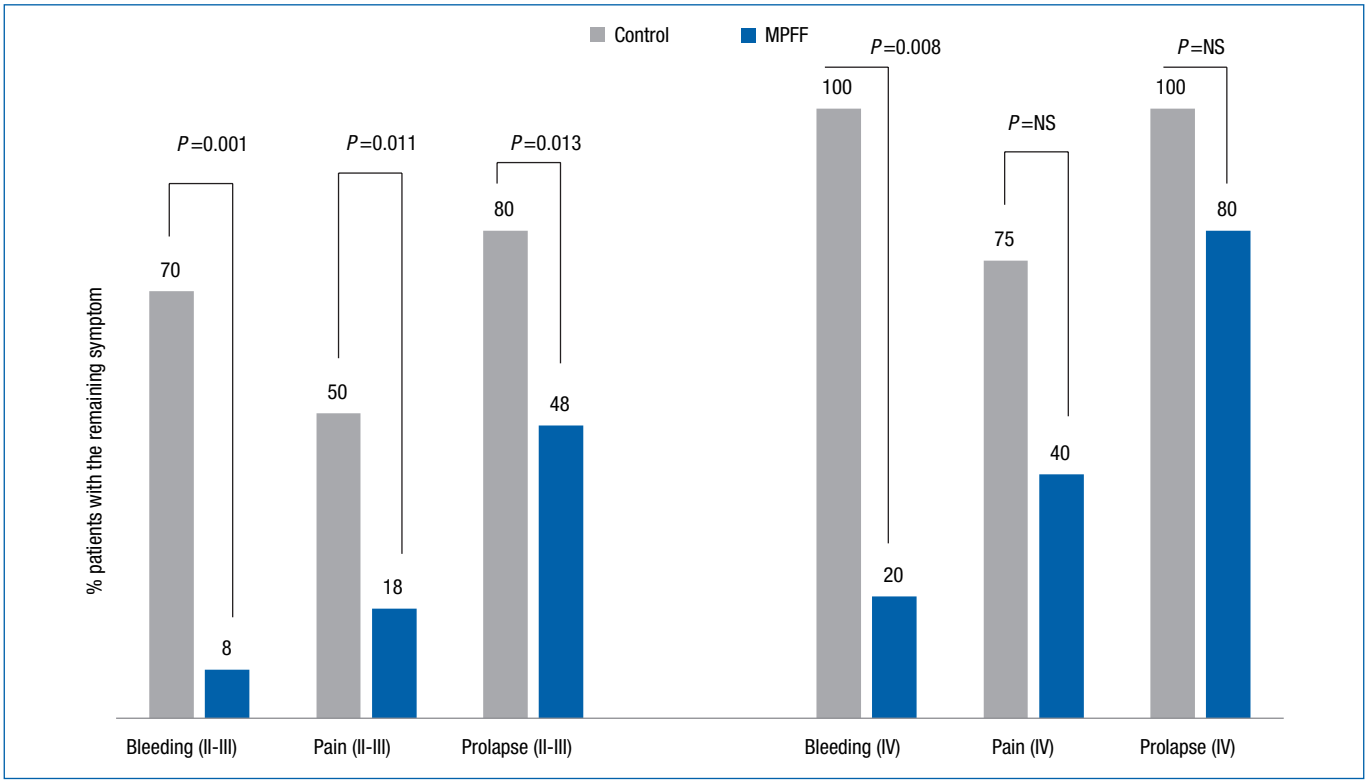


Figure 1. *Comparing remaining postsurgery symptoms between groups in patients with stages II+III and stage IV hemorrhoidal disease.*

We noticed that in the MPFF-treatment group, not only were symptoms reduced, but also the need for analgesics, anti-inflammatory drugs, and hemostatic agents were reduced, which may decrease the total cost of treatment substantially. *Figure 1* shows the comparison of the results (presence of postsurgery symptoms) between groups in stages II + III and stage IV HD patients.

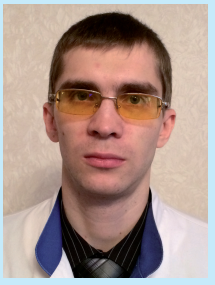
In stage III to stage IV HD control group patients, duration of wound healing lasted between 3 and 5 days, and in most cases we failed to remove all the hemorrhoids in a single operation due to the advanced stage of disease and high risk of postoperative complications.

CONCLUSION

The role of the venous component in the pathogenesis of HD should not be ignored, as well as its involvement in the occurrence of postsurgery symptoms. The early relief of symptoms when associating MPFF with HD surgery may reduce the duration of the hospital stay. In addition, the reduction in the need for analgesics, anti-inflammatory drugs, and hemostatic agents not only may decrease the total cost of treatment, but may also positively influence the psychoemotional status of the patients. Therefore, we recommend the use of MPFF in association with HD surgery.

Corresponding author
V.L. ASTASHOV
N.N. Burdenko Main Military Clinical Hospital of the Ministry of Defense of the RF, Moscow, Russia

E-mail: astashov095@mail.ru



Corresponding author
D.A. TIMCHENKO

E-mail: dimatim@yandex.ru

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Chronic venous disease and the genetic influence

Michel-René BOISSEAU

University Victor Segalen Bordeaux2, Department of Pharmacology, Bordeaux, France

ABSTRACT

The etiology and pathophysiology of chronic venous disease (CVD) have been intensively studied in the past decades. The elucidation of mechanisms leading to CVD is a challenging task because acquired phenomena alone are presumably insufficient to explain the full clinical course of the disease. CVD genetic screening adopted the most appropriate methodology to find out which chromosomal and/or gene defects could be responsible for the predisposition. They include family studies, gene expression methods (eg, single candidate gene expression, DNA microarrays), or genotyping methods (eg, single nucleotide polymorphisms, mutations). Investigations have so far only partially produced coherent results and there must be further collaborations in order to successfully advance the field of venous disease genetics. More acute definitions and better classification of patients should avoid major bias. The present review offers a panoramic view on the genetic propensity of venous disorders based on literature.

The venous system in humans is permanently submitted to high blood pressures, particularly in lower limb veins. Prolonged venous hypertension, due to standing, unknown among other mammalians, is responsible for diverse clinical aspects of chronic venous disease (CVD), mostly of primary etiology. Globally, CVD may affect more than 60% of the adult population,[1] and its high costs, both at individual and societal levels, have been well documented.[2]

Research in recent years has dramatically improved our understanding of the pathophysiology of CVD. Prolonged venous hypertension is linked to all theories regarding CVD pathogenesis and chronic inflammation, which maintains a vicious circle of disease progression. Numerous inflammatory factors, cytokines, growth factors, and tissue enzymes such as vascular endothelial growth factor (VEGF), tumor growth factor β (TGFβ), and tissue inhibitors of the matrix metalloproteinases (TIMPs) are involved in the loop, which ends with remodeling and fibrosis of the venous wall. These complex interacting events have been extensively studied.[3-5] Chronic hypertension is transmitted to the capillaries, which ultimately leads to ulceration[6] (*see below for more details*).

Keywords:
congenital; familial; genetics; hereditary; varicose veins; venous ulcer

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Whether CVD is mostly acquired rather than partly due to hereditary phenomenon remains to be elucidated. The aim of this review is to discuss the available data from literature concerning heredity of varicose veins from epidemiology to molecular disturbances and venous ulcers including their quality of healing.

HEREDITY OF VARICOSE VEINS

Evidence for family history in patients with varicose veins

Social and environmental factors

CVD evolution, at any stage, is linked to intricate social or environmental factors and to the field of physiology and biology. For example, obesity, which increases pressure in lower limbs veins, is linked to genetic factors because the heritability is close to 80%.[7,8] However, obesity is also linked to social food habits or may even be due to adenovirus infections or trendy eating fashions. In addition, fat tissue in obese patients usually delivers plasminogen activator inhibitor (PAI)-1, interleukin-6, and the adhesion molecule P-selectin, which all contribute to vein lesions. From a genetic point of view, these factors can all be altered by gene defects. CVD exhibits "multisided clinical phenotypes; characteristics of complex diseases."[9]

Large epidemiological surveys

Some studies have reliably examined the role of genetic factors in the overall clinical picture, but no study has examined it at the molecular level. For a long time, physicians have asserted that 70% to 80% of their patients with varicose veins have a family history of the disease,[10-12] and it was found that 42% of women with varicose veins had a family history.[13] In a study that analyzed 4033 nuclear families, heritability of CVD equaled 17.3%, suggesting a genetic component.[14]

Twins

Few studies have been conducted on twins. Available data shows a higher degree of concordance between monozygotic twins (75%) than between dizygotic twins (52%), although the difference was not statistically significant because the numbers involved were too few.[15] In a study based on impedance plethysmography in 46 pairs of twins, it was shown, after appropriate adjustments, that heritability of compliance was 90%; so a venous physical function, involved in the wall tonicity, is dependent on genetic factors.[16]

Case-control studies

A case-control study conducted on 134 families has properly analyzed the incidence of varicose veins in one or more of the parents examined clinically; this latter point being essential and far better than using questionnaires. The risk of developing varicose veins for the children was 90% when both parents suffered from this disease, and 25% for males and 62% for females when one parent was affected.[17] Using the Hospital Register in Sweden, and thereby eliminating recall bias, family history of hospital treatment for varicose veins was associated with an increased risk of similar treatment among relatives.[18] In an assay conducted in Finland, among a large population of people between 40 and 60 years of age, a reported positive family history of varicose veins was found to be an independent and significant risk indicator.[19] In another trial, 82% of patients with CVD and 22% without had a positive family history.[20] Misclassification of varicose veins may have introduced some bias in such studies, depending on whether 'varicose veins' were defined as visible dilated veins or as refluxing veins.[21,22]

Modes of heredity

Various modes of heredity have been hypothesized. Some authors have, from the outset, postulated a recessive mode of inheritance, which involves a pedigree segregation ratio as well as a discontinuous mode of heredity. Moreover, when only one parent was affected, no correlation was observed between the sex of the affected parent and varicose veins in the children. However, it was common to observe pedigrees where men and their fathers, but not their mothers, were affected. These factors tend, therefore, to exclude a sex-linked pattern of inheritance and to stress the multifactorial nature of varicose vein inheritance.[23] However, the data from the literature seem to indicate the existence of different types of heredity depending on the families studied.

Other investigators observed an autosomal dominant-like inheritance with an estimated 50% of varicose vein patients having some genetic linkage.[24] A Chinese study investigated the hereditary nature of varicose veins in a hospital population.[25] The analysis of nuclear families was compatible with autosomal dominant inheritance, with 70% to 92% penetrance, some pedigrees were compatible with autosomal recessive inheritance, and 37% of cases were sporadic.

Recently, an autosomal dominant mode of inheritance has been observed in nine families.[26] Varicose vein disease in these families was linked to the candidate marker *D16S520* on chromosome 16q24, which may account for the linkage to the transcription factor forkhead box protein C2 (FOXC2). Mutations in the *FOXC2* gene are associated with the lymphedema-distichiasis syndrome, and varicose veins are commonly observed as one of its phenotypic abnormalities at an early age.[27] Such findings suggest a possible role for the *FOXC2* gene in the pathogenesis of varicose vein formation and lymphatic dysfunction in such families.

Ethnicity

In some studies, the ethnic origin of subjects has been taken into account. In the San Diego multiethnic cross–sectional study on 2211 persons, CVD appeared to be more common in non-Hispanic whites than in Hispanics, African-Americans, and East Asians.[28] Though such results were obvious, they appear likely to be linked with social habits rather than genetics. In a prospective cohort study performed in aged residents, African-Americans exhibited higher levels of IL6, which it is considered to be a marker of both CVD and ulcers,[29] but in fact, they represented a group of obese patients, heavy smokers, etc. So a socially disadvantaged environment seems to be a main cause of CVD occurrence when ethnicity is taken into account, with the more possible underlying genetic factors being masked and not easily diagnosed. It should be noted that in the past, African tribes or other ethnic races were considered to have less prevalence of varicose veins that Europeans; however, that was related to the absence of sitting on chairs. After the use of tables and chairs were introduced to African families, the difference between African tribes and Europeans has disappeared.

Family history of varicose veins with mast cell infiltration

In one study, members of families with CVD exhibited higher mast cell counts in the adventitia of the varicose vein as a regular histological observation.[30]

Blood groups and varicose veins–a weak link

A case-control study, including 395 subjects, found a relationship between the A blood group and the presence of varicose veins, as well as a relation with vein thrombosis occurrence in non-O blood groups. It remains difficult, however, to keep the A blood group as an efficient risk factor of CVD![31]

In spite of the numerous nosological restrictions of studies focusing on the hereditary aspect of varicose veins, it can nevertheless be safely said that there is a significant genetic factor. However, its significance is interpreted in different ways and the nature of the genetic factor is still a topic of debate: is it due to heredity, family habits, or genetic transmission, and if so, by which genetic mode?

Inherited metabolic and catabolic disorders favoring varicose veins

Some general metabolic inherited disorders are known to constitute a background for alteration of tissues and organs, mainly with a link to vascular diseases and thrombosis.

Hyperhomocysteinemia

An increased level of plasma homocysteine is found in 65% of patients with CVD. Increased homocysteine levels are correlated with the CEAP classification grades, favors venous wall changes, and are also a risk factor for venous thrombosis. Prevalence of the 677C>T mutation in methylene tetrahydrofolate reductase was higher at the C4-C6 stages (20%) than in earlier stages (10%). It appears that around 15% of patients were homozygous, compared with 5% in a "healthy" white population.[32]

Unbalanced collagen types in the venous wall

Sansilvestri-Morel et al demonstrated that dermal fibroblasts from both the vein wall and the skin of subjects with varicose veins have an altered collagen profile.[33] The clinically observed vessel wall thickening appears to be associated with an increase in thick and disorganized collagen bundles.[34] Varicose veins are characterized by a smooth muscle cell and extracellular matrix component disorganization in the venous wall, which is associated with abnormal distensibility of varicose veins. The level of collagen type III is decreased in cultured smooth muscle cells and dermal fibroblasts derived from patients with varicose veins and hydroxyproline is overproduced in smooth muscle cells suggesting increased collagen content. This collagen augmentation appears to be correlated with an increase of collagen type I. Since collagen type I confers rigidity and collagen type III provides distensibility in tissues, such changes could contribute to the weakness and reduced elasticity of varicose veins. In conclusion, the collagen III defect seems to be generalized in different tissues and argues in favor of a genetic alteration in wall remodeling when submitted to prolonged pressure.[35,36] The importance of

such a systemic defect in the connective tissue has been stated in consensual reviews.[5,6] Unfortunately, there is a lack of epidemiological data related to the lesion frequency in a large population, which could be due to ethical problems and the need for skin biopsies.

Alleged genetic influence on wall remodeling

An imbalance in matrix metalloproteinases (MMPs) and TIMPs was observed in patients with varicose veins, which could be modulated genetically.[34] Altered apoptosis, either enhanced[37] or decreased,[38,39] in the varicose vein wall has been described and such results could be influenced by frequent single nucleotide polymorphisms (SNPs) on genes involved in apoptosis pathways. An observed downregulation of desmuslin, an intermediate filament protein, in smooth muscle cells of varicose veins may be due to defects in related structural genes.[40] Additionally, the thrombomodulin 1208/12O9TT deletion mutation has been associated with vein thrombosis and subsequently with varicose veins.[41]

Hemochromatosis factor XIII variants in the evolution of CVD

The HFE C282Y hemochromatosis gene mutation and factor XIII V34L gene variants have been identified in patients with varicose veins and may have long term implications for increased risk of more severe forms of CVI.[42,43] The main role of these factors appear to be in the ulcer formation as described below in detail.

Gene mutations and specific hereditary syndromes

The occurrence of varicose veins can be related to specific defects or well defined gene mutations, allowing groups of patients with CVD to be specifically included in defined syndromes.

CADASIL (Notch 3 gene mutation)

A heterogeneous mutation on the Notch 3 gene has been identified in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). In the CADASIL pedigree with varicose veins, a mutation of the Notch 3 gene (at the 3' acceptor site of intron 15) causes degeneration of venous smooth muscle cells that in turn can generate CVD.[44]

FOXC2 mutations with varicose veins

FOXC2 is an important gene for the development of venous and lymphatic valves. Mutations in the FOXC2 gene cause lymphedema distichiasis, which is often associated with varicose veins. These mutations are strongly related to venous valve failure.[45] Patients who have a homozygous cytosine to thymine mutation at position 598 (598C>T) of the von Hippel-Lindau gene (*VHL*) are likely to have varicose veins. This mutation is also linked to increased expression of hypoxia inducible factor-1 (HIF-1) genes, which induce VEGF and transferrin receptors (TfR).[46]

Angiodysplasias

Ehlers-Danlos syndrome comprises more than 10 types of connective tissue disorders with abnormal collagen synthesis. The syndrome is characterized by joint hypermobility, distensible skin, ocular disease, bone deformities and fragility, as well as cardiovascular disorders that render blood vessels and visceral tissue walls fragile and susceptible to rupture. Patients with Ehlers-Danlos syndrome type IV, which predisposes them to vascular pathologies, may present with varicose veins,[6,47] while surprisingly, the Marfan disease, another connective tissue syndrome, only affects the arterial system.[6] In the congenital Klippel-Trenaunay syndrome, the patient presents with varicose veins, limb hypertrophy, and dermal capillary hemangioma (port wine stain),[6] and 75% to 100% of patients exhibit venous valve hypoplasia.

A mutation of the Norrie disease gene (ND), an X-linked recessive disorder, is responsible for ocular anomalies and further sensory neural deafness, which develops by the second decade in up to 100% of individuals. The ND gene mutation can be associated with peripheral vascular diseases such as varicose veins, venous ulcers, and erectile dysfunction. It is present in nearly all males over the age of 50, perhaps as a result of small vessel angiopathy, and its age of onset is similar to that of the hearing deficit and the time course of progression is similar.[48]

Finally, 82 upregulated genes belonging to extracellular matrix molecules, cytoskeletal proteins, and myofibroblasts were identified in varicose veins using a cDNA microarray. These genes include: transforming growth factor 3-induced gene (BIGH3), tubulin, lumican, collagen type I, versican, actin, and tropomyosin.[49]

Table I summarizes the hereditary factors in varicose veins.

- Evidence for family histories with CVD
  - Shown in case-control studies
  - Positive in Twin studies
  - Recessive and/or dominant properties of the trait
  - No link to ethnicity
  - Families with numerous in situ mastocytes
  - A weak blood group influence
- Inherited metabolic disorders favoring CVD
  - Hyperhomocysteinemia (iron deposit)
  - Increased collagen type I in the vein wall and skin
  - Genetic influence on wall remodeling
    - Unbalanced matrix metalloproteinase tissue inhibitors
    - Smooth muscle cell desmuslin down regulation
    - Thrombomodulin mutation 1208/1209TT
- Gene mutation in specific hereditary syndromes
  - CADASIL (NOTCH 3 gene mutation)
  - FOXC2 mutations and syndromes related to varicose veins
  - Norrie disease mutation
  - Angiodysplasia
    - Ehlers-Danlos syndrome
    - Klippel-Trenauney syndrome

Table I. *Hereditary factors and varicose veins*

HEREDITARY FACTORS IN THE OCCURRENCE OF VENOUS ULCERS

Epidemiology, ethnicity, and venous ulcers

Epidemiological studies underline the prevalence of venous ulcers in around 0.3% of CVD patients, and that healed ulcers are observed in 1% of the adult population both in Europe and the USA.[50] Few data are available regarding family history, ethnic groups, and rapid ulcer occurrence. In a large review of longitudinal studies, the role of obesity in the occurrence of ulcers is identified, especially in the Framingham Study and the Bonn Study.[51]

In the West London Study, regarding patients presenting with leg ulcer(s) at their consultations over a one-year period, the prevalence of ulcer(s) were higher in white people than in a South Asian population (odds ratio=4.43), but the authors themselves pointed out a bias in recruitment.[52]

Previous history of DVT, age, arterial hypertension, and lifestyle (prolonged standing) are main actors in the development of ulcers, which constitutes a "cloud" preventing the discovery of potential underlying putative genetic factors. Particularly, it is unknown how many patients with superficial reflux will progress to venous ulceration.[50] Is venous ulceration, due to lifestyle, lack of exercise, family habits, or is there a genetic factor involved? The debate is still ongoing.

There is, however, an exception. Patients with homozygous sickle cell disease (homozygous for the hemoglobin mutation 6 glu>val; HbSS), frequently suffer from venous ulcerations of the lower limbs, which are often disabling. The mechanism appears complex and not related to venous disease by itself, but to arteriovenous shunting along with an abundance of hypoxic cells.[53]

Genetics factors in ulcer formation

Mechanism of the lower limb venous ulcer development

The ulcer develops over skin regions with predictive aspects such as corona phlebectatica, a varicose edema occurring mainly at advanced stages of the CEAP classification. Using capillaroscopy at the ankle, microvascular ischemia combined with venous and lymphatic edema, define areas of the skin where ulcers develop.[54] Inside the skin, the setting of previous biological events can also predict sites of ulcer development and are marked by: increased permeability, erythrocyte migration, iron deposits leading to free radical activity in the tissue, leukocyte migration (white cell trapping), and migration of macrophages and mastocytes.

The mechanism of ulcer formation is shown in *Figure I*. Two processes act separately:

1. Necrosis of the extracellular matrix, in which TGFβ, proteolytic hyperactivity of MMPs, and destruction of collagen microfibrils and proteoglycans (opening craters in the skin) play a role.[4,5]

2. Increased apoptosis of keratinocytes and caspase-2 activation leads to dermo-epidermal detachment that eventually progresses to an ulcer.[55]

Many biological factors and/or processes lead to ulcer formation, and are influenced, sometimes strongly), by the patient's heredity (ie, either an abnormal or dysfunctional gene due to a close acting SNP. The situations are diverse and implies either large metabolisms or precise genetic processes.

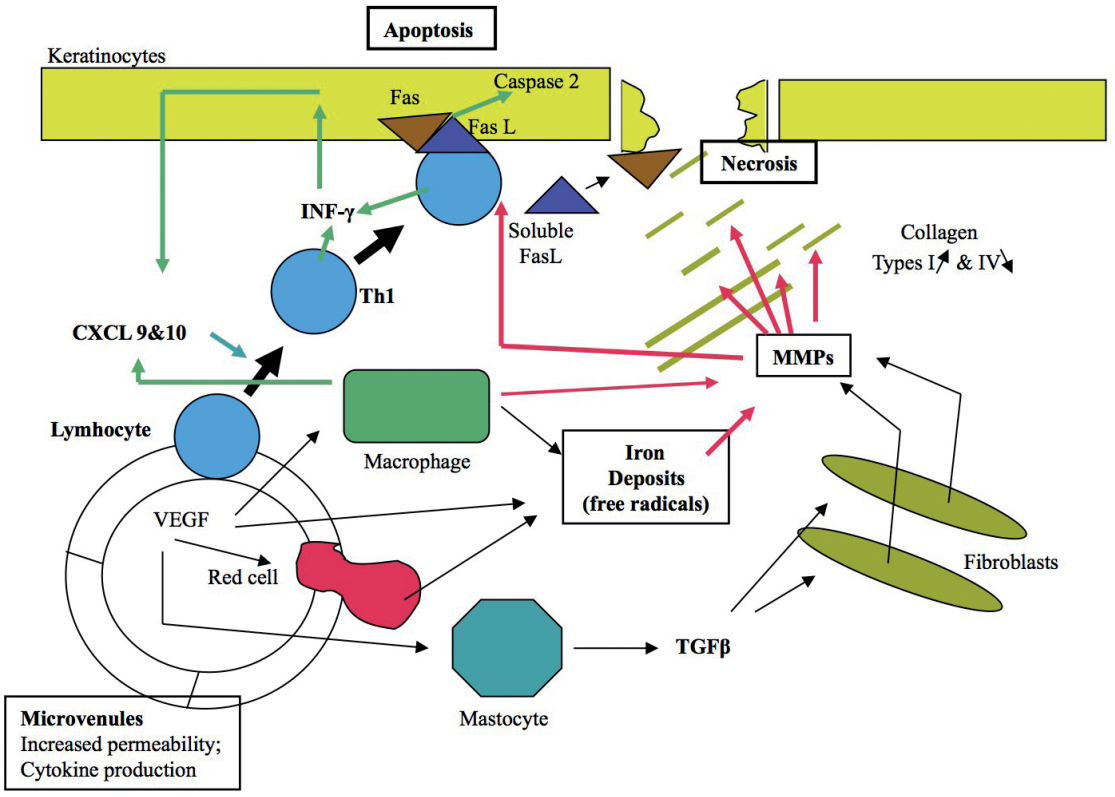


Figure 1. Venous ulcer pathogenesis[4, 5, 55]

Abbreviations: CXCL, chemokine; Th1, INFγ, interferon; Fas-L, soluble Fas ligand; TGFβ, tumor growth factor β; Th1 lymphocyte; VEGF, vascular endothelial growth factor.

Familial alterations of iron metabolism

Iron deposition is correlated with the occurrence of skin complications in chronic venous insufficiency (CVI). It was recently demonstrated that visible iron deposits cause lesions in some, but not all, individuals due to functional iron and related gene variants. As previously stated, a dysregulated iron cycle leads to local iron overload that could generate free radicals or activate a proteolytic hyperactivity on the part of MMPs or downregulate tissue inhibitors of MMPs.

Iron cycle

Figure 2 underlines the role of the membrane-linked HFE protein opposing TfR-1 that controls iron influx through ferroportin, however, other actors are potent players. Hepcidin, a low molecular weight protein, shuts down the iron influx by engulfing ferroportin at the intestinal barrier and from macrophages, which are also an important source of ferritin deposit in tissues. In the end, iron influx is blocked first by the receptor HFE and second by Hepcidin. Hepcidin regulators in the liver may be dysfunctional.

Familial Hemochromatosis

Hereditary hemochromatosis is incorrectly assumed to be due to a single gene. Actually, the overwhelming majority actually depends on mutations in the HFE gene, but there is non-HFE–related hemochromatosis. One can summarize as follows, excluding some other close SNPs influences.

1. Hemochromatosis Type 1:
   - Frequent
   - Autosomal recessive inheritance
   - Gene HFE mutations: HFE C282Y and HFE H63D
2. Hemochromatosis Type 2A:
   - Juvenile, rare
   - Autosomal recessive inheritance
   - Hemojuvelin decreases due to a HFE-2 gene mutation
3. Hemochromatosis Type 2B:
   - Juvenile, rare
   - Autosomal recessive inheritance
   - Hepcidin decreases due to a Hamp gene mutation.

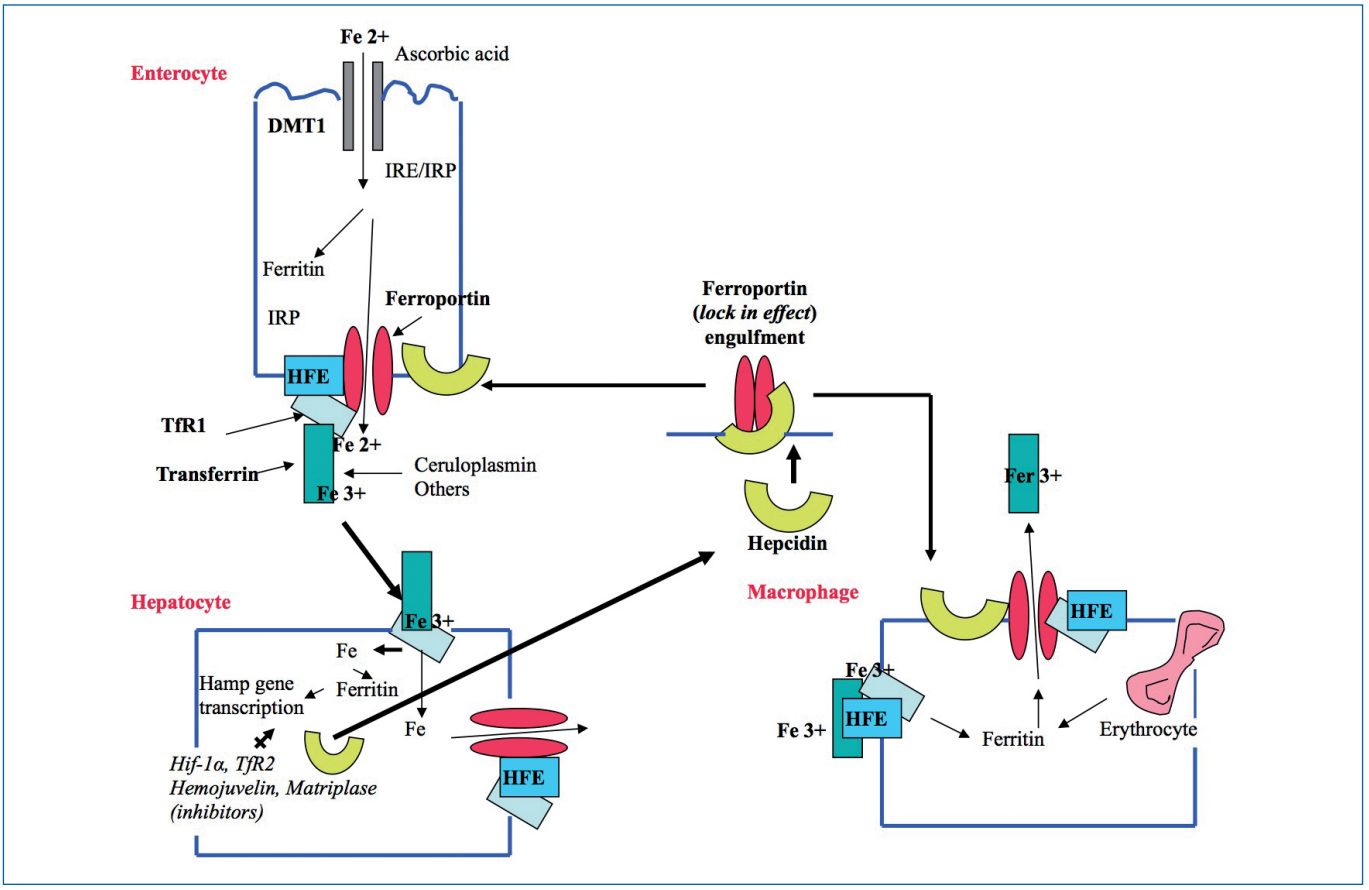


Figure 2. Iron transport: opposing effects of the proteins HFE and Hepcidin

Abbreviations: DMT1, divalent metal transporter 1; IRE, iron responsive element; IRP, iron regulatory protein; HIF-1α, hypoxia inducible factor 1α; Hamp gene, hepcidin gene; TfR, transferrin receptors (1 and 2); HFE, membrane protein HFE

4. Hemochromatosis Type 3:
   - Juvenile, rare
   - Autosomal recessive inheritance
   - TfR-2 gene mutation leading to dysfunctional transferrin and Hepcidin
5. Hemochromatosis Type 4:
   - Juvenile, African, rare
   - Autosomal dominant inheritance
   - Lack of ferroportin, due to a FNP1 gene mutation (SLC40A1)

HFE C282Y is very frequent in Europe and increases, by a factor of 7, the risk of developing a venous ulcer. Despite the low penetrance of the gene, its influence is high even in heterozygotes. The membrane bound proteins related to the HFE C282Y gene are no longer able to lock out the ferroportin mechanism (*Figure 2*).

In a case-control study, among 980 patients with severe CVD (C4-C6), 518 cases were genotyped for HFE mutations. The C282Y mutation significantly increases, by a factor of 7, the risk of an ulcer in primary CVD (odds ratio=6.69) by 7. Application of the research demonstrated an increased specificity (98%) and a positive value (86%).[42] The HFE H63D variant is rare, but ulcers form occur 10 years earlier in patients with CVD.[9,56] On the whole, including double heterozygotes, 10% of patients might be affected by hemochromatosis gene mutations.[42,57]

SNP on the ferroportin gene FPN1

Few data are available regarding studies related to SNPs and ulcer occurrence. Recently, a significant association was identified between FPN1-8CG, a SNP in the promoter region of the FPN1 gene, and ulcer susceptibility, showing that susceptibility increased 5-fold.[9] The FPN1-8CG polymorphism is close to the region of iron response element (IRE), and could act at macrophage membranes, paradoxically hampering efflux of iron from the cell, but leading to macrophage death. In this study, the risk of an ulcer appeared to be in addition to the HFE C282Y gene (3% of individuals).

Polymorphisms of the ON-exon and the ERβ gene ESR2

An elegant study showed that SNPs in the Estrogen receptor beta (ERβ) gene was associated with venous ulceration in elderly patients (SNPs close to the regulatory region of the ERβ gene including the ON exon and promoter). Such SNPs were found in 23% of the elderly persons investigated. A major susceptibility in haplotype, carried by 23% of cases, was significantly associated with an active ulcer. Furthermore, there was an association with elevated serum levels of tumor necrosis factor α. In such groups of patients, the "dampening" effect of estrogen on inflammation is decreased, thereby facilitating an ulcer, both in genesis and healing.[58]

Hereditary thrombophilia in ulcer formation

In a study performed on 88 patients with a venous ulcer, 41% have a thrombophilia prevalence rate that is 30 times higher than the rate of the general population.[59] Hemostasis disorders were quite diverse: antithrombin and protein S, C deficiencies, activated protein C resistance, factor V Leyden, presence of prothrombin 20210A, lupus anticoagulant, and cardio lipid antibodies. There was no relation with previous deep venous thrombosis. The prevalence of venous ulcers in patients having factor V Leyden had been previously reported.[60] It remains difficult to assert that coagulation disorders could play an actual role in ulcer formation, knowing that most of them, like factor V Leyden, are weak risk factors in thrombosis. A role in poor healing could be a more convincing possibility.

Matrix metalloproteinase (MMP) SNPs and ulcer occurrence

The proteolytic enzymes, MMP-1, -2, -8, and -9, play an important role in ulcer formation due to their ability to degrade extracellular matrix components (*Figure 1*). Particularly efficient is an imbalance in MMPs versus TIMPs-1, -2, and -3 activity ratios, and HIF-1β enhances their effects. MMP SNPs have been studied in several diseases, but there were only a few with regards to ulcer formation. Polymorphisms in the promoter regions of MMP-2, -9, and -12 have been studied in diseases where ECM destruction is an important process, (eg, diabetes, coronary arterial disease),[61,62] and recently it has been shown that the polymorphism MMP12-82AG, located in the coding region of the gene, induces a 2-fold higher risk of developing a venous ulcer in patients with primary CVD.[9]

Polymorphisms in inflammation (cytokines, growth factors) and venous ulcers

Tumor Necrosis Factor α polymorphism, the 308G>A polymorphism in the promoter region, has been associated with ulcer susceptibility.[63] It has been suggested to have a possible association with obesity.[64] Other cytokine SNPs (eg, VEGF isoforms) are likely to be involved in the evolution, onset, and duration of venous ulcers, and some particular roles in apoptosis.

Table II summarizes the hereditary factors in venous ulcer formation.

- Weak evidence for family history and ethnicity
  - Except obesity
  - Except sickle cell anemia
- Inherited metabolic disorders favoring venous ulcers
  - Familial Hemochromatosis (iron deposit)
    - Frequent European recessive type 1: HFE C282Y, HFE H63D
  - Ferroportin polymorphisms (iron deposit)
    - Frequent: FPN-1 8C>G
    - Rare: dominant African Type 4: FNP1-SL C40A1
- Estrogen receptor β: polymorphism of the ON exon (ERβ-SNP)
- Weak influence of thrombophilia
- Matrix metalloproteinases SNPs
  - MMP-12 82A>G
- Inflammation and growth factor polymorphisms
  - Tumor Necrosis Factor α -308G>A (obesity linked)

Table II. *Hereditary factors and venous ulcers*

VENOUS ULCER HEALING AND GENETICS

The healing process

Figure 3 shows the main factors leading to ulcer healing. The ulcer crater is recovered by a layer of thrombin-induced fibrin which must be of normal quality. The ECM must be rebuilt by fibroblasts with a normal balance between collagen I and III. Growth factors (eg, platelet factor 4, VEGF, etc) are needed, keratinocytes must proliferate, and the superficial lining of cells must be rebuilt. This latter process requires apoptosis to be stopped. A certain number of abnormalities with a link to the personal heredity in given patients have been reported.

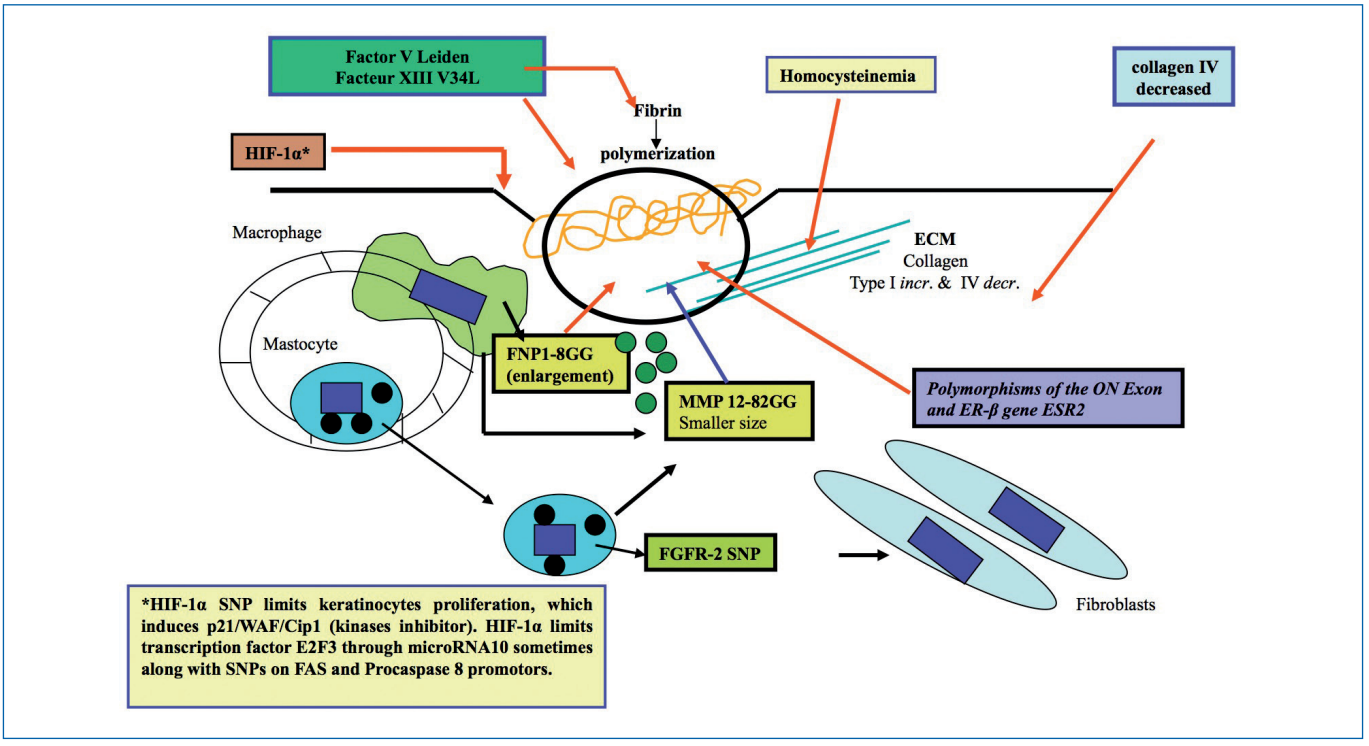


Figure 3. Venous ulcer healing and genetics

Abbreviations: ECM, extracellular matrix; ER, estrogen receptor; FAS, fas cell surface death receptor gene; FGFR-2: fibroblast growth factor receptor 2; FNP: ferroportin; HIF-1: hypoxy induced factor 1; MMP: matrix metalllo-proteinase .

A bad fibrin layer and the role of factor XIII

Thrombophilia could impair ulcer healing, and at the same time, favor its incidence. Such an assertion is poorly documented because fibrin in the ulcerous crater is due to tissue factors coming from altered neighboring tissues, without the involvement of the intrinsic coagulation cascade. There is a need for an efficient fibrin polymerization by factor XIII to improve fibroblast migration, and so the dysfunctional factor XIII-SNP-V34L has been shown to impair healing.[43,65]

Constituents of extra cellular matrix

Collagen IV deficiency and high levels of homocysteine are implicated in reduced ulcer healing.

Different factors involved in healing

In elderly patients, the ERβ-SNP (ON exon) is also a cause of poor venous ulcer healing.[58]

The fibroblast growth factor receptor 2-SNP is often present in CVD patients with venous ulcer and is also a cause for poor healing.[64]

Apoptosis alterations

Approximately, 50% of humans would have SNPs in the extrinsic apoptotic chain, according to many researchers in cancer, diabetes, and immunology fields. Although these SNPs have not specifically been found in the ulcer, we can speculate about a possible role for either increasing or decreasing the intensity of keratinocyte destruction. On the FAS ligand (FAS-L) promoter, the FAS-SNP-844T>C has been identified, which favors its induction (42% homozygotes and 9% heterozygotes). FAS promoter SNPs are able to diminish FAS-L joining and the same is true for the procaspase-8 promoter. Other proteins are involved in apoptosis such as the Bcl-2 family where other important SNPs could be located. HIF-1α, an important transcription factor, is induced by both hypoxia and oxidative stress. HIF-1α may contain two important SNPs (1772C>T and 179OG>A) that leads to an increased transactivation capability and may play a role in colorectal cancer.[66] Hypoxemia in the crater of an ulcer can induce HIF-1α, and subsequently, keratinocyte regeneration would dramatically decrease by upregulating the kinase inhibitor p21.[67]

The Paradox of the protective effects of SNPs

Some inverse observations showed that specific FXIII genotypes, such as FXIII V34L, also evaluated in venous ulcer healing following superficial venous surgery in patients with CVD, promote favorable ulcer healing rates. However, the HFE gene mutation, despite its importance in venous ulcer risk, had no influence on healing time. Also, it has been reported that homozygous MMP-12 SNP-82GG favors a smaller ulcer size.[9]

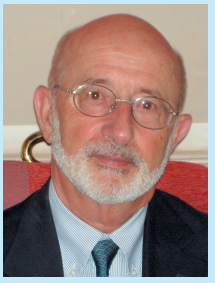
Table III summarizes the influence of genetics in venous leg ulcer healing.

- Increased healing time
  - Weak influence of thrombophilia
  - Factor XIII SNP-V34L (AA & AG types)
  - Homocysteinemia
  - Decreased collagen Type IV
  - ERβ-SNP (ON exon)
  - Fibroblast growth factor receptor-2 SNP
  - SNPs on the extrinsic apoptosis chain (promoters of FAS and procaspase-8)
  - HIF-1α SNPs
- Size of the ulcer
  - MMP 12-82AG: smaller with GG genotype
  - Factor XIII-V34L: smaller
  - FNP1-8GG: enlarged

Table III. *Hereditary factors and venous ulcer healing*

CONCLUSION

The list of hereditary factors, as discussed in this review, that influence the quality of the venous wall in CVD and the formation of an ulcer, is far from being complete. SNP discoveries will continue, but above all, there is a particular need for cross-sectional epidemiology studies in order to unveil the actual role of heredity, which is masked by a "cloud" of lifestyle and acquired factors. Critical functions of susceptibility genes and the translational pathways leading to the observed CVD or venous ulcer should be analyzed. Metabolomic technologies could help identify the metabolic pathways involved in varicose veins and how they are controlled by both genetic and environmental factors.[68] MicroRNA profiles of diseased veins could also help understand the remodeling pathways.[69]



Corresponding author
Michel-René BOISSEAU
University Victor Segalen Bordeaux2,
Department of Pharmacology,
168 rue Léo Saignat,
33076 Bordeaux cedex
France

Email: m.r.boisseau@wanadoo.fr

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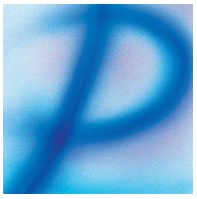

Critical Role of the Vasa Venarum in the Pathogenesis of Chronic Venous Disease. Part II: Therapeutic Implications

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Stephan NEES[1],
Dominik R. WEISS[2],
Gerd JUCHEM[3],
Hugo PARTSCH[4]

1 Department of Physiology, University of Munich (LMU), 80336 Munich, Germany

2 Department of Transfusion Medicine and Hemostaseology, University of Erlangen-Nuremberg (FAU), 91054 Erlangen, Germany

3 Department of Cardiac Surgery, University of Munich (LMU), 81377 Munich, Germany

4 Emeritus Professor of Dermatology, Medical University of Vienna, Austria

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ABSTRACT

Standing or sitting for a long duration is accompanied by venous distension and pooling of blood in the larger leg veins and the lower vena cava. Under these conditions, reflux from the vein lumen into the nutritive microvascular system of the vein wall can occur. Resulting acute inflammatory processes lead to a breakdown of the endothelial barrier in the corresponding venules, edema formation, and venular thrombosis, events that have the potential to spread into the lumen of the respective parent vein. To forestall the development of chronic venous insufficiency and obviate the dangers of venous thrombosis and postthrombotic syndrome, all measures aimed at improving venous return as well as the perfusion and tightness of the nutritive microcirculatory system in the vein wall are welcome. The most important treatment modalities to achieve this goal are compression, surgical intervention, and certain pharmacological measures that will be addressed and discussed against the background of their effectiveness and the current literature.

INTRODUCTION

As described in Part I, standing or sitting for a long duration is accompanied by venous distension and pooling of blood in the larger veins of the lower extremity, the pelvis, and the lower vena cava. Blood emerging from the microcirculatory beds of the leg organs must now mix with the pooled blood in the draining veins. This decreases the concentrations of unstable antithrombogenic mediators added to the blood from the microcirculatory endothelium (as is the case while lying or running). In addition, the high hydrostatic pressures in the capillaries and venules during standing increase the filtration of fluid, resulting in “hydrostatic edema,” an increase of the local hematocrit and a compensatory increase of lymph drainage. Should such a situation become chronic, the lymph drainage will decompensate and inflammatory processes can superimpose themselves on this hydrostatic background. Inflammatory mediators, synthesized and released locally, can elicit active contraction of the venular endothelial cells, thus strongly enhancing the exit of plasma into the interstitium. During this "inflammatory edema" formation, the vessel walls will be substantially remodeled and a final thrombotic occlusion of the lumina may occur.

Stasis in the microcirculation correlates with elevated pressure in the veins. As a consequence of gravity, this may happen in immobile patients who spend their lives in wheelchairs, in extremely obese patients with restricted mobility, or in patients with massive venous refluxes leading to ambulatory venous and capillary hypertension while walking. Due to steadily increasing pressure in the venules, there is an increase of the transcapillary pressure gradient and a decrease in the shear stress on the venular and capillary endothelium. Low shear stress promotes leukocyte adhesion and penetration into the endothelium, which triggers an inflammatory reaction,[1] as described in Part I.

In this situation and in the context of the novel pathophysiological insights described above (particularly in Part I), all measures aimed at improving venous return are welcome. The most important treatment modalities to achieve this goal are compression, surgical interventions, and pharmacological measures that will be addressed briefly in the following article.

COMPRESSION THERAPY

The most important mechanism of compression treatment of the lower extremities is to counteract gravity as the major hindrance affecting venous return while in the upright position.

Treatment of an edema occuring from a hydrostatic origin

In the lower extremities, sitting or standing for long periods of time leads to an increased shift of fluid from the microcirculation into the tissue causing the so-called physiological "evening edema" or "occupational edema." After a long day, shoes may no longer fit and an unpleasant feeling of tension in the legs may occur. Compression is very effective at preventing this hydrostatic edema and reducing subjective complaints. It could be demonstrated that compression stockings in a pressure range of around 20 mm Hg are able to prevent occupational edema and alleviate symptoms.[2] By measuring the capillary filtration rate, compression stockings with higher stiffness are superior to highly elastic products with low stiffness.[3] The prevention of leg edema after long flights, by using stockings, may also have a thromboprophylactic effect by preventing the increase of local hematocrit in leg veins occurring without compression after sitting for long periods due to increased filtration of fluid into the tissue.[4] Compression is also able to reduce manifest edema, which can be achieved with relatively low pressures in patients with pitting edema before it becomes indurated.[5] Reduction in skin edema is associated with an increase in capillary density.[6]

Compression in chronic venous insufficiency and during leg ulcer therapy

Chronic venous insuffiency (CVI) is characterized by a failure of the venous pump mechanism (see *Part I , Figure 2),* in association with venous reflux and/or venous obstruction. As demonstrated in numerous studies, compression reduces venous reflux and improves the venous pump. A prerequisite for this mechanism is a venous caliber reduction, which can be demonstrated by using magnetic resonance imaging, not only in the supine, but also in the standing position[7] (*Figure 1*). Together with Duplex-investigations, such studies were useful to find the minimal compression pressure required to narrow the leg veins in the upright position.[8] In patients with CVI, inelastic compression applied with a pressure >50 mm Hg reduces pathological reflux in both superficial and deep veins,[9] increases the ejection fraction of the venous pump,[10] and reduces ambulatory venous and capillary hypertension.[11,12] Pressure measurements in dorsal foot veins, performed in patients with ulcers due to a congenital absence of venous valves, showed an improvement in ambulatory

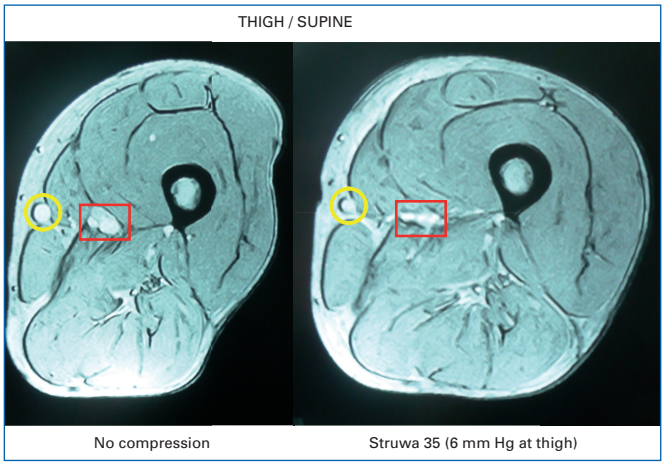

Figure 1: Cross section at mid-thigh level in a supine patient with a large great saphenous vein (yellow circle) obtained by magnetic resonance imaging.

Left without compression, right with a compression stocking exerting a pressure of 6 mm Hg at thigh level. Compression reduces the calibre of the superficial (yellow circle) and deep vein (red square) and leads to a more circular configuration of the thigh.[7]

venous hypertension by compression, disproving the popular concept that compression works by making distended valves competent again.[13]

The most severe form of chronic venous hypertension, which leads to a massive inflammatory reaction in the context of CVI, is the venous leg ulcer, for which compression is the cornerstone of management. Biopsies taken from the periphery of the ulcer and from healthy tissue have shown that compression treatment can reduce the raised levels of diverse inflammatory cytokines in the ulcer region, while TGFβis upregulated.[14] Additional studies, employing noninvasive confocal laser scanning microscopy in ulcer patients, have shown an increased cell flow rate in dermal capillaries and a reduction in the number of inflammatory cells after treatment with inelastic Pütter bandages when compared with local therapy without compression.[15] In addition, 4 weeks of compression therapy have been shown to enhance the expression of tight junction molecules in the vascular endothelium, which may play a role in preventing extracellular edema.[16]

In patients with mixed arterial-venous ulcers and concomitant peripheral arterial occlusive disease, inelastic compression bandages applied with a pressure of <40 mm Hg have been shown to increase arterial blood flow and the ejection fraction of the venous pump. This finding adds substantial weight to the empirical recommendation of modest compression (not more than 40 mm Hg) with inelastic bandages together with walking exercises as the basic conservative treatment approach.[17] Previous experimental studies, in healthy persons, have also reported an increase in arterial blood flow beneath a compression bandage at pressures up to 40 mm Hg.[18] Myogenic relaxation of the arterial wall, release of vasodilator mediators, and a reduction in the arteriovenous pressure gradient following improvement in the venous pump function are discussed as possible explanations. Nutritive microvessels in large artery and vein walls may play an important role in both myogenic relaxation of the arterial wall and release of vasoactive substances.

In the microcirculation, intermittent compression produced by walking with inelastic compression or with pumps will increase shear forces at the vessel walls and reduce leukocyte adhesion to the endothelium and increase release of diverse antithrombotic, anti-inflammatory, and vasodilatory mediators from the endothelium (eg, various platelet inhibitors, anticoagulants such as tissue factor pathway inhibitor [TPFI], and profibrinolytic tissue plasminogen activator [tpA], *(see Part I, Figure 3)*. This latter effect has been demonstrated during intermittent compression using appropriate pumping systems.[19]

Use in the prevention and therapy of deep leg vein thrombosis

An acceleration of venous blood flow velocity in the legs counteracting stasis is an important mechanism of action to prevent thrombosis. This can be achieved by either pneumatic pumps that squeeze the legs intermittently or by sustained compression[20].

In the supine position, reduction in the cross-sectional area with unchanged volume inflow will raise the linear venous flow velocity in the compressed parts of the leg (*Figure 1*). This could be demonstrated by measuring venous transit times with and without thromboprophylactic stockings using intravenous injections of tiny amounts of radioactive tracers.[21] Blood will arrive more rapidly in the lungs *(see Part I, Figure 2)*, where the enormous increase in the endothelial surface and hence the pivotal "clearance function" of the pulmonary endothelium comes into play. The continuous removal of activated coagulation factors, vasoactive compounds, and inflammatory mediators that eventually appear in the mixed venous blood is a complex function of the lungs that is certainly as vital as gas exchange.

Inflammatory processes in the vein wall obviously play prominent roles in the pathogenesis of venous thrombosis[22,23] *(Part I)*. In patients with superficial thrombosis, used as a model for deep vein thrombosis (DVT), excisions of thrombosed vein segments have been performed after intravenous injection of radioactively labeled ^{131}I-fibrinogen. The concentration of radioactivity was much higher in the adventitia and the rest of the vein wall, rather than in the clot itself.[24] This means that the substrate for a "positive fibrinogen uptake test," as used for the detection of DVT, is little to no accumulation of fibrin in the clot and far more accumulation in the vein wall (*Figure 2*). These findings support the concept that venous thrombosis is, in fact, more complex than the formation of an intraluminal thrombus, and highlights the currently proposed importance of the venular endothelial barrier and the pericytes within the vasa venarum network. The

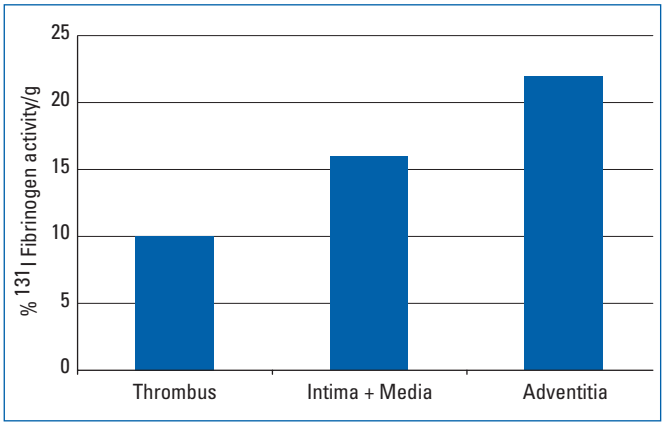

Figure 2: Radioactivity per 1 g of tissue measured in 3 patients with superficial leg vein thrombosis 24 hours after intravenous injection of ^{131}I fibrinogen and excision of the thrombosed vein segment. There is more fibrin in the vein wall and especially in the perivenous tissue than in the clot.[24]

accumulation of fibrin in such experiments is unlikely to be attributable to simple diffusion of fibrinogen from the lumen into the wall periphery due to the large distance from the vein lumen, the tight internal elastic lamina, and the whole media of the adventitia. Rather, the observed deposition of a surprisingly large amount of fibrin, particularly in the layer of the vessel wall enclosing the thrombus, is most likely the substrate of a massive thrombotic reaction occurring in the vasa venarum network and in the interstitial space surrounding the corresponding microvessels, which drain into the lumen of the respective parent vein. Hemostatic reactions are always immediately followed by local activation of the acute immune defense. This inflammatory response in the vein wall, which is associated with deep vein thrombosis, can be visualized by gadolinium magnetic resonance venography. Gadolinium extravasates into tissues during inflammation, producing a perithrombus enhancement, which can be visualized by magnetic resonance imaging. The typical "bulls-eye sign" corresponding to gadolinium enhancement in the vein wall has been described as a helpful discriminator to differentiate between acute and chronic DVT.[25]

Recent application of positron emission tomography after the uptake of radioactive fluorodeoxyglucose (^{18}F-FDG) during acute DVT resulted in documentation of an increased metabolic activity in the wall of the respective thrombosed veins, which extended into the "adjacent soft tissues."[26] This result probably reflects the high inflammatory activity in and around the vena venarum networks, which are the densest in the adventitia and its surrounding connective tissue (Part I).

For such reasons, compression therapy considerations for future studies must address mechanical influences on the thrombus and preventive effects on coagulation and inflammatory reactions within the vein walls. Such mechanisms are endorsed by studies demonstrating that compression therapy reduces proinflammatory cytokine levels and increases the level of the anti-inflammatory cytokine IL-1,[14] and that increases in shear stress releases anti-inflammatory substances from the endothelial cells.[19] Clinical research has demonstrated that during catheter directed thrombolysis, the use of intermittent pneumatic compression pumps in patients with proximal thrombosis achieves better early and late results compared with thrombolysis alone.[27]

In the past, patients with deep leg vein thrombosis were frequently immobilized due to fear of a pulmonary embolism. Controlled clinical studies have shown that immediate mobilization under adequate anticoagulation combined with compression, results in a more rapid reduction in swelling and pain than bed rest, without raising the risk of symptomatic pulmonary embolism.[20] When deep vein thrombosis develops in a mobile patient, multiple and often clinically silent pulmonary emboli can be detected in a large proportion of patients, which justifies the term "venous thromboembolism."[28] In such cases, it could also be argued that it is better to shift small fresh parts of the thrombus under compression and walking into the pulmonary capillary system than to leave them in the leg veins to avoid the risk of causing irreversible damage to vein walls and valves, or of developing into large and possibly life-threatening emboli.[29] The pulmonary microcirculatory system acts like a filter, and entrapped small thrombi are prone to prompt and complete lysis due to the extremely high ratio of endothelial surface area to blood volume and the profibrinolytic potency of the endothelial surface *(see Part I, Figures 1 and 4)*. As a consequence, the most recent guidelines now recommend compression with both ambulatory exercise and optimal anticoagulation as the conservative basal therapy for deep leg vein thrombosis.[20]

The postthrombotic syndrome

Signs and symptoms that may occur as long-term complications of DVT are included under the term "Postthrombotic syndrome" (PTS), also called

postphlebitic syndrome. Randomized controlled studies have documented a 50% reduction in the incidence of clinical signs and symptoms of a postthrombotic syndrome when compression stockings are worn for up to two years after an acute episode of deep vein thrombosis.[30] PTS, which presents with clinical signs of chronic swelling, skin changes, and ulceration in the leg with a previous thrombosis, is a classic model for chronic inflammatory changes particularly in the vein wall, in which the pathological processes described above play a key role. The resulting pathology is determined not only by a variable proportion between persisting venous occlusion and recanalization of vein-segments with valve damage and reflux, but also by fibrotic changes in the vein walls, which undergo continuous remodeling.[31] Calcification and even ossification of vein walls may be late signs of a previous, but sometimes asymptomatic thrombosis. A persistent inflammatory reaction initiated in the acute phase of DVT, may indeed be a more important risk factor for the development of PTS than hypercoagulability.[32,33] Pathological consequences are initiated in the acute phase of DVT, which explains the importance of an exact anticoagulation treatment together with avoiding stasis by immediate compression to reduce the incidence of recurrent thrombotic events and to prevent PTS.

Compression in the acute phase of DVT reduces pain and edema immediately[34] and continuation of compression is able to maintain this situation and prevent PTS.[35] If compression therapy is initiated too late, eg, several weeks after the acute phase of DVT, prevention of PTS may be less prominent. This is probably one explanation for the contradictory results of a recently published study that was unable to find differences between compression stockings and "placebo-stockings" regarding the development of signs and symptoms of PTS two years after proximal DVT.[36] In particular, the very low compliance rate for wearing stockings and the restriction to weak, subjective outcome parameters make this study unreliable.

Radionuclide scintigraphy has shown that the deep, subfascial lymph transport is disturbed not only during acute thrombosis, but also over the period of a subsequent postthrombotic syndrome.[37,38] It can be assumed that the mentioned fibrin deposition in the adventitia of occluded veins will also include the accompanying lymph collectors. In any case, 7 days of compression therapy with firm zinc paste bandages has been shown to consistently improve subfascial lymph transport.[39] This result can be explained by stimulation of fibrinolysis during intermittent pneumatic compression due to the massaging effect achieved during walking exercises under stiff bandages[40] and enhanced contractions of lymph collectors.

More precise concepts for the mechanism accounting for the clinically impressive effects of compression with respect to prophylaxis and treatment of PTS are still lacking. The effects of compression on the vessel walls and microcirculation have been widely neglected until now. The complex pathogenetic factors and self-propelling pathomechanisms *(Part I)*, open a wide scope for future histological, biochemical, and physiological studies.

ENDOVENOUS TECHNIQUES AND VASCULAR SURGERY

There is an ongoing dispute regarding the pathogenesis of varicose veins and their recurrence after treatment. In a simplified manner, this dispute involves two main concepts: (i) distal venous dilation ("descending, hemodynamic theory") is mainly caused by reflux due to valvular incompetence; and (ii) the origin of the illness ("ascending theory") is due to structural abnormalities in the vein wall. Based on the findings reported in Part I, both concepts involve cellular and molecular changes, which lead to histological alterations in the vein wall and the extracellular matrix. Actually, such changes in the vein wall and hemodynamic factors are linked together in a vicious circle.[1,41]

Regarding treatment options, the introduction of endovenous techniques has given new stimuli for the management of both venous reflux and proximal venous obstruction based on experience and a modern, anatomical/topological definition. Today, venous reflux can be followed downstream from the large venous trunks into the region of ulcers using Duplex ultrasound,[42] and can be eliminated by endovenous procedures including foam sclerotherapy. Obstructions to upstream venous flow in the pelvic region can be recanalized using dilating catheter techniques and stents. In both cases, the treatment aims to eliminate the hemodynamic triggers for chronic venous hypertension. In practice, unfortunately, the decision for such intervention is frequently made too late, ie, after irreversible tissue damage has already occurred.

All ablative endovenous techniques aim to occlude refluxing veins. To reach this goal, thermal ablation of incompetent superficial veins by laser fibers, radiofrequency, or steam are applied. Another effective method is chemical ablation by injecting sclerosing agents into the respective veins. The result is always the destruction of the endothelial layer, which progresses to variable structural damage to the vessel wall and the vasa vasorum.[43,44] Local thrombosis is initiated promptly after exposure to subendothelial pericytes *(see Part I, Figure 3)*, which illustrates the newly recognized ubiquitous distribution of the prothrombotic pericytes in the different branches of the circulatory system. Ideally, the vein will finally be remodeled to a fibrotic cord. Ingrowing new vascular networks, a phenomenon which had been called "intraluminal neovascularization,"[45] may originate from the nutritional vasculature in the outer layers of the treated vein. Due to this event, an unfavorable recanalization of the occluded vein may happen.

The critical involvement of pericytes in the development of venous disease described in part I of this publication has considerable impact on the outcome of classical varicose vein surgery. Pericytes nourish endothelial cells and are of central importance for angiogenic processes. In fact, after surgical ablation of saphenous veins, the pericyte-rich adventitial vasa venarum of the remaining stump and surrounding scar tissue are often involved in the development of progressive neovascularization, giving rise to the recurrence of varicosity.[46]

The influence of compression, specifically on the tissue changes initiated, by thermal or chemical vein ablation of refluxing veins, has been poorly investigated. Recent animal experiments were not successful in preventing reperfusion by compression (≤120 hours) after injection of sclerosing agents into rabbit ears.[47]

In the case of bypass operations or reconstruction of deep vein valves, measures that are sporadically performed in specialized centers only, care must be taken to ensure that the endothelium of the implanted vessel segments remain intact and undamaged.[48,49] Basic research on the reendothelialization of different stent material concentrated on arterial circulation and animal experiments. Lots of research, especially with regards to venous stents, still needs to be conducted. Understanding the underlying pathophysiological mechanisms better, as described in Part I, will provide helpful stimuli for future research.

NEW PHARMACOLOGICAL ASPECTS IN THE THERAPY OF CVI

Critical preliminary remarks

As described in Part I, CVI is a chronic disease, probably originating in the nutritive microvasculature in leg vein walls and/or leg organs, and in which local coagulation mechanisms and inflammatory reactions play a central, self-reinforcing role. It is clear that this is the site for intervention, both with effective and specific medications, and with the aim of inhibiting, or even permanently preventing, the chronic progression of the disease. The main benefit of physical or surgical therapies must be viewed in the context of prophylaxis or support: alone they are insufficient to prevent the spreading microcirculatory inflammatory processes. However, evaluation of venous drug therapy effectiveness is beset by diverse fundamental difficulties.[50] For example, the objective assessment of certain symptoms, eg, pain and edema, is difficult. In addition, quantitative assessment of fluid accumulation in the legs, a distinction should be made between hydrostatic and/or inflammatory causes (a distinction that can hardly be realized using the standard physical measurement methods). Further handicaps in the evaluation of medications, which are mostly of a phytotherapeutic origin, result from an unsatisfactory analysis of the composition of the active substances in the preparations and also lack detailed knowledge of their metabolic pathways in the human body. Appropriate studies are particularly difficult to carry out with patients and alternative animal experimentation is excluded by the lack of a recognized animal model for CVI. In addition, the use of many venous therapeutics, endorsed for decades, is based on clinical studies that would not satisfy today's standards, and moreover, the pathogenetic targets described in Part 1 of this publication have, to date, been largely ignored. Almost exclusively, purely physical parameters are at the forefront as the goal of current therapy (eg, venous pressure, leg circumference, "leg heaviness"), consistent with the classical concept that these are passive consequences of gravity. Unfortunately, therapeutic efforts frequently concentrate on cosmetic effects, neglect the causal pathogenetic mechanisms, and are often started too late. Moreover, clinical proof-of-effectiveness studies have rarely included

the determination of blood parameters, such as the concentration of certain inflammatory mediators. The latter have been employed successfully in modern laboratory studies on the pathogenesis of CVI to document its inflammatory nature.[11,51]

Therefore, in view of all the foregoing information, the great heterogeneity of pharmacological study results is not surprising. To improve this situation, Perrin and Ramelet have suggested guidelines for the further development of appropriate drugs.[52]

Questionable venous drugs

The spectrum of venoactive substances is wide and comprised of different substances (*Table I*). The site of action of several drugs, within the framework of accepted pathogenesis models, is unclear and the clinical evidence for a therapeutic success must be frequently considered

Class of compound	Claimed main active principle(s)	Origin	Trade names (Examples)	Dosage (mg/day)	Commercially available in (Country)[1]
		Plant extracts / semisynthetic compounds			
α-Benzopyrone	Coumarin	Foliage of the yellow meliot *(Melilotus officinalis)* or woodruff *(Galium odoratum)*	No single-substance preparations in the german «Rote-Liste®»	–	Only traditional preparations in Germany
Organic-chem. starting products	Calcium dobesilate	Organic-chemical synthesis	Doxium®	1-2 × 500-1000	Not Germany, but (e.g.) Switzerland (prescription only)
	Benzarone	Organic-chemical synthesis	–	–	Taken off the market in Germany in 1992 because of side-effects (liver damage)
	Naftazone	Organic-chemical synthesis	Mediaven® forte	1 × 30	Not Germany, but (e.g.) Switzerland (prescription only)
Saponines	"Escin" or "Aescin" (chemically not defined)	Seeds of the horse chestnut *(Aesculus hippocastanum L)*	Venostasin® retard, Aescorin® forte, Aescusan® retard, Venoplant® retard etc.	2 × 500	Germany and other European countries
	Ruscogenines	Berries of the butcher's broom *(Ruscus aculeatus L)*	Cefadyn®, Phlebodril®	1-2 × 86 2-3 × 150	Traditional preparation in Germany and other European countries
Terpenlactones, Flavonglycosides	"Ginkgolides" (chemically not defined)	Foliage of the gingko tree *(Ginkgo biloba)*	Tebonin®, Rökan®, Gingkobil-ratiopharm® etc.	No dosage recommendation for use with CVI; Off-label	Germany and other European countries, not licensed for treatment of chronic venous diseases
γ-Benzopyrones (Flavonoids)	Quercetin-glucuronide, kaempferol-glucoside	Red vine leaves *(Vitis vinifera L)*	Antistax® extra	1-2 × 360	Germany and other European countries
	Complex mixture of poly-(O-2-hydroxyethyl)-rutosides (semisynthetic, also known as "Oxerutin" or "Troxerutin"	Foliage of the Japanese pagoda tree *(Sophora japonica)*, common buckwheat *(Fagopyrum esculentum)*	Venoruton® intens, Venoruton® 300, Troxerutin-ratiopharm® 300 mg etc.	2 × 500 3 × 300	Germany and other European countries
	Diosmin (90%) + Hesperidin (10%) semisynthetic, especially finely ground, frequently termed «MPFF» ("micronized purified flavonoid fraction")	Dried bitter (or Seville) orange *(Citrus aurantium)*	MPFF*	2 × 450 or 500	France, Switzerland and other European countries (not Germany)

1. The commercial exploitation of these products is far more complex than can be represented in a table column. Most have a double status, being deemed to be medicinal products in some countries and food supplements in others. Antistax®, for instance, is a food supplement in Belgium, Cyprus, Greece, Irland, Italy, Malta, Portugal and the UK, but is a medicinal product in Austria, the Czech Republic, Germany, Hungary, Slovakia, Spain and the Netherlands. As food supplements, preparations are not subject to medical supervision and assessment, and even the medicinal products are not licensed uniformly: Doxium®, for instance, is approved in Spain only for the treatment of eye capillary fragility, whilst in other countries it is also approved for the symptomatic therapy of CVI.

** Registered as Ardium®, Alvenor®, Arvenum® 500, Capiven®, Daflon® 500 mg, Detralex®, Elatec®, Flebotropin®, Variton®, and Venitol®.*

Table I: Medication for therapy of chronic venous disease (adapted from ref 67 with permission)

with reservations.[52-54] For example, α-benzopyrone coumarin, contained in specially prepared plant extracts, is now rarely employed because of its now known hepatotoxicity and carcinogenicity.[55] The evidence for the effectiveness of various synthetic venous therapeutics is also dubious. Positive clinical findings for calcium dobesilate, for instance, were reported in one study,[56] while another multicenter and double-blind study found no useful effect whatsoever.[57] In addition, literature[57] provides no evidence for a positive effect of benzarone in the treatment of CVI, and there is no convincing evidence for naftazone effectiveness. The one positive report for the latter substance stems from a study in 1997 that does not meet today's standards.[57] The use of triterpenglycosides, (A)escin, extracted from the horse chestnut, was initially reported to be beneficial and widely prescribed,[58] but is now regarded by the same authors with more reservation.[59]

Target for a promising and specific CVI therapy: the venular endothelial barrier

To protect the venular endothelial barrier, a drug should inhibit the metabolic cooperation between platelets and polymorphonuclear leukocytes (PMN).[60] A potential intervention for a venoactive drug would be to inhibit the intercellular clefts in the venular endothelium from opening, although this still requires a detailed biochemical investigation. Preventing the cleft opening in situ would, in any case, avoid the collapse of the venular barrier, and consequently, prevent the prompt activation of the pericytes, plasma-extravasation, and the rapid and massive coagulation and inflammatory initiation. Such specific protection of the venular barrier would appear to be a promising approach for the prevention of thrombosis and would not increase the risk of hemorrhage (see below). Protection against reactive oxygen species from activated leukocytes, a so-called antioxidant therapy, is a further desirable action of a potent venoactive drug.[61]

Compounds that combine all these potential actions are members of the large class of flavonoids.[62] There is increasing evidence that some of these substances have a broad anti-inflammatory effect.[60,62-65] Quercetin glucuronide, the main flavonoid component of the extensively studied red vine leaf extract, stabilizes specific endothelial barrier functions of the human venular endothelium at submicromolar concentrations, even in the presence of activated platelets and PMN.[60,66,67] Quercetin also interferes with the proinflammatory signaling of thrombin, which results in the inhibition of adenine nucleotide secretion from activated platelets and decreased PMN function.[68] Flavonoid compounds are effective platelet inhibitors, can reduce blood pressure, and restore endothelial dysfunction characterized both by a loss of the vasorelaxant effect and by reduced bioavailability of endothelial nitric oxide (NO) in hypertensive animals.[69] In addition, quercetin improves vessel function by inducing endothelial NO-synthetase activity via phosphorylation of an AMP-dependent phosphokinase.[70]

Systemic administration of certain flavonoids has recently been recommended for the treatment of sepsis in the context of intensive care.[71] This acute, life-threatening disease is characterized by generalized platelet and granulocyte activation in the entire circulation and complete breakdown of the venular barrier in numerous organs that can lead to multiple organ failure and death. Such severe pathological reactions should also be inhibited within the framework of an improved conservation and revitalization of explanted organs intended for transplant. In accordance with the central involvement of venules and their pericytes in the initiation of thrombotic events, presented in Part I, the histological diagnosis of selective venular occlusion,[72] venular thrombosis,[73] or venulitis[74] is already regarded as the earliest reliable sign of impending organ rejection.[60] Our observations on an isolated, working, blood-perfused porcine heart (xenografts in a pig-to-man model of heart transplantation) show that it is extremely important to specifically prevent the venular barrier function breakdown and the resultant formation and spreading of thrombi into the venous limb of the microcirculatory system during explantation.[75] Cardiac function in these experiments was significantly improved in the presence of quercetin glucuronide. Subsequent specific microscopic examination of the ventricular myocardium of such preparations showed no evidence of venular thrombosis, venulitis, or excessive accumulation of leucocytes in the myocardium.

Flavonoids are very effective therapeutically and during CVI in clinical studies

Use in cases of mild-to-moderate chronic insufficiency (CEAP class 2 to 4)

The above-mentioned effects of quercetin glucuronides account for many aspects of their therapeutic effectiveness, as has been repeatedly demonstrated in double-blind placebo-controlled studies.[76,77]

In addition, a synthetically hydroxyethylated mixture of derivatives of rutin, a flavonoid extracted from plants (*Table 1*), has been shown to reduce leg edema and improve hemodynamics.[78-80] A meta-analysis has also shown that these flavonoid preparations reduce CVI symptoms,[81] and in a more recent Cochrane review, it is stated that Rutoside appears to help relieve the symptoms of varicose veins in late pregnancy.[82]

The clinical effectiveness of a micronized purified flavonoid fraction (MPFF) preparation has been tested frequently with respect to CVI.[83-85] Data from a large (5000 patients) multicenter study are especially convincing.[86] One consistent finding in clinical reports is the reduction in subjective complaints.[87] This fact may be explained by a reduction in capillary leakage, which stimulates nocireceptor fibers in the tissue.

Use in chronic venous leg ulcers (CEAP class 5 to 6)

For patients with chronic venous ulcers, the most frequently tested agent is MPFF.[88] A meta-analysis summarizes the data from investigations on over 700 patients.[89] Corresponding clinical studies with smaller patient numbers treated with (a)escin or oxerutin failed to show faster healing or reduced recurrence of venous leg ulcers.[90,91]

NEW ASPECTS IN THE PHARMACOLOGICAL TREATMENT AND PREVENTION OF THROMBOSIS

Short survey of the development of antithrombotic drugs

As described in Part I, with respect to microvessel wall and vascular intima functional classifications, (in particular the proinflammatory and procoagulatory roles of the pericytes) highly interesting changes are looming with relation to drug treatment and prophylaxis of thrombosis.

For almost 70 years, heparins and vitamin K antagonists (VKA) have been employed as complementary anticoagulants for prevention and treatment of thrombosis. The introduction of low-molecular-weight heparin (LMWH) was a big step forward with respect to both prophylaxis and treatment of DVT. Numerous studies have shown that LMWH is superior to unfractionated heparin and may even be considered for long-term treatment because it is safer than vitamin K antagonists.[92] LMWH may also have more favorable effects regarding the prevention of a postthrombotic syndrome. The small LMWH molecules may diffuse more readily into the vein wall and interfere with freshly formed thrombin at the surface of procoagulant pericytes, which could explain their superior effect when compared with conventional heparin. Thrombus resolution and vein wall remodeling have also been shown to be positively influenced by LMWH.[93,94]

DVT restitution–treatment concentrates on clot removal by mechanical means (thrombectomy; catheter-directed thrombolysis [CDT]), but does not consider the proinflammatory and prothrombotic potential of the vein wall (see Part I). This explains the rather disappointing results with respect to prevention of the postthrombotic syndrome even after a successful CDT. This led to the most recent ACCP guideline recommending anticoagulant therapy in preference to CDT in patients with acute proximal DVT.[95]

If thrombolytic agents dissolved in large volumes are injected into a vein of the thrombotic leg under regional circulatory arrest, the resulting high intravenous pressure (Biers block [retrograde intravenous pressure infusion]), will promote infiltration of large fibrinolytic molecules into the thrombus, and also via the numerous venule clefts of the vasa venarum system into the interstitial space of the vein wall. This procedure, in combination with subsequent thrombectomy, may achieve better results than conventional CDT, especially in distal vein involvement.[96]

Vitamin K antagonists (VKA) have not changed pharmaceutically for years, although treatment surveillance has been improved by the introduction of the International Normalized Ratio (INR) and self-monitoring/management. Recently, however, new oral anticoagulants have been authorized. These arouse high expectations, both in prescribers and patients, since they obviate the burdensome control investigations accompanying VKA treatment, without any loss of efficiency or safety. The major difference between VKA and new anticoagulants is the highly specific action of the latter against thrombin (dabigatran etexilat, Pradaxa®) or factor Xa (rivaroxaban and other "xabanes" currently under development). The half-life of these new substances is much shorter than the usual VKAs (eg, phenprocoumon, warfarin), so that "anticoagulation bridging" before surgery becomes unnecessary. The therapeutic window of the specific anticoagulants is wider, meaning that they can be administered at fixed

doses. Clinical studies have claimed that, with respect to prophylaxis of thrombosis, thromboembolism, and atrial fibrillation, these substances are as effective as conventional VKAs. Certain restrictions may become apparent with respect to gastrointestinal side effects, metabolism, renal excretion, and other routes of elimination; specific antidotes are not yet available for these effects. In short, considerable clinical experience will still be necessary before the new anticoagulants will finally replace VKAs.[97]

Pitfalls of modern anticoagulation therapies and flavonoids as promising prophylactic antithrombotics

The pharmaceutical and therapeutic developments (briefly addressed above) completely ignore the recently recognized importance of hemostasis on the venular endothelial barrier, and behind it, the procoagulant pericytes, as presented in Part I. In essence, all modern anticoagulatory therapies aim to specifically inhibit already activated coagulation factors, such as factors Xa or IIa (thrombin), formed in the middle or at the end of the coagulation cascade. However, on the basis of our proposed functional model, it would be more rational to interfere with the initiation of the extrinsic coagulation pathway by blocking the tissue factor/VIIa complex on the plasmalemma and in the extracellular matrix of the pericytes. This would attenuate the accumulation of free factor Xa or thrombin in the plasma, and a physiological thrombin concentration below 0.1 nM could be established and maintained via the intrinsic coagulation pathway. The resulting constant low rate of physiological fibrin synthesis in the blood stream would then foster necessary capillary tightness (therefore reducing the risk of hemorrhage). Simultaneously, the constant activation of protein C mediated by the endothelial thrombomodulin/thrombin complex at low thrombin concentrations *(see Part I, Figure 4)* would continuously prevent this "physiological intrinsic fibrin production" from overshooting. Clinically employable pharmaceuticals for direct prevention of plasma factor X activation, by the pericytes cell membrane tissue factor *(see Part I, Figure 4)*, are not yet available. However, as discussed above, certain flavonoids stabilize the integrity of the venular endothelial barrier and probably contribute to the physiological antithrombogenicity of the healthy intima, since they prophylactically prevent direct contact between pericytes and plasma coagulation zymogens. Moreover, recent studies indicate that naturally occurring flavonoids can inhibit tissue factor,[98] particularly when oligopolysulfated moieties are included in the typical ring structure.[98,99] In short, these substances would appear to have remarkable potential to become new, effective, and safe agents for a prophylactic anticoagulant therapy.

Flavonoid-induced sealing of the venular endothelial barrier implies possible prophylactic use, not only with respect to preventing initiation of the coagulation process in the adventitia (more precisely: at the plasmalemma and in the extracellular matrix of abundant microvascular pericytes), but also with respect to prevention of platelet activation since thrombin is the most potent physiological activator of platelet aggregation.[100] Indeed, antiplatelet drugs have also been rediscovered as promising agents with respect to early interaction at the beginning of a thrombotic process in the venous system. Several recent recommendations suggest their use for preventing arterial and venous thrombosis.[101,102]

Corresponding author
Professor Dr. Stephan NEES
Department of Physiology, University of Munich (LMU)
Schillerstr. 44, 80336 Munich, Germany

E-mail:
stephan.nees@lrz.uni-muenchen.de
stephan@snees.de


D. R. WEISS


G. JUCHEM


H. PARTSCH

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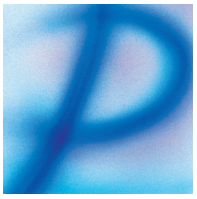

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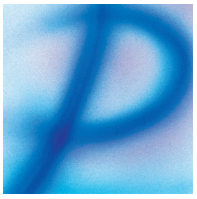

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A unique action at the core of chronic venous disease

First and unique position in international guidelines[1]

COMPOSITION UNIQUE & MICRONIZATION[2,3]

COMPOSITION*: Micronized, purified flavonoid fraction 500 mg: 450 mg diosmin; 50 mg flavonoids expressed as hesperidine. **INDICATIONS*:** Treatment of organic and idiopathic chronic venous insufficiency of the lower limbs with the following symptoms: heavy legs; pain; nocturnal cramps. Treatment of acute hemorrhoidal attacks. **DOSAGE AND ADMINISTRATION*:** *In venous disease:* 2 tablets daily. *In acute hemorrhoidal attacks:* the dosage can be increased to up to 6 tablets daily. **CONTRAINDICATIONS*:** Hypersensitivity to the active substance or to any of the excipients. **WARNINGS*:** The administration of this product for the symptomatic treatment of acute hemorrhoids does not preclude treatment for other anal conditions. If symptoms do not subside promptly, a proctological examination should be performed and the treatment should be reviewed. **INTERACTION*:** None. **FERTILITY*/ PREGNANCY*. BREASTFEEDING*:** Treatment should be avoided. **DRIVE & USE MACHINES*. UNDESIRABLE EFFECTS*:** *Common:* diarrhoea, dyspepsia, nausea, vomiting. *Rare:* dizziness, headache, malaise, rash, pruritus, urticaria. *Uncommon:* colitis. *Frequency not known:* isolated face, lip, eyelid oedema. Exceptionally Quincke's oedema. **OVERDOSE*. PROPERTIES*:** Vascular protector and venotonic. Daflon 500 mg acts on the return vascular system: it reduces venous distensibility and venous stasis; in the microcirculation, it normalizes capillary permeability and reinforces capillary resistance. **PRESENTATION*:** Pack of 30 film-coated tablets of Daflon 500 mg. Pack of 60 film-coated tablets of Daflon 500 mg.

** For complete information, please refer to the complete summary of product characteristics for your country.*

**IMS data worldwide (12 months to December 2012 in turnover)

Les Laboratoires Servier – 45520 Gidy - France. Correspondent: **Servier International** 50, rue Carnot - 92284 Suresnes Cedex - France. Web site: www.servier.com

2 tablets daily

SERVIER **Chronic venous disease**

1 - Nicolaides AN, Perrin M. The updated international guidelines on "The management of chronic venous disorders of the lower limbs" and the place of venoactive drugs. Abstract presented at the last UIP congress, Boston, United States. September 8th–13th 2013. **2** - Garner RC, Garner JV, Gregory S, et al. *J Pharm Sci.* 2002;91:32-40. **3** - Paysant J, Sansilvestri-Morel P, Bouskela E, Verbeuren TJ. *Int Angiol.* 2008;27:81-85.

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Correspondent:

Servier International - 50, rue Carnot - 92284 Suresnes Cedex - France
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