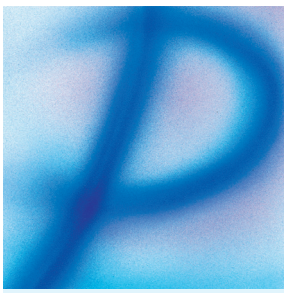
Phlebolymphology

ISSN 1286-0107

Vol 23 • No. 2 • 2016 • P57-120 No. 89



Phlebolymphology

Editorial board

Editor in chief

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.

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Indexed in EMBASE, Index Copernicus, and Scopus.

ISSN 1286-0107

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Editorial

Michel PERRIN

Dear Readers,

At the end of 2015, Servier asked me to become the editor-in-chief of Phlebolymphology. I accepted without hesitation as in the last two decades Phlebolymphology has become an excellent journal, particularly in terms of research updates and the treatment of venous and lymphatic disease. The Phlebolymphology website also lists:

- *All randomized control trials regarding treatment of varicose veins, classified either by author or topic, plus their abstracts.*
- *The references of all articles published since 1990 on the presence of varices after operative treatment (PREVAIT), under 8 headings.*

Randomized control trials on operative management of varicose veins and information on PREVAIT are both excellent tools for updating the knowledge of physicians who treat venous and lymphatic diseases and are particularly helpful for those who want to publish on these two topics.

***Françoise Pitsch** managed Phlebolymphology for more than 15 years by carefully selecting the articles to be published and I will do my best to continue this policy. As Servier informed me that the board contracts were over, I decided to revitalize the board by inviting younger people to sit on the board, and three women have agreed:*

- ***Marianne de Maeseneer**, Erasmus Medical Center, Rotterdam, Netherlands, who is in charge of the venous section of the European Journal of Vascular and Endovascular Surgery and an expert in the recurrence of varicose veins after operative treatment.*
- ***Lourdes Reina Gutiérrez**, Cruz Roja Hospital, Madrid, who has developed the use of ultrasound-guided sclerotherapy in Spain.*
- ***Marzia Lugli**, Hesperia Hospital, Modena, Italy, who has extensive European experience in treating deep venous obstruction.*

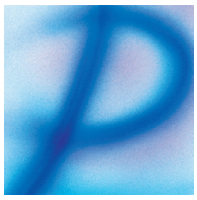
These three Graces are joined by five male colleagues:

- ***Athanasios Gianoukas**, University Hospital and University of Thessaly Medical School, Larissa, Greece, who is the general secretary of the European Venous Forum and who has wide-ranging experience in both acute and chronic venous disease.*
- ***Oscar Maleti**, Hesperia Hospital, Modena, Italy, who directs the Interuniversity Center of Phlebolymphology and has internationally recognized experience in treating deep venous reflux.*
- ***Armando Mansilha**, Faculty of Medicine, Angiology and Vascular Surgery, Porto, Portugal, who is an expert in venous surgery as well angiology.*
- ***Djordje Radak**, Faculty of Medicine, Vascular Surgery, Belgrade, Serbia, who has many publications to his credit.*
- ***Marc Vuylsteke**, Sint-Andriesziekenhuis, Tielt, Belgium, who has vast experience in vascular surgery and in thermal ablation of varicose veins.*

I am convinced that all of the new board members will help me to track down the most appropriate authors to write articles of excellence for publication in Phlebolymphology.

Happy reading.

Michel Perrin



An update on operative treatments of primary superficial vein incompetence: part 2.

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Abstract

In part 2 of "An update on operative treatment of primary superficial vein incompetence," all randomized controlled trials (RCTs) published since 1990 on operative treatments of varicose veins were collected and the references were gathered in tables according to either the procedure used or the patient's clinical status. Case series and meta-analyses were taken into account in this review when RCTs were not available. For more details regarding clinical or instrumental outcomes of the studies described, please go to www.phlebolymphology.org. In the second part of this article, the indications for operative treatment of varicose veins will be discussed. These indications are not specific, as many factors must be taken into account and, unfortunately, in practice it is not always based on evidence. Finally, the recently published international recommendations about the use of the various procedures for varicose vein ablation will be reviewed.

Keywords:

case series; meta-analyses; operative treatment; randomized controlled studies; recommendations; surgery; varices; varicose veins

Outcomes after operative treatment

Randomized controlled trials (RCTs) are very good tools for comparing the results of the various operative treatments for varicose veins. Yet, before drawing definitive conclusions on any of these procedures, an accurate publication analysis is mandatory as RCTs often contain hard-to-identify bias. For example, the short-term results of a procedure greatly depend on the type of anesthesia performed during varicose vein ablation (local tumescent anesthesia or general anesthesia).[1] In the absence of RCTs for evaluating a procedure, case series are considered even though they provide a weaker level of evidence. Well-designed meta-analyses can provide valuable information for clinicians. By combining RCTs, meta-analyses increase the sample size, and thus, the power to study the results of a given procedure. Study outcomes are usually divided into the following 3 categories: (i) postoperative outcomes (<1 month); (ii) short- to mid-term outcomes (1 month to 3 years); and (iii) long-term outcomes (>3 years for RCTs and >5 years for case series. Nevertheless, this review's outcome analysis has been divided into two parts: (i) postoperative and mid-term outcomes and (ii) long-term outcomes.

Phlebolymphology. 2016;23(2):59-75

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Postoperative and mid-term outcomes

Open surgery

Classic open surgery has been compared with conservative treatment both in C_2 and C_5-C_6 patients *(Tables I.1 and I.2)*.[2-13] In addition, classic open surgery has been compared with open surgery variants *(Tables I.3 and I.4)*, such as cryostripping[14,15] and tributary-powered phlebectomy[16-20]– techniques that are only rarely used in current practice. Some RCTs *(Table I.5)*[22-35] provide interesting information on how classical stripping influences nerve damage,[22,25,29] the short- and long-term outcomes according to the procedure used,[24,30,33] the results following saphenofemoral junction ablation and ligation[21,26,35] or associated perforator ablation.[30] The RCTs comparing classic open surgery with other ablative procedures are more interesting and are shown in *Table I.6 to I.15*.[36-86] Additionally, the CHIVA method (Cure Hémodynamique de l'Insuffisance Veineuse en Ambulatoire [conservative ambulatory hemodynamic management of varicose veins]) is performed under local anesthesia when other open surgery techniques need spinal or general anesthesia, and as a result, CHIVA shortens the length of the hospital stay *(Table I.6)*.[36,37]

All RCTs that compared the short-term results of classic open surgery with radiofrequency ablation (RFA), endovenous laser ablation (EVLA), endovenous steam ablation,[81] endovenous microwave ablation, ultrasound-guided foam sclerotherapy (UGFS), and high ligation with tributary phlebectomy concluded that both endovenous procedures and high ligation with tributary phlebectomy are less painful than classic open surgery and these procedures shorten the time required before returning to normal activity. Sensory impairment and ecchymosis are less severe with endovenous microwave ablation than open surgery, even though endovenous microwave ablation causes skin burns, 10% of which are related to slow probe withdrawal or using energy that is too high *(Table I.14)*.[82] However, when modern open surgery is performed under local anesthesia (unfortunately by very few teams), it is as effective postoperatively as any endovenous procedure.

Endovenous procedures

Endovenous procedures have been widely studied and compared with open surgery and other endovenous procedures.

Thermal ablation

Radiofrequency ablation. RFA has been compared with open surgery, cryostripping, invagination stripping, EVLA, and UGFS *(Table I.7, I.12, I.16, and I.17)*.[38-46,79,80,87-91] Studies of EVLA using bare fibers vs RFA favored the latter since it is less painful and results in less ecchymosis. However, it is now acknowledged that radial fibers, which are currently used, provide better postoperative results than bare fibers.[92] No differences in efficacy and undesirable effects were observed between RFA and UGFS in a 4-arm study.[79,80] At a 1-year follow-up, redo operations were less frequent after RFA compared with deleted or synchronized ambulatory incompetent tributary avulsion *(Table I.18)*.[93]

Endovenous laser ablation. Treating varicose veins with EVLA is a safe procedure in patients with active ulcers. Ulcers healed faster after EVLA than in patients undergoing compression therapy alone and no ulcer recurrence occurred during a 1-year period posttreament.[13] EVLA has been compared with open surgery, cryostripping, invagination stripping, EVLA has been compared with open surgery (*Table I.8*)[47-63], with open surgery and UGFS (*Table I.11*)[76-78], in a 4-arm RCT including open surgery, EVLA, RFA, UGFS (*Table I.12*)[79-80], with invagination stripping (*Table I.16*)[87-91], with steam ablation (*Table I.19*)[100], and with cryostripping (*Table I.29*).[94-96] All procedures were similarly effective in patients with varicose veins[94,95] and EVLA had a similar, but slightly higher cost.[96]

When comparing UGFS and EVLA *(Table I.11 and I.25)*,[76-78,97-99] no differences at 3 months[97,98] were observed for clinical results or vein obliteration, but UGFS outperformed EVLA in cost, treatment duration, postoperative pain reduction, and recovery. At 15 months,[99] there were no differences in clinical results, but vein occlusion was higher with EVLA. At a 1-year follow-up, Biemans et al found no difference between the EVLA and UGFS in complications and clinical results, but UGFS resulted in lower occlusion rates.[76] Brittenden et al showed similar clinical efficacy between UGFS and EVLA, but EVLA had fewer complications and UGFS had lower ablation rates at both 6 weeks and 6 months posttreatment.[77] Tassie et al showed that EVLA has the highest probability of being cost-effective compared with classic open surgery and UGFS.[78]

The 1-year treatment success of high-dose EVLA was not inferior to that of endovenous steam ablation. Several secondary outcomes (eg, painful legs, patients' satisfaction, duration of analgesia, and limitations in daily life) were in favor of endovenous steam ablation (P<0.001).[100]

Data from ten RCTs on EVLA variants *(Table I.20)*[92,101-111] show that: (i) below-knee EVLA was not associated with saphenous nerve injury[104]; (ii) lower postoperative pain

	Operative procedures	Reference(s)
1	Classic open surgery vs Conservative treatment	Michaels et al,[2] 2006 Michaels et al,[3] 2006 Ratcliffe et al,[4] 2006 Sell et al,[5] 2014
2	Classic open surgery ± SEPS or laser ablation + compression therapy vs Isolated compression therapy in C_5-C_6 or C_6 patients	Barwell et al,[6] 2004 Guest et al,[7] 2003 Gohel et al,[8] 2005 van Gent et al,[9] 2006 Gohel et al,[10] 2007 Zamboni et al,[11] 2003 Zamboni et al,[12] 2004 Viarengo et al,[13] 2007
3	Classic open surgery vs Cryostripping	Menyhei et al,[14] 2008 Klem et al,[15] 2009
4	Classic open surgery with various types of tributary phlebectomy	Aremu et al,[16] 2004 Scavée et al,[17] 2003 Ray-Chaudury et al,[18] 2003 Chetter et al,[19] 2006 Krasznai et al,[20] 2015
5	Classic open surgery: partial vs complete stripping	Holme et al,[22] 1990
	Classic open surgery: HL comparing two skin closure techniques	Corder et al,[23] 1991
	Classic open surgery: HL + tributary phlebectomy vs Isolated HL	Dwerryhouse et al,[24] 1999
	Classic open surgery with and without a tourniquet	Sykes et al,[25] 2000
	Classic open surgery with SFJ 1ush ligation + tributary phlebectomy vs SFJ distal ligation + tributary phlebectomy	Belcaro et al,[26] 2002
	Classic open surgery with saphenous stripping (Babcock) vs Pin stripping (Oesch)	Buttler et al,[27] 2002
	Classic open surgery under general + local anesthesia: Lidocaine + adrenaline vs Saline solution	Nisar et al,[28] 2006
	Classic open surgery with saphenous stripping (Babcock) vs Invaginated stripping	Scheltinga et al,[29] 2007
	Classic open surgery with HL + stripping + tributary phlebectomy vs Idem + SEPS	Kianifard et al,[30] 2007
	Redo open surgery with SFJ ligation vs Redo SFJ ligation + polytetra1uoroethylene patch insertion in recurrent great saphenous varicose veins	Winterborn et al,[31] 2007
	Chemical ablation (UGFS) + HL vs HL + stripping	Abela et al,[32] 2008
	Flush SFJ ligation vs Standard transfixion SFJ ligation	Winterborn et al,[33] 2008

	Operative procedures	Reference(s)
5	HL + stripping + tributary phlebectomy + antibiotic prophylaxis vs Idem without antibiotic prophylaxis	Mekako et al,[34] 2010
	Classic open surgery with HL of the SFJ vs Idem without high SFJ ligation	Casoni et al,[21] 2013
	HL vs HL + fascia cribriformis suture vs HL with inverting suture of the stump	Haas et al,[35] 2005
6	Classic open surgery vs CHIVA	Carandina et al,[36] 2008 Parés et al,[37] 2010
7	Classic open surgery vs RFA	Hinchliffe et al,[38] 2006 Kianifard et al,[39] 2006 Lurie et al,[40] 2003 Lurie et al,[41] 2005 Rautio et al,[42] 2002 Perälä et al,[43] 2005 Stötter et al,[44] 2006 Subromania et al,[45] 2010 Elkaffas et al,[46] 2011
8	Classic open surgery vs EVLA	de Medeiros et al,[47] 2005 Vuylstecke et al,[48] 2006 Lin et al,[49] 2007 Rasmussen et al,[50] 2007 Darwood et al,[51] 2008 Kalteis et al,[52] 2008 Theivacumar et al,[53] 2009 Christenson et al,[54] 2010 Pronk et al,[55] 2010 Rasmussen et al,[56] 2010 Carradice et al,[57] 2011 Carradice et al,[58] 2011 Rass et al,[59] 2012 Rasmussen et al,[60] 2013 Flessenkämpfer et al,[61] 2013 Samuel et al,[62] 2013 Roopram et al,[63] 2013
9	Classic open surgery vs Endovenous thermal ablation (EVLA, RFA)	Dzieciuchowicz et al,[64] 2014
10	Liquid chemical ablation vs Classic open surgery	Einarsson et al,[65] 1993
	Liquid chemical ablation + HL vs Classic open surgery	Rutgers et al,[66] 1994
	Liquid chemical ablation vs Classic open surgery + liquid chemical ablation vs Classic open surgery	Belcaro et al,[67] 2000
	Liquid and foam chemical ablation vs Various open surgery procedures	Belcaro et al,[68] 2003

	Operative procedures	Reference(s)
	Phlebectomy vs Liquid chemical ablation	de Roos et al,[69] 2003
	Chemical ablation + HL vs Classic open surgery (HL + stripping)	Abela et al,[32] 2008 Bountouroglou et al,[70] 2006 Liu et al,[71] 2011 Kalodiki et al,[72] 2012
	Chemical ablation (UGFS) vs Classic open surgery (HL + stripping)	Figueiredo et al,[73] 2009 Shadid et al,[74] 2012
	Chemical ablation (liquid or foam) vs HL or HL + stripping or phlebectomy	Wright et al,[75] 2006
11	Classic open surgery vs EVLA vs UGFS	Biemans et al,[76] 2013 Brittenden et al,[77] 2014 Tassie et al,[78] 2014
12	Classic open surgery vs EVLA vs UGFS vs RFA	Rasmussen et al,[79] 2011 Rasmussen et al,[80] 2013
13	Classic open surgery vs Endovenous steam ablation	Woźniak W et al,[81] 2015
14	HL + stripping + tributary phlebectomy + perforators ligation vs HL + EMA of the GSV + EMA tributary phlebectomy + EMA perforators ablation	Yang et al,[82] 2013
15	Classic open surgery (HL + stripping) vs HL + tributary phlebectomy ± perforator ligation	Campanello et al,[83] 1996 Hammarsten et al,[84] 1990 Hammarsten et al,[85] 1993 Winterborn et al,[86] 2004
16	RFA vs EVLA	Almeida et al,[87] 2009 Shepherd et al,[88] 2010 Gale et al,[89] 2010 Goode et al,[90] 2010 Nordon et al,[91] 2011
17	RFA vs Invagination stripping vs Cryostripping	Stötter et al,[44] 2006
18	RFA completed with deleted or synchronized ambulatory incompetent tributary avulsion	Lane et al,[93] 2015

	Operative procedures	Reference(s)
19	EVLA vs Endovenous steam ablation	van der Bos et al,[100] 2014
20	EVLA with different wavelengths	Kabnick et al,[101] 2006
	HL + EVLA vs EVLA without HL	Disselhoff et al,[102] 2008 Disselhoff et al,[103] 2011
	EVLA of above-knee GSV vs Above- and below-knee GSV ablation	Theivacumar et al,[104] 2008
	EVLA with and without nitroglycerin ointment	Hogue et al,[105] 2008
	EVLA using 980 nm bare-tip fiber vs EVLA using 1470 nm radial fiber	Doganci et al,[92] 2010
	EVLA using 1470 nm radial fiber comparing warm and cold tumescence anesthesia	Pannier et al,[106] 2010 Dumantepe et al,[107] 2015
	EVLA using 980 nm vs 1500 nm diode	Vuylsteke et al,[108] 2011
	EVLA using a bare fiber vs EVLA using a tulip fiber	Vuylsteke et al,[109] 2012
	EVLA with 2- vs 7-day postoperative compression therapy	Bakker et al,[110] 2013
	EVLA using 12 W laser power with intermittent withdrawal vs 14 W laser power with continuous withdrawal	Samuel et al,[111] 2013
21	Sclerotherapy using polidocanol vs Saline solution	Kahle et al,[112] 2004
22	Liquid sclerotherapy vs Foam sclerotherapy	Hamel-Desnos et al,[113] 2003 Yamaki et al,[114] 2004 Alòs et al,[115] 2006 Ouvry et al,[116] 2008 Rabe et al,[117] 2008
23	Sclerosing agent at various doses and concentrations	Hamel-Desnos et al,[120] 2005 Ceulen et al,[121] 2007 Hamel-Desnos et al,[122] 2007 Blaise et al,[123] 2010

	Operative procedures	Reference(s)
24	Different compression therapy regimens after foam sclerotherapy	O'Hare et al,[124] 2010
	Foam sclerotherapy with and without compression therapy	Hamel-Desnos et al,[125] 2010
	In vivo biological effects of foam sclerotherapy	Hamel-Desnos et al,[126] 2011
25	EVLA + phlebectomy vs UGFS	Lattimer et al,[97] 2012 Lattimer et al,[98] 2012 Lattimer et al,[99] 2013
26	Visual foam sclerotherapy alone vs Visual + UGFS	Yamaki et al,[118] 2012
27	Foam sclerotherapy in thrombophilic patients in combination with thromboprophylaxis: low-molecular-weight heparin vs warfarin	Hamel-Desnos et al,[119] 2009
28	Ulcer healing and ulcer recurrence according to the presence or absence of incompetent perforators after SEPS	van Gent et al,[153] 2015
29	EVLA vs Cryostripping	Disselhoff et al,[94] 2008 Disselhoff et al,[95] 2008 Disselhoff et al,[96] 2009

Table I. Randomized controlled trials, case series, and meta-analyses comparing operative procedures for the treatment of primary superficial vein incompetence.

For more information on the trials, please go to www.phlebolymphology.org.

Abbreviations: CHIVA, Cure Hémodynamique de l'Insuffisance Veineuse en Ambulatoire (Conservative ambulatory Hemodynamic management of VAricose veins); EMA, endovenous microwave ablation; EVLA, endovenous laser ablation; GSV, great saphenous vein; HL, high ligation; RFA, radiofrequency ablation; SEPS, subfascial endoscopic perforator surgery; SFJ, saphenofemoral junction; UGFS, ultrasound-guided foam sclerotherapy.

and better Venous Clinical Severity Scores (VCSS) were obtained with radial fibers compared with bare fibers[92] or tulip fibers[109]; (iii) cold tumescent anesthesia had fewer side effects and a reduction in analgesic intake than warm tumescent anesthesia[106,107]; and (iv) symptom intensity was lower and quality of life better when compression was applied for 2 to 7 days posttreatment.[110]

Chemical ablation

Sclerotherapy. Postoperative, short-term, and mid-term results are difficult to compare because many different protocols and outcome criteria were used *(Tables I.10 to I.12)*.[65-80] RCTs on variants of sclerotherapy provide some data on postoperative course and short- or mid-term outcomes. Foam sclerotherapy provides better results than liquid sclerotherapy *(Table I.22)*,[113-117] and occlusion rates are similar when using either a 1% or 3% polidocanol foam solution *(Table I.24)*.[124-126] The use of postoperative compression does not influence the percentage of patients with side effects after UGFS *(Table I.25)*.[97-99]

Glue. No RCTs evaluating glue vs other procedures have been conducted, but a case series has reported good results at a 2-year follow-up–occlusion rates were 92% and a significant improvement in VCSS was observed.[127]

Mechanochemical ablation

There are no RCTs for Clarivein®, but case series are available.[128-130] At a 6-month follow-up, the occlusion rate was 96% and the VCSS improved in a series of patients presenting with saphenous vein varices.[128] In the case series by Boersma et al on patients who underwent short saphenous vein ablation, the occlusion rate at 1 year was 94% and the VCSS improved.[130]

Long-term outcomes

Clinical parameters

PREVAIT

The term PREsence of Varices After operatIve Treatment (PREVAIT) was adopted in the VEIN-TERM transatlantic interdisciplinary consensus document.[131] PREVAIT is a frustrating problem for both the patients with varicose veins and the physicians who treat these varicose veins. Recurrent Varices After Surgery (REVAS) have been previously compared with classic open surgery.[132]

Severity scores

The Venous Clinical Score (VCSS), Venous Segmental Disease Score (VSDS), and Aberdeen Varicose Vein Severity Score (AVVSS)–are used in the literature to assess treatment success rates. VCSS is a very good tool for evaluating the treatment of complicated varices, but it is less informative for uncomplicated C_2 patients.[133,134]

Generic and specific health-related quality of life questionnaires

Many health-related quality of life questionnaires have been used, including AVVQ, the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ), the Specific Quality of Life and Outcome Response-Venous (SQOR-V), and the results have been compared with anatomic, hemodynamic, and clinical outcomes before and after operative treatment.[135] Patient-Reported Outcome Measures (PROMs) are new and very promising tools.[136]

Instrumental investigation measurements

These measurements rely on occlusion rates and hemodynamic function. It has been clearly identified that the correlation between clinical and investigational parameters is far from perfect.

Information provided by RCTs

Open surgery vs high ligation and tributary phlebectomy

These procedures were assessed in 2 RCTs with 4, 5, and 11 years of follow-up[24,83-86] and there were no differences in clinical outcomes. More redo surgery was performed in the group with high ligation and tributary phlebectomy, but preoperative and postoperative investigations were outdated in both groups.

Open surgery vs CHIVA

CHIVA was compared with classic open surgery in 2 RCTs with 5 and 10 years of follow-up *(Table I.6)*.[36,37] Both RCTs favor CHIVA in terms of PREVAIT reduction, but bias was identified to weaken the authors' conclusions.

Open surgery vs radiofrequency ablation

Only one RCT comparing long-term outcomes (3-year) of open surgery with RFA is available and there was no difference in clinical results between the two groups,[150] but the Closure® catheter used was older and less efficient that the Closure FAST® catheter.

Open surgery vs EVLA

At a 5-year follow-up, a RCT comparing EVLA with open surgery found no difference between the 2 groups in persistent reflux, PREVAIT, redo treatment, VCSS, and generic and specific health-related quality of life scores. In this trial, open surgery was minimally invasive and the EVLA procedure used a bare fiber with a 980-nm diode laser and a stepwise laser withdrawal.[60]

Sclerotherapy vs various open surgery procedures

Belcaro et al reported two series with long-term follow-up data, but no conclusive results were obtained.[67,68] The RCT comparing UGFS complemented by high ligation with open surgery at a 3- to 5-year follow-up was more informative, showing that the treatment was equally effective in both groups, which was demonstrated by improvements in the VCSS, VSDS, and the generic health-related quality of life scores. At 5 years posttreatment, the AVVQ was significantly better in the open surgery group.[72]

Information provided by case series

Open surgery

The most documented outcomes are provided by classic open surgery, but most studies are retrospective. In a 34-year follow-up study, varicose veins were present in 77% of the lower limbs examined and most were symptomatic–58% were painful, 83% had a tired feeling, and 93% showed a reappearance of edema.[137] Two prospective studies concerning classic open surgery are available with a 5-year follow-up.[138,139] In both studies, patients were preoperatively investigated with duplex scanning and treated by high ligation, saphenous trunk stripping, and stab avulsion. In the Kostas et al series, 28 out of 100 patients had PREVAIT after 5 years, where the recurrent varices mainly resulted

from neovascularization (8/28, 29%), new varicose veins as a consequence of disease progression (7/28, 25%), residual veins due to tactical errors (eg, failure to strip the great saphenous vein) (3/28, 11%), and complex patterns (10/28, 36%).[139]

In the van Rij series, 127 limbs (CEAP class C_2-C_6) were evaluated postoperatively by clinical examination, duplex scanning, and air plethysmography. At the clinical evaluation, recurrence of varicose veins was progressive from 3 months (13.7%) to 5 years (51.7%). In line with clinical changes, a progressive deterioration in venous function was measured by air plethysmography and reflux recurrence was assessed by duplex scanning.[138] These two studies showed that recurrence of varicose veins after surgery is common, even in highly skilled centers. Even if the clinical condition of most affected limbs after surgery improved compared with before surgery, progression of the disease and neovascularization are responsible for more than half of the recurrences. Rigorous evaluation of patients and assiduous surgical techniques might reduce the recurrence resulting from technical and tactical failures.

Other procedures

A 5-year follow-up of a large series of patients treated with RFA using a Closure plus catheter showed that vein occlusion and absence of reflux were present in 87.2% and 83.8% of patients, respectively. Symptoms, including pain, fatigue, and edema, significantly improved compared with the preoperative status. The rate of PREVAIT progressed from 6 months (7.7%) to 5 years (27.4%).[140] Currently, no long-term results are available for Glue and Clarivein®.

Information provided by meta-analyses

Since 2009, six meta-analyses on operative treatment of primary varicose veins by open surgery, RFA, EVLA, and UGFS were identified–all produced similar conclusions.[141-146]

Final remarks concerning outcomes after operative treatment

The immediate postoperative course, including side effects, recovery time, and convalescence, is better in all other procedures compared with classic open surgery, but this point is questioned if modern and minimally aggressive open surgery is used. No differences in recurrence between classic open surgery compared with RFA and EVLA are present at the mid- or long-term follow-up. PREVAIT is more frequent after UGFS compared with other mentioned procedures, but PREVAIT can be easily and effectively treated with redo UGFS.

Operative treatment indications

According to CEAP class and instrumental investigations

In patients with primary superficial reflux who are classified as C_2, indications for operative treatment rely on patient complaints, such as symptoms and cosmetics, and on the extent and size of the varices. For patients in the C_3 to C_6 classes, operative treatment must be considered in all cases, except for the usual contraindications. However, in all clinical classes, nonvenous causes must be identified because venous symptoms are not pathognomonic and some signs, including edema and ulcers may be due to other etiologies. In the presence of axial deep primary reflux combined with primary varices, varicose veins must be treated first. However, we know that, in about half of the patients, axial deep primary reflux is not corrected by varicose vein ablation[147] and its persistence is responsible for varices recurrence.[148,149]

When incompetent perforators are associated with primary varices, do they need to be treated in the same session? As no RCTs have compared the outcomes after varicose vein ablation with perforator ablation + varices ablation, no evidence-based information is available. Nevertheless, we know that, in half of these patients, incompetent perforators are no longer identified after varices ablation.* To summarize, perforator ablation can be reserved for patients with persistent incompetent perforator vessels, abnormal hemodynamic parameters, or continued symptoms and/or signs (C_{4b}-C_6) after superficial ablative surgery.[152] Nevertheless, one RCT favors treating perforators in C_6 patients to prevent ulcer recurrence *(Table I.28)*.[153]

Operative treatment indication in PREVAIT patients

PREVAIT represents a particular situation in terms of indication.[154] Managing patients with PREVAIT varies according to the clinical situation. Patients attending a routine follow-up, who are either asymptomatic or symptomatic, and not complaining of recurrences are managed differently than symptomatic patients who are complaining of cosmetic problems and presenting with complicated varices (C_3-C_6).[150] A consensus document agrees that UGFS is the first-line treatment in almost all cases, except in patients presenting with varicose veins of the lower limbs that are fed by pelvic refluxive veins. The European guidelines for sclerotherapy assigned a Grade 1B to this procedure.[156] In the absence of RCTs, this recommendation is based on case series.[157,158]

** Except in presence of associated axial deep reflux.[150-152]*

Operative treatment choice

In practice, the choice of the procedure is frequently not made on evidence-based data, but on other factors, such as: (i) personal mastery of the different techniques–practitioners will favor the procedures they have mastered; (ii) coverage/reimbursement by the health services/health insurance, which varies from country to country; (iii) the patient's choice, which is influenced by possible postoperative problems, recovery time, time off work, the procedure that provides the easiest control of recurrences, and information from friends, literature, or the internet.

Guidelines

Recommendations from five guidelines are summarized in *Table II*. The guidelines of the Society for Vascular Surgery/American Venous Forum (SVS/AVF) were published in 2011.[159] Most recommendations remain valid, but are not fully applicable in Europe. The SVS/AVF guidelines were analyzed by a European team.[160] In 2013, the European Guide for Sclerotherapy was made available, giving much information on sclerotherapy, including practical information.[156] In 2014, the European Venous Forum (EVF)

Operative procedure	SVS/AVF[159]	EVF/IUA[161]	ESVS[163]	ETAV/IUP[162]	EGS[156]
Classic open surgery	GSV 2B* SSV 1B*	2A*	IB**		
Modern surgery	*NG*	1B*	*NG*	*NG*	*NG*
CHIVA	2B*	*NG*	IIbB**	*NG*	*NG*
ASVAL	2C*	*NG*	IIaB**	*NG*	*NG*
EVLA or RFA	1B*	1A*	GSV IA** SSV IIaB**	1A*	*NG*
Steam				1A*	
Clarivein®	*NG*	*NG*	*NG*	*NG*	*NG*
Glue	*NG*	*NG*	*NG*	*NG*	*NG*
UGFS	*NG*	1A*	IIIA**	*NG*	1A-1C* according to vein diameter
Thermal ablation vs UGFS (GSV)	1B*	*NG*	IA**	*NG*	*NG*
Thermal ablation vs Surgery (GSV)	1B*	*NG*	IA**	*NG*	*NG*
Surgery for PREVAIT	2C*	*NG*	*NG*	*NG*	*NG*
UGFS for PREVAIT	2C*	*NG*	IIaB**	*NG*	*NG*
Endovenous thermal ablation for PREVAIT	2C*	*NG*	IIaB**	*NG*	*NG*

Table II. Recommendations for operative procedures for the treatment of superficial refluxing veins from the recent guidelines.

**Guyatt's grading[164]*

***Grading system of the European Society of Cardiology[165]*

Abbreviations: ASVAL, Ablation Selective des Varices sous Anesthésie Locale (Ambulatory Selective Vein Ablation under Local anesthesia); AVF, American Venous Forum; CHIVA, Cure Hémodynamique de l'Insuffisance Veineuse en Ambulatoire (Conservative ambulatory Hemodynamlc management of VAricose veins); EGS, European Guide for Sclerotherapy; EVLA, endovenous laser ablation; ESVS, European Society of Vascular Surgery; ETAV, Endovenous Thermal Ablation for Varicose Vein Disease; EVF, European Venous Forum; GSV, great saphenous vein; IUA, International Union of Angiology; IUP, International Union of Phlebology; NG, not graded; PREVAIT, PREsence of VArices after operatlve Treatment; SSV, small saphenous vein; SVS, Society of Vascular Surgery; UGFS, ultrasound-guided foam sclerotherapy.

and the International Union of Angiology (IUA) published a guidelines document on the management of chronic venous disorders.[161] The International guidelines on endovenous thermal ablation were published in 2015. This consensus document also provides many technical details.[162] The same year, the European Society for Vascular Surgery (ESVS) endorsed guidelines on the management of chronic venous disease.[163]

Most of these guidelines used the Guyatt grading scheme, which classifies recommendations as strong (grade 1) or weak (grade 2), according to the balance among benefits, risks, burdens, cost, and the degree of confidence in the estimates of benefits, risks, and burdens. It classifies quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors, such as study design, consistency of the results, and directness of the evidence.[164] Only the ESVS guidelines used the European Society of Cardiology's grading system. For each recommendation, the letter A, B, or C marks the level of current evidence. Weighing the level of evidence and expert opinion, every recommendation is subsequently marked as either class I, IIa, IIb, or III. The lower the class number, the more proven the efficacy and safety of a certain procedure.[165]

In 2013, the National Institute for Health and Care Excellence (NICE) published a document on varicose veins of the leg,[166] where the recommendations for people with confirmed varicose veins and truncal reflux were as follows:

- First, offer endothermal ablation (RFA for varicose veins [NICE interventional procedure guidance 8][167] and EVLA for the long saphenous vein [NICE interventional procedure guidance 52][168]).
- If endothermal ablation is unsuitable, offer UGFS (see UGFS for varicose veins [NICE interventional procedure guidance 440][169]).
- If UGFS is unsuitable, offer surgery.
- If incompetent varicose tributaries are to be treated, consider treating them at the same time.[166]

Conclusions

Operative treatment of primary varicose veins is currently performed using minimally invasive procedures, excluding spinal or general anesthesia. The problem is that the development of new procedures or devices is so rapid that when long-term outcomes are available, particularly for RCTs, the technique or material evaluated is frequently no longer used. Postoperative quality of life has improved, complications are far less frequent, and sick leave is shorter. The long-term frequency of PREVAIT is approximately the same for all techniques used, as long as the initial procedure has been correctly executed. To minimize the severity of PREVAIT, it is crucial to have regular patient follow-up and use ultrasound investigation to manage possible varices recurrence.

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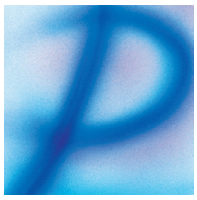

What is postthrombotic venous obstruction and how can it be avoided?

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Keywords:

postthrombotic obstruction; postthrombotic syndrome; vein obstruction

Phlebolymphology. 2016;23(2):76-81

www.phlebolymphology.org

Abstract

Postthrombotic venous obstruction is part of the pathophysiology of a postthrombotic syndrome. When the obstruction occurs in the iliofemoral segment, postthrombotic morbidity is often severe. In a recent study, the intraluminal contents of chronically occluded postthrombotic common femoral veins were analyzed. Approximately 80% to 90% of the tissues analyzed were composed of type I collagen, with type III collagen comprising the remainder. Vascular endothelial growth factor receptor 2 (VEGFR2) was more abundant in young specimens (≤1 year after the acute DVT); angiopoieton-1 receptor (TIE-2) was observed more often and at higher concentrations in mature specimens (≥10 years after the acute DVT); and the CD31 ligand was found equally in both young and mature specimens. Postthrombotic endoluminal obstruction can be avoided if the initial obliterating thrombus is successfully removed during the course of treatment for acute DVT. In fact, randomized trials, registries, and large observational experiences have demonstrated a reduction in the incidence of postthrombotic syndrome after successful thrombus removal. Another randomized trial, the ATTRACT trial, has recruited 692 patients with acute DVT in order to evaluate whether there is a reduction in or elimination of the incidence of postthrombotic syndrome with anticoagulation plus catheter-directed thrombolysis vs anticoagulation alone–results will be available in 2017.

Introduction

Postthrombotic syndrome is the consequence of acute deep vein thrombosis (DVT) of the lower extremities. Ambulatory venous hypertension is the underlying pathophysiology resulting from venous valvular incompetence and postthrombotic luminal obstruction. Patients with iliofemoral DVT have the most frequent and severe postthrombotic morbidity and suffer the highest risk of recurrence.[1-3] In a prospective observational study of patients treated for acute DVT with anticoagulation alone, Kahn et al[2] observed that the most powerful predictor of severe postthrombotic syndrome was iliofemoral DVT.

Qvarfordt et al[4] measured compartment pressures in patients with iliofemoral DVT before and after venous thrombectomy and showed that preoperative

compartment pressures exceeded 35 mm Hg and dropped to 10 mm Hg or less following iliofemoral venous thrombectomy. In this setting, compartment pressures can be used as a surrogate for venous pressures. Labropoulos et al[5] measured arm-foot pressure gradients in patients with chronic postthrombotic venous disease. Patients with iliofemoral venous disease had the highest resting and postocclusive hyperemic pressures compared with patients with infra-inguinal postthrombotic disease.

Treatment strategies of anticoagulation alone do not assure that the occlusive thrombus will resolve and they depend upon the body's endogenous thrombolytic activity to recanalize the obstructive thrombus. Unfortunately, a thrombus in the iliofemoral venous system frequently persists, causing central venous obstruction. As mentioned earlier, patients with iliofemoral DVT treated with anticoagulation alone have the highest risk for severe postthrombotic syndrome. This is largely due to persistent obstruction of the major venous outflow tract of the lower extremities.

Luminal obstruction

Based on ultrasound findings and phlebography, the obstructive nature of the thrombus in the vein lumen has been variously described as chronic thrombus, intraluminal fibrosis, or scar tissue. Until recently, no definitive description of the human tissue that chronically obstructs postthrombotic veins has been provided. In an attempt to resolve the extreme morbidity of these patients, those presenting with incapacitating postthrombotic syndrome due to chronic iliofemoral and inferior vena cava occlusion are fully evaluated. If the common femoral vein is obstructed, it is recommended to perform a common femoral vein endophlebectomy followed by transluminal recanalization of the occluded iliac veins and inferior vena cava (if involved).[6]

In a recent study, Comerota et al[7] analyzed the intraluminal contents of 18 chronically occluded postthrombotic common femoral vein specimens obtained from 16 patients undergoing endophlebectomy followed by intraluminal recanalization of their iliocaval venous segments. Specimens were studied using the hematoxylin/eosin and Masson's trichrome stains for collagen, immunohistochemical collagen staining, and von Kossa stains. Young specimens (those ≤1 year from the acute DVT) and mature specimens (≥10 years from the acute DVT) were evaluated to study the evolution of the function of endothelial cells lining neovessels and recanalization channels. Antibodies to four biomarkers were used to examine the specific function of these endothelial cells. The biomarkers included vascular endothelial growth factor receptor 2 (VEGFR2), angiopoieton-1 receptor (TIE-2), platelet endothelial cell adhesion molecule 1 (PECAM1), which is also known as CD31, and von Willebrand factor (vWF).

VEGFR2 is an important signaling protein for vascular neogenosis and angiogenesis that stimulates monocyte and macrophage migration. VEGF receptors are typically found on young endothelial cells populating neovascular channels. There are numerous subtypes of VEGF receptors; however, VEGFR2 is the predominant mediator of the cellular responses to VEGF.[8] TIE-2 is a tyrosine kinase receptor that is important for the development of blood vessels. TIE-2 promotes sprouting and branching from the primary capillary plexus and vascular remodeling, and it is necessary for normal embryonic vascular development and stabilization of blood vessels in adults.[9] CD31 is a type 1 transmembrane glycoprotein that has a number of biologic functions, such as regulating vascular integrity and affecting cell survival.[10] CD31 interacts with leukocytes to prevent transendothelial leukocyte migration and remove apoptotic leukocytes. Due to the sophisticated functions of CD31, it is thought that CD31 would most likely be expressed by mature endothelial cells. vWF is a glycoprotein produced by the endothelium, megokaryocytes, and subendothelial connective tissue[11] that is important for maintaining hemostasis, and it is expected that mature endothelium would have a higher concentration of vWF.

Results

Figure 1 shows three typical endoluminal images observed after venotomy of the common femoral vein. In our experience, a thrombus was absent in all but one patient. The one patient in which a thrombus was present had a documented recurrent DVT 2.5 months prior to the venotomy The hematoxylin/eosin staining confirmed that abundant collagen, neovascularization, recanalization, and inflammation were present in the common femoral vein *(Figure 2)*. The neovascular channels were observed in the loose collagen, whereas few neovascular channels (if any) occurred within the densely packed collagen. An interesting observation was the close proximity of recanalization channels to neovessels. This suggests that two processes–neovascularization and revascularization–are governed partly by a common stimulus.

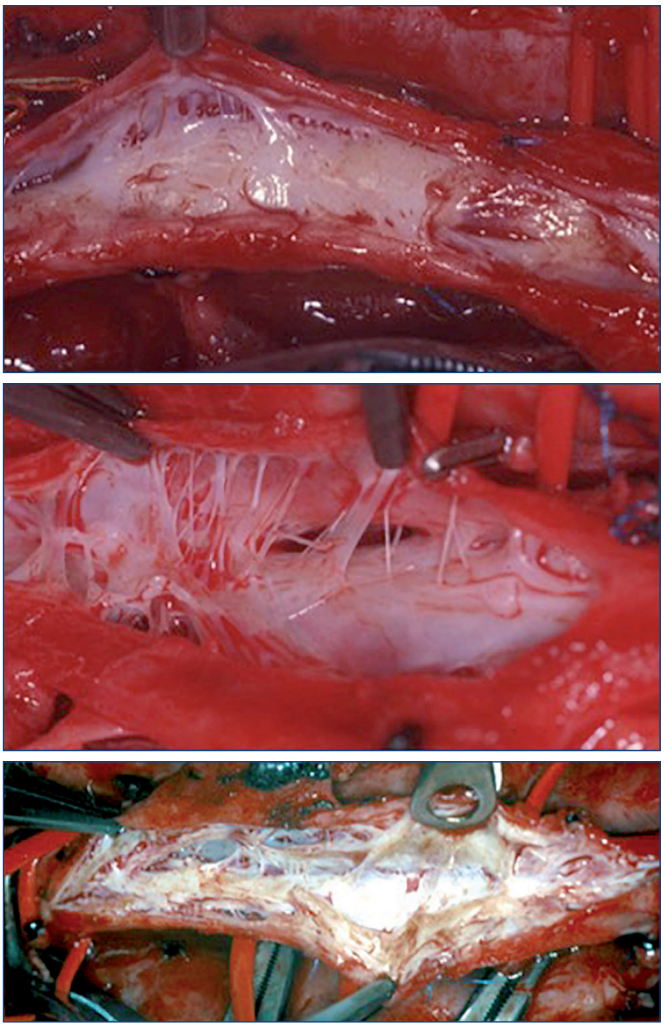


Figure 1. Endoluminal images after phlebotomy of the common femoral vein.

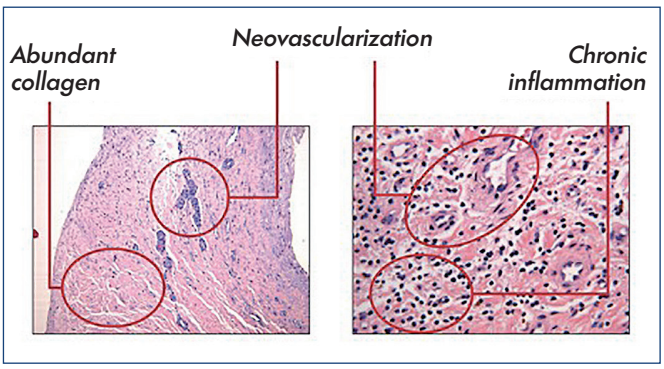


Figure 2. Hematoxylin/eosin staining showing abundant collagen, neovascularization, recanalization, and inflammation in the common femoral vein.

VEGFR2 was found in greater concentrations in younger specimens in both neovessels and recanalization channels. However, the neovessel endothelium was more densely stained than the recanalization endothelium. It is likely that VEGF plays a central role in both recanalization and neovascularization of the thrombus. CD31 was found in both young and mature specimens. CD31 has numerous physiological functions that include regulating vascular integrity, controlling cell survival, modulating angiogenesis and cell migration, and influencing vascular permeability. Which aspects of its many functions are operative in the earlier vs the later stages of thrombus resolution require further study. As anticipated, a greater number of channels were found in mature specimens expressing higher concentrations of vWF. Cells under the regulation of the endothelial–specific TIE-2 promoter were observed more often and at higher concentrations in mature specimens.

Can postthrombotic venous obstruction be avoided?

The answer to this question depends upon whether a strategy of thrombus removal is attempted and successful. The true question is "does a strategy of thrombus removal result in less postthrombotic morbidity?" Based upon current evidence, the answer to this question is yes!

Plate et al[12-14] reported the short-term and long-term results of their randomized trial of venous thrombectomy plus anticoagulation vs anticoagulation alone for patients with iliofemoral DVT. They observed that iliofemoral venous patency was significantly better and venous pressures, leg edema, and postthrombotic morbidity were lower in patients randomized to venous thrombectomy. The evolution of catheter-based techniques has significantly reduced the need for venous thrombectomy. Integrating mechanical techniques with catheter-directed lysis has reduced the dose of the plasminogen activator, reduced the length of the hospital stay, and improved the efficiency of thrombus removal.[15,16]

Figure 3A is a photograph of a patient with severe acute phlegmasia cerulea dolens after 5 days of treatment with low-molecular-weight heparin. The patient was markedly uncomfortable and could not ambulate. The iliofemoral phlebogram *(Figure 3B)* shows extensive venous obstruction. Following pharmacomechanical thrombolysis, patency was restored to the femoral vein *(Figure 3C)*, common femoral vein, and iliac venous system *(Figure 3D)*. The patient had persistent obstruction of the common iliac vein, which was corrected with a 16-mm bare-metal stent *(Figure 3E)*. At the 36-month follow-up, the physical examination was normal, the veins were patent with normal valve function, and the patient was fully active and asymptomatic *(Figure 3F)*.

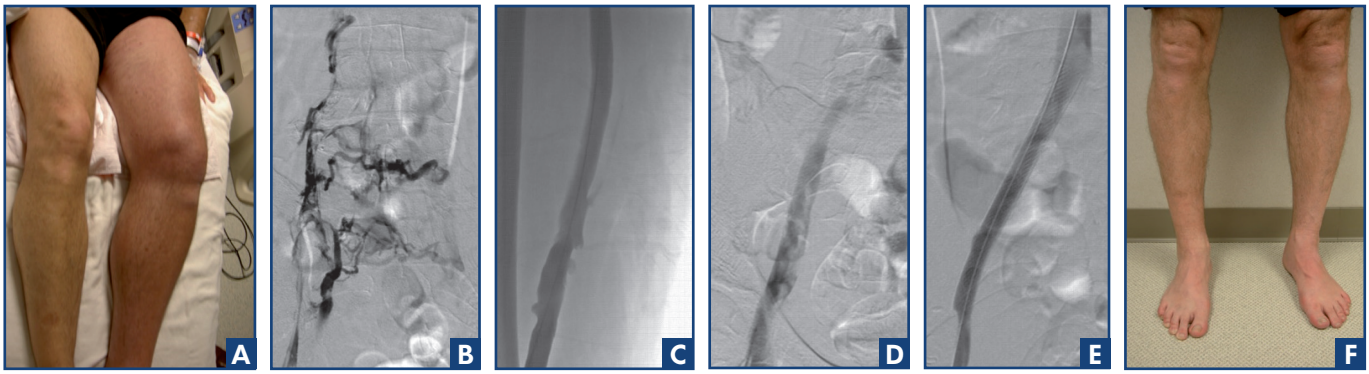


Figure 3. Posttreatment assessment of a patient with deep vein thrombosis treated by pharmacomechanical thrombolysis and stenting after unsuccessful anticoagulation.

Photograph of a patient with severe acute phlegmasia cerulea dolens after 5 days of treatment with low-molecular-weight heparin (Panel A). Iliofemoral phlebogram showing extensive venous obstruction (Panel B). Patency restoration to the femoral vein (Panel C) and the iliac venous system (Panel D) after pharmacomechanical thrombolysis. The patient had persistent obstruction of the common iliac vein, which was corrected with a 16-mm bare-metal stent (Panel E). At the 36-month follow-up, the physical examination was normal and the veins were patent with normal valve function (Panel F).

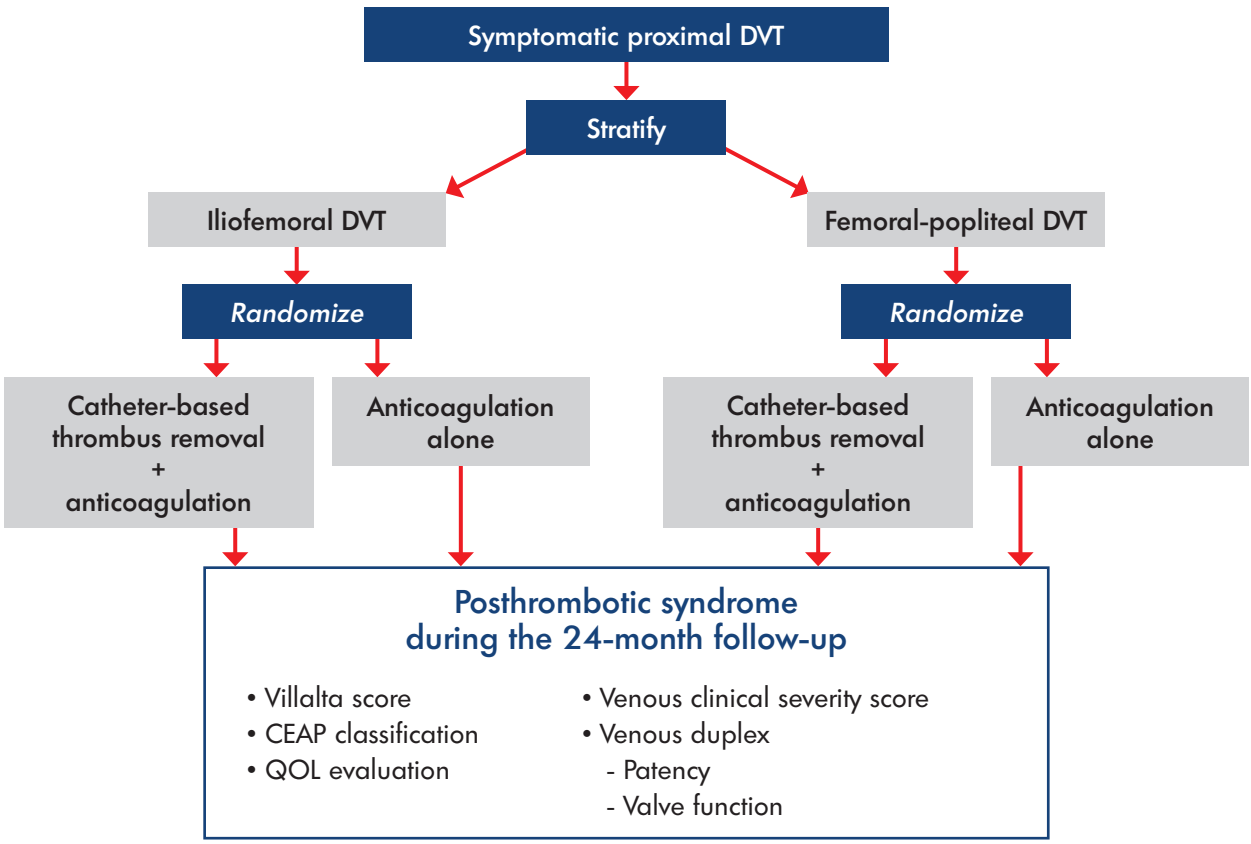


Figure 4. ATTRACT trial design.

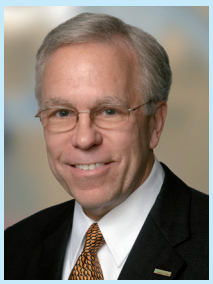
Abbreviations: ATTRACT, Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis; CEAP, clinical, etiological, anatomical, and pathophysiological classification; DVT, deep vein thrombosis; QOL, quality of life.

A cohort-controlled study of treatment for patients with iliofemoral DVT found that catheter-directed thrombolysis improved health-related quality of life compared with anticoagulation alone.[17] Furthermore, postthrombotic

morbidity was found to correlate with residual thrombus following catheter-directed thrombolysis.[18] Therefore, when starting a strategy of thrombus removal, the goal should be to remove as much of the thrombus as possible and restore unobstructed venous drainage to the vena cava.

The CaVenT (Catheter-directed Venous thrombolysis in acute iliofemoral vein Thrombosis) study investigators randomized patients to anticoagulation plus catheter-directed thrombolysis vs anticoagulation alone.[19] They found significant benefit with catheter-directed thrombolysis, which was correlated with patency of the iliofemoral venous segment. Since the majority of patients entered into the trial had a patent iliac venous system, the number needed to treat to prevent one postthrombotic syndrome was seven. If all patients had had iliofemoral DVT, it is the author's opinion that the number needed to treat to prevent postthrombotic syndrome would be much smaller, approaching unity.

The ATTRACT trial (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis)[20] is the largest trial to date randomizing patients with acute DVT to catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone. The target of 692 patients was reached in December 2014. The primary end point is postthrombotic syndrome at 2 years *(Figure 4)*. Patients were stratified at entry according to the level of their acute DVT and whether the DVT involved the iliofemoral vein or the femoral popliteal vein. The final follow-up visits will occur in December 2016, at which time, the data will be analyzed, presented, and published. While the results of the ATTRACT trial are anxiously awaited, the current body of evidence strongly supports the adoption of a strategy of thrombus removal for patients with iliofemoral DVT. Of course, removing the acute thrombus will restore patency and eliminate the substrate for luminal obstruction, thereby significantly reducing the likelihood of severe postthrombotic morbidity.



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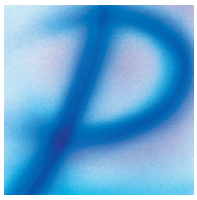

Chronic venous disorders: pharmacological and clinical aspects of micronized purified flavonoid fraction

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Keywords:

MPFF, micronization, flavonoids, venous tone, capillary, permeability, capillary leakage, lymphatic, drainage, dose-effect, chronic venous disorders

Abstract

Micronized purified flavonoid fraction (MPFF) is a flavonoid-based venoactive drug that is more potent than pure diosmin due to the presence of additional flavonoids, such as hesperidin, diosmetin, linarin, and isorhoifolin. In addition, the dissolution and absorption rates of MPFF increase due to the micronization of its active ingredients. The micronization process improves exposure to MPFF– derived metabolites that are responsible for its pharmacological activity. The positive impact of micronization on the pharmacological activity of purified flavonoid fraction has been demonstrated in both animal and clinical pharmacological trials.

MPFF improves venous tone by modulating noradrenergic signaling and reducing norepinephrine metabolism and MPFF also protects against inflammation-related valve damage by inhibiting the leukocyte-endothelium interaction, decreasing capillary permeability, improving capillary resistance, and increasing lymphatic drainage. The best dose-effect ratio is achieved with 1000 mg.

MPFF is an important treatment option for chronic venous disorders because it relieves symptoms at all stages, significantly alleviates venous edema, and, in more advanced stages, MPFF may be used in conjunction with sclerotherapy, surgery, and/or compression therapy for patients undergoing stripping or an endovenous operation for varicose vein ablation. MPFF may also be used as an adjunctive therapy in patients with active venous ulcers, especially in patients with chronic large ulcers.

Phlebolymphology. 2016;23(2):82-91

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Introduction

Flavonoids are one of the main active phytoconstituents found in plant extracts and the micronized purified flavonoid fraction (MPFF*) is included in this group. The use of plants and isolated phytochemicals for the prevention and treatment of various health ailments has been in practice for years. About 25% of the drugs prescribed worldwide are derived from plants and 121 such active compounds are currently in use. In addition, 11% of the 252 drugs on the World Health Organization (WHO)'s essential medicine list are exclusively plant based.[1]

Besides providing pigmentation, flavonoids play an important role in the growth and development of plants, such as protecting against UVB radiation, fungal infection, and microbial and insect attacks. Flavonoids have been reported to chelate metal, inhibit enzymes, inhibit cellular proliferation, induce apoptosis, stabilize membranes, and scavenge free radicals. Flavonoids have antioxidant, anti-inflammatory, antiallergic, antibacterial, osteogenic, cytotoxic, antitumoral, hepatoprotective, antithrombotic, and antiviral pharmacological properties.[2]

MPFF consists of diosmin (90%) and an additional flavonoid fraction (ie, diosmetin, hesperidin, linarin, and isorhoifolin; 10%) and it is widely used to treat symptoms related to chronic venous disorders and hemorrhoidal disease. This review contains an overview of the pharmacological activities and clinical benefits of MPFF on chronic venous disorders.

**Registered as: Alvenor®, Ardium®, Arvenum® 500, Capiven®, Daflon® 500 mg, Daflon® 1000 mg, Detralex, Elatec®, Flebotropin®, Variton®, Venitol®.*

MPFF Chemistry

Flavonoids are a class of low molecular weight, secondary plant phenolics with significant antioxidant and chelating properties and they are characterized by a flavin nucleus

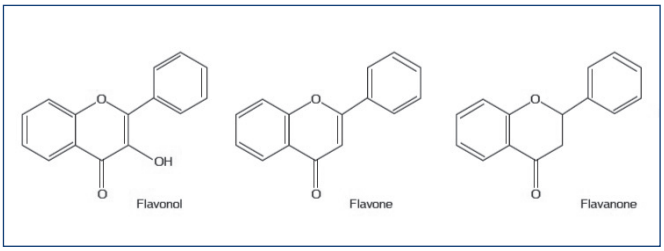

Figure 1. Chemistry of three types of flavonoid compounds.

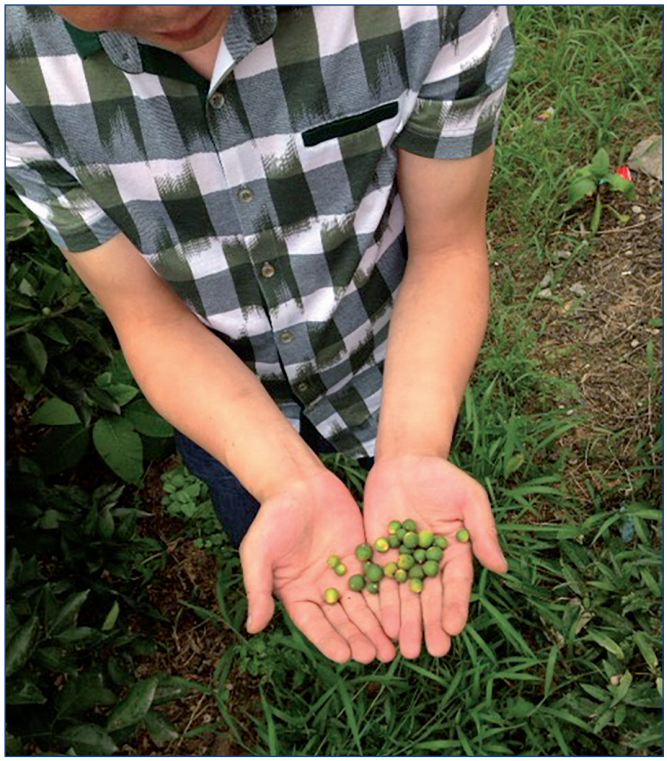

Figure 2. Harvest of small immature fruits (10 to 20 mm in diameter) to produce MPFF.

The fruit are harvested when they fall from the tree at the end of the flowering period. The sun-dried oranges are then ground and hesperidin is extracted in powder form.

and an oxygenated heterocyclic skeleton that is composed of two aromatic rings. Substitutions at different positions in the ring lead to various types of flavonoid compounds, including flavone, flavonol, and flavonone *(Figure 1)*. To date, more than 4000 flavonoids have been identified and they are widely distributed in the leaves, seeds, bark, and flowers of plants that constitute an integral part of the human diet. The most important groups are the anthocyanidins, catechins, flavones, flavanones, and flavonols *(Table I)*.

The MPFF components diosmin, diosmetin, linarin, and isorhoifolin are synthesized from hesperidin, which is extracted from *Citrus aurantium* var *amara*, a type of small, "bitter," immature orange *(Figure 2)*. Diosmin and its aglycone diosmetin (3', 5, 7-trihydroxy-4'-methoxyflavone) belong to the flavonol and flavone groups, while hesperidin, which differs from diosmin by the absence of a double bond between two carbon atoms, is part of the flavanone group *(Table I)*. These compounds also occur naturally in citrus fruit. Both linarin (Acacetin 7-rutinoside) and isorhoifolin are derived from flavones.

Chemical group	Plant of extraction Latin name (common name)	Major active ingredient (part of plant)	Brand
Flavonoids (flavones and flavonols)	Citrus species *Citrus aurantium* L. ssp *amara* (bitter orange)	Diosmin, (pericarp)	MPFF
	Ginkgo biloba L. (ginkgo)	Quercetol, rutoside (leaf)	Ginkor Fort
	Vitis vinifera L. (common grape vine)	Quercetol, isoquercetol (leaf)	
	Sophora japonica L. (Japanese pagoda tree)	Rutoside, troxerutin (bud)	Ginkor Fort Venoruton
	Viburnum prunifolium L. (blackhaw)	Amentoflavone (stem bark)	Jouvence
Flavonoids (flavanones)		Hesperidin Methylchalcone	MPFF Cyclo-3; Bi-Cirkan
Anthocyanines	*Vaccinium myrtillus* L. (blueberry)	Anthocyans (leaf, fruit)	Pycnogenol
	Ribes nigrum L. (blackcurrent tree)	Anthocyans (leaf, fruit)	
Tannins	*Hamamelis virginiana* L. (American witch-hazel)	Gallic acid, ellagique (stem bark, leaf)	Jouvence Hamamelis Boiron
Procyanidolic oligomers (PCO), precursors of tannins	*Pinus maritimus* (maritime pine)	PCO (branch)	
	Vitis vinifera L. (common grape vine)	PCO (grape seed)	Endotelon
Saponosides	*Aesculus hippocastanum* L. (horse chestnut)	Escin (stem bark, seed)	
	Centella asiatica L. (hydrocotyle)	Asiaticoside, centelloside, madecassoside (bud)	Madecassol
	Ruscus aculeatus L. (holly)	Ruscin (roots)	Cyclo-3
Coumarins	*Melilotus officinalis* L. (yellow sweet clover)	Melilotoside (bud)	SB-Lot

Table I. Main categories of venoactive drugs.

Pharmaceutical characteristics of MPFF

MPFF excipients

The excipients included in the MPFF-based drug composition are organic with a mineral, animal, or plant origin and they are known to be safe and well tolerated. The main excipients used in MPFF include microcrystalline cellulose, sodium starch glycolate, gelatin, magnesium stearate, and talc. They are used for the following reasons:

1. **Microcrystalline cellulose** is an inert substance that is widely used as a binder and diluent in many pills and tablets.[3] As an insoluble fiber, microcrystalline cellulose is not absorbed into the blood stream, so it cannot cause toxicity when taken orally, and as a result, it is often used as a placebo in controlled drug studies. Microcrystalline cellulose has no impact on the dissolution rate of any active ingredients; consequently, it cannot improve their absorption and cannot replace the benefits of the micronization

2. **Sodium starch glycolate** is derived from potato starch, is not contraindicated for celiac disease, and is a disintegrant.

3. **Gelatine** binds to the active molecules. It has a bovine, ovine, or poultry origin; therefore, it is compatible with the Muslim religion and a gout diet.

4. **Magnesium stearate and talc** are inert substances used as lubricants.

MPFF active ingredients

Contrary to "pure diosmins," such as Phlebodia®, MPFF includes diosmin (90%) and additional flavonoids (ie, diosmetin, linarin, isorhoifolin, and hesperidin) expressed as hesperidin (10%). Each flavonoid present in MPFF contributes to its pharmacological effect. In a hamster model of venous inflammation, where leaky sites are formed in the cheek pouch, each of these additional flavonoids administered separately displayed an antileakage effect comparable to or greater than diosmin.[4] These results illustrate that MPFF is more potent than pure diosmin and that each of the flavonoid substances present in the MPFF composition contributes to its action *(Figure 3)*. In a related article, Paysant et al concluded that "*it should be stressed that MPFF decreases the appearance of leaky sites more than any of its single constituents, which is most likely explained by the synergistic action of all the flavonoids present in its formulation.*"[4]

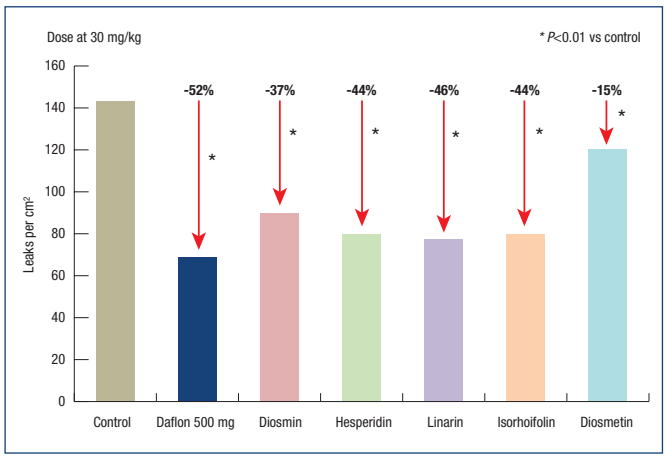

Figure 3. Effect of oral administration of MPFF or diosmin alone on permeability induced by ischemia and reperfusion.

Modified from reference 4: Paysant J et al. Int Angiol. 2008;27:81-85.

Pharmacokinetics of MPFF

There are no known drug interactions with MPFF since marketing authorization.[5]

Absorption and distribution of the MPFF active ingredients

Diosmin is a Biopharmaceutical Classification System IV (BCS IV) compound, which means that it has low solubility and low permeability.[6] Diosmin is not directly absorbed by the body, and, as shown in studies, it is not found in the circulation after oral administration. Metabolism studies showed that diosmin is metabolized by gut microbiota within the gastrointestinal tract to produce several metabolites

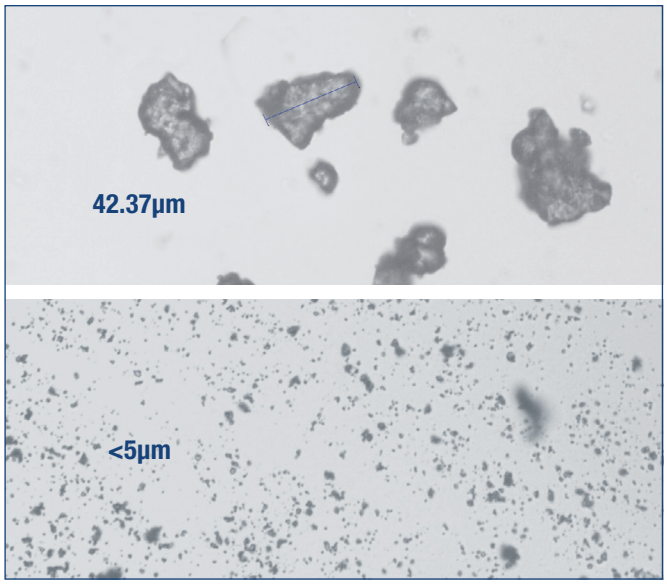

Figure 4. Nonmicronized and micronized purified flavonoid fractions.

Nonmicronized purified flavonoid fraction (top) and MPFF (bottom). The micronization process increases the bioavailability of the flavonoids comprised in the MPFF composition.

that are then further absorbed.[7] However, nonmetabolized diosmetin is not found in the circulation; therefore, it is not the active compound responsible for the venotonic action following oral administration of diosmin. Other metabolites of MPFF, such as glucuronide derivatives of diosmetin, and other metabolic breakdown products (phenolic acid derivatives) have been identified in the circulation and/or urine.[8]

Micronization enhances MPFF absorption

Micronization is achieved by using air jets operating at near supersonic velocities to create repeated particle-on-particle collisions that result in an average particle size that is <2 µm *(Figure 4)*. Absorption of compounds derived from diosmin metabolism, measured by the urinary excretion of total radioactivity following oral administration of ^{14}C-diosmin in humans, was significantly (P=0.0004, analysis of variance) improved with micronization (57.9±20.2%) vs nonmicronization (32.7±18.8%).[9] Micronization increases the dissolution rate of diosmin and enhances its metabolism, which in turn improves exposure to the metabolites that are responsible for its pharmacological activity.

The positive impact of micronization on the pharmacological activity of purified flavonoid fraction has been demonstrated in both preclinical and clinical pharmacological trials. In a study performed in hamsters, MPFF reduced the ischemia/reperfusion-induced macromolecular permeability in the

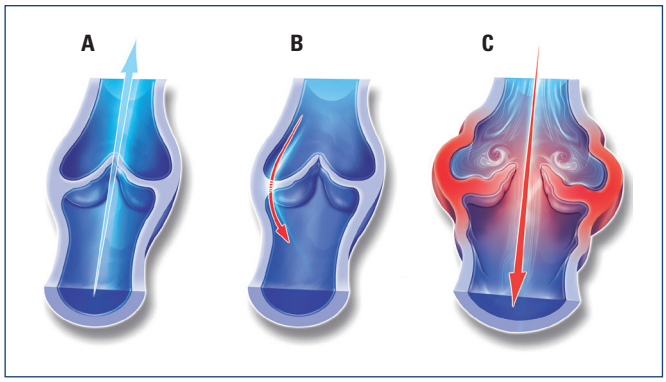

Figure 5. Illustrations of venous valves with and without reflux.

Illustrations of a normal venous valve without reflux (Panel A), a valve with a nonpathological commissural reflux usually seen in the evening after being in a prolonged upright position (Panel B), and a valve with a pathological intervalvular reflux (Panel C).

From reference 24: Tsoukanov Y et al. Phlebolymphology. 2015;22:18-24. Image courtesy of the author.

cheek pouch microcirculation to a greater extent than the nonmicronized purified flavonoid fraction (83.4% vs 47.9%, respectively).[10] In a former clinical study, 500 mg of MPFF taken twice daily for 2 months improved clinical symptoms and decreased venous outflow parameters more than 300 mg of nonmicronized diosmin taken thrice daily (900 mg dialy).[11] Therefore, micronization is essential for effective absorption of the active compounds.

Metabolism and elimination of the MPFF metabolites

In humans, elimination of micronized diosmin is relatively rapid, with 34% of the ^{14}C-labeled diosmin being excreted in urine and feces over the first 24 hours and 86% over the first 48 hours, with a 100% cumulative excretion of the dose in urine and feces after 168 hours (109±23%).[9] Similarly, the other citrus flavanone aglycones, such as hesperetin and naringenin, are recovered in plasma as their conjugated forms and are subsequently excreted in urine.[12-15]

Pharmacological effects of MPFF

MPFF activity on venous tone

Traditionally, venous hypertension, which underlies all clinical manifestations of chronic venous disease, was thought to result primarily from valvular incompetence related to excessive venous dilation due to a weakness in the vein wall and/or low venous tone. Consequently, much of the earlier research on MPFF was centered on its effects on venous tone. Treating patients with MPFF, two 500 mg tablets daily, reduced venous distension and venous capacitance and improved venous tone in women with various grades of venous insufficiency, ie, healthy women, women with venous insufficiency related to postthrombotic syndrome, or pregnant women.[16] In a another trial, MPFF, two 500 mg tablets daily, improved venous tone in female volunteers with abnormal venous elasticity and a high risk of developing varicose veins.[17] MPFF acts on venous tone by modulating noradrenergic signaling and reducing norepinephrine metabolism.[18]

Antioxidant properties of MPFF

MPFF inhibits oxygenated free radical production in vitro in zymosan-stimulated human neutrophils, rat leukocytes, and mouse macrophages. Additional trials demonstrated that MPFF leads to the following: (i) normalization of prostaglandin E_2 or F_2 and thromboxane B_2 synthesis in inflammatory granulomas in rats; (ii) reduction in the bradykinin- or ischemia-induced microvascular permeability in rat cremaster muscle; (iii) reduction in the histamine-, bradykinin-, leukotriene B_4-induced ischemia and reperfusion or oxidant challenge in the hamster cheek pouch; (iv) protection of endothelial cells from lipid peroxidation in bovine aortic endothelial cells and human skin fibroblasts.[7,19]

Leukocyte activation and adhesion

In the last 10 years, research focus has shifted toward determining the action of venoactive drugs on chronic inflammatory processes affecting large and small venous vessels and valves. Such inflammatory processes start with inappropriate activation of leukocytes in the veins. Former pharmacological studies in animals have demonstrated that MPFF inhibits venous inflammation by reducing leukocyte rolling, adhesion, and migration in rats, by decreasing the number of parenchymal dead cells after venular mesenteric occlusion in rats, and by reducing leukocyte adhesion and/or migration after ischemia-reperfusion injury in hamster skinfold or rat skeletal muscle. In clinical studies, MPFF reduced the expression of monocyte or neutrophil CD62L and the endothelial activation markers intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on human leukocytes from patients with venous ulcers.[7,19]

Protective effect against inflammation-related valve damage in chronic venous disorders

Pharmacological studies have shown that MPFF mitigates or blocks the effects of chronic inflammation in the micro- and macrocirculation. In a model of venous occlusion and reperfusion, elevation of venous blood pressure increased

inflammation and tissue injury.[20] In MPFF-treated animals, markers of inflammation decreased in a dose-dependent manner. MPFF also significantly reduced parenchymal cell death, leukocyte rolling, adhesion to postcapillary venules, and migration.[21] In rats with venous hypertension induced by creating an arteriovenous fistula, Takase et al showed that MPFF treatment resulted in a significant, dose-dependent reduction in the reflux rate in rats with higher than normal venous hypertension, demonstrating the protective effects of MPFF on the macrocirculation.[22]

By delaying or blocking the inflammatory reaction in venous valves and walls, these data suggest that MPFF may delay the development of venous reflux and suppress damage to valve structures in a rat model of venous hypertension. These observations were confirmed in a new study using the same animal model. MPFF reduced edema and fistula blood flow produced by an acute arteriovenous fistula and reduced granulocyte and macrophage infiltration into the valves, similarly to the previous study.[23]

In clinical trials, 1000 mg/day of MPFF for 2 months eliminated the transitory commissural reflux observed in patients presenting with subjective leg symptoms without visible signs of chronic venous disorders; these patients are categorized as C_{0s} according to the clinical, etiological, anatomical, and pathophysiological (CEAP) classification system *(Figure 5)*.[24] Transitory reflux elimination was paralleled with pain relief and an improvement in quality of life. In this trial, consecutive C_{0s} patients were enrolled and assessed for symptom intensity using the visual analog scale (VAS), quality of life using the ChronIc Venous Insufficiency quality of life Questionnaire (CIVIQ-20), and saphenous reflux duration and saphenous vein diameter using a twice-daily Duplex scan examination (morning and evening). A total of 41 C_{0s} patients were enrolled, and, of these patients, 15 had no reflux in either the morning or evening and 26 had transitory evening reflux with 22 being commissural and 4 intervalvular. The saphenous vein diameter was greater in the subgroup of patients with transitory reflux compared with patients without reflux (P<0.05). After MPFF treatment, there was a trend toward a reduction in intervalvular reflux length (despite being nonsignificant), while transitory commissural refluxes (n=22) no longer appeared. Additionally, vein diameter returned to normal. These results mirror the protective effect of MPFF on venous valve structures in humans.

Capillary permeability and resistance

MPFF decreases the volume of induced edema in the rat paw and improves microvascular reactivity and functional capillary density after ischemia and reperfusion in the hamster cheek pouch. In humans, MPFF significantly improved capillary hyperpermeability compared with placebo in patients with idiopathic cyclic edema,[25] decreased the abnormal capillary filtration rate in patients with chronic venous insufficiency as evaluated using strain gauge plethysmography, and improved capillary resistance significantly compared with placebo in patients with abnormal capillary fragility.[26]

Lymphatics

MPFF increased the contractility of mesenteric lymphatic collecting ducts in sheep, increased the frequency of spontaneous contractions in bovine mesenteric lymphatics, and improved lymphatic drainage in sheep and dogs. In clinical pharmacology, MPFF decreased intralymphatic pressure and increased the number of functional lymphatic capillaries, which resulted in an improvement in lymphatic drainage in patients suffering from skin changes.[27-29]

Dose-effect ratio for MPFF

Contrary to the statement that the administration of 600 mg of diosmin once daily is sufficient, Amiel et al reported that the best dose-effect ratio is achieved with 1000 mg of MPFF, which means at least 900 mg of diosmin.[30] No significant differences were found with the single MPFF tablet dosing; on the other hand, after administration of two or four tablets of MPFF 500 mg, legs with residual postphlebitic abnormalities showed significant improvements in venous capacitance, venous distensibility during occlusion at 40, 50, and 60 mm Hg, and total venous emptying time and its longest component (ie, time needed to empty the last 50%) compared with contralateral healthy legs. There was a linear relationship between the logarithm of the MPFF dose and the effect on venous hemodynamics in both abnormal and normal legs. For most measurements, the results obtained with four tablets were significantly reinforced compared with those obtained with two tablets, but the effect was not doubled. Definitely, the best dose-effect ratio was achieved with two tablets of MPFF 500 mg on the hemodynamic parameters previously described. Therefore, a single dose of 600 mg of diosmin is probably insufficient.

Safety of MPFF

In a study in rats, when MPFF was administered by gastric intubation for 26 weeks, no deaths, changes in weight, or abnormalities of standard functional tests were observed.[31] In a study in humans, MPFF administration resulted in minor side effects in only 10% of the subjects compared with 13.9% of those treated with placebo.[32] Adverse events were similar in nature and incidence between these patient groups. The rate of discontinuation due to adverse events (primarily of gastrointestinal origin) was comparable among patients receiving two tablets of MPFF 500 mg daily or placebo (1.1 vs 3.2%). In this analysis, the incidence of adverse events was not significantly different in patients >70 years old or with concomitant diseases (ie, hypertension, atherosclerosis, diabetes mellitus, neurological/psychiatric disease, or alcoholism) than the total population group.[32] In addition, MPFF did not appear to interact with the drugs used to treat these concomitant diseases. The incidence of adverse events did not increase with long-term treatment with two tablets of MPFF 500 mg daily.[33] Treatment with MPFF did not modify blood pressure or laboratory parameters. Systolic or diastolic blood pressure and laboratory values did not change during treatment with two tablets of MPFF 500 mg daily for 1 year in a clinical trial that monitored these parameters every 4 months.[33] Laboratory values (eg, red blood cells, leukocytes, hemoglobin, hepatic enzymes, blood urea, blood glucose and lipids, and creatinine) remained within normal physiological ranges.

Role of MPFF in the treatment of chronic venous disorders

Venous symptoms

MPFF plays a role in the management of symptomatic patients at the earliest stages of chronic venous disease, given that compression therapy may be the only other appropriate form of therapy for such patients. However, due to poor compliance with compression therapy in certain countries,[34,35] pharmacological treatment with venoactive drugs (including MPFF) may be the only available alternative. Rabe et al showed that approximately 20% of all patients consulting their general practitioner for any reason could be assigned to class C_{0s}; therefore, it is important to treat these patients effectively.[36] Studies of venoactive drugs on this specific C_{0s} patient are not yet available.

Despite a lack of homogeneity between studies, a Cochrane review of 44 controlled studies of venoactive drugs vs placebo[37] showed significant treatment benefits of the venoactive drugs compared with placebo for pain, cramps, heaviness, sensation of swelling, and paresthesia *(Table II)*. The only nonsignificant effects were for itching, but the sample size was the lower (n<500). The placebo effect in these studies is far from being insignificant and thus large samples are needed to observe any treatment effect on venous symptoms. Sample sizes in *Table II* are over 1000 patients for most variables.

In a recent double-blind, placebo-controlled trial including 592 symptomatic patients (leg pain and heaviness) randomly allocated to either MPFF treatment (n=296; 1000 mg/day for 4 months) or placebo (n=296; same process), symptom intensity as assessed using a 10 cm-visual analog scale decreased from 6.2±1.5 cm to 3.4±2.4 cm after 4 months of MPFF treatment (vs 6.0±1.4 cm to 3.7±2.5 cm in the placebo group; *P*=0.031). In addition, the CIVIQ quality of life questionnaire scores increased from 57.3±19.3 to 69.9±20.6 points in the MPFF treatment group (vs 59.5±17.9 to 69.1±20.6 points in the placebo group; *P*=0.040).[38] Between group differences favored MPFF for both symptom relief and quality of life improvement *(Figure 6)*. MPFF enhances quality of life by relieving symptoms right from the very beginning (C_{0s}) and at all stages of the disease.

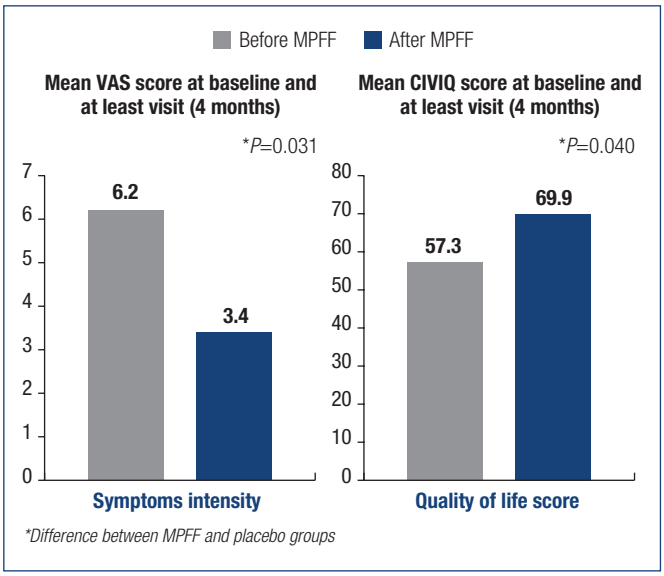

Figure 6. Benefits of the micronized purified flavonoid fraction on symptoms and quality of life of C3 and C4 patients.

Modified from reference 38: Rabe E et al. Int Angiol. 2015;34:428-436.

Outcome variable	Patients in the Cochrane review (N)	Patients in the treatment group (N)	Patients in the placebo group (N)	Patients with no symptom in the treatment group (%)	Patients with no symptom in the placebo group (%)	Test for treatment effect (*P* value)	Study heterogeneity
Edema	1245	626	619	59.4	42.5	5.81 (<0.00001)	no
Trophic disorders	705	355	350	33.8	23.7	3.76 (<0.0001)	no
Pain	2247	1294	953	63.4	37.0	4.70 (<0.00001)	yes
Cramps	1793	1072	721	67.6	45.5	3.02 (=0.003)	yes
Restless legs	652	329	323	46.2	33.4	2.77 (=0.006)	no
Itching	405	206	199	64.6	41.2	0.83 (NS)	yes
Heaviness	2166	1257	909	59.8	33.1	5.38 (<0.00001)	yes
Swelling	1072	544	528	62.9	38.4	3.86 (<0.0001)	yes
Paresthesia	1456	896	560	71.0	50.7	2.82 (=0.005)	yes
	Patients in the meta-analysis (N)	**Patients in the treatment group (N)**	**Patients in the control group (N)**	**Patients with no ulcer in the treatment group (%)**	**Patients with no ulcer in the control group (%)**	**Test for overall effect (P value)**	**Study heterogeneity**
Venous ulcer at 6 months	616	318	298	61.3	47.7	0.03	Yes

Table II. Global results of combined analyses for all venoactive drugs.

All outcomes were analyzed as a percentage of improved patients.

Adapted from the Cochrane review of phlebotonics for venous insufficiency[37] and the meta-analysis of adjunctive MPFF on venous ulcers.[43]

Venous edema

Although nonspecific, edema is one of the most frequent and typical signs of chronic venous disease. All other causes of edema should be excluded to confirm its venous origin. Venous edema is described as sporadic, unilateral or bilateral, and more frequently located at the ankle. Several well-conducted controlled trials vs placebo or compression stockings have shown a reduction in edema by oral venoactive drugs, such as MPFF.[18] The analysis of a pool of 1245 patients from the Cochrane review showed significant benefit of such drugs in alleviating edema *(Table II)*.[37]

In a meta-analysis of ten publications of randomized controlled trials comparing venoactive drugs with either a placebo or another venoactive drug (hydroxyethylrutoside,

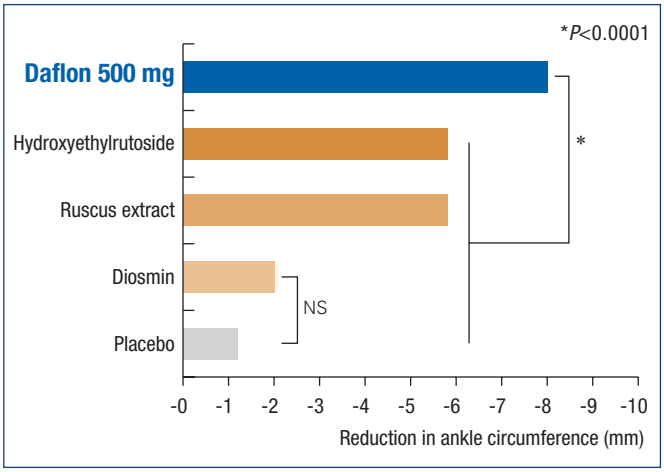

Figure 7. Superiority of the MPFF over placebo and other venoactive drugs in relieving venous edema.

Modified from reference 39: Allaert FA. Int Angiol. 2012;31:310-315.

ruscus extracts, and diosmin) on the reduction in ankle circumferences in 1010 patients complaining of venous edema at any CEAP stage, the mean reduction in ankle circumference was significantly greater with MPFF than with any other venoactive drug ($P<0.0001$; *Figure 7*). In addition, results for diosmin were not significant compared with placebo.[34] MPFF significantly alleviates patients from edema vs other venoactive drugs.

More advanced stages of chronic venous disease (C_2 to C_6 patients)

In more advanced stages of chronic venous disease, MPFF may be used in conjunction with sclerotherapy, surgery, and/or compression therapy in patients undergo stripping[35,36] or an endovenous operation for varicose vein ablation.[37] MPFF may be considered an adjunctive therapy in patients with active venous ulcers, especially in those with chronic large ulcers.[43]

Conclusion

The availability of multiple methods to treat chronic venous disorders necessitates a clinical evidence-based ranking to better inform and satisfactorily treat patients. An ideal treatment would rapidly and significantly reduce symptoms, stop disease progression, act on all components of the disease, protect against complications, remain effective in the long term, and be well tolerated. The aim is to improve patient's quality of life as quickly as possible.

MPFF is the only venoactive drug to demonstrate significant anti-inflammatory and venoprotective actions, which distinguishes this drug from other venoactive drugs to provide patients with rapid and substantial relief of symptoms. MPFF also provides a unique protection against complications by preserving the venous valves and walls. These facts have been recognized by systematic reviews[7,44] and both national and international guidelines,[18,45] where MPFF has the highest level of recommendation as a first-line treatment for the management of chronic venous disorder–related symptoms and edema at all stages and as an adjunctive therapy for venous ulcers.

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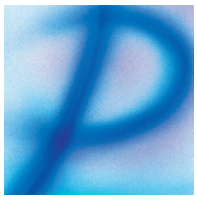

Testing the potential risk of developing chronic venous disease: Phleboscore®

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Abstract

Chronic venous disorders (CVD), a highly prevalent problem among populations worldwide, with which both general practitioners and specialists have to deal, include symptoms (leg pain, leg heaviness, and other types of discomfort) and signs as described in the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification. Symptoms appear early in the progression of the disease and with time may be associated with clinical signs of increasing severity. CVD is a chronic disorder that significantly alters the quality of life for the affected patient right from the early symptomatic stages, but may progress toward skin complications. Numerous risk factors have been postulated as possible causes for the development of CVD, but specific and validated instruments to adequately assess the impact that these risk factors may have on CVD progression were lacking. This article presents the steps that were needed to construct a self-assessment tool (Phleboscore®) for patients with leg problems to quantify the risks of developing further CVD complications.

Keywords:

assessment tools; CEAP classification; chronic venous disease; chronic venous disorders; diagnosis; management; Phleboscore®; risk factors; self-assessment

Introduction

Chronic venous disorders (CVD) are common among the general population worldwide,[1,2] and the prevalence of such disorders is likely to increase with population aging.[3] For a long time, wide differences have been observed between the reported rates of prevalence, probably due to recruitment bias and to the use of a definition of CVD that has long remained nonhomogenous. The clinical, etiological, anatomical, and pathophysiological (CEAP) classification, updated in 2004,[4] provides a framework that describes CVD in all its aspects. With the CEAP classification, the multiple variations of CVD can be communicated in a clinically and scientifically meaningful manner, allowing analysis and comparison of treatment modalities for like conditions. It describes the multifactorial nature of the condition that leads to very different rates of progression in different patients and allows comparisons between epidemiological data in various countries. The CEAP classification categorizes limbs into seven classes from C_0 to C_6. Each clinical class is further characterized by either a subscript S or A depending on whether the categorized limb is symptomatic or asymptomatic, respectively. This

Phlebolymphology. 2016;23(2):92-101

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classification has been used in recent population-based epidemiological surveys.[5-10]

Both general practitioners and specialists have to deal with this pathology. The management of CVD is usually based on clinical examination and on complementary investigations when needed. However, such evaluations do not take into account the patients' lifestyle, genetic inheritance, or family history of CVD–the factors known to be associated with the disease and its aggravation. A specific patient-oriented tool capable of allowing patients to identify the risk factors for CVD and self-assess the impact these factors may have on CVD progression is the key for efficient prevention and management of the disease.

Objective

The objective of this article is to present the steps that were needed to construct a self-assessment tool (Phleboscore®) for a patient with leg problems to quantify the risk for developing more severe stages of CVD.

Methods

The scoring system for "venous" risks was set up in several steps:

1. Listing the prevalence of all symptoms and signs of CVD from epidemiological surveys.

2. Identifying the risk factors for CVD.

3. Finding a relationship between the exposures to identified CVD risk factors and the appearance or aggravation of the symptoms and signs of the disease.

4. Quantifying and "weighting" each risk factor accordingly.

Results

Prevalence of the CVD-related symptoms and signs in epidemiological surveys

Recent population-based surveys that used the CEAP classification reported CVD prevalence rates of 44% in Bulgaria,[5] 49% in Poland,[6] 71% in the US,[7] 77% in Italy,[8] 85% in Scotland,[9] and 90% in Germany.[10] The Vein Consult program was a worldwide epidemiological survey involving 20 countries, 5 continents, and 91 545 screened adults consulting for any medical reason, found that the distribution of individuals among the CEAP clinical classes was as follows: 16 901 (21.7%) were C_1 (telangiectases, reticular veins), 13 888 (17.9%) C_2 (varicose veins), and 18 863 (24.3%) C_3 (edema) to C_6 (chronic venous insufficiency) for a total of 46 452 patients. The number of subjects complaining solely of symptoms, the so-called C_{0S} patients, was 15 290 (19.7%), indicating that almost 20% of the survey population had CEAP grade C_{0s}. Only 12 774 (16.4%) individuals had no symptoms or signs of CVD and thus were exempt from leg problems (C_{0A}).[2,11] *Figure 1* summarizes the epidemiological data of this program.

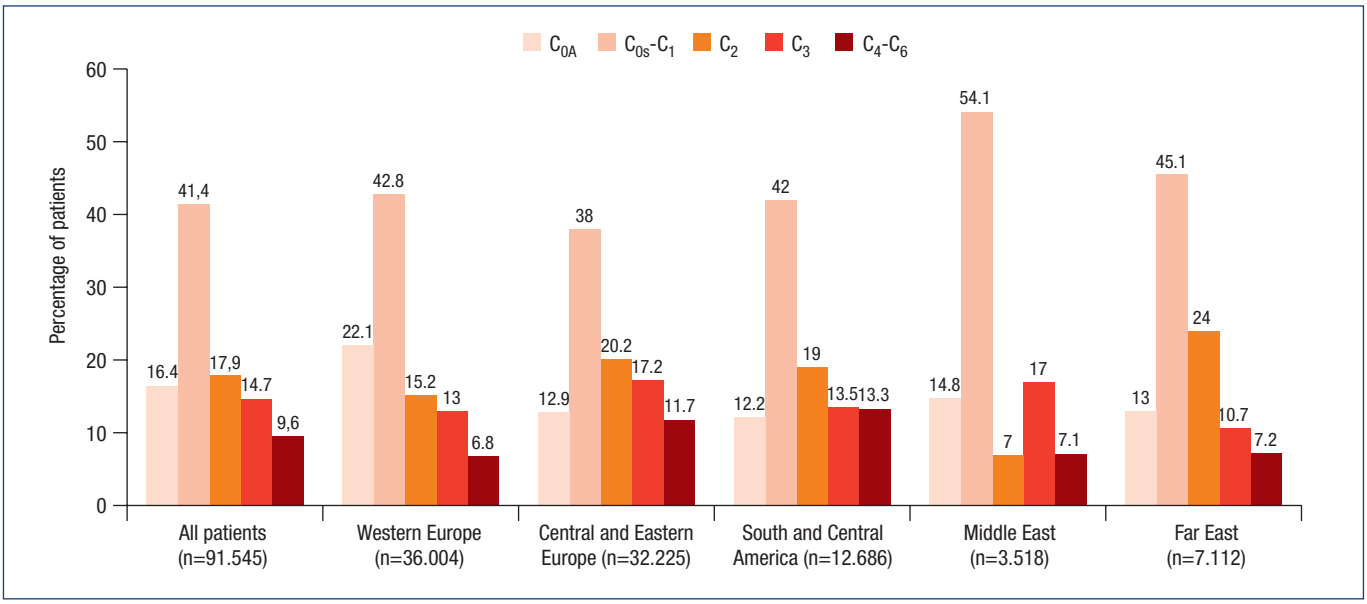

Figure 1. Distribution of the clinical, etiological, anatomical, and pathophysiological (CEAP) classifications according to geographical areas.

Finally, the incidence and prevalence of CVD depend on the age and sex of the surveyed populations. In the US, one branch of the Framingham study found that the annual incidence was 2.6% in women and 2.0% in men,[12] and one Finnish study reported an incidence rate of 13.5 per 1000 person-years (8.5 for men and 19.2 for women).[13]

CVD risk factors in the literature

Based on numerous CVD studies, the main risk factors found to be associated with CVD include age, sex, pregnancy, obesity, positive family history of varicose veins, and previous thrombophlebitis.[14] Environmental or behavioral factors may also be associated with CVD, such as smoking, prolonged standing, and a special sitting posture at work.[15] Moreover, tight clothes, constipation, diet habits, foot posture, or hypermobility showed variable associations with CVD.[6,14,16]

Age

A common finding in epidemiological studies is that the prevalence of CVD increases with age.[1-3,9,16] In the Bochum study, examination of a cohort of school children between the ages of 10 and 12 demonstrated the presence of discrete reticular veins in only 10% of the pupils, but 4 years later, this figure had increased to 30% and a few children had developed varicose veins.[17] The underlying mechanisms for changes in the venous system with aging are insufficiently understood. There is evidence for an association between age-related alterations of deep venous valves and high incidences of deep venous thrombosis[18] because deep venous valves change with age and are thicker in older individuals. The increase in valve thickness with age would explain the age gradient seen in the incidence of venous thrombosis. Likewise, in CVD, aging was established as an important factor responsible for changes in the venous wall and valves where inflammatory events play a pivotal role both in the aging process and the development of varicose veins.[19,20] Although the disease and aging processes run a parallel, overlapping course, the aging process may be accelerated in CVD, coinciding with the remodeling of the venous wall and valves that affect both its cellular component[19-22] and its extracellular component, as observed by Buján et al.[19]

Sex

Most studies have shown that CVD is more frequent in women.[12,23-26] Sex-related and lifestyle risk factors, such as genetic factors, obstetric history, work, and oral contraceptive use, could be considered partly responsible for the higher frequency of CVD in women. In the Edinburgh Vein Study,[9,26] the prevalence of varicose veins and chronic venous insufficiency was higher in men. Severe stages (C_3 to C_6) of chronic venous insufficiency were also more frequent in men than in women in the study by Scott et al.[27] Vlajinac et al[28] showed that chronic venous insufficiency was significantly more frequent in men, while more women reported the earlier stages (C_{0s}-C_1).[28] Fiebig et al[29] postulated that the higher proportion of women suffering from CVD may be partially explained by different timing in disease progression between the two sexes.

Hormones and pregnancies

It is a widely held view that hormones may be important in the development of postpartum varicose veins. Epidemiological studies have sought to determine whether the number of pregnancies or childbirths is related to the occurrence of CVD. Several studies found that a greater number of pregnancies[12,15,30] and childbirths[16,20] were related to an increasing prevalence of CVD signs, and this association was maintained after age adjustment. In the Serbian Vein Consult Program,[28] the average number of births was significantly higher in women with CVD compared with those without the disease. The higher number of births was a risk factor for CVD independently of other observed factors, including age.[28] The association of CVD with the use of oral contraceptive pills and hormonal replacement therapy is not clear and controversial results came up from a number of studies.[28] It is not well understood why pregnancy might increase the risk of developing CVD. The belief that pregnancy leads to varicose veins due to pressure from the uterus that obstructs venous return from the legs has been refuted because the majority of varices appear during the first trimester of pregnancy when the uterus is not large enough to cause mechanical obstruction. Hormonal factors or the additional burden of increased circulating blood volume could be important.

Obesity

Doubt remains about the relationship between obesity and CVD. Epidemiological studies, including the Basel study,[31] the Edinburgh Vein Study,[9] and the study by Jawien et al[6] observed a relationship between obesity and varicose veins in women, but not in men, while others failed to show an association in either sex.[32] Another French epidemiological study did not find any relationship between CVD and obesity in male patients,[33] while the Serbian Vein Consult Program concluded that obesity was a positive risk factor for varicose veins in both sexes, with the exception of a severe form of CVD in men.[28] The Framingham Study showed a higher incidence of varicose veins in women who were more likely to be obese than men.[12]

Since obese patients have more severe forms of CVD than nonobese patients with comparable anatomical patterns of venous incompetence, van Rij et al postulated that obesity exacerbates the severity of the varicose disease once venous reflux occurs,[32] and that this may be the result of increased intra-abdominal pressure leading to increased reflux, vein diameter, and venous pressures.

Family history of CVD

A strong body of evidence implicates genetics in the etiology of CVD. Cornu-Thenard et al studied the role of the family history in varicose disease in a prospective case-controlled study.[34] They showed that the risk of developing varicose veins was 90% for the children when both parents had varicose veins, 25% for men and 62% for women when one parent was affected, and 20% when neither parent was affected.[34] A Chinese analysis of nuclear families reported a penetrance between 70% and 92%, while 37% of their cases were sporadic.[35] A Finnish longitudinal study showed a 1.6-fold increased risk of developing varicose veins in those with a family history of varicosities.[36] Fiebig et al examined heritability of CVD and concluded that the additive genetic component was approximately 17%.[29] These studies suggest a strong genetic component in primary venous failure, but the genes involved have yet to be identified.

History of venous thromboembolism

In the Vein Consult Program, history of venous thromboembolism was the most important independent risk factor for CVD.[28] This confirmed the results of previous work in which venous thromboembolism was found to be the most important cause of secondary CVD.[27] Heit et al[3] and Carpentier et al[15] estimated that as many as 20% of CVD cases developed as a consequence of a prior deep venous thromboembolism. Venous thromboembolism would lead to CVD via the development of venous hypertension because of persistent venous outflow obstruction and/or venous valvular incompetence due to damage caused by thromboses.

Lifestyle factors

Smoking was found to be a risk factor for varicose veins in the Framingham study,[12] but only in men, not in women. In the San Diego survey[16] and the Vein Consult Program,[28] current smoking was associated with increased rates of chronic venous insufficiency in men. In a recent study from Finland,[37] the 5-year incidence of varicose veins in both sexes was higher in smokers compared with nonsmokers. The mechanisms responsible for the harmful effects of smoking on the venous system might involve the oxidative stress related to the smoke, which causes hypoxia and endothelial damage.[28]

There are many studies about the effect of prolonged standing on CVD, which has often been blamed for the development of CVD and, more particularly, varicose veins.[38] In the San Diego survey, prolonged standing was positively associated with more severe disease and prolonged sitting inversely associated with moderate disease in women. For men, increased daily walking was associated with moderate disease, and men who worked as laborers were more likely to have severe disease than those in positions that typically required more desk time. Regular movement when sitting for long periods was related to lower rates of moderate disease in men.[16] In the Framingham study, the 2-year incidence of varicose veins was higher with the length of time women spent sitting or standing.[12]

In theory, tight undergarments might promote the development of varicose veins by increasing intra-abdominal pressure. The prevalence of varicose veins increased with the stiffness of the corsets being worn in the 1960's by the female cotton workers in England and Egypt.[39]

Constipation and a low-fiber diet could be related to an increased CVD prevalence since this produces small, hard stools that are difficult to pass, leading to regular straining and repeated increases in intra-abdominal pressure. Increased intra-abdominal pressure from straining at stool may be transmitted down the veins of the legs, leading to dilation of the veins and nonapposition of the valve cusps, rendering the valves incompetent. Research is currently ongoing to determine the possible relationship between constipation and CVD occurrence (the CHORUS survey [Chronic venous and HemORrhoidal diseases evalUation for improvement of Scientific knowledge] from Servier).

Abnormal static posture of the foot may account for improper emptying of the plantar venous pump while walking. Since the venous pump of the human foot is the first step in venous return from the lower extremity to the heart, it has a role to play in the occurrence of CVD.[40]

The risk factors retained for constructing Phleboscore® are summarized in *Table I*.

Factors related to patients	Factors related to lifestyle habits
• Age • Sex • Weight • Height • Number of pregnancies • Hormonal treatments • History of venous thromboembolism • Family history of chronic venous disorders • Abnormal static posture of the foot	• Smoking • Diet • Constipation • Sport • Position at work • Clothing stiffness • Heaviness in the legs that are exacerbated after prolonged standing or sitting, with heat, or during menstruation for women

Table I. Risk factors for chronic venous disorders retained for constructing Phleboscore®.

Relationship between risk factors and CVD aggravation

The knowledge of the natural history (progression) of CVD relies on a few longitudinal studies, and much of the available information arises from cross-sectional studies. In patients awaiting surgery for a mean of 19 months, nearly one-third of those with venous reflux had progression in the CEAP clinical stage and either an extension of a preexisting reflux or reflux in a new segment.[41] In a prospective 7-year follow-up on patients with venous reflux, most of the limbs clinically deteriorated at the end of the observation period. Limbs that underwent a superficial or deep venous procedure remained stable or improved over time; those that underwent elastic compression alone had worsening hemodynamic and clinical status.[42]

The Bochum study, a large cohort investigation in Germany, explored the natural history of preclinical (C_0) and early stages (C_1) of the development of varicosities and the behavior and function of the venous calf pump from childhood to adulthood in subjects with healthy veins. Telangiectasias and reticular veins were noted early on, independently of the presence of reflux. Large varicosities appeared in older subjects, often preceded by reflux in the saphenous veins.[17]

In the Bonn Vein Study I that was conducted in 2000, 3072 participants of the general population of the city of Bonn and two rural townships, aged 18 to 79 years old, participated.[10] In the follow-up study (Bonn Vein Study II) that occurred 6.6 years later, the same population was assessed again. The incidence of progress to chronic venous insufficiency (C_3-C_6) was approximately 2.0% per year.[43] In a multivariate analysis, the main risk factors for developing severe stages of CVD (C_4-C_6) were age, arterial hypertension, and obesity. The presence of the symptom of a "sensation of swelling" significantly increased the risk for developing chronic venous insufficiency.[43]

Kostas et al evaluated long-term (5-year) characteristics of CVD progression and its correlation with the modification of specific risk factors. The contralateral (normal) limb of 73 patients undergoing varicose vein surgery for unilateral varicosities was prospectively evaluated using physical and color duplex examination and classified using the CEAP classification. In about half of the patients, CVD (reflux development and clinical deterioration) developed in the contralateral, but initially asymptomatic, limb in 5 years. In these patients, obesity, orthostatism, and noncompliance with the use of elastic stockings were independent risk factors for CVD progression, but estrogen therapy and multiparity were not.[44]

Clinical signs (eg, corona phlebectatica and other skin changes) may warrant early interventions to prevent later ulcer formation. The risk of ulceration is related to the severity of varicosities and venous insufficiency, and this risk is increased following deep vein thrombosis (incompetence). However, the risks may also be increased in those who smoke, are obese, and have restricted ankle movement and reduced power in the calf muscle pump.[45] Studies show that mechanical dysfunction of the calf muscle pump may enhance the development of leg ulceration.[46] Therefore, it is important to investigate ankle range of motion, function of the calf muscle pump, and patient activity in relation to disease progression.

Quantification of the CVD risk factors

The multifactorial evaluation of all risk factors for CVD appearance and progression led us to "weight" the factors according to sex *(Figures 2 and 3)*, which allowed us to build the Phleboscore® questionnaire (*Table II*).

Q1 – Sex
- Male = **0**
- Female = **1**

Q2 – Symptoms: do your legs ever feel heavy?
- No, never = **0**
- Occasionally = **1**
- Often = **2**
- Virtually all the time (considerable pain) = **3**

Q3 – Symptoms: if your legs feel heavy, is this heaviness increased by
- I don't have heavy legs / no worsening = **0**
- Hot weather = **1**
- The pill and hormone replacement therapy = **2**
- Systematically when I get my period = **3**

Q4 – Symptoms: do you ever have swollen ankles in the evening?
- No, never = **0**
- Only in hot weather or during long trips by plane, train, or car = **1**
- Yes, almost every day, but only in the evening = **2**
- Yes, every day, from the morning onward = **3**

Q5 – Your age
- Under 15 = **0**
- 15-29 = **3**
- 30-50 = **6**
- Over 50 = **9**

Q6 – Heredity: do you have a family history (father or mother) of varicose veins?
- No = **0**
- One parent = **3**
- Both parents = **6**
- Both parents, one with complications (leg ulcer) = **9**

Q7 – Pregnancy: how many full-term pregnancies have you had?
- I've never been pregnant = **0**
- One pregnancy = **3**
- Two pregnancies = **6**
- More than two pregnancies = **9**

Q8 – Hormonal imbalance: do you ever have any of the following symptoms?
- I've never have any hormonal imbalance = **0**
- Swollen eyelids and fingers = **3**
- Irregular menstrual periods = **6**
- Premenstrual syndrome and irregular menstrual periods = **9**

Q9 – Personal history of phlebitis: have you ever had phlebitis?
- No never = **0**
- One episode of phlebitis = **3**
- Two episodes of phlebitis = **6**
- More than two episodes of phlebitis = **9**

Q10 – Overweight: do you know your BMI?
- BMI under 25 = **0**
- 25-29 = **2**
- 30-39 = **4**
- 40 and over = **6**

Q11 – Imbalanced diet: which adjective(s) best describe your diet?
- Balanced and varied: I eat a lot of vegetables, some meat or fish, starchy vegetables, etc, and I keep up to date on the latest news regarding diet = **0**
- Home cooking, simple and easy-to-prepare dishes, while trying to follow a balanced diet consisting of vegetables, starch, some meat and fish = **2**
- Commercially prepared foods and dishes, frozen prepared vegetables = **4**
- Fast food, I go out a lot and eat in fast food restaurants = **6**

Q12 – Muscular fitness: do you walk, swim, cycle, jog, and/or go to the gym?
- Yes, at least 3 hours per week = **0**
- Less than 3 hours per week = **2**
- Occasionally (during vacation time) = **4**
- Never = **6**

Q13 – Posture at work: in your opinion, how long do you remain seated, standing, or standing in place during the working day?
- Less than 4 hours per day = **0**
- 4-8 hours per day = **1**
- More than 8 hours per day = **2**
- More than 8 hours per day, plus frequent traveling by car, train, or plane = **3**

Q14 – Tight-fitting clothing: what type of clothing do you usually wear?
- I mainly wear loose-fitting comfortable clothing = **0**
- I mainly wear beltless, single-breasted clothing = **1**
- I mainly wear skirts and dresses with a shaped waist or pants with pleats = **2**
- I mainly wear form-fitting clothing or tight fitting at the waist and thighs (slim-cut jeans, belts, ankle high tights or stockings, etc) = **3**

Q15 – Plantar aspect of the feet: do you have any problems with plantar posture?
- No, none = **0**
- I have hollow feet or flat feet with no lesions = **1**
- I have indirect lesions on my feet (corns, callouses, moderate hallux valgus) = **2**
- I have serious lesions on my feet (severe hallux valgus, toe deformities) = **3**

Table II. Content of Phleboscore®, a patient's self-questionnaire for the assessment of the risk of chronic venous disorder progression. Version from November 2015, printed with the kind permission of Dr Philippe Blanchemaison.

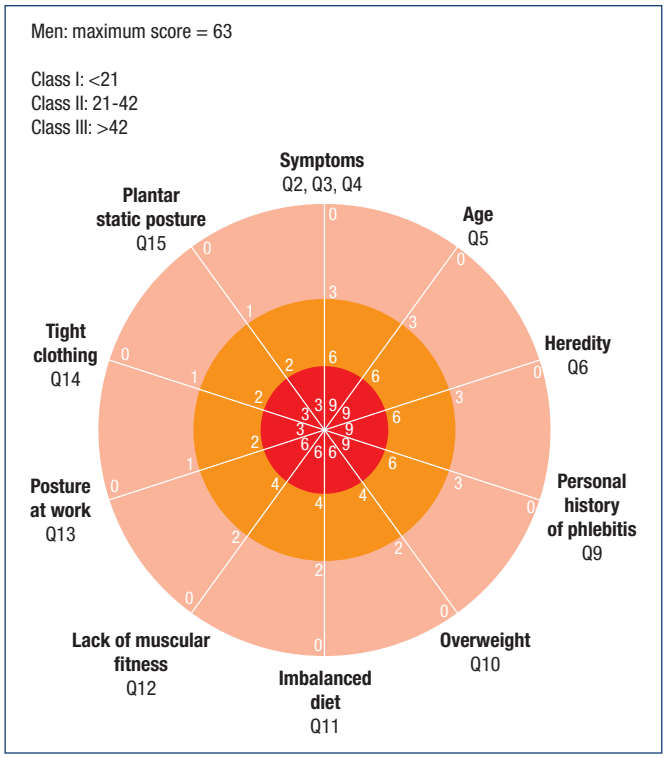

Figure 2. Multifactorial evaluation of the risk factors for chronic venous disorders in men.

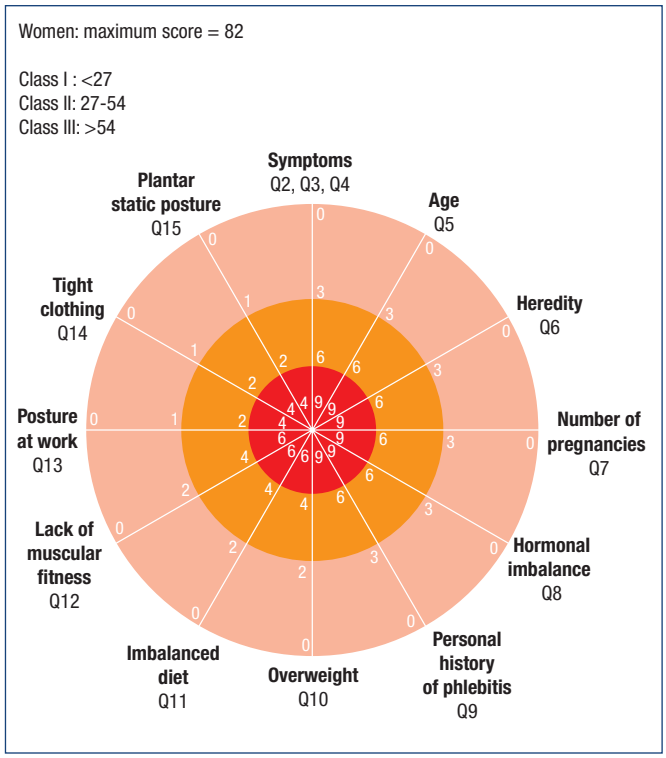

Figure 3. Multifactorial evaluation of the risk factors for chronic venous disorders in women.

Advice for CVD patients according to the Phleboscore® results

The advice for patients depends on the score that women or men with CVD received after filling out the Phleboscore® questionnaire. CVD patients are divided into 3 classes depending on their risk factors: low risk of CVD (class I), moderate risk of CVD (class II), and high risk of CVD (class III). Actions to take according to the patient's risk class are summarized in *Table III*.

Overall score	Subscore	Indications
Women ≤27 Men ≤21	Low risk of venous disease (class I). **Follow your doctor's advice to maintain the healthy condition of your veins.**	
	Symptoms Q2, Q3, and Q4 >6	Problem with fluid retention. Prefer an antifluid retention diet by drinking water, tea, and herbal tea and choosing vegetables known for their fluid elimination properties (artichokes, black radish, asparagus, leeks, etc).
	Medical history Q6, Q7, and Q9 ≥18 Q6 and Q9 ≥12	History that promotes occurrence of venous disease Monitor the appearance of your legs and symptoms related to fluid retention Consult your doctor in the case of varicose veins and swelling
	Diet Q10 and Q11 ≥8	Problem with being overweight Improve your diet and eat a balanced diet depending on basal metabolism Prefer fresh food and home cooking instead of commercially prepared food.
	Physical habits Q12, Q13, and Q14 ≥8	Walk 10 000 steps daily (at least 1 hour of walking) to stimulate circulation in the legs Stretch your legs even when seated and do not wear tight clothing, particularly at the waist and thighs

Overall score	Subscore	Indications
Women 27-54 Men 21-42	Moderate risk (class II): **risk of venous disease and/or disorder is already causing a certain number of signs indicating poor venous circulation. It is time to act decisively with personal action (eg, exercise, healthy venous lifestyle), and, in case of signs and symptoms of venous disease, with medical management (phlebotropic drug treatment, compression stockings, etc).**	
	Symptoms Q2, Q3, and Q4 ≥6	Problem with fluid retention. Prefer an antifluid retention diet by drinking water, tea, and herbal tea and choosing vegetables known for their fluid elimination properties (artichokes, black radish, asparagus, leeks, etc) Undergo lymphatic drainage.
	Medical History Q6, Q7, and Q9 >18	If you do not have varicose veins or edema, monitor your legs regularly and have them checked by your vascular specialist
	Diet Q10 and Q11 ≥8	Remember to eat a balanced diet depending on your basal metabolism. Prefer fresh foods Do not hesitate to consult a nutritionist
	Physical habits Q12, Q13, and Q14 >8	Engage in physical activity regularly, such as aqua biking, swimming, and walking Avoid tight clothing, particularly at the waist and thighs
Women >54 Men >42	High risk (class III): **you have a high risk for already chronic venous disease or you already suffer from the disease. You need to stop the progression of the disease by medical management (phlebotropic drug treatment, compression stockings, etc) and maintain the results obtained by a lifestyle that promotes healthy veins.**	
	Symptoms Q2, Q3, and Q4 ≥6	Problem with fluid retention. Prefer an antifluid retention diet by drinking water, tea, and herbal tea and choosing vegetables known for their fluid elimination properties (artichokes, black radish, asparagus, leeks, etc) Undergo lymphatic drainage and/or pressure therapy. Engage in an antifluid retention program (vascular exercises)
	Medical history Q6, Q7, and Q8 ≥18 Q6 and Q9 >12	Consult your vascular specialist
	Diet Q10 and Q11 >8	Consult a nutritionist Go on a diet to ensure the correct intake of essential nutrients for proper functioning of blood vessels (mineral and trace elements, amino acids, vitamins)
	Physical habits Q12, Q13, and Q14 >8	Wear compression stockings Engage in physical activity regularly, such as aqua biking, swimming, and walking Avoid tight clothing, particularly at the waist and thighs

Table III. Actions to take by subjects presenting with chronic venous disorders or disease according to their Phleboscore® results. Version from November 2015, printed with the kind permission of Dr Philippe Blanchemaison.

Conclusion

Phleboscore® is a medical tool to assess a patient's potential risk of developing chronic venous disease. Phleboscore® should help to more accurately identify the patients at risk of developing a more serious disease so that interventions can be offered at an early stage to those who will gain the most benefit.

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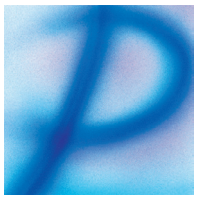

Role of duplex ultrasound investigation in the management of postthrombotic syndrome

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Keywords:

deep vein re1ux; duplex ultrasound; iliofemoral obstruction; postthrombotic syndrome; venous stenting

Abstract

Duplex ultrasound is a method for analyzing the anatomy and hemodynamic profile of lower-limb veins; it can also be used for pelvic and abdominal examinations. For postthrombotic syndrome, duplex ultrasound can recognize specific anatomical abnormalities in the venous lumen, wall, and valves. Reflux can be easily diagnosed with duplex ultrasound, although some controversy is present concerning the extent of the reflux detected compared with descending venography. Venous obstruction is more challenging to quantify; nevertheless, simple indirect signs, such as phasic-flow disappearance and low–flow velocity in the common femoral vein, suggest suprainguinal obstruction. Before operative recanalization, duplex ultrasound can be used to determine the procedure, feasibility, expected permeability, and safest venous access site; evaluate suprainguinal venous segments and infrainguinal vessels to determine the landing zone; distinguish between postthrombotic syndrome, primary and congenital incompetence, or compression. Duplex ultrasound is currently used during postoperative follow-up after repermeation and stenting to determine the permeability of the stented veins and recognize complications, such as thrombosis, residual stenosis, and intrastent intimal hyperplasia. Currently, duplex ultrasound is the first-line examination for postthrombotic syndrome diagnosis, preoperative investigation, and postoperative follow-up because it provides relevant information for the operative management of obstruction and reflux, even if the preoperative assessment must be completed by venography and other instrumental investigations.

Introduction

Postthrombotic syndrome includes all of the venous signs and symptoms occurring after a deep venous thrombosis in the lower limb. Major clinical features include dilated veins, edema, leg pain, and cutaneous changes. Obstruction of the deep venous system may lead to venous claudication. Diagnostic and quantification of postthrombotic syndrome are based on clinical criteria, which are described in the Villalta scale.[1]

Phlebolymphology. 2016;23(2):102-111

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Often underestimated, postthrombotic syndrome is responsible for important disabilities in daily life. The development of new endovascular interventional techniques offers appealing treatment possibilities, even for patients without tissue damage, that are complementary to conservative treatments. Deep endovenous stenting is safe, resulting in low morbidity and mortality, and effective, with a high rate of technical success, patency, ulcer healing, and clinical improvement.[2] The main objectives are to improve the patients' quality of life and possibly reduce the risk of recurrence by removing the obstruction.

In addition to a physical examination, duplex ultrasound is a mandatory and complementary assessment for patients presenting with chronic venous disease. Current guidelines strongly recommend using duplex ultrasound as the primary diagnostic test for superficial venous insufficiency, suspected abdominal or pelvic venous pathology, postthrombotic syndrome, or clinical suspicion of other forms of iliac or inferior vena cava obstruction.[3] Examining deep veins is more challenging than superficial veins, but duplex ultrasound may provide very useful information during all stages in the management of postthrombotic syndrome.

Duplex ultrasound techniques

Duplex ultrasound is a method for analyzing the anatomy and hemodynamic profile of lower-limb veins; it can also be used for pelvic and abdominal examinations. Duplex ultrasound techniques have been extensively described in consensus documents.[4,5]

For superficial veins, it is recommended to use a high-resolution linear ultrasound transducer (12-18 MHz) and to have the patient in a standing position. Basic duplex ultrasound examination of superficial veins includes assessing perforating veins and all of the saphenous vein junctions, trunks, and tributaries. The hemodynamic analysis is used to diagnose reflux elicited by the calf compression-release maneuver and/or the Valsalva maneuver. Cut-off duration for reflux is 0.5 seconds for superficial veins and 0.35 seconds for perforating veins. The anatomical analysis measures the diameter of the refluxing saphenous trunks, which is measured ≈15 cm away from the saphenofemoral junction for the greater saphenous vein, at mid-calf for the small saphenous vein, and at the fascia for perforating veins. In all cases, the sources and extension of the reflux must be recognized. Results of duplex examination are commonly reported on cartography.

Examination of deep veins requires different probes that are convex and/or microconvex and have a lower frequency (3-8 MHz). For postthrombotic syndrome, duplex ultrasound checks for deep venous reflux at the femoral and popliteal veins in patients who are standing and it uses a cut-off value of 1 second for reflux duration. Obstruction is measured using an augmentation maneuver in patients in a supine position.[6]

Postthrombotic syndrome diagnosis

Deep veins abnormalities

Anatomical abnormalities

At the acute stage of an obstructive deep venous thrombosis, the occluded vein appears as a dilated and noncompressible vein with a clot filling the lumen of the vein that is more or less echolucent according to the age of the thrombus. For a nonocclusive thrombosis, the thrombus is usually floating in the lumen of a nondilated vein.

During follow-up, different evolutions of the thrombus can be observed with the entire spectrum from a complete resolution with recanalization without any residual abnormality to a persistent occlusion with vein shrinkage.[7] Consequently, deep venous abnormalities can be very obvious, but they can also be very limited or absent, and, in such a case, distinguishing between postthrombotic and primary deep venous insufficiency can be challenging. On the other hand, according to the depth of the veins, duplex ultrasound is usually more precise for infrainguinal vein examination than for the inferior vena cava and iliac veins that require using a low frequency transducer for better penetration, even though this results in a lower resolution.

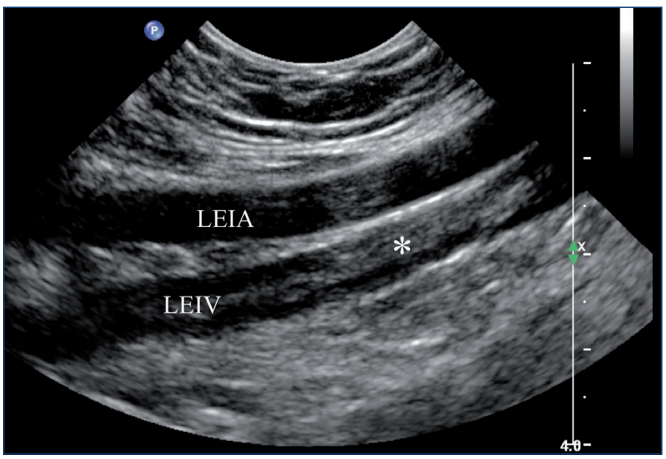


Figure 1. Residual fibrotic thrombus in the left external iliac vein (sagittal view).*

Abbreviations: LEIA, left external iliac artery; LEIV, left external iliac vein.

Postthrombotic changes may involve the venous lumen, wall, and valves. According to the extent of the lysis, the following can be observed in the venous lumen: (i) persistence of a thrombus that usually decreases in size and becomes more echogenic, and, in such cases, the vein is not totally compressible *(Figure 1)*; (ii) partial recanalization of the vein with residual intraluminal fibrotic material presenting as more or less extended webs or synechia that lead to compartmentalization of the lumen *(Figure 2)*; (iii) localized intraluminal calcifications-phleboliths *(Figure 3)*; and (iv) complete recanalization of the vein without any abnormality. The following can be observed in the vein wall: (i) more or less shrunken, with possible complete fibrosis and disappearance from ultrasound detection *(Figure 4)*; and (ii) isolated venous wall thickening and/or rigidity *(Figure 5)*.[8] Finally, venous valves are usually thin and mobile in the lumen of the vein and they can also present with the following abnormalities: (i) thickening and abnormally very

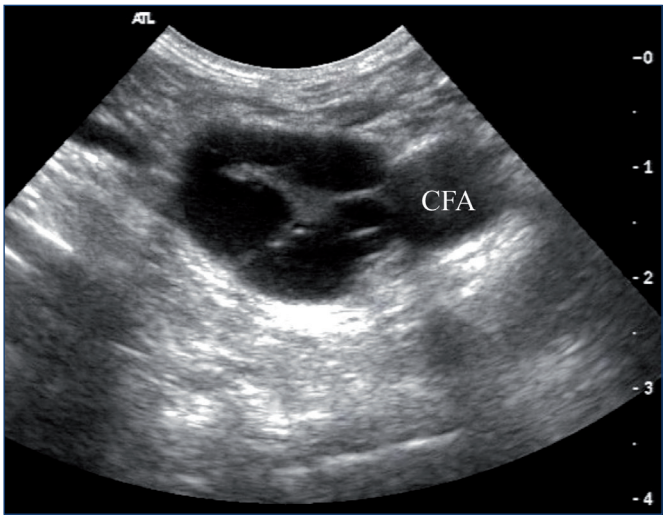


Figure 2. Intraluminal webs in the common femoral vein (transverse view).

Abbreviations: CFA, common femoral artery.

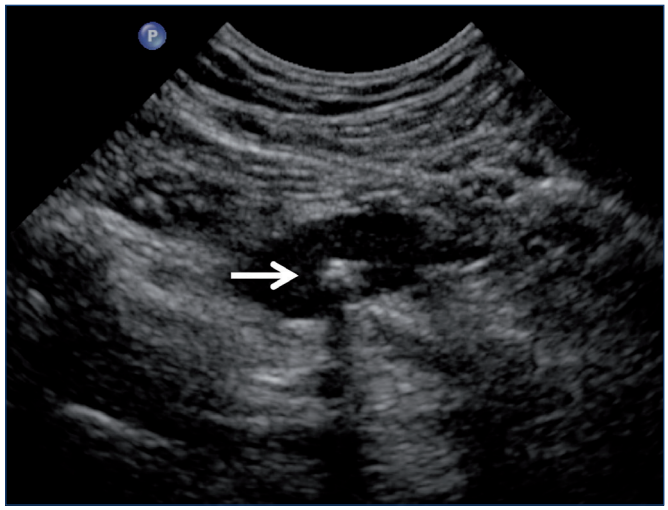
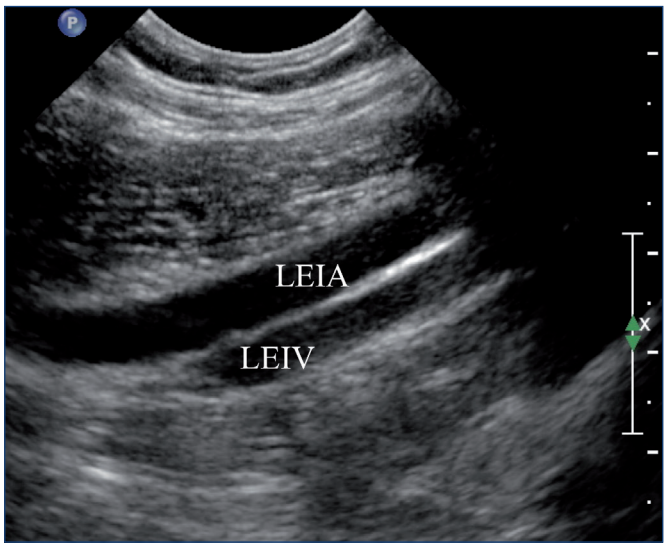


Figure 3. Phlebolith showing the transverse view of the soleal vein in the calf.



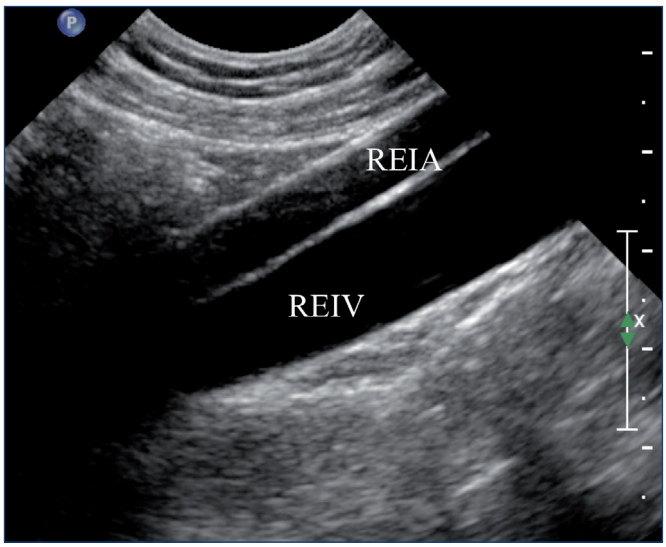


Figure 4. External iliac veins (longitudinal view).

Panel A shows shrinking of the LEIV. Panel B shows a healthy REIV.

Abbreviations: LEIA, left external iliac artery; LEIV, left external iliac vein; REIA, right external iliac artery; REIV, right external iliac vein.

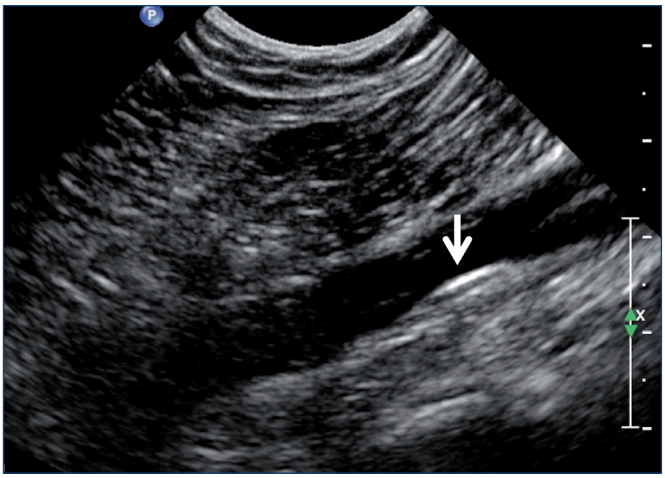


Figure 5. Popliteal vein with wall thickening (longitudinal view).

echogenic *(Figure 6)*; and (ii) rigid without spontaneous or induced valve movement. Nevertheless, in some cases, no anatomical abnormality can be observed with duplex ultrasound in patients with a confirmed history of deep vein thrombosis.

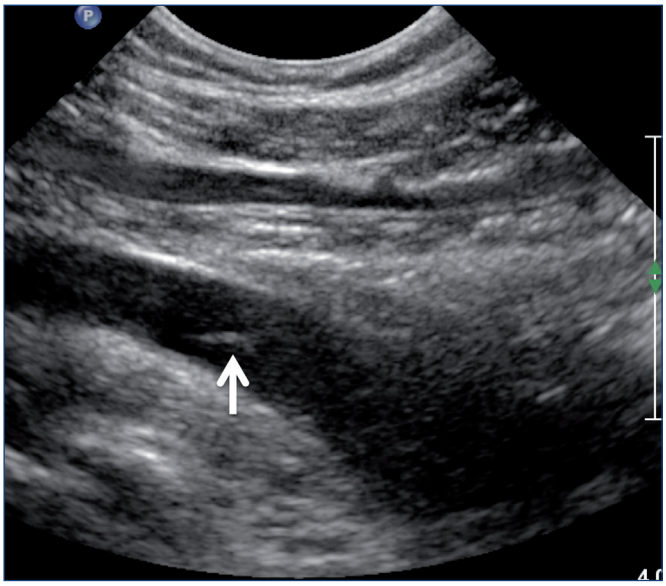


Figure 6. Popliteal vein with valve thickening (longitudinal view).

Hemodynamic abnormalities

Postthrombotic changes may be responsible for reflux, residual complete obstruction, or limited lumen stenosis. Reflux can be observed mainly at the popliteal and femoral veins using a compression-release maneuver of the limb distal to the point of examination in a patient that is standing. A color Doppler ultrasound investigation is used for reflux screening. In a second step, a power Doppler ultrasound can measure reflux duration that must exceed the 1-second threshold to be considered significant *(Figure 7)*. Duplex ultrasound is a very efficient technique, but there is some controversy concerning the evaluation of reflux extension compared with descending venography.[9]

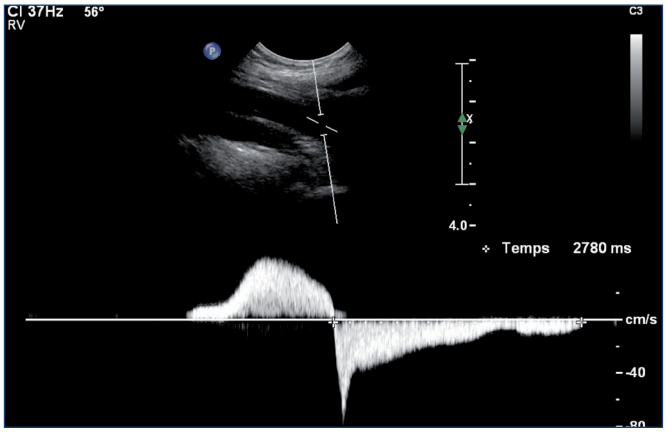


Figure 7. Popliteal vein with significant reflux (longitudinal view).

Obstruction is more challenging to diagnose and therefore to quantify with duplex ultrasound, which can only measure velocities at different locations of the venous network, but cannot provide any relevant quantification of the global venous flow of the limb. In a normal patent vein, spontaneous blood velocities are low and they increase significantly with an augmentation maneuver. In this case, color Doppler shows a complete and homogenous filling of the lumen and pulsed Doppler shows an increase in the flow velocities with a steep slope of the curve. Furthermore, proximal veins, such as the iliac and common femoral veins, present a phasic flow with respiratory modulation.

In obstruction analysis, a duplex ultrasound can demonstrate the following for a remodeled vein:

- Absence of any flux in case of obstruction.
- Low velocities in case of partial recanalization.
- Increase in velocity in case of venous stenosis with ratio over 2.5 *(Figure 8)*.[10]

Usually low velocities are registered cranially to a segmental obstruction area or at a long remodeled segment of the vein. An increase in velocity is observed at a segmental stenosis. In the last two cases, color Doppler shows an irregular colorization of the vein lumen compared with a patent healthy vein *(Figure 9)*. If the duplex analysis is performed proximally to an obstructive area, the duplex ultrasound will demonstrate a low increase in venous

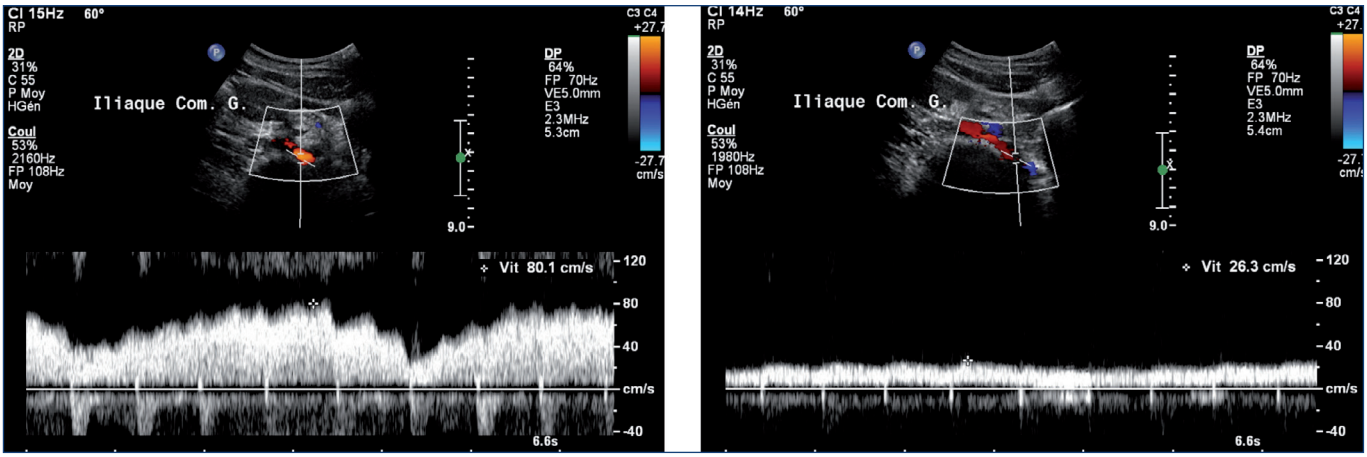


Figure 8. Increase in venous flux velocities at the termination of the left iliac vein (Panel A) compared with velocities measured distally to the stenosis (Panel B) (spontaneous flow).

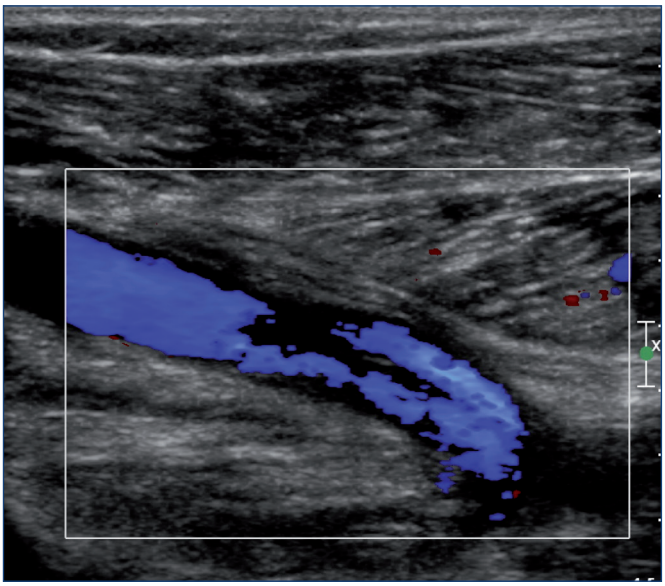


Figure 9. Color Doppler ultrasound of the popliteal vein (longitudinal view).

There is a partial recanalization with irregular colorization of the lumen vein.

velocity during an augmentation maneuver with a flat slope of the waveform that is asymmetrical compared with a healthy limb *(Figure 10)*.

For iliac vein obstruction, phasic flow measured in the common femoral vein usually disappears and a spontaneous low velocity flux can be observed *(Figure 11)*.[11] An analysis of the collateral veins is useful. As lower-limb veins are often duplicated or triplicated and connected with numerous collateral veins, a collateral pathway develops when deep vein thrombosis occurs and this network may or may not compensate for a residual occlusion of a deep vein. For example, for postthrombotic syndrome, spontaneous high-flow velocity in the great saphenous vein indicates that there is an obstruction of the infrainguinal deep vein. For supra-inguinal postthrombotic syndrome, retrograde flow into the internal iliac vein indicates that there is an obstruction of the common iliac vein and other deep collateral veins can also be identified.

Superficial and perforating vein tests

Postthrombotic syndrome may mimic primary superficial venous insufficiency, which is why deep veins must also be investigated, especially in patients presenting with a history of thromboembolic disease and/or with an advanced clinical class (C) of the clinical, etiological, anatomical, and pathophysiological (CEAP) classification. Superficial venous insufficiency can be present in postthrombotic syndrome and can sometimes be worsened by deep venous reflux or obstruction. Duplex ultrasound examination of the superficial vein for postthrombotic syndrome is the same as for primary superficial venous insufficiency. Nevertheless, two points must be highlighted. For postthrombotic syndrome, superficial collateral veins can be dilated and tortuous and they can mimic varicose veins. In such cases, duplex ultrasound shows a spontaneous and continuous antegrade flow and no reflux during a compression-release maneuver. These features are commonly observed at the thigh and abdomen. If the varicose vein reflux originates from an incompetent perforating vein or if it is connected with a bidirectional perforating vein, duplex ultrasound must search for the source of the perforating venous reflux, which can be increased by reflux in an axial or a major deep vein.

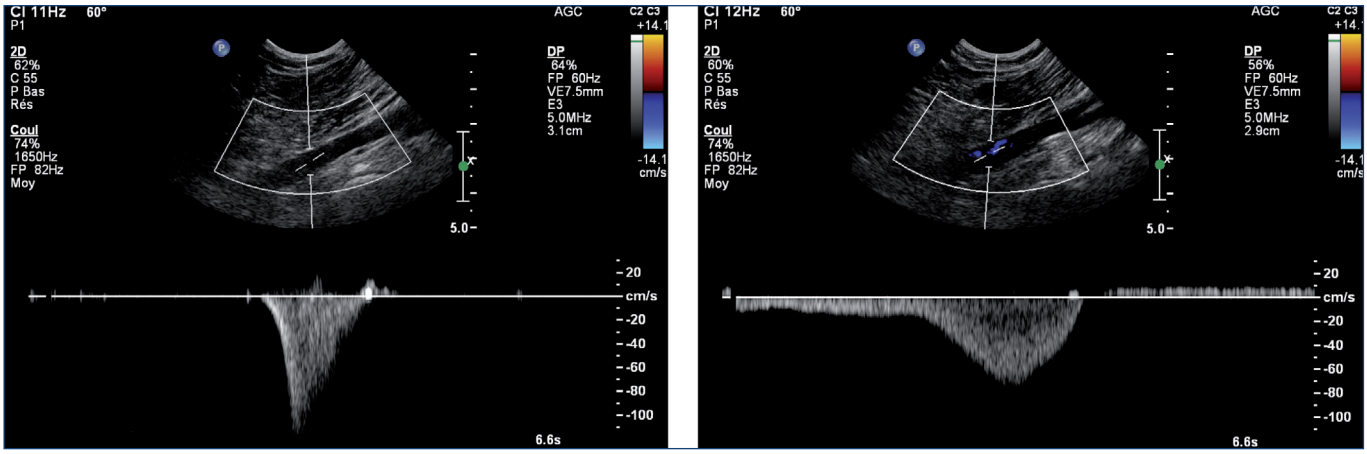


Figure 10. Left and right popliteal vein (longitudinal view).

Normal (Panel A) and pathological (Panel B) velocity profiles during an augmentation maneuver.

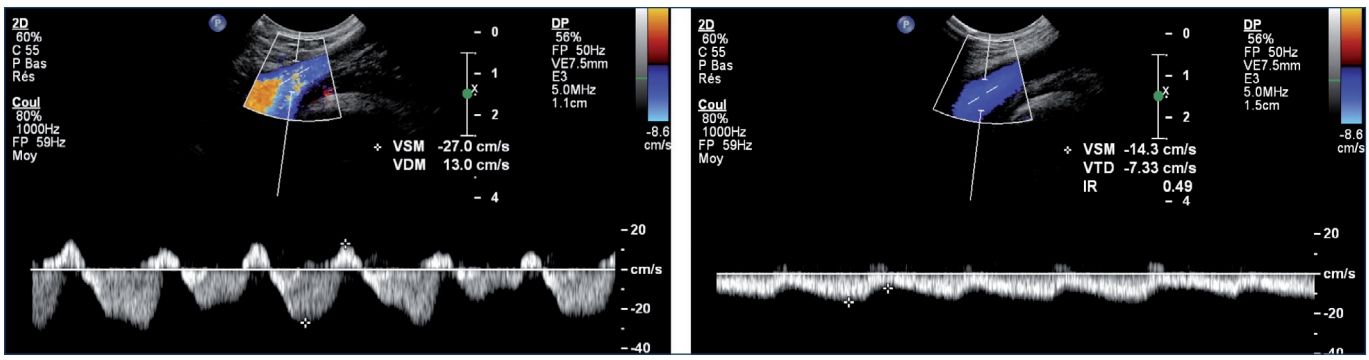


Figure 11. Left and right common femoral vein flux.

Right common femoral vein flux with a patent and healthy right iliac vein (Panel A) and left common femoral vein flux with left iliac vein obstruction (Panel B).

Hemodynamic analysis for postthrombotic syndrome

Supra-inguinal obstruction

Iliac vein obstruction can be related to postthrombotic syndrome, but also to other conditions, such as the May-Thurner syndrome (left common iliac vein compression between the right iliac artery and the spine), other iliac vein compressions, or congenital deep venous anomalies, such as inferior vena cava atresia. Duplex ultrasound searches for indirect signs of iliac obstruction at the femoral vein, ie, phasic–flow disappearance and low-flow velocity. High venous pressure can be responsible for an increase in the femoral vein diameter compared with the contralateral side.

For postthrombotic syndrome, anatomical and hemodynamic direct abnormalities (as described above) can be observed at the common iliac vein and/or at an external vein, which sometimes extends to the femoral vein and/or the inferior vena cava, according to the location of the initial deep venous thrombosis. Some collateral veins can usually be recognized with duplex ultrasound, such as the superficial suprapubic vein (Palma collateral veins) or the lateral abdominal collateral vein (for inferior vena cava obstruction), but also deep veins involving the latero-uterine, ovarian, and lumbar veins can be identified. In some cases, collateral veins can mimic the course of the iliac vein.

For the May-Thurner syndrome, indirect hemodynamic anomalies of obstruction are present on the left side and deep collateral veins can be observed. Left internal iliac vein retrograde flux is frequent. The termination of the common iliac vein appears to be compressed by the right common iliac artery with a decrease in the vein diameter and an increase in the flux velocity. Proximally to the compression,

the iliac vein diameter is larger with a decrease in venous flow velocities. For other compressions, duplex ultrasound can often identify the cause of the compression (tumor or retroperitoneal fibrosis). For inferior vena cava atresia, duplex ultrasound shows the absence of a normal inferior vena cava in the atretic area and usually obvious collateral veins *(Figure 12)*.

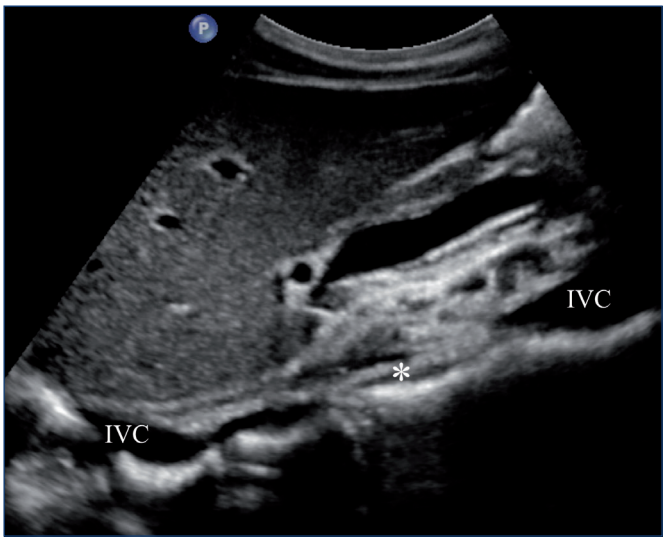


Figure 12. Inferior vena cava atresia (longitudinal view).*

Abbreviations: IVC, inferior vena cava.

Infrainguinal abnormalities

Combination of superficial and deep venous reflux

At the infrainguinal level, the combination of superficial and deep venous reflux is common, and normally, both can be easily evaluated. For combined reflux in the common femoral vein and the great saphenous vein or in the popliteal vein and the small saphenous vein above the saphenofemoral or the popliteal junction, respectively, deep venous reflux can be simply induced by the saphenous reflux. If the reflux occurs below the junction, it shows evidence of a true deep venous incompetence.

Combination of reflux and popliteal-femoral vein obstruction

As discussed previously, reflux in the deep veins is easier to demonstrate using duplex ultrasound than is obstruction. In current practice, duplex ultrasound is used to search for reflux at the popliteal and femoral veins, while obstruction is only searched for at the iliac vein. For postthrombotic syndrome, reflux and obstruction can coexist at the infrainguinal vein; therefore, these should both be analyzed.

For popliteal-femoral vein obstruction associated with great saphenous vein reflux, it can be challenging to evaluate the respective responsibility of deep venous obstruction and superficial venous reflux, insofar as refluxing superficial veins can also act as a collateral pathway. If the great saphenous vein appears to be refluxing in a standing position with a compression-release maneuver, it can also be efficient as a collateral pathway during exercise. In such a case, the decision to spare or ablate the refluxing great saphenous vein can be made by using the following tests: (i) a great saphenous vein duplex ultrasound can be performed during tiptoe-elevation movements to analyze the flux direction during exercise; and (ii) variations in the flow in the deep veins and other collateral veins of the thigh can be analyzed during compression of the great saphenous vein *(Figure 13)*. If the great saphenous vein appears to be refluxing during exercise and/or if the deep venous flow increases during great saphenous vein compression, reflux is probably predominant compared with the collateral efficacy.

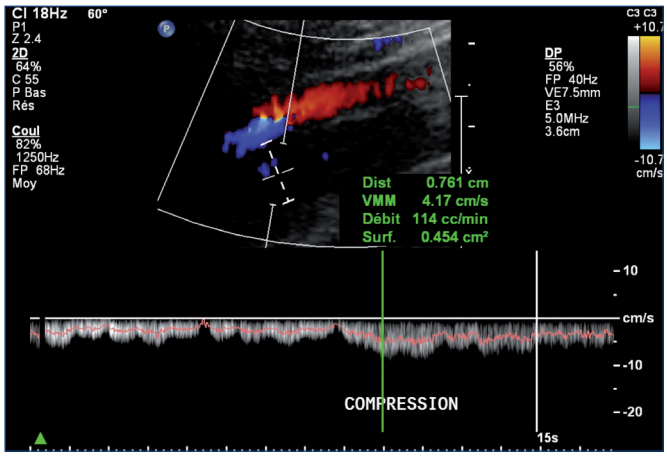


Figure 13. Increase in the femoral vein flow during great saphenous vein compression.

Interest in preoperative duplex ultrasound

Recanalization

Percutaneous transluminal angioplasty for iliocaval or iliofemoral obstruction can use a guidewire to go through the obstruction and then dilate and stent the obstructed vein segment. Preoperatively, duplex ultrasound provides relevant information about the extent of obstruction, the precise anatomy of affected segments to treat, the presence of collateral veins, and the association of deep and/or superficial venous reflux.

The entire deep venous system can be analyzed from the inferior vena cava up to the distal veins. Veins are described

as normal, dilated, or shrunken, and the vein diameter is measured at each level. Postthrombotic abnormalities are classified as an absence of a patent vein lumen (residual obliteration), the presence of a patent central channel (with vein wall thickening), or compartmentalization of the vascular lumen by postthrombotic webs and/or synechia *(Figure 1, 2, and 4)*. Moreover, duplex ultrasound identifies other anomalies, such as inferior vena cava atresia, May-Thurner syndrome, or vein compression.

Consequently, the duplex ultrasound examination focuses on selecting patients to be treated regarding feasibility; determining the expected mid- and long-term permeability; planning the procedure; choosing the most efficient site for safe venous access; selecting venous segments to be treated; evaluating infrainguinal vessels (ie, common femoral vein, deep femoral vein, femoral and popliteal veins, and saphenous veins) to determine the landing zone since proximal and distal termination of the stents have to be positioned in a normal healthy venous segment, even below the inguinal ligament. Infrainguinal dilatation and eventual stenting have not yet been validated, although they are considered interesting by some clinicians.[12]

Surgery for postthrombotic syndrome reflux

Duplex ultrasound is usually able to distinguish between postthrombotic, primary, and congenital incompetence. For primary incompetence, the refluxing vein appears as a normal vein, with a thin wall and no lumen abnormality. The vein can be compressed easily and completely. The only abnormality, except for an occasional, slightly enlarged vein, is valve incompetence *(Figure 14)*. Sometimes the valve structure remains intact and is therefore suitable for external or internal valvuloplasty. For postthrombotic syndrome, different therapeutic options can be considered, including the replacement of the refluxing vein segment by transplantation of a vein segment containing a competent valve, transposition of a refluxing vein onto a competent one, or creation of a neovalve from the thickened vein wall.[13]

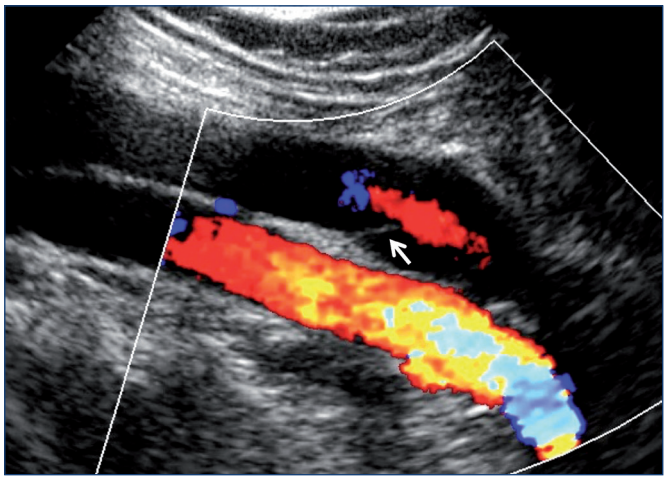


Figure 14. Popliteal vein as obtained from color Doppler ultrasound showing central reflux through a nonthickened valve (longitudinal view).

Even if the preoperative examination is based on phlebography, duplex ultrasound could be used to describe precisely the anatomical and morphological features of the vein to be transplanted or transposed and the features of the vein wall and lumen before neovalve creation.

Superficial and perforating vein ablation

If superficial vein ablation is planned, preoperative duplex ultrasound is mandatory. Duplex ultrasound examination will include an assessment of perforating veins and the saphenous vein junctions, trunks, and tributaries along their course with the results reported using cartography. Furthermore, duplex ultrasound will be used to guide endovenous treatment (thermal and chemical), which is largely used today, compared with conventional surgery.[14]

Intraoperative duplex ultrasound

Recanalization mainly uses fluoroscopic guidance. When available, intravascular ultrasound provides a precise evaluation of the venous stenosis and the result of the angioplasty. Nevertheless, transcutaneous duplex guidance as an adjunctive option should be considered, but it must first be evaluated. Duplex ultrasound can also be used for vein access guidance at the femoral and popliteal level. If the vein to be treated is clearly visualized with duplex ultrasound, echo guidance should be used for catheterization. Providing real time hemodynamic analysis, duplex ultrasound could also limit the use of contrast to manage and control venous recanalization.

Postoperative duplex ultrasound follow-up

Duplex ultrasound is the first-line imaging technique for the postoperative follow-up, regardless of the treatment modality–endovascular and open surgery (bypass or valvuloplasty). After recanalization, duplex ultrasound is used to check the patency of the treated vein and the collapse of collaterals. More precisely, duplex ultrasound measures flow into the stented veins. Complications are easily diagnosed with duplex ultrasound: (i) thrombosis usually occurs in the stented vein, which occurs more rarely

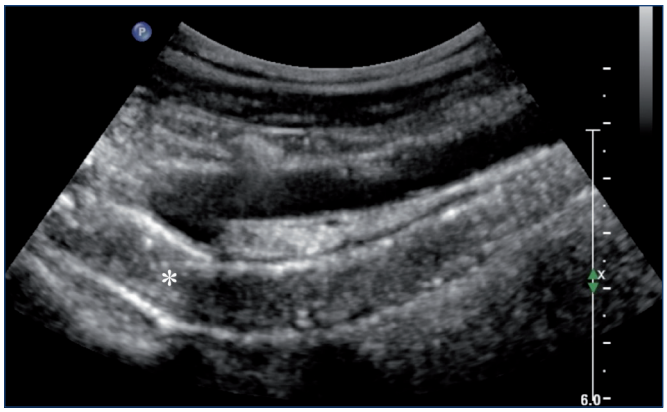


Figure 15. Thrombosis of the left iliac vein 1 day poststenting (longitudinal view).*

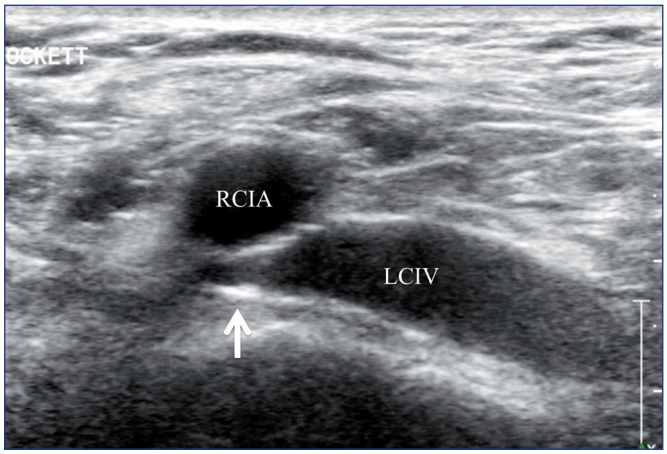


Figure 16. Inadequate angioplasty and stenting of the left common iliac vein with residual stenosis.

Abbreviations: LCIV, left common iliac vein; RCIA, right common iliac artery.

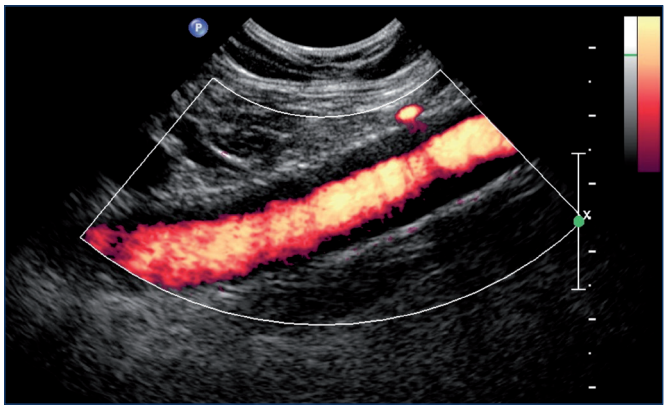


Figure 17. Power Doppler showing an intrastent intimal hyperplasia of the external iliac vein (longitudinal view).

in native veins *(Figure 15)*; (ii) residual stenosis can be observed for inadequate angioplasty or stenting *(Figure 16)*; (iii) can be observed during follow-up, intrastent intimal hyperplasia. For intrastent intimal hyperplasia, a power Doppler ultrasound can show a circumferential decrease in the diameter of the vein lumen with an echolucent area between the lumen and stented wall of the vein *(Figure 17)*. Regarding surgical techniques, duplex ultrasound checks the bypass permeability and the disappearance of reflux after valvuloplasty.

Role of duplex ultrasound in managing postthrombotic syndrome

Duplex ultrasound is recommended as the primary diagnostic tool for suspected abdominal or pelvic venous pathology to evaluate patients with postthrombotic syndrome or clinical suspicion of other forms of iliac or inferior vena cava obstruction or compression.[3] Nevertheless, because the use of Duplex ultrasound for assessing the iliac veins and collateral veins can be limited, additional pelvic imaging studies, such as conventional descending venography, computed tomography, or magnetic resonance imaging, are usually performed to assess the extent of the disease in the iliocaval segment and to exclude extravascular disease causing obstruction, such as tumors or retroperitoneal fibrosis.[15] Thus, duplex ultrasound is not systematically used as a preoperative examination before recanalization. Among 16 papers selected for a recent review of endovenous stenting in chronic venous disease secondary to iliac vein obstruction, duplex ultrasound was only used in 30% of the reported studies as a preoperative examination, and it was always associated with other diagnostic techniques, including ascending and descending venography, computed tomography and magnetic resonance venography, venous pressure measurement, and plethysmography.[16-20] However, in more recent publications on endovascular intervention, duplex ultrasound is always performed during follow-up to assess patency.[21-24]

Conclusion

Duplex ultrasound is a first-line examination for postthrombotic syndrome diagnosis and postoperative follow-up. It can provide relevant information for the operative management of obstruction and reflux, even if the preoperative assessment is based on computed tomography venography or magnetic resonance venography. Intraoperative ultrasound is not yet used, except for venous access.

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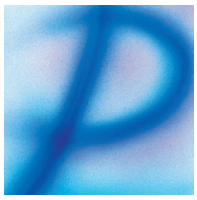

Management of combined venous and lymphatic malformations

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Keywords:

angiodysplasia; Klippel-Trenaunay syndrome; limb–length discrepancy; marginal vein; Parkes-Weber syndrome; vascular malformations

Phlebolymphology. 2016;23(2):112-120

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Abstract

Vascular malformations are congenital vessel malformations that include one or more venous, lymphatic, or arteriovenous defects. Klippel-Trenaunay syndrome occurs when there is a combination of venous and lymphatic malformations in the limbs; however, the definition is still controversial. The 2013 international venous malformation consensus established that Klippel-Trenaunay syndrome is a combination of venous malformations that involve the whole limb and lymphatic malformations. Although, if two venous malformations are present (eg, extratruncular and truncular), then a lymphatic malformation is not necessary to meet the definition for Klippel-Trenaunay syndrome. The classic triade of signs, ie, limb overgrowth, nevus and dilated superficial veins was not present in all cases of a patient series we analyzed (n=46). The diagnostic goal should be to recognize vascular malformations in individual patients. Investigations should involve the following (in the order presented): (i) a clinical examination; (ii) duplex scan to rules out arteriovenous malformations, study the morphology and flow in the veins, and establish flow in dysplastic peripheral vascular masses; (iii) MRI to confirm morphology of deep veins and determine the site of infiltrating malformations; and (iv) lymphoscintigraphy to identify the main deep and superficial lymphatic channels. Three treatment techniques–surgery, alcohol sclerotherapy of dysplastic vessels, and an interstitial or a superficial laser procedure–are available for Klippel-Trenaunay syndrome, which may be performed in stages and it may involve a combination of techniques. Significant improvement is possible if there is a complete diagnosis and correct treatment planning.

Introduction

Congenital vascular malformations arise due to an error in vessel development in the embryo. According to the type of vessel involved–artery, vein, or lymphatic duct–arterial, venous, lymphatic, and arteriovenous malformations can occur.[1] The anomalies are divided into defects of the main vessel, which are called truncular defects by the Hamburg classification,[2] or defects of the major named vessels according to the International Society for the Study of Vascular Anomalies (ISSVA)[3] and areas of dysplastic vessels in tissues, which are called extratruncular or simple according to the Hamburg classification or the ISSVA, respectively.

A combination of malformations may occur in the same patient, which often results in a more complex disease that can be difficult to understand and treat. In this paper, we will discuss combinations of venous and lymphatic malformations.

Venous malformations are the most common type of congenital vascular malformation with an incidence >50%, lymphatic malformations are less common, and combinations of venous and lymphatic malformations have a lower incidence.[4,5] *Table I* shows the distribution of congenital vascular malformations from a recent patient series. Venous malformations may be combined with lymphatic malformations in different truncular or extratruncular forms, resulting in the following possible combinations:

- Truncular venous malformations (aplasia, hypoplasia, or dilatation of the main venous trunks) with truncular lymphatic malformations (aplasia, hypoplasia, or dilatation of the main lymphatic ducts).
- Truncular venous and extratruncular lymphatic malformations (ie, mass of dysplastic lymphatics situated in the tissues).
- Extratruncular venous (ie, mass of dysplastic veins situated in the tissues) and truncular lymphatic malformations.
- Extratruncular venous and lymphatic malformations.[6]
- Truncular and extratruncular venous and lymphatic malformations may coexist in the same patient.

Vascular malformations	Number of cases (%)
Venous	624 (59%)
Arteriovenous	177 (17%)
Lymphatic	131 (12%)
Combined	57 (5%)
Capillary	70 (6.5%)
Arterial	6 (0.5%)
Total	1065

Table I. Distribution of congenital vascular malformations during 4 years of observation (2011-2015) in our Vascular Malformation Center of Castellanza (Italy).

Venous malformations may also have capillary defects (ie, the so-called port-wine stains) that vary from extensive cutaneous involvement to an almost complete absence of capillary skin defects *(Figure 1)*.

Figure 1. Diffuse cutaneous nevus in a case of Klippel-Trenaunay syndrome.

The combination of venous and lymphatic malformations in the limbs has been defined as the Klippel-Trenaunay syndrome, which comes from the original description by the French authors Maurice Klippel and Paul Trenaunay in 1900. They described cases with a triad of clinical signs on the lower limbs that included dilated superficial veins, nevus, and limb hypertrophy *(Figure 2)*.[7] At that time, no diagnostic instruments were available to recognize the vascular malformations existing in those patients. Some years later, the German dermatologist Frederick Parkes Weber described similar cases that presented with the triad of signs, but also clear signs of arteriovenous malformations.[8,9] With the introduction of angiography, it was possible to recognize that patients with Klippel-Trenaunay syndrome had venous malformations without arteriovenous fistulae, while the cases described by Parkes Weber (also known as Parkes-Weber syndrome) did, which helped distinguish between the two syndromes.

Figure 2. A case where the triad of signs for Klippel-Trenaunay syndrome is present–nevus, limb overgrowth, and dilated superficial veins.

The concept of Klippel-Trenaunay syndrome is still not clearly defined in the literature. Some authors have also used the term Klippel-Trenaunay-Weber syndrome, indicating cases with or without arteriovenous malformations, which increases the confusion between Klippel-Trenaunay syndrome and Parkes-Weber syndrome. Associated lymphatic malformations have been considered, but without a clear definition of the type of lymphatic malformations (truncular or extratruncular). Moreover, vascular malformations located in other parts of the body, such as the head or pelvis, have also been classified as Klippel-Trenaunay syndrome.

An attempt to clarify the concept of Klippel-Trenaunay syndrome has been done with the international consensus about venous malformations, where Klippel-Trenaunay syndrome was defined as a diffuse venous malformation that involved the whole limb and where a combination of two malformations was present (ie, truncular or extratruncular venous or lymphatic malformations), without arteriovenous malformations. Malformations involving only a part of the limb (thigh, calf, or foot) or locations only outside the limbs should not be defined as Klippel-Trenaunay syndrome. Diffuse arteriovenous malformations of a limb should be classified as Parkes-Weber syndrome.[10]

Clinical signs

Klippel-Trenaunay syndrome may manifest in the lower limbs with the clinical triad–dilated abnormal superficial veins, nevus, and limb–length discrepancy due to overgrowth or shortening of the affected limb. However, the nevus may be absent and limb–length discrepancies may not be constant *(Table II)*. Bilateral involvement *(Figure 3)* and deformity by overgrowth of the foot are possible *(Figure 4)*. An abnormal, lateral vein, called a marginal vein, is often present. This vein is valves and may create stasis, pain, and sometimes, a pulmonary embolism.[11] Patients often complain of heaviness, swelling, and pain, which may be localized to specific areas of the limb. Pelvic involvement is possible, including the genitals or the rectum with bleeding.

Figure 3. Bilateral Klippel-Trenaunay syndrome of the lower limbs.

Vascular malformations	Number of cases (%)
Right limb affected	18 (39%)
Left limb affected	18 (39%)
Bilateral disease	10 (22%)
Nevus	42 (91%)
Dilated superficial veins	46 (100%)
Limb overgrowth	18 (39%)
Limb shortening	3 (7%)
No limb length difference	25 (54%)
Foot overgrowth	4 (9%)

Table II. Clinical signs observed in 46 cases of Klippel-Trenaunay syndrome in our Vascular Malformation Center of Castellanza (Italy) from 2011 to 2015.

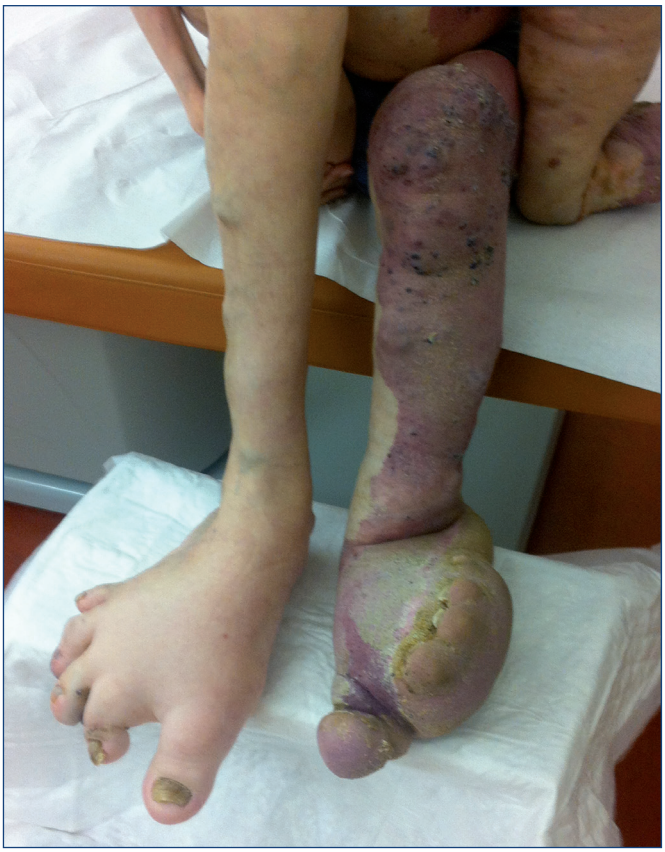

Figure 4. Foot deformity in a case of Klippel-Trenaunay syndrome.

Diagnostic

As Klippel-Trenaunay syndrome often appears as a complex of congenital vascular malformations, diagnosis may be difficult. Often unnecessary tests, such as angiography, were performed, while, in other cases, no examinations were done and the diagnosis was based on a simple clinical evaluation. To correctly diagnose the syndrome, a step-by-step procedure is recommended, beginning with the least invasive procedure, as follows:

- Clinical evaluation
- Comparative radiography of the limbs
- Duplex scan
- MRI with and without contrast
- Lymphoscintigraphy
- Other tests, if necessary

The clinical examination should focus on evaluating the extension of the nevus, recognizing and/or excluding differences in limb length, noticing the presence and extension of dilated superficial veins, and checking for signs of arteriovenous malformations, such as abnormal vascular pulsations (ie, thrills). The clinical signs of Klippel-Trenaunay syndrome vary and may include the classic triad of signs, but these may manifest with different frequencies, and some signs may not be constant. *Table II* shows the clinical signs that we identified in 46 cases of Klippel-Trenaunay syndrome.

Comparative radiography of the limbs is useful to recognize overgrowth or shortening of the affected limb, presence of phlebolythes (a typical sign of venous malformations), and bone structure anomalies *(Figure 5)*. Duplex scanning provides hemodynamic and morphologic data on the congenital vascular malformations. Analyzing the deep and superficial venous systems with duplex scanning may demonstrate anomalies of the deep and superficial veins *(Figure 6)*. Vascular masses situated in tissues should be analyzed to determine the type of flow: low flow indicates venous dysplasia; high flow is typical of arteriovenous malformations; and areas with liquid cysts with no flow (ie, no flow areas) indicate lymphatic extratruncular malformations. Combinations of low flow and no flow vascular areas may coexist *(Figure 7)*. MRI is an excellent diagnostic tool to identify the location and extent of the extratruncular venous and lymphatic malformations, which are often located inside the muscles. Truncular venous malformations have also been well documented *(Figure 8)*. Experience and knowledge of congenital vascular malformations is a requirement for the radiologist in order to acquire high-quality images that are specific for vascular malformations.[12]

Lymphoscintigraphy is necessary to study the lymphatic drainage system because anomalies are common in Klippel-

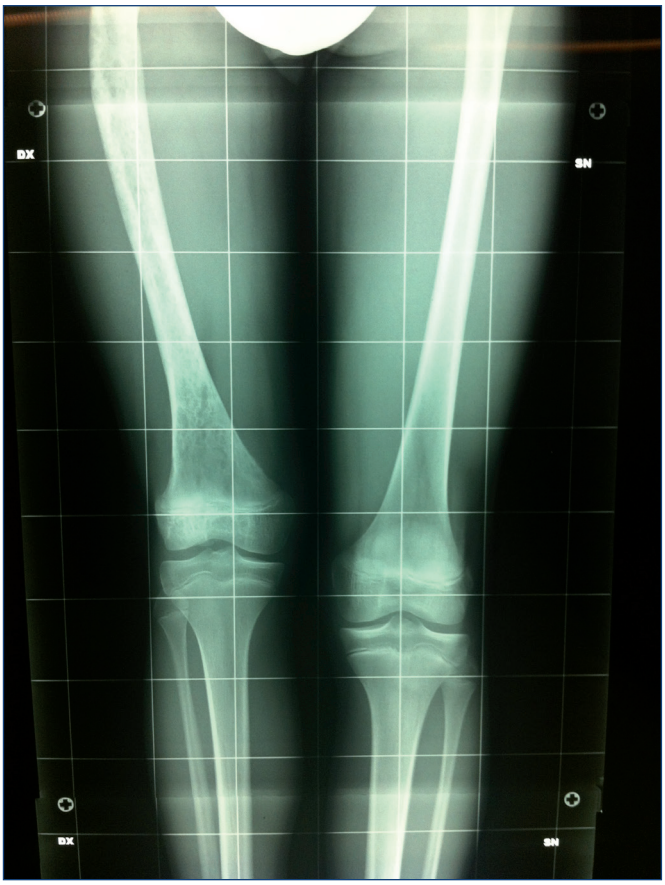

Figure 5. X-ray examination showing a limb–length discrepancy.

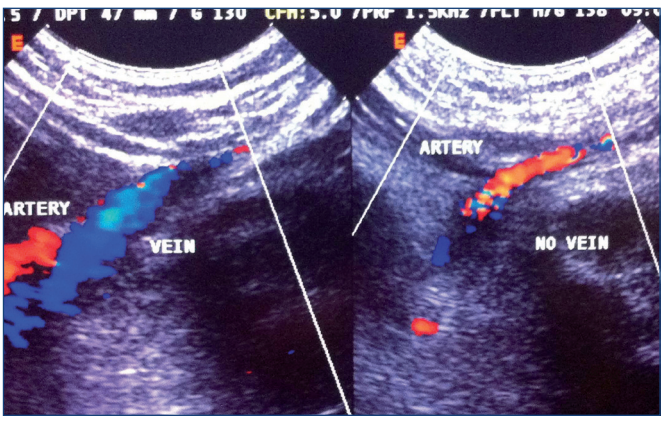

Figure 6. Duplex scan of the popliteal area showing aplasia of the left popliteal vein (right).

Trenaunay syndrome and these cannot be determined using other examinations. A separate study for deep and superficial lymphatic drainage systems is necessary to identify the location and extent of the malformations. Anomalies of the deep lymphatic trunks, such as aplasia or hypoplasia in segments or even the whole vessel, are the most common lymphatic malformations recognized in Klippel-Trenaunay syndrome *(Figure 9)*. However, nuclear

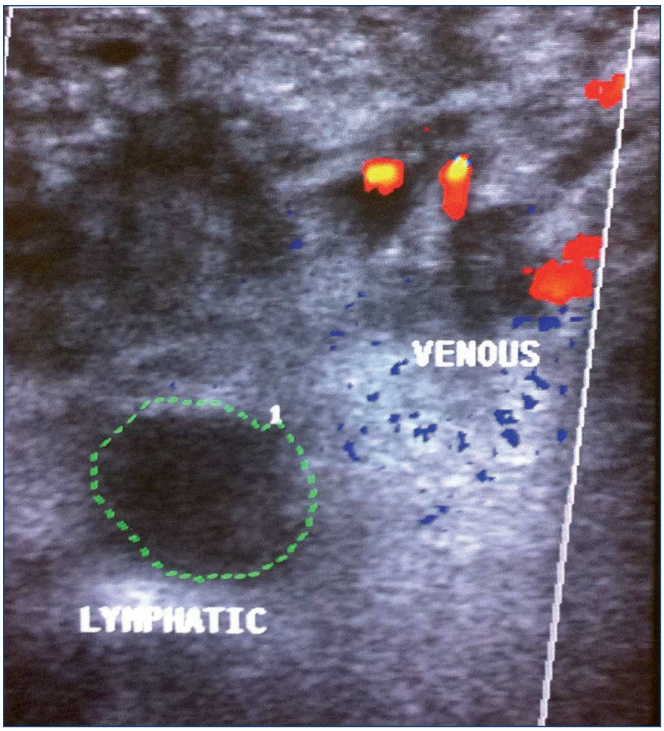

Figure 7. Duplex scan showing the presence of dysplastic intramuscular veins (low flow) and a large lymphatic area (no flow).

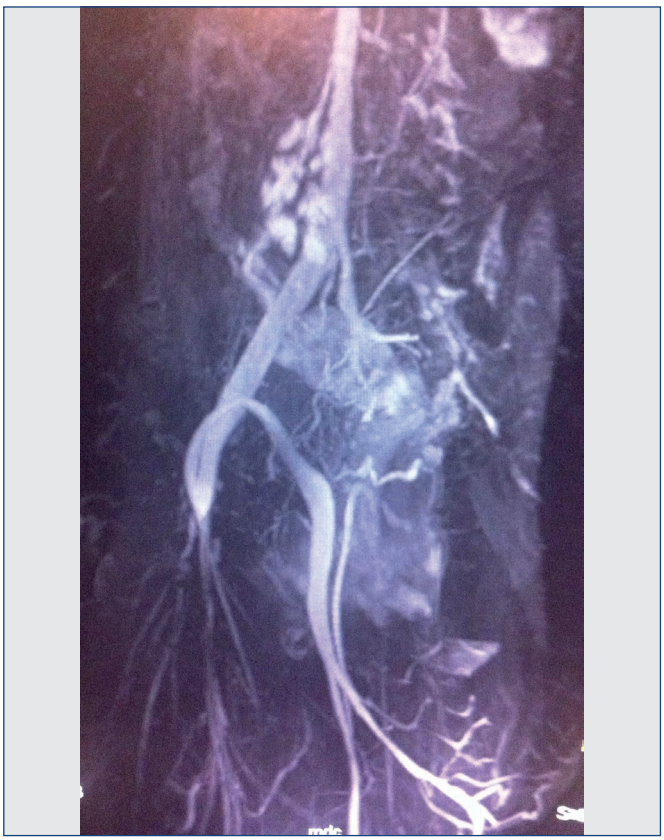

Figure 8. Magnetic resonance angiography demonstrating aplasia of the left iliac vein and spontaneous suprapubic left-right bypass.

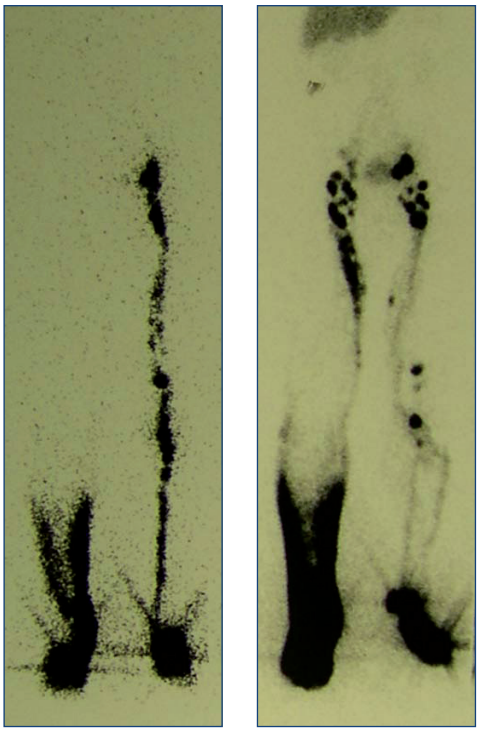

Figure 9. Lymphoscintigraphy of the deep and superficial lymphatic drainage system.

Panel A shows an absence of draining lymphatic vessels (right) and dermal backflow in the deep system. Panel B shows a slow drainage in the superficial system (right).

medicine laboratories usually do not perform this type of study because they are normally requested to analyze total lymph drainage of the limb in patients with lymphedema.[13]

The diagnostic process concludes when a precise definition of the vascular anomalies, according to classification, is possible. The incidences of different types of vascular anomalies discovered in our cases by diagnostic procedures are shown in *Table III*. This table shows that cases can be very different and that a complete diagnosis using the tests described is essential for complete recognition of the anomalies in a single case.

Vascular malformations	Number of cases (%)
Deep vein aplasia	9 (19%)
Deep vein hypoplasia	9 (19%)
Deep infiltrating veins	19 (41%)
Marginal vein	14 (30%)
Sciatic vein	3 (7%)
Superficial dysplastic veins	46 (100%)
Truncular lymphatic malformations	13 (28%)

Table III. Vascular defects observed in 46 cases of Klippel-Trenaunay syndrome in our Vascular Malformation Center of Castellanza (Italy) from 2011 to 2015.

Treatment

Treatment should be planned according to some priorities that include pain; clinical evolution of malformations, such as progression of limb elongation or shortening; risk of complications, such as a pulmonary embolism (ie, in the marginal vein); and esthetic discomfort (the last point to consider). Pain mainly occurs due to repeated thrombosis in venous extratruncular masses where blood stasis often occurs. Venous aneurysms in the femoral or popliteal vein may also cause pain due to blood stasis. Progression of limb elongation is often due to the marginal vein, which creates stasis, and due to a slight arteriovenous malformation located in the dysplastic tissues. Limb shortening is due to extensive venous dysplastic masses pressing on bones, which inhibits their growth. Pulmonary embolisms may originate from both large marginal veins and venous aneurysms.

Available treatment techniques include surgery, sclerotherapy, and laser treatment. Surgery is often the best technique; however, it should be well planned based on a complete recognition of the malformation and the causes of discomfort. Surgical removal of extratruncular masses that cause pain or affect limb growth can considerably improve a patient's condition *(Figure 10)*. In our experience, the best results are obtained with a step-by-step procedure, which avoids extensive single operations that may have complications, such as infection, difficult wound healing, and thrombosis. Marginal veins should be removed surgically in an open procedure; closed stripping should be avoided due to bleeding complications that can arise from the rupture of larger perforators, if present.[11] This procedure is not indicated for deep vein aplasia because, in this case, the marginal vein is the main draining vessel. For deep hypoplasia, the marginal vein can be resected, as deep veins are able to dilate spontaneously to an almost normal size after resection. Endovascular treatment of marginal veins using laser treatment has been reported.[14] Venous aneurysms can be treated by tangential resection and vein reconstruction using a Satinsky clamp, which is our preferred technique, or by resection and substitution with an autologous venous graft.

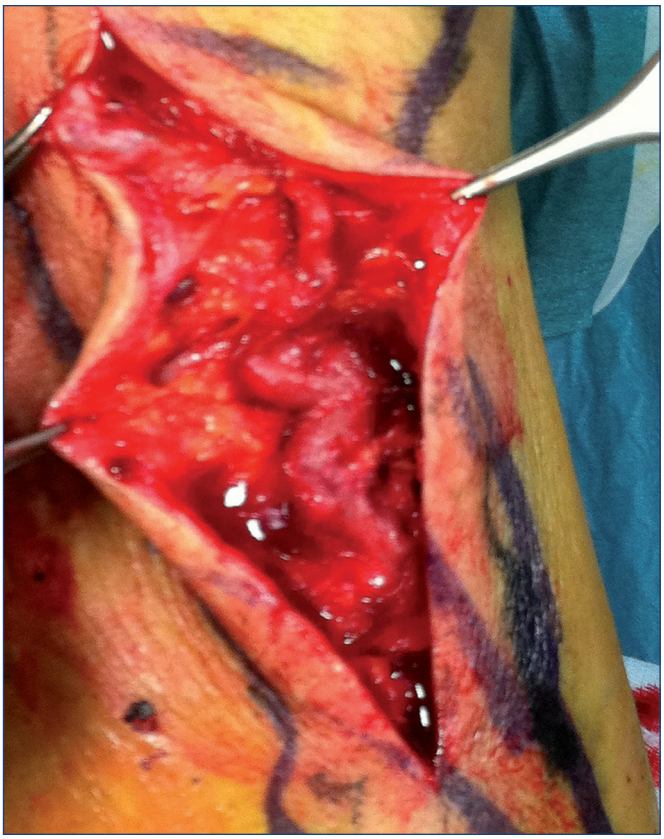

Figure 10. Abnormal superficial veins on the calf that need to be removed.

Sclerotherapy of dysplastic veins is an excellent and less invasive technique. However, classic sclerotherapy with sclerosants for varicose veins (eg, sodium tetradecyl sodium, polidocanol, etc) is less effective for venous malformations than for varicose veins and there is a high incidence of early recurrence. The presence of slight arteriovenous malformations in the dysplastic veins may explain the difference. The introduction of alcohol for sclerotherapy has dramatically improved the results because ethanol is the strongest sclerosant that can almost completely occlude the treated vessels. Ethanol is considered the reference sclerosant for venous malformations.[10] Alcohol is best used for treatment of extratruncular dysplastic venous malformations, whereas truncular malformations are treated better with surgery *(Figure 11)*.

For extratruncular vascular masses, laser treatment using an interstitial technique that positions the laser fiber in the mass can be used to occlude dysplastic vessels. Radial fibers may be useful to increase the effect of treatment. Leaking extratruncular lymphatic malformations with repeated inflammation can be treated successfully using laser treatment. Superficial and deep occlusion of leaky points is effective to treat inflammation, which occurs due to

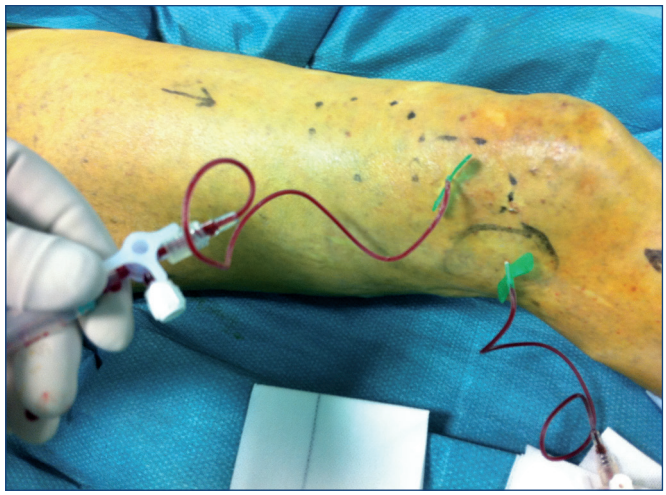

Figure 11. Alcohol is injected directly into the malformation and outflow is controlled using a contrast injection, which is administered before the alcohol.

an infection that enters through the leaky points. Superficial laser treatment of the nevus may have an esthetic goal, but this option should only be used after other, more severe, disturbances have been treated. Simple superficial laser treatments have no effect on deep malformations that result in severe symptoms. Treatment is often performed in stages by combining the three treatment modalities *(Figure 12)*.

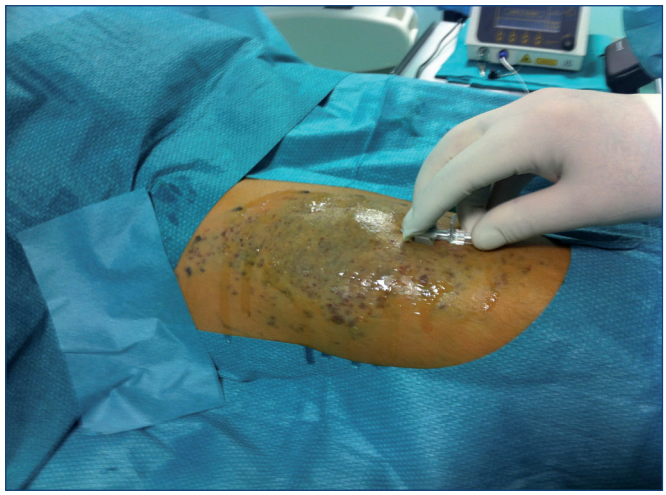

Figure 12. Interstitial laser treatment.

Orthopedic techniques are effective if limb–length discrepancies develop.[15] During childhood, epiphysiodesis is effective to temporarily block limb growth. The expected growth phase should be accurately predicted to determine when to implant the elongation device. In adults and after growth has stopped, limb elongation of the contralateral extremity is possible using the Ilizarov technique. Osteotomy to shorten the affected limb is performed less frequently.

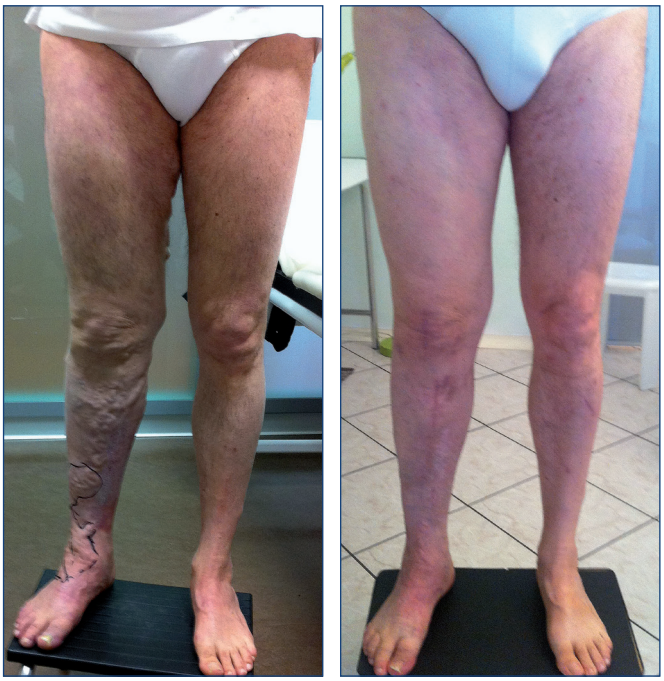

Figure 13. Results of surgical and alcohol treatment for Klippel-Trenaunay syndrome.

Diagnosis demonstrates abnormal, diffuse, superficial veins; hypoplasia of the superficial femoral vein; and deep lymphatic dysplasia. Panel A. Before treatment. Panel B. After treatment.

Limb shortening due to venous masses blocking limb growth is the least common condition, which requires occlusion or removal of the dysplastic veins. Correction of a short limb in adults is more complex as limb elongation may be dangerous due to bone fragility and the risk of fracture after removing the elongation device.

Conclusion

Klippel-Trenaunay syndrome is a complex congenital disease that has been defined in the past (and often even today) as an untreatable disease. That concept is not true today. Several treatment possibilities are available that can significantly improve the patient's condition *(Figure 13)*. However, the main condition for a successful treatment is to know what Klippel-Trenaunay syndrome is, to identify the vascular malformations that are present, and to perform a complete diagnosis. Moreover, treatment can be successful only if selected and performed by a team that has knowledge, experience, and the availability of the three treatment techniques: surgery, alcohol sclerotherapy, and laser. A correct treatment section can only be made if the three methods are available. In certain cases, the surgical team only knows how to perform one or two of the treatment options and they will choose these even if the third option is the best. "If the only tool you have is a hammer, you will treat everything as if it were a nail" – the law of the instrument of Abraham Maslow.[16]

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