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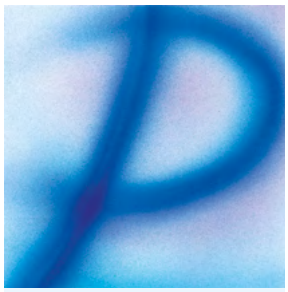

Phlebolymphology

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Aims and Scope

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

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

Phlebolymphology is scientifically supported by a prestigious editorial board.

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

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

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Editorial

Dear Readers,

In this new issue of Phlebolymphology, you will find the articles as below:

S. G. Gavrilov (Russia) *presents up-to-date data on the pathophysiology, epidemiology, classification, diagnosis, and treatment of the combination of May-Thurner syndrome and pelvic congestion syndrome.*

M. Josnin (France) *addresses venous thromboembolic risk after varicose vein procedures and provides an overview of the different interventional treatments for varicose veins and the recommendations, as well as the disparities, in practice.*

O. Maleti (Italy), F. Lurie (USA), G. Bergamo (Italy), S. Guerzoni (Italy), *and* ***M. Lugli (Italy)*** *present hemodynamics of the venous system of the lower limbs from a conversational angle to encourage further interest and pursuit of deeper understandings on the subject.*

N. Neaume (France) *discusses the management of venous ulceration with a particular focus on interventional treatments with perspectives from a recent meta-analysis and recommendations.*

O. Porembskaya (Russia) *elaborates on the literature review of microcirculatory disorders underlying the development of chronic venous diseases and also discusses the fundamentals of their systemic pharmacological correction, focusing on the effects of micronized purified flavonoid fraction.*

Enjoy reading this issue!
Editorial Manager
Dr. H. Pelin Yaltirik

Editorial

Chronic venous disease management: Thematic index of randomized controlled trials

Michel PERRIN, MD

Vascular Surgery; Editor in Chief of Phlebolymphology

There is currently no available index on chronic venous disease (CVD) management allowing the quick and easy identification of pertinent randomized controlled trials. Furthermore, it can be difficult to determine from article titles what precise treatment–whether interventional or not–and diagnosis tool were used in the studies, which can be problematic. To address this issue, we developed an index of treatment procedures and diagnosis methods as explained below (and in a simplified version in Table I). There are currently 11 chronic venous disease management headings, as follows:

1. Varicose vein interventional treatment

14 procedures are listed for varicose vein treatment.

All of them, except 1-9, have 2 subheadings specifying if the procedure is compared with another one or is a variant of the procedure.

Heading 1-9 is devoted to varices recurrence or more precisely to presence of varices after interventional treatment (PREVAIT) that include recurrence, varices not treated, and disease evolution when this data is available in the randomized controlled trial (RCT).

Examples:

Rasmussen LH et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous veins. *Br J Surg.* 2011;98:1079-1087. ***Management classification: 1-1-1, 1-5-1, 1-10-1, 1-11-1.***

Morrison N et al. Five-year extension study of patients from a randomized clinical trial (VeClose) comparing cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord.* 2020;8(6):978-989. ***Management classification: 1-3-1, 1-9, 1-10-1.***

Vuylsteke M et al. Endovenous laser treatment: is there a difference between using a 1500 nm and a 980 nm diode laser. A multicenter randomized clinical trial. *Int Angiol.* 2011;30(4):327-334. ***Management classification: 1-5-2.***

Nyamekye IK et al. A randomised controlled trial comparing three different radiofrequency technologies: short-term results of the 3-RF Trial. *Eur J Vasc Endovasc Surg.* 2019;58:401-408. ***Management classification: 1-10-2.***

2. Telangiectasia and reticular vein interventional treatment

Example:

McCoy S et al. Sclerotherapy for leg telangiectasia–a blinded comparative trial of polidocanol and hypertonic saline. *Dermatol Surg.* 1999;25:381-386. ***Management classification: 2.***

3. Perforator interventional treatment

This heading groups all the RCTs dealing with perforator ablation, either comparing perforator ablation procedures or varices ablation with or without complementary perforator division.

Examples:

Pierik EG et al. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: a randomized trial. *J Vasc Surg.* 1997;26:1049-1054. ***Management classification: 3.***

Kianifard B et al. Randomized clinical trial of the effect of adding subfascial endoscopic perforator surgery to standard great saphenous vein stripping. *Br J Surg.* 2007;94:1075-1080. ***Management classification: 1-1-2, 1-9, 3.***

4. Venous ulcer treatment

This heading has 4 subheadings.

4-1 Venous ulcer and medical compression.

Example:

Marston WA et al. Economic benefit of a novel dual-mode ambulatory compression device for treatment of chronic venous leg ulcers in a randomized clinical trial. *J Vasc Surg Venous Lymphat Disord.* 2020;8:1031-1040. ***Management classification: 4-1, 6-2.***

4-2 Venous ulcer and varicose vein interventional treatment

Example:

Campos W Jr et al. A prospective randomised study comparing polidocanol foam sclerotherapy with surgical treatment of patients with primary chronic venous insufficiency and ulcer. *Ann Vasc Surg.* 2015;29(6):1128-1135. ***Management classification: 1-1-1, 1-11-1, 4-2.***

4-3 Venous ulcer. Varicose vein interventional treatment combined with compression in venous ulcer

Example:

Gohel MS et al. Randomized clinical trial of compression plus surgery versus compression alone in chronic venous ulceration (ESCHAR study)- haemodynamic and anatomical changes. *Br J Surg.* 2005;92:291-297. ***Management classification: 1-1-1, 4-3.***

4-4 Venous ulcer and physical exercise

Example:

Jonker L et al. A multi-centre, prospective, randomised controlled feasibility study of plantar resistance exercise therapy for venous leg ulcers – results of the PREVUE study. *Phlebology.* 2020;35:237-246. ***Management classification: 4-4, 11.***

5. Deep venous reconstructive surgery

This heading has 2 subheadings.

5-1 For reflux

Example:

Wang SM et al. Effect of external valvuloplasty of the deep vein in the treatment of chronic venous insufficiency of the lower extremity. *J Vasc Surg.* 2006;44:1296-1300. ***Management classification: 5-1.***

5-2 For obstruction

Example:

Rossi FH et al. Randomized double-blinded study comparing medical treatment versus iliac vein stenting in chronic venous disease. *J Vasc Surg Venous Lymphat Disord.* 2018;6:183-191. ***Management classification: 5-2.***

6. Medical compression in CVD

This heading has 4 subheadings.

6-1 Medical compression. Interventional treatment combined with compression in varicose vein management

Examples:

Ayo D et al. Compression versus no compression after Endovenous Ablation of the Great Saphenous Vein: a randomized controlled trial. *Ann Vasc Surg.* 2017;38:72-77. ***Management classification: 1-5-2, 6-1.***

Onwudike M et al. Role of Compression After Radiofrequency Ablation of Varicose Veins: a randomised controlled trial. *Eur J Vasc Endovasc Surg.* 2020;60:108-117. ***Management classification: 1-10-2, 6-1.***

6-2 Medical compression variants

Examples:

Cavezzi A et al. Compression with 23 mmHg or 35 mmHg stockings after saphenous catheter foam sclerotherapy and phlebectomy of varicose veins: a randomized controlled study. *Phlebology.* 2019;34:98-106. ***Management classification: 1-11-2, 6-1, 6-2.***

Riebe H et al. Advantages and disadvantages of graduated and inverse graduated compression hosiery in patients with chronic venous insufficiency and healthy volunteers: a prospective, mono-centric, blinded, open randomized, controlled and cross-over trial. *Phlebology.* 2018;33(1):14-26. ***Management classification: 6-2, 6-3.***

6-3 Medical compression in noninterventional treatment

Example:

Gillet JL et al. Clinical superiority of an innovative two-component compression system versus four-component compression system in treatment of active venous leg ulcers: a randomized trial. *Phlebology.* 2019;34:611-620. ***Management classification: 4-1, 6-2.***

6-4 Medical compression vs interventional treatment

Example:

Barwell JR et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet.* 2005;363:1854-1859. ***Management classification of CV: 1-1-1, 4-3.***

7. Venoactive drugs (VADs) in CVDs

This heading has 2 subheadings.

7-1 VAD and interventional treatment

Example:

Saveljev VS et al. Stripping of the great saphenous vein under micronized purified flavonoid fraction (MPFF) protection (results of the Russian multicenter controlled trial DEFANCE). *Phlebolymphology.* 2008;15:45-51. ***Management classification: 1-1-2, 7-1.***

7-2 VAD in CVDs

Example:

Carpentier P et al. Clinical efficacy and safety of a new 1000-mg suspension versus twice-daily 500-mg tablets of MPFF in patients with symptomatic chronic venous disorders: a randomized controlled trial. *Int Angiol.* 2017;36(5):402-409. ***Management classification: 7-2.***

8. Venous malformations

Example:

Yamaki T et al. Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. *J Vasc Surg.* 2008;47:578-584. ***Management classification: 8.***

9. Investigations in CVD

Examples:

Blomgren LG et al. Late follow-up of a randomized trial of routine duplex imaging before varicose vein surgery. *Br J Surg.* 2011;98:1112-1116. **Management classification: 1-1-2, 9.**

Aherne TH et al. Does longitudinal or transverse orientation of the ultrasound probe improve cannulation success in minimally invasive venous surgery: a multicentre randomised controlled trial. *Phlebology.* 2020;35:686-692. ***Management classification: 9.***

10. Neuromuscular stimulation in CVD

Example:

Ravikumar R et al. A randomised controlled trial of neuromuscular stimulation in nonoperative venous disease improves clinical and symptomatic status. *Phlebology.* 2021;36:290-312. ***Management classification: 10.***

11. Physical exercise and rehabilitation

Example:

Jonker L et al. A multi-centre, prospective, randomised controlled feasibility study of plantar resistance exercise therapy for venous leg ulcers – results of the PREVUE study. *Phlebology.* 2020;35:237-246. ***Management classification: 11.***

In this classification, one or several numbers are attributed to each article; those numbers are added to the usual reference. To illustrate, all headings are listed as in Table 1 and Table 2 below. Many articles of RCTs have been attributed several numbers for CVD management classification in order to facilitate identification according to topic. This CVD management list is open to modification and can be supplemented with new treatments or investigations evaluated by RCT.

Chronic venous disease management headings

Heading No.	Headings	Examples	Management classification
1	**Varicose vein interventional treatment** 14 procedures are listed for varicose vein treatment. All of them, except 1-9, have 2 subheadings specifying if the procedure is compared with another one or is a variant of the procedure. Heading 1-9 is devoted to varices recurrence or more precisely to presence of varices after interventional treatment (PREVAIT) that include recurrence, varices not treated, and disease evolution when this data is available in the RCT.	Rasmussen et al,[1] 2011 Morrison et al,[2] 2020 Vuylsteke et al,[3] 2011 Nyamekye et al,[4] 2019	**1-1-1, 1-5-1, 1-10-1, 1-11-1** **1-3-1, 1-9, 1-10-1** **1-5-2** **1-10-2**
2	**Telangiectasia and reticular vein interventional treatment**	McCoy et al, [5] 1999	**2**
3	**Perforator interventional treatment** This heading groups all the RCTs dealing with perforator ablation, either comparing perforator ablation procedures or varices ablation with or without complementary perforator division.	Pierik et al,[6] 1997 Kianifard et al,[7] 2007	**3** **1-1-2, 1-9, 3**

Chronic venous disease management headings			
4	**Venous ulcer treatment** (4 subheadings)		
	4-1 Venous ulcer and medical compression	Marston et al,[8] 2020	**4-1, 6-2**
	4-2 Venous ulcer. Varicose vein interventional treatment combined with compression in venous ulcer	Campos Jr et al,[9] 2015	**1-1-1, 1-11-1, 4-2**
	4-3 Venous ulcer; Interventional treatment vs compression	Gohel et al,[10] 2005	**1-1-1, 4-3**
	4-4 Venous ulcer and physical exercise	Jonker et al,[11] 2020	**4-4, 11**
5	**Deep venous reconstructive surgery** (2 subheadings)		
	5-1 For reflux	Wang et al,[12] 2006	**5-1**
	5-2 For obstruction	Rossi et al,[13] 2018	**5-2**
6	**Medical compression in CVD** (4 subheadings)		
	6-1 Medical compression. Interventional treatment combined with compression in varicose vein management	Ayo et al,[14] 2017	**1-5-2, 6-1**
	6-2 Medical compression variants	Onwudike et al,[15] 2020	**1-10-2, 6-1**
		Cavezzi et al,[16] 2019	**1-11-2, 6-1, 6-2**
	6-3 Medical compression in noninterventional treatment	Riebe et al,[17] 2018	**6-2, 6-3**
	6-4 Medical compression vs interventional treatment	Gillet et al,[18] 2019	**4-1, 6-2**
		Barwell et al,[19] 2005	**1-1-1, 4-3**
7	**VAD in CVDs** (2 subheadings)		
	7-1 VAD and interventional treatment	Saveljev et al,[20] 2008	**1-1-2, 7-1**
	7-2 VAD in chronic venous disorders	Carpentier et al,[21] 2017	**7-2**
8	**Venous malformations**	Yamaki et al,[22] 2008	**8**
9	**Investigations in CVD**	Blomgren et al,[23] 2011	**1-1-2, 9**
		Aherne et al,[24] 2020	**9**
10	**Neuromuscular stimulation in CVD**	Ravikumar et al,[25] 2021	**10**
11	**Physical exercise and rehabilitation**	Jonker et al,[11] 2020	**11**
CVD, chronic venous disorder; RCT, randomized controlled trial; VAD, venoactive drug.			

Table I. Chronic venous disease management headings

THEMATIC INDEX of CHRONIC VENOUS DISEASE MANAGEMENT
1. VARICOSE VEIN INTERVENTIONAL TREATMENT 1-1 Open surgery. Classical open surgery (high ligation, saphenous stripping, +/-tributary avulsion, +/- perforator avulsion) or tributary phlebectomy 1-1-1 Versus other procedures 1-1-2 Variants 1-2 Cryostripping 1-2-1 Versus other procedures 1-3 Cyanoacrylate ablation 1-3-1 Versus other procedures 1-4 Electrocoagulation 1-4-1 Versus other procedures 1-5 Endovenous laser ablation 1-5-1 Versus other procedures 1-5-2 Variants 1-6 Mechanochemical ablation 1-6-1 Versus other procedures 1-6-2 Variants 1-7 Microwave ablation 1-7-1 Versus other procedures 1-8 Open surgery with saphenous preservation 1-8-1 Versus other procedures 1-9 PREVAIT/REVAS presence, prevention and treatment 1-10 Radiofrequency ablation 1-10-1 Versus other procedures 1-10-2 Variants 1-11 Sclerotherapy ablation including UGFS 1-11-1 Versus other procedures 1-11-2 Variants 1-12 Steam Ablation 1-12-1 Versus other procedures 1-13 Tributary ablation 1-13-1 Versus other procedures 1-13-2 Variants
2. TELANGIECTASIA and RETICULAR VEIN INTERVENTIONAL TREATMENT 2-1 Different procedures
3. PERFORATOR INTERVENTIONAL TREATMENT
4. VENOUS ULCER TREATMENT 4-1 Venous ulcer and medical compression. 4-2 Venous ulcer. W interventional treatment combined with compression in venous ulcer 4-3 Venous ulcer. Interventional treatment vs compression 4-4 Venous ulcer and physical exercise
5. DEEP VENOUS RECONSTRUCTIVE SURGERY 5-1 For reflux 5-2 For obstruction
6. MEDICAL COMPRESSION in CHRONIC VENOUS DISEASE 6-1 Medical compression. Interventional treatment combined with compression in VV management 6-2 Medical compression variants 6-3 Medical compression in non-interventional treatment 6-4 Medical compression vs interventional treatment
7. VENOACTIVE DRUG (VAD) in CHRONIC VENOUS DISORDERS 7-1 VAD and interventional treatment 7-2 VAD and chronic venous disorders
8. VENOUS MALFORMATIONS
9. INVESTIGATIONS in CVD
10. NEURO MUSCULAR STIMULATION in CVD
11. PHYSICAL EXERCISE and REHABILITATION

Table 2. List of topics in the Thematic index of RCTs
PREVAIT/REVAS, presence of varices after interventional treatment / recurrent varices after surgery; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein

Conclusion

More than 300 RCTs on CVD have been published in the last 30 years. In order to facilitate identification of the topic of a particular RCT, a modifiable index of CVD management, including treatment and diagnosis, has been created.

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Combination of May-Thurner syndrome and pelvic congestion syndrome: *terra incognita*

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Keywords:

diagnosis; gonadal vein embolization; iliac vein stenting; May-Thurner syndrome; pelvic congestion syndrome.

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Abstract

This review presents up-to-date data on the pathophysiology, epidemiology, classification, diagnosis, and treatment of the combination of May-Thurner syndrome (MTS) and pelvic congestion syndrome (PCS). It includes hypotheses to explain the predominant lesion of the pelvic veins in these patients and describes in detail the clinical symptoms of combined lesions of the iliac and pelvic veins. The article discusses modern methods of diagnosis of MTS and PCS, as well as advantages and disadvantages of ultrasound and radiological methods of investigation. It goes further to discuss the issues of choosing a method of treatment for combination of MTS and PCS and highlights the optimal sequence of using endovascular methods of treatment. It presents current data on the efficacy of iliac vein stenting in relieving PCS symptoms and discusses rational use of endovascular treatment methods to avoid unnecessary interventions on the gonadal veins. Altogether, these data indicate the lack of our knowledge both in regard to pathogenesis of the MTS and PCS combination and in determining the optimal set of diagnostic tests for verifying the diagnosis and choosing a treatment method. Multicenter randomized trials are needed to address many of the controversial issues in the diagnosis and treatment of MTS and PCS.

Introduction

Pelvic congestion syndrome (PCS) and May-Thurner syndrome (MTS) are two nosologies that have long been considered separately from each other. This is understandable because PCS is the common cause of chronic pelvic pain (CPP)[1-3] and MTS is a factor in the development of deep-vein thrombosis (DVT), venous claudication, and edema of the left lower extremity.[4,5] The situation changed within the last decade with the publication of studies[6-8] reporting case series of the combination of PCS and MTS; at that time, the main clinical end point was pelvic pain, not the symptoms of chronic venous disease (CVD) or venous thrombosis. The paradigm shift was reflected both in the updated Clinical, Etiology, Anatomic, Pathophysiology (CEAP) classification[9] and in changes in terminology, as well as in the direction of research.[10,11] The authors proposed use of the umbrella term "pelvic venous disorder" (PeVD) to describe various disorders of the pelvic veins (PCS, MTS, nutcracker syndrome, and ovarian vein syndrome). Despite a significant number of studies on the diagnosis and treatment

of MTS and PCS, more and more questions arise about the optimal method for assessing the degree of stenosis of the left common iliac vein (CIV) and the approaches to treatment of patients with a combination of MTS and PCS. This article aims to provide an overview of current trends in the diagnosis and treatment of the combination of MTS and PCS.

Epidemiology

The reported prevalence of MTS varies widely from 4% to 60% depending on the degree of CIV stenosis and the size of the studied population.[12,13] In the study of Kibbe et al, a narrowing of the left CIV of greater than 50% was identified in 24% of patients, and stenosis greater than 25% was diagnosed in 66% of the examined asymptomatic patients.[14] Liu et al reported the presence of MTS in 11% of symptomatic patients.[15] PCS is diagnosed in 15% of women of reproductive age and in 30% of women seeking medical help from a gynecologist for CPP.[16] According to different authors, one in every 10 women has a dilation of the gonadal veins (GV), and 60% of them eventually develop PCS.[17,18]

However, the real prevalence of the MTS and PCS combination is difficult to determine, as the screening for pelvic venous disease in a large population requires reliable imaging techniques. Pelvic vein dilation or left CIV stenosis does not necessarily indicate the presence of PCS or CVD.[19,20] As such, the prevalence of combined MTS and PCS is mostly reported for certain groups of patients, most often with CPP or DVT. Thus, in a study of 277 patients with pelvic venous insufficiency, Santoshi et al reported an 80% prevalence of CIV stenosis greater than 50%.[8] According to data from our clinic, the prevalence of combined MTS and PCS in patients with CPP is 23%, and 8% of patients have a left CIV stenosis greater than 50% as assessed by multiplanar pelvic venography (MPPV).[21]

Pathophysiology

The morphological substrate of MTS is the narrowing of the left CIV lumen due to its pulsatile compression between the overlying right iliac artery and the fifth lumbar vertebrae. To date, it is unclear why some patients with MTS present with CVD symptoms and signs while others develop PCS. Probably, in patients with MTS, the lesion of the left internal iliac veins (IIV), parametrial veins (PV), uterine veins (UV - uterine veins), and GV is one of the variants of the disease course, which is genetically determined (*Figure 1*). It can be speculated that, in such patients, the valves in IIV, PV, GV are absent or underdeveloped, and with worsening stenosis, blood reflux initially occurs in the left IIV and triggers a cascade of abnormalities in other veins.

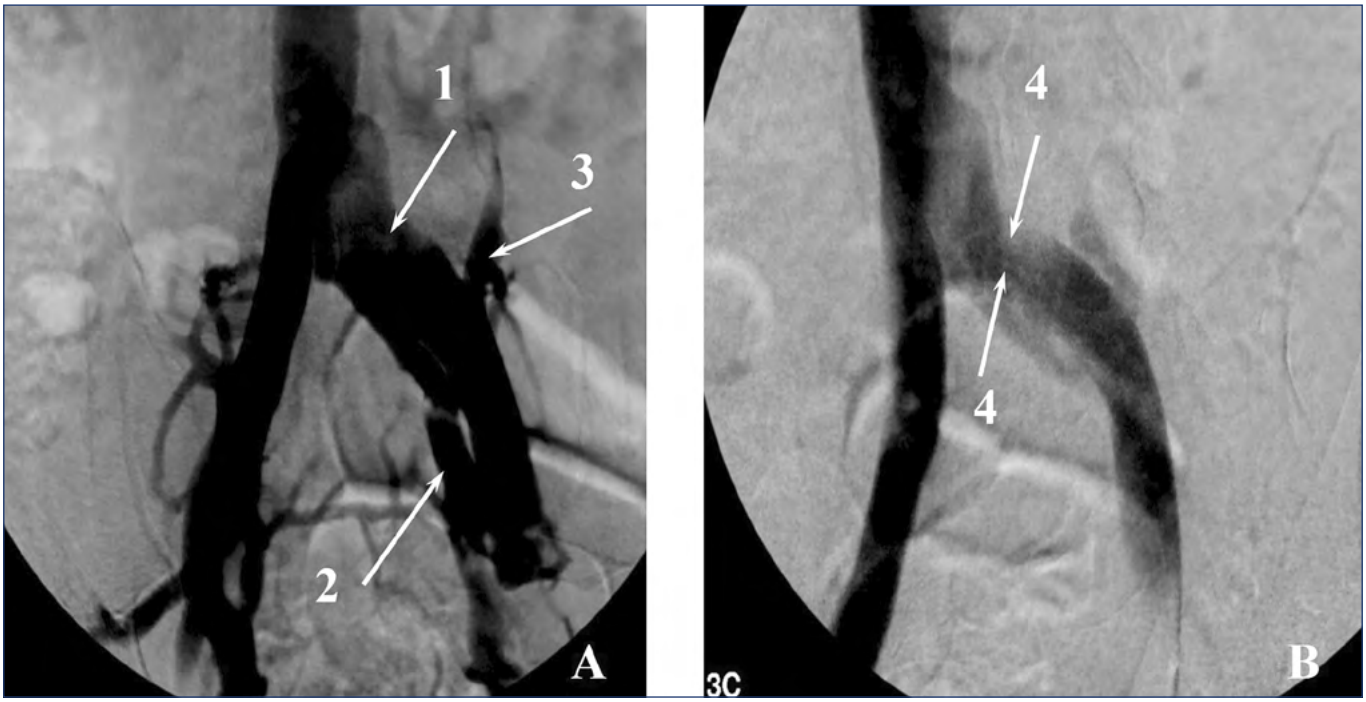

Figure 1. Pelvic venography. (A) Direct projection. (B) Lateral projection. 1, dilated left common iliac vein; 2, dilated left internal iliac vein; 3, reflux of contrast media in the left iliolumbar vein; 4, compression of the left common iliac vein by the right common iliac artery.

Nevertheless, MTS is an obvious morphological substrate for the development of pelvic varicose veins and occurrence of reflux and venous congestion in the pelvic organs. Disruption of normal blood flow in the left CIV is accompanied by active collateralization of venous outflow from the pelvis. This is manifested by the left IIV dilation and occurrence of reflux in its trunk and tributaries, PV, UV, and in the left iliolumbar vein. GV, same as collaterals, are probably affected at the late stage, as dilation of these veins and reflux in them are caused by an increase in hemodynamic load and in the volume of blood flowing through these thin-walled vessels, which are not adapted to such intense blood flow. As a result, the dilation of PV and reflux in these veins lead to the development of PCS. Combined lesions of the pelvic and lower-extremity veins can be a variant of MTS. In such patients, the clinical picture also includes symptoms and signs of CVD.

Classification

The symptomatic and asymptomatic course of MTS is distinguishable, which largely determines treatment strategy. Conventionally, left CIV stenosis is considered hemodynamically significant or insignificant if a reduction in lumen diameter is greater or lesser than 50%, respectively.[8,12] Significant CIV stenosis requires intervention, whereas insignificant CIV does not affect blood outflow from the pelvis and lower extremities. Patients with a combination of MTS and PCS should be classified using the updated revision of the CEAP classification.[9] Although the clinical part of that classification section does not include symptoms and signs of PCS, the other three parts are quite applicable for such patients. Meissner et al proposed a new classification of pelvic venous disorders (PeVDs),[11] which includes the following three domains: Symptoms (S), Varices (V), and Pathophysiology (P), with the pathophysiology domain encompassing the Anatomic (A), Hemodynamic (H), and Etiologic (E) features of the patient's disease. An individual patient's classification is designated as SVP A, H, E. For patients with pelvic origin of the lower-extremity signs or symptoms, the SVP classification is complementary to and should be used in conjunction with CEAP classification. Indeed, the development of the SVP classification is an important step forward in the implementation of new terminology and stratification of patients with PeVD. Whereas it is the first that is focused on pelvic venous insufficiency; it does contain controversial statements and generalizations that require further clarification. It is appropriate here to recall the well-known quote from Albert Einstein: "Everything should be made as simple as possible, but no simpler." Nevertheless, it should be recognized that the foundation for further research has been laid and clinicians now have something to work on.

Clinical manifestations

Regarding clinical manifestations, it's better to start not with the description of venous-specific symptoms and signs, but with a presentation of the general status of patients with a combination of MTS and PCS. Typically, they are young women aged 25 to 40 years who have given birth several times, who have a low body mass, bad mood, and are presenting numerous emotional complaints. Exaggerating, I would designate three signs of such a woman: young, thin, and angry (or emotionally labile). This is supported by studies that indicate that patients with PCS have a reduced body mass index.[22] Behavioral changes are understandable, as long-term pelvic pain affects the personality.[23]

Patients with a combination of MTS and PCS most often have symptoms and signs of venous congestion of the pelvic organs, such as pelvic pain, feeling of heaviness or discomfort in the hypogastric region, coital and postcoital pain, urination disorders, vulvar varicose veins, and varicose veins on the posterior surface of the thigh.[24,25] Pelvic venous pain (PVP) is typically described as a constant, dull, and aching pain localized in the hypogastric, left or right iliac regions, which increases in the second phase of the menstrual cycle, after static load or physical exertion, and with intake of gestagenic drugs, and decreases when the patient is in the horizontal position, after a night's rest, and with use of venoactive drugs. The PVP is characterized most often as a dull and aching feeling; however, a number of patients describe pain as stabbing, burning, or cramping.[26-28] PVP is noncyclic pain lasting more than 6 months and arising with dilation of the pelvic veins, which is localized in the lesser pelvis. It worsens the patient's quality of life and requires medical or surgical treatment.

A feature of dyspareunia in PCS is the persistence of pain after intercourse for a period of time lasting from 15 minutes to a day.[29] The superficial dyspareunia, which occurs in patients with vulvar varicose veins, is distinguished from deep dyspareunia characteristic of venous congestion of the uterus. The presence of deep dyspareunia is an unfavorable prognostic sign indicating significant pelvic venous congestion.[26,29,30] Vulvar (gluteal, perineal) varicose veins and varicose veins of the posterior surface of the thigh are pathognomonic signs of pelvic vein abnormalities (*Figure 2*).

It is notable that a number of patients with a combination of MTS and PCS have symptoms and signs of CVD, including leg pain, edema, telangiectasias, and varicose veins of the lower limbs.[31] One of the signs of iliocaval obstruction

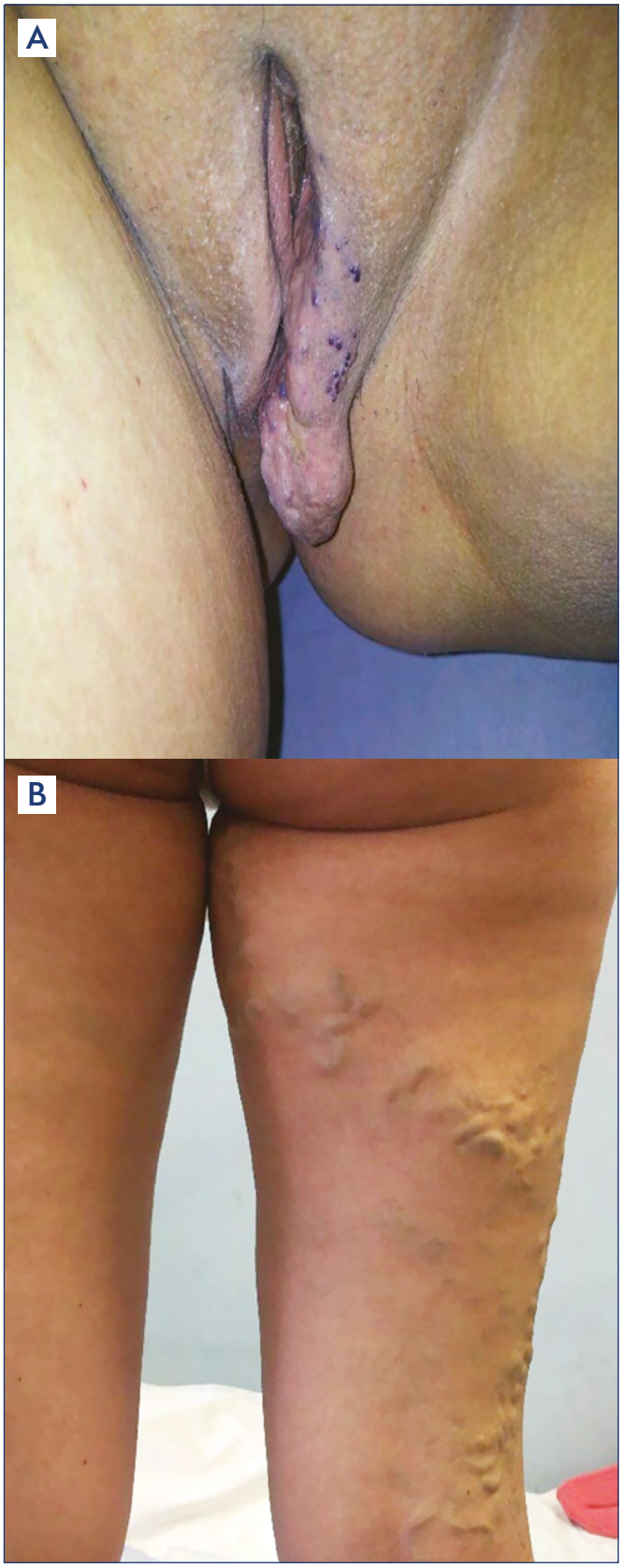

Figure 2. Photos of patients with (A) vulvar varicosities and (B) varicose veins on the posterior surface of the thigh at the confluence with the pelvic veins.

is venous claudication.[32] Thors et al revealed symptoms and signs of CVD in 75% of patients with PCS, and 6% of them had MTS.[33] Left CIV stenosis is also considered one of the factors in the development of DVT. In a study by Larkin et al, iliac vein obstruction was considered more important in the development of CPP than valvular incompetence of GV.[34] Although the authors point to a high prevalence of CVD symptoms and signs, it should be understood that they are related to post-thrombotic syndrome and not MTS. This emphasizes the significance of differentiation between thrombotic and nonthrombotic obstructions of the left CIV, as clinical manifestations and treatment approach in such patients are cardinally different. Esposito et al presented an analysis of 27 publications focused on MTS, but for some reason there is not a single mention of MTS as the reason for the development of PCS.[35]

Based on experience from our clinic, where, annually, we treat more than 5000 patients with various venous disorders, it can be argued that symptoms and signs of CVD in patients with a combination of MTS and PCS are rare and in 80% of cases are limited to CEAP class C1.[21]

Other clinical manifestations of the combination of MTS and PCS include urination disorders characterized by frequent urge to urinate.[26] This is due to the venous congestion of the bladder wall. Women with MTS and PCS often report various irregularities in the menstrual cycle, including irregular heavy and prolonged periods. Venbrux et al have demonstrated the absence of the effect of GV embolization (GVE) on the menstrual cycle in such patients.[36] Dysmenorrhea is likely due more to hormonal disorders than PeVD.

Thus, the clinical manifestations of the combination of MTS and PCS are highly variable and nonspecific. Perhaps only vulvar varicose veins can be used as a pathognomonic sign of such combined lesions. Additional diagnostic tests are required for the timely and precise diagnosis of this combined pathology.

Diagnosis

Detection and assessment of pelvic veins is impossible without the use of ultrasound and radiological techniques. This is determined by the deep location of pelvic veins, the nonspecific clinical picture, and the need to obtain accurate information about the diameters of the pelvic, iliac, and renal veins and to establish the presence and duration of pelvic venous reflux in numerous pelvic veins. This is especially true for patients with a combination of MTS and PCS because the

disorders of pelvic vein hemodynamics are the most complex in this category of patients.

Duplex ultrasound scanning (DUS)

Duplex ultrasound scanning (DUS) of the pelvic veins is considered the gold standard method for the diagnosis of pelvic varicose veins.[37,38] With DUS it is possible to measure diameters of pelvic (parametrial, uterine, gonadal) veins, establish the presence of reflux and its duration, as well as objectively assess the state of the left renal vein (nutcracker syndrome) and the patency and diameters of the iliac veins.[39] Other advantages of DUS include its noninvasiveness, the reproducibility of results, and the absence of radiation exposure. Disadvantages include operator dependence and the need for bowel preparation and following of a diet before the examination for better imaging of the pelvic veins. Whiteley et al report a high informative value of DUS in detecting pelvic-perineal reflux (PPR) and valvular incompetence of the internal pudendal, obturator, and inferior gluteal veins.[37] Our experience with DUS in patients with MTS and PCS suggests the opposite: the reliable imaging of the IIV tributaries with DUS is unlikely and, most importantly, is completely unnecessary.[40] If the treatment of vulvar varicose veins consists of sclerotherapy or excision of the vulvar veins, the presence of reflux in the IIV tributaries makes no difference. But if the task is localization diagnosis of PPR and embolization of IIV tributaries, pelvic venography is essential. Therefore, there is no point in wasting time and effort to identify reflux in the IIV tributaries using DUS. The main purpose of performing DUS in PeVD is to detect pelvic varicose veins and pelvic venous reflux and to assess the left renal vein (*Figure 3*).

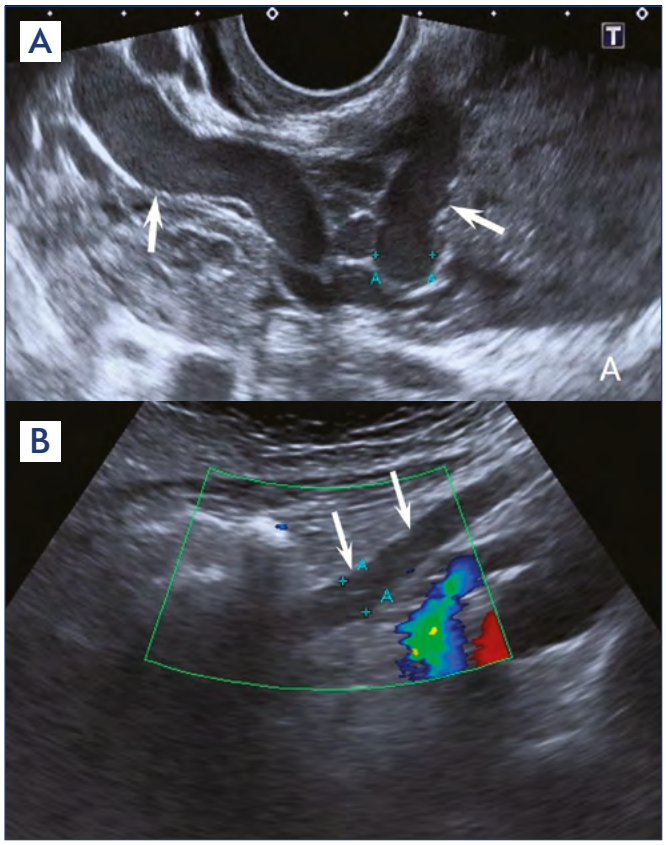

Figure 3. Duplex ultrasound scanning. (A) Arrows indicate dilated parametric veins. (B) Arrows indicate a dilated left gonadal vein.

The ability of DUS to detect stenosis of the left CIV is limited. A number of authors use various functional tests to diagnose compression of the iliac veins and to measure the blood flow velocity in the iliac veins in order to verify MTS.[41] This can only indirectly indicate a narrowing of the left CIV. Additional methods should be used to accurately assess the iliac veins.

Multispiral computed venography (MSCV)

Multispiral computed venography (MSCV) has been successfully used in the diagnosis of venous pelvic disorders. MSCV provides reliable visualization of GV, PV, UV, inferior vena cava, iliac, and renal veins.[30,42-44] MSCV does not allow detection of venous reflux and measuring blood flow velocity; however, it shows venous anatomy very well (*Figure 4*). The possibility of obtaining frontal, sagittal, transverse, and three-dimensional images also contributes to a qualitative assessment of the status of pelvic veins and to the accurate assessment of the degree of left CIV stenosis. Many authors report a high accuracy of MSCV in the verification of MTS and PCS, as well as the correlation between the results of computed venography and intravascular ultrasound (IVUS).[45] According to Jayaraj and Raju, three-dimensional computed venography represents a noninvasive and accurate technique for measuring the degree of left CIV stenosis and can be successfully used to determine the required caliber and length of the stent.[46] It should be noted that the results of MSCV are very indicative in the nutcracker syndrome, and native computed tomography can reveal the pathology of organs and tissues of the abdominal cavity and pelvis.[47,48] This is important for differential diagnosis of the causes of CPP. The disadvantages of the techniques are radiation exposure and the need to use contrast media.

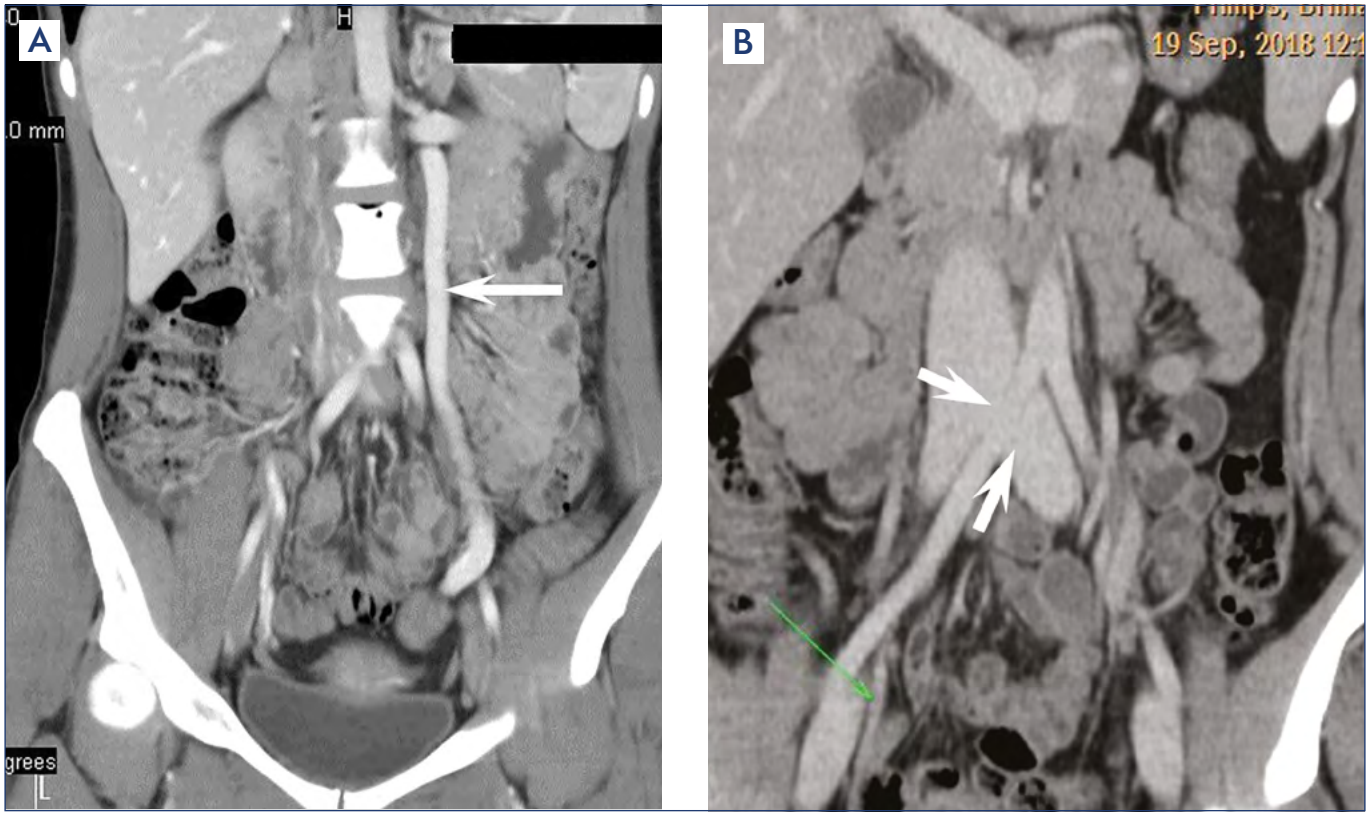

Figure 4. Computed venography. (A) Arrow indicates a dilated left gonadal vein. (B) Arrows indicate compression of the left common iliac vein.

Magnetic resonance venography (MRV)

Magnetic resonance venography (MRV) provides the same information about the pelvic veins as MSCV.[49-51] However, unlike computed tomography, it is possible to obtain images of the veins without using contrast media, and there is no radiation exposure. The use of contrast media increases the sensitivity of the test, and the dynamic scanning mode allows visualization of pelvic venous reflux. MRV detects pelvic varicose veins, and compression of the left CIV and left renal vein. According to McDermott et al, MRV does not always allow an objective assessment of the degree of left CIV stenosis.[52] The study is contraindicated in patients with pacemakers or metal implants.

Ovarian venography (OV) and multiplanar pelvic venography (MPPV)

Despite the availability of such high-tech modalities as MSCV, MRI, and IVUS, conventional venography has not lost its relevance to date.[53,54] Until embolization and stenting of veins are used, it will not be possible to refuse venography because it is a part of these procedures. The classic venographic sign of pelvic venous congestion is reflux of the contrast media in the left or right GV with the cross flow of contrast agent to the opposite side through the incompetent PV and UV. Renal venography always precedes left GV imaging in order to detect or exclude stenosis of the left renal vein. Pelvic venography in patients with MTS should be performed in frontal and lateral views. This provides the most accurate assessment of the degree of left CIV stenosis. Signs of hemodynamically significant MTS are narrowing of the left CIV in combination with its prestenotic dilation, substantial reflux of contrast media into the left IIV and visualization of pelvic collaterals, and reflux of the contrast media into the dilated left iliolumbar vein (*Figure 5*). In addition, during venography, it is possible to measure the pressure in pre- and poststenotic parts of the left CIV. A pressure gradient greater than 2-4 mm Hg is considered a sign of hemodynamically significant stenosis of the left CIV.[55]

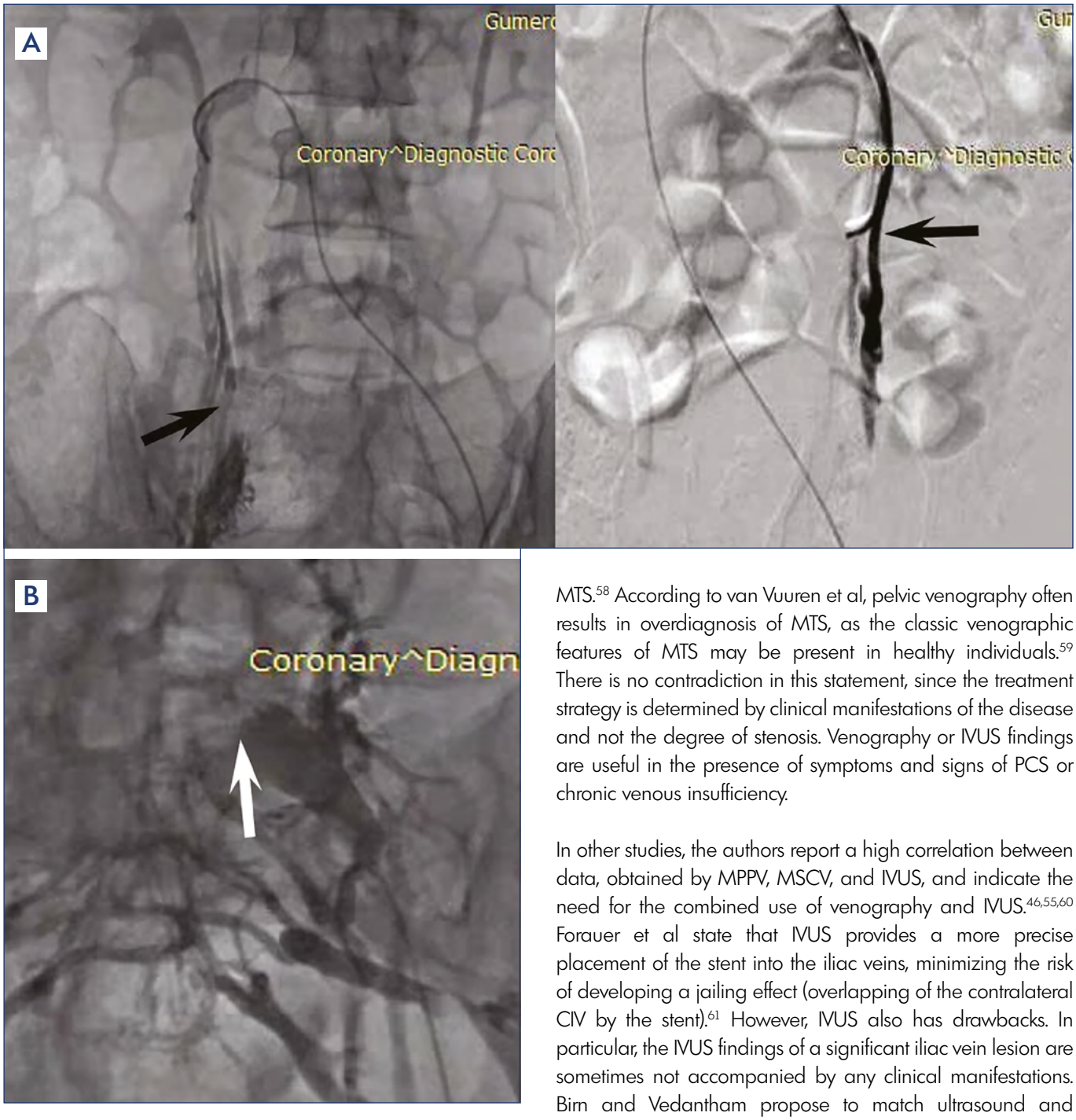

Figure 5. Ovarian and pelvic venography. (A) Arrows indicate dilated left and right gonadal veins. (B) Arrow indicates compression stenosis of the left common iliac vein.

Intravascular ultrasound (IVUS)

IVUS is a reliable method for assessing the status of iliac veins. According to many authors, the possibility to assess the status of the venous wall and to determine the diameter and area of the CIV stenosis significantly increases the accuracy of the technique.[56,57] Knuttinen et al suggest that IVUS in combination with conventional venography is the standard for diagnosing MTS.[58] According to van Vuuren et al, pelvic venography often results in overdiagnosis of MTS, as the classic venographic features of MTS may be present in healthy individuals.[59] There is no contradiction in this statement, since the treatment strategy is determined by clinical manifestations of the disease and not the degree of stenosis. Venography or IVUS findings are useful in the presence of symptoms and signs of PCS or chronic venous insufficiency.

In other studies, the authors report a high correlation between data, obtained by MPPV, MSCV, and IVUS, and indicate the need for the combined use of venography and IVUS.[46,55,60] Forauer et al state that IVUS provides a more precise placement of the stent into the iliac veins, minimizing the risk of developing a jailing effect (overlapping of the contralateral CIV by the stent).[61] However, IVUS also has drawbacks. In particular, the IVUS findings of a significant iliac vein lesion are sometimes not accompanied by any clinical manifestations. Birn and Vedantham propose to match ultrasound and clinical data in order to determine the optimal treatment for a patient with iliac vein lesion.[55]

Therefore, a variety of diagnostic tests including DUS, MSCV, and venography with or without IVUS should be used in patients with concurrent MTS and PCS. IVUS is not a panacea. Our experience suggests that successful diagnosis and treatment of patients with a combination of MTS and PCS is possible without the use of IVUS. Severe symptoms of venous congestion of the pelvic organs and disturbances of pelvic venous blood flow, according to DUS, MSCV/MRV, and

venography, substantiate the need to restore blood flow in the pelvic and iliac veins.

Treatment

Regarding a combination of MTS and PCS, we *a priori* consider symptomatic patients, as PCS cannot exist without pelvic pain, dyspareunia, etc. Furthermore, in such patients, the disturbances in venous outflow from the pelvis are significant, consistently confirmed by the results of ultrasound and radiopaque methods. When choosing a technique for restoring venous outflow from the pelvis in patients with MTS and PCS, the main factors are: (i) the degree of left CIV stenosis; (ii) involvement of GV, as PCS may be a result of an isolated PV and UV dilation without ovarian venous insufficiency; and (iii) the presence of vulvar/gluteal varicose veins, varicose veins on the posterior surface of the thigh, and detection of PPR by imaging.

The indication for endovascular intervention on the left CIV depends on the severity of its stenosis. Carr et al argue that narrowing the left CIV to 4 mm increases the risk of DVT and requires CIV stenting.[62] Ahmed et al expressed the same opinion about stenting in MTS.[7] Daugherty and Gillespie considered the following indication for stenting: reduction in CIV lumen diameter to 2–6 mm and stenosis area from 65% to 99% by IVUS.[31] For patients in our clinic with a combination of MTS and PCS, we consider compression stenosis of the left CIV greater than 50%, as assessed by venography, to be an absolute indication for stenting.[21]

GV reflux is a significant factor in the development of severe venous congestion of the pelvic organs. Therefore, reduction in blood flow through GV is one of the necessary steps in PeVD treatment. However, in patients with combined MTS and PCS, the role of ovarian venous insufficiency may be secondary. It was shown that isolated excision of varicose tributaries of the great saphenous vein or crossectomy in combination with excision of tributaries (ASVAL [Ambulatory Selective Varicose vein Ablation under Local anesthesia] and CHIVA [*Conservatrice Hémodynamique de l'Insuffisance Veineuse en Ambulatoire*] methods) is accompanied by restoration of great saphenous vein valvular function in 60% to 70% of cases.[63,64] It is likely that the restoration of normal blood flow in the left CIV would reduce reflux in the left GV. In patients with PCS, we observed the elimination of the dilation of PV and UV and the restoration of their valvular function after GVE.[65]

In patients with PeVD, the occurrence of vulvar varicosities (VV) and varicose veins on the posterior surface of the thigh is associated with reflux in the IIV tributaries (internal pudendal, obturator, and inferior gluteal veins).[66,67] Vulvar vein dilation most often occurs during pregnancy; the rate of its detection in pregnant women ranges from 10% to 20%.[68] However, in two-thirds of these women, VV disappears after childbirth without any treatment. This suggests that IIV reflux is reversible. Khan et al presented the case of a woman with combined MTS, PCS, and VV[69] and who had no detectable images of IIV tributaries or PPR on venography despite a severe VV. Our experience shows that the reflux in the IIV trunk, internal pudendal vein, and obturator vein is found in only 8%, 8%, and 6% of patients with VV, respectively.[40] These data should be taken into account when choosing a method for eliminating VV.

Stenting or embolization?

What is the first intervention to perform in patients with a combination of MTS and PCS? Is it really necessary to perform GVE? Should the IIV inflows be embolized in patients with a combination of MTS, PCS, and VV? These and a number of other questions arise for surgeons when taking into account clinical, ultrasound, and radiological data in this cohort of patients.

Findings from recent studies suggest that CIV stenting is the first intervention on the pelvic veins to perform in patients with concomitant MTS and PCS. Daugherty and Gillespie reported elimination of PCS symptoms in 79% of patients after CIV stenting.[31] Santoshi et al successfully used isolated CIV stenting in 22% of patients with combined MTS and PCS.[8] Ahmed et al managed to relieve symptoms of venous congestion of the pelvic organs in 68% of patients with MTS and PCS via stenting and without GVE.[7] A study by Gavrilov et al showed complete relief of PCS symptoms in 17% of patients with left CIV stenosis.[21] Lakhanpal et al noted a significant reduction or complete relief of PCS symptoms in 76% of patients.[70] These data indicate the possibility of curing patients who have a combination of MTS and PCS through CIV stenting alone, without GVE.

In the presence of hemodynamically significant CIV stenosis in these patients, the treatment of choice is stenting of the iliac veins (*Figure 6*). At the same time, there is a certain proportion of patients (from 30% to 70%) in whom stenting does not significantly improve PCS symptoms. Various explanations include a long history of the disease (more than 5-7 years), incorrectly chosen stent size, and erroneous stent implantation in patients with hemodynamically insignificant stenosis of the iliac veins. Persistence of PCS symptoms after CIV stenting is an indication for GVE.

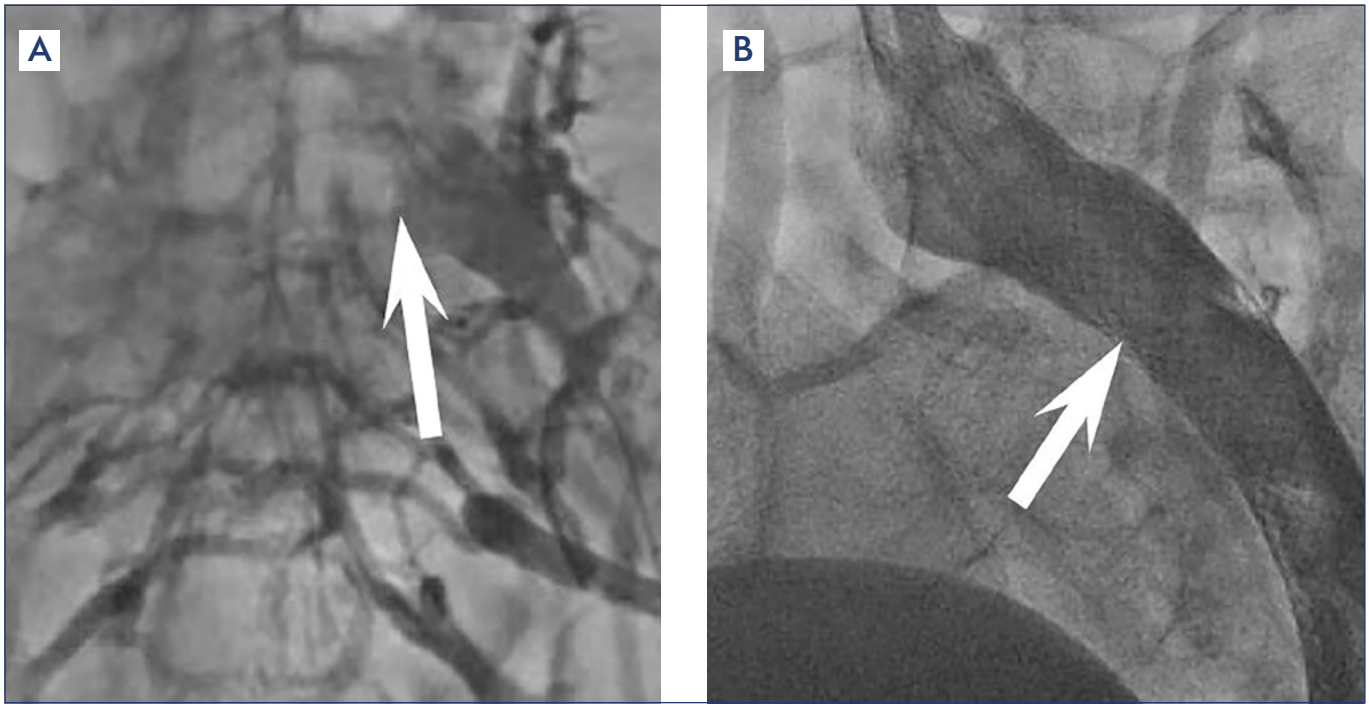

Figure 6. Pelvic venography (A) before and (B) after stenting of the left common iliac vein. The arrows indicate a stenosis of the left common iliac vein and stents in the lumen of the left iliac veins.

It is inappropriate to perform GVE without elimination of hemodynamically significant CIV stenosis. Patients report an increase in pelvic pain, and some of them develop VV.[71] Left GV occlusion in persisting MTS will increase pelvic venous congestion (*Figure 7*). Our clinical experience indicates the need to use a staged approach to the endovascular treatment in patients with a combination of MTS and PCS: stenting in the first stage and then, depending on its clinical effect, deciding whether GVE is needed.[21,71] In the case of CIV stenosis less than 50%, GVE can be performed as a primary intervention. It may be used as the sole treatment in patients with MTS and PCS when symptoms are resolved. To date, there is no indication for iliac-vein stenting in patients with PCS and hemodynamically insignificant (<50%) stenosis of the left CIV. If clinical signs persist, stent placement should probably be considered after careful reassessment of the iliac veins and exclusion of any other cause of persistent pelvic pain.

GVE is a widely accepted treatment for PCS. Most often, it is performed using coils (nitinol, platinum, fibered or not fibered). However, published data and our own clinical experience indicate that coils are not the optimal agent for treating GV occlusion. Frequent complications of GVE are postembolization syndrome (10%-53%), protrusion of the coils (4%-8%), and nickel allergy.[72-74] This indicates the need to use other embolizing agents for GVE (Amplatzer devices, cyanoacrylate glue).[75,76]

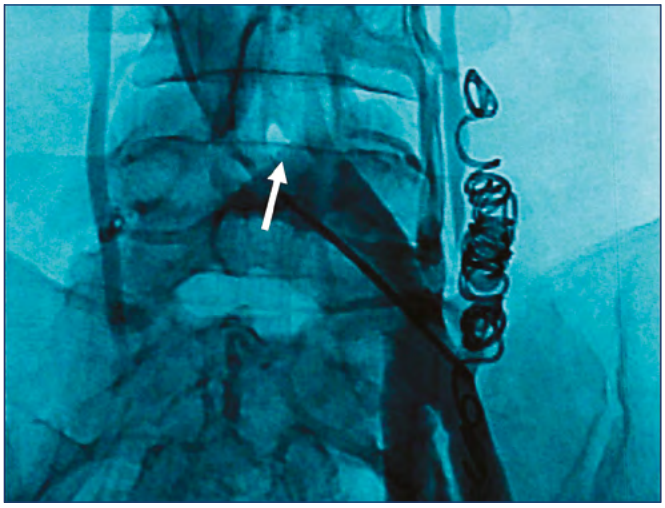

Figure 7. Pelvic venography of a patient with unresolved compression stenosis of the left common iliac vein (indicated by an arrow) after embolization of the left gonadal vein. Marked pelvic collaterals and reflux of the contrast media into the dilated left internal iliac vein are visualized.

Choice of a stent

The stenting procedure is well developed and adequately described in the literature.[5,77,78] An important point is choice of stent. Raju et al proposed to use stents that have a diameter of 16-18 mm to restore the normal lumen of the CIV.[79] Furthermore, these authors prefer to install stents having a diameter 2 mm greater than the recommended size. This makes it possible to

perform aggressive post-dilation to eliminate residual stenosis and to achieve better fixation of the stent in the vein lumen.

Another issue in choosing an optimal stent is braiding and length. A wide range of venous stents have been developed to date. They are distinguished by flexibility, strength, and radial resistance force, and they have various braiding, etc.[80] The authors recommend using Z-stents. The length of iliac vein stents should be at least 90 mm. The experience of our clinic is based on the use of Wallstent stents (Boston Scientific). These devices have been used in the treatment of MTS for 15 years, and there have been no cases of reported breakage, migration, or thrombosis of these stents.[71]

Placement of the stent in the CIV lumen should also be touched on. The ideal position is placement within the immediate area of confluence of the iliac veins. However, this is almost impossible to achieve in real practice because stent placement within the same plane as the CIV orifice is associated with a risk of proximal residual stenosis after stenting. Therefore, most authors recommend placing a stent in a vein so that it protrudes 0.5-1 cm into the lumen of the inferior vena cava.[78] Other authors point out that even 2-cm displacement of the stent in the inferior vena cava should not be regarded as a serious defect in stenting technique.[78] The "jailing" effect leads to thrombosis of the contralateral OPV in no more than 1% of cases.[81] This is demonstrated by tomograms of a patient with MTS and PCS who underwent CIV stenting with two stents in our clinic 15 years ago (*Figure 8*). PCS symptoms were completely eliminated and are absent to date; stents remain completely patent; and there have been no episodes of thrombosis of the iliocaval segment.

Venoactive drugs (VAD) in the treatment of patients with a combination of MTS and PCS

When using endovascular methods of treatment, it should be understood that CIV stenting and/or GVE does not result immediately in a decrease in the diameter of the pelvic veins, elimination of reflux in them, and restoration of venous outflow from the pelvic organs. Given this fact, patients should be advised to take venoactive drugs (VADs); these have a beneficial effect on the walls of the pelvic veins and improve microcirculation in the pelvic organs. The only VAD studied in PCS patients is the micronized purified flavonoid fraction (MPFF, Detralex, Daflon). Several studies have shown a positive effect of MPFF on venous outflow from the pelvis, pelvic pain, and other symptoms of the disease.[82-85] This drug is characterized

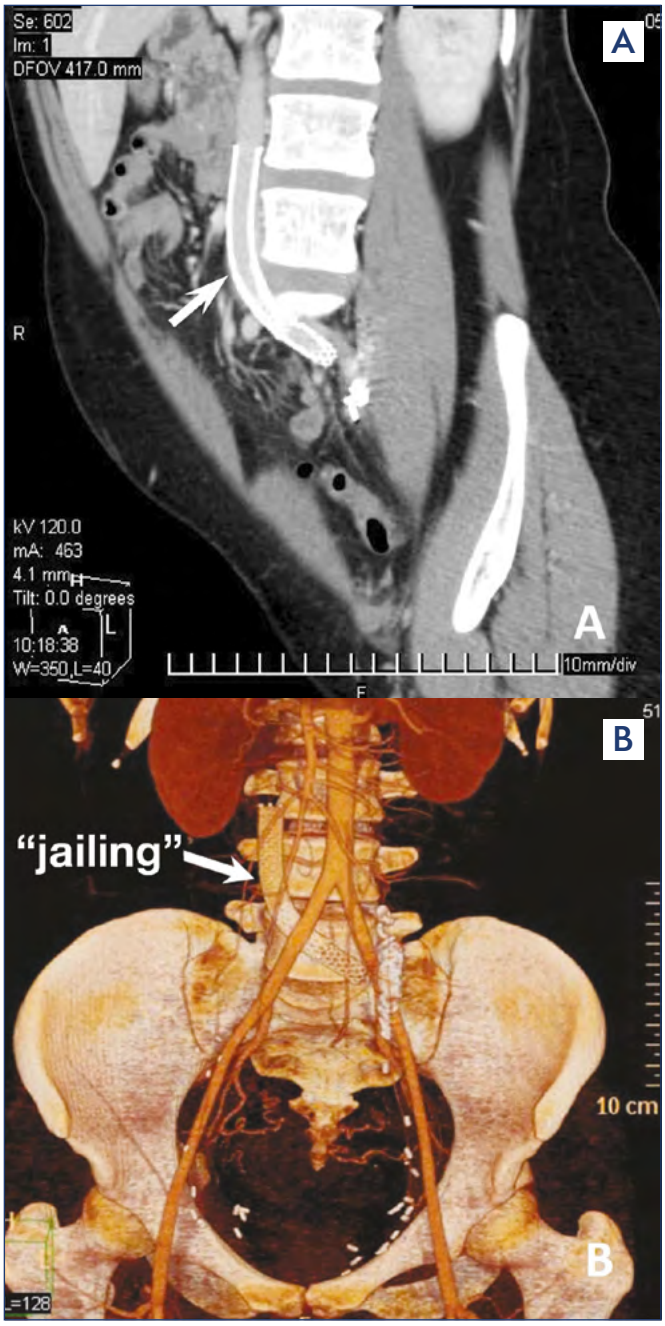

Figure 8. Computed tomography in a patient who underwent stenting of the left iliac veins with two Wallstent stents and embolization of the left gonadal vein with coils. (A) Sagittal projection. (B) Frontal projection. The stents are patent. The arrow indicates the "jailing" effect.

by high efficacy and safety in the treatment of patients with PCS. The use of MPFF in the pre- and postoperative period provides early relief of symptoms of the disease and facilitates rehabilitation of patients with MTS and PCS after endovascular treatment.

Conclusion

It is difficult to address all the issues and nuances of diagnosis and treatment of patients with a combination of MTS and PCS in one review; there are many anatomical and clinical variants of the course of this combined pathology. MTS and PCS are the most common causes of pelvic vein disease. The main directions of research are clear, focusing on the study of pathophysiological processes in PeVD, adequate and reliable diagnosis of disease, and determination of optimal approaches and methods for correction of venous outflow disturbances in MTS and PCS. It is also obvious that these issues are impossible to resolve without international consolidation of the efforts of surgeons, phlebologists, vascular, and interventional surgeons. Large multicenter studies are needed, sharing international experience in the diagnosis and treatment of PeVDs.

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Anticoagulation and interventional treatment of varicose veins

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Abstract

Venous thromboembolic risk is very low after varicose vein procedures. This risk is often cited as less than 1%; however, studies also show the risk to be highly variable. Overall, literature in the field does not typically conclude thromboprophylaxis to be necessary in low-risk patients, owing to the low incidence of the event studied and the often-insufficient number of patients included. Despite the low incidence, venous thromboembolic risk is important in terms of mortality and morbidity. Varicose veins affect an average of 1 in 3 individuals, and there is still great variability in practices concerning thromboprophylaxis throughout the world. The parallel must also be considered with regard to interventional treatment of varicose veins in patients already receiving anticoagulant therapy. Endovenous treatment of varicose veins of the lower limbs has taken precedence over conventional surgery more or less rapidly depending on the country and the level of health care reimbursement. Recommendations advocate for an endovenous rather than a surgical approach whenever possible. However, questions remain unanswered, and a standardization of practices through clear recommendations needs to be drawn.

Keywords:

anticoagulant therapy; thromboprophylaxis; varices endovenous ablation or surgery; varicose veins.

Overview of the different interventional treatments for varicose veins and their recommendations

Open surgery is the oldest interventional treatment technique for varicose veins and remains in the phlebology practice in many countries.

Thermal endovenous treatment techniques have been developed over the last 2 decades with the advent of ultrasound, which has allowed a better understanding of venous anatomy and hemodynamics. Overall, there are 3 types of endovenous techniques (*Table I*): (i) tumescent thermal ablations, including endovenous laser treatment (EVLT) and radiofrequency ablation (RFA), which are the most widely used and best-studied techniques; (ii) nonthermal, nontumescent ablations, of which sclerotherapy, and more particularly ultrasound-guided foam sclerotherapy (UGFS), often also classified as "chemical ablation," is the most widely practiced and the technique with the greatest recoil; and finally, (iii) combined ablations, a combination of thermal and nonthermal techniques, such as the treatment of a saphenous trunk by laser/RFA, and the treatment of tributaries by echosclerotherapy.[1,2] All these procedures can be used with tumescent and nontumescent local anesthesia.

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Tumescent thermal ablation • Radiofrequency • Laser • Steam • Microwave
Nonthermal nontumescent ablation • Sclerotherapy • Mechanochemical methods: MOCA (ClariVein and Flebogrif) • Physicochemical methods (LAFOS technique) • Obstructive methods (cyanoacrylate glues) • HIFU: high-intensity focused ultrasound
Combined ablation: thermal ablation + sclerotherapy

Table I. Classification and overview of the different techniques for endovenous treatment of varicose veins.

LAFOS, laser-assisted foam sclerotherapy;
MOCA, mechanical occlusion chemically assisted ablation

So-called "conventional" varicose vein surgery has remained the gold standard of varicose vein treatment for decades. The concept of "modern surgery" recognized in 2014[3] could in 2021 be summarized as the combination of minimally invasive treatment of the saphenous trunk and incompetent tributaries, with stripping being replaced by laser or RFA. Most often, crossectomy or flush ligation is abandoned.

The European Venous Forum and the International Union of Angiology[3,4] recommend thermal ablation (RFA or laser), modern open surgery, or UGFS for grade 1A conditions. In 2018, the recommendations of the European Venous Forum added steam, cyanoacrylate glue, and mechanical occlusion chemically assisted ablation (MOCA) for grade 1B conditions.

The European Society of Vascular Surgery (ESVS)[5] recommends endovenous thermal ablation (EVTA) as first-line interventional treatment for grade IA venous insufficiency of the great saphenous vein before surgery or UGFS.

The American Venous forum[6] recommends EVTA for grade 2B classified conditions of the great saphenous vein, before UGFS and before conventional surgery.

The National Institute for Health and Care Excellence (NICE)[7] recommends EVTA by RFA or EVLT as the first-line interventional treatment for the great saphenous vein. Finally, the Guidelines of the First International Consensus Conference on EVTA for varicose vein disease[8] recommend EVTA for the great saphenous vein (grade 1A), the small saphenous vein (grade 1A), the accessory saphenous vein (intrafascial portion; grade 1B), and the Giacomini's vein (grade 1B).

The "minimally invasive" nature of endovenous techniques allows them to be performed on an outpatient basis with the shortest possible immobilization of the patient, with rapid resumption of ambulation and little or no time off work. This has been well demonstrated compared with conventional surgery.[9,10]

Thrombotic risk

Sclerotherapy

Sclerotherapy via a sclerosing agent in liquid form has long been the reference treatment for spider veins and telangiectasias. The foam form was described during the Second World War but was really developed in the middle of the 1990s.

Development of ultrasonography then made it possible to combine injection and foam form, thus increasing the efficacy and safety of this remarkable technique, its indications being high grade and allowing the practitioner to treat all varicose veins.[11] The thrombotic risk is described as low: Jia in his meta-analysis reports a thrombotic risk of around 0.6%.[12] Among other things, the author notes that the large volumes of the sclerosing agent injected increase the thromboembolic risk and that the thrombotic risk factors to be taken into consideration include history of venous thromboembolic disease, thrombophilia, obesity, and sedentary lifestyle. For Kulkarni,[13] the risk is about 0.9%.

Thermal endovenous treatments

The thermal endovenous treatment techniques that have been evaluated in the greatest number of quantitative and qualitative studies and for which there is the greatest hindsight are laser and RFA. The long-term safety and efficacy of these techniques has already been demonstrated.[14,15] The risk of thromboembolism has also been reported to be less than 1% in most studies.[16-19] The Marsh study[20] found rates of around 1% for endovenous laser treatment, and this was slightly lower, at 0.7%, for RFA.

Nonthermal nontumescent endovenous treatments

For mechanochemical ablation methods (MOCA: ClariVein and Flebogrif), obstructive methods (cyanoacrylate glues: VenaSeal, Variclose, VenaBlock), physicochemical methods (LAFOS technique [laser assisted foam sclerotherapy]), and high-intensity focused ultrasound (HIFU), the studies are far fewer in number and the follow-up is less important. For MOCA, the thromboembolic event rate is less than 1% and remains lower than for endovenous thermal treatments according to the recent meta-analysis by Nugroho.[21] As regards VenaSeal,

the 2019 French Health Authority (HAS) report shows a low rate of thromboembolic events, again less than 1%,[22] and this rate is also very low in the VeClose study (VenaSeal Sapheon Closure System Pivotal Study).[23]

Conventional surgery

Here again, the figures for the incidence of thromboembolic events are low, on the order of 1%.[24] For Sutton, there is no difference in risk between all varicose vein interventional treatment procedures, from conventional surgery to endovenous treatments.[25]

For all techniques, the studies carried out have often been retrospective. It is important to bear in mind that retrospective studies necessarily show fewer thromboembolic events than prospective studies because use of Doppler ultrasound is not systematic in retrospective studies and events could have been diagnosed by another team without the team that performed the procedure being informed. What is important to remember is that despite some rare and disparate data, the majority of studies report a thromboembolic event rate of around 1%.

Finally, the European Society of Vascular Surgery[5] estimates the incidence of venous thromboembolic events at 0.2% to 1.3%, with no difference between endovenous techniques and conventional surgery.

With regard to endovenous treatments, practitioners need to take into account the risk of occurrence of endovenous heat-induced thrombosis (EHIT) for thermal treatments and endovenous foam-induced thrombosis (EFIT) for sclerotherapy. For example, Sufian[26] found rates of EHIT after RFA treatment of around 3%, most EHITs being asymptomatic and not all of them requiring curative treatment, as noted in the recently updated recommendations of the American Venous Forum and the Society of Vascular Surgery.[27] In addition to a very precise therapeutic course of action, these recommendations give a precise definition of the entities "EHIT" and "venous thrombosis": "EHIT, any thrombus detected by ultrasound within 4 weeks of EVTA, originating from the treated vein and protruding into a deep vein. Non-EHIT venous thrombosis: deep venous thrombosis occurring in a venous segment not contiguous to the thermally ablated vein."

There is no scientific evidence to support the use of thromboprophylaxis or venous compression to prevent EHIT occurrence.

With regard to EFITs, the study by Kulkarni[13] also found a very low rate.

Recommendations

Most recommendations agree on the need to stratify thromboembolic risk according to the type of treatment and the patient's predisposition to develop a thromboembolic event. For example, this is well described in the Caprini score, in which it is interesting to note that the presence of varicose veins is a risk factor for developing a venous thromboembolic event perioperatively. Despite this, thromboembolic risk stratification for the treatment of varicose veins is very poorly defined.

With regard to sclerotherapy, European recommendations[11] indicate that anticoagulation should be proposed in patients with a history of venous thromboembolism or severe thrombophilia. For these patients, venous compression and rapid resumption of activities are recommended, as well as avoidance of injection of too-large volumes of sclerosing foam. Overweight patients or those with limited mobility should also be considered. However, no notion of severe thrombophilia is defined.

This notion can be better understood by looking at the study of Hamel-Desnos,[28] which included 105 patients with thrombophilia (heterozygous Factor V, homozygous Factor V, heterozygous Factor II, elevated Factor VIII, combination of heterozygous Factor II and V mutations, combination of heterozygous Factor V and elevated Factor VIII mutation). Thromboprophylaxis was given to all patients. No thromboembolic events occurred.

A distinction must be made between patients with minor thrombophilias, those at low risk of venous thromboembolic events, and those with major thrombophilias at higher risk of thrombosis. Two major thrombophilia groups are particularly at risk: those with antithrombin III deficiency and those with antiphospholipid syndrome. Classically, for these 2 major thrombophilias, sclerotherapy should not be performed, as there is not enough experience to date. For other thrombophilias, a benefit/risk balance should always be established before considering treatment, as recommended.

The Society of Vascular Surgery and the American Venous Forum[6] recommend thromboprophylaxis in patients at risk without recommending one regimen over another.

The Venous Forum and the Royal Society of Medicine published this year, in the context of the SARS-CoV-2 pandemic, recommendations concerning thromboprophylaxis of patients treated with thermal and nonthermal endovenous

treatments.[29] The authors note a lack of recommendations on this subject and a disparity in practices. The authors propose a risk stratification and suggest taking into account the intermediate-risk patient, who would not necessarily have received thromboprophylaxis outside the pandemic. With regard to the low-risk patient, it was indicated that there were no arguments for using a single-dose or a short 3-day treatment. The risk factors to be taken into account are personal or family history of thromboembolism, known thrombophilia, reduced mobility, body mass index (BMI)>30, hormone therapy, active cancer, postthrombotic syndrome, and superficial venous thrombosis.

With regard to the ESVS[5] and the NICE,[7] they do not make any specific recommendations concerning thromboprophylaxis. The ESVS recalls that to reduce the risk of thrombosis, the patient should be treated as an outpatient, under tumescent local anesthesia, and should be ambulatory as soon as possible. The ESVS recommends assessing risk factors according to a score such as the Caprini score and specifies a history of thromboembolism, thrombophilia, obesity, immobilization, cancer, and older age as risk factors.

The guidelines of the first international consensus on EVTA of varicose veins[8] do not recommend systematic thromboprophylaxis. As for ESVS, it is recommended to evaluate the thrombotic risk by the Caprini score, for example, and to take into account age over 60 years, oral contraception, hormone therapy, history of thromboembolism, severe thrombophilias, obesity, immobilization, and cancers.

Some authors note that certain interventional characteristics will increase the thrombotic risk with regard to varicose vein surgery: bilateral procedure, treatment of a recurrence, treatment of a small saphenous vein, and concomitant phlebectomies.

In France, the Health Authority (HAS; *Haute Autorité de Sante*)[30] states that "the postoperative prescription of low molecular weight heparins (LMWH) has not been the subject of a consensus among the professionals previously consulted, except for subjects considered to be 'at risk' for whom preventive treatment would be prescribed."

In 2020, the French Society of Vascular Medicine (SFMV) updated its guidelines on endovenous thermal treatments.[31] It proposes prophylactic anticoagulation in patients at high risk of thromboembolism: personal history of venous thromboembolism or known major thrombophilia. It proposes a therapeutic regimen with anticoagulation via direct oral anticoagulant or LMWH or fondaparinux at a preventive dose for 7 days, and it proposes to combine it with a class 2 venous compression.

What stands out today is the need to treat patients on an outpatient basis, with the shortest possible intervention time and the fastest possible return to ambulation.

Technological progress, such as the almost systematic use of the 1470-nm wavelength for endovenous laser with radial fibers, has helped minimize undesirable effects; this is no longer in question. A new wavelength has recently been commercialized: 1940 nm. This higher wavelength allows a better absorption of the energy in the water of the venous wall, allowing basic power to be decreased. We do not have enough experience with this wavelength yet, but it will be interesting to study this aspect.

With regard to the type of thromboprophylaxis, apart from the French recommendations, there is no therapeutic scheme or recommended molecule. It has been shown that direct oral anticoagulants are safe and effective compared with LMWH and fondaparinux in the same indications, particularly in orthopedic surgery.[32,33] Keo[34] showed that rivaroxaban (10 mg, once daily, 3 consecutive days) was as effective in preventing the occurrence of EHIT and deep-vein thrombosis as fondaparinux.

As regards venous compression, here too we do not have any recommendations concerning the treatment of varicose veins, but we can cite the guidelines for vascular surgery published in 2006,[35] which indicate a benefit in relation to the risk of thromboembolism in general surgery and vascular surgery. Despite the absence of recommendations, many articles have been published on this subject and there is still considerable controversy, but this is not the subject of this article.

Disparities in practice

What is frequently observed from one country to another, but also from one team to another within the same country or even within the same health care institution, is an incredible disparity of practices concerning thromboprophylaxis. Therapeutic strategies vary greatly: from single dose to longer duration (3 days, 7 days, 10 days, etc).

As indicated by Dattani,[36] for patients at low thromboembolic risk, practices vary enormously according to practitioner and patient preferences. In the randomized controlled trial (RCT) of San Noberto[37] aimed at evaluating thromboprophylaxis in the

context of venous surgery, although the power of the study was considered too low to conclude, the patients included were at moderate thrombotic risk and 2 groups were formed: in the first group, thromboprophylaxis for 10 days was prescribed, whereas in the second group no pharmacological treatment was administered. No thromboembolic events occurred.

There are no consistent RCTs on the subject of thromboprophylaxis, and once again, the low incidence of thromboembolic events would require a very large cohort, and given the disparities in practice, one can imagine that there might be some difficulty in acceptance, particularly in the process of randomizing patients.

However, many articles have been published that are not controlled studies. We may cite the publication by Boyle,[38] which shows that in Ireland the majority of practitioners use a single dose of thromboprophylaxis. One-third of the procedures in Ireland in that publication were endovenous treatments. The most relevant thrombotic risk factors are recognized to be thrombophilia, cancer, bilateral procedures, and obesity.

Another publication by Nikolopoulos[39] also provides evidence of practice in a survey of Greek vascular surgeons. What is interesting in this study is to see that half of the patients treated by open surgery and also half of those treated by endovenous treatments received thromboprophylaxis for 2 to 5 days and in 95% of cases by LMWH. The risk factors taken into account were mainly thrombophilia, history of venous thromboembolic disease, cancer, and estrogen-progesterone contraception, but bilateral procedures, older age, or duration of surgery were not taken into account.

With regard to single-dose therapy, there is no evidence to date of its efficacy; in the study by Enoch,[40] thromboembolic events occurred in the group that received single-dose therapy, whereas in the group that received no thromboprophylaxis, there were no thromboembolic events. For Boyle,[38] given that varicose vein surgery is known to be the most contentious area of vascular surgery, it may therefore be advisable to administer at least a routine dose periprocedure. This remains totally debatable given the lack of demonstrated efficacy but also owing to the possible downside of such an attitude: why prescribe thromboprophylaxis for a duration that is known to be ineffective rather than stratifying the risk and prescribing, as recommended, thromboprophylaxis for a longer duration?

Risk of bleeding

What about patients who are being treated with anticoagulants and for whom varicose vein interventional treatment is being considered?

This case should not be underestimated, as the overall trend in long-term anticoagulation is increasing for all causes. In France, we know that more than 2% of the general population is treated with long-term anticoagulants. It is therefore important for the practitioner not to ignore this condition.

First of all, it is necessary to know for what reason(s) the patient is treated with an anticoagulant. There are 2 cases: cardiac pathologies and venous thromboembolic disease. In both cases, it is of course imperative that the benefit-risk balance of the planned treatment of varicose veins, as well as the consequences of the absence of treatment, always be raised in these fragile patients.

Next, the practitioner should ask himself a few questions: for patients with a history of venous thromboembolic pathology, has a thrombophilia screening been performed? As we have seen previously, for certain thrombophilias, even in a patient who is anticoagulated, sclerotherapy is not indicated. Another very important point to take into account in these patients, who have already had 1 or more venous thromboses, is the possible presence of obstructive or occlusive sequelae of the deep venous network and the possible need to preserve suppleance veins.

In this field, the literature provides us with some information. The first series on this subject date back to the 1980s with Dastain[41] and then Franchitti[42] who, in 2 small series, demonstrated that sclerotherapy in patients with long-term anticoagulation was safe and effective, with no significant difference in terms of efficacy compared with patients without anticoagulation.

Another publication from 2002 by Gachet[43] showed, in long-term anticoagulated patients, that sclerotherapy is safe, but the author suggests it takes more sclerotherapy sessions to bring about venous occlusion than in nonanticoagulated patients. This is also the conclusion of a study by Stücker.[44]

In 2009, Darvall[45] published a study of 27 patients who underwent sclerotherapy for venous ulcer treatment. Four of these patients were treated with warfarin. No difference in efficacy or safety was shown in these patients. Hager in 2016[46] published a study whose objective was to highlight the factors

influencing the occlusion of incontinent perforating veins according to 3 treatment modalities: UGFS, RFA, and EVLT. In each of these 3 groups, one-third of the patients were on long-term anticoagulants. It was shown that anticoagulation was not a predictor of failure.

Sharifi[47] also studied the effect of anticoagulation in the context of thermal endovenous treatment of the great saphenous vein. This was also a small series, and no significant difference was found between the groups studied.

Takahashi's team[48] also published a study including 1136 patients who received thermal endovenous treatment of the great saphenous vein or the small saphenous vein. Of the patients included, 12% had antiplatelet aggregation treatment and 8% were receiving anticoagulation treatment. There was no significant difference between the different groups of patients regarding the rate of recanalization and postoperative complications.

A study by Theivacumar[49] published in 2009 shows that warfarin does not influence the success of endovenous treatment by laser of the great saphenous vein.

Finally, Sufian[50] did not find more bleeding when evaluating RFA procedures in anticoagulated patients and showed a slight decrease in the incidence of EHITs and an increase in the incidence of treatment failure in these patients.

Finally, it should be noted that the European guidelines[11] for sclerotherapy report that anticoagulation is not a contraindication to the practice of sclerotherapy.

What emerges from these different studies is that there is no difference in effectiveness and safety. Of course, these are small series, uncontrolled studies.

The practitioner should remember that there is no need to increase in the first instance, for example, the concentration of the sclerosing agent in a patient treated with an anticoagulant for fear of a decrease in its effectiveness. We must continue to follow the recommendations in terms of therapeutic procedures, whatever they may be, and not forget that the indication for the treatment of varicose veins must always be weighed on a case-by-case basis. It should also be remembered that patients with long-term anticoagulation are fragile and have other comorbidities that need to be taken into account, and that interventional approach will be more appropriate for these patients than open surgery.

Conclusion

Practices concerning thromboprophylaxis for the treatment of varicose veins remain very heterogeneous.

Varicose vein procedures are still the most widely performed in the world, and there is no doubt that the increase and aging of the world's population will only reinforce this observation.

The low incidence of venous thromboembolic events leads practitioners to doubt the usefulness of this procedure for certain patients.

Endovenous treatments are overtaking open surgery more or less rapidly depending on the country concerned and for various reasons (reimbursement, habits, lack of mastery of sonography, etc).

There is no doubt that in the years to come other endovenous treatment techniques that do not require an operating area will become the rule.

The practitioner must ask himself the question of the thromboembolic risk of his patient: either the risk is present and a thromboprophylaxis of 8/10 days must be prescribed, or his patient does not have this risk and no thromboprophylaxis must be instituted. This is of course within the recommended practice conditions; the treatment of varicose veins must be as short as possible, with local anesthesia, and ambulation must be resumed as soon as possible. Under these conditions, the analysis of the thrombotic risk is simplified and remains intrinsic to the patient.

To support the practitioner, publication of national and international guidelines is needed in order to harmonize our practices, make them safer, and limit their economic impact.

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Dialogue on venous hemodynamics

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Abstract

Hemodynamics of the venous system of the lower limbs is very complex, its explanation typically evoking formulas and concepts that can be daunting for those new to the subject. Here, we approach the task from a more conversational angle, introducing a dialogue between expert and student as they discuss the matter. Such an approach aims to encourage further interest and pursuit of deeper understandings.

Introduction

The hemodynamics of the venous system of the lower limbs is very complex. The explanation of physiology and pathophysiology takes place through the application of mathematical formulas and physical concepts not always well understood by young phlebologists who approach the subject. The result is that you discourage them from studying instead of encouraging them. This dialogue between the teacher (Prof Smith)–a senior phlebologist–and his student (Dr Paul) tries to explain in a very simple way and without using any formula the most elementary concepts that characterize the venous system of the lower limbs. We hope to arouse interest and push young phlebologists to deepen this fascinating and still in some ways obscure field of physiopathology.

Take-home message

The premise for improving each therapeutic gesture is to try to understand how it acts and which pathophysiological element it modifies. Understanding some basic elements of the lower-limb venous system improves our daily decisions about phlebological actions.

Dialogue

Dr Paul: Today my legs feel a bit heavy. Maybe I have venous hypertension.

Prof Smith: In that case you can relax. What we normally call "venous hypertension" doesn't exist.

Dr Paul: What do you mean "it doesn't exist"?

Prof Smith: I'm joking, but only in part. It's a long way to the Convention. If you like, we can spend the journey talking about some basic principles in venous pathophysiology.

Dr Paul: Sure. It would be a pleasure.

Prof Smith: Excuse me for asking. I assume you know the basic difference between arteries and veins?

Dr Paul: I think so.

Prof Smith: Ok, but let me give you a briefing. The venous system is quite different from the arterial system.[1,2] As you know, in the arterial system we find high pressure, low volumes, non-collapsible arterial vessels, and high peripheral resistance in the limbs. Whereas in the venous system, we see lower pressure, higher volumes, collapsible venous vessels, with low peripheral resistance.

Dr Paul: Low pressure? How come low pressure? I thought that in a subject of average height, venous pressure at the ankle exceeded 100 mm Hg.[3]

Prof Smith: Of course. I see what you mean. Let's backtrack a bit.

Being on planet Earth, we are subject to the law of gravity. This means that when we stand still, a column of blood of a certain weight forms in the venous system.

Dr Paul: I see ... and increasing the vein caliber, I suppose we increase the weight.

Prof Smith: Wrong! The weight in question depends on a person's height. The vein diameter has nothing to do with it.[4] You remember Torricelli!

Dr Paul: Vaguely ...

Prof Smith: Torricelli took a series of wine-butts like the ones you use at home to make "*aceto balsamico.*" He filled them with water and connected tubes at various heights and with various diameters. He also filled the tubes with water.

Dr Paul: Then what happened?

Prof Smith: When the column of water reached a certain height, the wine-butt broke. The amazing thing was that the wine-butt broke regardless of the tube's diameter – narrow or wide (*Figure 1*).

Dr Paul: You mean the liquid exerts pressure proportional to its height, and the diameter is not a key factor.

Prof Smith: Exactly! You got it!

Dr Paul: So, what you're saying is that an incontinent, great saphenous vein of wide caliber has the same pressure as an incontinent great saphenous vein of small caliber, in subjects of the same height.

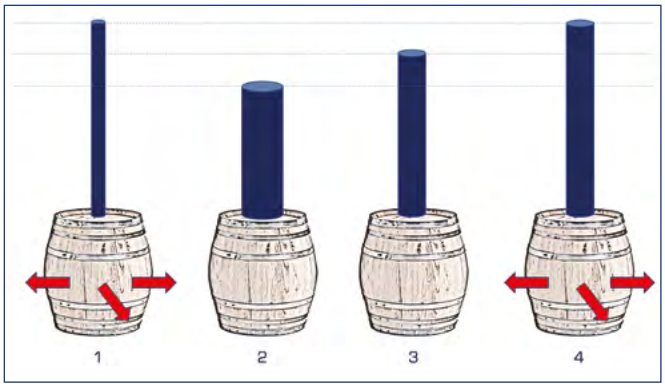


Figure 1. Torricelli's law. The pipes above the barrels are filled with liquid. The pressure exerted will break first barrels, number 1 and 4 (of equal height), regardless of the caliber of the tube.

Prof Smith: Exactly! Those veins have the same hydrostatic pressure.

Dr Paul: But a patient with a wide varicose vein usually is more symptomatic than a patient with a narrow vein.

Prof Smith: That's right. But to explain the difference we don't look at the pressure.

Dr Paul: What do we look at?

Prof Smith: Other parameters. But let me first finish what I was saying about venous pressure.

Dr Paul: I'm all ears. You were talking about pressure, so that means hydrostatic pressure. Is that right?

Prof Smith: That's right. We ought really to call it "hemostatic pressure" because we are talking about a column of blood, and not water. Even if the term "hydrostatics" is usually used.

Dr Paul: I'm with you. This pressure is the force that makes the blood return to the heart, right?

Prof Smith: Wrong again! It's not this pressure that moves the blood. Let me give you an example to make things clear. If I take a cylinder 1 meter in height and fill it with water, the hydrostatic pressure at the bottom of the cylinder is 73 mm Hg. Although the pressure at the bottom is higher than it is at the surface, the liquid doesn't move.

Dr Paul: Why not?

Prof Smith: Because at the surface the liquid has *a potential energy* equal to that at a height of 1 meter. So, the 2 forces are equal and opposite. Otherwise, we'd have discovered perpetual motion!

Dr Paul: Let me see if I understand. At ground level, the hydrostatic pressure is high, and the potential energy is zero. And vice versa at a height of 1 meter.

Prof Smith: Exactly.

Dr Paul: And at half-way up?

Prof Smith: At half-way up, the 2 energies are perfectly equal (*Figure 2*).

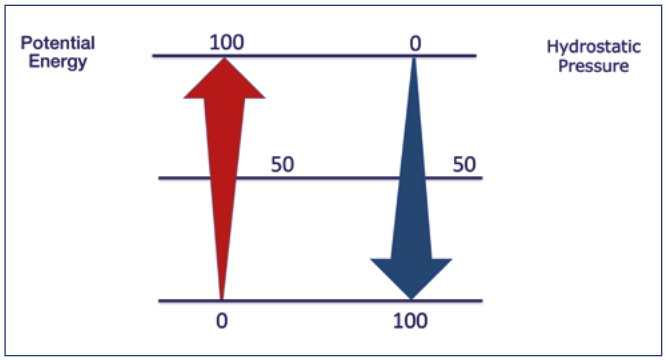


Figure 2. Hydrostatic pressure and potential energy. Where the hydrostatic pressure is maximum, the potential energy is minimum and vice versa.

Dr Paul: I get it. But I don't quite understand the concept of *potential energy*.

Prof Smith: *Potential energy* can also be called *gravitational energy*. Think about the water level in a dam serving a hydroelectric power plant. The *potential energy* is the difference in height between the height of the water in the dam and the base of the dam itself.

Dr Paul: So, in that case, it isn't the difference in pressure that moves the blood.

Prof Smith: You've got it! It isn't the *pressure gradient* but the *energy gradient*.

Dr Paul: But who or what supplies this energy?

Prof Smith: When a patient is standing still, the energy comes from cardiac contraction.

Dr Paul: I know that. But if I remember correctly, this energy is dissipated at the capillary level.

Prof Smith: So how do you think the blood returns from the foot to the heart?

Dr Paul: Respiration, cardiac aspiration, the artery pulsing next to the vein, muscle contraction, and so on.

Prof Smith: Wrong. The blood also returns when you hold your breath and when there are no muscular contractions. What makes the blood return to the heart is a principle known as *vis a tergo*, which is provided by the heart.

Dr Paul: Give me another example, please.

Prof Smith: Think of an elevator. Do you know how an elevator works?

Dr Paul: More or less.

Prof Smith: Maybe it's more helpful if you think of a U-shaped tube, with its two branches filled with a liquid. The level of the liquid will be equal in both branches. You only have to blow lightly into one end to see the liquid overflowing at the other end. That's not the whole story, because you don't find a system of rigid tubes in nature. Still, the analogy is valid for the time being (*Figure 3a*).

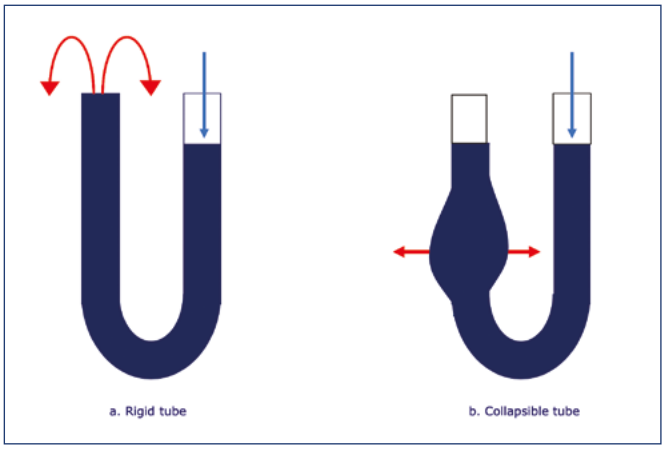


Figure 3. a) In a rigid tube containing liquid, the pressure exerted on one end produces a displacement of the liquid toward the other end. b) In a partially collapsible tube, the transmitted energy initially expands the tube itself.

Dr Paul: But if the pressure in the vein is due exclusively to the distance from the heart, when is it correct to talk of venous hypertension?

Prof Smith: Apart from particular pathologies, such as vein occlusion (mainly acute) and vein malformations, venous hypertension, as such, in the standing (orthostatic) position… does not exist.

Dr Paul: But what about hypertension in de-ambulation? I mean when a patient is walking and has damaged or absent valves? You remember the graphs that are presented at every convention? What's happening there?

Prof Smith: Right. I'll show you that photo. I have it in my phone. Here we are. This is not a case of venous hypertension. Rather, it is the absence of a reduction in venous pressure. It is not that the pressure goes up, but simply that it fails to go down.[5,6]

Dr Paul: Let's have a cup of coffee while I have a good think about all this ...

Prof Smith: In healthy subjects with valves, hydrostatic pressure in the veins decreases while they walk *(Figure 4)*. This is because continent valves break up the column of blood we mentioned earlier.

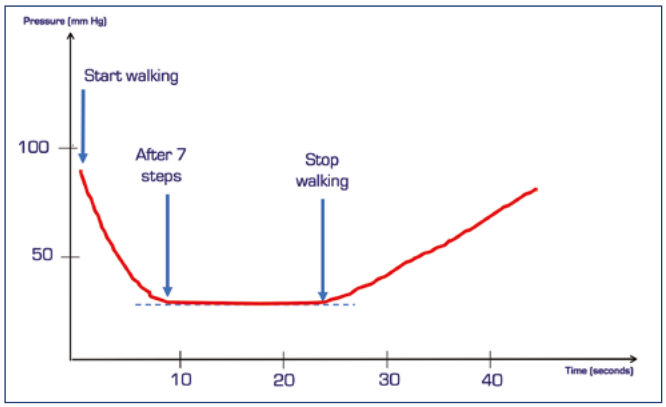


Figure 4. Venous pressure, detected with a needle placed in a dorsal vein of the foot, during walking.

Dr Paul: In other words?

Prof Smith: In other words, when the valve closes at femoral level, the column of blood in question will be the one that goes from that point (ie, the femoral valve) to the foot, and not the one that goes from the right atrium to the foot. Practically half the length. If a valve then closes at a lower point, say at popliteal level, the length is further reduced, and so on until a minimum, which is around 25-30 mm Hg.

But we're oversimplifying. It doesn't happen simultaneously this way in all the veins in a limb.[7] The column of blood doesn't divide if there are no continent valves *(Figure 5)*.

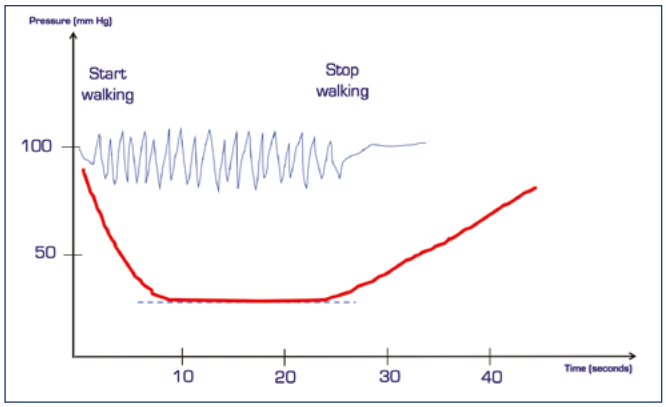


Figure 5. When the valves do not work, venous pressure is not reduced during walking. This represents the absence of physiological hypotension.

In such cases, we always used to talk about "venous hypertension." As you can now see, it was actually a decrease in pressure that failed to take place.[8]

Remember that in the orthostatic position, hydrostatic pressure accounts for 80% of venous pressure. That's why it's so important. To get an idea of what happens, we can take a plastic bottle and make holes in it at various levels. What we observe is that the lowest hole produces a jet of water that goes further than the others (*Figure 6*).

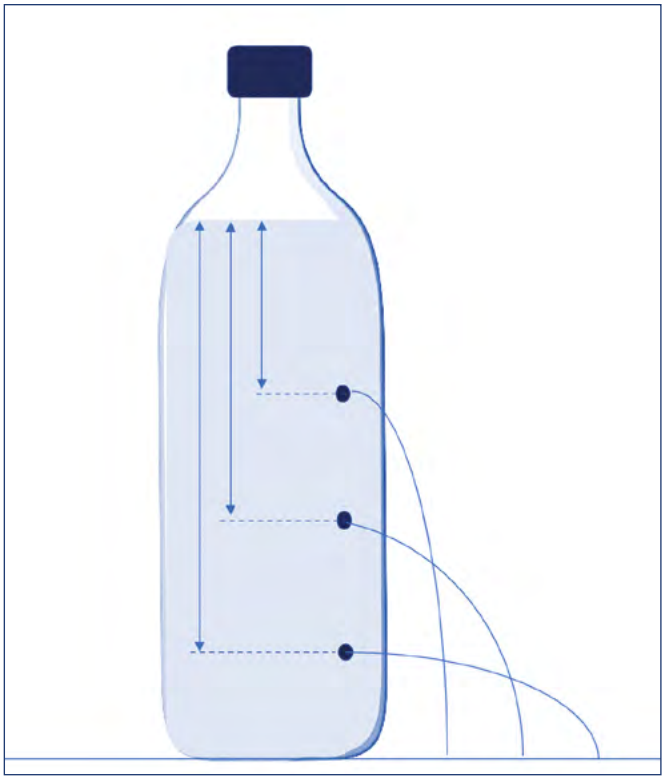


Figure 6. The lowest point has a higher hydrostatic pressure. By making a hole at this level, there will be a longer jet of water.

Dr Paul: But I thought you said that the system is immobile.

Prof Smith: That's right, I did. But if you make holes in the system, the situation changes from a static to a dynamic one. If we inject liquid to keep the level constant, the lowest hole has a longer jet, and the highest hole has a shorter one.

This shows that pressure-derived energy is being transformed into kinetic energy.

Dr Paul: Got it. Apart from hydrostatic pressure, what other factors are involved in venous pressure?

Prof Smith: Static pressure directed toward the vein walls, and dynamic pressure, derived from the *vis a tergo*; but other factors are involved.

During muscle contraction, when intramuscular veins are squeezed, an increase in velocity is created, which can modify the energy. This is because the sum of the various energies is constant, in line with Bernoulli's law.

Dr Paul: I'm not quite with you.

Prof Smith: Remember that the three kinds of energy–hydrostatic, static, and dynamic–act in combination.

As one kind increases, the others diminish in quantity. Incidentally, dynamic energy is more correctly defined as "kinetic energy" and is correlated to the speed of flow.

However, blood volume is also a key factor. Now, we need to talk about vein anatomy.

Dr Paul: I'm still listening.

Prof Smith: Veins are collapsible tubes.

Dr Paul: Right.

Prof Smith: Collapsible tubes vary in diameter according to the amount of liquid they contain. Imagine a plastic bag filled with water and then empty.[9] The venous system is a kind of expanding reservoir that can change its capacity to cope with the amount of blood it needs to contain.[10]

Dr Paul: You mean *compliance*?

Prof Smith: Exactly. This ability to vary its capacity is called *compliance*. Compliance is one of the key factors in the venous system. When empty, a vein presents a flattened profile. When it fills, it takes on a spherical shape in transversal section. When particularly full, it can widen to a point of maximum expansion. This depends on vein-wall pliability.

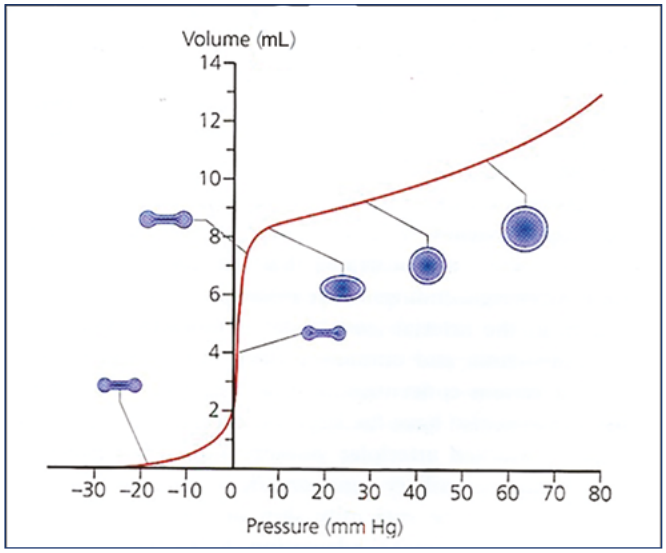


Figure 7. Comparing volume and pressure, pressure will increase only after reaching full volume.[9]

When the vein begins to fill, it maintains a very low pressure until a spherical shape is achieved. From then on, the pressure will increase, and even small variations in volume will be enough to create high increases in pressure (*Figure 7*).

Volume and pressure also vary depending on the anatomical location of the vein and on the position of the body. Take the lower cava system, for example.

Dr Paul: So, the legs.

Prof Smith: Exactly. In the lying position, in certain locations, the leg veins can collapse, whereas in the standing position they fill up. The venous system will accumulate energy by means of wall distension. Before reaching this energy, the blood in the large veins is practically motionless. If you want proof of this, take a duplex probe and place it on the femoral vein in a lying subject. Now have the subject stand up and you will see that there will be a certain amount of time before you can hear a signal. This is due to the filling time of the system and the accumulation of parietal energy.

The analogy of the U-shaped tube I mentioned before is slightly misleading. In veins, one of the branches of the U has a collapsible tube (*Figure 3*). So, before it transfers its energy, it needs to acquire parietal pressure and distend to its maximum. Also, each vein has a different degree of compliance.

Dr Paul: When you speak about collapsible tubes, what happens in the superior cava system?

Prof Smith: Thank you for the question because jugular veins offer a good example of what we mean when talking about collapsible veins.

Let me first say that each system has its own particular characteristics. So, we can't extend these principles to all the veins in the body. However, to give you a better idea of what we mean when we talk about collapsible veins, I want to use the example of the jugular veins.

Dr Paul: Please do.

Prof Smith: When a patient suddenly stands up from supine position, blood will flow rapidly toward the heart, whereas blood from the arterial system can't fill the vein fast enough to maintain the volume at what it was when the patient was lying down. So, the vein caliber has to adapt to a lower volume of blood. In other words, the container adapts to the contents. And when this happens, the various resistances adjust to each other.

Let me give you a more graphic example. Imagine you have a bathroom sink full of water. Now remove the plug, leaving the tap running. Once the sink has emptied, the only flow of

water going down the plughole will be what is coming out of the tap. All you see is the water going down the plughole. But in the part of the sink where there is no water, there is air! In veins there is no air, and that is why the vein has to adapt to the contents.

In a collapsible tube (ie, the vein), the wall has to distend to accumulate the energy required.

During muscle contraction, when intramuscular veins are squeezed, an increase in velocity is created, which can modify the energy. This is because the sum of the various energies is constant, in line with Bernoulli's law.

Dr Paul: What other factors accelerate blood flow?

Prof Smith: Another factor is anatomic. Throughout the system, the global vein section narrows from foot to heart. This is what explains the increase in velocity. The leg often has a double system, but we have a single common femoral vein. Remember that the amount of blood flowing through the common femoral artery is equal, per unit of time, to that flowing through the common femoral vein. That is when other smaller pathways are excluded.

Dr Paul: Is this always the case?

Prof Smith: No, this situation changes continuously according to the collapsible vein concept. Take the example of a sprinter. As he or she runs, three things increase: cardiac output, arterial flow to the legs, and venous return. But after a few seconds, peripheral vasodilation occurs. This leads to a decrease in peripheral arterial resistance, and an increase in arterial flow. It's Poiseuille's Law. The volume of blood circulating redistributes to benefit the legs. Increased flow in the veins reduces lateral pressure, which minimizes venous dilation. When the sprinter stops running, cardiac output goes down rapidly. The venous flow slows down, and the lateral pressure increases, so the vein dilates, accumulating a lot of extra blood volume. As this happens, the flow through the common femoral artery becomes greater than that flowing through the common femoral vein. This is a good example of the way the venous system adapts. The high compliance of the venous wall means that the veins act as a buffer between the arterial flow to the leg and the venous return needed to maintain cardiac output at the right level.

Dr Paul: Are there other factors that increase velocity?

Prof Smith: Yes, valves. In the healthy subject, the valve not only prevents reflux, but also accelerates flow.

Dr Paul: How does this work?

Prof Smith: It's due to the position of the valve cusps, which maintain a semi-open state (*Figure 9*).

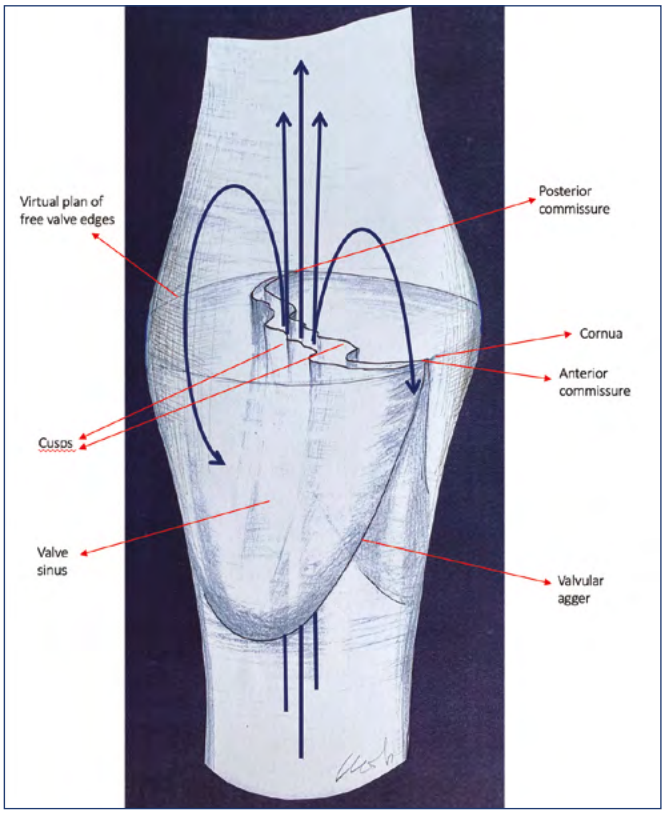


Figure 8. In a valve, the cusps are almost always in a half-open position.

Dr Paul: But if they are in a semi-open state, don't they also create higher resistance?

Prof Smith: Yes. In certain situations, a valve that doesn't open correctly can be an obstacle to flow. This results in higher resistance.

Dr Paul: And when it opens correctly?

Prof Smith: When blood flows through a valve of a standing patient, we normally see only the central portion of the flow; this is not a smooth flow, but a turbulent one. When the muscle contracts, the valve leaflets open, but never fully. Valve resistance is therefore a flow-control mechanism to cope with changed needs.[11,12]

Actually, each of the valves works as a resistor in the venous system. However, there are several mechanisms that compensate for the increased resistance. The valve orifice has a "fish mouth" shape. When the shape shifts from the cylindrical to the fish-mouth shape (that of the valve funnel), a rotational momentum occurs in the blood moving through the vein. As the venous flow increases, it becomes helical (or

spiral). This flow pattern is maintained due to a mechanism whereby each valve in a pair of valves orients at an angle to its partner. Finally, all venous tributaries join the vein at an angle, reinforcing the spiral flow pattern. Spiral flow is much more energy-efficient, which compensates for increased resistance in the valves.[13]

Dr Paul: We talked about resistance, and this reminds me of something. I heard in the last conference that obstruction through increased resistance is also important in determining the signs and symptoms of chronic venous disease.

Prof Smith: That's right, reflux alone has long been valued; however, both obstruction and reflux are important. In a system of collapsible vessels, resistance plays a fundamental role, and given that in PTS they are associated with reflux in two-thirds of cases, you can understand its importance.[14,15]

Resistance is an obstacle to blood flow. The main obstacles are reduced diameter and length of the vein. Resistance is proportional to 8 times the length and inversely proportional to the vein radius to the fourth power.

Acute vein occlusion creates the highest resistance.

During an acute obstruction, the pressure is immediately distal to obstruction, similar to what you see during surgical clamping. Then a collateral pathway forms or dilation takes place, and the pressure drops. When you remove the clamp, the system empties, and the veins return to their usual size. They don't follow the filling and emptying mechanism. At first, emptying is instantaneous, and then it gradually drops off.

A non-ideal elastic system, when distended, does not follow the same process of an ideal material.

Dr Paul: That is?

Prof Smith: When you apply a force and you obtain a linear elongation of the material, this is defined as "ideal." A blood vessel is a viscoelastic tissue. If you apply a force, it changes shape. When the force decreases, the elastic tissue returns to its previous shape. But by reducing the force, we don't get a reverse version of the widening process.

Dr Paul: Could you give me a clear example of pressure/volume correlation in acute phase?

Prof Smith: The clearest proof of the way volume and pressure are related comes from occlusion plethysmography. When you inflate the pressure sleeve to 80 mm Hg, at a certain point you see a plateau.[16,17]

Dr Paul: What does this plateau mean?

Prof Smith: It means the blood is flowing in the veins again. The sleeve has simply created a dam effect.

Dr Paul: And what happens if we increase the pressure to 100 mm Hg?

Prof Smith: We get another plateau. It means the blood is flowing in the veins again. The sleeve has simply created a dam effect.

Dr Paul: But can't the veins get blocked?

Prof Smith: Sure, but the values remain close to those of arterial pressure.

Yes, like those you see during a total blockage, as in surgical clamping. Then what happens is a collateral pathway forms or dilation takes place and the pressure drops.

In the chronic phase, the occlusion will be compensated by collateral pathways and a decrease in resistance.

Dr Paul: I've seen several phlebograms showing compensating collateral pathways.

Prof Smith: Yes, but pay attention, because when we look at a compensation circle during an investigation like phlebography, we are inclined to think that the system is compensated. This is not always the case. To compensate an occluded iliac vein with a diameter of 16 mm (that is, to equalize the flow with the same pressure and length) 256 veins are required with a calibre of 4 mm. So, a radiological image of a collateral pathway does not mean that the flow is normal.

Dr Paul: We spoke about resistance, but what happened with venous pressure?

Prof Smith: An increase in pressure gradient. In all events, during the chronic phase in basic conditions, you can't increase the pressure distally, but during movement, things are different. In this case, pressure may increase, even if only slightly when collateral pathway is not efficient.

Dr Paul: What happens if these collateral pathways can't compensate the obstruction?

Prof Smith: Think of what happens when you dam a river. With a chronic obstruction, where there's a collateral pathway, the pressure must show up as normal.

Dr Paul: So, the leading actor in vein hemodynamics is volume. To sum up: most procedures for treating varicose veins, including thermal ablation, phlebectomy, and so on, work because they reduce the volume.[18]

Prof Smith: Stockings as well. More exactly, they reduce the residual volume. The same is true for procedures aimed at correcting superficial[19] and deep venous reflux.[20,21]

Well, we just arrived at the Conference venue.

Dr Paul: Thanks for the chat. Now I know venous hemodynamics.

Prof Smith: Are you kidding? Venous hemodynamics is very complex,[22,23] and I have only introduced some basic concepts. Many aspects of venous physiology and pathophysiology are not yet known, and others not yet studied. Only those who ignore the structural and functional complexity of this system can claim to have understood everything.

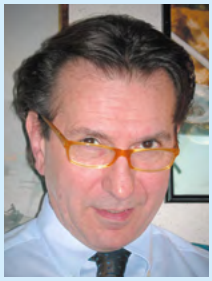
Dr Paul: I understand. I still want to thank you for introducing me to the problem without having to understand complex formulas.

Prof Smith: The complex formulas that you find applied to hemodynamics are often applied in an arbitrary way, as they are based on different experimental models. You will have the opportunity in the future to study all this, and you will probably be the one to master everything that I have not yet understood.

Conclusion

The complexity and partial knowledge of the hemodynamics of the venous system of the lower limbs makes it difficult to understand the mechanism of action of many therapeutic interventions, applied automatically by the phlebologist.

A simple approach could pave the way to better understanding them, as well as encourage more complex studies. Those who find interest in this simple approach will be able to deepen their knowledge by reading the texts and the countless publications on this topic.



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Management of venous ulceration (interventional treatments) with perspectives from a recent meta-analysis and recommendations

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Abstract

Venous leg ulcers still affect about 1% of the adult population despite recent advances in chronic venous insufficiency treatment, and they represent a significant public health cost, estimated at between 1% and 2% of the annual health budget of Western European countries. Venous leg ulcers may be treated conservatively, with compression bandaging and wound care, medically, surgically, or with a combination of approaches, depending on the severity of the ulcer and available resources. The randomized trial of early endovenous ablation in venous ulceration demonstrated that early removal of a superficial venous reflux in patients with leg ulcer, combined with appropriate elastic compression, reduces healing time and increases time to recurrence without ulcer, assessed at 1-year follow-up. Thus, current National Institute for Health and Care Excellence (NICE) clinical guidelines recommend early endovenous treatment in patients with venous ulcers. However, the relative benefit or indications for use of these interventional treatments (surgery, thermal ablation, nonthermal nontumescent techniques, subfascial endoscopic perforator surgery [SEPS], valvuloplasty, and stenting) remain to be definitively shown.

Keywords:

glue cyanoacrylate; laser; mechanochemical endovenous ablation; radiofrequency; SEPS; surgery; ultrasound-guided foam sclerotherapy; venous leg ulcer.

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Introduction

Ulcers of the lower limbs are a major public health problem for which management requires further improvement, particularly in terms of healing time, prevalence, and recurrence rate. Ulcers of venous, or mixed arteriovenous and predominantly venous, origin represent the majority of leg ulcers with an estimated proportion of 70% to 80% of cases. They are painful, disabling conditions that are difficult to treat in a lasting way.

Venous leg ulcers (VLUs) are common and affect up to 1% of the adult population; they represent a significant public health cost, estimated at between 1% and 2% of the annual health budget of Western European countries. Risk factors for venous ulcer correspond to those for chronic venous insufficiency: advanced age (peak between 60 and 80 years old), female sex, history of deep-vein thrombosis, family history of leg ulcer, personal history of obesity, trauma or leg surgery, number of pregnancies,

and prolonged standing. The cost of in-home care for leg ulcers is about 235 million euros (nurses, dressings, antibiotics, and analgesics).

There are various guidelines around the world for the treatment of VLUs, which leads to a disparity in the treatment of patients worldwide. VLUs may be treated conservatively, with compression bandaging and wound care, medically, surgically, or with a combination of approaches, depending on the etiology, pathology, physiopathology, and the severity of the ulcer and available resources.

The current standard of care for chronic venous ulcers involves the use of compression bandages, and this is recommended as the initial standard treatment[1,2]; it exerts its effects in two ways: by reducing ambulatory venous pressure and raising interstitial tissue pressure by directly compressing at the ulcer and surrounding tissue, consequently reducing edema.[3]

In the prevention of recurrence of venous ulceration, a class 3 compression stocking should be used as it significantly reduces the recurrence rate over class 2.[4]

Dressings are applied beneath the compression and are used to control the exudate and to maintain the wound in a moist environment. In the case of a dry wound, a hydrogel and hydrocolloid dressing should be used, whereas highly absorbent dressings such as alginates, hydrofibers, or foam are more appropriate in the case of a highly exuding wound. Dressing changes should be as frequent as necessary.[5,6]

Other adjunct strategies include physical therapy; systemic drug treatments such as micronized purified flavonoid fraction (MPFF), sulodexide, pentoxifylline, aspirin; split-thickness skin graft; and home- or community-based management.[7-13]

An international survey published in 2020 by Heatley et al shows that compression is used in 95% of cases if not contraindicated. Of the respondents (n=787), 78% believe that the treatment of superficial truncal venous reflux by endovenous intervention (radiofrequency or laser) or by surgery improves ulcer healing. Similarly, 80% of respondents believe that treatment of superficial truncal venous reflux by endovenous intervention or surgery reduces the recurrence rate in patients with chronic venous ulceration. Thermal ablation (laser or radiofrequency) alone was the most commonly used, followed by a combination of foam sclerosis and thermal ablation, followed by foam sclerosis alone and open surgery. Mechanochemical ablation (MOCA) and glue were the least used, probably for financial reasons. Finally, 59% of respondents perform endovenous intervention or surgery before the ulcer heals, 19% after healing, and 19% depending on circumstances.[14]

Interventional treatments

Apart from conservative methods, there are currently several techniques for correcting venous hypertension, which is at the origin of trophic disorders, including surgery but also sclerotherapy and endovenous thermal or nonthermal treatments.

The care strategy takes into account several criteria, specified in the Clinical, Etiological, Anatomical, Physiological (CEAP) classification:

- anatomical distinction specifying whether they are superficial, deep, or perforating veins.
- aspects related to etiology, specifying whether it is a primary degenerative venous insufficiency or a secondary pathology, including post-thrombotic.

Treatment of superficial venous reflux

The EVRA study (Early Venous Reflux Ablation)[15] provides the first level of evidence for the benefit of early endovenous treatment of superficial venous reflux in VLUs.

The complete healing time is significantly shorter in the "early removal" group (hazard ratio, 1.38; confidence interval, 1.13-1.68; *P*=0.001) with a mean healing time in this group of 56 days, compared with 82 days in the delayed ablation group.

The mean healing rate at 1 year is 93.8% in the early ablation group versus 85.8% in the delayed ablation group.

The average duration without ulcer is 306 days in the early ablation group and 278 days in the delayed ablation group with a recurrence rate at 1 year of 11% in the early ablation group and 16.5% in the delayed ablation group.

However, there was no significant difference on any of the quality-of-life measurement scales.

This study tends to demonstrate that early removal of a superficial venous reflux in patients with leg ulcer, combined with appropriate elastic compression, reduces the healing time and increases time to recurrence without ulcer as assessed at 1-year follow-up.

Surgery

The ESCHAR study (Effect of Surgery and Compression on Healing And Recurrence) has shown that surgical correction of superficial venous reflux in addition to compression bandaging does not improve ulcer healing but reduces the recurrence of ulcers at 4 years and results in a greater proportion of ulcer-free time.[16] Ulcer healing rates at 3 years were 89% for the compression group and 93% for the compression plus surgery group (P=0.73, log rank test). Rates of ulcer recurrence at 4 years were 56% for the compression group and 31% for the compression plus surgery group (P<0.01).

In their study, Van Gent et al[17] also report that the addition of surgical treatment in patients with venous ulceration leads to a significantly higher chance of being ulcer-free than ambulatory compression therapy alone. This effect persists after 10 years of follow-up, and the number of incompetent perforating veins has a significant effect on the ulcer state and recurrence.

Ultrasound-guided foam sclerotherapy

Sclerosant is a chemical agent that damages the endothelium after injection. Foam can be obtained by mixing liquid sclerosant with air. The most frequently used method of producing foam is the Tessari technique, which consists of rapidly mixing 1 cc of liquid sclerosant with 4 cc of air. Sclerosing foam is more effective than liquid sclerosing agent and is injected by direct puncture or by catheter under ultrasound guidance.[18]

The technique of foam sclerotherapy has been described in a prospective study[19] concerning C5/C6 diseases, with, for Pang et al, a healing rate comparable to that of surgery but a recurrence rate which appears to be lower.

O'Hare et al have published a randomized study comparing foam sclerotherapy associated with compression and compression alone in wound healing. The difference between the two groups is not significant, but recruitment is considered insufficient to conclude.[20]

Finally, a study published by Campos et al compares polidocanol foam sclerotherapy with surgery (n=56, C6, follow-up for 502±220 days): the ulcer healed in 100% and 91.3% of patients treated with surgery or foam sclerotherapy, respectively (P>0.05).[21]

Thermal treatments

Endovenous thermal ablation includes endovenous laser ablation, radiofrequency ablation (RFA), and steam ablation. Tumescent anesthesia is usually applied to prevent adjacent tissue injury from heat, compression, and of emptying the vein for proper contact of the catheter with the endothelium, and it pushes skin away from the catheter in case of shallow varicose veins (<1 cm from skin).

A randomized study evaluating the healing rate (n=52, C6) was carried out in two groups: endovenous laser plus compression or compression alone. After 12 months, Viarengo et al reported a healing rate of 81.5% in the group associated with compression and 24% in the group with compression alone. No recurrence was observed in patients treated with endovenous laser.[22]

In their randomized controlled trial (RCT) VUERT (Venous Ulcer: Endovenous Radiofrequency Treatment trial), Puggina et al compared radiofrequency plus compression (n=27) versus compression alone (n=29) and showed that RFA of insufficient saphenous and perforating veins plus multilayer compressive bandaging is an excellent treatment protocol for venous ulcer patients, because of its safety, effectiveness, and impact on ulcer recurrence reduction and clinical outcome (recurrence was lower in the radiofrequency group [P<0.001]).[23]

Nonthermal nontumescent treatments

Non-thermal techniques including MOCA and cyanoacrylate vein ablation have been developed with a view to removing thermal injury risk. The various techniques of nonthermal ablation that completely avoid the need for tumescent anesthesia reduces the time of the intervention, the per-intervention pain, the bruises, and the sensory nerve lesions.

O'Banion et al reported that a multi-institutional retrospective review of all CEAP 6 patients who underwent closure of their truncal veins from 2015-2020 was performed. A total of 119 patients were included with median follow-up of 105 days; 68 limbs were treated with RFA; and 51 limbs treated with VenaSeal. Median time to wound healing after procedure was significantly shorter for VenaSeal than RFA (43 vs 104 days, P=0.001). ClosureFast and VenaSeal are both safe and effective treatments to eliminate truncal venous insufficiency, and the ulcer recurrence rate was 19.3% (22.1% RFA vs 13.7%).[24]

In a retrospective review, Kim et al compared MOCA and thermal ablation (RFA and endovenous laser therapy) for venous ulcer healing in patients with clinical class 6 chronic venous insufficiency. They conclude that MOCA is safe and effective in treating VLU; younger age and use of MOCA favored wound healing, but randomized studies are necessary to further support their findings.[25]

Synthesis

In a Cochrane review aiming to look at potentially promising treatment with endovenous thermal ablation for healing venous ulcers and preventing recurrence as compared with compression therapy alone, Samuel et al found no RCTs that met inclusion criteria. They concluded that high-quality RCTs are urgently needed for implementation of this treatment in practice."[26]

There is a meta-analysis of RCTs and observational comparative studies that we can refer to, which analyzes the effectiveness of all these surgical and intravenous methods in the context of ulcers. It concludes that such methods are not superior to compression alone on healing and rate of venous ulcer recurrence.[27]

There is a review showing the importance of the EVRA study,[15] which tends to demonstrate that early removal of a superficial venous reflux in patients with leg ulcer, combined with appropriate elastic compression, reduces healing time and increase time to recurrence without ulcer, as seen at 1-year follow-up.

Treatment of perforating veins

The Society for Vascular Surgery (SVS)/American Venous Forum (AVF) Guideline Committee defines "pathologic" perforating veins as those with outward flow of 500 ms, a diameter of 3.5 mm, and location beneath a healed or open venous ulcer (CEAP class C5-C6).[28]

There is an RCT evaluation of the use of conventional surgery to eliminate the flow of perforating veins.[29] The author notes a benefit of surgery in cases of recurrent or medial ulcers, where the time spent without ulcer is longer.

In their RCT, Nelzén et al report that adding subfascial endoscopic perforator surgery (SEPS) to superficial venous surgery is safe and effective for removing incompetent perforating veins in patients with a venous ulcer; however, they do not observe any detectable clinical benefit within 12 months of follow-up.[30]

In a Cochrane review of SEPS for treating VLUs, Lin et al report that the role of SEPS for the treatment of VLUs remains uncertain.[31] However, percutaneous ablation either by ultrasound-guided sclerotherapy or endothermal ablation is recommended to avoid incision on the damaged skin in advanced chronic venous disease.[32] The initial success rate after percutaneous ablation varies between 50% and 70%, and repeated procedure is common. Successful ablation is associated with ulcer healing in recalcitrant cases.[33,34]

Treatment of deep venous reflux

Venous reflux is a retrograde venous flow in an incompetent vein during ambulation in upright position. Treatment of reflux results in decreasing mean ambulatory venous hypertension, logically leading to ulcer healing and decreased recurrence.[27]

Surgery has a very specific place here: in the context of a primitive reflux, the most appropriate technique appears to be valvuloplasty, which has a 70% absence of recurrence of ulcers at 5 years. In the framework of a post-thrombotic syndrome, Maleti and Perrin report a 50% success rate at 5-year follow-up for clinical and hemodynamic results from transposition and transplantation. The clinical results for the new valves are encouraging.[35]

Treatment of deep venous obstruction

Iliocaval vein obstruction can occur after deep-vein thrombosis or can be related to external compression. Iliac vein lesion has been shown to be the significant cause of chronic venous disease, with a 20% prevalence in two studies.[36,37]

The standard treatment in iliocaval vein obliteration is endovascular angioplasty with mandatory stenting.

Treatment of chronic venous ulcer

We include in this overview from "ESCHAR to EVRA" a multicenter retrospective cohort study that used a standardized database to evaluate patients with chronic venous ulcers treated between January 2013 and December 2017 (n=832).[38]

At 36 months of follow-up, the ulcer healing rates according to treatment were: 75% of the 187 patients treated by compression and wound care management alone, 51% of patients who underwent truncal vein ablation alone, 68% of patients who received both superficial and perforator ablation, 77% of those who underwent stent placement alone, and 87% of those who underwent deep-venous stenting and ablation of both incompetent truncal and perforator veins.

Interventional treatment when deep anomalies (combination of obstruction and reflux) are associated with superficial venous reflux

Currently, the literature does not define precisely whether deep or superficial treatment should be performed first. However, 3 articles give us some interesting insights, discussed here.

The May-Thurner syndrome (also known as Cockett's syndrome) is thought to be a relatively rare contributor to chronic venous disease, predominantly affecting the left lower extremity of young women. In his study, Raju[36]shows that stenting alone (nonthrombotic iliac vein lesions), without correction of associated reflux, often brings relief. The cumulative results observed 2.5 years after stent placement in the nonthrombotic-iliac-vein-lesion subsets with reflux and without reflux indicated complete stasis ulcer healing in 67% and 76%, respectively. The relationship between superficial and deep venous reflux and why deep venous reflux is sometimes resolved after greater saphenous treatment needs further investigation.

In Puggioni's series,[39] after greater saphenous vein ablation, deep reflux disappeared in only 24% of limbs, and reflux time and velocity did not significantly improve.

Maleti et al[40] show in their study that the failure to correct deep axial reflux by superficial ablation in patients with superficial and associated primary deep axial reflux may be related to asymmetry in the leaflets of the incompetent deep venous valve. If the valves are symmetrical, it is advisable to first treat the superficial system alone. Conversely, if they are asymmetrical, valvuloplasty associated with varicose vein ablation might be indicated.

Recommendations

Gianesi et al published "Global guidelines trends and controversies in lower limb venous and lymphatic disease: Narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics, 23–25 January 2019"[41] and summarize the indications to interventional procedures for venous ulcer management in *Table I* below.

Although a general agreement toward the application of procedures in venous ulcer management exists in all the guidelines evaluated, there is significant heterogeneity in the reported grade of evidence.

The EVRA trial demonstrated that early removal of a superficial venous reflux in patients with leg ulcer, combined with appropriate elastic compression, reduces healing time and increases time to recurrence without ulcer as assessed at 1-year follow-up. Thus, NICE currently recommends early endovenous treatment in patients with venous ulcers.

Siribumrungwong et al summarized treatment modalities other than compression therapy to manage VLU according to pathophysiology and includes guideline evidence in *Table II* below.[42] *Table III* indicates adjunct treatment strategies to compression therapy alone.[42]

	USA AVF/SVS 2011 (GRADE)	AUSTRALIA 2001 (A-D)	UK NICE 2013-2016	USA AVF/SVS 2014 (GRADE)	EUROPE ESVS 2015 (I-III; A-C)	LATAM 2016 (GRADE)	EUROPEAN DERMATOLOGY FORUM 2016 (I-IV)
Venous procedure	**IA** ablation of the incompetent vein	Possible beneficial effect, but not enough evidence to overcome standard care	Patients with chronic venous leg ulcer and superficial venous reflux should be considered for superficial venous surgery for recurrence	**IB** For healing **IC** For recurrence risk reduction	**IB** The possibility of active venous intervention should be explored for venous ulcer healing **IIaB** Foam sclerotherapy as primary treatment in elderly and frail patients with venous ulcers	**IA** ablation of the insufficient superficial venous system plus compression to reduce recurrence **2B** Treatment of the incompetent perforating vein located around an open or closed ulcer **2C** SEPS, ultrasound-guided sclerotherapy or thermoablation for the incompetent perforating vein treatment	**I** Short Stripping + SEPS for combined superficial and perforator insufficiency **III** Sclero-compression therapy to improve healing

Table I. Indications for interventional procedures for venous ulcer management.
After reference 41: Gianesini et al. Phlebol J Venous Dis. *2019;34(1 suppl):4-66. © 2019, SAGE Publications.*
AVF, American Venous Forum; ESVS, European Society for Vascular Surgery; LATAM, Latin American Working Group; NICE, National Institute for Health and Care Excellence; SEPS, subfascial endoscopic perforator surgery; SVS, Society for Vascular Surgery.

Pathophysiology	Treatment	Evidence and grade of recommendation
Reduce ambulatory venous hypertension		
Outflow occlusion		
Iliac vein stenosis or occlusion	• Endovascular angioplasty and stenting • Open bypasses procedure (after failed endovascular treatment and recalcitrant ulcer) • Deep venous obstruction should be treated first, before considering treatment of deep venous reflux	1C[a]; Class IIa, B[b] 2C[a] Class I, C[b]
Infrainguinal stenosis or occlusion	• Endophlebectomy, or autogenous venous bypass (only recalcitrant ulcer) to aid healing and prevent recurrence	2C[a]
Valvular incompetence and reflux		
Deep venous reflux	• Valve repair (external banding, external, and internal valvuloplasty), valve transposition or transplantation • In the absence of deep venous obstruction, and after abolition of superficial venous reflux, open repair of deep venous reflux in severe CVD should be considered	2C[a] Class IIb, C[b]
Superficial venous reflux with active venous ulcer	• Ablation to aid ulcer healing • Ablation to prevent recurrence	2C[a] 1B[a]
Superficial venous reflux with healed venous ulcer	• Ablation to prevent recurrence	1C[a]
GSV reflux	• Endothermal ablation is preferred over surgery and foam sclerotherapy	Class I, A[b]
SSV reflux	• Endothermal ablation should be considered	Class IIa, B[b]
Pathologic perforator in CEAP C5-6	• Ablation to aid ulcer healing and prevent recurrence in pathologic perforator with/without superficial reflux • Percutaneous technique is preferred over open surgery	2C[a] 1C[a]
Calf muscle function and limited ankle range of motion	• Supervised exercise to reduce pain and edema	2B[a]

Table II. Non–compression therapy treatment modalities for venous leg ulcer management, according to pathophysiology.

After reference 42: Siribumrungwong et al. Compression and Chronic Wound Management *[Internet]. 2019:81-103. Cham: Springer International Publishing. http://link.springer.com/10.1007/978-3-030-01195-6_5. © 2019, Springer Nature Switzerland.*

CEAP, Clinical, Etiological, Anatomical, Pathophysiological classification; CVD, chronic venous disease; GSV, great saphenous vein; SSV, small saphenous vein.

[a]Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum 2014.[2] Grade of recommendation: 1, strong; 2, weak recommendation. Level of evidence: A, high; B, moderate; C, low quality.

[b]Clinical practice guidelines of the European Society for Vascular Surgery 2015.[1] Class of recommendation: I, treatment beneficial, recommended; II, conflicting evidence and/or divergence, opinion; IIa, favor of usefulness and efficacy; IIb, usefulness/efficacy is less well established; III, treatment not useful, not recommended. Level of evidence: A, from meta-analysis or multiple randomized controlled trials; B, single randomized controlled trial, or large nonrandomized studies; C, consensus, retrospective studies, or registries.

Treatment	Strategy	Evidence and grade of recommendation
Local inflammatory effects		
Micronized purified flavonoid fraction or pentoxifylline	• Should be combined treatment with compression therapy to fasten and aid in ulcer healing	1B[a]
Sulodexide and micronized purified flavonoid fraction	• Should be considered as adjuvant therapy in venous ulcer	Class IIa, A[b]
Other modalities		
Split-thickness skin grafting	• In selected patients with large ulcer that failed conservative treatment for 4-6 weeks	2B[a]
Leg elevation	• May be considered when compression is not tolerated and in conjunction with compression during resting	Class IIb, C[b]

Table III. Adjunct treatment strategies for venous leg ulcer management (in combination with compression therapy).
After reference 42: Siribumrungwong et al. Compression and Chronic Wound Management [Internet]. 2019:81-103. Cham: Springer International Publishing. http://link.springer.com/10.1007/978-3-030-01195-6_5. © 2019, Springer Nature Switzerland.
[a]Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum 2014.[2] Grade of recommendation: 1, strong; 2, weak recommendation. Level of evidence: A, high; B, moderate; C, low quality.
[b]Clinical practice guidelines of the European Society for Vascular Surgery 2015.[1] Class of recommendation: I, treatment beneficial, recommended; II, conflicting evidence and/or divergence, opinion; IIa, favor of usefulness and efficacy; IIb, usefulness/efficacy is less well established; III, treatment not useful, not recommended. Level of evidence: A, from meta-analysis or multiple randomized controlled trials; B, single randomized controlled trial, or large nonrandomized studies. C; consensus, retrospective studies, or registries.

Conclusion

VLUs still affect about 1% of the adult population despite recent advances in chronic venous insufficiency treatment.

After confirming the diagnosis of venous ulcer, 3 main lines of treatment are considered: adjunctive treatment, concomitant treatment of the cause of venous hypertension, and compression therapy.

A recently published RCT (EVRA) suggests benefit of early, as compared with deferred, endovascular ablation for those with VLUs in terms of reduced healing time and extended ulcer-free recurrence time.

However, the relative benefit or indications for use of these interventional treatments (surgery, sclerotherapy, thermal ablation, nonthermal nontumescent techniques, SEPS, valvuloplasty, and stenting) remain to be definitively shown.

Percutaneous ablation either by ultrasound-guided sclerotherapy or endothermal ablation is recommended to avoid incision on the damaged skin in advanced chronic venous disease; the potential benefits, in particular a reduced risk of nerve damage associated with nonthermal techniques, might be of considerable clinical importance and may lead to a preference for such techniques in the future.

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Microcirculatory disorders in chronic venous diseases and fundamentals of their systemic pharmacological correction

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Abstract

This article reviews the literature on microcirculatory disorders underlying the development of chronic venous diseases (CVD) across all the CEAP (Clinical-Etiology-Anatomy-Pathophysiology) clinical classes from C0s to C6 and the fundamentals of their systemic pharmacological correction particularly with micronized purified flavonoid fraction (MPFF). Anatomical and functional changes specifically in the vessels of the microvasculature are the main pathogenetic mechanism for the development of most vein-specific symptoms and determine CVD progression. The altered vessels of the microvasculature are characterized by valvular incompetence and tortuosity that make them similar to glomerular capillaries. The main morphological alterations are a decrease in the functional capillary density; an increase in the dermal papilla diameter, capillary glomerulus, and capillary diameter; as well as an increase in the ratio of abnormal capillaries. These early changes are already observed at clinical class C0s. Atypical microcirculatory vessels lose their ability to maintain venoarteriolar reflex and vasomotor function. Increased vascular wall permeability leads to formation of perivascular extravasates. Inflammation and congestion decrease transcutaneous O_2 pressure and increase CO_2 pressure, which is associated with an increased generation of free radicals and triggers of tissue damage. Evidence from clinical and experimental studies suggests that MPFF can reduce permeability and diameter of microvasculature vessels, modulate leukocyte-endothelial interactions and, therefore, reduce leukocyte activation and vein-specific inflammation by inhibiting the secretion of adhesion molecules and proinflammatory cytokines. In addition, MPFF has free-radical scavenging properties and increases venous contractility. These properties substantiate a high efficacy of MPFF and strong recommendation for its use in the recent international CVD guidelines for the treatment of pain, heaviness, feeling of swelling, functional discomfort, cramps, leg redness, skin changes, edema and quality of life, as well as for the healing of leg ulcers in patients with CVD. Given the scarce data on the reversibility of microcirculatory changes in the management of CVD, it is reasonable to consider MPFF in the management of CVD patients.

Introduction

Chronic venous diseases (CVD) refer to a diverse group of morphological or functional abnormalities of the venous system affecting deep, superficial, and/or intradermal veins.[1] Despite the etiological heterogeneity, all CVD forms share a common pathogenesis, in particular, the microcirculatory alterations, which underlie the development of venous symptoms and the progression of skin trophic disorders.[2] Microvasculature changes have a number of typical morphological and functional features. In general, morphological alterations are similar to those in the saphenous veins and are manifested by the vein tortuosity and formation of venous reflux, which can occur in this vascular territory with or without the concomitant hemodynamic changes in the saphenous veins.[3]

Studies have revealed the presence of valves in the arteriovenous anastomoses at the level of postcapillary venules, as well as efferent venules, with a typically bicuspid structure, although in rare cases the unicuspid and tricuspid valves have been described.[4] In the lower limbs, valves are found in the veins with a diameter of greater than 18-20 μm.[1,4] Structurally, the valves are composed of 2 layers of endothelial lining on the basal membrane consisting of collagen fibers.[4]

In a study with retrograde venous filling of amputated lower limbs with a contrast media, microvalves were identified down to the sixth generation of tributaries from the great saphenous vein (GSV).[3] They were most prevalent in the third generation of tributaries, constituting the "boundary" microvalves that prevented reflux extension into the microvenous networks in the skin. In addition, the third and higher generation veins without valves were identified, which played the role of collaterals, shunting blood flow to the distal branches of the capillary bed bypassing the competent veins.[3]

In the lower limbs with signs of severe chronic venous insufficiency (CVI), the reflux of contrast media was extended down to the venules of the capillary network of the skin, which had a dilated tortuous structure and stretched valves.[3] The advanced classes of CVI were characterized by retrograde blood flow in both the conducting veins and skin venules.

In a number of patients, reflux in the capillary network in the skin is observed even if GSV is competent.[3] Instrumental studies have shown that the occurrence of venous symptoms in patients with clinical class C0s is associated with an isolated retrograde blood flow in the microvasculature vessels, with retention of residual venous volume in them.[2] In such patients, venous occlusion plethysmography reveals the reduced emptying of the venous reservoir and reduced venous refilling time, compared with healthy individuals.[2]

As CVD progresses from low to high grade, the number of functional capillaries in the skin decreases.[5,6] The remaining capillaries acquire a tortuous shape with a large number of loops, which makes them similar to the renal glomeruli.[5,6] The transition from C0 to C5 class was shown to be associated with the reduction in the number of capillaries amenable for the assessment from 8 (5-10) to 4 (2-5), whereas the number of convoluted loops in capillary glomeruli increases from 1 to 8 (5-10).[5] In the center of white atrophy spots, no capillaries are visible (avascular fields).[6]

Orthogonal polarization spectral (OPS) imaging is a method used to quantify morphological features of glomerulus-like capillaries.[7] The CVD progression from C1 to C5 class was found to be associated with a reduction in the functional capillary density (FCD), ie, the density of capillaries with flowing red cells (from 20.9 ± 6.1 to 12.1 ± 8.1 cap/mm^2) and an increase in the diameter of dermal papilla (from 111.4 ± 13.5 to 223.9 ± 126.9 μm), diameter of capillary bulk (from 52.8 ± 8.8 to 149.1 ± 56.3 μm), and capillary diameter (from 8.1 ± 0.8 to 11.1 ± 2.9 μm), as well as with changes in capillary morphology (% of abnormal capillaries within the field of view; from 3.6 ± 5.5% to 75.2 ± 37%).[7]

Comparison of atypical capillaries revealed significant differences in the above parameters between patients with clinical class C1 and healthy individuals.[7] Moreover, the alterations were also observed in patients with clinical class C0s. Compared with healthy individuals, the latter group had a significantly lower FCD and a significantly greater diameter of dermal papilla, which can be considered the first morphological response to the development of venous hypertension.[1] In addition, there was a trend toward an increase in the diameters of the capillary bulk and of capillaries; however, this finding did not reach statistical significance versus healthy controls.[1]

Structural changes in the microvasculature vessels are associated with the loss of a number of their functions, including the ability to produce the venoarteriolar reflex (VAR), which explains an increase in intradermal blood flow in the orthostatic and sitting positions.[2] VAR is a local protective axonal reflex with arteriolar vasoconstriction in response to a change in the body position, which provides a decrease in cutaneous blood flow by 40% to 50% or more and prevents the development of hypertension and edema at the microcirculatory level.[2,8] The laser Doppler flowmetry shows

a reduction in the difference in microcirculatory blood filling between the supine and orthostatic positions by up to 30% already in clinical class C0s.[2]

Dysfunction of microcirculation vessels results in a reduction in their vasomotor activity, as evidenced by laser Doppler flowmetry data. In patients with CVD, the microcirculatory index, which depends on the number of red blood cells (RBCs) reflecting the laser beam, is significantly increased due to venous stasis.[9,10] The skin flux (the concentration of moving blood cells multiplied by the magnitude of the median velocity) also decreased and became smaller with CVD progression and at higher clinical class levels.[10] Starting from C4 class, these variations in some patients can be smoothed to a straight line.[10]

Atypical capillaries show increased wall permeability, as determined by microscopy and verified by intravenous administration of a fluorescent dye.[6] With light microscopy, a "cobblestone pavement" pattern is clearly visualized around the altered capillaries, which is explained by various-diameter extravasates of capillary bed contents, consisting of fibrin/fibrinogen, other proteins, and polysaccharides.[9,11,12] Hyperpigmentation can be observed along the edges of such "halo" due to accumulation of hemosiderin, a product of hemoglobin degradation.[9] The injected fluorescent dye, spreading beyond the capillary wall, creates a high-intensity glow in the pericapillary space, which is most pronounced in patients with CVD of clinical class C3 or higher.[9] At the same time, a high concentration of the dye is achieved much faster than in healthy individuals. Differences in the diameter of the glow zone were also observed (138 ± 13 μm and 81 ± 15 μm, respectively).

In severe CVI, the filling of capillaries with a fluorescent dye in the observation area is slowed down, which is explained by the inhomogeneity of the perfusion of microvasculature.[9] In some areas, the distribution of contrast agent is halted due to the occurrence of RBC sludges, which may be explained by microthromboses.[9,12] The latter, in turn, can result in micronecroses in the perivascular space.[12]

Pericapillary edema, as a consequence of high permeability of the vascular wall, creates conditions for an increase in the intraneural pressure in adjacent nerves, which, in turn, activates their alpha fibers and leads to the occurrence of pain and a feeling of heaviness in the lower limbs.[13]

Blood congestion in the abnormal vessels of the microvasculature is accompanied by a decrease in the transcutaneous oxygen pressure ($TcPO_2$), an increase in the transcutaneous carbon dioxide pressure ($TcPCO_2$), and high concentrations of free oxygen radicals.[6] The $TcPO_2$ is measured using the Clark electrode. The current on the probe exposed to the tissue oxygen is measured and is proportional to the oxygen content in capillaries.[6] A reduction in the $TcPO_2$ from 56.8 ± 9.9 to 47.7 ± 14.5 mm Hg was revealed in patients with CVD, compared with healthy individuals. The reduction was even greater (down to 22.5 ± 7.0 mm Hg) and achieved statistical significance in patients with trophic changes (hyperpigmentation, lipodermatosclerosis, healed trophic ulcer). In the late stages of CVI with the development of lipodermatosclerosis, there is an increase in type IV collagen synthesis, which results in the vessel wall thickening and an increase in its permeability.[14] The concomitant fibrosis in the pericapillary space creates a barrier preventing transmembrane diffusion.[15] Disturbance of microcirculatory tissue perfusion is associated with an increase in $TcPCO_2$.[16,17] One of the effects of CO_2 is vasodilation of capillaries, which contributes to the further progression of stasis and results in an even more significant increase in CO_2.[16] The reduction in stasis during topical treatment with a venoactive combination agent (escin + heparin + essential phospholipids) results in an improvement in tissue perfusion, which is manifested by an increase in $TcPO_2$ and a decrease in $TcPCO_2$.[16,17] The severity of venous symptoms correlates with these parameters and decreases with the improvement in tissue perfusion.[18]

Venous stasis and hypoxia are associated with an increase in expression of plasma free radicals (PFRs) in capillary blood, which are considered one of the triggers of tissue damage and which slow down tissue repair.[19] The major source of PFRs are leukocytes, which are active participants in inflammation of the vascular wall in microvasculature in patients with CVD.[20] Spectroscopy of blood obtained from the skin puncture site in the area of interest showed that concentration of oxidation products in patients with high ambulatory pressure and low venous refilling time is significantly higher than in healthy individuals.[19,21] The treatment targeted at improving microcirculation is associated with changes in PFR levels.[21] Studies have demonstrated a reduction in the PFR level in patients who received compression therapy (stockings with compression level of 20 mm Hg) in combination with a venoactive drug (VAD), or topical therapy with venoactive combination agent (escin + heparin + essential phospholipids).[19,21] In patients with CVD, a significant difference from baseline was reported after 2 and 4 weeks of treatment.[19,21] The reduction in PFRs was associated with a decrease in the severity of venous symptoms, such as edema, pain, feeling of swelling, and restless legs.[21]

Pharmacological effects in microcirculatory disorders

Experimental animal models of venous hypertension have been developed to study pathophysiological mechanisms underlying CVI, as well as to investigate opportunities for pharmacological correction. The animal model most closely representing the pathogenesis of venous hypertension is a rodent (hamster) model based on external iliac vein ligation, which results in substantial changes in saphenous veins without inducing systemic fluctuations in venous pressure.[20] All changes were significant compared with those in hamsters after sham surgery without vein ligation. Chronic venous hypertension reaches its maximum severity in 6 to 10 weeks and is manifested by an increased pressure in the saphenous veins, decreased number of functional capillaries (with preserved blood flow), as well as signs of intensive rolling of leukocytes, their adhesion to the walls of capillaries, and dilation of venules while maintaining the diameter of arterioles. In this rodent model, oral administration of MPFF or diosmin alone was found to be effective in reducing these changes.[20] During the pharmacotherapy, a decrease in the rolling and adhesion of leukocytes and an increase in the number of functional capillaries were observed. The beneficial effects of MPFF were significantly greater than with diosmin alone, and only MPFF provided a decrease in the diameter of venules in venous hypertension.

The MPFF effect on the microvascular function can also be assessed using the models of angiopathy in other vascular territories. Stimulation of the vasculature of hamster cheek pouch by the application of bradykinin or histamine for 5 minutes causes abundant diffusion of the fluorescent dye through the vascular wall.[22] The effects of systemic therapy with MPFF for 10 days compete with the vascular effect of topical agents, contributing to a decrease in the permeability of postcapillary venules.[22] The same effect of MPFF is also observed in the experiment with reperfusion of the microvascular bed of hamster cheek pouch after 30-minute ischemia induced by clamping of the main feeding artery.[22,23] A reduction in the venular permeability is associated with a decrease in leukocyte adhesion to the venular endothelium.[22,23]

In the model of ischemia-reperfusion in the hamster skin flap, the MPFF treatment was associated with a weak adhesion of leukocytes to the endothelium of venules, compared with controls without the MPFF treatment.[24] This effect of the drug prevails over the hemodynamic effect, as evidenced by the absence of changes in the parameters of blood flow velocity in the venules of the skin flap after reperfusion.[24]

In mesenteric venous hypertension, the effects of MPFF are similar to those in the CVD model.[25] Thus, 1-week treatment with MPFF in rats resulted in a faster return of the diameter of venules to normal values during reperfusion of the mesenteric territory, without changing the blood flow velocity parameters. Besides the inhibition of local leukocyte-endothelial adhesion in the experiment, the anti-inflammatory action of the drug is manifested by a systemic reduction in the activity of circulating leukocytes, with suppression of CD62L gene expression, a decrease in pseudopodia formation, and negative results for a nitroblue tetrazolium (NBT) test.

MPFF also modulates leukocyte-endothelial adhesion in postcapillary venules of skeletal muscles after ischemia, accompanied by an increase in levels of adhesion molecules (P-selectin and intercellular adhesion molecule 1 [ICAM-1]),[26] and results in a decreased rolling and adhesion of leukocytes in the damaged muscle.

In an experiment with injection of a sclerosing agent in the dorsal vein of a rabbit ear, the effect of MPFF on microcirculation was manifested by a decrease in the diameter of venules, an increase in the number of functional capillaries, and a decrease in their permeability.[27] This experiment has also demonstrated the characteristic effect of reducing leukocyte rolling and adhesion.

The MPFF effect on the capillary bed is manifested by a reduction in vascular permeability, an improvement in vascular resistance, a decrease in blood stasis, and an increase in blood flow and RBC flow rates.[28,29]

In clinical practice, MPFF administration in patients with clinical class C1 of CVD undergoing sclerotherapy alleviates the local inflammatory response to the procedure.[30] This is confirmed by a significant decrease in the local concentration of inflammatory markers (C-reactive protein, interleukin [IL]-1, tumor necrosis factor [TNF], vascular endothelial growth factor [VEGF], and histamine), compared with the control group without MPFF.[30] The VEIN ACT PROLONGED-C1 observational program (Administration of Micronized Purified Flavonoid Fraction During Sclerotherapy of Reticular Veins and Telangiectasias) has shown that in patients undergoing sclerotherapy, MPFF treatment is associated with an improvement in the patient's quality of life (QOL), and a significant decrease in sensation of leg heaviness, pain, swelling, and itching.[31] Similar clinical results were obtained in the SYNERGY survey, which included patients with CVD of clinical classes C1-C3.[32] In patients undergoing sclerotherapy, MPFF administration allowed an achievement of treatment satisfaction in 81% of patients, not

only in terms of a cosmetic effect of the procedure, but also in reduction in the severity of venous symptoms.

The treatment efficacy of MPFF has been demonstrated in a large number of studies, which provided grade A evidence for the use of MPFF in monotherapy for CVD.[33] MPFF treatment is associated with a reduction in the severity of leg pain and heaviness, feeling of swelling, nocturnal cramps, and edema of the lower limbs, as well as with a QOL improvement both in clinical classes C0s-C1s and in CVI, including those with trophic disorders up to active venous ulcers (C4 and C6).[33-35] The efficacy of MPFF as regards accelerating ulcer healing in the comprehensive treatment of venous ulcers is determined by improvement of microcirculation and reduction in venous inflammation, as demonstrated in a meta-analysis.[36]

Pathogenetic basis of microcirculatory disorders in CVD and the MPFF action

Blood reflux, stasis, and tissue hypoxia at the microcirculation level determine changes in the activity of the endothelium, with modulation of the expression of adhesion molecules on endothelial cells, including vascular cell adhesion molecule 1 (VCAM-1), ICAM-1, lymphocyte function-associated antigen 1 (LFA-1), and very late antigen 4 (VLA-4).[28,37,38] Changes in endothelial cell phenotype result in an increased adhesion of leukocytes and their activation. Activated leukocytes are a source of enzymes and oxygen free radicals that are released into the environment.[39] Unlike saphenous veins, capillaries do not have a typical 3-layer wall structure, and as a result, lytic enzymes of leukocytes destroy subendothelial and pericapillary structures.[28] Activated cells secrete various cytokines, including IL-8; regulated on activation, normal T-cell expressed and secreted (RANTES; also known as chemokine [C-C motif] ligand 5); monocyte chemoattractant protein-1 (MCP-1); macrophage inflammatory protein 1beta (MIP-1ß); and VEGF.[40] A variety of cytokines, which are secreted by activated leukocytes and endothelial cells, contributes to the activation of fibroblasts and further attraction of monocytes and mast cells, which are also a source of enzymes and mediators.[28,39] One of the significant mechanisms of damage to the capillary wall is the destruction of extracellular matrix by matrix metalloproteinases (MMP), which are secreted by activated leukocytes, endothelial cells, and other cells.[41,42] MMPs destroy both collagen and elastin[43] and also damage glycocalyx on the endothelial surface, which results in an exposure of adhesion receptors and increased leukocyte-endothelial adhesion.[41]

Changing properties of the endothelium–due to its activation and cytokine aggression, as well as enzymatic damage to subendothelial structures–result in an increase in capillary permeability, with the possibility of extravasation of not only plasma, but also large molecules.[28,39]

MPFF has anti-inflammatory properties, reduces vein-specific inflammation in the vessel wall, and has a protective effect on the surrounding parenchyma.[25] MPFF was shown to decrease expression of adhesion molecule CD62L on leukocytes and levels of plasma-soluble markers of endothelial activation–sVCAM-1, sICAM-1–which results in modulating the endothelial-leukocyte interactions without affecting leukocyte function and provoking leukopenia.[44-47] In patients with trophic changes of skin, MPFF decreases the levels of lactoferrin and VEGF; normalizes the levels of prostaglandins E2, F2, and thromboxane B2; and suppresses platelet activation.[28,45,48]

Treatment with MPFF suppresses the production of oxygen free radicals by activated polymorphonuclear neutrophils and macrophages, which contributes to a decrease in capillary permeability and a damaging effect on tissues.[49,50]

An experiment has shown that in veins of a larger caliber containing a muscle layer, MPFF treatment prolongs the action of norepinephrine and increases the sensitivity of the contractile apparatus of the vascular wall to Ca^{2+}, as well as venous contractions.[51-53] The restoration of normal venous tone in large veins can indirectly reduce blood stasis in the microvasculature and, therefore, the severity of clinical manifestations of venous symptoms.[54]

Conclusion

Microcirculatory disorders underlie the development of CVD and its progression across all its clinical classes. Anatomical and functional changes specifically in the vessels of the microvasculature are the main pathogenetic basis for the development of most vein-specific symptoms and determine CVD progression. Treatment aimed at elimination of microcirculatory disorders is associated with an improvement in the QOL of patients and a decrease in the severity of CVD symptoms. Today, the effects of MPFF in the treatment of CVD have been assessed in a large number of clinical and experimental studies, clearly demonstrating its undoubted efficacy. In recent international CVD guidelines, MPFF is strongly recommended for the treatment of pain, heaviness, sensation of swelling, functional discomfort, cramps, leg redness, skin changes, edema, and QOL, as well as for the healing of leg ulcers in patients with CVD.[33] When choosing treatment

strategy in patients with any class of CVD, it is necessary to consider the lack of data on the reversibility of microcirculatory disorders on top of any conservative or surgical treatment. The probable persistence of changes in the microvasculature may cause relapses in venous symptoms and indicate the need for regular supportive courses of conservative therapy with VADs, primarily with MPFF.

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