Phlebolymphology

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The vein of Giacomini: an in-depth review of its anatomy, hemodynamics, and treatment alternatives *4*
Agnieszka NOWAK-TARNAWSKA, Lourdes REINA-GUTIERREZ *(Spain)*

Microcirculatory alterations in chronic venous disease: observation from $C0_s$ to C5 patients (CEAP classification) *13*
Carlos Eduardo VIRGINI-MAGALHÃES, Eliete BOUSKELA *(Brazil)*

Lipedema, lymphedema, lipohypertrophy, and obesity: how do we differentiate? *20*
Erika MENDOZA *(Germany)*

Optimal management of combined iliac vein stenosis and ovarian vein reflux in patients with pelvic venous disease (PeVD): which patients should be treated for both and what comes first? *28*
Karem HARTH, Gloria SALAZAR *(USA)*

Mechanochemical ablation (MOCA), a nonthermal nontumescent ablation (NTNT) technique for the treatment of chronic venous disease (CVD): our experience and its benefits in Latin America *38*
Paola ORTIZ *(Uruguay)*

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Phlebolymphology

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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Content

Vol 31, No. 1, 2024

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4

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Editorial

Dear Readers,

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

A. NOWAK-TARNAWSKA and **L. REINA-GUTIERREZ** ***(Spain)*** review the anatomy of the Giacomini vein, its hemodynamics and reflux variations depending on its valve arrangement that leads to 2 different types of reflux, and the minimally invasive treatment modalities for Giacomini-vein-related venous insufficiency that must be focused on the point of reflux.

The progression of chronic venous disease is associated with the perpetuation of an inflammatory process that translates early into microscopic changes at the level of the venous wall and valve structures, and the extensive cutaneous capillary network of the lower limbs. **C. E. VIRGINI-MAGALHÃES** and **E. BOUSKELA** ***(Brazil)*** show that it's possible, by observing images of the cutaneous circulation, to identify the degree of microangiopathy and associate its findings with the evolution of chronic venous disease. The more advanced the clinical class, the more changes are observed in the cutaneous capillary, which grows and takes on an atypical shape.

The increasingly prevalent lipedema, lipohypertrophy, obesity, and lymphedema and their mixed forms are frequently overdiagnosed, underdiagnosed, or misdiagnosed, with undesirable repercussions for the patients and health systems. In her practical review, **E. MENDOZA** ***(Germany)*** explains the differential diagnosis based on descriptions on visual inspection and palpation of the affected legs, supported with many pictures.

The optimal management of combined iliac vein stenosis and ovarian vein reflux in patients with pelvic venous disease is a challenge that is approached by **K. HARTH** and **G. SALAZAR** ***(United States)***. This article describes insights to accurately diagnose the disease with its different clinical and anatomical presentations, focusing on the management of combined iliac vein stenosis and ovarian vein reflux in patients with nonthrombotic disease.

P. ORTIZ ***(Uruguay)*** explains in her review how the mechanochemical ablation with ClariVein and Flebogrif catheters can be an effective and safe ablation technique in selected patients with non-large-diameter saphenous trunks and using appropriate concentrations of sclerosants. This technique is producing good results in environments with limited resources and long surgery wait times such as in Latin American countries.

Enjoy reading this issue!

Co-Editor
Dr Lourdes Reina-Gutierrez

The vein of Giacomini: an in-depth review of its anatomy, hemodynamics, and treatment alternatives

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ABSTRACT

The vein known as the "vein of Giacomini" or "Giacomini vein" is part of the venous network of the lower limb and is involved in the drainage of the posterior part of the thigh. This vein owes its name to the Italian professor of anatomy who was the first to describe it in 1873. Giacomini observed that this vein acts as a proximal extension of the small saphenous vein and may follow multiple anatomical courses. Moreover, its most intriguing feature is that it can have more than 1 hemodynamic pattern depending on its valve arrangement and, most interesting, it leads to 2 different types of reflux when this vein becomes incompetent. Minimally invasive surgical options for this vein insufficiency include thermal ablation or ultrasound-guided foam sclerotherapy. These options allow for focused treatment of the leak point for both types of reflux. This article reviews the anatomy of the Giacomini vein, its hemodynamics and reflux variations, and the current treatment modalities for Giacomini-vein-related venous insufficiency.

Keywords

Giacomini vein | Giacomini vein insufficiency treatment | paradoxical reflux | superficial venous insufficiency | thigh extension of the small saphenous vein

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Definition

The saphenous system, located within the saphenous compartment delimited by the superficial fascia and the muscular fascia, deserves special attention as it is not a classic "superficial" venous system.[1] This compartment contains the great saphenous vein (GSV), the small saphenous vein (SSV), their accessories, and the "vein of Giacomini" or "Giacomini vein" (GV).

The GV, which is essentially a proximal extension of the SSV into the thigh, can have several anatomical variations. It may have various proximal endings, including the common variation of joining the GSV, albeit in some cases it may not be present at all.

Historical background

Carlo Giacomini, who studied the anatomy of lower-limb veins, observed the frequent presence of a thigh extension (TE) of the SSV. He described it in 1873 after dissecting 51 lower limbs. In his study, some type of TE of the SSV was present in 94% of the legs, with different anatomical patterns.[2]

Georgiev[2] summarized those findings and grouped them into types, such as an intersaphenous anastomotic branch to the GSV, branches terminating as a vein of the small ischiatic nerve, branches communicating with perforators of the thigh, or branches ending in the thigh muscles (*Figure 1*). These types may or may not coincide with the presence of a saphenopopliteal junction (SPJ).

Georgiev also noted the contribution of Giacomini in determining that the presence of different proximal terminations of the SSV was a normal, most common condition and recognizing that the TE and the SSV, due to their fascial location, were parts of the same vein.

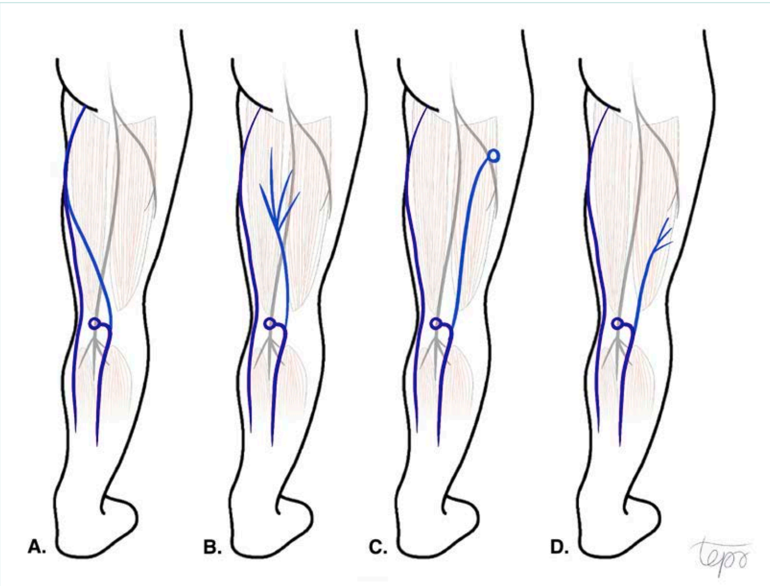

Figure 1. Schematic representation of Giacomini's findings.

A) An intersaphenous anastomotic branch to the great saphenous vein (GSV). B) Termination as a vein of the small ischiatic nerve. C) Branches communicating with perforators of the thigh. D) Branches ending in the thigh muscles.

These types may or may not coincide with the presence of a saphenopopliteal junction.

Drawn by Topo (IG: @artsy.topo) for the author's personal collection.

Anatomy and nomenclature

After Giacomini, there have been many subsequent anatomic postmortem studies that have confirmed Giacomini's findings, albeit with varying results until the advent of ultrasound imaging.

Venous ultrasound plays a crucial role in visualizing the TE. The TE appears as an ascending branch of the SSV in the lower thigh, situated in the interfascial layer between the semitendinosus and semimembranosus muscles medially

Figure 2. **A transverse ultrasound image of the thigh extension at the lower thigh (blue arrow) in the interfascial layer between the semitendinosus and semimembranosus muscles medially (on the left) and the long head of the biceps laterally (on the right).**

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

and the long head of the biceps laterally (*Figure 2*). More proximally, it can penetrate deeper layers to join the deep venous system or end laterally in a muscle or have a circumflex course toward the GSV.

Recent studies using duplex ultrasound scanning (DUS) have reported the presence of the TE in 63.2%,[3] 65%,[4] and up to 70.4%[5] of cases. According to Giacomini's research, the TE of the SSV can differ anatomically between individuals. However, the most frequent variation is the anastomotic connection between the SSV and GSV (72%).[2] This anastomotic connection, as observed by Giacomini, was the most frequent variation in Delis' ultrasound study (49.5%).[5] The Vascular Surgery Department in Cruz Roja Hospital in Madrid conducted an ultrasound observational study in 2022 that revealed the TE presence in 90% of 100 venous ultrasound explorations of lower limbs, and 48% of these showed an intersaphenous anastomotic variant.[6,7]

Considering the different anatomical courses that TE can adopt, the International Union of Phlebology (UIP) published a consensus on using different names based on the anatomy of the vein. The vein that ascends between the biceps femoris and semimembranosus muscles and ends in either deep or superficial veins of the thigh via perforators or via venous branches is referred to as the TE of the SSV.[8] The one that connects to the GSV through the posterior thigh circumflex vein is referred to as the GV.[8]

Hemodynamic features

There is an additional discovery by Giacomini concerning these veins.

He discovered that they can have one of 2 possible and opposite valve arrangements that enable either normal upward or normal downward flow.

The intersaphenous GV is a classic example of the valve arrangement that permits upward blood flow. Some other proximal projections of the SSV may also exhibit this pattern, particularly when the SPJ is not present. *Figure 3* shows a schematic representation of an upward-flowing valve arrangement.

On the other hand, the TEs that work as tributaries to the SPJ, such as the TE that terminates as muscular thigh branches, have valves that work in reverse in order to facilitate downward blood flow into the popliteal vein.[2] *Figure 4* shows a schematic representation of a downward-flowing valve arrangement.

Veins with normal upward blood flow may become incompetent due to a proximal leak point, eg, the GSV, proximal perforators, or pelvic connections. This leads to a conventional gravitational reflux, which is observed

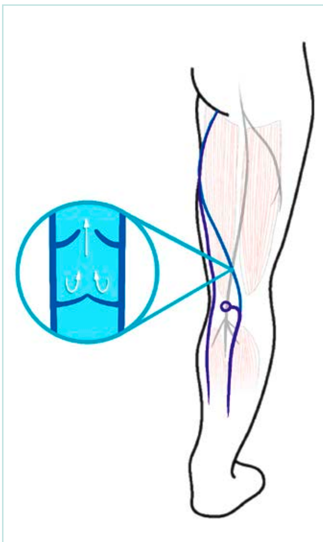

Figure 3. **Schematic representation of an upward-flow-allowing valve arrangement.**

Drawn by Topo (IG: @artsy.topo) for the author's personal collection.

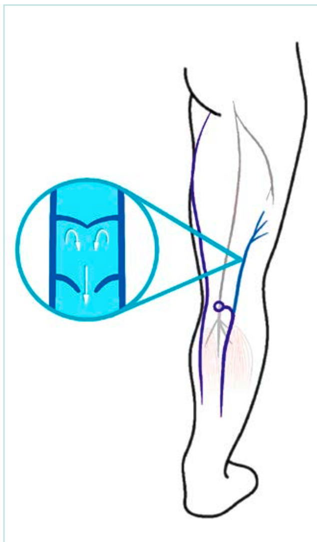

Figure 4. **Schematic representation of a downward-flow-allowing valve arrangement.**

Drawn by Topo (IG: @artsy.topo) for the author's personal collection.

as diastolic reflux when the calf muscles are released after the squeezing maneuver (*Figure* 5). This reflux can end at the SPJ, draining into the popliteal vein, or may continue toward the SSV axis.

Veins with normal downward blood flow have valves that prevent the upward flow from the SPJ. Therefore, in cases of valvular malfunction and vein incompetence, a completely different reflux is observed: an upward reflux becomes noticeable (paradoxical antigravitational reflux).

The upward reflux may be difficult to detect with a duplex examination due to its paradoxical pattern and occasional low flow. It is considered paradoxical because during muscular diastole the flow goes in the same upward direction as the manually induced systolic flow (*Figure* 6).

It may seem contradictory to consider an upward flow as pathological. However, in a duplex exam, the absence of venous flow during muscular diastole is normal, whereas both downward and upward flows lasting over 0.5 seconds during the diastolic phase should be considered pathological. For this reason, upward flow during diastole is a reflux that arises from a distal leak point such as the SPJ.[2,9]

The information about these 2 possible flow and reflux patterns is important to keep in mind during clinical and duplex examinations in order to anticipate identifying them.

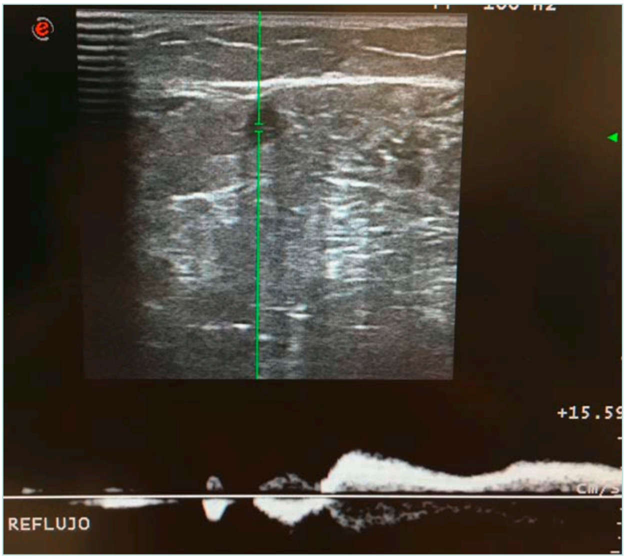

Figure 5. A transverse duplex image of the thigh extension at the lower thigh, with gravitational diastolic reflux that is opposite to the manually induced systolic flow (squeezing maneuver).

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

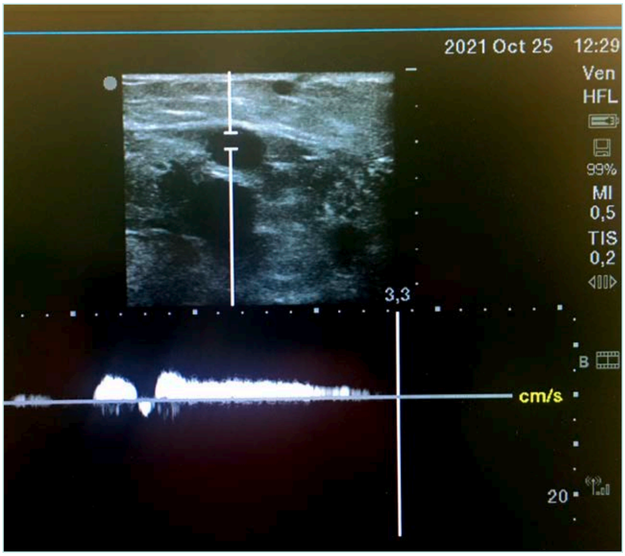

Figure 6. A transverse duplex image of the thigh extension at the lower thigh, with paradoxical diastolic reflux that goes in the same direction as the manually induced systolic flow (squeezing maneuver).

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

Giacomini vein and thigh extension reflux prevalence

DUS is an ideal method for examining the pattern and magnitude of venous reflux.

Studies vary in methodology but provide insight into the prevalence of GV insufficiency.

Georgiev et al found GV reflux in 6.2% of 1226 limbs with GSV or SSV insufficiency. It corresponded to paradoxical reflux in 30% of cases.[2] Delis et al[5] observed GV reflux in 3.3% of 301 limbs with suspected chronic venous disease; Labropoulos et al[10] found it in 17.4% of 226 limbs with isolated reflux in the SSV system; and Escribano et al[9] detected GV paradoxical reflux in 1.1% of 1350 limbs with varicose veins. In our department's study at Cruz Roja Hospital, 5% of 100 examined limbs showed GV or TE insufficiency. Out of that, 1% had paradoxical reflux.[6,7]

Considering these findings, although somewhat varied, they confirm the potential for incompetence in veins within the Giacomini system and that they can exhibit both typical/gravitational and paradoxical/antigravitational reflux.

Treatment options reports

The popliteal fossa, where Giacomini-system veins rise, is a complex anatomical area.

It can be challenging to perform surgical treatment due to the complex neurovascular relationships and anatomical variability of the venous structures.[11]

In view of this, a simple removal of superficial varicose branches, without surgical dissection of the insufficient Giacomini vein could be done as a single procedure.

Regarding this option, Escribano et al[9] noticed a significant number of varicose veins recurrences (57%) after a 12-month follow-up. Thus, he suggested a CHIVA procedure (CHIVA—a French acronym for *Conservatrice Hémodynamique de l'Insuffisance Veineuse en Ambulatoire*) that involves surgically interrupting an insufficient GV (with paradoxical reflux) at the junction with the SSV as a more effective treatment, with only 13% of recurrences after a 12-month follow-up.[9]

More recently, endovascular treatments have emerged as convenient, effective, and secure options for treatment, especially for incompetent saphenous veins. In the same way, reports have emerged regarding endothermal laser treatment for GV insufficiency.

Bush et al[12] used a combination of endolaser thermal ablation and ultrasound-guided foam sclerotherapy (UGFS) to treat 14 patients who had varicose veins due to TE insufficiency (including both TE and GV variants). The laser fiber was advanced proximally from the SSV as far as possible within the GV or TE for thermal ablation. Foam sclerotherapy was necessary for the proximal angulated or subcutaneous portions of the GV or TE, as well as for the posterior thigh perforators. The author did not report complications such as sural nerve damage or deep vein thrombosis nor were there any recurrences after 2 years of follow-up.

Theivacumar et al[13] documented 2 cases of endolaser ablation of the GSV as a treatment of the paradoxical reflux of the GV. This approach served as a solution for reflux transmitted from the SPJ to the GSV through the intersaphenous connection. The ablation was performed on the GSV by puncturing it in the calf, from behind to above the point where the GSV joins the GV. He stated that the SPJ and the GV regained competency within 12 weeks. The reasoning behind this approach is that the SPJ is not responsible for this type of reflux. It is not a common approach, and an extensive follow-up should be done to rule out recurring disease.

Park el al[14] reported endolaser ablation of 18 incompetent GV (16 with gravitational reflux and 2 with anterograde "paradoxical" reflux), utilizing the SSV or GV as the primary access point, but employing the proximal GSV as a secondary option if needed. The observed endolaser-related adverse effects included bruising (56%), which had resolved by the 1-month follow-up, and tightness or pain at the treatment site (12.7%), both of which improved or resolved by 6 months. The author acknowledges the study's limitations, including the loss of 66.7% of patients at the 12-month follow-up and the absence of anatomical details regarding the incompetent GV. However, he concluded that endolaser ablation provided a safe, effective, and technically successful solution for GV insufficiency.

The Guzelmansur et al[15] retrospective study represents the largest group of patients (32 patients, 39 limbs) treated for GV insufficiency through endovenous ablation. The authors treated both the intersaphenous GV and the TE but did not identify the reflux type as conventional or paradoxical. Endolaser thermal ablation was used for treating straight incompetent GV (29 limbs), whereas UGFS was used on tortuous veins that were unfit for endolaser treatment (10 limbs). Likewise, endolaser therapy was employed for treating coexisting incompetent saphenous trunks. The authors did not report any complications, only transient discomforts. With a maximal follow-up up to 12 months, there was complete success in the endolaser group and only 1 recanalization in the UGFS group.

Targeted endovenous treatment of varicose disease associated with GV insufficiency (any type of reflux) demonstrated safety and efficacy in a study by Atasoy et al[16] involving 17 patients. Straight GVs were treated with endolaser and tortuous GVs with UGFS (in 3 cases). As a treatment focused on reflux sources, it allowed the unnecessary ablation of healthy saphenous veins to be avoided.

Discussion

The presence of different proximal endings of the SSV that extend toward the thigh is a common and prevalent condition known as the TE of the SSV. Due to their contiguous location, both the TE and the SSV can be considered components of the same vein.

The most common anatomical variation of the TE is the intersaphenous anastomotic branch, also referred to as the Giacomini vein (GV).

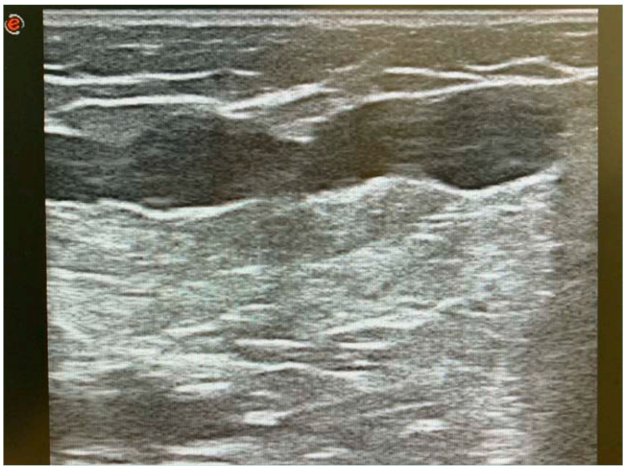

Figure 7. **A longitudinal ultrasound view of a tortuous thigh extension located in the middle third of the thigh.**

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

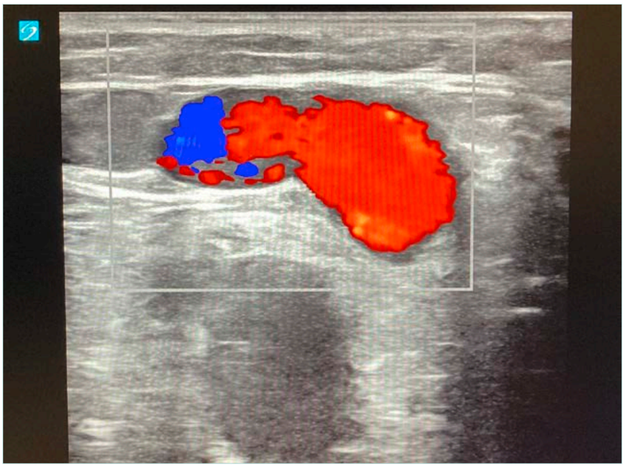

Figure 8. **A transverse duplex image of a tortuous thigh extension located in the distal third of the thigh.**

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

Although the GV is a connection between 2 subfascial saphenous veins, it frequently has 3 segments, with the middle segment located superficially within the subcutaneous tissue.[2,4,9] On the other hand, when the GV is incompetent, it often becomes tortuous and angulated. These anatomical features are important to consider when deciding on treatment options (*Figures 7 and 8*).

Another important consideration for treatment decisions is these veins' ability to exhibit 2 possible types of reflux, which are opposite to each other, due to 2 distinct and opposite valve arrangements. As a result, GV insufficiency can cause either a conventional, gravitational reflux or a paradoxical, antigravitational reflux.

It is important to think about the likelihood of paradoxical reflux in order to spot it in an ultrasound exam. By extension, reflux identification enables the reflux-oriented and therefore more effective treatment.

Based on current recommendations, the reflux source should be treated using a minimally invasive technique.

There is currently no established standard treatment for varicose vein disease associated with GV insufficiency. Therefore, extrapolating the recommendations for saphenous vein treatment may be an option.

The European Society for Vascular Surgery (ESVS) clinical practice guidelines[17] on the management of chronic venous disease (CVD) of the lower limbs recommend endovenous thermal ablation as the first-choice technique for treating the GSV and SSV insufficiency, whereas UGFS can be considered for trunks with a diameter less than 6 mm. On the other hand, UGFS "is the technique of choice for anatomical configurations that make endovenous cannulation or advancing the ablation device challenging and is suitable for treating tortuous varicose veins."[17]

So, although thermal ablation is the preferred technique for saphenous trunks, it has certain drawbacks when used for GV insufficiency; for example, due to the frequently tortuous or partially subcutaneous course of this vein. In fact, only 1 of the aforementioned authors[14] reported a completely endolaser-based thermal ablation of GV insufficiency, although it is not possible to know the anatomical characteristics of the veins in this study. The remaining authors considered it necessary to use a combined treatment approach, using endolaser for straight vein segments and UGFS for elongated ones.

On the other hand, the possibility of thermal damage to adjacent nerves is a logical concern, especially in the popliteal fossa, a high-risk area due to its numerous nerves and variable anatomy. This includes the possibility of anatomical proximity between the GV and the sciatic bifurcation, as well as the tibial and peroneal nerves.[18] In *Figure 9*, imaging shows the tibial nerve located near the TE vein in the distal part of the thigh. Regarding the GV in particular, it has its neural companion in the thigh, the posterior femoral cutaneous nerve (*Figure 10*).

According to Uhl and Gillot's theory of "angio-guiding" nerves that determine the venous development of the embryo, the posterior femoral cutaneous nerve corresponds to the former postaxial nerve that guides the TE of the SSV.[1] The posterior femoral cutaneous nerve is a sensory nerve, and its neuropathy causes pain in the inferior gluteal area and the posterior part of the thigh.

Of the published studies of thermal ablation for GV insufficiency, Park et al[14] reported mild transient symptoms of neuronal distress (in 12.67% of cases). It is important to note that in this study, the entire length of the GV was treated solely with thermal ablation, without the use of foam sclerotherapy.

In the field of Peripheral Nerve Surgery and Research, there is a report of a common peroneal nerve injury following

Figure 9. **Tibial nerve located near the thigh extension vein in the distal part of the thigh, indicated by 2 white crosses.**
Image from the collection of the Vascular Department at Cruz Roja University Hospital.

Figure 10. **The white arrow indicates the posterior femoral cutaneous nerve located near the thigh extension vein in the middle/upper part of the thigh.**
Image from the collection of the Vascular Department at Cruz Roja University Hospital.

endolaser thermal ablation of the GV.[18] The article mentions an endovenous laser treatment from 10 centimeters below the knee to 20 centimeters above the knee, delivering 4010 J at 14W. The patient experienced immediate postoperative numbness and was unable to evert their ankle. Electromyogram demonstrated a severe peroneal neuropathy. There was no motor or sensory recovery after 9 months of follow-up. In conclusion, the authors emphasize the importance of precise preoperative ultrasound-guided mapping of venous and neural structures. The relative anatomic relationship between these structures should be the guiding principle in selecting the level of venous thermal ablation.[18]

In summary, data on thermal neuropathy after GV ablation are still too limited to draw definitive conclusions.

As previously mentioned, the ESVS guidelines highlight UGFS as a recommended treatment option for anatomically challenging and tortuous venous configurations, which frequently happen in the case of the GV. The Vascular Surgery Department in Cruz Roja Hospital considers UGFS as the preferred approach for treating GV insufficiency. In our experience, UGFS can be used as a single technique for any type of GV or TE, regardless of the complexity of its anatomical course or depth. In addition, UGFS does not endanger nerve integrity.

To implement the leak-point–focused strategy while performing UGFS, it is crucial to conduct a comprehensive duplex mapping of GV insufficiency to determine the type of reflux. This allows for a hemodynamic treatment, as the leak point is targeted first.

In the case of varicose TE or GV caused by upward reflux (paradoxical antigravitational reflux), the initial puncture for foam injection is performed near the SPJ, which corresponds to the leak point. Then, the next venous segment not filled with foam is punctured and filled, and the treatment is completed from a distal to a proximal part of the thigh. See *Figures 11-13*.

To treat downward reflux (conventional gravitational reflux), staged injections should be administered from the upper part of the thigh toward the calf, along the targeted vein.

Figure 11. **Patient with varicose veins caused by upward paradoxical reflux of the thigh extension vein. Picture before treatment.**
Image from the collection of the Vascular Department at Cruz Roja University Hospital.

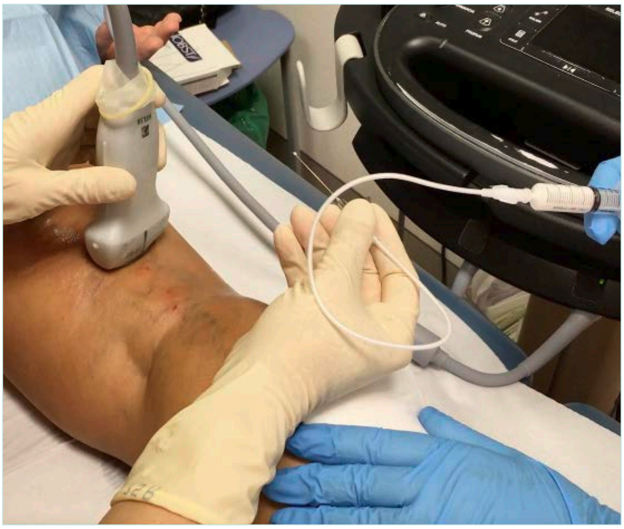

Figure 12. **Ultrasound-guided foam sclerotherapy is used to treat the incompetent thigh extension vein. The first injection is administered near the saphenopopliteal junction. Subsequent injection involves filling the next unfilled segment with foam, moving toward the proximal part of the thigh.**

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

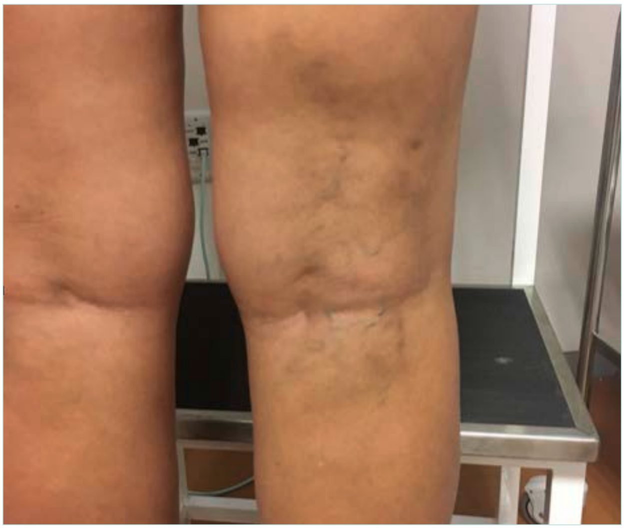

Figure 13. **Six months after 1 session of ultrasound-guided foam sclerotherapy of the incompetent thigh extension vein.**

Image from the collection of the Vascular Department at Cruz Roja University Hospital.

Conclusions

The so-called "Giacomini vein" (GV) refers to a range of anatomical courses of the TE of the SSV that can vary anatomically between individuals. They are commonly found in the human lower limb and the most frequent variation is the anastomotic connection between the SSV and GSV, which should actually be referred to as the GV.

Aside from exhibiting anatomical variability, these veins can have one of 2 possible (and opposite) valve arrangements, depending on their drainage function. Due to this feature, when the vein becomes insufficient, it can result in one of 2 types of reflux that are opposite to each other. During duplex examinations, it is important to keep in mind the 2 possible flow and reflux patterns, especially the likelihood of paradoxical (or upward) reflux.

For GV and TE venous insufficiency, minimally invasive surgical options include thermal ablation or UGFS. These options enable targeted treatment of the leak point in both upward- and downward-directed reflux.

In cases of endothermal ablation, a thorough preoperative ultrasound examination of venous and neural relationships is crucial to minimize the risk of thermal nerve injury.

UGFS is a suitable treatment option for anatomically challenging varicose veins, which are particularly common within the GV system. Additionally, it is a nerve-safe technique.

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Microcirculatory alterations in chronic venous disease: observation from $C0_s$ to C5 patients (CEAP classification)

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ABSTRACT

Over the last few decades, knowledge of microcirculation has expanded in its pathophysiological and molecular bases and its correlations with clinical practice. By observing images of the cutaneous circulation, it is possible to identify the degree of microangiopathy and associate its findings with the evolution of chronic venous disease (CVD). With the progression of venous disease, the cutaneous capillaries lose their typical hairpin shape of healthy individuals and early stages of the disease, become progressively enlarged and tortuous, and form masses or tangles described as glomerulus-like capillaries. In more advanced stages of CVD, there is a reduction in functional capillary density. This reduction in the number of capillaries begins to be observed in C3 and is more important in classes C4, C5, and C6. The result is the replacement of healthy capillaries by large coiled vascular masses, reduced skin perfusion, and the replacement of healthy connective tissue by a chronic fibrosing inflammatory process characteristic of lipodermatosclerosis found in class C4, which eventually leads to skin ulceration. There is currently a consensus that these evolutionary changes in microcirculation are caused by the association of different hemodynamic forces and an intricate inflammatory cascade that results in a vicious cycle of proteolytic remodeling of the venous wall and further inflammation, as well as degradation of the protective endothelial glycocalyx, producing a broad spectrum of clinical symptoms ranging from varicose veins to venous ulcers.

Keywords

CEAP classification | chronic venous disease | microcirculation | orthogonal polarization spectral imaging | varicose veins

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Introduction

Since the work of Fagrell,[1] in the late 1980s, the role of microcirculation in chronic venous disease (CVD) has been gradually revealed. Over the last few decades, the knowledge of microcirculation has expanded in its pathophysiological and molecular bases and, above all, in its correlations with clinical practice.

By observing images of the cutaneous circulation, it is possible to identify the degree of microangiopathy and associate its findings with the evolution of CVD. The aim of this work is to describe the interfaces between the microcirculatory changes observed in CVD and their correlation with clinical practice

CEAP classification

The clinical-etiological-anatomical-pathophysiological (CEAP) classification for CVD, created 30 years ago, has become a universally accepted tool for describing patients in clinical practice and ensuring the standardization of scientific literature. Throughout this period, it was reviewed and updated at different times.[2,3] The assessment of the 4 dimensions of CEAP is fundamentally based on information from history and accurate clinical examination, and ultrasound findings. CEAP is a descriptive tool. Although established, CEAP is also the target of criticism that includes the lack of precise definitions and reproducibility.[2]

The C (clinical) domain of CEAP is by far the most used in clinical practice and research. Each category describes a specific moment of CVD, it is not associated with the progression of the disease; although tempting, CEAP should not be used to assess the evolution of CVD in an individual. Therefore, it is not possible to guarantee that in the natural history of an individual's disease, class progression will occur over time. For example, there are patients considered C1 who will never become C2 over the years. Therefore, when we describe the different clinical classes of CEAP, we limit ourselves to discussing that specific clinical picture. Several instruments are more effective for objectively measuring the evolution of the disease, as well as the results of different therapeutic approaches.

Microcirculation, a dimension completely unrelated to the aspects addressed by CEAP, can be assessed using different instruments generally used in clinical research. Despite the knowledge about the existence of microcirculatory changes in CVD, their importance in diagnosing the severity and progression of the disease is not yet considered in clinical practice. Although pathophysiology has been included in CEAP with its constant updates, we consider that detailed microcirculatory analysis should, at some point, be part of the classification owing to its importance in understanding CVD.

Microcirculatory evolution in CVD

Microcirculation is the term used to describe vessels with an internal diameter of less than 100 μm. Several methods have been used to study the microcirculation directly or indirectly, such as laser Doppler flowmetry, plethysmography, fluorescence videomicroscopy, orthogonal polarization spectral (OPS) imaging technique, and more recently the superb microvascular imaging (SMI) technique.

Microcirculatory changes in CVD have been known since the end of the last century. By observing images of the cutaneous circulation, it is possible to identify the degree of microangiopathy and associate the findings with the severity of CVD.

Cutaneous capillaries are extensions of a network composed of 2 to 4 parallel layers of arterioles and venules organized beneath the skin. They are shaped like a hairpin and are positioned perpendicular to the surface of the skin within the dermal papillae.[4] The imaging tests used, such as videomicroscopy or Cytocam™, usually obtain images only of the most superficial segment of the capillary, the capillary loop. As venous disease progresses, cutaneous capillaries lose their normal hairpin-like appearance, become progressively enlarged and tortuous, and form masses or kinks described in the literature as glomerulus-like capillaries.[1] In addition to capillary remodeling, there is also hypertrophy of the dermal papillae.[5] These vessels of aberrant morphology with dilated interendothelial pores and irregularity of the vascular wall present increased permeability to large molecules and blood cells such as fibrinogen, macrophages, red blood cells, and plasma. It has already been suggested that the dilatation of the dermal papillae in CVD may be translated into the beginning of interstitial fluid extravasation, corresponding to a preclinical phase of limb edema found from C3.[1,6]

In more advanced stages of CVD, there is a reduction in functional capillary density, ie, a reduction in the number of capillaries that nourish the skin. The result is the replacement of healthy capillaries by large coiled vascular masses (*Figure 1*), reduced skin perfusion, and replacement of healthy connective tissue by a chronic fibrosing inflammatory process that affects the subcutaneous cellular tissue, eventually leading to skin necrosis.[7]

It has been suggested that microangiopathy precedes trophic skin changes and even in areas of normal skin, it is possible to observe morphological changes in capillaries with experimental methods at different stages of CEAP. No microcirculatory parameter alone can discriminate between different CEAP classes. There is an overlap of findings between classes and low interobserver reproducibility, depending on the imaging method used. In any case, microcirculation is likely to represent the bridge between macroscopic and clinical events and molecular biology.[8]

Figure 1. These images show the appearance of microcirculation in individuals with CEAP classification C0 (A and B) and C5 (C and D). The dashed circles (A and C) represent the dermal papilla, the functional cutaneous unit. Observe the difference in size of the dermal papilla and the capillary inside it in the 2 individuals. The normal capillary (A) transforms into a large vascular coil (C).

Images courtesy of Virgini-Magalhães CE.

A study using electron microscopy analyzed the ultrastructure of the wall and venous valves of the great saphenous vein (GSV) in different CEAP classes. The authors observed that with the progression of the disease, the elastin content appears to increase, and it is possible to observe progressive damage to the endothelium of the wall and the venous valve in a similar way, with areas of absent endothelial cells and denuded basement membrane.[9] There is also vascular wall heterogeneity with alternation of atrophic and hyperplastic areas, disorganized patterns of elastin layers, and micro herniations of smooth muscle cells.[4]

In another line of research, the group led by Professor Van Rij has been studying the role of the network of small cutaneous veins less than 2 mm in diameter in the clinical expression of CVD. Initially, a study using resin casts of amputated limbs revealed that valvular incompetence may exist in valves of small GSV tributary veins in stages C0 and C1, even though no truncal reflux can be observed on Doppler.[10] More recently, a new technology known as SMI has obtained better images than color Doppler to evaluate reflux of these microvalves located in the most superficial layer of the skin surface.[10,11]

Previously, it was believed that these small veins did not have valves. However, the studies by Van Rij and coworkers point to some interesting aspects that could change our view about the pathophysiology of CVD. According to these authors, valve incompetence may exist even in small veins of the skin regardless of valve competence in GSV and its tributaries. In practice, many veins of the subcutaneous venous system present degenerative changes, in the absence of truncal reflux detectable on duplex scan or in the presence of clinical varicose veins. On the other hand, when there is GSV reflux, these small microvalves would be able to prevent reflux into the skin, playing a critical role in the progression of cutaneous changes in venous insufficiency.[11] Such findings suggest an important role for this system of small subcutaneous veins in the CVD pathophysiology.

Remodeling of microcirculation and macrocirculation

Microcirculation is the term used to describe vessels with an internal diameter of less than 100 μm. In the skin, capillaries are mainly located in the superficial papillary layer of the dermis where venules and arterioles are organized in a composite network formed by 2 to 4 parallel and superimposed layers with the purpose of guaranteeing thermoregulation.[4]

There is currently a consensus that the pathophysiology of CVD has an important inflammatory component, at its origin or in the progression of the disease. The purely mechanical view that valve insufficiency is the sole cause of stasis and venous hypertension and the origin of CVD may not be sufficient to explain all aspects of its pathophysiology.[10,11]

The remodeling of macrocirculation and microcirculation depends in part on the strength of the hemodynamic insult and its effects on the genetic resilience of each individual.[12] However, the common factor in all theories is the perpetuation of a chronic inflammatory process, which insidiously causes venous macrocirculation and microcirculation remodeling and extends to the skin and subcutaneous cellular tissue in more advanced stages of the disease.

This process involves an intricate inflammatory cascade with the participation of proinflammatory factors including reactive oxygen species (ROS), metalloproteinases (MMPs), and also adhesion molecules such as E-selectin, P-selectin, and von Willebrand factor, released by the endothelium, which in turn attract and stimulate neutrophils and platelets, and progressively cause damage to the vascular wall and extracellular matrix.[4,13] Macrophages/monocytes and mast cells play an important role in this inflammatory cascade. These cells release proteolytic enzymes and ROS, participating in damage to the vascular wall.[14] On the other hand, growth factors cause migration, proliferation, and dedifferentiation of smooth muscle cells that stimulate the formation of neointima and vascular remodeling.[15] The result is a vicious cycle of proteolytic remodeling of the venous wall and further inflammation, as well as degradation of the protective endothelial glycocalyx, resulting in a wide spectrum of clinical symptoms ranging from varicose veins to venous ulcers.

Using the OPS technique, it is possible to obtain noninvasive images of the cutaneous microcirculation in patients with CVD and compare its findings between different CEAP classes. The more advanced the clinical class, the more changes are observed in the cutaneous capillary, which grows and takes on an atypical shape. These observations had already been published by Howlader and coworkers using videomicroscopy in different CEAP classes.[16] As CVD progresses, the cutaneous capillaries with their usual hairpin-shaped appearance are being replaced by increasingly larger, glomerulus-like, coiled vascular masses. This altered morphology is found in 20% of capillaries in C1 patients and becomes increasingly common as the CEAP class advances, reaching 75% of capillaries in C5 patients (*Table I*). The remodeling involves the dermal papilla, a functional cutaneous unit that doubles in size when comparing patients C1 and C5.

Besides normal capillaries being replaced by large vascular coils, a gradual reduction in functional capillary density is observed, ie, the number of active capillaries decreases on the skin surface. C1 and C2 individuals have approximately the same number of functioning capillaries when compared with healthy individuals, around 20 capillaries/mm^2. As the CEAP class advances, a gradual reduction is observed, where only 12 capillaries/mm^2 are counted in C5.[5] In more advanced stages of the disease, therefore, we find a scarce cutaneous capillary network with vessels of completely anomalous morphology.

In more advanced stages of CVD, the chronic inflammatory process extends to the surrounding tissues, subcutaneous layers, and skin. Elevated levels of MMPs in these chronically inflamed tissues contribute to excessive degradation of the extracellular matrix and collagen, which can lead to impaired healing and skin ulceration.[17] The development of subcutaneous fibrosis can occur due to high levels of growth factors produced by activated leukocytes, which stimulate the excess production of fibrinogen and collagen, causing scarring fibrosis. Finally, the degradation of extravasated red blood cells and the subsequent release of hemoglobin and iron into the surrounding structures increases the oxidative state of the tissue, increasing the activity of MMPs, exacerbating tissue damage and further impairing wound healing.[18]

Microcirculatory parameters/CEAP	C0	C1	C2	C3	C4	C5
Functional capillary density (cap/mm^2)	20.9 ± 6.1	20.6 ± 4.8	20.9 ± 6.6	18.0 ± 4.4	14.5 ± 4.5	12.1 ± 8.2
Diameter of dermal papilla (µm)	111.4 ± 13.5	125.1 ± 26.5	141.0 ± 21.1	150.5 ± 31.7	169.5 ± 23.7	223.9 ± 126.9
Diameter of capillary bulk (µm)	52.8 ± 8.8	77.1 ± 31.6	75.8 ± 17.9	87.8 ± 26.9	103.2 ± 35.4	149.1 ± 56.3
Capillary diameter (µm)	8.1 ± 0.8	8.7 ± 1.2	9.7 ± 1.3	9.1 ± 1.6	9.5 ± 1.8	11.1 ± 2.9
Capillary morphology (%)	3.6 ± 5.5	20.3 ± 12.8	27.5 ± 17.7	44.9 ± 32.6	58.5 ± 28.7	75.2 ± 37.0

cap, capillaries; **CEAP**, clinical-etiological-anatomical-pathophysiological classification.

Table I. Observe changes in the measurements of microcirculatory parameters as the CEAP classification progresses. Although there are overlapping values, it is possible to observe that as the severity of the disease increases, the functional capillary density decreases at the same time as the dermal papilla and capillary vessel grow, transforming into a large, coiled vascular mass.

Based on reference 5: Virgini-Magalhães et al. *J Vasc Surg*. 2006;43:1037-1044.

$C0_s$ and C1 patients

The CEAP C0 class included individuals who did not present visible signs or symptoms of CVD in the lower limbs, that is, individuals with no venous disease. Even so, a significant proportion of these individuals chronically experience complaints typical of venous hypertension. CEAP incorporated the $C0_s$ nomenclature, clearly recognizing that some individuals present characteristic symptoms of CVD, even if they do not present objective visible signs of venous disease. In recent years, this clinical picture has been defined under different names: hypotonic phlebopathy, phlebopathic diathesis, prevaricose syndrome, functional phlebopathy, functional chronic venous insufficiency, or functional venous disease.

In epidemiological studies, the prevalence of $C0_s$ patients ranges from 13.9% to 19.7% of the general population.[19] Complaints of numbness, burning sensation or leg heaviness, edema, muscle cramps, or restless legs may suggest the condition, especially when associated with heat, long periods of standing, specific situations such as pregnancy, type of occupation, and some seasons of the year such as spring or summer. On the other hand, resting and limb elevation tend to improve symptoms. The difficulty in diagnosis lies in the low specificity of the symptoms and the absence of clinical or imaging signs. Although some patients may or may not present permanent changes on echo-Doppler, as already described in the literature, most individuals do not present objective data to corroborate the diagnosis.[3,20]

The absence of specific diagnostic instruments and the lack of longitudinal studies evaluating individuals diagnosed as $C0_s$ bring uncertainty in the diagnosis and early therapeutic management of these patients, even though in the literature the use of venoactive drugs is recognized as an effective approach in controlling the symptoms in this condition.[20] Considering the anti-inflammatory and antioxidant properties, platelet inhibition, improvement of endothelial homeostasis, leukocyte-endothelium interaction, among other actions, flavonoids, saponins, and some plant extracts target exactly the steps involved in the pathophysiology of symptoms and evolution of CVD even in early stages, such as in $C0_s$ patients.[15]

At the microcirculatory level, C0 individuals have capillaries with normal luminal diameters and dermal papillae of usual sizes. Capillary morphology is the typical hairpin shape, although a small percentage of capillaries present different degrees of coiling, characteristic of more advanced stages of CVD.[5] These findings are not sufficient to ensure an adequate distinction between healthy individuals and patients in initial stages of CVD. Therefore, microcirculatory imaging parameters in $C0_s$ patients are not very different from healthy individuals when evaluated by currently available imaging research instruments.[5,21]

A study in the early 2000s attempted to demonstrate functional changes in the microcirculation even before the onset of capillary remodeling in CVD. Using photoplethysmography and strain-gauge plethysmography, the authors suggest hyperdistensibility of the venous wall in this class of patients. The study also refers to ultrasound findings of reduced calf muscle pump and increased venous compliance.[22] Lugli et al [23] showed differences in flow when comparing $C0_a$ and $C0_s$ individuals using a highly sensitive flat probe continuous wave Doppler, finding the presence of bidirectional flow in symptomatic individuals and only unidirectional flow in the control group.

These changes in the microcirculation (*Figure 1* and *Table I*) associated with genetic and environmental factors such as sedentary lifestyle, type of occupation, and personal habits may be at the origin of symptoms and the onset of an insidious chronic inflammatory process in C0 and C1 patients. Evidence shows the role of several inflammatory mediators released in the activation of type C nociceptors, located in the middle layer of the venous wall and in the perivenous connective tissue, as responsible for the symptoms in these patients.[5,24]

C2 and C3 patients

Patients considered C2 class have varicose veins with at least 3 mm in diameter and no limb edema. The clinical picture can vary considerably, from completely asymptomatic individuals to complaints of constant heaviness and pain associated with standing. At the level of microcirculation, changes in the diameter of the dermal papilla and the growth of the capillary bulk are already evident. Thirty percent of capillaries present morphological changes due to vascular remodeling, but functional capillary density has normal values. Microcirculatory parameters gradually change. As the disease progresses to C3 class, when edema appears on physical examination, around half of the capillaries have already undergone remodeling.[5]

C3 class seems to be the point of no return for microcirculatory changes in CVD. Although there is a large overlap in values between CEAP classes, it is possible to observe changes in microcirculatory parameters at this stage of the disease, especially the number of active capillaries that begin to reduce, albeit in a soft way, and a large contingent of remodeled cutaneous ones, when about half of the normal hairpin-shaped vessels were replaced by glomerulus-like capillaries (*Figure 1* and *Table I*).

C4, C5, and C6 patients

In advanced stages of CVD, especially those recognized as chronic venous insufficiency equivalent to CEAP clinical classes C4, C5, and C6, clinical signs and symptoms tend to be more exuberant. There may be evident skin pigmentation, and healthy skin gives way to fibrotic tissue that compromises the dermis and subcutaneous cellular tissue and the lymphatic system.

Capillary remodeling and changes in vascular permeability are associated with elevated levels of vascular endothelial growth factor in patients at these stages of CVD. The development of skin fibrosis may be caused by high levels of transforming growth factor β type 1 (TGF-β1) present in the skin of these patients. TGF-β1 is produced by activated leukocytes, and it stimulates the production of excess fibrinogen and collagen, causing subcutaneous fibrosis.[18]

In addition to skin fibrosis, it is also from C4 stage of CVD that skin pigmentation occurs. Cutaneous deposits of hemosiderin are caused by extravasation of red blood cells, which in turn release hemoglobin and iron into the interstitial space, increasing the activity of MMPs and causing tissue damage.

In the cutaneous capillaries, the predominant morphology is large vascular coils, reaching 75% of the capillaries in C5 patients. The remodeling also involves the dermal papillae, which doubles in size when comparing C1 and C5 patients (*Figure 1* and *Table I*).[5] There is already a significant reduction in functional capillary density. In C4 and C5, only 12 capillaries/mm^2 are counted, approximately half of the active functional capillary units compared with early stages of CVD. In more advanced disease stages, therefore, we find a scarce cutaneous capillary network with vessels of completely anomalous morphology. It is possible to identify avascularized areas that correspond to lesions known as atrophie blanche sign found on clinical examination.[25]

Classes C4, C5, and C6 represent the terminal stage of CVD, presenting irreversible sequelae in most cases, a consequence of chronic inflammatory effects over years of disease acting on the venous network of the macrocirculation and microcirculation, and even after successful interventions. Successful treatments at this stage of the disease are not capable of restoring the physiological status of these patients.

Conclusion

The progression of CVD is associated with the perpetuation of an inflammatory process that translates early into microscopic changes at the level of the venous wall and valve structures, and the extensive cutaneous capillary network of the lower limbs. Over the last few decades, knowledge of the microcirculation has expanded its pathophysiological and molecular bases and, above all, its correlations with clinical practice. As this understanding advances, new insights and possibilities emerge for research in this territory that represents the interface between biomolecular changes and clinical practice in the care of patients with CVD.

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Lipedema, lymphedema, lipohypertrophy, and obesity: how do we differentiate?

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ABSTRACT

Lymphological and fatty tissue disorders of the legs are increasingly tying up capacities in the health care system. This is related to the increase in obesity disease to almost endemic proportions in our society. Although the term lipedema was coined in the 1950s, it has only now become really well known. Women with lipedema suffer from symmetrical and disproportional fat deposition on both legs, accompanied by tenderness or strong pain especially on touch. Over 50 years, this condition has been underdiagnosed. Women with lipohypertrophy (same fat disproportion without pain) fear they suffer from lipedema and are misguided by false information, claiming treatment, as well as liposuction reimbursed by health care systems. Affected women suffer greatly from misinformation but also from overdiagnosis. The aim of this work is to make differential diagnosis easier for the health practitioner. On the basis of descriptions on visual inspection and palpation of the affected legs, the differential diagnosis is explained here, supported with many pictures. As a result, differentiation of the entities lipedema, lipohypertrophy, obesity, and lymphedema and their mixed forms is made easier for health practitioners in their daily work. Many studies are still needed to better understand the entity lipedema, and efforts are underway to change the name to avoid misunderstandings, as the condition "lipedema" does not seem to have water in the fatty tissue.

Keywords

edema | differential diagnosis | lipedema | lipohypertrophy | lymphedema | obesity

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Introduction

Obesity, disproportion between abdomen and extremities (lypohypertrophy), and fat tissue pain are conditions that particularly affect women.[1-6] It is possible that women have a genetically disposed capacity to store energy in the leg and gluteal fatty tissue.[2] This might be an evolutionary selection criterion, as these fatty tissue deposits help in nursing a baby during hunger episodes (author's speculation). These days, obesity is endemic in rich countries, where we do have fridges to prevent us from having weather-dependent hunger. Perhaps this also explains the yo-yo effect after diets, eg, during periods of hunger, the body "remembers" hunger periods from 10 000 years ago and is conditioned to store any food, as soon as it is available (author's speculation). And this is exactly what happens after a diet, especially in women, and it is hard to overcome (author's speculation).

In modern times, societal beauty standards show models that are slim and have perfect legs; thus, women often consider their legs to be part of their beauty and sex appeal. Thus, fat deposition on the legs is disturbing for women; they feel undesirable themselves and are surrounded by women held up as "wonderful" in the media. This makes the problem of obesity and disproportion not only an issue of health but also a complex issue involving psychology and self-acceptance.[3]

Independent of these disproportion and obesity problems, there are 2 clinical pictures that are very closely related to those described above and that can easily be confused; these are lipedema and lymphedema. Even though first described in the 1950s,[7] it wasn't until 2000 that interest was focused on knowledge of the condition lipedema.[2] Parallel to this, we've had a pandemic increase in obesity since the late 20th century, contributing to obesity-related lymphedema as well as asymptomatic lipohypertrophy, increasing confusion.

The term lipedema suggests an edema component. This is reinforced by the fact that compression reduces the pain.[1,2,6] A lot of investigation is needed to find the real reason for the pain in the affected women; there is very probably a high inflammatory component.[1,4] The suggestion that manual lymphatic drainage is necessary in lipedema is derived from the misleading name.[2]

The differential diagnosis is even made more difficult by incorrect information spread through social media, suggesting that disproportion (ie, lipohypertrophy) equals lipedema, that lipedema inevitably causes psychological harm to the affected women, and that increase in body weight is unavoidably associated with lipedema. This places affected women in a helpless and hopeless situation. They approach the health care system in desperate need of help.[1-3]

A lot of work is needed to address this misleading information with 2 goals. One aim is to provide health care workers with information about these conditions, empowering them to support affected women in their concerns. The other is to correct public opinion with true information about the conditions lipedema, lipohypertrophy, lymphedema, and obesity, especially with an aim to correct confusion about the following: i) lipedema and obesity are often concomitant, but not related to each other; ii) obesity increases the disproportional shape of lipedema, but is not caused by lipedema[1,2]; iii) psychological disease is present in 80% of women before lipedema symptoms such as pain in the legs appear[3]; iv) psychological therapy reduces the pain of lipedema[3]; v) pain levels can be influenced by a ketogenic diet[4]; and vi) wearing compression garments during sport activities reduces the pain in lipedema.[5]

This article aims to provide tools to help easily distinguish the following: i) lipedema; ii) lipohypertrophy; iii) lymphedema; and iv) obesity of the legs. The diagnosis of these 4 entities is based on medical history, visual inspection, and palpation. Further investigation, such as with duplex ultrasound, is only helpful as an adjunct, to detect the extent of the edema and to exclude concomitant venous disease.[1,2,6]

Definitions of lipohypertrophy, lipedema, lymphedema, and obesity with leg deformity

Lipohypertrophy is described as symmetrical, disproportional deposition of fatty tissue on the legs and/or arms, respecting hands and feet, with a slim waist.[1,2,6] The clinical picture is possibly hereditary.[1,8] The women do not feel pain in the fatty tissue on touch or on movement.[2] Compression holds the disproportional, often smooth, tissue together and gives a better shape. During sports, compression avoids wobbling.

Lipedema has an optical presentation like lipohypertrophy, but with additional tenderness to the touch and sensitivity to pressure in the increased fatty tissue.[1,2,5,6] In other words: a painful, symmetrical increase in fatty tissue on the legs and arms, with a slim waist.[1,2,6] The condition seems to be hereditary. Classification into stages has been abandoned in some countries, as they were merely morphologic, not reflecting the pain intensity.[1,2] The volume and shape of lipedema legs is mostly influenced by the degree of concomitant obesity, not by the lipedema itself.

Lymphedema is characterized by an alteration of the lymphatic drainage pathways, so that tissue-lymph is not drained physiologically, resulting in congestion and edema of the region.[9] Lymphedema can be congenital, with early or late onset, can appear without any apparent reason, or as a result of an injury (trauma, surgery, radiotherapy).[9] Currently, one of the most common causes of lymphedema is obesity, which delays the drainage of lymph via the groin and retroperitoneum and is often accompanied by a lack of exercise.[10] On touch, the subcutaneous fatty tissue is consistent, not wobbling when moved back and forth, pressure on the skin creates a dent (like in a short-crust pastry), which remains for a few seconds. In an advanced degree of lymphedema, the accumulation of protein in the tissue increases and fibrosis of soft tissues occurs, then the texture changes from soft to hard or ''stony'' and only leaves a slight impression after half a minute of hard pressure.[9]

Lymphedema is divided into 3 stages, as follows: i) Grade I, reversible overnight; ii) Grade II, not spontaneously reversible; and iii) Grade III, with fibrosis and tissue sclerosis.[9]

Obesity with leg deformity could be described as extreme degrees of obesity causing deformities of the legs with dents, furrows, and dewlap formation. In these cases, the fatty tissue is distributed harmonically on the whole body. There is no pain on touch in the fatty tissue.[1,2] Frequently, these women have leg pain due to other obesity-related illnesses, such as knee osteoarthritis, hip disorders, fascial pain, and muscle pain.

Diagnosis

Lipedema and lipohypertrophy

Visual inspection of lipedema and lipohypertrophy

Both conditions look similar, which is why their visual inspection is described here together. They differ only according to palpation findings. They can affect the entire leg and arm or only some parts, always excluding hands, abdomen, thorax, and feet.

Both conditions only affect women, and the appearance is always symmetrical.[1,2] These 2 diagnoses cannot be distinguished by visual inspection alone, as their appearance is identical.

In women of (high) normal weight

In lipohypertrophy and lipedema, there is disproportion between the waist and legs *(Figure 1, left)*. Typically, the ankle is the lower end of the increased fatty tissue, the foot is not changed in shape,[1,2,6] and often a groove or furrow is observed at the ankle[2] *(Figure 1, middle)*.

In obese women

In this case, the disproportion between the waist and legs has been partially lost due to obesity. Typically, the furrows are also found on the thighs and knees or calves. The foot remains without an increase in volume, with the typical furrow at the ankle *(Figure 1, right)*.

Figure 1. **Left:** Dorsal aspect of a woman with disproportion between a slim waist and high fat deposition in gluteal and thigh region. This could be lipedema or lipohypertrophy. **Middle:** Calf and ankle of a woman with fat deposition on the calf, respecting ankle and foot. A furrow is found at the ankle. This could be lipedema or lipohypertrophy. **Right:** Obese woman with furrows on the legs, no fat tissue deposition at the foot. As there is no disproportion, we cannot consider lipohypertrophy. Only if the history demonstrates disproportion in earlier years (before increasing the weight) and there is tenderness on palpation can we consider lipedema.

Palpation of lipedema and lipohypertrophy

In both lipedema and lipohypertrophy without accompanying lymphedema, we do not find any dents when we press into the tissue,[2] as we do with lymphedema. The difference between the two lies in the spontaneous pain or pain on palpation, which is pathognomonic for lipedema.[1,2,5,6] It is typically symmetrical and can be reduced by compression stockings.[1,2,6]

What does lipohypertrophy feel like?

The increase in fatty tissue in lipohypertrophy is soft and mobile. The fatty tissue is painless to the touch.[2] However, if there is muscle or fascia pain or back-related leg pain, this can be confusing. In case of muscle pain, this appears after "deeper" pressure reaching the fascia with the fingers on palpation. Touching, wobbling, or pressing superficially on the fat layer does not provoke pain.

What does lipedema feel like?

With lipedema, the fatty tissue is more compact on touch (unless the patient has just lost weight). Superficial palpation is immediately painful.[1,2] This typical lipedema pain is greatly reduced by wearing compression garments. If there is any doubt, the patient might try support leggings or capri pants to sort out the effect. If support stockings help, the patient might be provided with compression stockings or panties. If there is no relief or the stockings are even bothersome, lipedema can be safely ruled out. The reason for the pain may be orthopedic pain that can be treated otherwise.

How can we tell the difference?

Not all patients with increased fatty tissue on the legs and certain leg pain suffer from lipedema. We therefore need to differentiate between the various possibilities, to find the correct diagnosis but also to give the patient the deserved help against the pain. For example, different types of pain include the following: i) symmetrical pain—probably lipedema (especially if compression helps)[1,2,5,6]; ii) pain on superficial contact—probably lipedema (especially if compression helps); iii) deep pain to the touch—possible neuromuscular or rheumatological cause, fascial adhesions[1]; iv) asymmetrical pain that is dependent on posture (more so when standing or sitting) or movement patterns, suggesting an orthopedic, eg, joint condition; and v) asymmetrical pain that is dependent on posture (more so when recumbent), suggesting a spine condition.[11]

Labeling the patient with the diagnosis "lipedema" often means that no doctor looks for other causes of the pain, leaving the patient with no diagnosis on the real cause of the pain and the needed treatment.

Coexistent obesity and lipedema or lipohypertrophy

The condition lipedema or lipohypertrophy by definition means a higher fat deposition on the extremities. This automatically increases the body weight, even if the rest of the body is slim. Thus, the body mass index (BMI) as a measurement of being overweight can be misleading. Nevertheless, weight is still a tool to help distinguish between obesity and lipedema or lipohypertrophy.[1,12]

The waist-to-height ratio (WHtR) has been introduced to overcome this problem. The ratio is calculated as follows: waist circumference (in cm) divided by height (in cm). *Table I* shows the normal and overweight values calculated for women by BMI and WHtR.[1,12]

Edema in lipedema and lipohypertrophy

Patients with lipedema or lipohypertrophy may develop coexisting edema, perhaps at the end of the day, especially if there are coexisting conditions, such as obesity, sedentarism, and intake of edema-promoting drugs.[1] Patients report swelling of the ankles, calves, or feet in the evening. They may show pitting edema on palpation in the evening. If clinically not visible, the feeling of bursting of the ankles the patients describe can be visualized in ultrasound as lines of water between the fatty layer and the bone or the muscle fascia next to the ankle. This is always an indication to wear knee-long compression stockings to treat and prevent this condition. This edema is not pathognomonic for lipedema but can coexist with the disease.[1,2]

Thigh swelling in lipedema

Some women affected by lipedema describe a subjective perception of turgidity and swelling in the thighs that increases during the course of the day. A small pilot study was run to confirm if the thighs actually swell during the day in lipedema or not.[13]

In an in-hospital setting, 14 female patients with a confirmed diagnosis of lipedema and who reported suffering from swelling of the thigh throughout the day would have their thigh circumferences measured by the same person in the morning and the evening, all on the same day. They remained without compression. The investigation took place on a Saturday, with no treatments scheduled apart from a walk. Ten control, female patients, adjusted for BMI and hospitalized for arm lymphedema after breast cancer, underwent the same measurements on the same day.

The mean circumferential change during the day ranged from 0 to 0.64 cm for the women with lipedema and from 0.3 to 0.8 cm for the subjects in the control group, none of which were large amounts. No statistically significant differences were found.

	Normal	Overweight	Obesity		
			Grade I	*Grade II*	*Grade III*
BMI	18.5 – 25	25 – 30	30 – 35	35 – 40	>40
WHtR	<0.8	0.8 – 0.84	>0.84		

BMI, body mass index; **WHtR,** waist-to-height ratio.

Table I. Values indicating normal weight, overweight, and obesity measured by BMI (body mass index) or WHtR (waist-to-height ratio).

Based on reference 1: Faerber G. S2k-Leitlinie Lipödem. AWMF-Registernummer 037-012. https://register.awmf.org/de/leitlinien/detail/037-012 (English translation expected online at the same web address August 2024).

Lymphedema

Visual inspection of lymphedema

Lymphedema in the legs can start in the thigh (often after cancer surgery in the pelvis, *Figure 2, left*), in the feet (*Figure 2, middle*), or affect all parts of one or both legs (*Figure 2, right*). Particularly with lymphedema of the thigh, you can see the imprint of the edge of the seat after standing up (*Figure 2, right*).

Lymphedema often also affects the feet. The forefoot then bulges, and thickening of the toes can be observed, which develop the appearance of "boxes" with grooves at the base of the toes ("box toes") (*Figure 3, left*). Particularly in summer, when compression is often omitted due to the heat, small blisters may appear on the skin, with clear fluid oozing out (*Figure 3, middle*). Depending on the extent of the lymphedema, the skin can turn reddish-brown (Grade III) (*Figure 3, middle and right*) and even lead to an ulceration. In advanced cases, but also with additional poor skin care, wart-like skin changes with scaling occur (*Figure 3, right*).[9]

Palpation of lymphedema

Lymphedema feels like cake batter or Plasticine; if you press into the tissue with your finger (*Figure 4, left*), a dent remains, which only fills up again after a few minutes[9] (*Figure 4, right*). Depending on the degree of lymphedema, the accumulation of protein in the tissue increases, then the texture changes from soft (*Figure 5, left and center*) to hard or "stony" (*Figure 5, right*) and only leaves a slight impression after half a minute of hard pressure.[9]

Figure 2. **Left:** Lymphedema of the left leg after iliofemoral tumor (sarcoma) with surgery and radiation. The leg difference is caused by the lymphedema deposition in the subcutaneous tissue without treatment over a long time. **Middle:** Lymphedema in a woman with terminal cervix cancer after Wertheim surgery and radiation. The patient is underweight (43 kg) and still has lymphedema on the legs with box toes. **Right:** An 82-year-old man with lymphedema after prostate-carcinoma with surgery and radiation. He usually sits and is no longer able to move. Lymphedema accumulates in the dependent areas and has a high plasticity. After the patient sits 3 minutes on the examination couch, a depression in the edema is apparent.

Images courtesy of © Erika Mendoza.

Figure 3. **Left:** Typical changes at the toes of lymphedema patients: furrows at the base of the toes, filling with lymphedema, so that the form of the toe is no longer round, but like a box. It is impossible to take a skin fold at the toes (Stemmer sign). **Middle:** After a longer period of persistence of the lymphedema, the skin develops sclerosis with discoloration and atrophy of the fatty tissue. Without compression, the lymphatic fluid will ooze out of small blisters on the skin. **Right:** Lymphedema at an advanced stage, with furrows and caused by poor skin care; wart-like skin changes with scaling.

Images courtesy of © Erika Mendoza.

Figure 4. Testing for lymphedema: compressing with a finger (left), a depression develops that stays throughout a period of minutes (right). In this case, with early lymphedema, the tissue is soft on touch.

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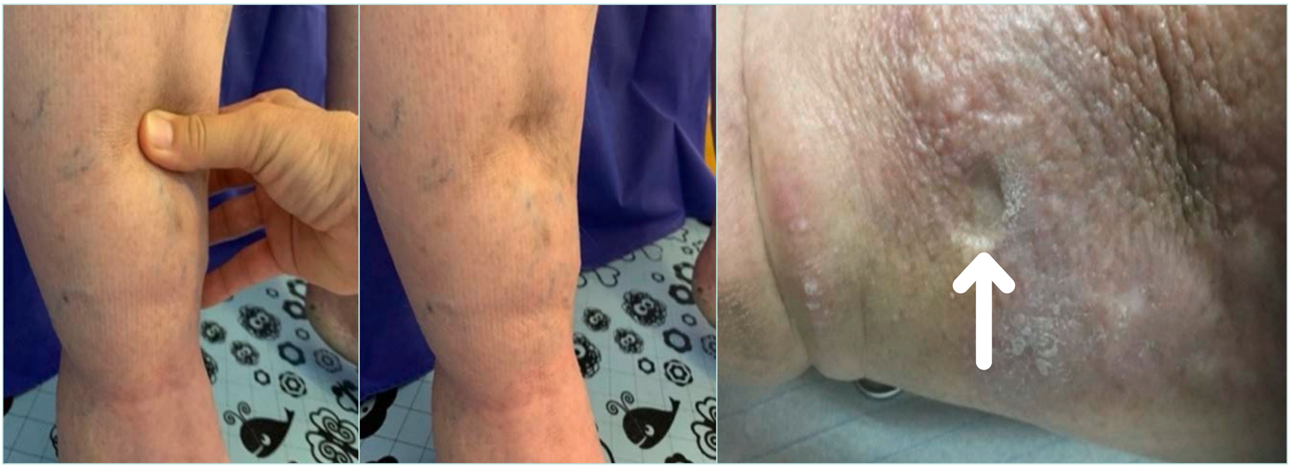

Figure 5. **Left and center:** Lymphedema in Grade II, it takes more force to provoke the depression and it stays longer. **Right:** In very advanced protein-rich lymphedema, it takes some minutes to pinch a finger cusp inside the tissue—the dot provoked (see arrow) stays for hours.

Images courtesy of © Erika Mendoza.

Coexistence of lymphedema and lipohypertrophy or lipedema

If women with lipedema or lipohypertrophy develop massive obesity, "obesity-related" lymphedema can also occur. *Figure 6* shows a case of lipedema with bulge formation and furrows, obesity, and obesity-related lymphedema with box toes at the feet on the same leg. We know that this is lipedema and not lipohypertrophy, as she has pictures from her youth showing disproportion between abdomen and legs and she reports that she has always suffered from pain. She has worn compression stockings regularly since she was 18 years old. Prior to this image, the patient had lost 30 kg, dropping from 180 kg to 150 kg, to be admitted for a knee-joint surgery.

Some people call this "lipo-lymphedema," which is an inappropriate term, as the lymphedema is not secondary to the lipedema, but to the obesity. Lymphedema and lipedema are completely different clinical entities.[14] An overview of characteristics for the 4 conditions is given in *Table II*.

Table II. Overview of characteristics from lipedema, lipohypertrophy, lymphedema, and obesity.

[a] Please distinguish between pain in the fatty tissue or pain on deep touch with compression of the fascia or muscular tissue, often painful in sedentary persons.
[b] Unless there are other causes, such as muscle pain, lumbar spine problems, fibromyalgia, fascial pain.

	Lipohypertrophy	Lipedema	Lymphedema	Overweight
Disproportion between abdomen and legs	Yes	Yes	Possible	No
Symmetric	Yes	Yes	Possible	Yes
Sensitive to touch in the fatty tissue[a]	No	Yes	Possible	No
Painful	No[b]	Yes	Possible	No[b]
Pain relief through compression	No	Yes	Yes	No
Subcutaneous tissue indentable like cake dough	No	No	Yes	No
Forefoot swelling, box toe	No	No	Yes	No

Leg changes with obesity

Some patients have generalized obesity. The furrows in the tissue are caused by the excess weight; it is present all over the body and does not cause pain to the touch.[1,2] This is obesity and not another disease entity. However, this obesity will often lead to lymphedema (see *Figure 6*). The degree of lymphedema reduces or the condition even disappears after weight reduction.[14]

Figure 6. Women with lipedema with "dewlaps" (ie, excessive, almost hanging fatty tissue) and furrows, in a patient after losing 30 kg with additional lymphedema. Note the reddish discoloration of the very bulging tissue in front of the shin, here a "kneadable" consistency when touched, with involvement of the forefoot with furrows between the toes and the back of the foot.

Summary

Lipedema, lymphedema, lipohypertrophy, and obesity are 4 conditions with similar manifestations, making differential diagnosis challenging. However, differentiation can be made easier if basic concepts are clear.

Diagnosis is based on medical history and physical exam, visual inspection, and palpation being the key items. An improvement of the definitions of these entities including the renaming of lipedema disease to avoid conception of edema associated with lipedema is needed. Educational activities promoting these fundamental keystones among health care workers and the general population will improve diagnosis, and consequently management.

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Optimal management of combined iliac vein stenosis and ovarian vein reflux in patients with pelvic venous disease (PeVD): which patients should be treated for both and what comes first?

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ABSTRACT

The increased recognition of iliac vein stenosis in the causative effect of venous origin–chronic pelvic pain has led to an ongoing debate of the evaluation, diagnosis, and treatment of patients with pelvic venous disease (PeVD) who present with both iliac venous stenosis and ovarian vein reflux. While ovarian reflux has been thought to play a primary role in the pathophysiology of this disease process, increased evidence suggests that iliac vein stenosis can also lead to chronic pelvic pain and other associated conditions present in these patients, such as chronic venous disease and postural orthostatic tachycardia. Moreover, patient evaluation is confronted by associated nonspecific pelvic symptoms and various anatomical presentations, which are becoming more diagnosable. This is leading to an increase in incidence of patients presenting with combined patterns, which poses a challenge in choosing a treatment algorithm. This article will describe insights to accurately diagnose the disease with its different clinical and anatomical presentations, focusing on the management of combined iliac vein stenosis and ovarian vein reflux in patients with nonthrombotic disease.

Keywords

iliac vein stenosis | nonthrombotic disease | ovarian vein reflux | pelvic venous disease | venous origin–chronic pelvic pain

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Introduction

Pelvic venous disease (PeVD) is defined as the spectrum of signs and symptoms secondary to abnormal venous flow in the pelvic area. However, it remains poorly understood and frequently misdiagnosed, partly due to nonstandard anatomical terminology and limited diagnostic criteria for the venous conditions it encompasses.[1] This issue is further complicated by the presence of "mixed" anatomical pathways implicated in the development of venous origin–chronic pelvic pain (VO-CPP), highlighting the varied presentations of disease state in different patients. Recently, the Symptoms-Varices-Pathophysiology (SVP) classification of pelvic venous disorders was created to improve patient categorization for further understanding of causative factors leading to VO-CPP.[2] Moreover, there is increased evidence of comorbidities associated with this entity (interstitial cystitis and postural orthostatic tachycardia), that may further contribute to the patients' clinical presentation.[3]

Given all these anatomical and clinical contributors to VO-CPP, the interventional treatment of PeVD needs to be optimized for each patient and may involve several treatments needed to achieve clinical success. This may include the following procedures: ovarian vein embolization (OVE), internal iliac vein embolization (IVE), and venous stent placement. Whereas the pathophysiology contributing to the patient's symptoms will determine the best endovascular treatment, a major issue relates to the different clinical presentations in women of various ages[4] and the need for venous stent placement occurring more commonly in older patients.[5,6] In this article, we will describe how to evaluate these patients and discuss treatment strategies in nonthrombotic patients with both ovarian vein reflux (OVR) and iliac vein stenosis (IVS).

Anatomy and pathophysiology of chronic pelvic pain in compression syndromes

The SVP classification defines PeVD as the spectrum of symptoms and signs arising from the veins of the pelvis (gonadal veins, internal iliac veins and their tributaries, venous plexuses of the pelvis) and their primary drainage pathways (left renal vein, iliac veins, and pelvic escape points).[2] Traditionally, PeVD has been described in patients with pelvic venous reflux (ovarian and internal iliac veins) leading to resultant pelvic varices around the periuterine area.

The uterine plexus is drained by 4 primary veins, the lower portion of the uterus is drained through the bilateral internal iliac veins, and the upper portion of the uterus is drained through the uterine or the ovarian plexus to the ovarian veins (OVs). The left OV drains directly into the left renal vein (*Figure 1 A, B*), whereas the right OV drains at an acute angle into the inferior vena cava (*Figure 2*) in most cases. These pelvic veins typically are extensively collateralized with

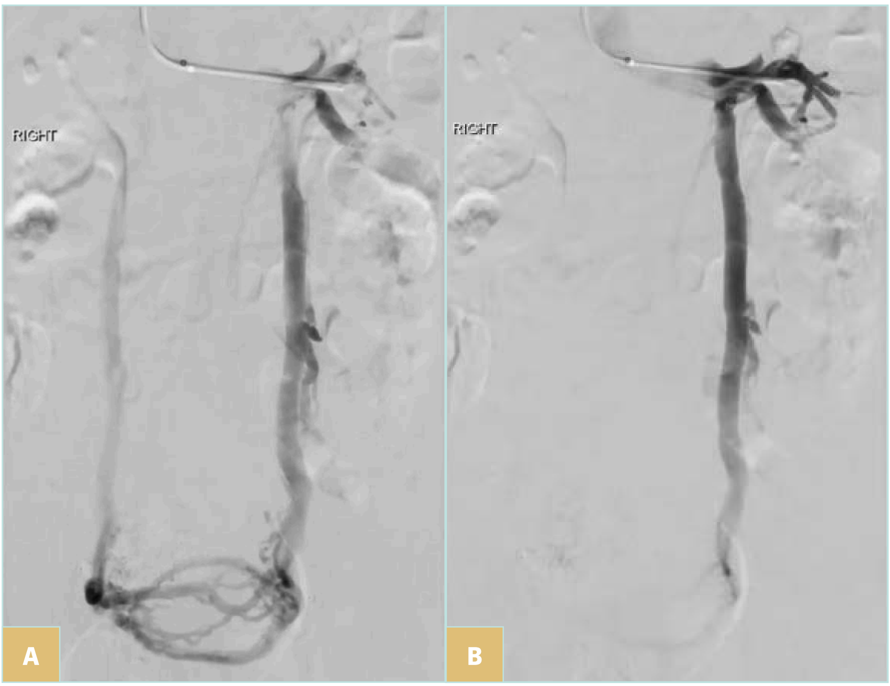

Figure 1. **A)** Uterine/ ovarian plexus drainage to bilateral gonadal veins. **B)** Left gonadal vein drainage.

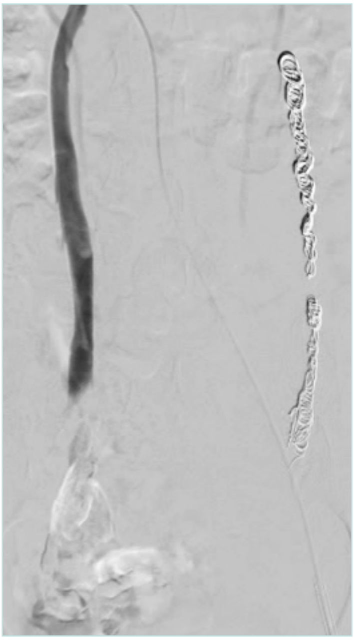

Figure 2. Right gonadal vein draining into inferior vena cava.

connections with the superficial veins of the genitalia and the lower extremities, which can result in extra-pelvic symptoms—"so called" S3 symptoms in the SVP classification system (*Table I*).

Recently, studies have challenged the causative effect of OVR in PeVD, given that OVR is symptomatic in only up to 59% of patients,[7,8] and some evidence shows that iliac vein outflow abnormalities such as stenosis, not OVR, are more common underlying causes of PeVD.[5,9,10] One large case series of 1280 patients found that IVS was present in 53% of patients with PeVD, whereas 40% had IVS in combination with OVR.[5] In another report of 421 patients, Larkin et al found that 46.7% had iliac vein obstruction, and 40.1% had OV incompetence.[9] However, of those who had chronic pelvic pain (CPP), common iliac vein (CIV) obstruction, with and without gonadal vein incompetence (33% and 35%, respectively), was more common than OV incompetence (14%).[9] In cases with combined iliac and gonadal venous abnormalities, the OV is acting as a compensatory escape vein rather than the primary pathologic vein.[10] This has been supported by a small study demonstrating the resolution or improvement of symptoms in patients with combined IVS and gonadal vein reflux with iliac stenting alone.[5] Moreover, IVS has been reported as a cause of intractable pelvic neuropathic pain, in patients with PeVD who had evidence of left OVR and IVS, suggesting a correlation to CPP.[11] Lastly, a recent study demonstrated that 69% of female patients with postural orthostatic tachycardia syndrome (POTS) had significant left CIV compression and clinical improvement of dysautonomia symptoms after treatment for their PeVD.[12]

S0	**No symptoms of pelvic venous disease**
S1	**Renal symptoms of venous origin**
S2	**Chronic pelvic pain of venous origin**
S3	**Extrapelvic symptoms of venous origin**
a	**Localized symptoms associated with veins of external genitalia**
b	**Localized symptoms associated with pelvic-origin nonsaphenous veins of the leg**
c	**Venous claudication**

Table I. Symptoms-Varices-Pathophysiology classification: symptoms categories (S).

When should we consider the possibility of iliac vein stenosis in patients with PeVD?

The major clinical challenge in the proper diagnosis of combined patterns is to obtain a proper clinical history and evaluation of presenting symptoms, with patients being categorized in 2 major groups according to the SVP classification system (*Table I*): S_2 and $S_{2,3}$ patients.[2]

Consensus documents define the following symptoms: pelvic pain, perineal heaviness, urgency of micturition, and postcoital pain (S_2 symptoms), caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices (S_3 symptoms).[13] In addition, symptoms can range from CPP (S_2) and renal manifestations (S_1 symptoms), if one considers left renal vein compression.[14] However, renal symptoms (S_1) such as hematuria, dysuria, and urinary frequency in the absence of infection can be present in women with PeVD without left renal vein compression.[14] However, if patients report hematuria and or left flank pain, it is important to rule out left renal vein stenosis for proper management of symptoms.

Regardless, the classic description of PeVD includes CPP with dyspareunia and postcoital pain with worsening after prolonged periods of standing (postural pain). It is important to ask patients about the temporal relationship of onset of symptoms and pregnancies, whether the patient has developed vulvar varices or not during that time, and finally, the venous characteristic of the pain: postural CPP (heaviness, cramping) relieved by lying flat, with some patients needing to have a "break" in the middle of the day to relieve the pain. The 3 "P" s (pelvic pain, provoked by gravity, and prolonged postcoital ache) are the most frequent clinical findings in VO-CPP in women, based on the literature.[15] Whereas most patients presenting with S_2 symptoms have overlapping OVR and IVS, patients with combined venous claudication and edema and or varicose veins in the leg should be evaluated with imaging and ruled out for venous outflow obstruction.

Imaging evaluation and treatment planning

Most patients with CPP will have already undergone limited evaluation with transvaginal ultrasonography (TVUS) (*Figures 3 and 4*). Most recently, a study demonstrated that the presence of pelvic veins or venous plexus of 8 mm or larger, observed by TVUS, can predict 79% of patients with pelvic congestive syndrome.[16] Whereas there is a high association of VO-CPP and evidence of periuterine veins of diameters larger than 8 mm in TVUS, when suspecting iliac stenosis in addition to reflux, the ideal imaging tool for assessment includes either an abdominal ultrasound and/or cross-sectional imaging, such as computed tomography (CT) venography and magnetic resonance venography (MRV), to specifically diagnose stenosis. The imaging choice will depend on local availability and ultrasonography expertise. There are published ultrasound protocols to evaluate both pelvic venous reflux and stenosis[17]; however, patient body habitus and presence of overlaying bowel gas can limit the evaluation in about 50% of patients.[18] In these instances, CT offers superior spatial resolution over ultrasound, and the use of intravenous contrast can improve characterization of the pelvic vasculature (*Figure 5*). A drawback is the supine positioning for acquiring the study, which prevents recreation of flow dynamics seen in venous reflux. However, data suggest a significant correlation between left iliac vein cross-sectional area and diameter ratios to reflux start-up time in digital subtraction venography.[19] Of note, a 50% or greater iliac stenosis may be present in 25% to 33% of the population. Therefore, anatomic stenosis alone should not be considered a criterion for intervention, and presence of stenosis should be interpreted in the context of patients' clinical symptoms.[20,21]

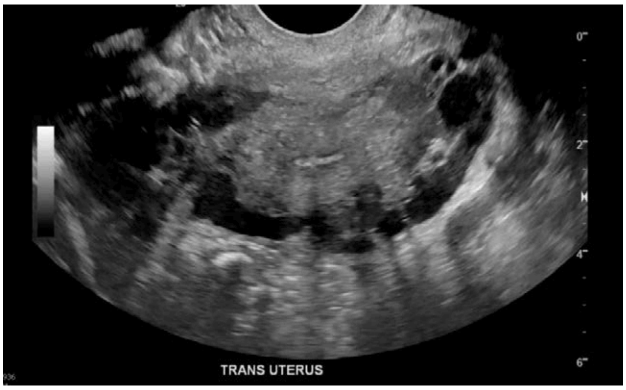

Figure 3. Ultrasound with utero-ovarian plexus >5 mm in diameter.

Time-resolved contrast-enhanced MRV does allow for dynamic evaluation of the direction of flow, but MR venography provides a high 42% false-positive rate[22]; moreover, dehydration status can mimic stenosis, resulting in false-positive exams.[23] Despite these drawbacks, MRV is favorable in situations where ultrasound imaging is unsuccessful, such as in patients with large body habitus.

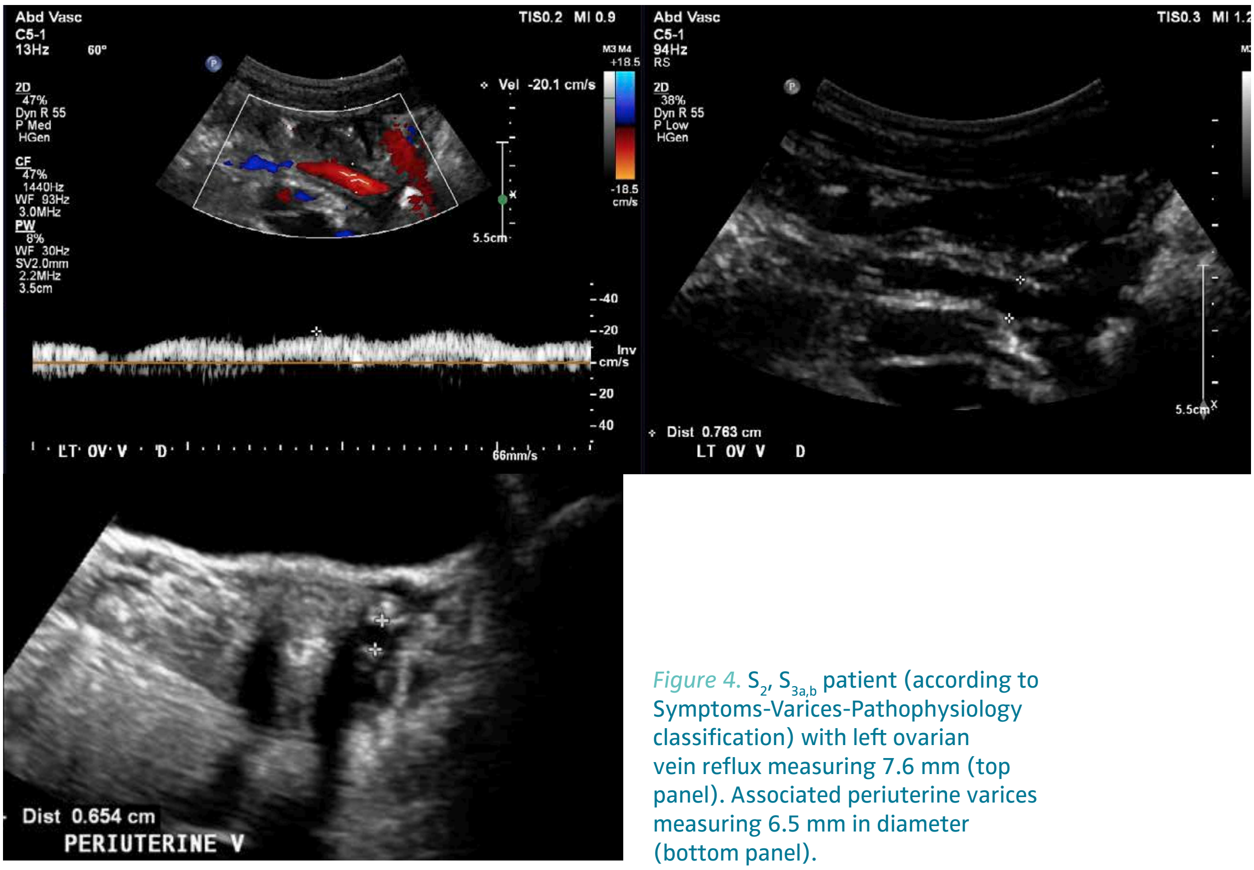

Figure 4. S_2, $S_{3a,b}$ patient (according to Symptoms-Varices-Pathophysiology classification) with left ovarian vein reflux measuring 7.6 mm (top panel). Associated periuterine varices measuring 6.5 mm in diameter (bottom panel).

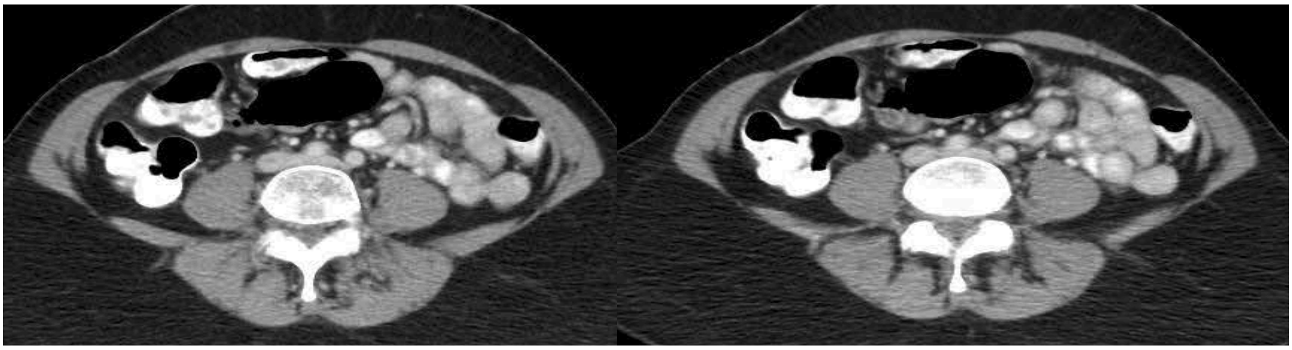

Figure 5. Computed tomography venography demonstrating left iliac vein compression.

Catheter venography has emerged as the standard of care in diagnosing PeVD, but due to advances in noninvasive imaging and ionizing radiation, it is typically indicated for definitive imaging at the time of treatment. Generally, a catheter venography study involves the placement of a diagnostic catheter into high-frequency points of obstruction where contrast is injected to image for potential areas of compression, scale magnitude of distention, reflux, and pooling (*Figure 6*). Diagnostic criteria for pelvic varices on catheter venogram include 5 mm or greater diameter of gonadal vein, uterine vein, and utero-ovarian arcade. Free reflux in the gonadal vein with valvular incompetence or filling of contrast material across the midline are also diagnostic criteria (*Figure 1B*).[24] Additionally, described criteria include timing duration of contrast pooling after venography.[25] For the diagnosis of IVS with associated reflux, there has been description of a grading system, varying from normal findings (Grade 0) to presence of internal iliac venous reflux (Grade 1), pelvic venous collaterals (Grade 2), and iliolumbar venous collaterals (Grade 3).[19]

The use of intravascular ultrasound (IVUS), which provides additional information regarding the severity of stenosis (*Figure 7*), is considered the gold standard for diagnosing CIV compression and planning of iliac vein stenting; however, adequate imaging thresholds correlating with clinical outcomes are lacking.[26] In the VIDIO study (Venogram vs IVUS for Diagnosing Iliac vein Obstruction),[27] Gagne et al evaluated IVUS stenosis and outcomes, indicating that diameter stenosis was the only significant predictor of future improvement in clinical symptoms in iliac stenosis, with a threshold of >61% by IVUS.[27] In addition to being superior to single-plane venography, IVUS is helpful in assessing lesion response to angioplasty, guiding stent placement, and identifying in-stent stenosis.[28]

Figure 6. S_2 patient (according to Symptoms-Varices-Pathophysiology classification) with combined presentation of ovarian vein reflux (OVR) and iliac vein stenting (IVS).

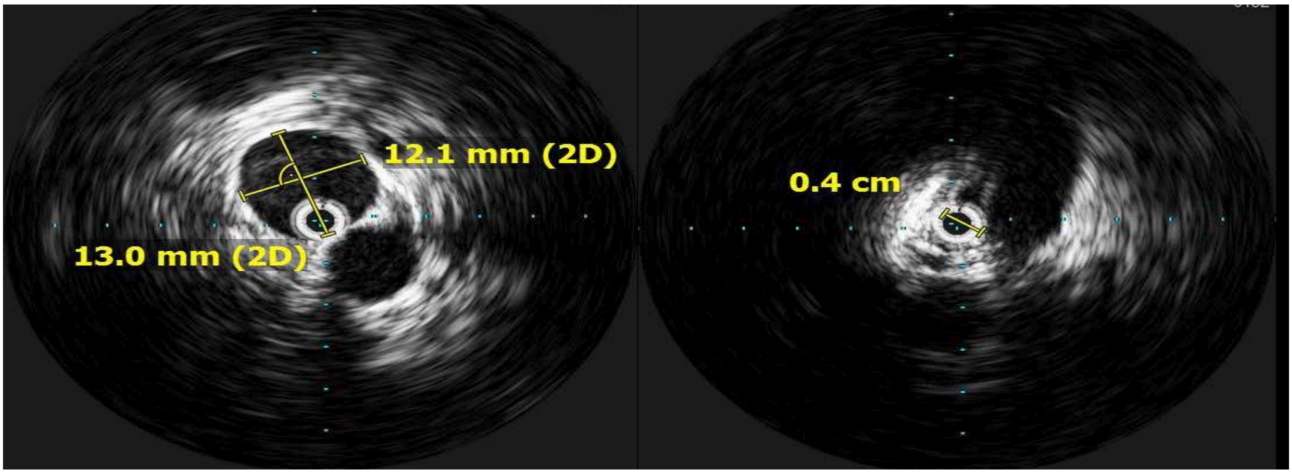

Figure 7. Intravascular ultrasound (IVUS) evaluation.

Therapeutic considerations

When creating a treatment plan, it is important to note that many patients with PeVD have multiple venous abnormalities contributing to their symptoms, and effective treatment defined by symptomatic improvement or resolution is dependent on the identification of the underlying venous conditions contributing to the patient's presentation. Careful assessment for presence of the previously described patterns that contribute to this disease, including OV incompetence/reflux, venous stenosis, escape points, and anatomical variant, are critical for effective treatment and determining the treatment plan in each patient. Most patients present with a combination of these pathophysiologic variants, so optimization of treatment strategies is critically important.[4]

The reality for several patients is that a large proportion have more than one of the above abnormalities contributing to their symptoms. Initial data based on 19 patients suggested that in patients with both common IVS and left OVR, addressing the venous stenosis alone with a stent placement was effective in symptom improvement in most patients.[29] However, a more recent study including 12 patients reported symptomatic relief in only 16.6% of patients with PeVD when only stenting was performed and indicated that OVE should be performed 6 months after stenting.[30] These findings supported the data from a previous study involving a larger number of patients (n=277) published in 2018, which found that 80% of patients had both OV insufficiency and iliac vein compression. The authors advocated for the treatment of venous stenosis first, followed by OVE if symptoms persisted, but suggested simultaneous treatment in patients with large pelvic reservoirs.[10]

The order of and timing of optimal treatment is not yet fully elucidated, and there are heterogeneous practice patterns. Below we describe the most current literature on this subject.

Current evidence of literature supporting ovarian vein embolization first

Despite extensive publications highlighting the role of OVE in isolated nonobstructive OVR, there is growing evidence demonstrating the role of left iliac vein stenting, challenging whether the primary source of pelvic varices (periuterine varices) and symptoms are secondary to OVR or IVS.[9] The role of OVE as a treatment option for PeVD, demonstrates a technical success rate ranging from 96.7% to 100%, and clinical improvement of pain between 50% and 100%,[31] with recurrence in up to 25% of patients[32] in patients with isolated left OVR. Whereas no large randomized control trials exist comparing percutaneous embolization with medical and or surgical therapies, OVE has emerged as a treatment of choice due to low morbidity, effectiveness, and durability, and is usually the first approach in patients with combined patterns, with stenting being performed at later stages if patients present with persistent VO-CPP.[4] Part of the challenge relates to the lack of understanding of the primary physiologic mechanism responsible for VO-CPP in these patients. Moreover, OVR or IVS grading has been based on venographic/imaging criteria and not appropriately defined yet,[1] without a quantitative tool to reliably assess hemodynamic flow in these mixed patterns. That said, a few studies retrospectively described the role of OVE first. In a subset of patients with staged OVE and stent (n=94), only 9 patients presented with symptomatic improvement after OVE alone, and most patients required additional venous stenting.[10] These results are contrasted by the smaller, above-mentioned study reporting symptom relief in only 16.6% with stenting alone and that recommended additional OVE at 6 months for these patients.[30]

In another study of 43 women with PeVD, authors found the following anatomical distribution of lesions: OVR (61%), internal iliac vein reflux (9%), reflux combination of both (30%), and 42% of patients with anatomical obstruction (inferior vena cava, common iliac or left renal veins). Treatments among these patients included OVE (86%), internal IVE (9%), and venous stent placement (35%), with subsequent improvement in the leading symptom of pelvic pain in up to 93% of patients, whereas 14 (33%) became symptom free.[33]

Current evidence of literature supporting stenting first

Most of the data published represents a total of 254 women presenting with VO-CPP as a predominant symptom. Associated chronic venous disease ($S_{2,3}$ patients) was present in about 78% of patients (n=199), of which 27% (n=69) were treated primarily with CIV stent alone.[10,29,30]

In one of the first series to address iliac vein lesions in PeVD, CIV stent placement was effective in the treatment of CPP even if there was observed untreated left OVR.[29] As previously mentioned, a larger study from 2018[10] in patients with combined patterns suggested that pelvic venous outflow lesions should be treated first, with a subset of patients with large pelvic reservoir needing to have simultaneous treatment with both iliac vein stenting and OVE. However, as mentioned above, a smaller study reported symptom relief in only 16.6% with stenting alone and recommended additional OVE at 6 months.[30]

Stenting in the setting of PeVD is performed in the same fashion as described for patients with nonthrombotic IVS. The technique has changed with the advent of dedicated venous stents, but in short, the left femoral vein is accessed with a 9F introducer sheath, and an IVUS system is utilized to confirm venous stenosis and estimate the size of stent to be placed based on intraluminal measurements. The assessment begins at the inferior vena cava and continues into both CIVs, external iliac veins, common femoral veins, and femoral veins. In addition, multiplanar venography is performed from the left femoral vein access. Lesions are treated first with balloon angioplasty with an appropriate-length balloon of 12 mm to 14 mm in diameter, and then stenting. Stent sizing is based on the landing venous zone diameters (normal vessel), extending just to the iliac confluence, usually at L4, using IVUS guidance for proper length and diameter, typically measuring 14 mm in diameter with minimum length of

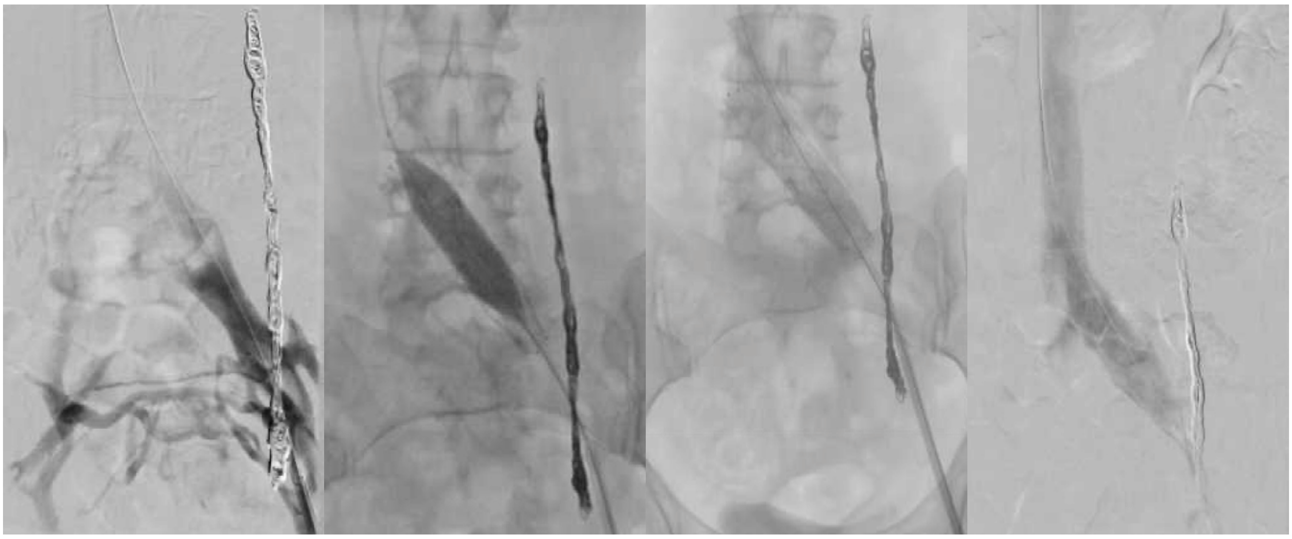

Figure 8. Procedural steps for stent placement. Venography shows Grade 2 reflux and a 14-mm dedicated venous stent placement after left ovarian vein embolization (OVE) in an S2 patient (according to Symptoms-Varices-Pathophysiology classification) with persistent chronic pelvic pain.

100 mm to avoid stent migration[34] and allows for proper positioning within the pelvic vasculature (*Figure 8*). Stent placement has been associated with back pain in up to 66% of patients 1 week after stent placement, with improvement of symptoms at 1 month.[35]

Despite most data regarding venous stenting arising from the chronic venous disease literature, data suggesting the effectiveness of venous stenting in patients with VO-CPP as a major manifestation of PeVD is emerging. It is debated whether stenting of the iliac vein alone results in successful outcomes or if other interventions are needed for significant clinical improvement. Therefore, stenting should be done in symptomatic patients whose symptoms are attributable to the stenosis (S_2 and/or $S_{2,3}$ patients), particularly in the younger patient population.[36] This is determined through a combination of history, medical work-up, and imaging. Since there is a high prevalence of IVS in asymptomatic patients, it can be a challenge to determine the degree of stenosis that becomes clinically relevant, and treatment would result in symptomatic relief in those with PeVD when there are multiple factors at play.[37]

Nevertheless, in a small series of 38 women with VO-CPP and chronic venous disease secondary to combined IVS and OVR, 76% of patients achieved complete symptom resolution with iliac vein stenting alone, with authors recommending that iliac vein stenting alone should be the primary treatment, with staged OVE to be reserved only in cases of persistent symptoms.[5]

Long-term effects of ovarian vein embolization and iliac vein stenting for women of reproductive age and anticoagulation management

OVE seems to be safe in patients of reproductive age and attempting to become pregnant.[38,39] In a small series, subsequent pregnancies were reported in up to 66.7% of women undergoing OVE who had complete symptomatic relief.[38] However, pregnancy is associated with recurrent reflux in the pelvic veins in women who had previously been treated with coil embolization, and a repeat procedure may be needed afterwards.[39]

On the other hand, there have been questions about long-term patency of stents during pregnancy, and the decision of placing an iliac venous stent in the PeVD woman of childbearing age remains controversial, particularly in cases of isolated S_2 symptoms.[36] To that end, initial studies recommended perinatal anticoagulation management[40]; however, most recently, a systematic review demonstrated that in the heterogenous patient population with a subset treated for nonthrombotic iliac stenosis (46%), the following outcomes were recorded: 1.14% experienced stent occlusion, 2.29% developed asymptomatic nonocclusive in-stent thrombus, and 2.29% experienced permanent stent compression.[41]

There is marked variation in anticoagulation and antiplatelet management after stenting for nonthrombotic central venous stenosis. A Delphi consensus was performed to generate consensus statements among venous stenting experts. They stated that anticoagulation is preferred to antiplatelet therapy for the first 6 to 12 months after stenting for nonthrombotic venous stenosis. Low-molecular-weight heparin is the first-choice anticoagulation the first 2 to 6 weeks after stenting. In the case of postthrombotic venous stenting, anticoagulation can be discontinued 6 to 12 months after stent placements if the following criteria are met: i) negative results are obtained on thrombophilia screen; ii) the thrombotic event was the first for the patient; and iii) stent patency is demonstrated on ultrasound. In patients who have multiple deep venous thromboses and iliac vein stenting, anticoagulation should be continued indefinitely barring contraindications.[42]

In our practice, patients who are in a hypercoagulable state or have a history of prior deep venous thrombosis are placed on anticoagulation for 6 months only. All other patients are treated on an antiplatelet agent (clopidogrel 75 mg) for 6 to 8 weeks after the procedure. Our rationale is that, in general, our patient population is young and healthy and presents with nonthrombotic disease. The risks of both bleeding and thrombosis are discussed with patients prior to making the decision of using antiplatelets versus anticoagulation.

Future trials considerations

The major challenge in the interpretation of results reported in the literature relates to heterogenous patient cohorts and to nonstandard terminology in describing the anatomical lesions and patient symptoms. Given the overlapping presentations and heterogeneity of clinical studies published thus far, it is prudent to optimize treatment using proper categorization of patients and data on existing literature. In terms of patients who present with IVS, most studies are based on patients who have associated chronic venous disease, predominantly manifested as VO-CPP. Daugherty et al[29] demonstrated successful clinical outcomes in patients with PeVD and iliac vein stenting alone, whereas Gavrilov et al[30] found that stenting alone was not sufficient to completely improve symptoms in a patient population with VO-CPP and $S_{2,3}$ symptoms.

For future trials, we need first to study patients with S_2 symptoms in a randomized controlled study with a comparator treatment. Whereas patients with OVR and IVS, would need to be evaluated separately, to understand the value of OVE and iliac vein stenting, a prospective evaluation of patients with both reflux and stenosis with S_2 symptoms alone would be helpful to elucidate the order of treatments. Diagnostic criteria, as it relates to defining a clinically significant IVS threshold, needs to be further investigated to determine which lesions should be treated. At this point, the SVP classification has been designed as a new tool for defining the anatomy and symptoms of patients with PeVD. Prospective registries applying the SVP tool will help to evaluate treatment outcomes and understand the incidence and contribution of reflux versus obstruction. Long-term data would then include controlled, prospective analysis of different treatment strategies and comparative studies to support interventional treatments in these patients. Actually, the lack of validated patient-reported–outcome tools limits the evaluation of the clinical benefit of treatment, and most studies rely on patients' self-reported levels of pain as a clinical outcome metric.

Conclusion

Whereas there are different anatomical presentations, the management of combined patterns in PeVD has gained increased attention, with considerable variation in the literature in terms of patient selection, treatment order, and reported clinical outcomes. Although we are still debating the proper pathophysiology in these patients, and given the lack of high-quality scientific evidence, staged OVE followed by stenting seems to be a reasonable approach, particularly in patients with significant venous stenosis. However, there are still concerns about long-term outcomes in younger patients, particularly in women of childbearing age. Future research should focus on individual trials evaluating patients with isolated OVR, IVS, and S_2 symptoms separately. This would then follow with the development of protocols to further elucidate the hemodynamic differences in patients with combined patterns. Ultimately, this would help define the appropriate criteria to choose therapy for the presenting clinical picture and underlying pathophysiology.

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Mechanochemical ablation (MOCA), a nonthermal nontumescent ablation (NTNT) technique for the treatment of chronic venous disease (CVD): our experience and its benefits in Latin America

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Keywords

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Flebogrif
Latin America
nonthermal nontumescent
polidocanol
tetradecyl sulphate sodium
sclerotherapy
varicose veins
venous ulcers

ABSTRACT

The treatment of chronic venous disease (CVD) has evolved since its inception in 1891, when Trendelenburg introduced the saphenofemoral junction ligation. In 1905, Keller performed the first saphenectomy and, for over a century, arch ligation flush ligation of the junction and saphenectomy have been the methods of treatment. In 1999, the United States Food and Drug Administration approved the treatment of CVD by means of endovenous thermal ablation. These endovenous techniques are currently the preferred choice due to their minimally invasive characteristics, resulting in less pain during and after the procedure, and a faster postsurgical recovery.

Nonthermal nontumescent (NTNT) techniques have arisen in the last 15 years as an even less invasive option for treating CVD, as they do not require the use of thermal energy nor tumescent anesthesia with the benefit of being able to be performed on an outpatient basis. Mechanochemical ablation with ClariVein or Flebogrif catheter is one of the NTNT methods. Endovenous treatments have replaced conventional surgery in the United States and most European countries. In recent years, we have witnessed significant progress in initiatives, knowledge, experience, and availability of technology for treating CVD through endovenous techniques in Latin America. However, there are still several regions in Latin America and around the world where the implementation of these techniques has not yet been fully achieved due to the considerable social and economic variability of the countries. Conventional surgery remains the most prevalent choice in most Latin American countries, accompanied by long waiting lists in many of them. Venous disease has a high prevalence in the population, significantly impacting on the patient's quality of life and the health system. In many countries, it remains an unresolved health issue.

Thermal ablation techniques, when available, are predominately conducted in hospitals, whereas NTNT techniques are performed in outpatient settings, which may be an advantage in reducing waiting lists for varicose vein surgery. In this paper, we will briefly review the topic and the published literature on NTNT focused on MOCA methods. We will also share experiences and analyze the benefits of NTNT techniques in the Latin American population.

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Introduction

Chronic venous disease (CVD), as defined by the Vein Term consensus document, encompasses any morphological and functional abnormalities of the venous system of long duration (especially in the lower extremities), and chronic venous insufficiency (CVI), a term reserved for advanced clinical stages (C3-C6),[1] exhibits a high prevalence and incidence worldwide according to epidemiological studies.[2,3]

The international survey program "Vein Consult" (2010)[2] estimates a prevalence of CVD of clinical stages C0-C6 at 83.6% and a prevalence of C1-C6 at 63.9%. In the DETECT–IVC 2006 study conducted in Spain in 2006, the prevalence of CVD was reported as 67.3%.[3] In Latin America, the prevalence of CVD was 68.11%, with 26.6% corresponding to stages C3-C6; the Latin American countries included in that survey were Brazil, Colombia, and Mexico.[4]

At present, insufficiency of the superficial venous system can be treated conservatively by compression and venoactive drugs, as well as by ablative invasive treatment options, including modern open surgery (ultrasound guided) with saphenous vein stripping by invagination and flush ligation of saphenous femoral and popliteal junctions and phlebectomy, and endovenous treatments.[5-7]

Endovenous treatments are the recommended first-line treatment for CVD, according to the latest European and American guidelines.[5-7]

Thermal techniques using radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) were the first ones to receive US Food and Drug Administration (FDA) approval in 1999 and 2002, respectively. They have shown remarkable success in achieving anatomical closure of the great saphenous trunk (GSV) in the long term[8,9] and have been associated with less pain during and after the RFA procedure and a faster postsurgical recovery compared with saphenous vein stripping.[9-11]

Nonthermal nontumescent (NTNT) techniques are procedures that do not require the use of tumescent anesthesia nor do they require thermal energy. They include mechanochemical ablation (MOCA), cyanoacrylate closure (CAC), and chemical ablation with ultrasound-guided sclerotherapy (UGFS).

Two devices are available for MOCA: one using liquid sclerosant, polidocanol or tetradecyl sulphate sodium (STS) and a ClariVein catheter (Merit Medical, South Jordan, Utah, USA),[12] and another using sclerosing foam made with polidocanol or STS and a Flebogrif device (Balton, Warsaw, Poland).[13]

For CAC, there are 3 devices on the market: VenaSeal (Medtronic, USA),[14] VariClose (Biolas, Turkey),[15] and VenaBLOCK (INVAMED, Turkey),[16] presenting different polymerization characteristics.

For UGFS, there is physician-compounded foam performed with the Tessari technique[17] and polidocanol endovenous microfoam (PEM).[18]

All these endovenous methods and devices are supported by studies demonstrating their effectiveness and feasibility. They have a low incidence of periprocedure pain[9,19,20] and a low risk of neurological adverse effects.[21]

The rate of anatomical closure varies among these techniques. Important key points to achieve a successful closure for a long period of time is the proper selection of the patient—the diameter of the vein to be treated is crucial—and an optimal performance of the technique.

The rate of anatomical closure of CAC is similar to thermal techniques in the medium term.[22] The anatomical success of UGFS is better in saphenous trunks under 6 mm of diameter, although these results depend on the strategy and technique applied, which is very variable.[23]

MOCA techniques include 2 types of catheters with different mechanisms of action, therefore they should be analyzed separately. Results of MOCA with the ClariVein catheter techniques improve in saphenous trunks under 8 mm of diameter.[24] The European Society for Vascular Surgery guidelines recommend thermal ablation (TA) for the treatment of GSV of ≥12 mm in diameter (IIaC).[6]

Endovenous treatments are recommended as the first-line approach by both American (American Venous Forum [AVF], American Vein & Lymphatic Society [AVLS], Society for Vascular Surgery [SVS])[5,7] and European (European Society for Vascular Surgery (ESVS) guidelines.[6] The current recommendation is grade I, level of evidence A (IA) for TA of the GSV, IIaA for CAC, and IIbA for MOCA. For the small saphenous vein (SSV), the recommendation from the European guidelines[6] is IA for TA, and IIbB for CAC, MOCA, and UGFS (NTNT methods). For the accessory anterior saphenous vein (AASV), the recommendation is IIaC for TA and IIbB for UGFS; there is still no recommendation for the AASV with CAC or MOCA.[5-7]

In this paper, we will analyze a review of literature about MOCA. The literature analyzed in this paper derives from searches conducted using PubMed and Cochrane Embase databases, employing the following keywords: "Ablation Techniques" AND "Saphenous Vein" OR "Varicose Veins" OR "Venous Insufficiency"AND "MOCA". These searches were carried out in 2 periods, one in December 2023, and the other in February 2024. Additionally, we have also analyzed meta-analysis studies arising from another search performed by a scientist specialized in the subject and basic sciences.

We have selected 35 articles that include outcome studies with MOCA, in addition to 4 randomized clinical trials (RCTs) comparing MOCA versus EVLA and 3 RCTs comparing MOCA versus RFA. We have also analyzed meta-analyses, including one comparing all thermal and nonthermal techniques and saphenectomy. We have examined the results from these articles, highlighting the following information.

Outcome studies with MOCA

Great saphenous vein

In relation to the closure of the GSV at 1 year with ClariVein catheter, the results vary according to different studies, but range from 84.5%[25] to 92%.[26] Additionally, the closure rate for the SSV at 1 year is reported to be 92.6%.[27]

From the meta-analysis published by Sun et al in 2017,[28] 101 studies were identified, 14 of which met the criteria for inclusion, and it was concluded that MOCA with ClariVein catheter proved to be effective in the short term with minimal complications. The analysis also emphasized the need for standardized consensus guidelines and definition of reports in order to facilitate comparison with other techniques.

From the study published by Witte et al in 2017, it was concluded that after a mean of 36 months of follow-up of patients who underwent MOCA with ClariVein catheter for the treatment of GSV insufficiency, the rate of recanalization occurred in 15% of the 102 successfully treated patients. The anatomical success rates were 92%, 90%, and 87% at 1, 2, and 3 years, respectively. This represents the longest follow-up study of patients who underwent MOCA with the ClariVein catheter. This study demonstrates that MOCA with ClariVein catheter is effective in the medium term, but the outcome seems to decline over time.[26]

From the analysis of an RCT published by Vähäaho et al in 2019[21] comparing the results of GSV closure obtained with MOCA versus EVLA and RFA (TA), involving 117 patients, the success of closure at 1 year was 100% for TA and 82% for MOCA (P=0.002). The preoperative GSV diameter was associated with the recanalization rate of the proximal GSV in the MOCA group. At 1 year after treatment, disease-specific life quality was similar in the 3 groups. The GSV occlusion rate 1 year after treatment was significantly higher after EVLA and RFA than after MOCA. Quality of life was similar for both groups.[21] The conclusion of this study was that the failure of closure in the group of NTNT ablations was linked to the diameter of the vein.

From the 2-year results of a multicenter RCT comparing MOCA with ClariVein catheter to RFA in the treatment of primary GSV incompetence (MARADONA study), that included 213 patients, it was concluded that treatment with MOCA with ClariVein catheter resulted in more anatomic failures mostly driven by partial recanalizations, more hyperpigmentation, but less postoperative pain and a faster improvement in venous clinical severity score (VCSS). Both techniques were associated with similar clinical outcomes at 1 and 2 years.[29]

Results of the RCT study published by Vähäaho et al in 2021,[24] involving 117 patients, comparing EVLA and RFA (TA) versus MOCA with ClariVein catheter, show that at 3 years the occlusion rate was significantly lower with MOCA with ClariVein catheter than with either EVLA or RFA (82% vs 100%; P=0.005). Quality of life was similar between the groups. In the MOCA group, GSVs that were larger than 7 mm in diameter preoperatively were more likely to recanalize during the follow-up period. The partial recanalizations of proximal GSV observed at 1 year progressed during the follow-up.[24] The authors concluded that MOCA with ClariVein catheter is a feasible treatment option in an outpatient setting, but its technical success rates are inferior compared with endovenous thermal ablation. Its use in large-caliber veins should be considered carefully.[24]

A meta-analysis and systematic review published in 2022,[30] comparing MOCA with the ClariVein device with TA, showed that MOCA is as effective as standard TA within the first postoperative month. However, this approach was associated with less success after 12 months; in most studies, pain was less severe in cases of MOCA. This data suggested that MOCA was safe for varicose veins. However, large-scale and long-term studies are required to define the role of MOCA.

The MOCA technique by Flebogrif shows, according to the published studies, a closure success of up to 93.2% at 1 year. This information comes from a systematic review and meta-analysis of MOCA using the Flebogrif device (Balton, Warsaw, Poland) for varicose veins, recently published by Alozai et al, in 2022.[31]

In this meta-analysis, 5 articles met the criteria for inclusion, reporting 348 procedures in 392 patients. Closure success at 12 months was 93.2% (95% CI, 90.3%-96.1%). This study concluded that MOCA using Flebogrif catheter was a safe and well-tolerated treatment for GSV insufficiency. However, well-designed studies with a higher number in follow-up are required to compare the effectiveness with other modalities, and thus define the definitive role of the Flebogrif device.[31]

Small saphenous vein

For the SSV, the results of treatment with MOCA appear to have similar closure success to that of GSV treatment. According to the retrospective study of 60 patients with SSV incompetence treated with ClariVein in a single center published by Baccellieri et al in 2021, the closure success at 1 year was 92.6%.[27] In the prospective cohort study published by Boersma et al in 2013, with 50 patients treated with the ClariVein device, the 1-year follow-up with Echo-Doppler showed an anatomical closure success of 94% (95% CI, 0.87-1).[32]

In a comparative retrospective study of treatment of the SSV with MOCA with ClariVein catheter versus saphenopopliteal junction ligation and stripping published by Apruzzi et al in 2022,[19] involving 118 limbs, at 10 months follow-up, the closure success rates were similar (recurrence rates were 7.5% [4/53] for MOCA vs 5.7% [3/52] for the stripping group), but the report of 3.4% of neurological adverse effects in the stripping group was noteworthy. In the MOCA group, there were no neurological adverse effects, less postoperative pain was reported, and the patients returned faster to their usual activities (MOCA 3.5 ± 2.3 days vs open surgical treatment [OS] 14.2 ± 3.8 days, *P*<0.0001).[19]

In the meta-analysis of mechanochemical ablation with Flebogrif, 3 of the 5 studies analyzed reported a closure rate of 90% to 96% at 1 year[31]; Iłżecki et al performed the longest follow-up, with an occlusion rate of 93% after 24 months.[31]

Sclerosant dose in MOCA

From this review of the literature, we have found studies providing important technical and histological information that may help physicians to choose the proper technique and dose of sclerosant for performing MOCA.

A notable study is the double-blind multicenter RCT trial published by Lam et al in 2022[33] with a follow-up period of 6 months, which evaluated the technical outcome (defined as an open part of the treated vein segment of ≤10 cm in length) of MOCA of 375 GSVs treated with ClariVein catheter using polidocanol at different concentrations and different vein diameters. The technical outcome at 6 months was 69.8% in the 2% polidocanol group versus 78.0% in the 3% polidocanol group (*P*=0.027). A better technical outcome was observed in GSV of ≤5.9 mm compared with GSV of >5.9 mm (84.3% vs 59.5%, respectively *P*<0.001). In that study, 2 pulmonary embolisms and 2 deep venous thromboses were seen. Superficial venous thrombosis occurred more often in the 3% group (18 vs 8 in the 2% group; *P*=0.033).[33]

The results of this study show better closure success for ClariVein catheter with 3% polidocanol in liquid form compared with ClariVein catheter with 2% polidocanol in liquid form at a 6-month follow-up. However, the difference in quality of life was not significant. Long-term studies are required to investigate whether these results are sustainable over time.[33]

Other advantages of MOCA

MOCA of the GSV has the advantage of being an ablation without tumescent anesthesia and without thermal ablation, thus making it a less painful procedure.[27,34,35]

In addition, MOCA is associated with a significant improvement in VCSS and in health-related quality of life (HRQOL) measured in several studies.

A retrospective study published by Kim et al in 2019[36] was conducted in 66 patients with venous leg ulcer (VLU). Seventy-four percent of patients who underwent MOCA with ClariVein catheter achieved ulcer healing, in comparison with 35% of those treated with EVLA and RFA (TA). The mean time to heal was 4.4 months in the TA group, compared with 2.3 months with MOCA (*P*=0.01). However, there were notable differences between treatment groups. Patients who received MOCA were significantly older than the TA group (mean 67.9 vs 57.2 years, *P*=0.0003), and a greater proportion of MOCA patients had multiple vein segments treated (63% vs 16%, *P*=0.0010). The MOCA group had more treatment of the SSV and perforator veins (*P*<0.05). The duration of venous ulcers was slightly longer in the MOCA group (mean 11.2 ± 14.4 months vs 9.2 ± 13.9 months in the TA group, *P*=0.5414). The length of follow-up was longer in the TA group (mean 12.8 months, range 0–46 vs mean 7.9 months, range 0.5–20; *P*=0.0220). This study concludes that MOCA is an effective and safe technique in the treatment of venous ulcers and appears to provide results comparable to TA. According to this study, young age of patients and the use of MOCA promotes wound healing. MOCA, in this study, was an independent predictor of ulcer healing. However, RCTs are required to further support these findings.[36]

The feasibility and effectiveness of the MOCA techniques have also been shown in the treatment of venous malformations such as Klippel-Trénaunay syndrome (KTS), as evidenced in the study conducted in Argentina for the treatment of children with KTS, published by Lambert et al in 2021.[37]

Systematic reviews and meta-analysis comparing thermal vs NTNT techniques

A health-technology assessment of CAC and MOCA was conducted in Ontario, Canada in 2021,[38] evaluating effectiveness, safety, and cost-effectiveness among other issues. This systematic review and meta-analysis included 19 primary studies reported in 25 publications comparing either MOCA or CAC, with at least one other invasive treatment for symptomatic varicose veins. No studies compared MOCA with CAC. All RCTs up to 2021, since January 2012, were included.[21,24,29,35] Findings from this meta-analysis included the following: MOCA and CAC were shown to be equally effective in achieving clinical improvement and enhancing the quality of life compared with TA. CAC demonstrated a similar anatomical closure outcome, whereas MOCA exhibited poorer anatomical closure outcomes. Recovery time was slightly reduced with nonthermal endovenous procedures compared with TA. The complication profiles of both nonthermal endovenous procedures were generally minor, though the nature of adverse events differed somewhat from those following EVLA or RFA, as expected. Most adverse effects were mild, transient, and resolved either entirely or to a point of being a minimal interference with people's lives. However, most studies that reported complication data were not powered to statistically test differences in complications between treatment groups. EVLA was most likely to be the most cost-effective strategy.

In patients with ulcers, MOCA presented a similar anatomical outcome compared with RFA and EVLA. In patients with active ulcers, MOCA showed a higher ulcer healing rate among patients with similar healing time and recurrence.[36,38]

In this meta-analysis, the publication of Vähäaho et al in 2019[21] is highlighted, which describes a significant association between the preoperative diameter of the GSV and the success of closure in the proximal segment of the GSV. The mean diameter of patients who reported recanalization of proximal thigh at 1 year was 8.6 mm, compared with those who did not recanalize, which was 6.5 mm.[21,38]

A study published by Shaprynskyi VO et al in 2023[39] compared the treatment of CVD with superficial venous insufficiency in 228 patients with C2-C6 stages using EVLA, RFA, MOCA, CAC, and UGFS. EVLA was demonstrated to be the most effective method for treating CVD, providing the best long-term results. The advantage of NTNT techniques was that they do not injure the perivascular tissue or spaces, and there was no need of tumescent anesthesia—this is important in cases of patients allergic to anesthesia. Additionally, after applying cyanoacrylate, no compression stockings were required. Foam sclerotherapy had the advantage of lower cost compared with other methods, and it was used to address postoperative technical failures associated with other methods.[39]

A meta-analysis comparing MOCA with endothermal ablation that included 4 RCTs comprising 654 patients was recently conducted and published in April 2023.[40] A lower occlusion rate at 1 year was observed after MOCA than with TA (risk ratio 0.85, 95% CI, 0.78 to 0.91; *P*=0.001). No significant differences were observed in procedural or postprocedural pain. No significant differences were observed in Aberdeen Varicose Vein Questionnaire score at 1 year (mean difference 0.06, -0.50 to 0.62; *P*=0.830) or incidence of venous thromboembolism (risk ratio 0.72; 95% CI, 0.14 to 3.61; *P*=0.690).

Summary of the literature

In summary, whereas most of the studies have involved a low number of patients and are not RCTs, MOCA techniques offer the advantages of being associated with fewer neurological adverse effects, less pain during and after the procedure, faster recovery after the procedure, no need for anesthesia, and that they can be performed on an outpatient basis in clinics. From the analysis of the studies, we can conclude that to obtain good long-term results, patients should be selected based on the diameter of the vein to be treated. The type of sclerosant, along with its concentration, is also crucial. The best outcomes are obtained with veins of 7 to 12 mm, or even smaller diameters, using 3% polidocanol or STS, at least in the proximal segments. The device that uses foam sclerosant has also shown positive results. Better results were observed for patients with ulcers.

It is recommended that randomized control studies, more extensive in terms of sample size and duration of follow-up, should be carried out to obtain more conclusive results.

Our experience, progress, and application of endovenous techniques in Latin America

Latin America exhibits considerable social, political, and economic diversity.[41] In recent years, we have witnessed in Latin America substantial progress as regards the treatment of CVI using endovascular methods.

In many countries, the first option is conventional saphenous stripping surgery in the operating room, and currently, there are long waiting lists to address the venous pathology. The efforts of the medical community and the population, caused in part by globalization, have led to improved accessibility to technical knowledge and devices for treating various pathologies, especially CVI. Nevertheless, there is still a long way to go.

In many areas of Latin America, as well as worldwide, accessibility to invasive treatments is limited and CVD progresses to advanced stages with ulcers and phlebolymphedema, which not only impacts the patient's quality of life but also has social, economic, and health care system implications for the countries.

The possibility of performing NTNT ablations in authorized clinics enables addressing an unresolved health issue, at least in certain patients, such as those with saphenous veins smaller than 7 mm, as suggested in the literature.

Based on an experience of more than 10 years with NTNT techniques across various centers and academic and humanitarian activities in Latin America, and having performed over 1000 cases of MOCA, we have observed the benefits these techniques may bring to a segment of the Latin American population.

With the support of foundations such as the Hackett Hemwall Patterson Foundation, with headquarters in Wisconsin, the United States of America, and the Naples Cardiac and Endovascular Center foundation, along with other foundations working to provide help, we have observed the benefits of MOCA techniques in these activities and in this population.

From the experience and data records of patients assisted by the foundations, it should be noted that, with the aid of donations, 150 MOCA procedures using the ClariVein catheter have been performed annually from 2015 to 2019. In total, 750 ablations were conducted during that period, and we have observed a low incidence of adverse effects, with no instances of deep venous thrombosis, and we also observed self-limited hyperpigmentation. The success of vein closure treated by MOCA techniques during the activities of these 2 foundations was similar to that reported in the international literature. The technique is performed following the guidelines, resulting in an improved quality of life and faster ulcer healing time (*Figure 1*).

In relation to our experience in private clinics and public hospitals in Uruguay with MOCA for the treatment of CVI, we present an unpublished work conducted at Centro Venoso E.C.S.A., Uruguay. This work aims at determining the effectiveness and feasibility of the NTNT MOCA technique with the ClariVein device in clinics in Latin America, with a 5-year follow-up.

This study shows that, although the success of saphenous vein closure was 86.4% at 5 years (*Figure 2*), patients experienced an improvement in their quality of life, as measured by

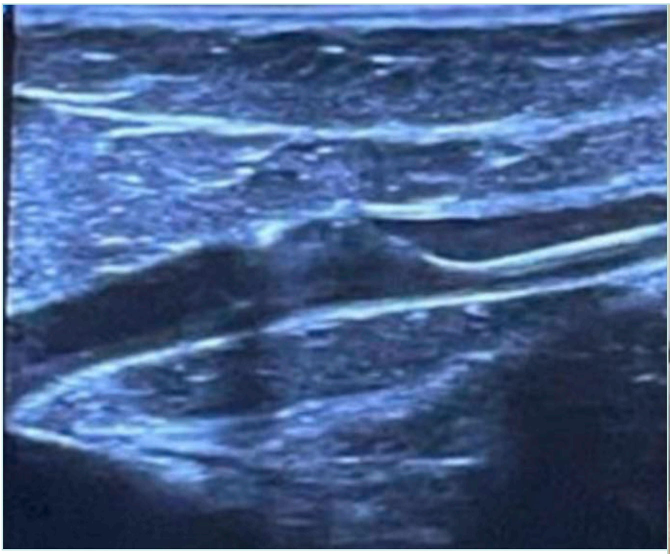

Figure 1. Ultrasound image of a catheter during mechanochemical ablation.

the CIVIQ 20 scale (ChronIc Venous dIsease quality-of-life Questionnaire). The VCSS improved from an average of 12.3 before treatment to 1.7 at 1 year and 1.6 at 5 years (*Figure 2*). Recanalization was observed in patients with a body mass index (BMI) greater than 30 and saphenous vein diameter greater than 10 mm. All ulcer patients maintained closed ulcers, despite an axial vein closure success rate of 86.4% at 5 years.

We have attached *Figure 3* and *Figure 4* with the results of another more recent study involving 57 cases of MOCA with the ClariVein device conducted also at Centro Venoso E.C.S.A., Uruguay. This study was aimed at demonstrating the feasibility of performing these procedures in clinics.

The procedure proved to be fast and well-tolerated, with no major adverse effects recorded. There were 2 cases of

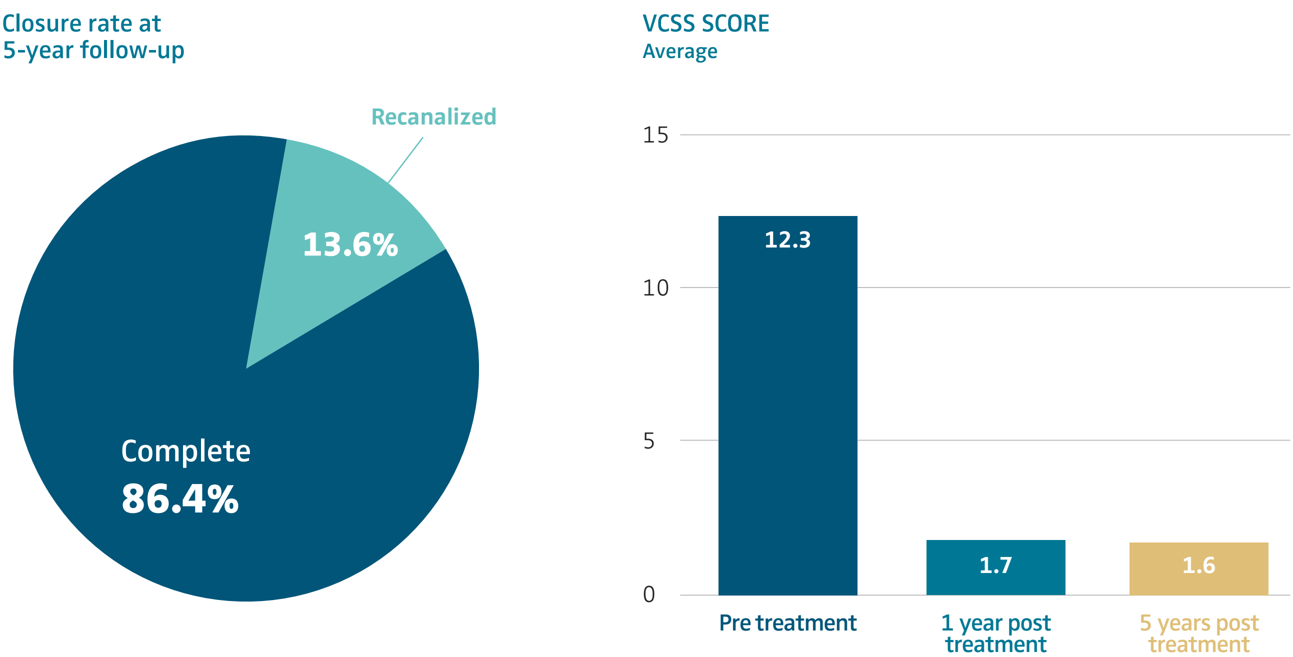

Figure 2. Closure rate at 5 years after treatment with mechanochemical ablation (MOCA) (left panel). Evolution of venous clinical severity score (VCSS) at 1 and 5 years (right panel).

hyperpigmentation, both of which were resolved within less than 6 months. The study highlights the improvement in the quality of life and the satisfaction of the patients. Statistically, results are similar to those reported in the international literature.

The benefits, similar to those reported in the literature, include its feasibility in clinics, rapid return to work, reduced pain, lower incidence of adverse effects and similar closure success rates in the short-term considering the diameter of the vein to be treated and the BMI.

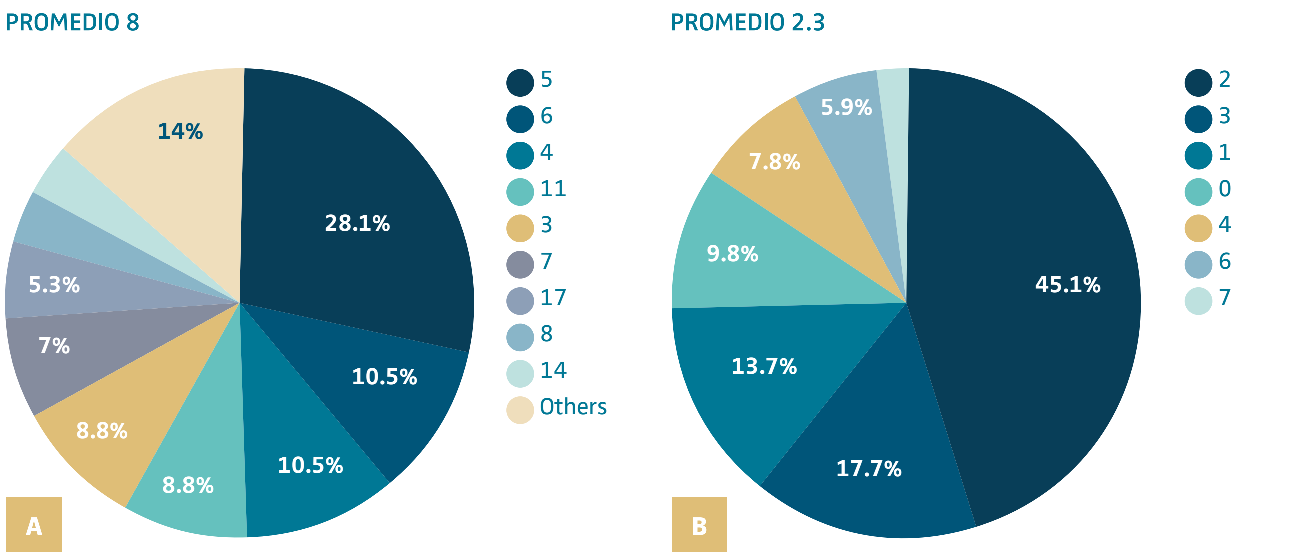

Figure 3. Venous clinical severity score (VCSS) in the studied population A) before treatment with nonthermal nontumescent ablations (mechanochemical ablations) and B) at 1 year after treatment with nonthermal nontumescent ablations (mechanochemical ablations) at Centro Venoso E.C.S.A. Uruguay.

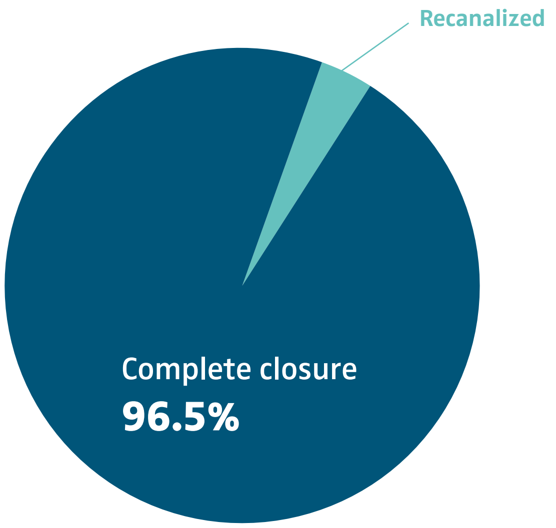

Figure 4. Rate of great saphenous vein closure at 1 year after treatment with mechanochemical ablations (MOCA) at Centro Venoso E.C.S.A. Uruguay.

Benefit for Latin America

Within the framework of the socioeconomic and health system situation in Latin America described above, NTNT and thermal treatments help to reduce the incidence of CVI and the waiting list for surgery, offering an alternative to conventional surgery and the prevalent conservative option in Latin America.

Based on the analysis of the data reported in the literature and our own experience, MOCA techniques are feasible and effective also in Latin America, especially in insufficient veins considering diameters under or equal to 8 mm.

More long-term multicenter randomized comparative trials with a larger number of patients would be needed to support their benefits.

Given the progress achieved in recent years in Latin America, the application of endovenous techniques is a present and promising future solution to address a health problem that remains unresolved.

Conclusions

Although studies have shown that MOCA techniques have a lower anatomical closure rate for large insufficient venous trunks compared with thermal techniques, they have demonstrated a low incidence of adverse effects, less pain before and after the procedure, a rapid return to work and normal daily activities, the possibility of being performed on an outpatient basis in authorized clinics, and an undeniable improvement in the quality of life with similar effectiveness, especially in patients with veins with diameters less than 8 mm.

Although more randomized trials are needed to assess adverse effects and long-term results, MOCA ablations in well-selected patients are currently highly advantageous, as demonstrated in studies conducted so far and in humanitarian activities.

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