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Phlebolymphology

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Aims and Scope

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

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

Phlebolymphology is scientifically supported by a prestigious editorial board.

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

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

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Editorial

Dear Readers,

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

As venous and lymphatic systems are inseparable "dual" outflow systems with mutually complimentary function, failure of one system to compensate for underperformance in the other results in phlebolymphedema. ***B. Lee (USA)*** *provides an overview on phlebolymphedema, explaining the pathophysiology behind it, its classification, how it's diagnosed, and how it can be managed.*

In acute and chronic venous diseases and in lymphedema, basic treatment options include compression treatment with medical compression stockings (MCS), compression bandages (CB), or intermittent pneumatic compression (IPC). ***E. Rabe et al. (Germany)*** *summarizes the results of an international expert consensus paper reviewing recent literature on reported risks and recommended contraindications for elastic compression treatment.*

Next, ***N. Baekgaard et al. (Denmark)*** *describes venous anatomy and hemodynamic characteristics for venous return in the upper limbs, including main differences in comparison with venous drainage in the lower limbs.*

Finally, ***I. Suchkov et al. (Russia)*** *presents a literature review and an analysis of the published data on the efficacy and safety of venoactive drugs (VADs) and also discusses the aspects of timing and duration of a course of VAD treatment in accordance with the clinical class of chronic venous disease and the use of VADs in combination with surgical treatment or sclerotherapy.*

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

Phlebolymphedema: is it a *new* concept?

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Keywords:

chronic lymphatic insufficiency; chronic venous insufficiency; Klippel-Trenaunay Syndrome; phlebolymphedema, primary and secondary

Abstract

Venous and lymphatic systems are inseparable "dual" outflow systems with mutually complimentary function so that such mutual interdependence between these two systems causes a new condition to affect both systems simultaneously when one of the two systems should fail to provide sufficient compensation to the other system, known as "phlebolymphedema" (PLE): combined condition of chronic venous insufficiency (CVI)/chronic venous hypertension and chronic lymphatic insufficiency (CLI)/chronic lymphedema. PLE is, therefore, an unavoidable outcome of the joint failure of this "inseparable" venous-lymphatic circulation system, presenting as a combined condition of venolymphatic edema caused by CVI and CLI due to various etiopathogenesis. PLE can be managed more effectively when open and/or endovascular therapy is added to basic compression therapy to control the CVI and CLI together. Primary PLE is caused mostly by vascular malformation components of Klippel-Trenaunay syndrome as the combined condition of CVI attributed to marginal vein (MV)/venous malformation and CLI attributed to primary lymphedema/lymphatic malformation. CVI attributed to reflux of MV can be treated with MV resection, whereas CVI attributed to deep-vein dysplasia can usually be treated with conventional compression therapy alone. Secondary PLE is usually the outcome of deep-vein thrombosis (DVT)/postthrombotic syndrome (PTS). CVI attributed to PTS can be further improved with correction of the venous outflow obstruction with angioplasty and stenting, especially when the DVT sequalae is involved at multiple levels of the iliac-femoral-popliteal vein system.

Introduction

Phlebolymphedema is not a new concept! Indeed, this "combined" condition of venolymphatic disorders has been well recognized and reported all along for many decades, but the term "phlebolymphedema" has not been properly defined, partly due to ignorance.[1-4]

Phlebolymphedema is an unavoidable outcome of joint failure of the "inseparable" venous-lymphatic circulation system. These two systems are a mutually interdependent "dual" outflow system of the circulation to transport used blood away from the tissue; these two systems maintain a hemodynamically unique relationship that means they share the same destiny. When one system goes bad, the other follows.

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Indeed, the more we learned about this unique relationship between the venous circulation and the lymphatic circulation over the last three decades, the more we realized how "overlooked and underappreciated" phlebolymphedema is.[5-8]

Although these two systems' hemodynamic principles, venodynamics and lymphodynamics, are based on totally different rheodynamics, both systems are mutually complimentary. Furthermore, the crucial role of the lymphatic system in comparison with the venous system was "underestimated" for many decades and recently reevaluated through a revised Starling principle based on the glycocalyx model of transvascular fluid exchange.[9-12]

The venodynamic is based purely on a passive low-pressure system of 10 mm Hg during an average run, via heart, diaphragm/breathing, and muscle contraction, etc; however, the "normal" lymphodynamic is based on "self-propelled" peristalsis via chains of multiple units of "lymphangion" to overcome the pressure gradient in excess of 30 mm Hg (~40 cm H_2O) in human legs. Indeed, the lymphangion system reduces the pressure downstream before additional fluid arrives from upstream segments through coordinated contractility.[13,14] However, a critical aspect of lymphodynamics is that should this normal peristaltic function of lymphangion be lost, due to various conditions, the "abnormal" lymphodynamic essentially becomes the same as the venodynamic.

When one of these two systems is overloaded, the second/other system is able to play an auxiliary role to assist the return of fluid to the circulation system to compensate for the insufficiency/failure of one system. However, this role/function of the two systems to help each other in case of overload is possible *only when* they are in a normal functional state.

Indeed, when the failure of one system contributes to overloading the other system and this exceeds the limit of compensatory function, resulting in the long-term failure of one system, it eventually results in "total" failure of this "inseparable" dual system altogether, so-called phlebolymphedema.[15-18]

Such mutual interdependence between the venous and lymphatic systems causes a new condition to affect both systems simultaneously when one of the two systems fails in its normal function to provide sufficient compensation to the other system. Thus, phlebolymphedema is the combined condition of chronic venous insufficiency (CVI)/chronic venous hypertension and chronic lymphatic insufficiency (CLI)/chronic lymphedema.

Pathophysiology

Phlebolymphedema represents a clinical condition of limb swelling as the result of the accumulation of excess intercellular/interstitial fluid in the legs and feet by the "combined" conditions of phlebogenic leg edema (ie, phleboedema) and lymphogenic leg edema (ie, lymphoedema) by various etiologies. Hence, this unique condition can be defined as "lymphaticovenous edema" caused by CLI and CVI (*Figure 1*).

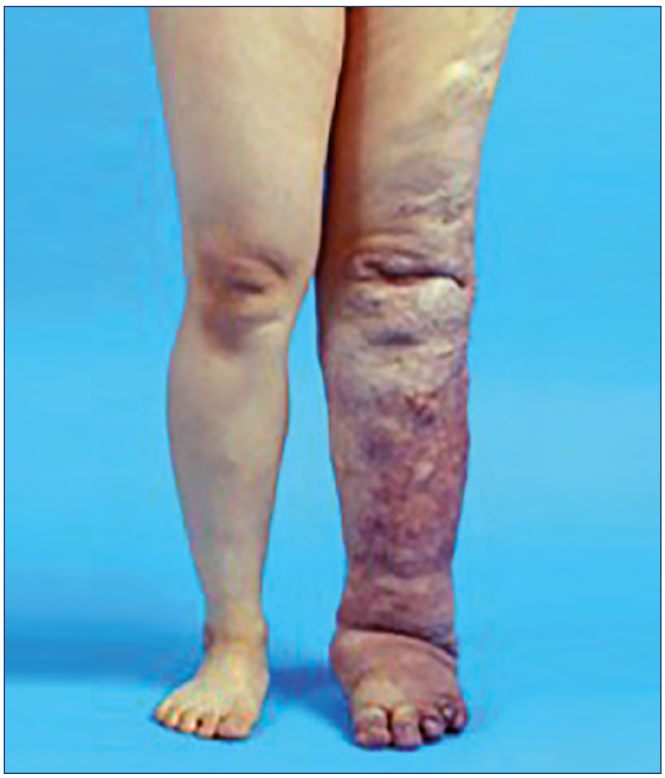

Figure 1. Phlebolymphedema of Klippel-Trenaunay syndrome origin.

This clinical condition of limb swelling represents "lymphaticovenous edema" caused by chronic lymphatic insufficiency and chronic venous insufficiency.

When CVI[19-22] results in an excessive fluid load within tissue, it disrupts the "checks and balance" function of the capillary system, allowing an additional load to the lymphatic system as well. If this overloading exceeds the maximum capacity of the normal lymphatic compensatory function, the lymphatics themselves are also damaged following an initially enhanced function to compensate for the insufficient venous system.

Indeed, the lymphatic system is a dynamic system, with limits in the volume of capillary ultrafiltrate that it can handle varying considerably. The fragile vessels of the lymphatic system can be easily damaged by infection, trauma, tissue inflammation, or radiation.

Lymphatic overloading caused by CVI can lead to valvular failure in lymphatic vessels, and increased tissue edema stretches the skin to cause the lymphatic capillaries to be pulled open by anchoring elastic fibers/filaments, widening interendothelial junctions; extreme distention causes rupture of these filaments, damaging the lymphatic capillary walls. Greater permeability of blood capillaries leads to further extravasation of proteins into the interstitial space, with their critical oncotic pressure to hold water molecules, creating a swollen extremity. Subsequently, *safety valve insufficiency* of the lymphatic system becomes inevitable, allowing the "lymphostasis" that results in CLI.[23-26]

Accordingly, when venous stasis/phleboedema exceeds this maximum lymphatic compensatory capacity, the insufficiency becomes "phlebolymphatic," and the inability of the lymphatic system to drain interstitial fluids and macromolecules effectively results in accumulation of protein-rich fluid in the interstitial space, initiating a cascade of events leading to major fibrosis of the interstitial tissue, called lipodermatosclerosis (*Figure 2*).

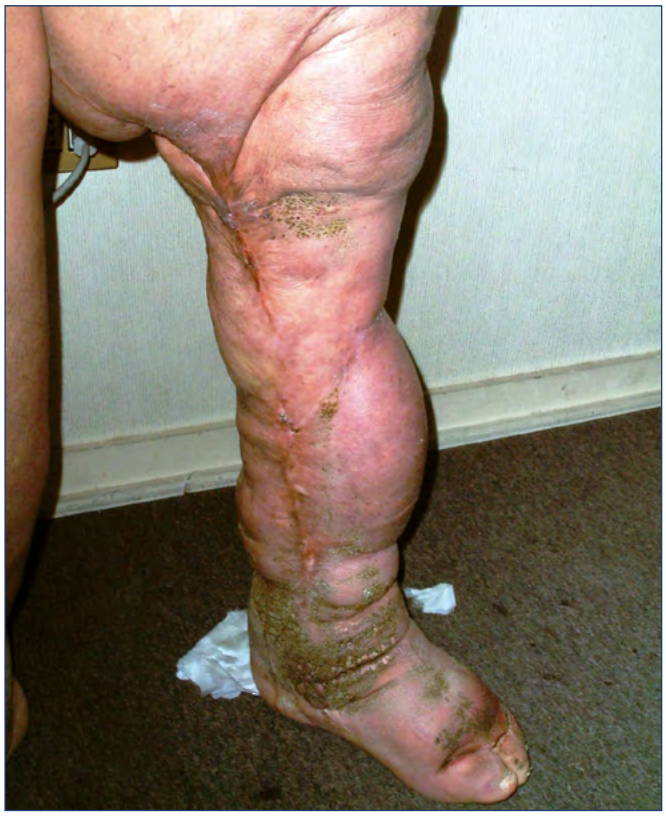

Figure 2. Phlebolymphedema with lipodermatosclerosis.

This clinical condition known as lipodermatosclerosis is the inevitable outcome of lymphostasis caused by chronic lymphatic insufficiency. Accumulation of protein-rich fluid in the interstitial space initiates a cascade of events of a major fibrosis.

Accumulation of these proteins and proinflammatory cytokines in the interstitial space creates a proinflammatory state that leads to a complicated inflammatory process resulting in tissue fibrosis.

Protein-rich fluid causes collagen deposition and a scarring process (lipodermatosclerosis) that impedes absorption of the interstitial fluid by lymph vessels and reduces permeability of lymph vessels, permanently compromising the microvascular and lymphatic systems. Indeed, increased protein concentration in the tissue further reduces the cellular oxygen and nutrients, interfering with wound healing and accelerating the degenerative phlebolymphatic process, which results in dystrophic ulcers and skin infections, etc.[27-30]

This CLI becomes more prominent when the lymphatic drainage condition is "compromised" by various etiologies (eg, surgery/radiotherapy associated with cancer treatment). Depending upon etiology (primary and secondary) and the degree/extent of the CVI and CLI, the clinical manifestation of phlebolymphedema varies greatly and, infrequently, multiple factors are involved, including systemic disease (eg, congestive heart failure, cirrhosis, or nephropathy), compounding the inability to drain interstitial fluids and macromolecules by the lymphatic system.

Definition

For the last two decades, lymphedema that develops along with advanced CVI has been called phlebolymphedema. However, this condition represents only one form of phlebolymphedema, with lymphedema as the outcome of valvular failure of lymphatic vessels due to lymphatic overloading to compensate for venous insufficiency caused by CVI.

For example, chronic "indolent" venous stasis ulcers on the distal lower leg are a typical model of phlebolymphedema that represents a "combined" condition of CVI and CLI despite having for many decades been considered a hallmark of "advanced" CVI as the sequalae of deep-vein thrombosis (DVT). Although these ulcers might have started as a single venous condition of the CVI, they no longer

remain a sole venous condition when the local condition changes/advances to a "combined" condition of venous and lymphatic insufficiency, becoming incalcitrant and resistant to healing (*Figure 3*).[27-30]

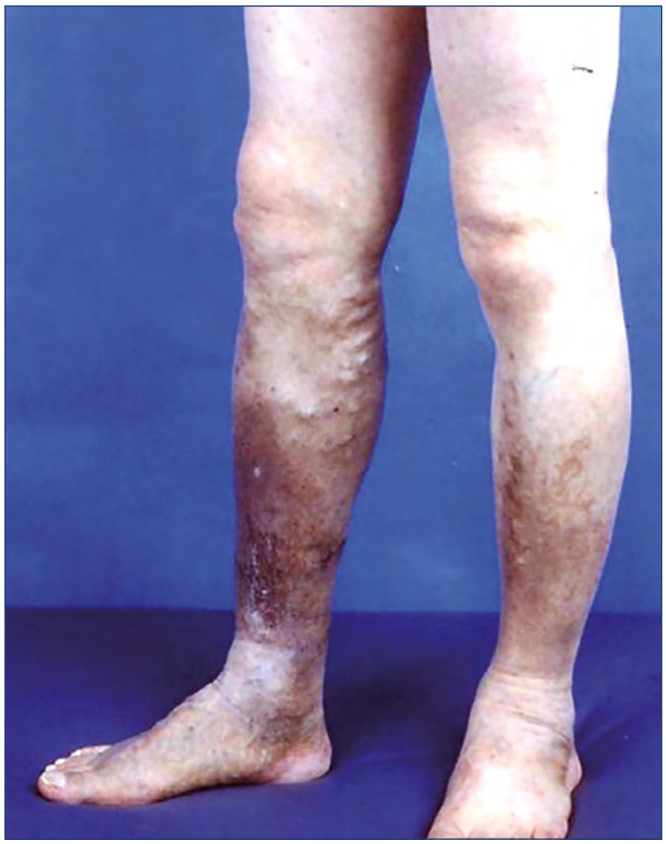

Figure 3. Phlebolymphedema with chronic "indolent" ulcers.

This clinical condition often starts as a single chronic venous insufficiency (CVI) condition as the sequalae of deep-vein thrombosis but becomes a "combined" condition of CVI and chronic lymphatic insufficiency (CLI) when the local condition changes/advances to precipitate lymphatic insufficiency, with CLI becoming incalcitrant, resistant to healing.

If ulcers become incalcitrant, resisting healing, they are considered a new condition—secondary phlebo-lymphedema—caused by the lymphatic failure/CLI that was precipitated by the initial CVI.

Therefore, this is a unique condition of "safety valve insufficiency" as the combined effect of increased lymph flow and reduced drainage capacity in the diseased lymphatic system, often having the outcome of advanced postthrombotic syndrome (PTS).

In other words, CLI involved with phlebolymphedema is not simply a condition that represents mechanical insufficiency only, with low lymph flow due to defects in the lymph system, or that represents dynamic insufficiency only, with high lymph flow overwhelming the maximum load-carrying capacity of the lymphatic system, but both conditions.

Classification

Primary phlebolymphedema

A combined form of congenital vascular malformation, known as Klippel-Trenaunay Syndrome (KTS),[31-34] represents the unique condition of primary phlebolymphedema[35-38] as a combined condition of CVI and CLI caused by its two vascular malformation components: venous malformation[39-42] and lymphatic malformation (*Figure 4*).[43-46,47]

Among many different types of venous malformation as vascular malformation components of KTS, marginal vein (MV) is the most common lesion to cause CVI with venous reflux/hypertension. However, other forms of deep-vein dysplasia (eg, iliac vein agenesis, hypoplastic femoral vein) or defective vein (eg, web, stenosis, aneurysm, ectasia) would also cause CVI with various degrees of venous outflow obstruction/hypertension, either alone as an independent lesion or combined with MV.[48-51]

MV is a relatively common venous malformation lesion in KTS patients. However, MV is not like other truncular lymphatic malformation lesions; it is an embryonic vein remnant, a birth defect that failed to involute after developmental arrest during the vein trunk formation period in the "later stage" of embryonic development. Therefore, MV has a defective vessel wall and, though they look similar, is not like a varicose vein with matured vascular structure.

Indeed, MV often runs along the lateral aspect of the lower extremity, very superficially beneath the skin, with minimum soft tissue coverage for the most part and so looks similar to ordinary varicose veins (*Figure 5*).

Nevertheless, MV accompanies a special condition called "avalvulosis/avalvulia" with a congenital absence/lack of venous valves so that it allows severe reflux, resulting in chronic venous hypertension/stasis with subsequent CVI. Besides, abnormal vessel wall structure due to defective/deficient media of the vein wall, often with a lack of smooth muscle layers (cf. varicose vein), accompanies a high risk of intravascular thrombosis resulting in venous thromboembolism (VTE) in addition to severe CVI, which then precipitates CLI.

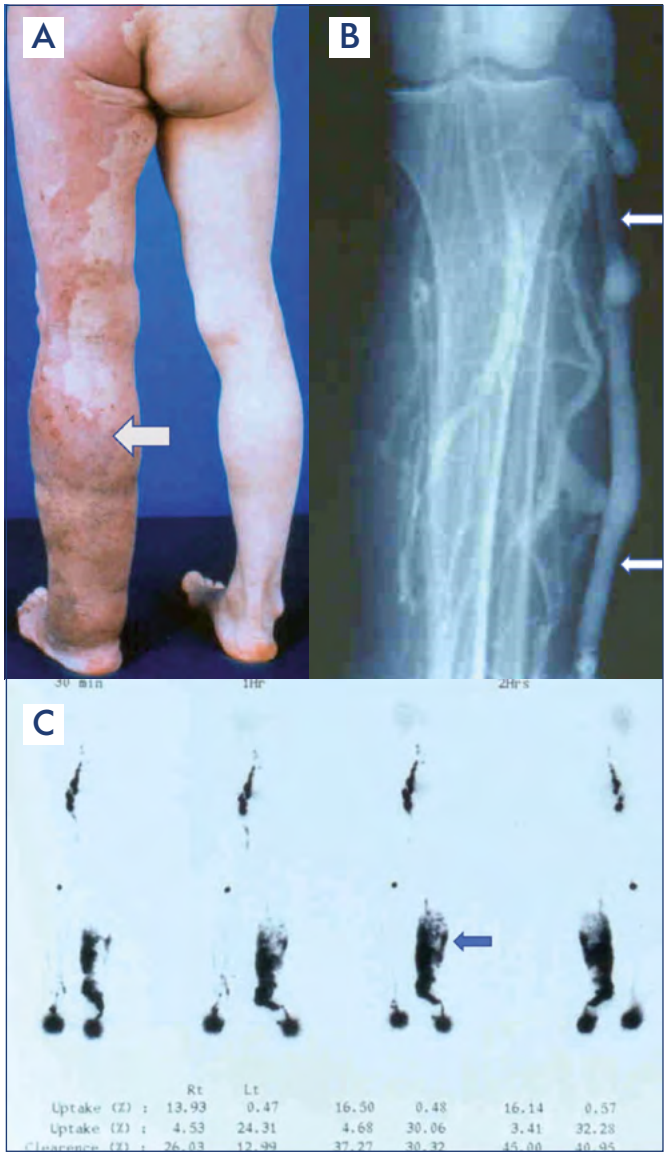

Figure 4. Primary phlebolymphedema.

A) *A clinical condition of primary phlebolymphedema along the left lower extremity (arrow) caused by the vascular malformation components of Klippel-Trenaunay syndrome: chronic venous insufficiency by venous malformation and lymphatic malformation.*

B) *Marginal vein, embryonic vein remnant/ vascular malformation, along the left lower extremity (arrow) with defective development of normal deep-venous system, to cause chronic venous insufficiency/phlebolymphedema.*

C) *Radionuclide lymphoscintigraphic findings of massive dermal backflow (arrow) resulting from chronic lymphatic insufficiency. It was caused by primary lymphedema as the outcome of defective development of the lymphatic system along the later stage of lymphangiogenesis known as truncular lymphatic malformation.*

After reference 47: *Lee and Villavicencio. Figure 170-2 Hemo-lymphatic malformations. A–I, Klippel-Trénaunay syndrome (KTS). Chapter 171. General considerations. Congenital vascular malformations. Section 26. Vascular Malformation. In: Sidawy AN, Perler BA, eds. 9th ed. Rutherford's Vascular Surgery and Endovascular Surgery. Philadelphia, PA, USA: Saunders Elsevier; 2019:2236-2250.*

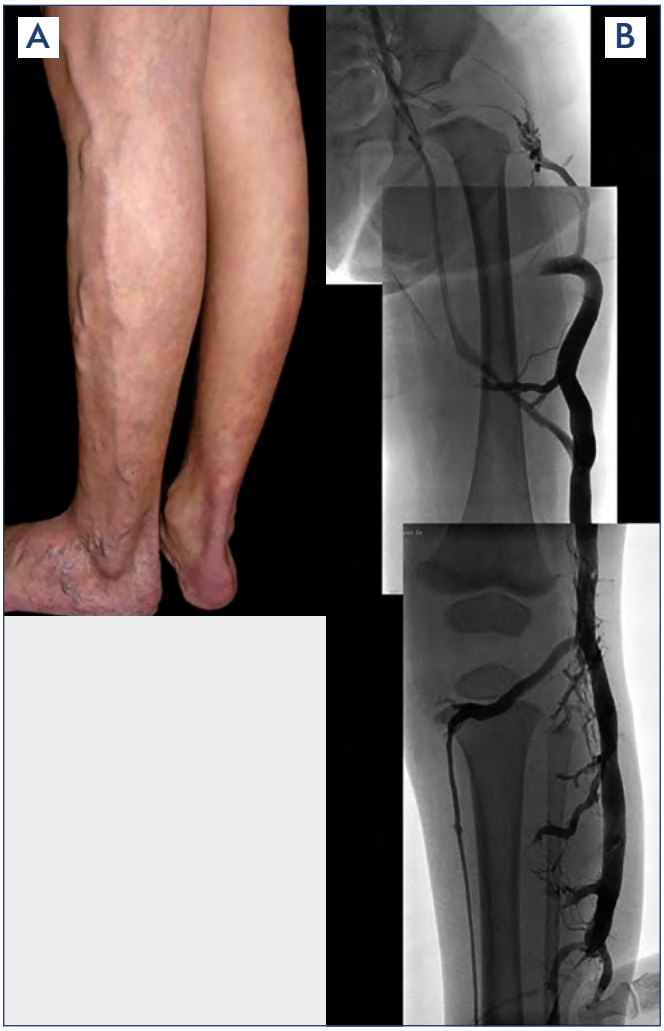

Figure 5. Marginal vein.

A) *Clinical findings of marginal vein (MV) running along the lateral aspect of the lower extremity very superficially to mimic common varicose veins. However, MV is not a varicose vein but rather an embryonic vein remnant remaining as a birth defect after it failed to involute.*

B) *Angiographic finding of MV revealing its extent to compensate for a deficient deep-vein system.*

CLI in KTS causes phlebolymphedema together with the venous malformation lesions, mostly due to primary lymphedema by truncular lymphatic malformation lesion alone (eg, lymphatic dysplasia: aplasia, hypoplasia, or hyperplasia) and extratruncular lymphatic malformation (lymphangioma) seldom involved with CLI.[52-55]

When these two conditions of CVI attributed to MV and CLI due to primary lymphedema are combined, they exert a synergistic impact on the mutually interdependent and inseparable venous-lymphatic system, worsening the limb swelling and making its management much more difficult.

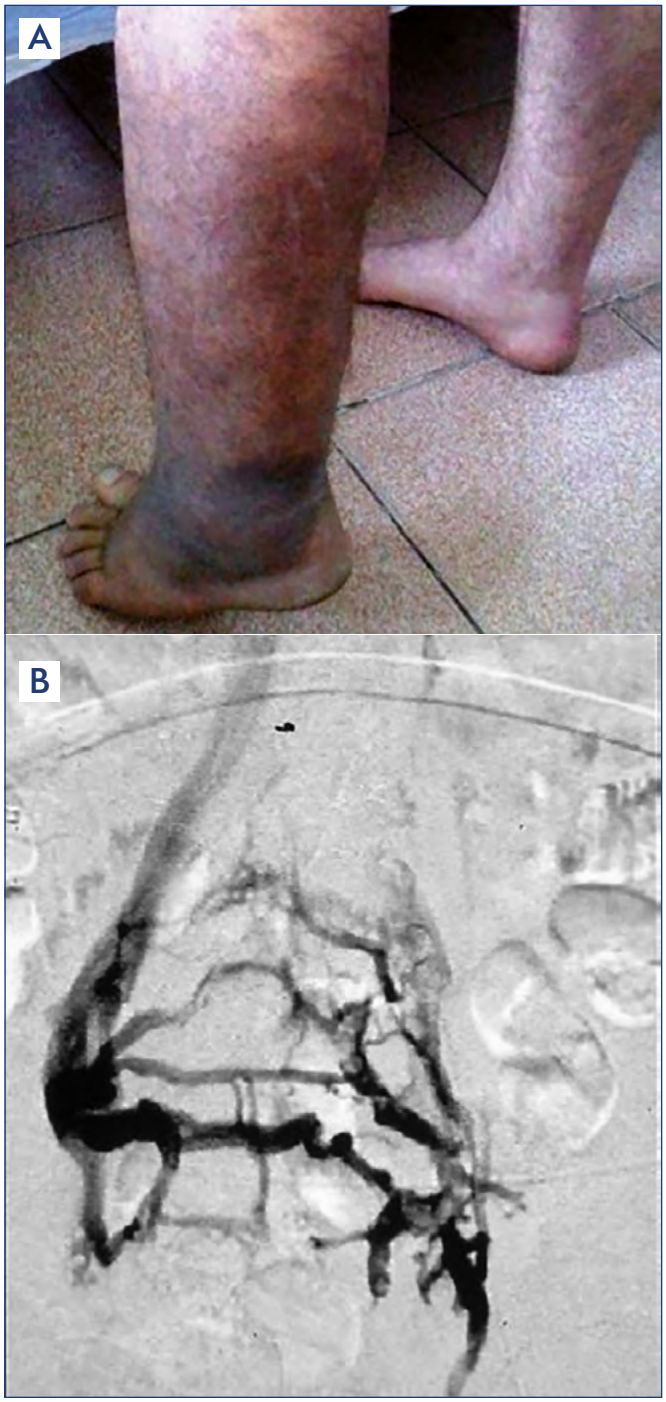

Figure 6. Secondary phlebolymphedema.

A) *Depiction of a clinical condition of secondary phlebolymphedema along the left lower extremity representing the end-stage of chronic venous insufficiency (CVI) as the sequalae of postthrombotic syndrome (PTS) following deep-vein thrombosis. Steady progress of the local tissue damage (eg, ulcer) by the CVI/PTS caused chronic lymphatic insufficiency, resulting in secondary regional/local lymphedema.*

B) *Angiographic findings of thrombosed left iliac vein with extensive collaterals to contralateral/right iliac veins through pelvic veins to illustrate the cause of this secondary phlebolymphedema.*

Secondary phlebolymphedema

Secondary phlebolymphedema develops along the end stage of CVI, mostly as the sequalae of PTS after DVT, as explained previously. After steady progress of local tissue damage (eg, ulcer) resulting from CVI/PTS, CLI generally begins as a secondary regional/local lymphedema showing a visibly strained lymphatic system as a victim of abnormal venous condition. CLI of secondary phlebolymphedema often makes the condition more complicated to manage, as a newly added condition of local/regional lymphedema; it becomes a major obstacle to clinical management due to the complexity of the local circulation (*Figure 6*).[56-59]

Occasionally, however, the clinical/subclinical condition of primary lymphedema exists as the cause of CLI, unnoticed until it accelerates the deterioration of the underlying benign primary venous disorder (eg, reflux), resulting in CVI.

Diagnosis – general strategy

Appropriate appraisal of CVI and of CLI should start with differential diagnosis between *primary* phlebolymphedema of congenital origin and *secondary* phlebolymphedema with various backgrounds. However, the diagnostic evaluation of phlebolymphedema should be initiated with the appraisal of these two closely linked conditions (CVI and CLI) together regardless of the etiology, either primary or secondary.[15-17,20-23,33-37,40,46,50,53,57]

All chronic venous conditions that carry suspicion of further progression to phlebolymphedema, including stasis ulcers that resist conventional care, should undergo assessment not only of the venous system itself but also together with the lymphatic system as a two-system assessment.

Similarly, for chronic lymphedema assessment among those with clinically suspected phlebolymphedema, the evaluation of the venous system should also be part of a mandatory evaluation of these two inseparable systems. In other words, if phlebolymphedema is suspected, such simultaneous evaluation of the two systems is essential as for any two-system assessment.

Nevertheless, the evaluation of limb swelling/edema should exclude or confirm the involvement of systemic causes of edema: (eg, cardiac failure, renal failure, hepatic failure, hormonal disturbances, malignant tumors) as a basic appraisal; other iatrogenic causes for edema should be investigated, including the use of calcium antagonists, vasodilators, and anti-inflammatory drugs.

The evaluation of CVI as the venous component of phlebolymphedema should start with a thorough evaluation of the anatomy of the entire venous system, including evaluation of the presence, size, and extension of refluxes both in the deep and superficial veins, and also evaluation of the presence of an obstruction of congenital or acquired origin.

Such basic information is essential for proper diagnosis of phlebolymphedema, and it has to be completed before proceeding to more specific investigation on chronic DVT/PTS resulting in CVI in secondary phlebolymphedema, and truncular venous malformation lesions, such as marginal vein/lateral embryonic vein, in primary phlebolymphedema as mentioned previously.

CLI as the lymphatic component of phlebolymphedema is equally important for determining primary, as well as secondary nature, but additional investigation on the lymphatic malformation, other than in primary lymphedema (eg, lymphangioma), is extremely important when primary phlebolymphedema is attributed to KTS with the risk of coexistence of additional vascular malformations.[60-63]

Diagnosis - laboratory assessment

Clinical diagnosis of primary as well as secondary phlebolymphedema should be confirmed based on proper combination of various available laboratory tests, mostly on the basis of being noninvasive to less invasive, so that proper treatment strategy can be formulated by the multidisciplinary team on the basis of the laboratory-assessed extent of CVI and CLI.

A limited exam for laboratory evaluation of the venous system (*Table I*)[41-46,48-60] for phlebolymphedema to assess the extent/severity of the CVI is generally sufficient, with tests to determine noninvasive to less-invasive status based on duplex ultrasonography (DUS), magnetic resonance imaging (MRI), and/or computerized tomography (CT).

Indeed, DUS remains a gold standard of morphofunctional studies for the evaluation of the venous system, especially for primary phlebolymphedema with MV as the cause of CVI. This technique makes possible the visualization of the entire length/course of the MV, which is located supra- and subfascially, together with the perforators, and also simultaneously provides crucial information on the hemodynamic status of the MV and the deep-vein system (eg, extent and severity of the reflux and outflow resistance).

- Venous duplex ultrasonography (DUS) – test of choice/mandatory
- Air plethysmography: functional assessment – optional
- Computerized tomography (CT) with/without contrast – optional
- Magnetic resonance imaging (MRI); standard & MR venography (MRV) – optional
- Radioisotope venography – optional
- Ascending & Descending venography – optional
- Percutaneous direct puncture phlebography – optional
- Volumetry – optional
- Whole-body blood pool scintigraphy (WBBPS)* – optional
- Transarterial lung perfusion scintigraphy (TLPS)* – optional

Table I. Laboratory evaluation for the venous system.[41,60]

** For the congenital vascular malformation assessment*

Since more than one-third of KTS patients with MV are known to have an additional defective deep-venous system (eg, hypoplasia of femoral vein, aplasia of iliac vein) that makes CVI more complicated, such DUS information remains crucial to the management plan.

However, various plethysmographic assessments, as listed, would also be needed as additional tests for further accurate evaluation to set up a management plan especially for secondary phlebolymphedema caused by DVT/PTS. Aside from that, ascending/descending phlebography is also needed together with direct puncture phlebography as a roadmap, especially for the primary phlebolymphedema involved in MV/venous malformation in KTS.

Laboratory evaluation for the lymphatic system (*Table II*)[23,25] for phlebolymphedema to assess functional status in CLI

- Radionuclide lymphoscintigraphy – test of choice (mandatory)
- Indocyanine green lymphangiography – optional
- Magnetic resonance (MR) lymphangiography – optional
- Lymphangiography (oil contrast): for the candidate of venolymphatic reconstructive surgery – optional
- Ultrasonographic lymphangiography – optional
- Computerized tomography (CT) scan – exclude underlying malignancy– optional
- Standard magnetic resonance imagery (MRI) – potentially most useful – optional
- Volumetry – optional
- Miscellaneous: dermascan, tonometry, ultrasonographic measurement of subcutaneous edema – optional

Table II. Laboratory evaluation for the lymphatic system.[23,25]

is a bit more complex. Morphological evaluation based on the DUS or CT scan with contrast medium makes it possible to visualize the edema with respect to size and depth, as well as lymph nodes for possible neoplastic pathology. However, the functional test remains crucial, and radionuclide lymphoscintigraphy[64-67] is still the examination of choice although a few other advanced tests are now available with limited usage/indication.

Clinical management

Depending upon the type of phlebolymphedema, the long-term care strategy will have to be organized to meet specific needs to control its pathoetiology, namely venous malformation/lymphatic malformation for the group of primary phlebolymphedema, and DVT/PTS for the secondary phlebolymphedema group, as previously pointed out above.

However, the basic approach for the management of phlebolymphedema, of either primary or secondary origin, should aim at maximum control of *both* conditions of CVI and CLI together since this unique condition is the outcome of simultaneous failure of two inseparable (dual) outflow systems.[17,20,27,29,35,36,58,59]

As the principles of management of CLI for primary phlebolymphedema is basically the same as those for secondary phlebolymphedema, the baseline therapy for both conditions is compression therapy, according to the manual lymphatic drainage (MLD)-based complex decongestive therapy (CDT) principle regardless of its etiology, which effectively controls the CVI as well.[68-71] Also, additional care with palliative and/or reconstructive surgical treatment modalities can be effectively accommodated to improve management of CLI in phlebolymphedema patients as well.[72,73]

However, CVI for the group of primary phlebolymphedema is mandated for further specific management, especially when MV becomes the cause of CVI, precipitating DVT, with the risk of pulmonary embolism. Therefore, contrary to deep-vein dysplasia—another cause of CVI in primary phlebolymphedema—MV should be aggressively controlled, preferably via resection whenever possible and, if not, embolosclerotherapy, as long as the deep-vein system is able to tolerate the sudden influx of the diverted blood volume from the MV once it's excised.[48-51]

In other words, ablation of the MV to relieve CVI can be done safely only when the deep system is in normal condition. If not, it would accompany a high risk of acute venous stasis to precipitate acute venous gangrene and cause further exacerbation of CLI via overloading of the lymphatic system, which would already be in jeopardy. In such case, prophylactic anticoagulation with weight-adjusted low-molecular-weight heparin (LMWH) is generally recommended (eg, DVT/pulmonary embolism).[74,75]

However, deep-vein dysplasia (eg, aplastic or hypoplastic iliac-femoral venous system) as a common truncular venous malformation that causes CVI/phlebolymphedema can usually be controlled with conventional compression therapy alone and seldom requires more than conservative management unless there is clear evidence for hemodynamic gain via bypass surgery of hypoplastic/aplastic iliac/femoral veins.

Finally, CVI in secondary phlebolymphedema caused by DVT/PTS should be treated more aggressively to relieve the cause of obstruction/reflux with open surgical (eg, bypass) and/or endovascular therapy (eg, angioplasty and stenting) as much as possible.[20,76-78] When CVI is caused by multilevel DVT sequalae (eg, indolent ulcer), even minimal correction of the obstruction/stenosis is able to provide significant relief of venous hypertension to improve the efficacy of compression therapy–based conservative management.

Conclusion

- Phlebolymphedema is a joint failure of the "inseparable" venous-lymphatic system as a mutually interdependent dual-outflow circulation system.

- Phlebolymphedema is, therefore, a combined condition of CVI and CLI caused by various etiopathogeneses.

- Phlebolymphedema can be managed more effectively when open surgical and/or endovascular therapy is added to basic compression therapy to control CVI and CLI together. Primary phlebolymphedema is caused mostly by vascular malformation components of KTS: CVI by MV/venous malformation, and CLI by primary lymphedema/lymphatic malformation. CVI attributed to reflux of MV can be treated with MV resection, whereas CVI attributed to deep-vein dysplasia can usually be treated with conventional compression therapy alone.

- Secondary phlebolymphedema is usually the outcome of DVT/PTS. CVI attributed to PTS can be further improved with correction of the venous outflow obstruction via angioplasty and stenting, especially when the DVT sequalae is involved at multiple levels of the iliac-femoral-popliteal vein system.

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Risks and contraindications of medical compression treatment

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Background

Medical compression treatment with medical compression stockings (MCS), compression bandages (CB), or intermittent pneumatic compression (IPC) belongs to the basic treatment options in acute and chronic venous diseases and in lymphedema. In a recent international consensus paper, well-known experts in the field reviewed the recent literature on reported risks and recommended contraindications for elastic compression treatment. **Results:** Reported nonsevere adverse events (AEs) included skin irritation, allergic skin reaction, discomfort and pain, forefoot edema and lymphedema, and bacterial or fungal infections. Only skin irritations and discomfort and pain were reported commonly with an incidence between 1% and 10%. All reported severe AEs such as soft tissue damage and necrosis, nerve damage, arterial impairment, venous thromboembolism, and cardiac decompensation were reported very rarely with an incidence below 0.01%. The contraindications for compression treatment are: severe peripheral arterial occlusive disease (PAOD) with ankle brachial pressure index (ABPI) <0.6, ankle pressure <60 mm Hg, toe pressure <30 mm Hg, or transcutaneous oxygen pressure < 20 mm Hg; suspected compression of an existing epifascial arterial bypass; severe cardiac insufficiency (New York Heart Association [NYHA] class IV); routine application of MC in NYHA III without strict indication, and clinical and hemodynamic monitoring; confirmed allergy to compression material; and severe diabetic neuropathy with sensory loss or microangiopathy with the risk of skin necrosis. **Conclusions:** Compression treatment is a standard treatment in venous and lymphatic diseases. Most of the published AEs are caused by incorrect indication or application of the compression material. The contraindications must be respected to avoid severe complications.

Introduction

Medical compression treatment by medical compression stockings (MCS), compression bandages (CB), or intermittent pneumatic compression (IPC) is a basic treatment option in acute and chronic venous diseases and in lymphedema.[1] However, despite widespread acceptance in patients, there are conflicting reports in the literature about risks and contraindications. In a recent international

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consensus paper, well-known experts in the field reviewed the recent literature on reported risks and recommended contraindications for elastic compression treatment.[2]

Methods

The experts identified 62 publications reporting adverse events (AEs) of medical compression treatment in PubMed.[2] The reported risks were critically reevaluated, and recommendations were given on how to prevent and manage AEs.

Results

Nonsevere reported AEs included skin irritation, allergic skin reaction, discomfort and pain, forefoot edema and lymphedema, and bacterial or fungal infections (*Table I*). Only skin irritations and discomfort and pain were reported commonly with an incidence between 1% and 10%.[3,4] All reported severe AEs such as soft tissue damage and necrosis, nerve damage, arterial impairment, venous thromboembolism, and cardiac decompensation were reported very rarely with an incidence below 0.01%.

Nonsevere adverse events

- Skin irritation
- Discomfort and pain
- Forefoot edema
- Infection

Severe adverse events

- Soft tissue damage and necrosis
- Nerve palsy
- Arterial impairment
- Venous thromboembolism
- Cardiac decompensation

Table I. Adverse events of compression treatment
After reference 2: Rabe et al. Phlebology. *2020;35:447-460.*

Adverse events

To prevent itching or dry skin below compression garments, adequate skin care in sensitive patients was recommended.[2] Discomfort and pain may be due to inadequate fit and application of compression devices or incorrect indication. Inflammatory skin reactions may be due to occlusive effects and dry skin below compression material. Real allergic reactions to compression material are very rare as modern devices no longer contain allergizing colors but may still be caused by rubber-based materials.[5,6]

In rare cases, forefoot edema has been described after compression. In those patients with a tendency to foot edema or in lymphedema patients, adequate compression of this region is required. This may include specific foot or toe compression parts.

Bacterial or fungal colonization of the skin may be present in patients with venous ulcers, lymphedema, or other skin diseases in which compression is indicated. Occlusive effects between the toes, promoting fungal infection, may be avoided by toe-free compression devices.[7] Erosive pustular dermatosis (EPD) has been described as a rare event below long-term, permanent compression with four-layer bandages.[8] In at-risk patients, long-term permanent compression should be avoided. Consideration of topical antiseptics is recommended if local infection beneath compression occurs, and systemic antimicrobiologic treatment is recommended for systemic symptoms.[2]

More-severe complications of compression treatment are mechanical tissue and nerve damage, which have been described in rare cases below compression bandages, stockings, and for intermittent pneumatic compression.[9-26] According to the Law of Laplace, areas with a smaller radius are subject to higher pressure beneath compression material.[27] On the leg, this appears in the ankle region, in the lateral aspect of the foot, and above other bony or tendinous prominences such as the tibia head and the Achilles tendon.[2] Local pressure that is too high may cause tissue necrosis and ulceration or nerve damage in regions where the nerve is compressed, such as the fibular head. Additional risk factors are reduced ankle brachial pressure index (ABPI), sensory loss as in diabetic neuropathy, frail skin, or strangulation by wrongly applied compression material. To prevent tissue damage or necrosis and nerve damage in regions with a small radius, the authors of the consensus suggest protecting these regions from inappropriately high pressure, particularly in sensitive patients, via decreasing the local pressure by inserting soft padding material, by using low overall pressure, and by taking appropriate circumference measurements so that the compression devices fit properly.[2] As peripheral arterial occlusive disease (PAOD) is a risk factor for tissue necrosis below compression, ankle pressure and ABPI or toe pressure should be measured and calculated before compression treatment is initiated. The authors recommend checking the arterial circulation status before any kind of compression therapy is initiated. If foot pulse and/or ankle pulse is weak or not palpable, ABPI should be measured and calculated prior to initiating medical compression

(MC) therapy.[2] In severe PAOD, sustained compression is contraindicated if the systolic ankle pressure is <60 mm Hg or the toe pressure is <30 mm Hg.[2]

After bypass surgery with improved peripheral arterial pressure, compression may be indicated if edema is present. In most of the cases, there is no direct compression effect on the bypass itself. However, it is recommended to avoid external compression in epifascial bypasses.[2]

Previously, it was discussed that compression may not be indicated in acute deep venous thrombosis (DVT). Today, there is a clear recommendation for early compression in acute DVT as part of the standard therapy.[28-30] A tourniquet effect on varicose veins should be avoided as it may cause superficial venous thrombosis, as Scurr has shown in prolonged sitting on long-haul flights.[31]

In recent guidelines, compression is contraindicated in decompensated cardiac insufficiency.[32] According to the published data, cardiac insufficiency per se does not constitute a contraindication for compression therapy today.[2] In the disease stages New York Heart Association (NYHA) I and II, appropriate compression is possible.[2] In the disease stages NYHA III and IV, careful use of compression therapy is possible to a limited extent if there is a strict indication and clinical and hemodynamic monitoring.[2]

Borderline indications

In former times, compression was contraindicated in several situations that are today considered good indications. Among these are deep and superficial vein thrombosis, and different kinds of edema and inflammatory diseases and infections.[2]

DVT and SVT

The avoidance of compression in DVT or SVT appears to be based only on the fear that compression might promote the dislodgment of clots and cause pulmonary embolism (PE).[2] This theory is not supported by published data.[28,29] In a study comparing patients with acute DVT treated with either low-molecular-weight heparin (LMWH) plus compression and walking or LMWH plus bed rest, new PEs occurred in less than 7.4% in both groups.[33]

Edema

Compression treatment is effective in the treatment of edema caused by different reasons.

In patients with venous or lymphatic edema and compensated heart failure (NYHA I or II), compression is not contraindicated but should start at the lower legs before being extended to the thigh.[2,34] In patients with venous leg ulcers and/or venous or lymphatic edema and PAOD, the ABPI must be measured. An ABPI below 0.6 is a contraindication, but in less severe cases, compression therapy may be beneficial for ulcer healing and edema reduction.[2]

Edema after bypass graft surgery and post-reconstructive edema after arterial revascularization are both improved with mild compression for edema reduction.[35-39]

Inflammatory diseases and infections

Compression used to be contraindicated in acute infections of the skin because compression may facilitate bacteria transfer into the circulation. However, compression can reduce inflammatory reactions of the skin and thus have a beneficial effect in addition to standard antibiotic or anti-inflammatory treatment.[40] In several centers, compression is used routinely in the management of erysipelas and vasculitis.[41-43] Recently, a retrospective study by Eder et al showed that compression is not contraindicated in acute leg erysipelas.[44] Compression is also able to prevent recurrent cellulitis in edema patients.[45,46] Compression is widely used in vasculitis of the skin, but prospective comparative studies are missing.[47]

Contraindications

Table II lists recommended contraindications for elastic compression garments based on the available literature.[2]

Contraindications of elastic compression therapy

- Severe PAOD with: ABPI <0.6 or ankle pressure <60 mm Hg or toe pressure <30 mm Hg or transcutaneous oxygen pressure < 20 mm Hg
- Suspected compression of an existing epifascial arterial bypass
- Severe cardiac insufficiency (NYHA IV)
- Routine application of MC in NYHA III without strict indication, and clinical and hemodynamic monitoring
- Confirmed allergy to compression material
- Severe diabetic neuropathy with sensory loss or microangiopathy with the risk of skin necrosis

ABPI, ankle brachial pressure index; PAOD, peripheral arterial occlusive disease; MC, medical compression; NYHA, New York Heart Association

Table II. Contraindications of elastic compression therapy
After reference 2: Rabe et al. Phlebology. *2020;35:447-460.*

Discussion

Prospective randomized studies investigating for AEs in compression treatment are rare or nonexistent. Most of the data we have comes from occasionally reported single AE cases. Most of these AEs are due to incorrect indication, application, or use of compression material. Another reason is the disregard of contraindications, such as severe PAOD. Main contraindications are severe PAOD, severe cardiac insufficiency, and severe diabetic neuropathy and microangiopathy. In addition to the described contraindications and risks of compression treatment, a limitation of the method is patient adherence to compression. Even in strong indications, such as venous leg ulcers, complete adherence to compression was described to be as low as 40%.[48]

Conclusions

If contraindications are respected and correct indications, application, and use is guaranteed, treatment with elastic compression is safe and effective in venous and lymphatic diseases.

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Duplex ultrasound as first-line imaging for morphology and hemodynamics in the upper limb venous system

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Abstract

This review describes venous anatomy and hemodynamic characteristics for venous return in the upper limb, including main differences in comparison with venous drainage in the lower limb. Duplex ultrasound (DUS) is the first-line imaging modality even it seems less standardized than other investigation approaches for veins in the lower limb. This article presents useful instructions to assess veins from the peripheral to the thoracic outlet via the costoscalene hiatus. Without basic understanding, it is even more difficult to diagnose acute and chronic changes, such as deep-vein thrombosis (DVT), by far the most frequent disease, considered primary idiopathic or effort-induced (Paget-Schroetter syndrome), and secondary after central venous cannulation if cancer-related. Furthermore, imaging with DUS is also indispensable for assessing the usefulness of superficial veins for arteriovenous fistula and sometimes as a conduit for arterial bypass. Computed tomography venography (CTV) and magnetic resonance venography (MRV) should be offered if DUS is inconclusive due to obesity and/or technical problems and in cases with normal DUS despite strong suspicion of disease.

Keywords:

anatomy; Duplex ultrasound; hemodynamics; upper limb; venous system

Introduction

The venous system in the upper limb has not attracted the same amount of attention as the venous system in the lower limbs. The hemodynamic influence, owing to lower involvement of gravity and limb weight, is less pronounced, as are complications after acute thrombosis, which do not exhibit the same clinical impact in the long run as observed in lower limbs. Although thrombosis in the upper limbs, either superficial or deep, plays a lessor role than deep-vein thrombosis (DVT) in the lower limbs, it is important to know how the venous system is constructed and how the venous return functions under normal conditions. Furthermore, such knowledge is useful for clinicians performing procedures that require vein access such as making arteriovenous (av) fistula for dialysis or for

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implanting feeding catheters and other devices for cardiac use. In some cases, arm veins are useful as bypass material for chronic arterial disease and, even more seldom, are used for segmental vein transplantation in case of chronic valve incompetence in the lower limb.

Duplex ultrasound (DUS) is useful as a first-line imaging modality for all these tasks.[1] In general, DUS examination in the upper limb is more difficult than in the lower limbs. It is advisable to compare findings with those from a normal site from the opposite side in case of doubt. Otherwise, another imaging modality is needed.

Anatomy

Like in the lower limbs, the venous system in the upper limbs is composed of superficial and deep veins. Perforating connections in the arm system are few and unimportant. Both systems have valves, which play a minor role owing to a less-pronounced influence of gravity than in the lower limb. Such valves are absent in the most central veins. The shoulder region is filled with various vein connections that allow development of collaterals as an important return possibility in a postthrombotic stage.[2]

Superficial veins

The cephalic and basilic veins arise from the dorsal venous plexus of the hand and the palmar part, respectively. The cephalic vein runs along the anterior aspect of the forearm and hereafter in a lateral direction into the deltopectoral groove ending through the clavipectoral fascia into the axillary vein. The basilic vein runs on the ulnar side of the forearm and connects with the brachial vein midway along the upper arm. The two systems are connected in the cubital region with the median cubital vein, which is inconstant in location.

Deep veins

The ulnar, radial, brachial veins are often paired and run along the arteries. The axillary vein begins at the border of the teres major muscle and continues at the border of the first rib into the subclavian vein entering the thoracic aperture. Connecting to the internal jugular vein at the medial border of the scalenus anterior muscle, the vein is named the brachiocephalic vein, and hereafter receiving the vein from the opposite side to be named the superior vena cava behind the first right costal cartilage. Two ribs further distally, the cava inters the right atrium. Grooves are typically found on the upper surface of the first rib with imprint of the vein going anterior and the artery going behind the anterior scalenus muscle (*Figure 1*).

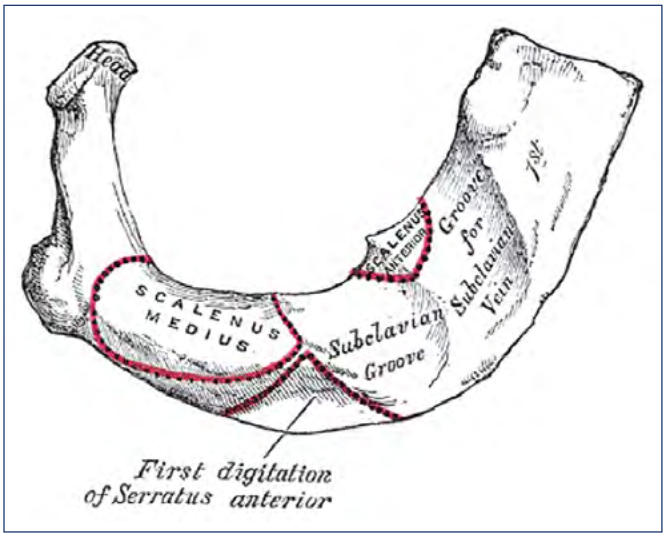

Figure 1. The vessel grooves on the first rib.

Azygos veins

Two veins constitute this system. The azygos vein is placed on the right side of the vertebral column, arising from the renal veins, and enters the superior vena cava from behind. The hemiazygos vein lies on the left side of the vertebral column and connects to the azygos vein at the level of the eighth thoracic vertebra. An accessory azygos vein continues on the left side and enters the left brachiocephalic vein. The azygos veins play an important role for collateral drainage in case of obstruction in the inferior vena cava, as well as in the superior vena cava, for which reason the system is mentioned here, even though not accessible for DUS.[3]

The thoracic outlet

The term thoracic outlet is used to describe the passage of nerves, arteries, and veins between the thorax and the region of the shoulder. It is actually called the inlet passage, addressing the veins. The subclavian vein is surrounded by the first rib and pleura at the bottom, posteriorly by the scalenus anterior muscle, medially by the costoclavicular joint and ligament, and anteriorly by the clavicle with the subclavian muscle (*Figure 2*). This passage has more or less of a congenital narrowing, and in 70% of all individuals, a stenosis can be visualized by venography, especially with the arm in hyper abduction. Another cause of stenosis is related to muscular enlargement. Another term is the thoracic outlet syndrome (TOS), referring to symptoms from compression of the nerves and arteries as well as veins passing through this region.[4] The Paget-Schroetter syndrome refers to vein thrombosis in the axillary and/or subclavian vein after strenuous arm exercise or repetitive effort.[5]

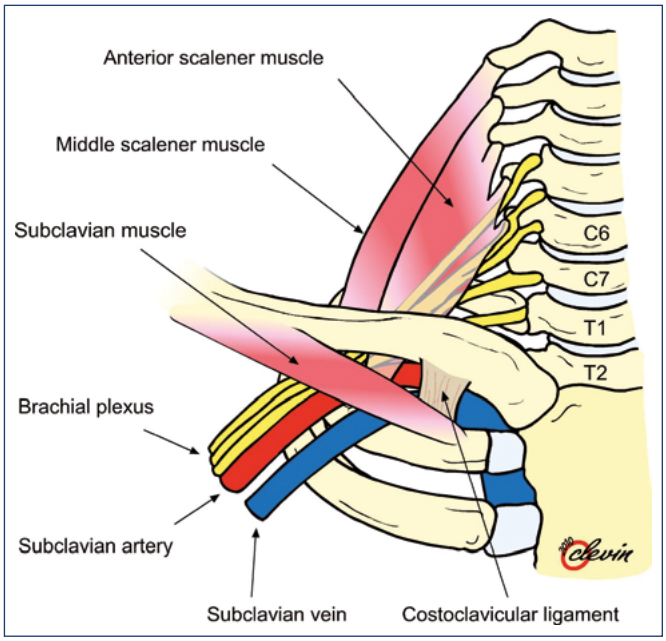

Figure 2. The thoracic outlet/inlet anatomy.

Hemodynamics

Normal veins

The venous return in a supine position is a result of a slightly higher pressure post capillary in the hand than in the right atrium. It is obvious that the importance of gravity is less pronounced in this extremity. In a standing position with the arm in a neutral hanging position, the hydrostatic pressure in the hand is about 45 mm Hg in a person of normal height, thus much lower than in the lower limb. Involuntary muscle activity and, of course, active movements act as a venous pump, as we know from the pumping principles in the lower limbs. The hydrostatic pressure facilitates flow to the atrium in an arm elevated above horizontal level. The return is also influenced by the respiratory pressure changes during inspiration and expiration with enhanced return during expiration.[3] Veins in an elevated arm over the head are visualized as nearly collapsed, whereas the veins in the opposite position are more elliptical in form.[6]

Vein pathology

Acute thrombosis is characterized by venous stasis with decreased flow distal to the occlusion without any collaterals. In a postthrombotic state, the veins are more or less occlusive, with caliber-varying flow channels; collateral flow is seen as another sign along with reflux, which can be demonstrated in a hanging arm by release of compression with retrograde filling distal to the compression point. The test for reflux can also be done with a powerful and firm handshake. The most important factor for pathophysiological changes in the upper limbs is the obstructive element, because valve incompetence is of less importance owing to the less-pronounced involvement of gravity than in the lower limbs.

Duplex ultrasound (DUS)

DUS is the most used imaging modality because it gives morphological and hemodynamic information at the same time. The patient is placed in a supine position with the arm relaxed and slightly abducted and rotated laterally, and the head slightly turned to the opposite side. A high-frequency linear transducer, typically 7.5-14 MHz, is used, but sometimes a 5-MHz curved array transducer is used for the subclavian vein. Both color Doppler and spectral Doppler are required for optimal flow assessment. As mentioned, other modalities such as computed tomography venography (CTV) and magnetic resonance venography (MRV) are helpful if DUS is inconclusive and/or imaging to determine etiology in adjacent structures is needed.

DUS of normal veins, morphology

A routine investigation of vein morphology begins at the level of the cubital region, whereas the veins in the forearm only are of importance for creating an av fistula at that level. The cephalic, basilic, and cubital veins are examined in a transverse scan plane, whereas the brachial and axillary veins are examined in the longitudinal and transverse scan plane. Normal veins are elliptical and easy to compress. The lateral part of the subclavian vein is investigated via an infraclavicular approach and the medial part via a supraclavicular view. It is not usually possible to compress this vein. The internal jugular vein is easy to identify and followed in the transverse plane to the junction with the subclavian vein. The brachiocephalic vein can be evaluated via a suprasternal approach with a minor high-frequency curved-array probe, which can also be used for larger individuals. It is not always easy to visualize the superior vena cava (*Figures 3-5*).

DUS of normal veins, waveform

The spectral Doppler waveform is characterized by a pulsatile configuration in the central veins (*Figure 6*). The action of the right atrium is reflected back and is manifested as a biphasic flow pattern with a flow peak forward in mid diastole, whereas the flow slows or reverses as the tricuspid heart valve closes. The respiratory phasicity is also reflected into the waveform, increased during inspiration and decreased during expiration (*Figure 7*). The influence of the heart and the respiration is less pronounced the more peripherally the examination is performed.

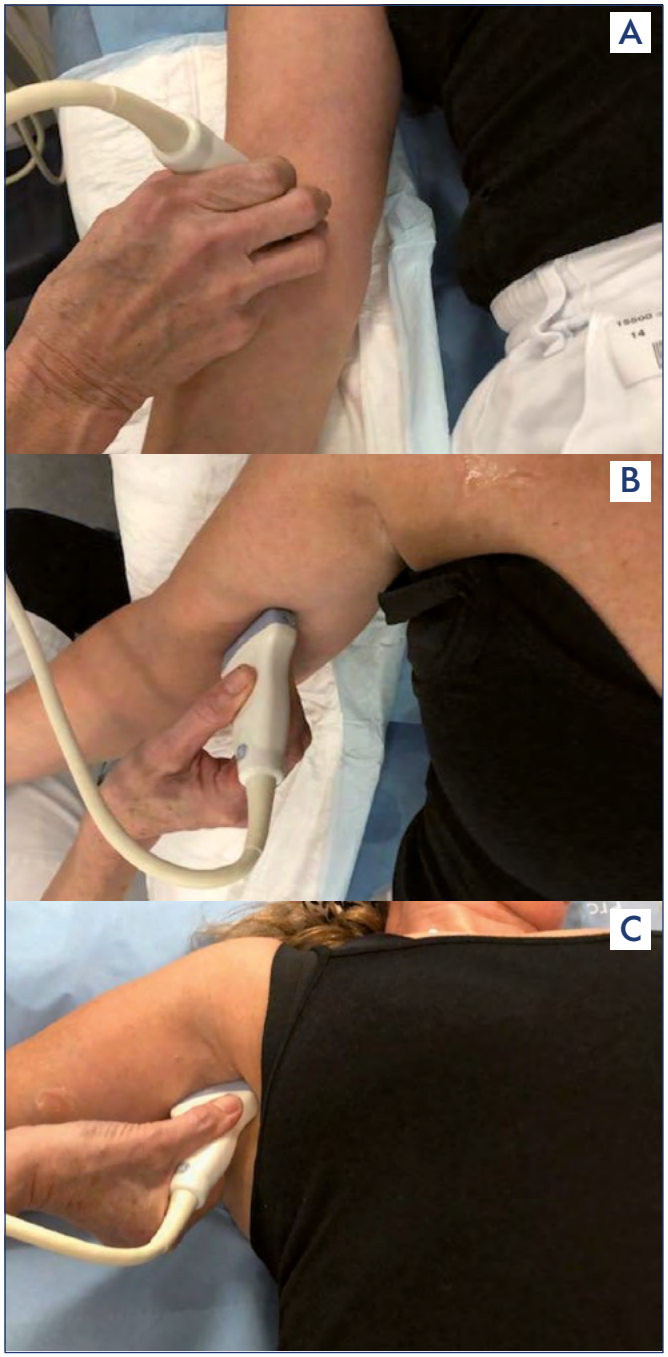

Figure 3A-3C. A linear transducer typically 7.5-14 MHz searching for the median cubital, brachial and axillary vein.

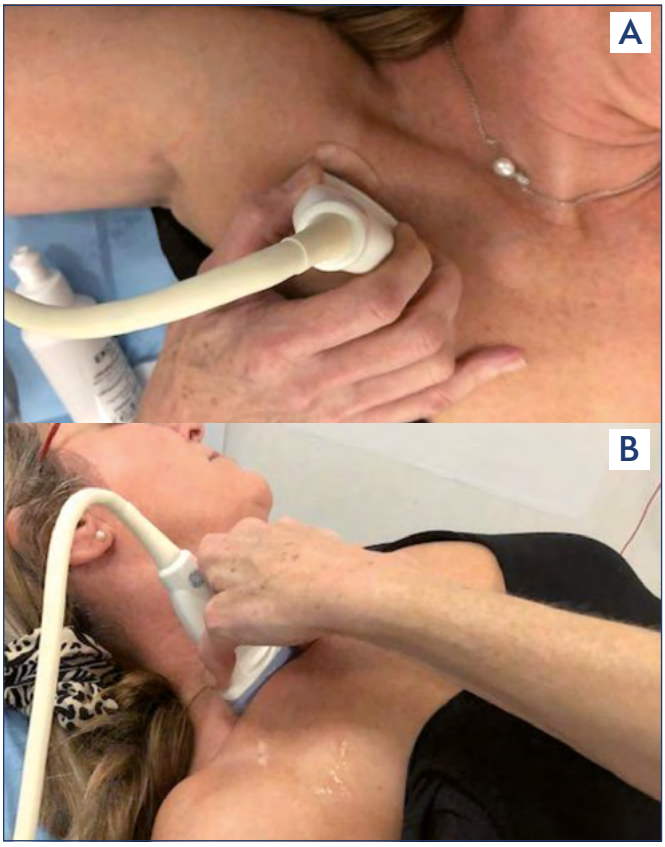

Figure 4A, 4B. Infraclaviculat view of lateral and supraclavicular view of medial part of subclavian vein.

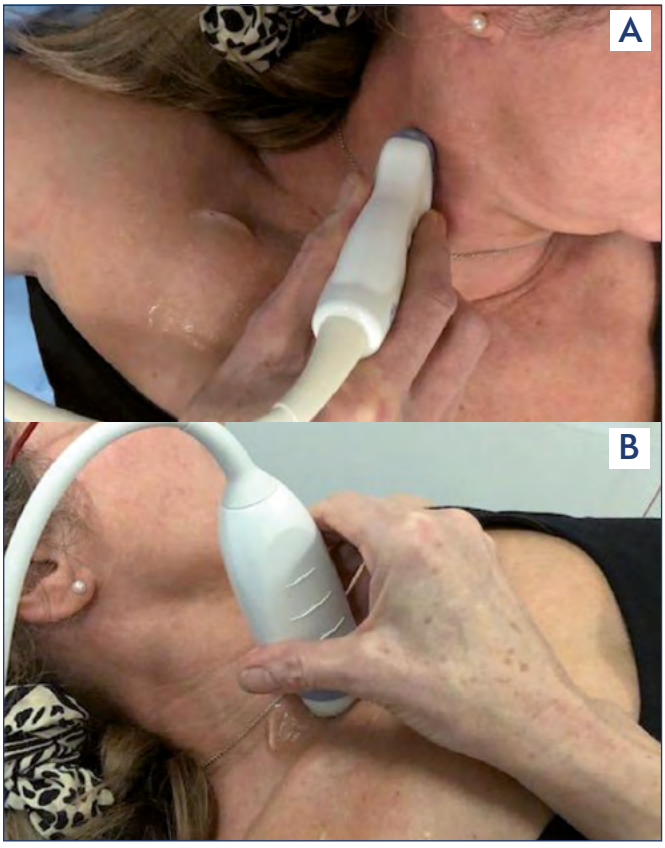

Figure 5A, 5B. The Jugular vein. The brachiocephalic vein and cava visualized with 5 MHz curved array transducer.

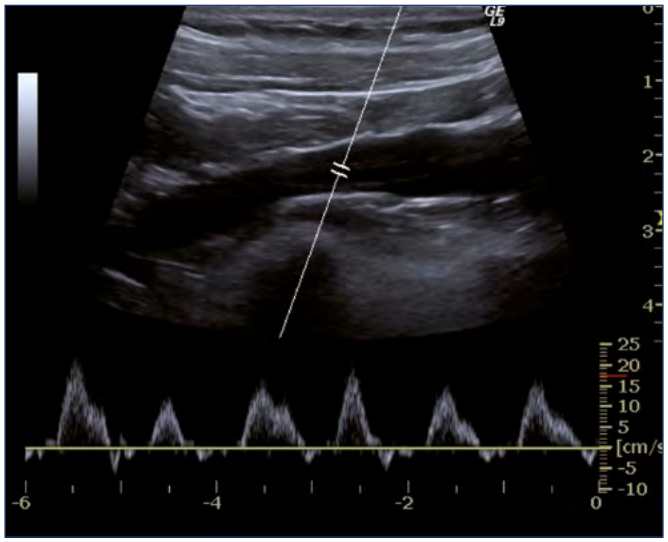

Figure 6. Doppler curve from the subclavian vein.

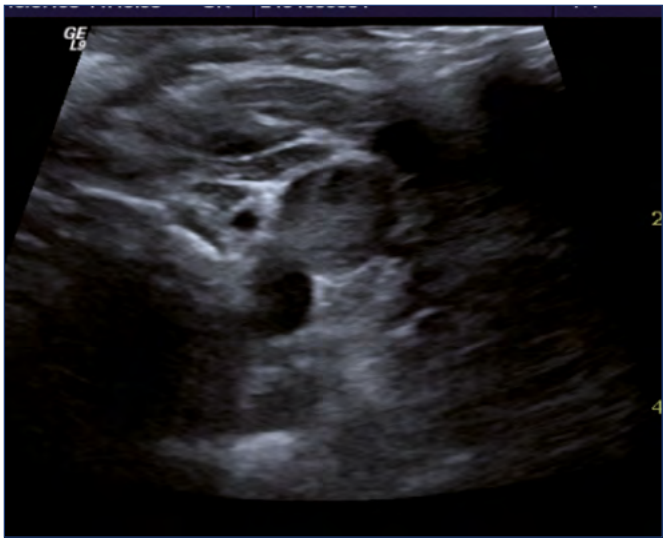

Figure 8. A thrombus in the subclavian vein seen with B-mode.

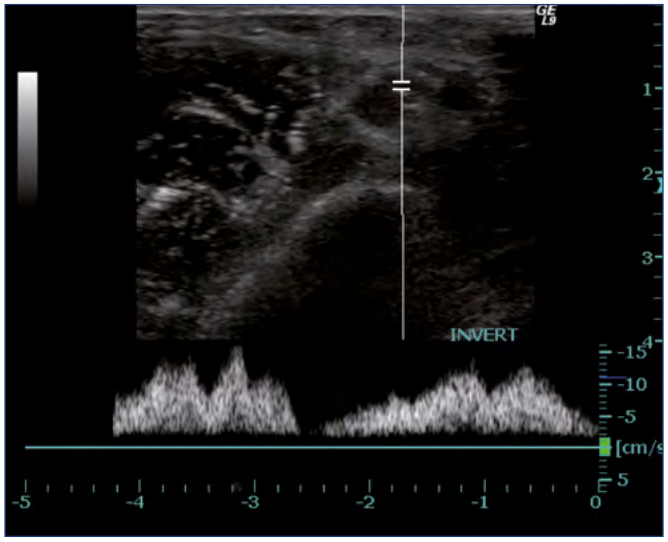

Figure 7. Fluctuations from breathing seen in the brachial vein.

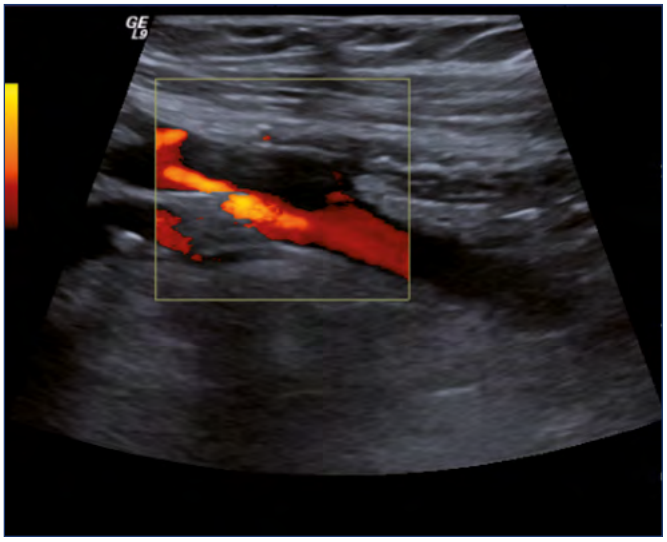

Figure 9. A partly thrombosed vein seen with color Doppler.

DUS of thrombosis

Thrombosis in the upper limb counts for about 5% of total DVT incidence, secondary being most frequent.[7] The examination for thrombosis concerns location, extension, compressibility, and flow. The B-mode modification can demonstrate the appearance of a hypo- or hyper-echogenic thrombus (depending on thrombus age) combined with noncompressible, except in very small nonocclusive thrombus and dilated vein structures (*Figures 8, 9*). The central veins such as the subclavian and brachiocephalic veins are also almost impossible to compress. Therefore, color flow imaging or spectral analysis is essential for diagnosis.

The absence of a Doppler signal means there is a thrombus. Hampered cardiac or respiratory fluctuations as well as lack of flow augmentation after distal compression raises suspicion of a central blockage (*Figure 10*).[8] In general, the sensitivity and specificity for detection of DVT with DUS was concluded on the basis of 11 studies in comparison with venography as reference, to be greater than 90%.[9] In a postthrombotic stage, color Doppler makes possible the visualization of the recanalized veins with internal channels in addition to small-caliber veins with noncompressible, thickened walls, and foci of echogenic thrombi may be seen. The spectral appearance in a stenosis typically shows accentuated turbulent and pulsatile flow. Multiple visible

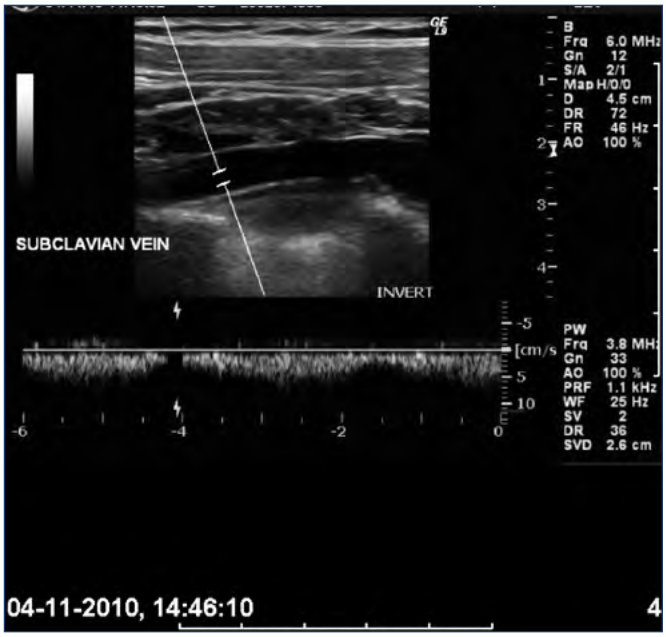

Figure 10. Doppler curve with lack of pulsatile flow in the subclavian vein indicating a more central obstruction.

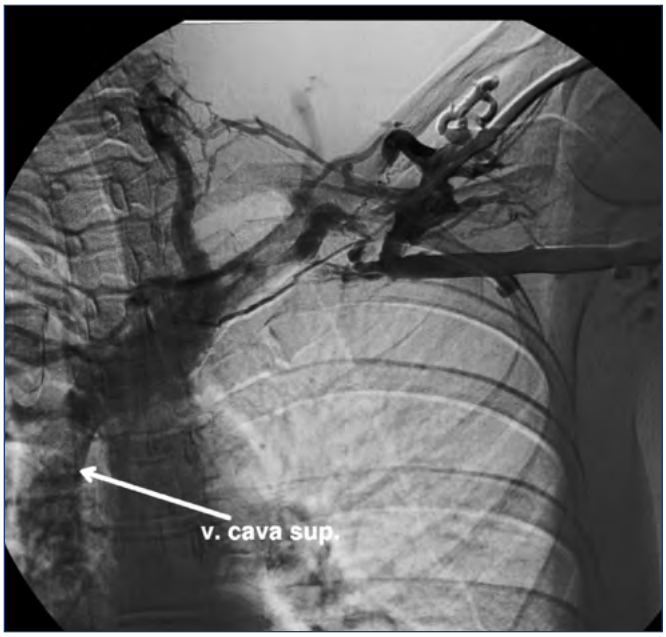

Figure 11. A central upper vein thrombosis seen with phlebography.

collateral veins point out chronic obstruction in the central veins.

Limitations with DUS

Duplicated veins, hypovolemia, obesity, and edema may limit the quality of the examination. The fact that the hemodynamics do change with different arm positions can make the interpretation difficult. A recent publication has demonstrated false negative findings with DUS in 21% of patients with suspected thrombosis. The group of patients in this investigation had primary DVT episodes with subclavian vein thrombosis due to TOS as a more difficult diagnosis. The interpretation means use of CTV/MRV should be encouraged in case of negative results in patients having idiopathic/primary arm thrombosis.[10]

Other modalities

Phlebography

This imaging modality was considered the "gold standard" for diagnosing acute thrombosis 15-20 years ago (*Figure 11*). It is preferable to administer the contrast medium in the deep veins, which can be difficult. The axillary vein can be overlooked if the contrast medium is injected in the cephalic vein. The procedure is usually painful as well. DUS has overcome all these disadvantages.

Chest radiography

Chest radiography can be useful when suspicion of underlying disease arises; eg, cervical rib, extreme callus after fracture of the clavicula, and seldomly, some osteal malformations all causing secondary thrombosis.

Computed tomography venography (CTV)

Multiple spiral CTV with 3D reconstructions is an ideal minimal invasive technique for rapid venous assessment. Bilateral arm injection is optimal for visualizing the central veins, including superior vena cava. However, this tool has limitations such as requirement for radiation and the possible occurrence of allergic reactions to the iodinated contrast medium.[11]

Magnetic resonance venography (MRV)

This modality with and without contrast medium is an alternative method if DUS is inconclusive; it is used for central veins.[12] Limitations involve claustrophobia (which may be triggered in some patients) and those involving the presence of metallic devices.[12,13]

Conclusion

DUS is a rapid and repeatable method for examination of the veins in the upper limbs. It is a first-line imaging method for diagnosing DVT, either primary or secondary, as well as postthrombotic changes. CTV and MRV are mandatory alternatives if DUS is technically insufficient and if DUS results are normal despite strong suspicion of disease. Knowledge of the normal anatomy is also useful for deciding if the veins can be used for different access strategies and av fistula. There is notable absence of a consensus document for DUS in the upper limbs such as we have for this imaging modality in the lower limbs.[14]

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Course duration for venoactive-drug treatment in chronic venous disease

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Keywords:

endothelial dysfunction; leukocyte activation; vein-specific inflammation; venoactive-drug treatment duration

Abstract

Chronic venous disease (CVD) is currently the most common vascular disorder of the lower extremities. The gradual progression of CVD has a negative impact on patients and also leads to high economic costs of medical care, especially for the advanced forms of chronic venous insufficiency (CVI). Conservative management of CVD includes the use of compression stockings and pharmacological therapy. Despite the efficacy of compression therapy, patients may often experience difficulties with the daily use of medical hosiery, which leads to lower adherence than pharmacotherapy. Venoactive drugs (VADs) exert a systemic effect on various components of the pathogenesis of CVD, leading to improvement in patient quality of life and slowing disease progression. This article presents a literature review addressing the issues of prescribing pharmacotherapy to patients with CVD. It includes an analysis of the published data on the efficacy and safety of VADs and discusses the aspects of timing and duration of a course of treatment with VADs in accordance with clinical class of CVD and their use in combination with surgical treatment or sclerotherapy. It describes the effects of VADs on pathophysiological mechanisms of the development and progression of CVD and reviews clinical studies assessing the effects of VADs on various components of CVD pathogenesis (endothelial dysfunction, activation of leukocytes, vein-specific inflammation, and activation of proteolytic enzymes that contribute to the degradation of the extracellular matrix). In this regard, it focuses particularly on micronized purified flavonoid fraction as having the largest evidence base for proven efficacy, safety, and long-term use. This article proposes, based on the data discussed here, several approaches to determine course duration of VAD treatment according to clinical class of CVD. It also emphasizes the importance and necessity of a personalized approach when choosing the optimal duration of VAD therapy.

Introduction

Chronic venous disease (CVD) is an important medical and social problem, holding a leading place among the most common peripheral vascular diseases, as shown in a number of epidemiological studies.[1,2] The pathogenesis of CVD is a complex and multifactorial process and has been studied in detail in patients with varicose veins of the lower extremities (VVLE). It is a cascade of changes triggered by venous stasis that occurs at molecular and cellular levels. In this

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cascade, certain changes develop in endothelium due to a change in the shear stress, inducing inflammatory and thrombogenic phenotypes of endotheliocytes.[3,4]

Leukocyte activation, with their subsequent interaction with endothelial cells, leads to the production of cell adhesion molecules and proteolytic enzymes, in particular matrix metalloproteinases (MMPs; synthesized by endothelial cells and macrophages), and cause degradation of the extracellular matrix of the venous wall and its varicose transformation.[3,5-9]

One of the important factors in the pathogenesis of varicose transformation of superficial veins in VVLE is dysregulation of collagen synthesis. Studies have identified various changes in the content of different types of collagen in the venous wall. Most attention has been given to the content of types I and III interstitial collagens, which form large fibrils in the venous wall.[8,10,11]

In this regard, it seems relevant to select optimal treatment regimens with venoactive drugs (VADs; ie, venotonics, vein-protective agents) that will be effective on these components of pathogenesis. VADs are a large group of biologically active substances produced from plant materials or by chemical synthesis, characterized by the ability to reduce the severity of vein-specific symptoms and syndromes and to increase venous tone. VADs for systemic use are produced in various forms (tablets, suspensions, powders for oral administration, etc).[12] The classification of the main VADs is presented in *Table I*.[12]

Class/Group	Active substance
Naturally occurring drugs	
γ-Benzopyrones	Micronized purified flavonoid fraction (MPFF) Nonmicronized, hemisynthetic diosmin Rutin and rutosides, hydroxyethylrutosides (HR)
Saponins	Escin (horse chestnut seed extract) Ruscus extract
Other plant extracts	Proanthocyanidins (oligomers) Ginkgo biloba extract
Synthetic drugs	
	Calcium dobesilate

Table I. Classification of venoactive drugs.

Based on reference 12: Kirienko et al. Flebologiya. *2018;12(3):146. doi:10.17116/flebo20187031146.*

In addition to VADs, other pharmacological agents (eg, antiplatelets, heparin-like compounds, enzymes, prostaglandins) are also used for systemic pharmacotherapy.

Issues in prescribing VAD therapy

When prescribing these drugs, differences in the mechanisms of action and in therapeutic effect should be taken into consideration. The main principle in the prescription of VADs is the effect on a particular clinical outcome as shown in randomized controlled clinical trials confirming the efficacy and safety of a certain drug. The main indications for prescribing VADs are the combination of patient complaints and well-known CVD symptoms and signs.

Although indications for VAD use and their therapeutic effects have been determined in numerous studies, many questions remain, including those on duration of use and frequency of treatment courses.[13]

Aspects of timing and duration of VAD treatment courses

For many VADs, recommendations for duration of treatment remain vague: it may not be specified in the instructions for use; if it is, instructions may note that the treatment course can last several months, and that in case of a recurrence of symptoms, the treatment course can be repeated according to physician recommendations. Thus, there are currently no specific guidelines on the duration of VAD therapy in accordance with the disease severity and its class according to the CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification.

In clinical practice, VADs are prescribed for periods of continual treatment, ie, courses, the frequency and duration of which are most often selected based on empirical evidence, taking into account the experience of a particular phlebologist. The specialist makes a decision based on the course of disease and a combination of symptoms, considering possible adverse events. At the initial stages of CVD, the standard VAD course is usually 2 to 3 months, and in classes C3 to C6 (CEAP), it is possible to prescribe treatment up to 6 months, preferably twice a year. Moreover, in severe chronic venous insufficiency (CVI) or obesity, if patients have difficulties using compression hosiery, VADs may be prescribed for an indefinite time. Regarding the safety of long-term use (up to 12 months), the largest evidence base has been obtained for micronized purified flavonoid fraction (MPFF).[12,13] *Table II* presents the

Reference	Year	Patients	Drug	Dosage	Duration	Outcomes
Shoab et al[14-16]	1999-2000	20 patients with CVD	MPFF	500 mg BID	2 months	Decrease in L-selectin / CD62-L expression; decrease in ICAM-1 and VCAM concentration by 32% and 29%, accordingly; decrease in plasma VEGF concentration by 42%
Jantet et al; RELIEF Study Group[17]	2002	5052 patients with CVD class C0-C4 (CEAP)	MPFF	500 mg BID	6 months	Venous pain relief and QOL improvement
Arceo et al[18]	2002	352 patients with CVI class 1-2 (CEAP)	Calcium dobesilate	500 mg TID	9 weeks	Reduction in severity, pain, and cramps in the lower limbs
Roztocil et al[19]	2003	150 patients with CVD class C6s	MPFF	500 mg BID	6 months	Ulcer healing within a year (64.6% vs 41.2% in the control group)
Kalus et al[20]	2004	129 patients with CVD class C1-C2 (CEAP)	Red vine leaf extract	360 mg OD	6 weeks	Increase in microvascular blood flow, blood oxygenation
Veverkova et al[21]	2006	181 patients with VVLE undergoing phlebectomy	MPFF	500 mg BID	14 days before and 14 days after surgery	Reduction in postoperative pain and hematomas
Pokrovsky et al (DEFANS trial)[22]	2007	245 female patients with VVLE undergoing phlebectomy	MPFF	500 mg BID	14 days before and 28 days after surgery	Reduction in postoperative pain and bruising; QOL improvement
Allaert et al[23]	2010	2862 patients with VVLE class $C1_S$–$C3_S$ (CEAP) undergoing sclerotherapy	MPFF	500 mg BID	1 month	Reduction in CVD symptoms
Rabe et al[24]	2011	248 patients with CVD class C3-C4a (CEAP)	Red vine leaf extract	720 mg OD	3 months	Clinically and statistically significant reduction in the lower limb volume and severity of symptoms
Bogachev et al, (DECISION trial)[25]	2012	230 patients with VVLE class C2–C4s undergoing EVLA	MPFF	500 mg BID	14 days before and 28 days after the intervention	Reduction in postoperative pain and bruising; QOL improvement
Allaert (Meta-analysis)[26]	2012	1010 patients with CVD class C3 (CEAP)	MPFF, HR, diosmin, ruscus extract		2-6 months	MPFF is effective in reducing edema syndrome in patients with CVD of class C3
Andreozzi et al (SURVET study)[27]	2015	615 patients with venous thromboembolism	Sulodexide	500 U BID	24 months	Reduction in the risk of VTE recurrences with no apparent increase in bleeding risk
Rabe et al[28]	2015	1137 patients with CVD class C3-C4 (CEAP)	MPFF	500 mg BID	4 months	Reduction in pain, heaviness in the lower limbs; QOL improvement
Elleuch et al[29]	2016	450 patients with CVD class C4 (CEAP)	Sulodexide	250 U BID	3 months	QOL improvement
Rabe et al[30]	2016	351 patients with CVD class C3-C5 (CEAP)	Calcium dobesilate	500 mg TID	3 months	Reduction in edema of the lower limbs

Reference	Year	Patients	Drug	Dosage	Duration	Outcomes
Pitalluga et al[31]	2017	Patients with VVLE undergoing ASVAL	MPFF	500 mg BID	3-6 months	Reduction in sizes of the preserved saphenous veins, the consequences of surgical trauma
Tsukanov Yu et al[32]	2017	96 patients with CVD class C1 (CEAP)	MPFF	1000 mg OD	3 months	QOL improvement (CIVIQ-20); reduction in CVD symptoms and transient venous reflux
Tsukanov Yu et al[33]	2017	294 patients with CVD class C0-C2 (CEAP)	MPFF	1000 mg OD	3 months	QOL improvement (CIVIQ-20); reduction in CVD symptoms and situational venous reflux
Maggioli et al[34]	2019	256 patients with CVD class C0s-C1 (CEAP)	MPFF	1000 mg OD (suspension)	8 weeks	QOL improvement (CIVIQ-20); reduction in discomfort in the lower extremities (VAS)

ASVAL, ambulatory selective varicose vein ablation under local anesthesia; BID, twice daily; CEAP, Clinical, Etiological, Anatomical and Pathophysiological classification; CIVIQ-20, Chronic Lower Limb Venous Insufficiency Questionnaire, 20 items; CVD, chronic venous disease; CVI, chronic venous insufficiency; EVLA, endovenous laser ablation; HR, hydroxyethylrutosides; ICAM-1, intercellular adhesion molecule 1; MPFF, micronized purified flavonoid fraction; OD, once daily; QOL, quality of life; TID, thrice daily; U, units; VAS, visual analog scale; VCAM, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism; VVLE, varicose veins of the lower extremities.

Table II. Results of the main studies on the duration of CVD treatment.

results of studies on the duration of VAD treatment in CVD patients.[14-34]

Effect of VADs on CVD development and progression

The initiation of conservative therapy at early stages of varicose veins, ie, before onset of pathomorphological transformation of the venous wall and its valves, can lead to a reduction in the number of patients with severe CVD. The main determinants in CVD pathogenesis are leukocyte-endothelial reactions, followed by an inflammatory process in the venous wall. Therefore, systemic pharmacotherapy in patients with VVLE should be based on the elimination of these changes. Considering this fact, the most promising are pharmacological agents than can improve endothelial function.[7,35]

At present, the main drug with proven efficacy in suppressing leukocyte-endothelial interaction is MPFF. A number of clinical trials have been conducted with various durations of treatment with this VAD, and their results have demonstrated efficacy and safety of MPFF in patients with various forms of CVD.

MPFF relieves signs and symptoms of CVD and improves QOL

The RELIEF study (Reflux assEssment and quaLity of life ImprovEment with micronized Flavonoids), one of the largest international trials for VAD treatment, was conducted in 23 countries for 2 years and included 5052 patients with CVD classes C0 to C4 (CEAP). The study showed that 6-month treatment courses with MPFF significantly reduced venous pain in patients with VVLE.[17]

The study of Rabe et al included 1137 CVD patients with classes C3 to C4 (CEAP) who were randomized to 4-month treatment with MPFF or placebo. MPFF use was associated with a reduction in pain and heaviness in the lower extremities, an improvement in quality of life (QOL).[28]

As for the effect of VADs on venous edema, a meta-analysis of 10 studies that included 1010 patients with CVD class C3 was carried out in 2012. MPFF demonstrated the highest efficacy in the treatment of venous edema.[26]

In several clinical studies assessing the efficacy of MPFF in patients with early stages of CVD (C0-C2 classes), treatment lasted for 2 to 3 months and was associated with QOL improvement (20-item Chronic Venous Insufficiency Questionnaire [CIVIQ-20]) and a reduction in CVD symptoms with the drug used in either tablet form[32,33] or suspension.[34]

MPFF mediates components of VVLE pathogenesis

Randomized clinical trials have also been carried out to evaluate the effect of MPFF on various components of VVLE pathogenesis. A few studies showed that a 2-month

treatment course with MPFF was associated with a reduction in L-selectin/CD62-L expression by monocytes and neutrophils, a reduction in intercellular adhesion molecule 1 (ICAM-1) and vascular adhesion molecule (VCAM) plasma levels by 32% and 29%, respectively, and in vascular endothelial growth factor (VEGF) plasma levels by 42%.[14-16]

These data demonstrate the benefits of MPFF in terms of improvement in venous endothelial function, as well as prevention of activation and adhesion of leukocytes. In experimental studies, MPFF has been proven to be effective in reducing the inflammatory response in venous valves and slowing down the development of venous reflux.[36]

In severe forms of CVD, a 6-month treatment course with MPFF has been studied. In patients with venous ulcers, MPFF was associated with better outcomes in terms of ulcer healing after 1 year (64.6% vs 41.2% in the control group with compression therapy only).[19]

VADs in combination with surgical intervention

The duration of conservative therapy in patients undergoing surgery or sclerotherapy is of special interest. In a pioneer study of perioperative use of venotonics, Veverkova et al assessed 181 patients aged 18 to 60 years who underwent crossectomy or stripping of the great saphenous vein. Patients were allocated to treatment with MPFF at a dose of 1000 mg daily for 14 days before and 14 days after surgery (n=92) or to the control group (n=89). Treatment with MPFF was associated with a reduction in the intensity of postoperative pain and, consequently, in the use of analgesics, as well as smaller size of postoperative hematoma, compared with the control group.[21]

The Russian trial DEFANS (Detralex - Assessment of Efficacy and Safety for Combined Phlebectomy) also evaluated the efficacy and safety of MPFF in patients undergoing phlebectomy. The main group consisted of 200 female patients with VVLE class C2s (CEAP) who received MPFF. The control group included 45 females who did not receive VADs. In this study, the duration of MPFF treatment was different: 500 mg twice daily (BID) for 2 weeks before surgery and 4 weeks after surgery.[22] The study showed similar QOL parameters at baseline (CIVIQ); postoperative hematomas in the main group on days 7, 14, and 30 after phlebectomy were significantly smaller ($P<0.05$), and the greatest differences (over 70%) were observed 4 weeks after surgery. Moreover, the rates of symptoms (pain) were significantly lower in the MPFF group than in the control group (2.9 and 3.5 visual analog scale [VAS] scores, respectively, at day 7 after the procedure). The DEFANS trial proved the feasibility of prescribing VADs in the preoperative period and for 1 month after surgery.

VADs in combination with minimally invasive surgical techniques

In addition to studies of the adjuvant treatment with VADs after open surgery, there are data on the duration of conservative therapy after minimally invasive surgical procedures such as endovenous laser ablation (EVLA). Thus, the DECISION trial (Observational Study Among Patients with Varicose veins of the Lower Limbs Undergoing Endovenous Ablation Alone or in Association with Venoactive Drugs), which was conducted in eight Russian clinical centers, included 230 patients with VVLE classes C2 to C4s (CEAP) and indications for endovascular treatment. The study group received MPFF 1000 mg daily for 2 weeks before and 4 weeks after endovascular treatment. Venous clinical severity score (VCSS) scales and the CIVIQ-14 questionnaire were used. Patients' satisfaction with MPFF treatment was significantly higher than in the control group.[25]

In addition, VADs were evaluated in patients who underwent sclerotherapy. Allaert et al conducted a study involving 2862 patients with VVLE class $C1_S$ through $C3_S$ (CEAP). The 1-month treatment course with MPFF at a dose of 1000 mg daily after sclerotherapy was associated with improvement of the main CVD symptoms.[23]

There are alternative (vein sparing), minimally invasive techniques for which it is also advisable to provide treatment with VADs. For example, in the studies performed by Pittaluga, VAD treatment (MPFF 1000 mg daily) was prescribed for a period of 3 to 6 months after surgery. According to Pittaluga, due to certain pleiotropic effects, MPFF not only reduces the consequences of surgical trauma, but also leads to a decrease in the diameter and to restoration of the working capacity of superficial veins spared with the Ambulatory Selective Varices Ablation Under Local Anaesthesia (ASVAL) technique.[31]

According to the Russian National Guidelines, sulodexide may be used for the treatment of advanced stages of CVD.[12] Although not a venotonic, sulodexide may be beneficial in affecting CVD pathogenesis and attenuating

the inflammatory cascade. Sulodexide inhibits the release of interleukin (IL)-2, IL-12 (p70), IL-10, and VEGF from wound-fluid–stimulated THP-1 monocytes in subjects with venous trophic ulcers, and also inhibits the synthesis of MMP-9, which slows down the degradation of the extracellular matrix.[37,38]

In a study that included 450 patients with CVD, participants received sulodexide at a dose of 250 units BID for 3 months. The results showed an improvement in the QOL of patients with CVD class C4 (CEAP). Adverse events were registered in only 2 patients (epigastric pain in one patient and abdominal pain with vomiting in another).[29] In addition, sulodexide can be used for treating postthrombotic syndrome (PTS). In the SURVET study (Multicenter, Randomized, Double Blind, Placebo Controlled Study on Long-term Treatment with Sulodexide for Prevention of Recurrent Deep Vein Thrombosis in Patients with Venous Thromboembolism), sulodexide demonstrated a reduction in the risk of venous thromboembolism (VTE) recurrences without an apparent increase in bleeding risk.[27]

In patients with severe CVI and venous ulcers, combination therapy with sulodexide and MPFF has been shown to be more effective than MPFF monotherapy.[39]

Approaches to determine course duration of VAD treatment according to clinical class of CVD

The analysis of various studies of VADs has demonstrated that in patients with early manifestations of CVD, the treatment benefits become apparent within 1 to 2 months of conservative therapy.[18,20] In patients with severe forms of CVD, treatment duration should be extended up to 3 to 6 months.[24,30]

The Society for Vascular Surgery (SVS) and American Venous Forum (AVF) guidelines do not provide clear recommendations on duration of the VAD treatment course. On the basis of data provided by American colleagues, VADs (diosmin, hesperidin, rutosides, MPFF, escin) in combination with compression therapy are indicated for patients with CVD-related pain and edema in countries where the above-mentioned drugs are available (class 2, level C), and the duration of the course of therapy should be up to 6 months.[40]

According to the European Venous Forum (EVF) guidelines, the treatment with MPFF for 3 to 6 months is effective in the reduction in CVD symptoms, including pain, feelings of heaviness or tightness (level of evidence A), cramps (level B), functional discomfort (grade A), skin changes (grade A), and severity of ankle edema (grade B).[41]

Conclusion

CVD is a gradually progressive disorder, and given the pathogenetic mechanisms of its development, it is the vein-specific inflammation that leads to the occurrence and worsening of symptoms and severe forms of the disease complicated by trophic changes. Through results of many studies, VADs have proven their efficacy and safety in the treatment of CVD in terms of their influence on the various components of pathogenesis. At present, MPFF is the VAD with the largest evidence base for safety and long-term use and the main one with proven efficacy in suppressing leukocyte-endothelial interactions, in treatment of venous edema and reducing venous pain and heaviness in VVLE, and improving QOL. Duration of VAD treatment course and frequency, as well as the optimal dosing schedule, depends on many factors, mainly on the current status of the patient's venous system. At the early stages of the disease, it is possible to prescribe short courses of VADs (up to 2 months), but with the worsening of CVD symptoms and development of CVI, it is necessary to prescribe prolonged VAD treatment courses: for at least 3 months in case of edema and at least 6 months for trophic skin changes. VADs are also advisable to be used in the perioperative period, before the invasive treatment of CVD and in the early postinterventional period. A personalized approach to the prescription of VADs is required, taking into account the stage of the disease and the status of the venous system, in order to improve treatment outcomes and QOL in patients with CVD.

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