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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:*

*The introduction and wide use of the CEAP classification for chronic venous disorders has made it possible to conduct large epidemiological studies and develop a set of clinical practice guidelines. Global use of this uniform classification has led to multiple comparable studies that have provided new evidence and improved understanding of chronic venous disease.* ***Fedor LURIE (USA)*** *reports the highlights from the 2020 update of the CEAP classification, which was realized by a task force of the American Venous Forum.*

*Air plethysmography (APG) and ambulatory venous pressure (AMVP) measurements, once popular, have gradually declined in use to near extinction. However, they can provide a more quantitative evaluation of reflux and disease severity than duplex ultrasound alone.* ***Seshadri RAJU (USA)*** *shares experience with these tests in 8456 CVD limbs seen over a 20-year period.*

*Iliofemoral venous obstruction is increasingly recognized as a major cause of post-thrombotic syndrome.* ***Gerard O'SULLIVAN (Ireland)*** *discusses the optimal method for imaging the iliofemoral venous segment.*

***Vadim BOGACHEV (Russia)*** *presents the results of a study, assessing the effectiveness of the micronized purified flavonoid fraction–based conservative treatment in patients with chronic venous edema as part of a prospective, observational program (VAP-C3; Vein Act Prolonged-C3) that evaluated the management of patients with chronic venous edema caused by the primary forms of CVD in real clinical practice.*

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

# 2020 Update to classification of chronic venous disorders

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Keywords:

CEAP; classification; varicose veins; vein; venous disease; venous ulcer.

## Abstract

In 2017, the American Venous Forum (AVF) created a task force to determine if the CEAP classification needed a revision. An extensive literature review led the task force to conclude that there was sufficient evidence to update it to align with the newest knowledge of chronic venous disorder (CVD) and to clarify terminology. Using the modified Delphi methodology, the AVF task force concluded its 2-year project by publishing the CEAP 2020 update, which also became a reporting standard for studies of patients with CVD. The updated CEAP classification remains a discriminative instrument designed to describe the signs and symptomatic status of each limb of a patient with CVD at a specific time point. The CEAP 2020 update added a subclass C4c for corona phlebectatica. This modification reflects current understanding that corona phlebectatica has a similar natural history to the C4a and C4b subclasses. Another update for the "C" component is a modifier "r" describing recurrent varicose veins (C2r) or recurrent venous ulcer (C6r). The update for the "E" component of CEAP includes creation of two subclasses for secondary CVD (Es) as follows: (i) Esi–intravenous causes; and (ii) Ese–extravenous causes. Finally, the numbering of the venous segments in the "A" component of the CEAP is replaced by commonly used anatomical abbreviations.

## Introduction

Classifications of diseases and pathological conditions have a very long history. Perhaps the first practical classification was developed in 1662 by John Graunt who published an index of causes of mortality. A century later in 1768, François Boissier de Lacroix developed a systematic classification of all known diseases at that time. Around the same time, in 1780, William Cullen published the classification of disease that became widely used by clinicians, especially in the United Kingdom. As multiple classifications began to emerge, the need for a unified single classification became apparent. William Farr wrote in 1839, "the advantages of a uniform nomenclature, however imperfect, are so obvious as weights and measures in the physical sciences. It should be settled without

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delay and kept without change." This need was addressed in 1855 at the International Statistical Congress in Paris, where Mark D'Espine and William Farr established the first international classification of diseases–a compromise between Farr's phenotypical approach and d'Espine's pathological approach to classification.

This international classification of diseases is an example of a descriptive classification that defines distinct diseases and conditions for public health and statistical purposes. Clinical classification is similar to descriptive classification in that it defines distinct diseases or conditions, but perhaps its greater purpose is to standardize communication among practitioners and clinical researchers. As a descriptive tool, clinical classification defines diseases based on their phenotypical manifestations, such as symptoms and signs. However, to address the needs of clinical practice, these disease definitions should be connected to treatment options. Evolving knowledge of the pathological mechanisms of diseases does not justify a change in a clinical classification until the treatment options targeting specific mechanisms become available. Oncologic classifications exemplify a transition from empirical phenotypical clinical classification to molecular classifications of cancer that are based on both an understanding of pathological mechanisms and the availability of therapeutics targeting these mechanisms.

## CEAP classification of CVD

The current understanding of CVDs includes knowledge of key pathological mechanisms, such as reflux and obstruction, that can be targeted by interventions in some anatomical locations. It also includes empirical knowledge that some of the CVD phenotypes have a similar natural history and impact on a patient's quality of life. However, the biological and pathological basis for these phenotypes is poorly understood. This complex situation has required a different classification. First introduced in 1996, the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification addressed the complexity of CVD by incorporating four different taxonomical approaches. The clinical class "C" is a description of signs and the symptomatic status of a lower extremity (LE). These clinical classes are based on the most frequently seen manifestations of CVD that also have a similar natural history. The "E" (etiology) of the CEAP reflects the current understanding of what causes the signs and symptoms in an affected LE. The "A" of CEAP describes which anatomical segments of the LE venous systems are affected. Finally, the "P" (pathophysiology) describes identified hemodynamic abnormalities in the affected anatomical segments. Because of the complexity associated with CVD, an individual component of the CEAP classification alone cannot provide an appropriate clinical description of an affected LE, but a combination of the components gives the clinician a more complete understanding of each patient's disease and guides the subsequent clinical management.

## Evolving CEAP classification: 2004 revision

The introduction and wide use of the CEAP classification has made it possible to conduct large epidemiological studies and develop a set of clinical practice guidelines.[1-4] Global use of this uniform classification has led to multiple comparable studies that have provided new evidence and improved our understanding of CVD. As new knowledge has developed, the classification itself has required revisions and updates. Thus, significant revision of the CEAP was done in 2004.[5] Although that revision substantially improved the classification, the transition to a new version of CEAP took several years. Studies that were initiated before the revision continued to report their findings using the previous version, whereas some publications were utilizing the revised classification. The experience suggested that future revisions of CEAP should be backward compatible, so the revised version of the CEAP may add more specific subcategories but leave the previous categories unchanged.

## Evolving CEAP classification: 2020 update

In 2017, the American Venous Forum (AVF) created a task force to determine if the CEAP needed further revision. An extensive literature review led the task force to conclude that there was sufficient evidence to update it to align with the newest knowledge of CVD and to clarify terminology. The task force was extended to include four groups, each group to focus on one of the four components of the CEAP. The advisory group of experts who participated in the creation and previous revision of CEAP was assembled to ensure continuity of the process (*Table I*). Realizing that revision of the CEAP is essentially a consensus process, the modified Delphi methodology was used.[6] During a 2-year process with multiple discussions, several proposed changes were rejected because they either lacked supportive evidence, violated one of the predefined revision criteria, or affected practicality of using the CEAP. These rejected proposals are described in the CEAP 2020 publication.[7]

| Group | Group leader | Group members |
|---|---|---|
| Group C | Mark Meissner | Marston W, Shortell C, Urbanek T, Santiago F |
| Group E | Elna Masuda | Dalsing M, Blebea J, Carpentier P |
| Group A | Harold Welch | Gasparis A, van Rij A, DeMaeseneer M |
| Group P | Ruth Bush | Labropoulos N, Rafetto J, Uhl JF |
| Advisory group | Eklof B, Gloviczki P, Kistner R, Lawrence P, Moneta G, Padberg F, Perrin M, Wakefield T | |

*Table I. The CEAP (clinical, etiological, anatomical, and pathophysiological classification) Task Force of the American Venous Forum.*

The updated CEAP classification remains a discriminative instrument designed to describe the signs and symptomatic status of each limb of a patient with CVD at a specific time point. Manifestation of CVD changes significantly over time, so the same patient may have a different CEAP description at different time points. The interpretation of such changes is beyond the ability of discriminatory instruments, and the CEAP cannot and should not be used to interpret these changes as improvement or deterioration. These terms require evaluatory instruments capable of measuring the disease severity and its change over time or as a result of an intervention. The Venous Clinical Severity Score (VCSS) is an example of such an instrument.

All four components of the CEAP should be treated as nominal variables. This includes the clinical class "C" and its subclasses. It is not appropriate to state that a patient with a manifestation of CVD classified as C4 has a more severe condition than a patient classified as C2. This also applies to the subclasses of the CEAP. The CEAP 2020 update added a subclass C4c for corona phlebectatica. This modification reflects current understanding that corona phlebectatica has a similar natural history to the C4a and C4b subclasses. It was assigned to "c" subclass of C4 in order to preserve the previous version of CEAP, so the C4a and C4b subclasses remain unchanged. This order of subclasses reflects neither the severity of disease nor a different prognosis. Another update for the "C" component is a modifier "r" describing recurrent varicose veins (C2r) or recurrent venous ulcer (C6r).

The update for the "E" component of CEAP includes creation of two subclasses for secondary CVD (Es). The CEAP 2020 separates intravenous and extravenous causes of the Es. Intravenous causes are conditions that are caused by venous wall or valve damage. Intravenous subclass Esi includes venous wall and/or valve damage caused by deep-vein thrombosis (DVT), primary intravenous sarcoma, or other intravenous lesions. Extravenous causes are pathological conditions that affect venous hemodynamics locally or systematically but are not located in the venous wall or venous lumen. The extravenous subclass of the Es includes CVD caused by congestive heart failure, external vein compression, perivenous fibrosis, muscle pump dysfunction (paraplegia, arthritis, chronic immobility, frozen ankle, or severe sedentary state), and obesity.

## CEAP: classification of CVD, not syndromes

The CEAP is a classification of CVDs, not syndromes. The difference becomes clear when comparing the CEAP definition of the secondary etiology of CVD and the definition of the post-thrombotic syndrome (PTS). Acute DVT can damage venous valves causing reflux–which will be classified as Esi; Ad; Pr by the CEAP–or cause an obstruction to venous flow by intravenous organized thrombus or synechia–which will be classified as Esi; Ad; Po. Each of these descriptions are specific to the sequelae of the DVT. In contrast, the definition of the PTS is based on a combination of symptoms and signs that are not

specific, and in more than 50% of patients, are not related to the sequelae of DVT but are caused by preexisting primary CVD.[8,9] This means that studies that use the PTS as an outcome, such as the SOX (Compression Stockings to Prevent Post-Thrombotic Syndrome) and ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) trials, are subject to significant misclassification bias.

## Use of CEAP 2020

As with the previous versions, CEAP 2020 can be used in two different ways. The abbreviated CEAP lists the highest clinical class with the symptomatic status ("s" for symptomatic, "a" for asymptomatic). This is followed by the description of etiology (congenital, primary, or secondary), anatomy (superficial, deep, perforators, or their combination), and pathology (reflux, obstruction, or their combination). Such descriptions provide minimum information about the patient but still may be sufficient for some purposes. The complete CEAP provides more specific information that is frequently sufficient for clinical management decision.

For example, two patients (*Figure 1 A, B*) with a healed ulcer in the left leg can be described as LLE (left LE): C5s; Es; Ad; Po by the abbreviated CEAP. Such description indicates that both patients have a healed ulcer, are symptomatic, and have secondary venous disease caused by obstruction in the deep veins. However, the complete CEAP description of these patients may be very different. The first patient is described as LLE: C3,5s; $Es_e$; Ad; $Po_{CIV}$. This patient has edema and a healed ulcer caused by extravenous obstruction of the left common iliac vein (May-Thurner Syndrome) and requires a work-up for possible iliac vein angioplasty and stenting. The second patient is described as LLE: C4b,5s; $Es_i$; Ad; $Po_{FV,POPV}$. He has lipodermatosclerosis and post-thrombotic obstruction of the left femoral and popliteal veins and is unlikely to be treated surgically. A complete CEAP provides all the information that otherwise would be missed.

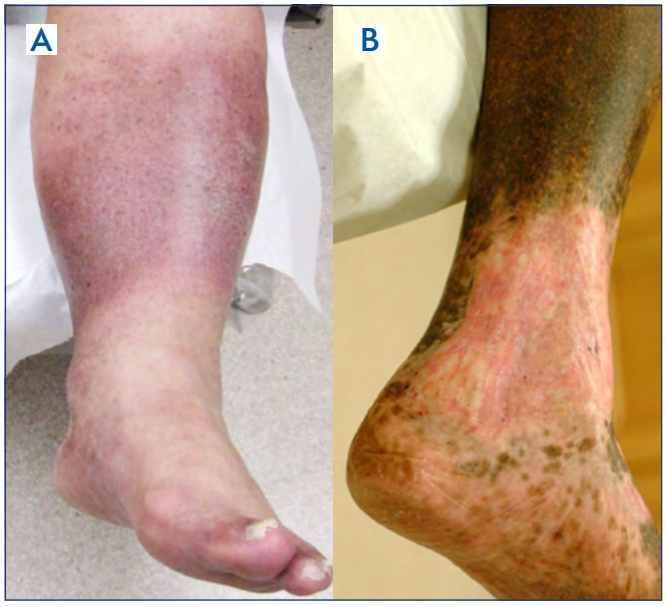


*Figure 1. Left lower extremities (LLE) of two patients who can be described as LLE: C5s; Es; Ad; Po. The complete clinical, etiological, anatomical, and pathophysiological (CEAP) classification for **patient A** is LLE: C3,5s; Ese; Ad; $Po_{CIV}$ (edema and a healed ulcer caused by extravenous obstruction of the left common iliac vein; May-Thurner Syndrome). The complete CEAP classification for **patient B** is LLE: C4b,5s; Esi; Ad; $Po_{FV}$, $Po_{PV}$ (lipodermatosclerosis and post-thrombotic obstruction of the left femoral and popliteal veins).*

## Limitations

As with any other instrument, the CEAP has a number of limitations. Future revisions and updates on the CEAP classification may include some of the proposed modifications that have been rejected by the task force. It may be considered, for example, that some of the CEAP classes should include subcategories for the complications. A sufficient level of evidence is required for such revisions, including establishing the incidence of such complications in each of the specific CEAP classes and how they change the natural history of the CVD.

## Conclusions

Although an imperfect instrument, the CEAP has proven to be an essential tool for practitioners and clinical researchers. Its worldwide utilization since 1996 has contributed to substantial progress in our understanding of CVD and development of new treatment options. Ultimately it has led to improved outcomes in the management of patients with venous disorders. CEAP 2020 is the evidence-based update of the CEAP classification that reflects the progress of the field of phlebology during the last two decades.

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# Use of air plethysmography and ambulatory venous pressure measurement in chronic venous disease

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Keywords:

air plethysmography; ambulatory venous pressure; APG; calf pump; chronic venous disease; quantifying venous reflux; venous pressure; venous reflux.

## Abstract

Air plethysmography (APG) and ambulatory venous pressure (AMVP) measurement are functional tests used in chronic venous disease (CVD). We review our experience with these tests in 8456 CVD limbs seen over a 20-year period. The venous filling index ($VFI_{90}$) parameter in the APG test shows progressive significant worsening as reflux and disease severity increase. Venous volume (W) also increases–a sign of venous pooling–with reflux and disease progression. This is compensated to a large extent by a parallel increase in ejection volume to as much as three times normal. There is little correlation between any of the APG and AMVP parameters. APG is a sensitive test and is abnormal in 70% of a wide spectrum of CVD limbs. AMVP measurement is more selective and abnormal in only 37%. There is an overlap of about 30% between the tests, which increases to 66% in advanced disease. AMVP is seldom abnormal (7%) if APG is normal. Venous refilling time (VFT) is the preferred AMVP parameter, as percentage drop in AMVP is abnormal in only 4% of limbs with normal VFT. Ambulatory venous hypertension is a feature of reflux, not obstruction. In conclusion, APG is a reliable test to assess severity of reflux. AMVP is recommended in advanced CVD as ambulatory venous hypertension indicates end-stage disease.

## Introduction

Duplex ultrasound is the preferred screening test in chronic venous disease (CVD) and in most centers the only test used for evaluation. Air plethysmography (APG) and ambulatory venous pressure (AMVP) measurement, once popular, have gradually declined in use to near extinction. However, these are functional tests based on sound basic physiology. They can provide a more quantitative evaluation of reflux and disease severity than duplex ultrasound alone.

## Techniques

### Air plethysmography

Water plethysmography has been used by physiologists to study calf-pump function and venous flow for many decades. APG is a commercial version of

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plethysmography that popularized its use in the clinical realm. Christopoulos and Nicolaides laid out the technical protocol and parameters for clinical use of this technique in CVD.[1]

The main parameters of interest (shown in *Figure 1*) are the base resting venous volume (VV), venous refilling time ($VFT_{90}$, commonly referred to as venous filling index [$VFI_{90}$]), ejection volume, ejection fraction, and residual volume fraction (RVF).

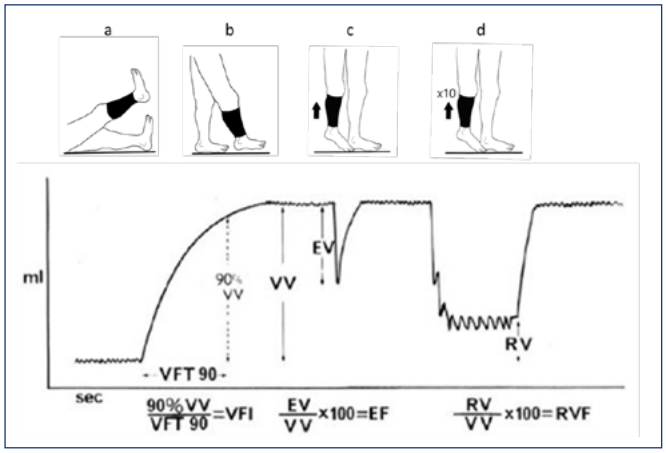


*Figure 1. Components of air plethysmography.*

*EF, ejection fraction; EV, ejection volume; RV, residual volume; RVF, residual volume fraction; VFI, venous filling index; VFT, venous refilling time; VV, venous volume.*

### Ambulatory venous pressure measurement

AMVP measurement is often described as a global test of calf-pump function. This rests on the belief that abnormalities in the complex mechanism that ejects blood from the calf will be reflected in AMVP. Earlier versions of the test used a variety of test protocols. Nicolaides and Zukowski standardized the protocol that has since been widely adopted.[2] Access is obtained through a vein on the dorsum of the foot. It is useful to record supine foot venous pressure at the start, as this measure is informative for assessing venous obstruction. The patient is asked to stand still, holding on to a support and bearing weight on the opposite leg. Resting erect foot venous pressure is measured with the transducer taped to the foot by the needle. The patient is asked to perform 10 tiptoe stands and then resume the resting position. The venous pressure drop (% drop) during exercise and the VFT per second are recorded. A percent drop less than 50% and VFT under 20 seconds are considered abnormal.

## Results

In our clinic, duplex ultrasound is the main screening instrument in CVD. APG is used at the next level as the main hemodynamic instrument. In complex cases, AMVP measurement is used simultaneously with APG (*Figure 2*),[3] as the maneuvers are the same.

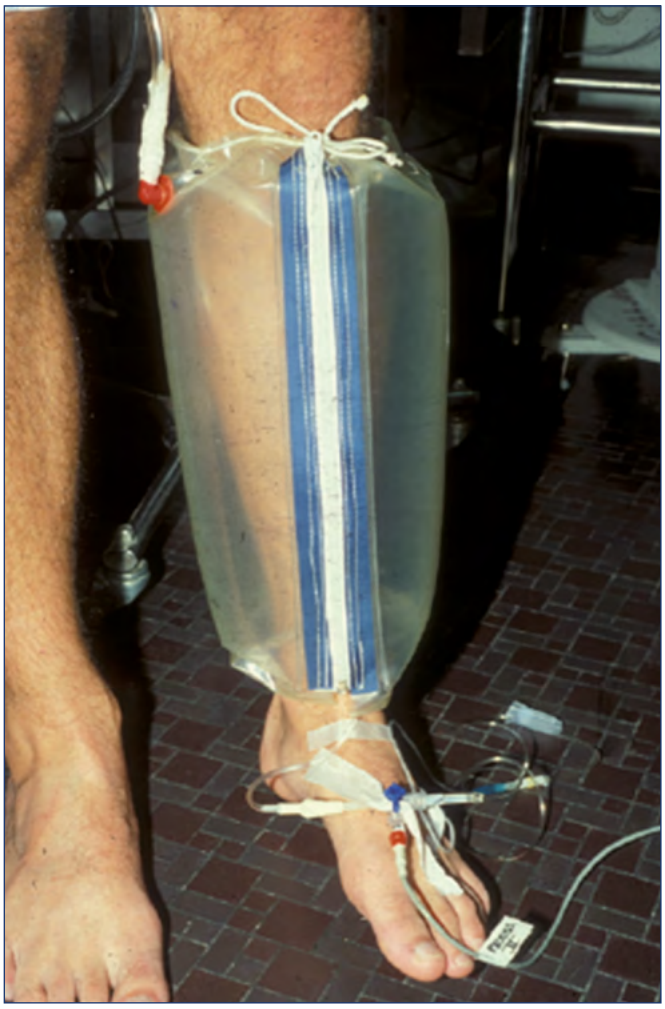

*Figure 2. Air plethysmography (APG) and ambulatory venous pressure (AMVP) measurement can be performed simultaneously, as the tiptoe calf exercise maneuver is the same for both.*

*After reference 3: Raju et al. J Vasc Surg Venous Lymphat Disord. 2019;7(3):428-440. © 2019, Society for Vascular Surgery. Published by Elsevier Inc.*

The results reported below are from an analysis of 8456 CVD limbs in 4610 patients treated over a 20-year period (1995-2016). APG data were available in 7910 limbs; simultaneous APG and AMVP data, in 4766 limbs. Reflux distribution by anatomic system is shown in *Table I*. No reflux was present in 33% of the limbs. Obstruction was evidenced in 967 limbs on the basis of intravascular ultrasound (IVUS) examination.

Main APG and AMVP findings are shown for the dataset, organized by CEAP (clinical-etiology-anatomy-pathophysiology classification; *Table II*), anatomic reflux distribution (*Table III*), reflux segment score (*Table IV*), and Kistner Axial reflux grading (*Table V*).

| Reflux location | Total limbs (n=8456) |
|---|---|
| **No reflux** | **2745 (33%)** |
| **Reflux** | **5711 (67%)** |
| **Superficial only** | 3616 (63%) |
| **Deep only** | 2324 (40%) |
| **Perforator isolated** | 621 (11%) |
| **Superficial & deep** | 1459 (25%) |
| **Superficial, deep, & perforator** | 288 (5%) |

*Table I: Anatomic distribution of reflux* in limbs investigated for chronic venous disease*

** Reflux was defined as reverse flow >1-second duration both for the deep and superficial veins*

| APG parameters (Normal values) | CEAP class 0-2 n=1105 | CEAP class 3 n=4045 | CEAP class 4 n=974 | CEAP class 5-6[a] n=465 |
|---|---|---|---|---|
| **VV** | 90 (0-325) | 87 (0-447) * | 103 (0-240) *** | 100 (0-373) ** |
| **VFI 90 (2.2 cc/s)** | 1.3 (0-18.2) | 1.3 (0-21) | 2.1 (0-21) *** | 2.7 (0-21) *** |
| **RT** | 11 (0-117) | 11 (0-86) | 10 (0-45) | 9 (0-100) *** |
| **AMVP** | **CEAP class 0-2 n=462** | **CEAP class 3 n=2387** | **CEAP class 4 n=606** | **CEAP class 5-6[b] n=270** |
| **% Drop (>50%)** | 74 (18-94) | 76 (5-98)* | 71 (4-95) ** | 63 (15-95) **** |
| **VFT (>20s)** | 40 (15-141) *** | 40 (19-274) | 20 (0-127) *** | 11 (0-84) *** |

*Table II. Air plethysmography and ambulatory venous pressure parameters; median (range) by CEAP class.*

*AMVP, ambulatory venous pressure; APG, air plethysmography; CEAP, clinical-etiology-anatomy-pathophysiology classification; EF, ejection fraction; EV, ejection volume; RT, refill time; RV, residual volume; VFI 90, venous filling index; VFT, venous filling time; VV, venous volume.*

*Note: P vs CEAP classes 0-2: * P≤0.05, ** P≤0.01, *** P≤0.001*

*[a]CEAP classes 5-6 were significantly worse than CEAP class 4 in VFI 90 (P≤0.001), EF (P≤0.001), and RT (P≤0.001). CEAP classes 5-6 were significantly worse than CEAP class 3 in VV (P≤0.001), VFI 90 (P≤0.001), and RT (P≤0.001; and better in EV (P≤0.01), RV (P≤0.001), and RVF (P≤0.05).*

*[b]CEAP classes 5-6 were significantly worse than CEAP classes 3 and 4 in % Drop (P≤0.001), and VFT (P≤0.001).*

| APG parameters (Normal values) | Superficial reflux only (n=3434) | Deep reflux only (n=2197) | Superficial & deep reflux (n=1379) [a] | Superficial, deep, & perforator reflux (n=269) [b] |
|---|---|---|---|---|
| VV | 101 (0-373) | 101 (0-388) | 106 (0-370) * | 126.5 (0-330) *** |
| VFI 90 (2.2 cc/s) | 2.2 (0-21.1) | 2.3 (0-21.1) | 2.7 (0-21.1) *** | 3.8 (0-15.7) *** |
| RT | 10 (0-185) | 9 (0-185) | 9 (0-185) *** | 8 (0-28) *** |
| **AMVP** (Normal values) | **Superficial reflux only (n=2007)** | **Deep reflux only (n=1348)** | **Superficial & deep reflux (n=868) [a]** | **Superficial, deep, & perforator reflux (n=188) [b]** |
| VFT (>20s) | 21 (0-185) | 18 (0-185) | 15 (0-185) *** | 9 (0-99) *** |
| % Drop (>50%) | 70 (4-98) | 67 (6-98) | 65 (6-98) **** | 58 (18-94) **** |

*Table III. Air plethysmography and ambulatory venous pressure parameters; median (range) according to anatomic distribution of reflux.*

*AMVP, ambulatory venous pressure; APG, air plethysmography; RT, refill time; VFI 90, venous filling index; VFT, venous filling time; VV, venous volume.*

**P≤0.05, *** P≤0.001, **** P≤0.0001*

*[a]Compared with superficial reflux only.*

*[b]Compared with deep reflux only.*

| | Segmental score | | | | | | |
|---|---|---|---|---|---|---|---|
| APG parameters (Normal values) | 0 (n=2536) | 1 (n=2623) | 2 (n=1373) | 3 (n=693) | 4 (n=402) | 5 (n=166) | 6 & 7 (n=85) |
| VV | 79 (0-447) | 90 (0-331) *** | 99 (0-388) *** | 104 (0-351) *** | 111 (0-319) *** | 120.5 (11-262) *** | 134 (30-248) *** |
| VFI 90 (2.2 cc/s) | 1 (0-101) | 1.4 (0-21.1) *** | 2 (0-16.6) *** | 2.3 (0-21.1) *** | 3.1 (0-20.5) *** | 4 (0.45-14) *** | 4.3 (0.9-13.9) *** |
| RT | 12 (0-117) | 10 (0-86) *** | 10 (0-185) *** | 9 (0-53) *** | 8 (0-71) *** | 7 (2-42) *** | 7 (1-15) *** |
| **AMVP** (Normal values) | **0 (n=1428** | **1 (n=1439)** | **2 (n=796)** | **3 (n=441)** | **4 (n=256)** | **5 (n=105)** | **6 & 7 (n=60)** |
| VFT (>20s) | 52 (0-274) | 36 (0-155) *** | 24 (0-141) *** | 19 (0-185) *** | 12 (0-99) *** | 10 (0-65) *** | 6 (0 -79) *** |
| % Drop (>50%) | 79 (10-98) | 76 (7-98) **** | 72 (4-98) **** | 69 (6-95) **** | 58 (11-95) **** | 61 (16-93) **** | 44 (17-95) **** |

*Table IV. Air plethysmography and ambulatory venous pressure parameters according to reflux segmental scores median (range).*

*AMVP, ambulatory venous pressure; APG, air plethysmography; RT, refill time; VFI 90, venous filling index; VFT, venous filling time; VV, venous volume.*

** P≤0.05, ** P≤0.01, *** P≤0.001, **** P≤0.0001 (segmental score 1-7 vs 0 segmental score).*

## APG findings

There was a significant stepwise increase in $VFI_{90}$ with increasing clinical and reflux severity, as reflected in these tables. The reflux segment score assigns one point each for the following vein segments if they are refluxive: great saphenous vein, small saphenous vein, femoral vein, deep femoral vein, popliteal vein, posterior tibial vein, and perforator vein; a score of 0 implies no reflux; and a score of 7 implies all segments are refluxive.[4] A similar progressive increase in VV representing venous congestion is also seen in parallel with an increase in $VFI_{90}$. These twin increases are also seen in other tables that use different classifications to grade disease severity.

## AMVP findings

AMVP results in the various categories represented in *Tables II-V* are shown as percentage drop and VFT. AMVP findings are different from APG results in several respects: AMVP abnormalities appear to be less common and more selective; AMVP abnormalities are (generally) found only in more advanced CVD with severe clinical or reflux manifestations. In less severe categories, neither percentage drop nor VFT breaches normal thresholds. In some tables, only the VFT is abnormal, whereas the percentage drop remains within normal parameters. Nevertheless, a general deterioration in AMVP is recognizable with disease progression (eg, see *Table V*). An abnormal AMVP test result is arguably more important than an abnormal APG result, as many believe that there is a pathophysiologic connection between venous hypertension and CVD.

## Relative prevalence

One or more APG abnormalities shown in Figure 1 occurred in about 70% of CVD limbs with reflux; AMVP abnormalities occurred in about 37%–roughly half that observed for APG abnormalities.

Both APG and AMVP were abnormal in about 30% of CVD limbs, which progressively increased to co-occurrence in 66% of the limbs with increasing clinical/reflux severity.

AMVP was abnormal in only 7% of CVD limbs that have normal APG findings. So, APG and clinical/reflux severity can be used to decide when to perform an AMVP test.

Percentage drop in AMVP was almost always abnormal when VFT was abnormal. An abnormal percentage drop occurred with a normal VFT in only 4% of CVD limbs. The AMVP test can be simplified by omitting percentage drop and measuring only the VFT.

## APG/AMVP correlations

There is substantial support in the literature for the usefulness of $VFI_{90}$ to assess reflux severity.[5-7] Support for other parameters provided by the instrument (ejection fraction; RVF) is mixed.[8] Although previously suggested that RVF may serve as a noninvasive measure of ambulatory venous hypertension,[9] with earlier work appearing to support this notion, recent analysis found poor correlation between the two measures (*Figure 3*).[3] There is little correlation between APG and AMVP parameters, considered loosely

| APG (normal values) | Grade 0 (n=5631) | Grade 1 (n=245) | Grade 2 (n=632) | Grade 3 (n=239) |
|---|---|---|---|---|
| VV | 87 (0-447) | 112.5 (0-322) *** | 109 (15-388) *** | 109 (11-284) *** |
| VFI 90 (2.2 cc/s) | 1.3 (0-101) | 2.2 (0-15) *** | 3 (0-20) *** | 3.7 (0-14) *** |
| RT | 11 (0-185) | 10 (0-26) *** | 8 (1-81) *** | 7 (1-23) *** |
| **AMVP (normal values)** | **Grade 0 (n=3157)** | **Grade 1 (n=139)** | **Grade 2 (n=415)** | **Grade 3 (n=172)** |
| % Drop (>50%) | 77 (4-98) | 65 (15-98) **** | 64 (6-95) **** | 56 (11-95) **** |
| VFT (>20s) | 40 (0-274) | 16 (0-120) *** | 17 (0-120) *** | 9 (0-79) *** |

*Table V. Air plethysmography and ambulatory venous pressure parameters; median (range) according to Kistner's reflux1 classification.*

**** P≤0.001, **** P≤0.0001*

*Grade 0, no reflux; Grade 1, reflux to the thigh; Grade 2, reflux below knee; Grade 3, reflux to ankle.*

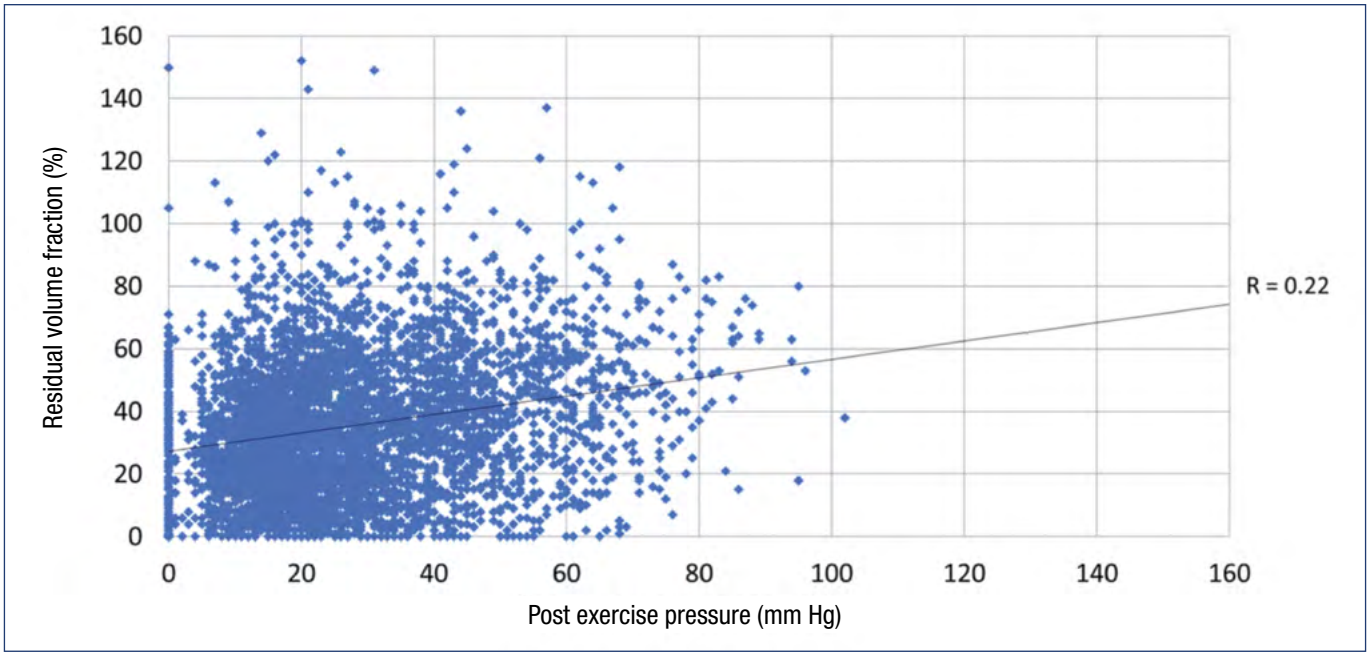


*Figure 3. There is poor correlation between residual volume fraction (RVF) and post exercise pressure in 7877 chronic venous disease (CVD) limbs (R=0.22). This is due to the nonlinear relationship between volume and pressure in veins. Air plethysmography (APG) and ambulatory venous pressure (AMVP) measurement each measure different parameters in different domains. APG and AMVP abnormalities also appear to occur in different populations of CVD limbs. See text.*

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as surrogates (*Table VI*). This is not surprising as the two techniques measure different physical properties in different parts of the leg (*Figure 4*).[3] A significant correlation would require a linear volume/pressure relationship, known not to exist in veins.

| APG/AMVP parameters | R-value |
|---|---|
| VV vs Base Pressure | 0.22 |
| VFI 90 vs VFT | 0.3 |
| EV vs % Drop | 0.1 |
| EF vs VFT | 0.09 |
| RT vs VFT | 0.31 |
| RVF vs % Drop | 0.24 |
| VFI 90 vs % Drop | 0.2 |
| VV vs VFT | 0.14 |
| RVF vs VFT | 0.11 |
| RVF vs AMVP | 0.22 |

*Table VI. Correlations (R-value) between Air plethysmography and ambulatory venous pressure parameters*

*AMVP, ambulatory venous pressure; APG, air plethysmography; EF, ejection fraction; EV, ejection volume; RT, refill time; VFI 90, venous filling index; RVF, residual volume fraction; VFT, venous filling time; VV, venous volume.*

*Figure 5* shows ejection volume plotted against venous volume (VV) in a large cohort of CVD limbs.[3] As the VV increases with advancing disease, so does the ejection volume with a high degree of correlation (r=0.7), increasing its output two to three times, keeping up with the increase in VV. This powerful compensatory mechanism tends to maintain a normal RVF (<50%) even in severe reflux categories. VV was normal in groups shown in *Tables II-V* including in the worst categories. This refers to means, not individual cases.

Calf ejection is known to be compromised by mechanical deficiencies of the calf pump, such as joint immobility or neuromuscular calf-muscle disease.[10-12] A "calf-pump failure" of a different sort, one that is functional rather than mechanical has been frequently mentioned in the literature. The definition of calf-pump failure has varied from a reduction in ejection fraction to the more often used increase in RVF. It is possible to define four different groups using different combinations of normal and subnormal ejection fraction and RVF as shown in *Table VII*. Mean values and prevalence of APG and AMVP parameters in those categories are also shown. Isolated RVF abnormality appears to be rare. A combination of reduced ejection volume and increased RVF (Group 4) occurs more often,

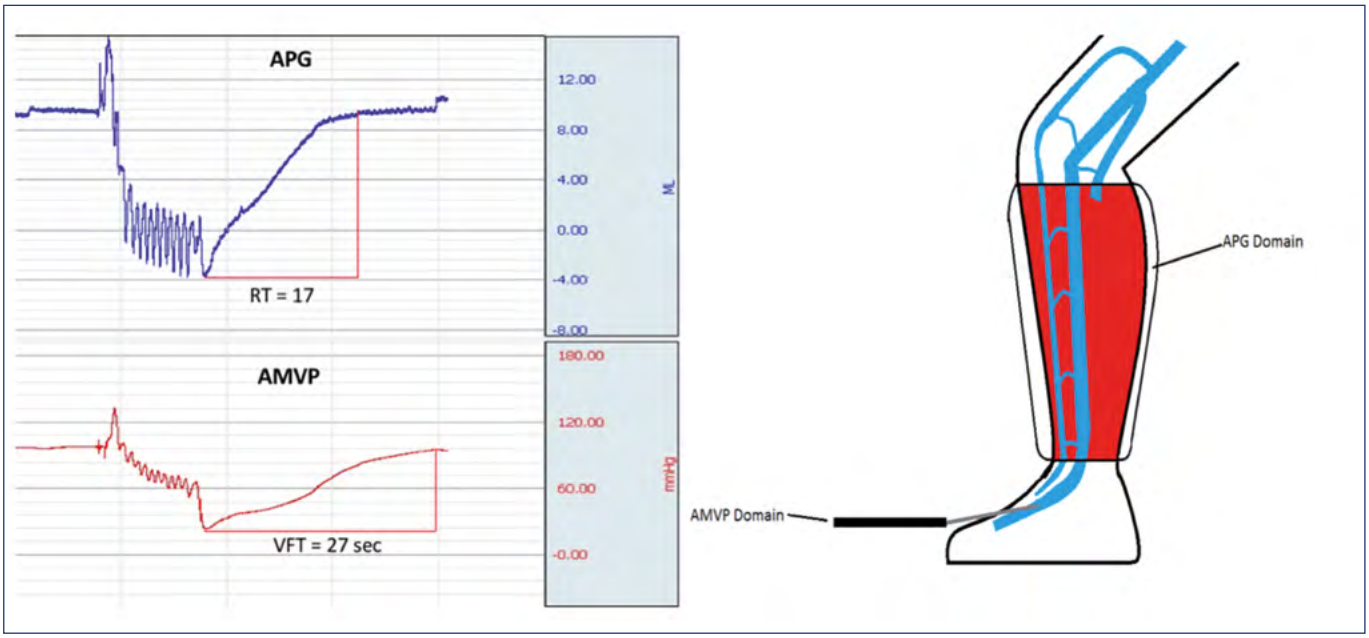


*Figure 4. Air plethysmography (APG) measures volume-related parameters in the calf, while ambulatory venous pressure (AMVP) measurement indicates pressure-related parameters in the axial flow channel (right panel). The flow channel volume is <5% of the calf volume. The calf volume, though larger, refills faster (refill time, RT) before refill of the axial flow channel is complete (venous refilling time, VFT) as shown in the left panel. The two tests (APG and AMVP) operate in different anatomic and hemodynamic domains. The volume-pressure curve is necessarily an intermediary between the two. Note also that abnormalities in the two tests have different distribution in Venn diagrams. See text.*

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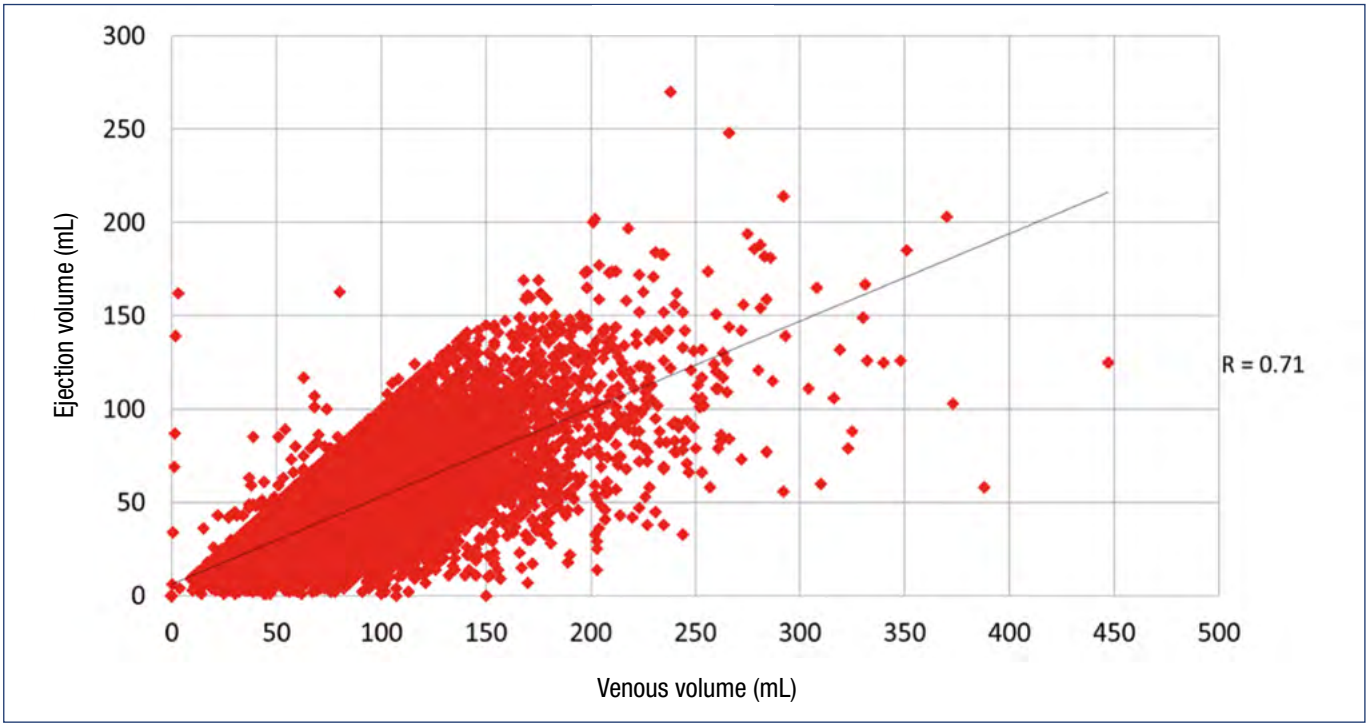


*Figure 5. Correlation between ejection volume (EV) and venous volume (VV) in 7877 chronic venous disease (CVD) limbs (R=0.71). The calf pump appears adaptable to pump a wide range of volumes presented to it. In the figure shown above, EV ranges up to 150 mL, or three times normal (50 mL). The higher the calf venous volume, the higher the EV with good linear correlation.*

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| AMVP parameter (Normal values) | Group 1 Normal EF & RVF (n=1992) | Group 2 Normal EF & Abnormal RVF (n=80) | Group 3 Normal RVF & Abnormal EF (n=1083) | Group 4 Abnormal EF & RVF (N=865) |
|---|---|---|---|---|
| **% Drop (>50%)** | 77 (19-97) | 76 (9-95) * | 74 (12-98) **** | 67 (4-96) **** |
| **VFT (>20s)** | 35 (0-274) | 25.5 (0-120) | 36 (0-145) | 21 (0-155) *** |
| **VENN Abnormal incidence** | 0% | 11% | 19% | 10% |

*Table VII. Ambulatory venous pressure, median (range) and abnormal incidence (VENN) in calf-pump failure.*
*AMVP, ambulatory venous pressure; EV, ejection volume; RVF, residual volume fraction; VFT, venous filling time.*
** P≤0.05, *** P≤0.001, **** P≤0.0001 (Group 1 vs Group 3 & 4)*
*Normal EF is ≥50%; Normal RVF is ≤50%; Abnormal EF is <50%; Abnormal RVF is >50%.*

but an overall clear pattern is not visible. Group prevalence of AMVP abnormality was also worst in Group 4. Further clarification in this area is needed.

Nicolaides has pointed out that with each calf-pump action, a portion of reflux volume will be retained, adding to RVF. Ejection fraction seldom is higher than 75% even with very efficient calf ejection; an ejection fraction approaching 100% would be required to completely prevent reflux-volume accumulation.[13]

## Venous obstruction

There is general agreement that APG evaluation according to the standard protocol provides little diagnostic information of value in venous obstruction. A new protocol described by Lattimer has drawn considerable interest. It is undergoing evaluation in several centers.[14]

It is commonly assumed that venous obstruction is associated with ambulatory venous hypertension. AMVP abnormalities

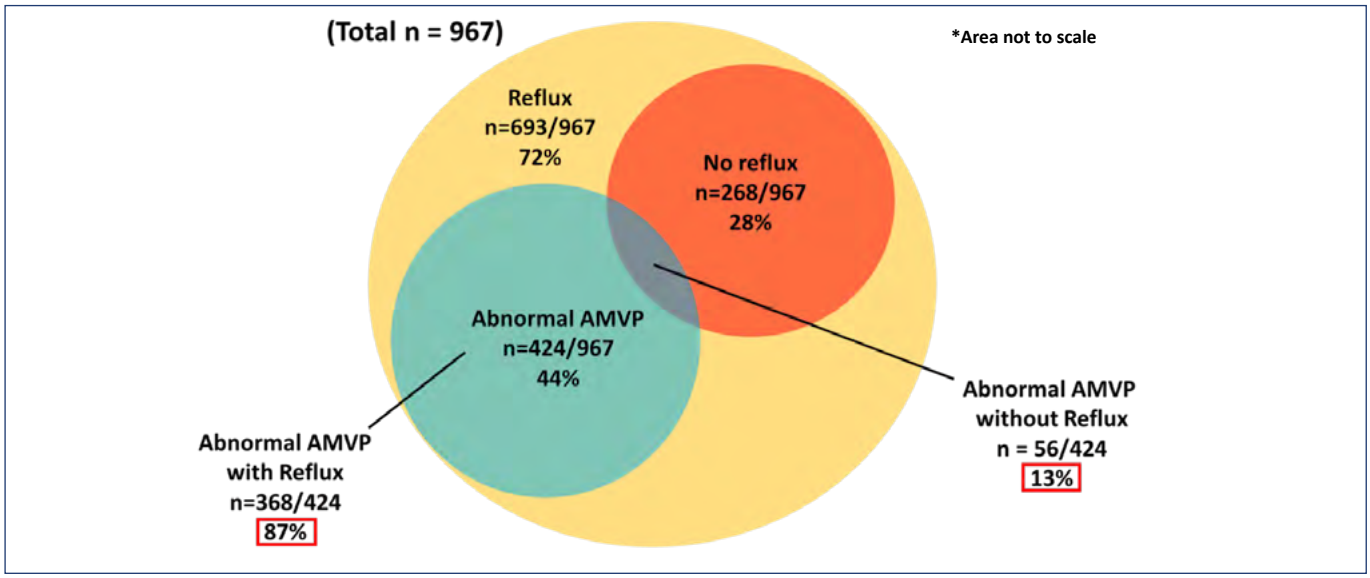


*Figure 6. Of limbs with intravascular-ultrasound–proven obstruction, 72% had reflux and 28% did not. Abnormal ambulatory venous pressure (AMVP; % drop and/or VFT) was present in 44% of the obstructed limbs. The overwhelming majority (87%) occurred in association with reflux in obstructed limbs. The incidence of AMVP abnormalities was small (13%) in obstructed limbs without reflux. *Area not to scale.*

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were observed in IVUS-proven obstruction (generally) only in cases where associated reflux was present (*Figure 6*).[3] Ambulatory venous hypertension largely appears to be a property of reflux, not obstruction. Curiously, resting foot venous pressure in the erect position is also elevated, likely related to partial erasure of arteriolar-venous reflux in CVD.[15] Elevated supine venous pressure appears to be associated with obstruction, not reflux.[15]

## Conclusion

APG is a reliable functional test for assessing severity of reflux, whereas AMVP measurement is recommended in the setting of advanced CVD, as ambulatory venous hypertension indicates end-stage disease.

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# What is the best method of imaging in iliofemoral venous obstruction?

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Keywords:

color Doppler ultrasound; computed tomographic venography; iliofemoral deep-vein thrombosis; iliofemoral venous obstruction; magnetic resonance venography; post-thrombotic syndrome

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## Abstract

Iliofemoral venous obstruction is increasingly recognized as a major cause of post-thrombotic syndrome. Patients can be left with significant symptoms after just one episode of iliofemoral deep-vein thrombosis; ranging from milder problems, such as varicose veins, to itching, leg swelling, and even venous ulceration. With the advent of endovascular techniques to reconstruct the iliofemoral segment has come an understanding that accurate recognition and diagnosis form a central part of the puzzle. Clinical evaluation is limited, and imaging has assumed a central role. This article looks at the optimal method for imaging the iliofemoral venous segment.

## Introduction

Iliofemoral venous obstruction (IF-VO) has emerged as one of the principal causes of lower extremity post-thrombotic syndrome (PTS), following iliofemoral deep-vein thrombosis (IF-DVT).[1]

A landmark study by Tom O'Donnell and Norman Browse in 1977 detailed the socioeconomic effects after IF-DVT; it demonstrated that 50% of men were unable to hold down a job just 5 years after IF-DVT, and after 10 years the majority had venous ulcers.[2] Adherence to anticoagulation treatment, the clinical efficacy of the newer anticoagulants, and the use of compression stockings (the latter have come under scrutiny after the large SOX trial [Compression Stockings to Prevent Post-Thrombotic Syndrome][3]) have all somewhat improved this dismal outcome; nonetheless, the morbidity from this condition is severe. The majority of post IF-DVT patients who go on to develop venous ulceration typically pass through the following stages (although the order may vary): venous claudication, weight gain, development of varicose veins, skin changes, and eventually venous ulceration. The first two problems are not captured at all by current clinical methods for evaluation of venous problems.[4,5] It is fairly obvious that one of the reasons patients continue to do so poorly clinically is that we are identifying patients much too late in their clinical trajectory–when they already have established PTS as opposed to earlier in its course. There is a mindset among physicians that all DVTs result in similar outcomes for patients, and the ATTRACT trial (Acute

Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) did not help to alter this perception.[6,7]

Over the last quarter of a century, the advent of endovascular stenting has meant that there are now treatment options that are less invasive than an open surgical procedure to bypass the affected area.[8-11] Therefore, there is increasing interest in identifying the best imaging options to identify this critical condition at an earlier stage in their disease trajectory.[12-16] *Table I* shows advantages and disadvantages of various imaging modalities.

| Imaging modality | Advantages | Disadvantages |
|---|---|---|
| Ultrasound | Cheap, radiation free, quick, real time, enables physiological parameters to be measured | Superb below the groin<br>Much more difficult above the groin particularly with increasing levels of obesity |
| Computed tomography | Quick, reproducible, accurate, excellent "rule-out" test | Uses ionizing radiation<br>Uses iodinated contrast |
| Magnetic resonance venography | Radiation free<br>Multiplanar<br>Superb image resolution<br>Can be performed with and without contrast | Time consuming<br>Limited availability<br>Despite impressive advances, still not widely used.<br>Significant artefact from stents<br>Cannot reliably identify in-stent restenosis |
| Intravascular ultrasound | Considered the gold standard for intraoperative measurement of venous stenosis | Invasive- 9F sheath<br>Cost |
| Venography | Identification of collaterals<br>Flow rate | Invasive<br>Employs radiation<br>Easily misses subtle lesions |
| Isotope scintigraphy | Cheap, does show evidence of flow | Probably obsolete now<br>Time consuming |

*Table I. Advantages and disadvantages of imaging modalities for evaluating venous segments in post-thrombotic syndrome.*

## Ultrasound

Color Doppler ultrasound (CDUS) by skilled operators is an excellent method (*Figure 1*). Although identification of occluded iliofemoral venous segments on its own may be difficult, CDUS is certainly excellent in identifying physiological flow issues below it, in terms of lack of respiratory variability and lack of response to augmentation.[17-19]

With IF-VO, the external iliac or common femoral vein Doppler waveform is typically flat and shows minimal to no change during respiration, deep Valsalva or a Müller maneuver (*Figure 2*).[20]

Often, the most useful aspect of ultrasound is the ability to compare one side with the other. In a patient with an occluded left iliofemoral venous segment, the right side will typically have grown to accommodate the extra flow, and then by comparison, the left will clearly be abnormally small. Obviously, this becomes more important in subtle

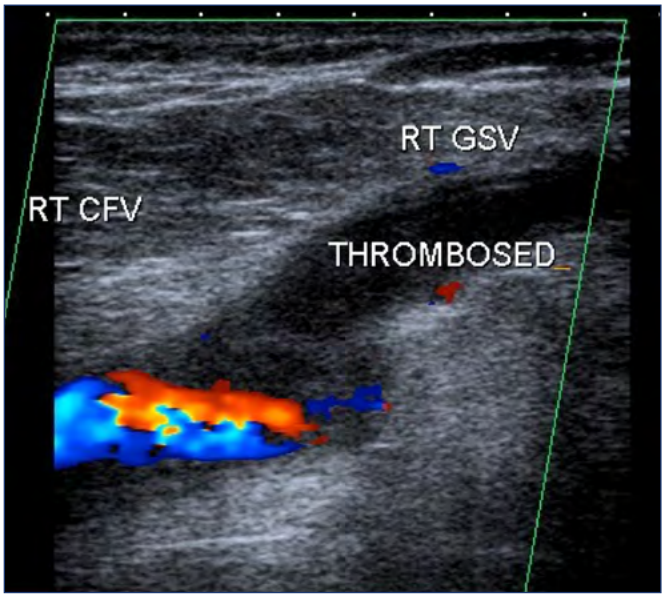


*Figure 1. Longitudinal ultrasound image demonstrating color flow in the main section of the right common femoral vein (RT CFV) and thrombosis extending from the right greater saphenous vein (RT GSV) just into the CFV.*

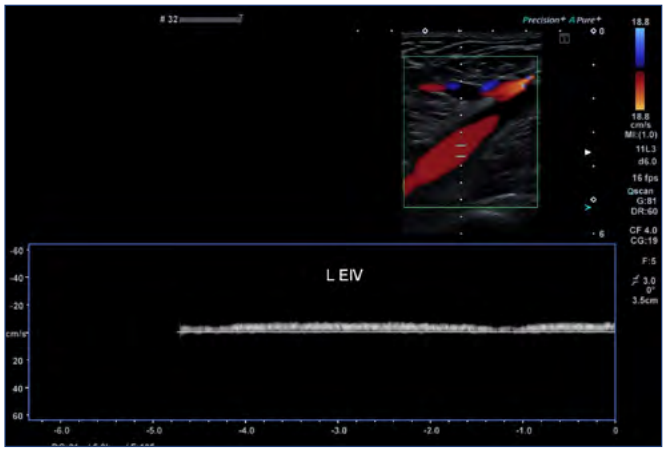


*Figure 2. Although there is normal color flow in the left external iliac vein (L EIV), the Doppler signal suggests otherwise–note the flat tracing with minimal to no respiratory variability. There is a more central inferior vena cava (IVC) and iliac venous obstruction. Ultrasound demonstrates physiological changes as well as simple anatomical abnormalities.*

lesions, where the discrepancy from side to side may well be less obvious. In slim patients and in skilled hands, it is *the* method of choice and should be used in every patient as an initial screening tool. If it is clearly normal, then the patient may not require any further investigation. If abnormal, the patient *may* require further investigation depending on symptoms, etc. Ultrasound is operator dependent, and if not personally performed by the endovascular specialist, the sonographer needs a special understanding of precisely what the specialist requires (inflow, outflow, potential access sites, etc). This information may not typically be obtained during a standard lower-limb venous ultrasound, which for obvious reasons, tends to concentrate on reflux more than obstruction. Comparison between sides (right groin vs left groin) and identification of the profunda femoris vein (*Figure 3*) are both often neglected unless specifically requested.

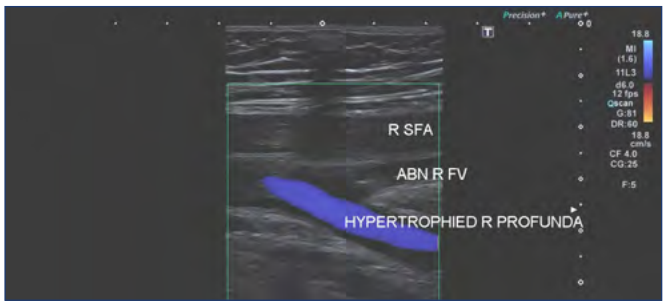


*Figure 3. Previous right iliofemoral deep-vein thrombosis with extension into the right femoral vein. Note the compensatory hypertrophy of the profunda femoris vein.*

*Abbreviations: ABN R FV, abnormal right femoral vein; R SFA, right superficial femoral artery; hypertrophied R profunda, hypertrophied (enlarged) right profunda femoris vein.*

Ultrasound is the imaging modality of choice in follow-up of previously stented areas because the stent segment can usually be identified with certainty (unlike in unstented iliac veins) and, obviously, it is radiation free. The evaluation of in-stent restenosis is also possible (*Figure 4*) with this method, and it is the most practical for performing serial follow-up on patients.[21] Computed tomographic (CT) venography (discussed below), which provides excellent data, might be considered–but not repeatedly–because of its high radiation dose. Magnetic resonance (MR) venography (discussed below) achieves variable results depending on the composition of the stented segment; ie, those stents with less stainless steel give rise to less artefact, and thus MR venography may be somewhat useful, whereas with those stents containing more stainless steel, the signal drop out means that establishing stent patency is not possible. In-stent restenosis cannot currently be quantified on MR venography, whereas it is possible on CT venography and CDUS.

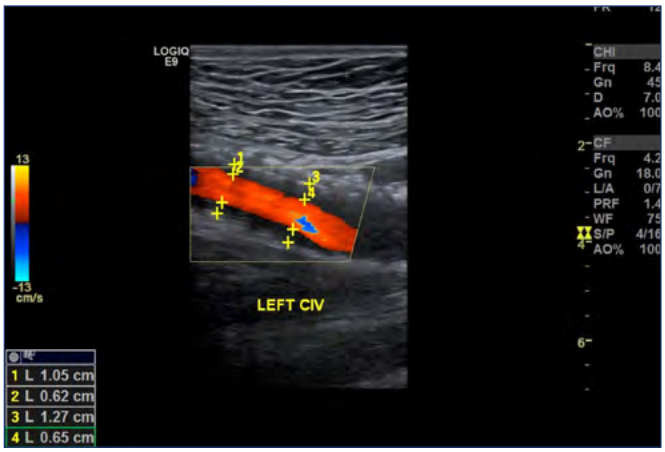


*Figure 4. The degree of in-stent restenosis after iliac venous stenting can be quantified: (1.05-0.62)/1.05=40.9% stenosis. This patient was symptomatic with recurrent venous claudication at this time.*

*Abbreviations: CIV, common iliac vein.*

## CT venography

CT venography is probably the most widely used imaging modality for investigation of iliofemoral and inferior vena cava pathology worldwide. It is quick, simple, reproducible, and most radiologists are comfortable interpreting it. CT venography may be divided into "indirect CT venography" and "direct CT venography."[22-25]

***Indirect CT venography*** is the more commonly used modality; the aim is to achieve systemic levels of opacification. This is performed by injection through a

peripherally sited IV cannula (arm, usually) at a rate of 3 cc to 5 cc/sec, typically with 100 to 150 cc of iodinated contrast at a delay of 60 to 120 seconds depending on cardiac output and the rate of injection.

Indirect CT venography is excellent for evaluation of acute deep-vein thrombosis to "rule- out" swollen legs (if normal, the deep venous system is unlikely to be at fault; this is especially so in bilateral lower-extremity swelling), in malignancy,[26] and during stent follow-up in certain patients in whom CDUS is difficult (scarring/obesity, etc). However, if patients' symptoms are unremitting or otherwise inexplicable with a "normal" indirect CT venography, we have learned to favor either direct CT venography or intravascular ultrasound (IVUS) (*Figures 5-7*).

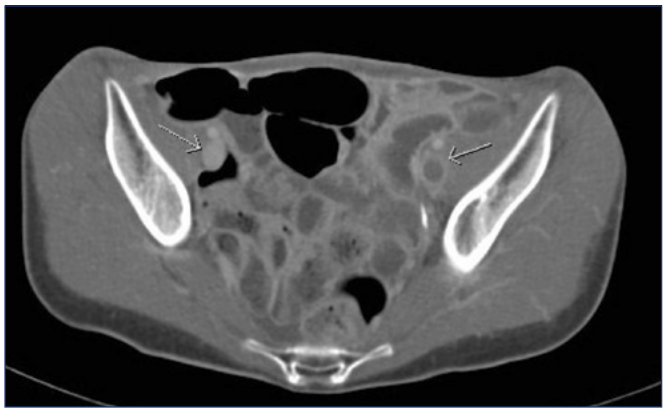

*Figure 5. Indirect computed tomographic (CT) venography. Acute left iliofemoral deep-vein thrombosis; note the difference in attenuation between the two sets of external iliac veins.*

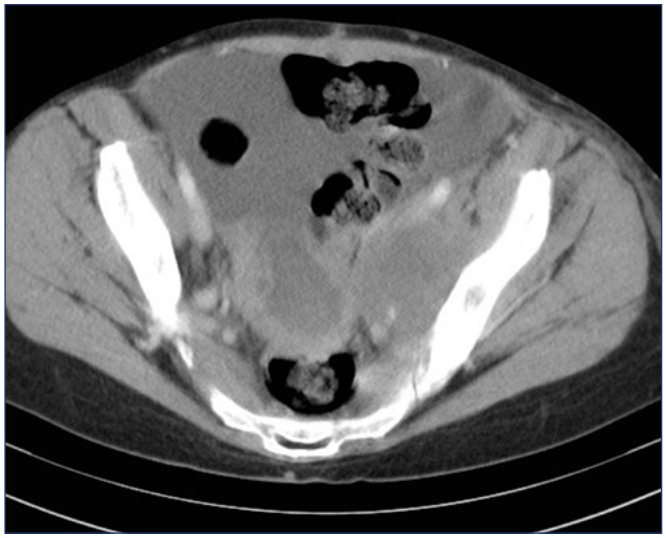

*Figure 6. Indirect computed tomographic (CT) venography. Large centrally necrotic midline pelvic mass with nearly confluent left external iliac vein lymph node mass: compare external iliac veins–right normal; left stretched over lymph node.*

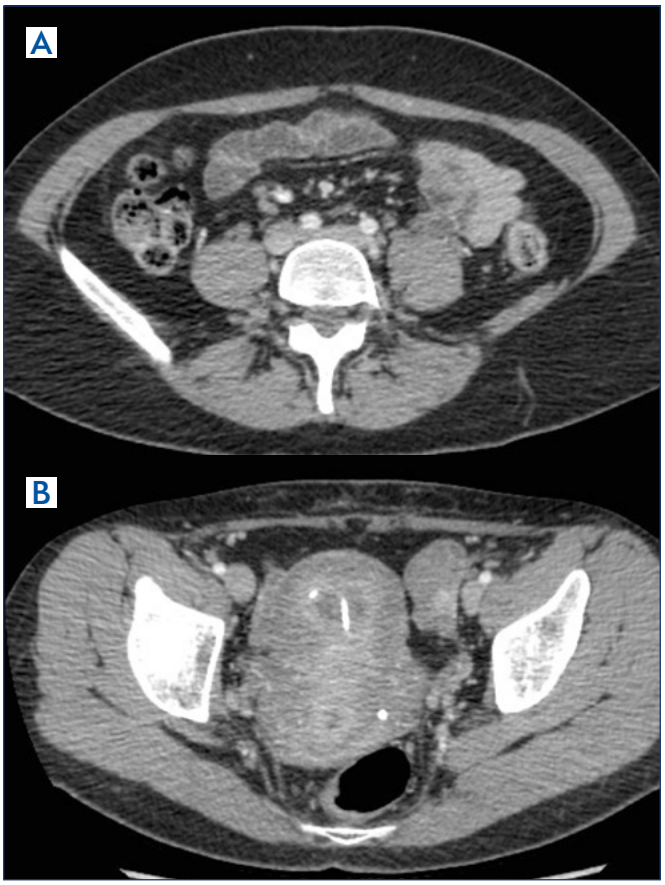


*Figure 7. A) Indirect computed tomographic (CT) venography. Left iliac system appears nearly the same as the right. B) Unremitting symptoms prompted us to perform a direct CT venography.*

***Direct CT venography*** is performed by injection of contrast into the affected limb, typically into the foot (*Figures 8-9*). The purpose of direct CT venography is to achieve a high level of contrast concentration in the venous system of the affected extremity; essentially, a "venous angiogram" can be obtained and therefore multiplanar reformats (MPRs) and maximum intensity projection (MIPs) images can be performed on the data set required.

Direct CT venography was first shown to us by the experts from Grenoble, France; it was a "Road to Damascus" moment; we immediately realized this would be an extremely useful technique in the investigation of patients with post-thrombotic venous obstruction prior to venous reconstruction.[27] In fact, it has proven to be exactly this; namely, it identifies which of the veins leading into the common femoral venous "sump" carries the most blood, what we call the "dominant inflow"; we believe this is critical for planning ahead of endovascular reconstruction, in that subsection of post IF-DVT patients whose scarring extends down to the common femoral vein or below.[28]

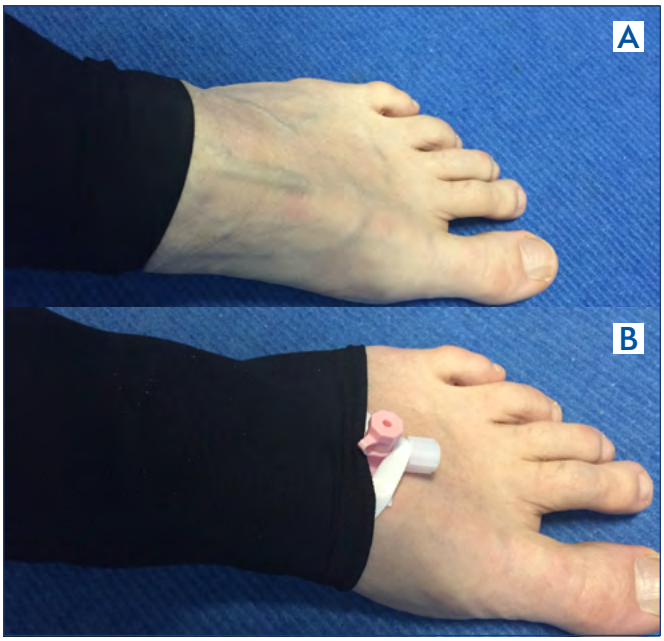


*Figure 8. How to perform a direct computed tomographic (CT) venography. A) Roll up the Class 2 compression stocking to expose a vein. B) Place 20G IV cannula with injection port into vein; tape it down; roll stocking back over the IV cannula. It is now ready for injection.*

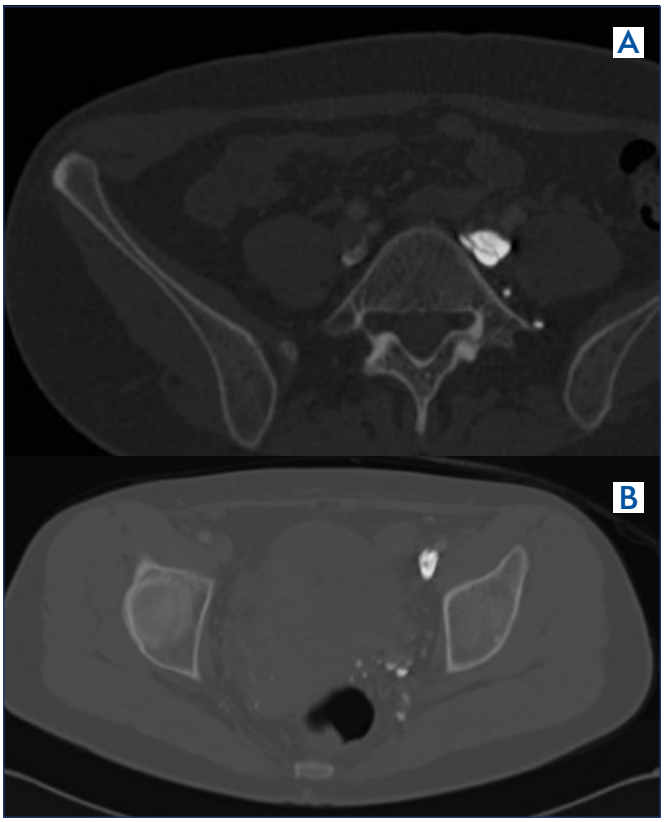


*Figure 9. A and B) Note synechiae/scars inside the vein lumen in same patient from Figures 7 A and B, which was read as "normal."*

We reserve direct CT venography for those patients whom we consider potential candidates for endovascular reconstruction, ie, their symptoms need to merit it (significant venous claudication, severe weight gain related to same, venous ulceration).

## Magnetic resonance venography

MR venography is now finally achieving the prominence it deserves in investigation of the iliofemoral venous segments.[16,29-32] The techniques have improved considerably in the last decade and it has gone from being a cumbersome, slow, poorly performed, and difficult-to-reproduce technique to one that is now achieving mainstream acceptance and applicability. It offers huge advantages in terms of lack of radiation and lack of iodinated contrast. With increasing knowledge, it will, in my opinion, become the go-to method for investigation of IF-VO. In certain centers, it has already achieved that distinction, and the images acquired are excellent in terms of spatial resolution, identification of scarring, wall thickness, intraluminal synechiae, and so on.

The technique for performing MR venography is beyond the scope of this chapter. Interested readers are directed toward the references; it does require an interested and expert radiologist, as well as well-trained radiographic staff and top-of-the-line machines with the appropriate coils and software algorithms to produce diagnostic images. Many patients undergo MR imaging; as yet, unfortunately, relatively few patients have a good quality MR venogram (*Figures 10, 11*).

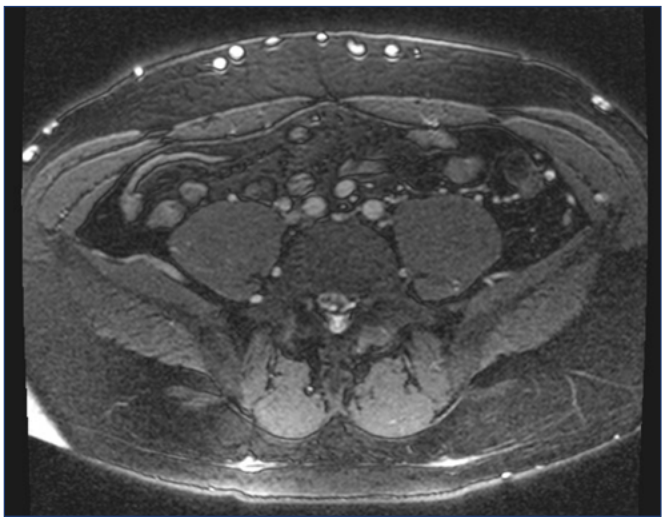

*Figure 10. Magnetic resonance venography. Note multiple collaterals along the skin's surface. The common iliac arteries are readily identified, but the veins are occluded and not seen.*

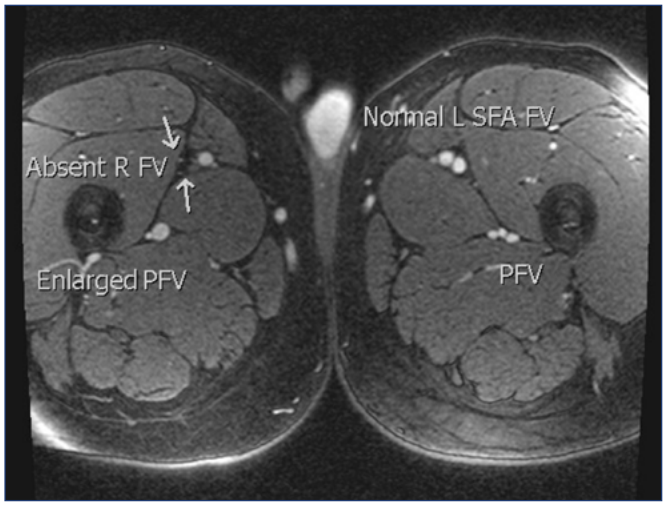


*Figure 11. Magnetic resonance venography is the best noninvasive imaging modality; in many centers, it is already the dominant modality. It provides excellent anatomical detail and uses zero radiation. Sequences are becoming faster.*

*Abbreviations: PFV, profunda femoris vein; R FV, right femoral vein; SFA FV, superficial femoral artery, femoral vein.*

## Intravascular ultrasound

IVUS is an invasive technique that provides superb imaging of the internal lumen and surrounds of the iliofemoral venous system. IVUS has been around for quite some time,[33,34] and its use has been extensively documented in the coronary circulation and more recently in both the venous and arterial systems. In some ways it was a technique looking for a "home," but it has most assuredly found that in the iliofemoral venous segment, as well as through much of the peripheral vasculature, particularly to guide therapy.[35] It offers huge advantages in terms of identification of luminal problems that are not readily seen on venography, even multiplanar venography.[36-38]

The VIDIO trial (Venogram vs IVUS for Diagnosing Iliac vein Obstruction)[38] has demonstrated quite eloquently that IVUS changes the decision algorithms in a significant percentage of patients, and it is far superior even to multiplanar venography in identifying subtle lesions. It is fair to say that in patients with marked obstruction–for instance, due to tumor compression–IVUS may not be required (*Figure 12*); nonetheless, it improves many aspects of endovascular reconstruction, including stent diameter, stent length, and accurate identification of landing zones; post treatment, it can confirm adequate wall apposition and expansion as well as measure the stent diameter and area (*Figure 13*). In the future, it will almost certainly provide physiological data in the same way that standard transabdominal ultrasound currently offers, demonstrating Doppler characteristics as well as color flow.

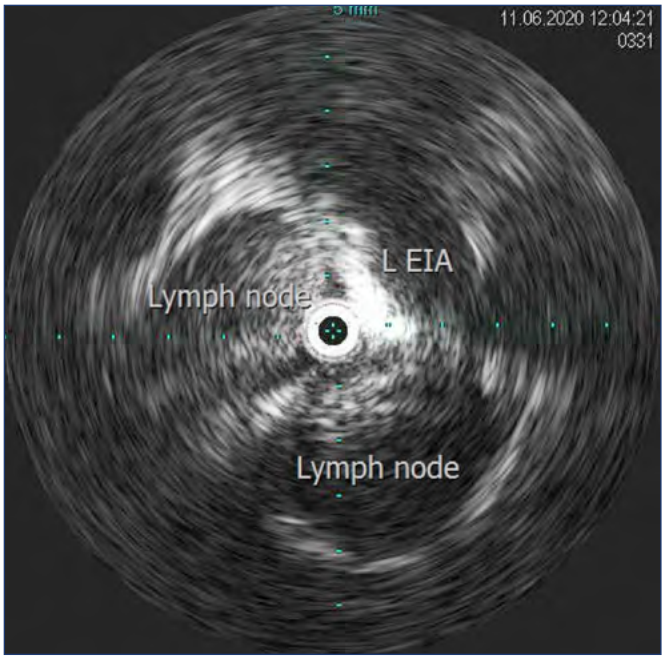


*Figure 12. Intravascular ultrasound (IVUS) demonstrating compression of the left external iliac vein by surrounding lymph nodes.*

*Abbreviation: L EIA, left external iliac artery.*

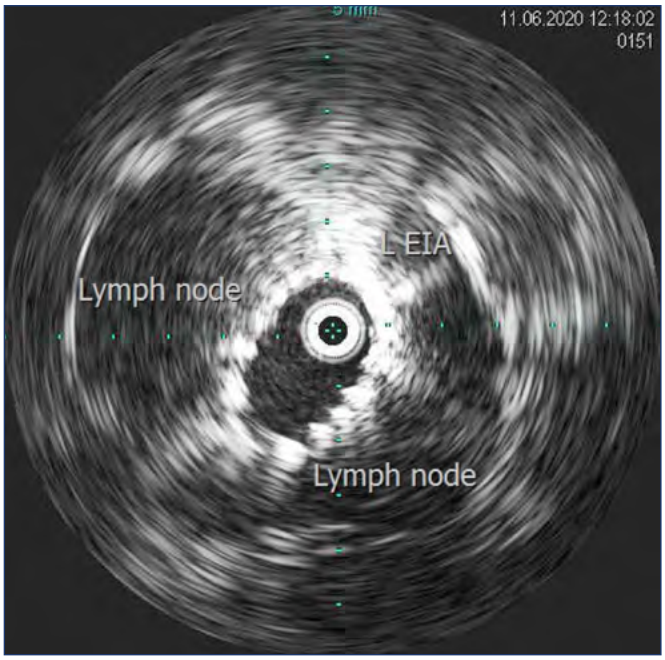


*Figure 13. Same patient post stent placement; lymph nodes have been pushed aside and stent expansion is confirmed; area can be measured.*

*Abbreviation: L EIA, left external iliac artery.*

## Venography

Venography for many years was the gold standard in identification of iliofemoral venous pathology but has gradually been replaced by cross sectional methods and now by IVUS. It is still very useful for identifying flow rate during a procedure, but more skill is required in identification of more subtle characteristics, in particular, subtle compression of the vein in an anteroposterior fashion, which can easily be missed even by the experienced observer unless a lateral projection is equally obtained.

For this reason, it is mainly reserved simply for identification of the correct path to follow during iliofemoral venous reconstruction, (*Figure 14*) and obliques are often essential for this. After stent placement, demonstration of rapid inline flow with abolition of collaterals is an excellent marker of success (*Figure 15*). Most experienced workers in this field do not perform catheter venography as a preoperative imaging investigation.

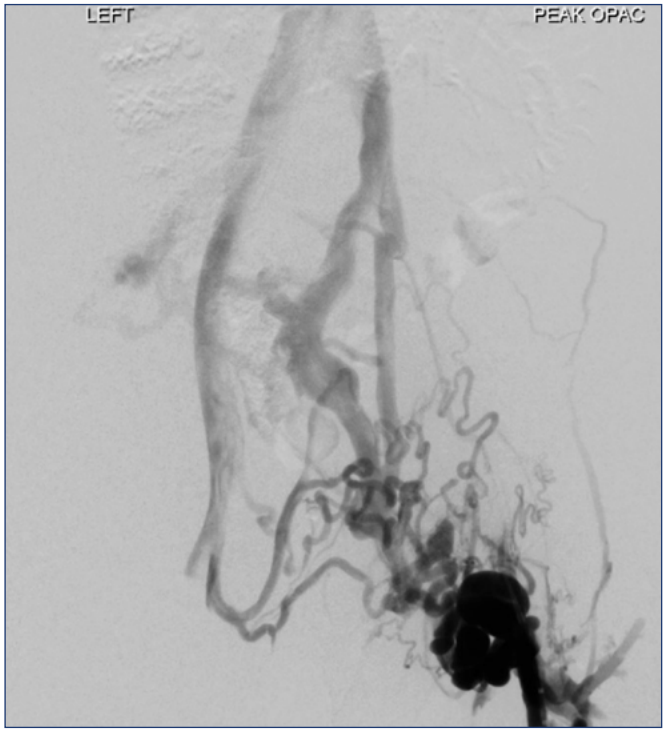


*Figure 14. Initial venogram in left groin showing large collaterals and no in-line flow from left common femoral vein to inferior vena cava.*

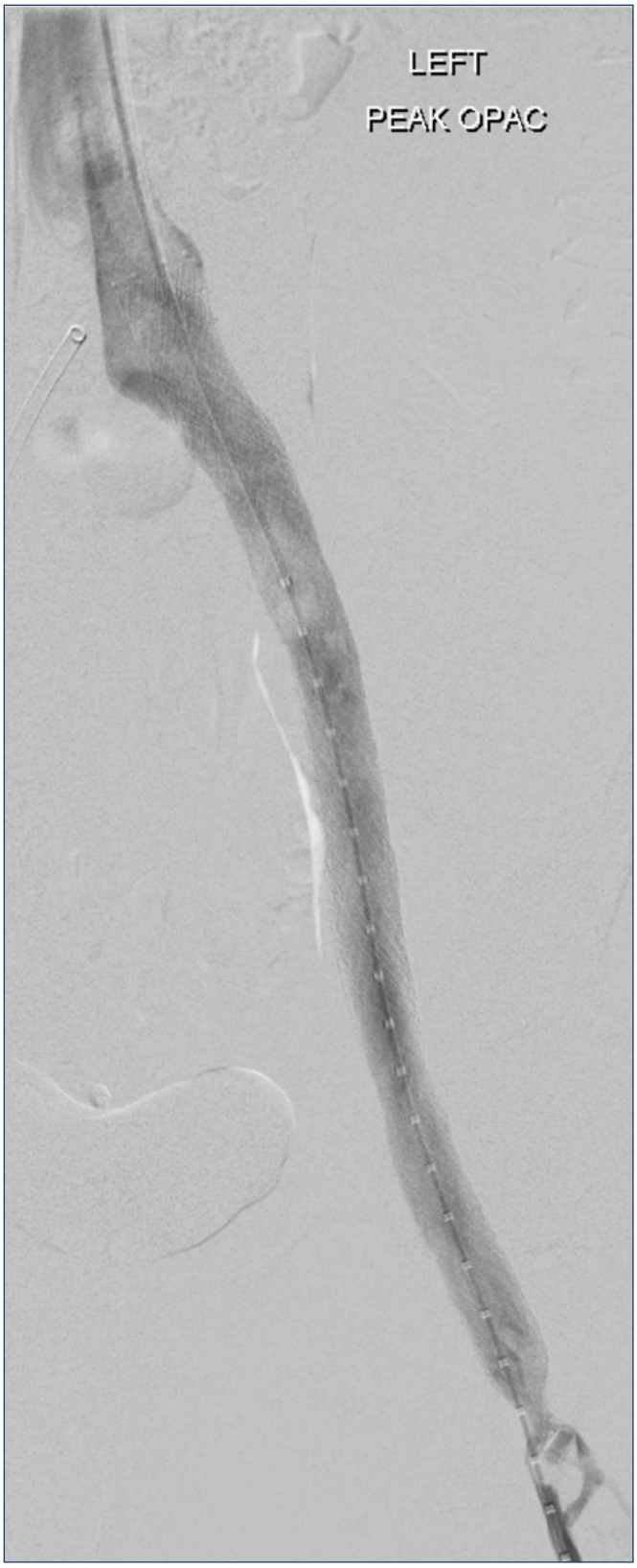


*Figure 15. Completion image demonstrating perfect in-line flow from left common femoral vein (LCFV) to inferior vena cava (IVC); abolition of collaterals, rapid passage of contrast.*

## Conclusion

We are fortunate to have so many excellent methods of imaging of the iliofemoral venous segment. Currently, CT venography is probably the work horse, but in experienced centers, MR venography is already, rightfully, taking over this role owing to its many advantages.

Intraoperatively, a combination of IVUS and venography is the current ideal combination, whereas post operatively, follow-up of the patient with ultrasound appears the most prudent and sensible option.

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# Effectiveness of micronized purified flavonoid fraction–based conservative treatment in chronic venous edema

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Keywords:

chronic venous edema; chronic venous insufficiency; CEAP class C3; micronized purified flavonoid fraction; MPFF

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## Abstract

**Aim:** This study assessed the effectiveness of micronized purified flavonoid fraction (MPFF)-based conservative treatment in patients with chronic venous edema (CVE) as part of an observational program that evaluated the management of patients with CVE caused by the primary forms of chronic venous disease (CVD) in real clinical practice. **Materials and methods.** The VAP-C3 (Vein Act Prolonged-C3; NCT03722836) prospective, single-arm, observational study was conducted in Russia in adult outpatients with CVD of CEAP (clinical-etiological-anatomical-pathophysiological) class C3EpAsPr (CVE). Patients' CVD symptoms, symptom severity, characteristics and location of edema, and ankle volume were recorded. Patients were treated by medical specialists according to conventional clinical practice and received compression and/or phlebotropic therapy with/without surgical intervention and returned for follow-up visits. Primary efficacy end points were changes in severity of main CVD symptoms (by visual analog scale) leg heaviness, leg pain, and sensation of leg swelling, ankle volume (by disc-model method), and quality of life (QOL) parameters of the disease-specific questionnaire CIVIQ-14. This analysis is focused on the effectiveness of MPFF-based conservative treatment in patients with CVE. **Results.** VAP-C3 enrolled a total of 708 patients, including 176 (24.86%) males and 532 (75.14%) females; mean age was 48.6±12.6 years, with 25.56% of participants older than 65 years of age; 64.8% had a body mass index ≥ 25 kg/m$^2$, and 61.30% had a family history of CVD. Mean study duration was 2.5±0.5 months. With MPFF-based conservative treatment, there were significant improvements in the main CVD symptoms such as leg heaviness, pain, and swelling and in CIVIQ-14–assessed QOL, and significant reduction in ankle volume. In comparative intergroup analysis, the reductions in ankle volume with MPFF-based conservative therapy and such therapy together with surgical intervention did not differ, whereas CIVIQ-14–assessed QOL was significantly improved when MPFF-based conservative therapy was used in combination with surgical intervention. **Conclusion.** MPFF-based conservative treatment, irrespective of addition of surgical intervention, was associated with a significant reduction in the ankle volume in patients with CVD of CEAP class C3EpAsPr. The antiedematous effect of conservative therapy with MPFF alone or in combinations including compression therapy suggests that it is reasonable to consider predominant use of MPFF in routine clinical practice in patients with CVD of CEAP class C3.

## Introduction

Chronic venous edema (CVE) of the lower limbs, defined as a visible or palpable increase in the volume of interstitial fluid due to chronic venous disease (CVD), is the main objective criterion of the CEAP (clinical, etiological, anatomical, pathophysiological) clinical class C3 and also reflects the transition of the disease to a difficult-to-reverse stage of chronic venous insufficiency (CVI).[1] The prevalence of CEAP class C3 CVD not only reflects the epidemiological situation of CVD, but also identifies the potential risks of trophic skin disorders and venous ulceration.[2]

The prevalence of CVE in the population is not clearly established and can vary significantly (from 7% to 20%) depending on the assessment method, age, and ethnic characteristics of the respondents, as well as circadian rhythms.[3]

Recent studies have shown that the development and progression of CVE is a complex pathophysiological process, caused not only by severe macro- and microcirculatory disturbances in the venous bed, but also by a significant deterioration in lymphatic drainage.[4]

CVE worsens the quality of life (QOL) of patients, causes technical issues during surgical interventions, and also increases the risk of adverse effects after surgery. In addition, it has been shown that even radical surgical intervention does not guarantee elimination or reduction in CVE.

For this reason, the complex conservative therapy, either as standalone method or in combination with surgery plays a crucial role in CVE treatment. According to the International Union of Phlebology (UIP) guidelines, a conservative approach in CVE is based on compression therapy and venoactive drugs (VADs). Other therapeutic techniques, such as intermittent pneumatic compression, neuromuscular electrical stimulation, and unloading exercises, play a secondary role.[5]

This publication presents an analysis focusing on the effectiveness of micronized purified flavonoid fraction (MPFF)-based conservative treatment in patients with CVE and is based on the results of the Russian national multicenter observational program Vein Act Prolonged-C3 (VAP-C3; an extension of the VEIN Act Program[6]), which was designed to evaluate treatment effectiveness on CVE in real clinical practice.

## Materials and methods

The VAP-C3 observational program (CinicalTrials.gov identifier NCT03722836) was carried out in 2018–2019. It was a multicenter study performed in the framework of ordinary consultations and examinations of CVD patients with CEAP class C3. All the treatments were fully consistent with the established clinical practice, instructions for the use of drugs, and a specific clinical situation. In the program, the parameters that are usually assessed during the examination of patients with CVD, as well as additional linear dimensions and the volume of the parts of leg with the most severe edema at inclusion, were evaluated. This is the routine method in the sites included in the study. According to the study protocol, each doctor was to include at least 10 patients meeting all of the following inclusion criteria and none of the following exclusion criteria.

The main inclusion criterion was the presence of CVE of the ankle caused by CVD of class C3EpAsPr, according to the CEAP classification. Additional inclusion criteria were age over 18 years, patient's written informed consent, absence of allergic reactions to a topical anesthetic and sclerosing agent, no intake of VADs within 4 weeks before inclusion in the program, and ability to come for a follow-up visit after the intervention.

Exclusion criteria were history of alcohol or drug abuse, secondary varicose veins, angiodysplasia, or neoplasm, lymphatic edema of the lower limbs, peripheral artery disease (ankle-brachial index <0.9), infectious disease within 6 weeks before inclusion, presence of one or more concomitant diseases that are able to affect treatment outcomes (ie, diabetes mellitus; hypertension; connective tissue diseases, including rheumatoid arthritis, intermittent claudication, diseases of bones or joints of the lower limbs; inflammatory bowel disease; renal failure; emphysema or chronic obstructive pulmonary disease; malignant neoplasm); history of deep-vein thrombosis within 1 year before inclusion; superficial thrombophlebitis within 3 months before inclusion; inability to walk (regardless of the cause); obesity (body mass index [BMI] ≥30 kg/m$^2$); poor predicted adherence to the study protocol; participation in another clinical trial within the last 3 months before inclusion; for women: pregnancy, breast-feeding, or willingness to become pregnant within 2 months after the study.

A total of five visits for each patient were scheduled during the VAP-C3 program: inclusion visit (V0) and four follow-up visits (V1, V2, V3, and V4) at 14, 30, 60, and 90 days after

V0. The schedule used with data sources and measurements of the observation research program VAP-C3 in order to assess treatment efficacy is presented in *Table I*.

Based on a specific clinical situation, the doctor independently decided on the rationale of the prescription of compression therapy (and its type) and also recommended one VAD or another.

The criteria to evaluate the treatment outcome were changes in the severity of CVD symptoms as assessed by the VAS scores, changes in the QOL parameters of the CIVIQ-14 (14-item ChronIc Venous Insufficiency Quality of life questionnaire), as well as patient satisfaction with treatment outcome using the Darvall questionnaire (not addressed here). To measure and monitor ankle edema, the disc method was used.[7,8] Moreover, all measurements were performed on the extremity with more pronounced edema.

Before inclusion in the observation program, all patients provided written informed consent, as well as gave permission to process personal data. Data processing and post hoc statistical analysis were carried out by an independent expert in medical statistics using two-sided parametric and nonparametric tests with a significance level of 0.05.

## Results

Eighty-six Russian phlebologists from private clinics enrolled 708 patients (75% females; mean age 48.6±12.6 years; 25.6% patients aged over 65 years) with CVD of CEAP class C3, who fulfilled all the protocol requirements as stated in the methodology section. After the inclusion visit (V0), the patients were followed-up with four visits (V1, V2, V3, and V4) during a mean study period of 2.5±0.5 months. No adverse drug reactions were reported during the study.

| Procedures | V0 | V1 | V2 | V3 | V4 |
|---|---|---|---|---|---|
| Eligibility with inclusion and exclusion criteria | * | | | | |
| Age and gender | * | | | | |
| Height, body mass, body mass index | * | | | | |
| Risk factors for CVD of the lower limbs | * | | | | |
| History of CVD of the lower limbs | * | | | | |
| Previous treatment of CVD of the limbs | * | | | | |
| Clinical assessment of CVD of the lower limbs (VCSS) | * | | | | * |
| Clinical examination of both limbs (CEAP) | * | | | | * |
| Measurement of the ankle volume (disk method) | * | * | * | * | * |
| Prescription and control of treatment with MPFF or other VADs | * | * | * | * | * |
| Prescription and control of compression therapy (at the doctor's discretion, including its type) | | | | | |
| Surgical intervention (could be performed at any visit at the doctor's discretion) | | | | | |
| Assessment of the main CVD symptoms (leg heaviness, pain, sensation of swelling) by VAS | * | | | | * |
| Patient's QOL assessment using CIVIQ-14 | * | | | | * |
| Patient satisfaction with the outcome treatment using the Darvall questionnaire | * | | | | * |
| Presence of re1ux and occlusion using duplex ultrasound | * | | | | * |
| Assessment of adverse events | | * | * | * | * |

*Table I. Schedule of the observation research program VAP-C3.*

*CEAP, clinical, etiologic, anatomic, and pathophysiologic classification; CIVIQ-14, 14-item ChronIc Venous Insufficiency Quality of life questionnaire; QOL, quality of life; CVD, chronic venous disease; VAD, venoactive drug; VAS, visual analog scale; VCSS, Venous Clinical Severity Score.*

The demographic and baseline clinical characteristics of these patients are presented in *Table II.*

| Parameter | All patients with C3 class CEAP (n=708) |
|---|---|
| **Gender, n (%)**<br>Male<br>Female | <br>176 (25)<br>532 (75) |
| **Age**<br>Mean, years<br>Over 65 years, % | <br>48.6±12.6<br>25.6 |
| **BMI**<br>Mean, kg/m$^2$<br>≥ 25 kg/m$^2$, % | <br>26.8±4.10<br>64.8 |
| Family history of CVD, % | 61.3 |
| History of acute venous thrombosis, % | 2.3 |
| **Smoking status, n (%)**<br>Never smokers<br>Former smokers<br>Current smokers | <br>66.2%<br>16.7%<br>17.1% |
| **Mean duration of daily static loads, hours**<br>in the upright position<br>in the sitting position | <br>5.7±2.4<br>5.7±2.3 |
| Regular physical activity | 19.1% |
| **Previous treatment of CVD, %**<br>Venoactive drugs<br>Compression therapy<br>Liquid sclerotherapy<br>Microfoam sclerotherapy<br>Open phlebectomy<br>Endovascular treatment<br>Other | **48.2%**<br>39.8%<br>33.2%<br>4.8%<br>2.5%<br>7.9%<br>2.3%<br>9.5% |
| **Occupational history, %**<br>Job change due to CVD<br>Hospital admission due to CVD<br>Disability in the past 5 years due to CVD | <br>5.7%<br>9.5%<br>8.5% |
| Use of female sex hormone preparations for contraception or as replacement therapy* | 4.1% |
| **Number of births, %***<br>1<br>2<br>3<br>>3<br>Never given birth | <br>37.6%<br>43.2%<br>11.4%<br>0.8%<br>7.0 % |

*Table II. Demographic and baseline clinical characteristics of patients included in the study (n=708).*

*BMI, body mass index; CEAP, clinical, etiological, anatomical, pathophysiological classification; CVD, chronic venous disease.*

**only for women*

All patients in the study underwent ultrasound examination according to standard protocol. In the total sample, pathological reflux was identified in 78.7% of patients and was located in superficial veins (74.6%), perforating veins (3.7%), or deep veins (0.4%). The location and characteristics of the venous edema are presented in *Table III and Table IV.*

| Location of venous edema | n | % of total number of patients |
|---|---|---|
| Both calves | 301 | 42.51 |
| Right calf only | 201 | 28.39 |
| Left calf only | 206 | 29.10 |
| No | 0 | 0.00 |
| Total | 708 | 100.00 |

*Table III. Location of venous edema (n=708).*

*n, number of patients.*

| Characteristics of venous edema | n | % of total number of patients |
|---|---|---|
| Morning edema above ankle, requiring elevation of the lower limb | 48 | 6.78 |
| Afternoon edema above ankle | 467 | 65.96 |
| Evening ankle edema only | 193 | 27.26 |
| None | 0 | 0.00 |
| Total | 708 | 100.00 |

*Table IV. Characteristics of venous edema (n=708).*

*n, number of patients.*

The allocation of patients depending on the treatment regimen is shown in *Table V.*

## Duration of phlebotonic therapy

With regard to systemic phlebotonic therapy, 97.7% of patients were prescribed MPFF. The dosing regimen included intake of MPFF in the form of one 1000-mg tablet once daily in 77.9%, one 500-mg tablet twice daily in 4.8%, or a 1000-mg oral suspension once daily in 15% of patients. The duration of phlebotropic therapy recommended by doctors in the study are presented in *Figure 1.* The recommended duration for phlebotonics was for 8-12 weeks in 45.8%, 4-8 weeks in 46.3%, under

| Group | Treatment regimen | n | % of total number of patients |
|---|---|---|---|
| 1 | MPFF | 32 | 4.5 |
| 2 | MPFF + compression | 145 | 20.5 |
| 3 | MPFF + compression + topical treatment | 158 | 22.3 |
| 4 | MPFF + compression + topical treatment + surgical intervention | 197 | 27.8 |
| 5 | MPFF + surgical intervention | 3 | 0.4 |
| 6 | MPFF + compression + surgical intervention | 155 | 21.9 |
| 7 | No treatment with MPFF | 16 | 2.3 |
| 8 | MPFF + topical treatment | 2 | 0.3 |
| **Total** | | **708** | **100** |

*Table V. Allocation of patients by treatment regimen (n=708).*
*MPFF, micronized purified flavonoid fraction; n, number of patients.*

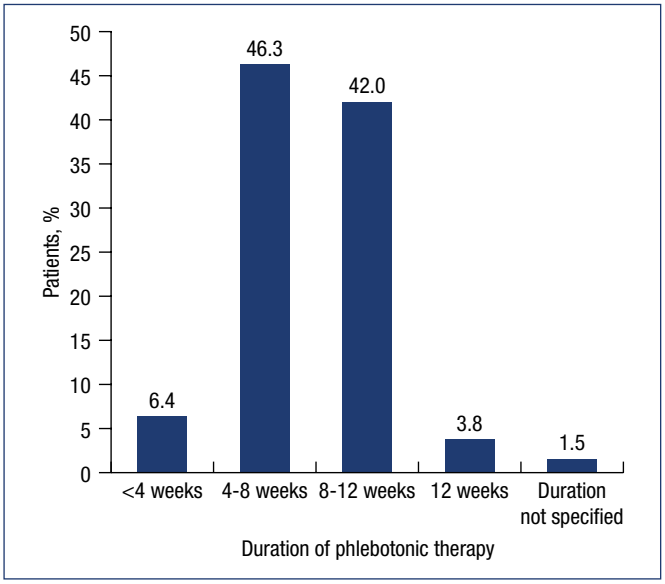


*Figure 1. Duration of phlebotonic therapy recommended by doctors in the VAP-C3 program.*

4 weeks in 6.4%, and unspecified in 1.5% (calculated percentages exclude those not prescribed MPFF).

MPFF was used at V1, V2, V3, and V4 visits by 96.61%, 94.77%, 81.07%, and 54.94% of the total number of patients in the study, respectively.

## Duration of compression therapy

Graduated medical compression hosiery was prescribed at V0 visit to 92.5% of patients. The recommended durations for compression therapy as prescribed in the study are shown in *Figure 2*, with 8-12 weeks being most recommended, in 60.5% of patients, followed by 4-8 weeks in 20.6%, under 4 weeks in 14.3%, and over 12 weeks in 4.6% (calculated percentages exclude those not prescribed compression therapy).

Compression treatment was used at V1, V2, V3, and V4 visits by 91.95%, 84.60%, 75.56%, and 61.16% of total number of patients in the study, respectively. The compression class by RAL standard (European compression standard) was 1, 2, and 3 in 5.5%, 85.3%, and 0.3% of them, respectively.

## Topical treatment

Topical treatment was prescribed at V0 visit to 50.4% of the total number of patients in the study and was used at V1, V2, V3, and V4 visits by 36.44%, 35.03%, 28.11%, and 16.67% of patients.

## Surgical intervention

Surgical intervention for CVI (including mostly endovenous laser treatment [EVLT], but also liquid sclerotherapy, radiofrequency ablation (RFA), miniphlebectomy or a combination of these techniques) was performed in 50.1% of the total number of patients in the study in combination with conservative treatments.

## Treatment effectiveness: CVD symptoms, QOL and ankle edema

Due to an insufficient number of subjects in groups 5, 7 and 8, which are listed in *Table V,* these groups were excluded from further analysis. Characteristics of the 687 patients in the remaining groups thus selected for final analysis are provided in *Table VI.*

The study revealed significant positive changes at the final visit, compared with baseline, in the severity of the

main CVD symptoms assessed by VAS, such as leg heaviness *(Table VII)*, leg pain *(Table VIII)*, and sensation of leg swelling *(Table IX)* in patients using MPFF alone, as well as in groups using MPFF in combinations including compression (*P*<0.001 in all groups).

Leg heaviness improved 52.8% in those receiving MPFF alone, 60.5% for MPFF+compression, 66.1% with MPFF+compression+topical treatment, 80.3% with MPFF+compression+topical treatment+endovenous surgery, and 78.5% with MPFF+compression+surgical intervention *(Table VII)*.

| Treatment regimen | Gender, M/F | Age, years | Body mass index, kg/m$^2$ | History of acute venous thrombosis, % | Current smoker, % | Previous venoactive therapy, % |
|---|---|---|---|---|---|---|
| MPFF (n=32) | 1/31 | 48.8±11.7 | 26.0±4.9 | 0 | 15.6 | 46.9 |
| MPFF + compression (n=145) | 42/103 | 50. ±12.9 | 26.8±3.8 | 2.8 | 15.2 | 41.4 |
| MPFF + compression + topical treatment (n=158) | 35/123 | 49. ±12.4 | 27.4±4.4 | 1.3 | 16.5 | 50.0 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 56/141 | 47.3±12.8 | 26.6±3.8 | 3.1 | 20.8 | 55.3 |
| MPFF + compression + surgical intervention (n=155) | 39/116 | 48.1±12.8 | 26.7±4.3 | 2.6 | 16.8 | 47.1 |

*Table VI. Characteristics of patients allocated to groups included in the final analysis (n=687).*

*MPFF, micronized purified flavonoid fraction.*

| Treatment regimen | V0 | V4 | *P* value |
|---|---|---|---|
| MPFF (n=32) | 5.27±2.31 | 2.49±1.97 | < 0.001 |
| MPFF + compression (n=145) | 4.99±2.22 | 1.97±1.61 | < 0.001 |
| MPFF + compression + topical treatment (n=158) | 5.66±2.18 | 1.92±1.56 | < 0.001 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 5.79±2.18 | 1.14±1.48 | < 0.001 |
| MPFF + compression + surgical intervention (n=155) | 5.03±2.01 | 1.08±1.01 | < 0.001 |

*Table VII. Changes in leg heaviness, as assessed by visual analog scale (n=687).*

| Treatment regimen | V0 | V4 | *P* value |
|---|---|---|---|
| MPFF (n=32) | 3.64±2.20 | 2.25±1.69 | 0.004 |
| MPFF + compression (n=145) | 3.98±2.57 | 1.42±1.56 | < 0.001 |
| MPFF + compression + topical treatment (n=158) | 4.58±2.43 | 1.39±1.35 | < 0.001 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 4.70±2.28 | 0.82±1.21 | < 0.001 |
| MPFF + compression + surgical intervention (n=155) | 3.78±2.21 | 0.64±0.88 | < 0.001 |

*Table VIII. Changes in leg pain, as assessed by visual analog scale (n=687).*

Leg pain improved 38.2% in those receiving MPFF alone, 64.3% with MPFF+compression, 69.7% with MPFF+compression+topical treatment, 82.6% with MPFF+compression+topical treatment+surgical intervention, and 83.1% with MPFF+compression+surgical intervention *(Table VIII)*.

Sensation of swelling improved 73.7% in those receiving MPFF alone, 65.9% with MPFF+compression, 71.3% with MPFF+compression+topical treatment, 82.7% with MPFF+compression+topical treatment+surgical intervention, and 82.4% with MPFF+compression+ surgical intervention *(Table IX)*.

These positive changes were accompanied by significant improvement in the QOL of the patients, assessed by CIVIQ-14 global index score in all the respective treatment groups (all *P*<0.001; *Table X*).

| Treatment regimen | V0 | V4 | *P* value |
|---|---|---|---|
| MPFF (n=32) | 5.02±2.44 | 1.32±0.98 | < 0.001 |
| MPFF + compression (n=145) | 5.45±2.47 | 1.86±1.82 | < 0.001 |
| MPFF + compression + topical treatment (n=158) | 5.89±2.42 | 1.69±1.66 | < 0.001 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 6.17±2.53 | 1.07±1.57 | < 0.001 |
| MPFF + compression + surgical intervention (n=155) | 5.28±2.21 | 0.93±1.10 | < 0.001 |

*Table IX. Changes in sensation of swelling, as assessed by visual analog scale (n=687).*

| Treatment regimen | V0 | V4 | *P* value |
|---|---|---|---|
| MPFF (n=32) | 21.5±14.6 | 8.3±9.6 | <0.001 |
| MPFF + compression (n=145) | 29.4±18.1 | 12.4±10.8 | < 0.001 |
| MPFF + compression + topical treatment (n=158) | 35.6±20.0 | 12.5±9.4 | < 0.001 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 36.6±17.6 | 8.2±10.9 | < 0.001 |
| MPFF + compression + surgical intervention (n=155) | 29.2±17.1 | 7.0±6.5 | < 0.001 |

*Table X. Changes in the CIVIQ-14 global score (n=687).*

| Treatment regimen | V0 | V4 | *P* value |
|---|---|---|---|
| MPFF (n=32) | 2.57±0.91 | 2.38±0.81 | <0.001 |
| MPFF + compression (n=145) | 2.95±0.89 | 2.72±0.83 | < 0.001 |
| MPFF + compression + topical treatment (n=158) | 3.23±0.81 | 3.04±0.76 | < 0.001 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 3.37±0.84 | 3.08±0.77 | < 0.001 |
| MPFF + compression + surgical intervention (n=155) | 2.69±0.63 | 2.47±0.57 | < 0.001 |

*Table XI. Changes in ankle volume (liters; n=687))*

The ankle volume, as a main efficacy parameter during the study, significantly decreased in patients using MPFF alone, as well as in groups using MPFF in combinations including compression (all P<0.001; *Table XI*). Total reductions in ankle volume (ranging from 0.19 L to 0.29 L) with respect to different treatment strategies are shown in *Table XII*.

### Comparative intergroup analysis: effectiveness of conservative treatment with or without surgical intervention

In the total treatment group (n=708), no differences in the CVE reduction were found between patients with or without surgical intervention (conservative treatment only) during the study period as presented in *Table XIII*.

Comparative intergroup analyses were also performed between patients who underwent surgical intervention and those who received only MPFF-based conservative treatments (excluding the 16 patients from the study who did not take MPFF; n=692). As in the total treatment group, no differences in observed CVE reduction were found between patients with or without surgical intervention (MPFF-based conservative treatment only) at the end of the treatment *(Table XIV)*. However, there was significantly better improvement in the CIVIQ-14 global score in patients who were treated with both MPFF-based conservative treatment and surgical intervention *(Table XV)*.

| Treatment regimen | Volume (liters) |
|---|---|
| MPFF (n=32) | 0.19±0.14 |
| MPFF + compression (n=145) | 0.23±0.17 |
| MPFF + compression + topical treatment (n=158) | 0.19±0.15 |
| MPFF + compression + topical treatment + surgical intervention (n=197) | 0.29±0.20 |
| MPFF + compression + surgical intervention (n=155) | 0.22±0.17 |

*Table XII. Total reduction in ankle volume (liters; n=687).*

| Visits | Conservative treatment + surgical intervention (n=355) | Conservative treatment only (n=353) | *P* value |
|---|---|---|---|
| V0 | 2.9±0.8 | 2.9±0.8 | 0.188 |
| V1 | 2.9±0.8 | 2.8±0.8 | 0.255 |
| V2 | 2.8±0.8 | 2.7±0.8 | 0.383 |
| V3 | 2.8±0.8 | 2.7±0.8 | 0.416 |
| V4 | 2.7±0.7 | 2.6±0.8 | 0.593 |

*Table XIII. Comparison of changes in ankle volume (liters) in all patients with or without surgical intervention for chronic venous disease during the study (n=708).*

| Visits | MPFF-based conservative treatment + surgical intervention (n=355) | MPFF-based conservative treatment only (n=337) | *P* value |
|---|---|---|---|
| V0 | 3.08±0.83 | 3.08±0.87 | 0.983 |
| V4 | 2.82±0.75 | 2.87±0.82 | 0.505 |
| *P* value | <0.001 | <0.001 | |

*Table XIV. Changes in ankle volume (liters) in patients with MPFF-based conservative therapy with or without surgical intervention (n=692).*

| Visits | MPFF-based conservative treatment + surgical intervention (n=355) | MPFF-based conservative treatment only (n=337) | *P* value |
|---|---|---|---|
| V0 | 33.4±17.8 | 31.5±19.2 | 0.176 |
| V4 | 7.7±9.2 | 12.0±10.1 | <0.001 |
| *P* value | <0.001 | <0.001 | |

*Table XV. Changes in the CIVIQ-14 global score in patients with MPFF-based conservative therapy with or without surgical intervention (n=692).*

## Discussion

The presence of CVE correlates with the worsening of other CVD symptoms and suggests decompensation of the drainage function of venous and lymphatic systems. Patients with CVD of CEAP class C3 not only report a significant reduction in all QOL parameters, but also fall into the high-risk group for the development of trophic disorders of the soft tissues of the ankle.[9,10]

Regarding the conservative approach for CVD, a combination of compression therapy with VADs is often prescribed, which is sometimes complemented by other techniques, such as intermittent pneumatic compression, neuromuscular electrical stimulation, and various types of manual drainage massage. If a more aggressive approach is necessary, the preference is given to endovascular surgery. However, there is a large amount of evidence suggesting that even in such a case it is advisable to first reduce or eliminate CVE, ie, to transition the patient from class C3 to class C2 CEAP. Moreover, the UIP guidelines emphasize that surgical intervention or sclerotherapy does not guarantee a reduction in or elimination of baseline CVE, which suggests prolonged conservative therapy in the postoperative period may be necessary.[11,12]

The study aimed to assess the effectiveness of MPFF-based conservative treatment in patients with CVE in real clinical practice. The medical focus group comprised selected medical specialists who were regularly and professionally involved in the treatment of this population of patients. Thus, the doctors' awareness in regard to this population of patients may also have played a role in decision making in this study.

All doctors started to treat patients with conservative therapy, including compression hosiery and VADs. The vast majority of patients were prescribed with class 2 medical hosiery (RAL standard), which is consistent with the International Compression Club guidelines. Rationale behind prescription of compression hosiery of RAL class 3 or to refuse prescription of compression therapy at all is unclear.[13]

Of interest is the recommended duration of compression therapy. Compression hosiery was prescribed for a period of more than 12 weeks, optimal for treating CVD, in only 4.2% of total patients, and not prescribed at all in 8.6% of patients. The reason for this finding is unclear. It can be assumed that the data shown in *Figure 2* indirectly reflects patient adherence to compression therapy, which decreases with longer duration of prescribed therapy and which is aligned with the findings of VEIN Act Program.[6]

Regarding the phlebotropic therapy used in this study, the choice of MPFF in various forms and in a standard daily dose of 1000 mg was based on the Russian National Clinical Guidelines and findings from the meta-analysis of Allaert.[14] This meta-analysis demonstrated the significant superiority of MPFF therapy for venous edema, assessed as the decrease in ankle circumference when compared with

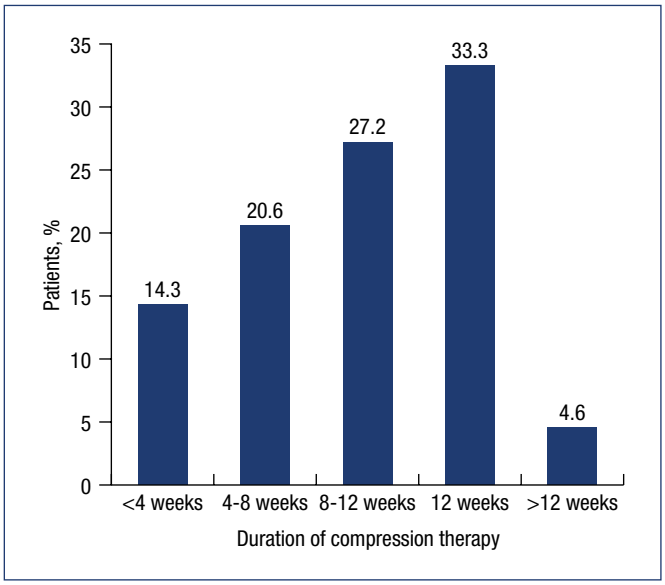


*Figure 2. Duration of compression therapy recommended by doctors in the VAP-C3 program.*

other VADs such as hydroxyethyl-rutosides, ruscus extract, and diosmin.[14]

In the study population that used MPFF-based conservative treatment, there were significant improvements in the main CVD symptoms such as leg heaviness, leg pain, and leg swelling, in CIVIQ-14–assessed QOL, as well as significant reduction in ankle volume. Whereas the observed improvement in ankle volume with MPFF-based conservative therapy was irrespective of surgical intervention, use of MPFF-based conservative therapy in combination with surgical intervention was associated with a significant improvement in CIVIQ-14–assessed QOL.

There is a need for a clearer management strategy in patients with CVD in respect to the duration of conservative therapy before referral to surgery, as well as in preparation for and following surgery.

Study limitations include its observational nature and the absence of equivalent comparison groups. In addition, the location of patient enrolment being in specialized phlebology centers rather than general medical institutions might also affect the study results. Nevertheless, the design of the VAP-C3 program and the acquired results reflect real clinical practice to a greater extent than standard refined comparative studies. The data obtained in the VAP-C3 program and the current evidence from other studies have already allowed us to recommend the routine perioperative administration of MPFF in patients with CVD in real clinical practice.[18]

## Conclusion

The results of the Russian national multicenter observational program VAP-C3 showed that treatment with MPFF-based conservative therapy significantly decreased the severity of CVE with reduction in the ankle volume and improved the main CVD symptoms, such as leg heaviness, pain, and sensation of swelling in patients with CVD of CEAP class 3. Such therapy also improved the quality of life of the patients, as assessed by the CIVIQ-14 global index score.

In addition, comparative intergroup analysis demonstrated a strong antiedematous effect of MPFF-based conservative therapy irrespective of surgical interventions, which may support the predominant use of MPFF in routine clinical practice in patients with CVD of CEAP class C3.

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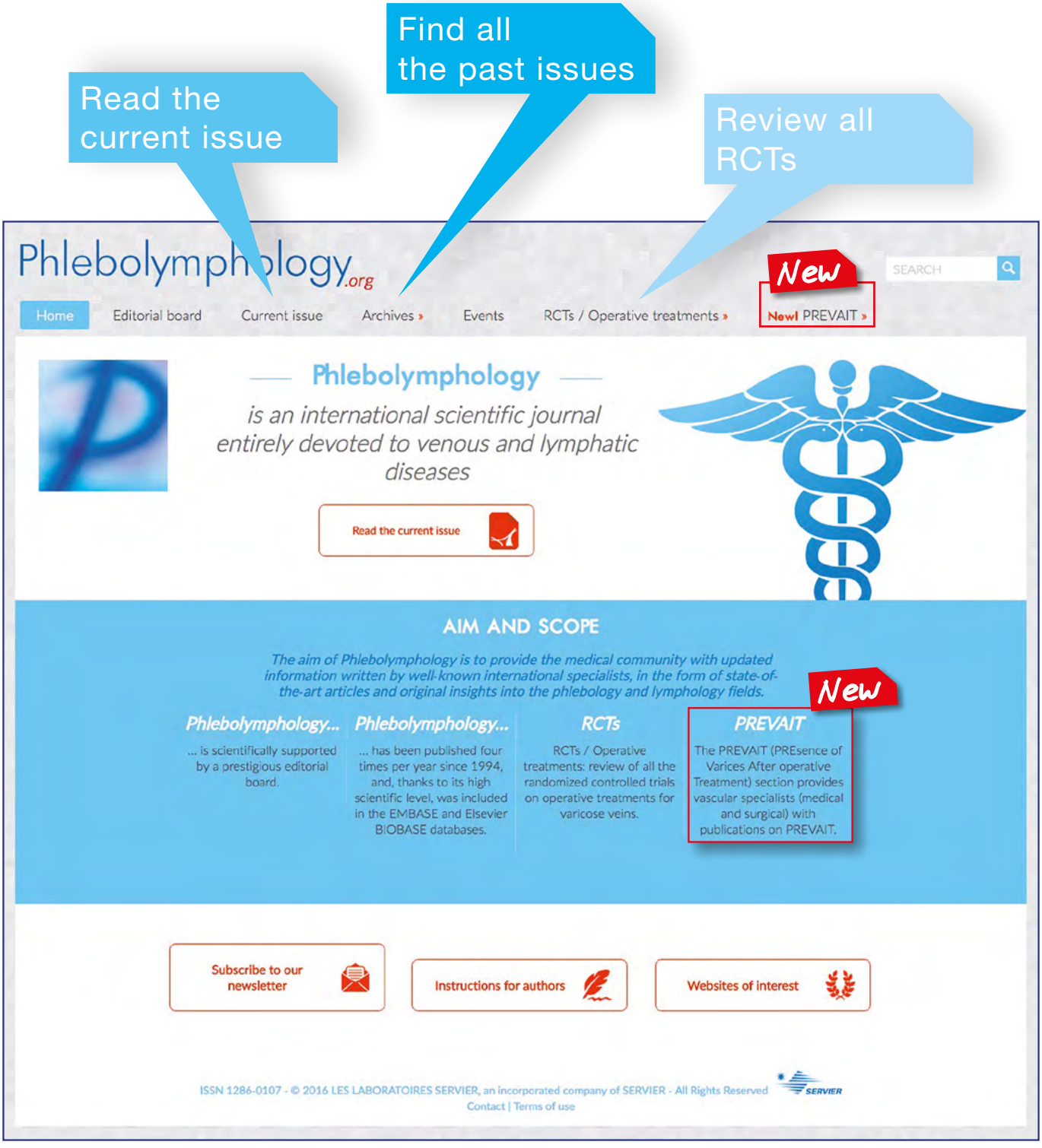

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