eISSN 2279-7483
https://www.pagepressjournals.org/index.php/vl/index

Veins and Lymphatics 2025 [online ahead of print]

To cite this article:
Didier Rastel, Amalric Montalibet, Cyril Chaigneau, Etienne Grenier. Lower limb oedema in mild to moderate superficial venous disorders is not only an ankle oedema: results of an exploratory study. Veins and Lymphatics. 2025;14:14092. doi:10.4081/vl.2025.14092

Lower limb oedema in mild to moderate superficial venous disorders is not only an ankle oedema: results of an exploratory study

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Key words: leg volume, venous oedema, water-displacement method.

Contributions: DR, design and conception of the protocol, analysis of results, writing; AM, conception of the protocol, measurements, analysis of results, review of the manuscript; CC, EG, conception of the protocol, analysis of results, review of the manuscript. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

Conflict of interest: The authors state that they have no conflict of interest in relation to this work since it is not linked to any commercially available product sold by SIGVARIS GROUP.

Funding: this study was funded by SIGVARIS Group. DERSMCAN was the CRO in charge of administrative follow-up, logistic and statistics. D. Rastel, is a private practice Vascular Physician. A. Montalibet is a research engineer at INSA Lyon.

Ethics approval and consent to participate: this trial was carried out in France, registered under code 17E0726, ANSM 2017-A01063-50. Approval of the national ethics committee was granted according to the principles of the Declaration of Helsinki.

Informed consent: the manuscript does not contain any individual person's data in any form.

Patient's consent for publication: the patients gave their written consent to use their personal data for the publication of this case report and any accompanying images.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Acknowledgments: we thank the Dermscan and INSA Lyon team for their involvement and implication, as well as Madeleine Kelly for the revision of the English and Sabrina Serpillon for her comments on the manuscript.

Abstract

The monitoring and treatment of leg oedema rely on the assumption that it is primarily localized in the ankle area. However, previous studies suggest that it may equally affect the entire leg. Such a finding may impact the disease management.

The objective of this study was to investigate the distribution of leg oedema in superficial venous disease.

Twenty-nine female patients suffering from mild to moderate superficial venous disease with oedema were enrolled. Forty-three legs were tested (15 unilateral oedema)**.** The variation of leg volumes between the morning (t0) and 6 hours later (t6), was measured using the water displacement method. To differentiate ankle oedema from lower leg oedema, two different water heights were used: 50 cm (lower leg) and 32 cm (ankle only).

At t0, the volume of lower legs and ankles were 327.2±28.3 cL and 154.5±11.2 cL, respectively. Between t0 and t6, it significantly increased by 4.9±3,1 cL and 2.3±1.3 cL respectively ($p<0.0001$). Consequently, the volume above the ankle had also increased by 2.6±2.3 cL ($p<0.0001$).

The present study demonstrates that in patients with moderate Chronic Venous Diseases (CVDs), leg oedema is not limited to the ankle.

Introduction

Lower limb oedema is an early complication of Chronic Venous Diseases (CVDs), that must be diagnosed then treated according to recent international recommendations.[1]

When permanently present over a long period of time, it reduces quality of life, changes normal skin to fibrosis resulting in limited movement of ankle joints.[2]

The causes of oedema are multiple leading to excessive venous filtration at capillary level and, to some extent, an overload of lymphatic drainage.[3,4] Due to gravity, in certain physio-pathological situations, lower limb oedema achieves its maximum volume in the ankle area and fluid accumulates in the dermis and sub-dermal layers of the skin.[5,6]

However, several studies suggest that, at an early stage, oedema might be evenly distributed in the area from below the knee to the foot.[7-11]

Consequently, the present study aimed at confirming this concept in mild to moderate CVDs.

Materials and Methods

Study design

This study is a sub-analysis of a prospective, monocentric, exploratory, controlled trial using intra-individual comparison. The primary objective was to compare bioimpedance and water-displacement methods in measuring lower leg oedema variation in patients over a day.[12,13]

This trial was carried out in France, registered under code 17E0726, ANSM 2017-A01063-50. Approval of the national ethics committee was granted according to the principles of the Declaration of Helsinki.

The present sub-analysis compares entire lower leg and ankle swelling over a day, measured by the Water Displacement Method (WDM) in patients with oedema associated with mild to moderate superficial venous disorders. The WDM is the gold standard in measuring variations of lower leg oedema.[14-16]

Population

Study subjects were female aged 18 to 75, with a Body Mass Index (BMI) ranging from 18 to 30, able to stand up for at least 10 minutes, agreeing not to wear compression stockings for 24 hours before inclusion visit and, if enrolled, for 24 hours before the test.

A standing phlebology ultrasound consultation at the end of the day established that they had oedema in at least one lower limb, varicose veins and/or reticular vein dilations. Deep and superficial veins were considered affected if reflux was present with a venous reflux time >1000 ms for deep veins and >500 ms for superficial veins during Valsalva or manual compression-decompression maneuvers.

Oedema was diagnosed either by a positive pitting test or when the patient reported a feeling of lower leg swelling associated with anechoic sub-dermal bands detected using ultrasounds.[17-20] The cutaneous layers were imaged in the transverse plane using a multifrequency 10-18 MHz linear probe (reference VF135; MyLab 25 Gold, Esaote, Genoa, Italy). Anechoic bands are black elongated images of different shapes, parallel to the skin and not coloured by Doppler. They are considered oedema if at least one of them has an antero-posterior dimension greater than or equal to 0.8 mm (threshold based on previous works).[5,6,17-20]

The severity of the disease was also described according to the CEAP classification[21,22] and the Venous Clinical Severity Score (VCSS).[23-25]

Exclusion criteria were oedema resulting from underlying medical conditions such as kidney, heart or liver diseases; post thrombotic syndrome; deep venous thrombosis sequelae or deep venous reflux; healed or active ulcer; lipodermatosclerosis, severe skin changes; lymphoedema; daily wearing of compression stockings or bandages; pregnancy up to 6 months after the delivery period; breast feeding.

All subjects provided written informed consent before entering the study.

Assessments

Leg volume was measured in the morning (t0) and 6±0.5 hours later (t6), using the WDM.

To differentiate ankle oedema from lower leg oedema, two pairs of polymethyl methacrylate were used: i) tall boxes, 22 L, water height of 42 cm to measure the lower legs volume and ii) small boxes, 14 L, water height of 23.5 cm to measure the ankle volume. Displaced water flowed into two containers placed laterally and was weighed with precision scales (KERN CKE 6K0.02) (Figure 1).

The investigator was trained before the trial until reaching 0.1% accuracy.[14,15]

Ankle (8 cm above the tip of the malleolus) and calf (at the greatest girth) circumference and the floor-popliteal fossa height were also reported using a digital measuring tape (HDTM012DQ-69 Health-o-meter®).

Study organization

On test day, patients were asked to be normally active, not to lie down, not to play sport or walk for more than one hour consecutively. In the morning (t0), patients were checked for adverse events, both legs were tested for oedema using ultrasounds and the measuring tape recordings were performed. The patients were then asked to put simultaneously their right and left legs in the tall boxes first, and then in the small boxes. The same procedure was conducted at t6.

Both legs, including unselected legs, were tested for all subjects.

Sample size

The required number of patients was estimated empirically. Significant results were expected with 40 legs. Assuming a <10% dropout rate, 43 legs were required for the study. Twenty-nine subjects were enrolled. All subjects enrolled in the clinical trial were included in this sub-analysis.

Statistics

Quantitative variables were presented as mean, standard deviation, quartiles and ranges; qualitative variables as percentages. A Student t-test was used to compare quantitative criteria with paired measurements between groups (alpha risk 5%, power 90%). A p-value <0.05 was considered statistically significant. A per-protocol analysis was conducted.

Results

Twenty-nine subjects (43 legs) were included in the trial with no dropout between t0 and t6 (Figure 1). Fifteen patients (51.7%) had unilateral oedema. The inclusion examination was performed approximately 9 hours after awakening (ranging from 6.5 to 13 hours).

Demographic data and detailed CEAP classification of patients are presented in Table 1.

All legs had telangiectasias while dilated and refluxing reticular veins were present in 41 legs (95%). Seventy-two percent of patients had a venous clinical severity score ≤5 (median=5, range 2-8). Eleven patients (37.9%) previously had superficial varicose vein surgery. No patient had deep or superficial vein thrombosis morphological sequelae on ultrasounds or deep venous reflux. The mean floor-popliteal fossa height of tested legs was 43.5 cm, ranging from 39.5 to 47 cm (Figure 2).

At t0, the average volume of the entire lower leg measured by WDM was 327.2±28.3 cL, whereas the average ankle volume was only 154.5±11.2 cL, representing 47.2% of the lower leg volume.

From t0 to t6, 90.7% of the legs tested increased in volume. Both lower leg and ankle volume increased significantly and equally: the volume of lower leg increased by 4.9±3.1 cL (+1.4%, $p<0.0001$) while the ankle volume increased by 2.3±1.3 cL (+1.4%, $p<0.0001$, Figure 3). Thus, the ankle swelling accounts only for 47% of the entire lower leg swelling.

Regarding the upper part of the lower leg (above the ankle), the oedema volume deduced by subtracting the volume increase of the ankle from that of the lower leg, is significant and reaches 2.6±2.3 cL ($p<0.0001$). This result is supported by the tape measurements at t0 and t6, which showed an increase in ankle circumference at the smallest perimeter (+0.2±0.3 cm, $p<0.0001$) but also in calf circumference at the largest perimeter (+0.3±0.3 cm, $p<0.0001$).

Interestingly, the increase in lower leg volume measured with the tall box between t0 and t6, was similar whether the pitting test was positive or negative.

We also compared the volume gain measured for lower leg and ankle in subgroups: i) selected legs with varicose veins, ii) selected legs without varicose veins and iii) unselected legs.

No significant difference was observed.

The comparison between operated and non-operated legs was also tested. The t0-t6 difference in oedema between the two boxes was of 2.6±3.1 cL in the operated legs and 2.6±1.8 cL in the non-operated legs, which is not statistically different. The proportion of oedema at the calf level was of 50.5% in the operated legs and 46.5%. There is a trend toward a greater part of oedema at the calf level in the operated legs, but it is not significant.

Discussion

The present results establish that the increased leg volume after 6 hours is evenly distributed along the lower leg in patients with mild to moderate superficial CVD. Of note, the mean lower leg volume variation observed in our study (4.9±3.1 cL) is consistent with results from previous studies for people standing at work or suffering from mild to moderate CVD.[7,26]

International guidelines suggest that moderate oedema is preferentially localized to the distal part of the leg where skin indentations are observed following thumb pressure during a pitting test.[27] However, not only is there no volumetry data supporting this notion, but clues from previously published work suggest otherwise.

Caggiati *et al*. have showed that in 20 legs of healthy volunteers, the leg volume increase over a daytime was higher in the calf aspect than in the ankle and foot regions.[11]

Indirect clues are from compression trials, for example, in a trial including 28 patients (40 legs), G. Mosti observed, after a 2-week treatment with inelastic bandages or compression stockings, a significant reduction in leg circumference from the malleolus to 28 cm above it; the maximum reduction being observed at mid-leg and distal section respectively.[28] Their results showed a trend towards a lower efficacy of graduated stockings in reducing leg circumference. An explanation could be that bandages are currently applied at a higher pressure than stockings to compensate for rapid loss of pressure, which could also exert a more constant pressure all over the leg compared to stockings.[28]

Graduated compression stockings, which apply greater pressure at the ankle than at the calf, is the most frequent compression device used to treat oedema.[7] Conversely, progressive stockings which exert the higher pressure at the calf give almost similar leg volume reduction than graduated stockings.[29,30]

This would be consistent with a distribution of oedema throughout the lower leg, as shown in our study. The issue of how the different modes of compression act should be addressed with respect to oedema distribution.

Similarly, the results presented in the present paper help to clarify why low and very low compression pressure is effective, as shown in previous studies.[31-33] In one of these, placebo stockings were used for the first time.[33] However, to prevent them from slipping down, a very low pressure of 3-6 mmHg was still exerted by the placebo stocking along the entire length of the lower leg. Surprisingly this "placebo" was able to reduce oedema by 1.2±6.8 cL in 116 standing patients at 28 days. An explanation could be linked to the skin area. At the ankle, there is a lower skin surface area and more impact of gravity. At calf level, gravity has less effect, but the skin surface area is greater.

Another point to be discussed is the management of oedema in CVD patients. Interestingly, our results show that oedema volume was not significantly different in patients with varicose veins compared to those without. Nevertheless, Partsch *et al*. observed a trend towards greater oedema occurrence in varicose vein patients.[31] In our study, the number of subjects may have been too small to observe a difference.

More generally, we still know very little about oedema in CVD patients. The definition, "a perceptible increase of fluid", although clear, is not practical as the diagnosis is based on clinical findings, which obviously are subject to variations, confirmed by the minimum agreement on clinical evaluation of oedema.[34] Our results show that oedema is not greater when a pitting test is positive than when it is negative, again emphasizing the need for a clearer definition of oedema in CVD patients, particularly to clarify the oedema aspect of VCSS.

Study limitations

The WDM was chosen to measure oedema variation because it remains the gold standard for chronic venous insufficiency. However, due to its technical and implementation constraints, it limited the study to the leg, excluding the knee and preventing analysis of the thigh, which could have provided additional information on the distribution of oedema.

This study has some other limitations that preclude a more extensive generalization of our results. One is the absence of a control group, e.g. healthy volunteers.[34] Another one is that we did not strictly divide the leg into two sections of equal length to ascertain that the oedema was evenly distributed all over the leg. Gravity probably plays a role since the anechoic subdermal ultrasounds' bands corresponding to an excess of fluid, are observed distally and not proximally on the leg. Consequently, oedema is more likely to be present at ankle level than in the upper part of the lower leg; but to what extent? More than simply considering leg height, we could have considered the skin area of each part of the leg tested in the different boxes.

Finally, the haemodynamic evaluation of our population was not precise enough to go further in the explanation of comparisons such as the absence of difference between operated and non-operated legs.

Conclusions

The present study demonstrates that in patients with moderate CVD, leg oedema is not limited to the ankle. More generally, we still know very little about oedema in CVD patients. The definition, "a perceptible increase of fluid", although clear, is not practical as the diagnosis is based on clinical findings, which are subject to variations.

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Table 1. Demographic data presented as number (%) or mean ± standard deviation and range and detailed CEAP classification of the patients.

Characteristics	**Population**
Patients / Legs included	29/43
Age	58.3±1.9 (31-71)
BMI	24.7±0.5 (19.1-29.2)
Menopausal status	21 (72 %)
Hormone replacement therapy / oestrogenic	04-mar
Contraception (oestrogenic)	3 (10 %)
Hypertension	2 (7 %)
Calcium blocker	1
Converting enzyme inhibitor	1
Venous clinical severity score ≤5	31 (72 %)
C1,3, Ep, As1, Pn	15 (%)
C1,3,4a, Ep, As1, Pn	1 (2 %)
C1,3, Ep, As1, 4, Pr	5 (%)
C1,3 Ep, As1, 5, Pr	5 (%)
C1,2,3, Ep As1,5 Pr	11
C1,2,3, Ep As1,3 Pr	4

C1,2,3, Ep As1,3,4 Pr	2
Varicose vein	17 (40 %)
Telangiectasias	43 (100 %)
Corona phlebectatica	4 (9 %)
Dermatitis	2 (4 %)
Pigmentation	1
Non-CVD dermatitis	1
Positive pitting test (total)	11 (25.5 %)
With varicose veins	6 (13.9 %)
Without varicose veins	5 (11.6 %)
Reflux on saphenous veins	6 (13.9 %)
Reflux on saphenous tributaries	15 (34.8 %)

BMI, Body Mass Index