A NEW NON INVASIVE METHOD FOR THE ACCURATE AND PRECISE ASSESSMENT OF VARICOSE VEIN DIAMETERS.

Damiano Baldassarre, PhD; Linda Pustina; Samuela Castelnuovo; Alighiero Bondioli, MD; Matteo Carlà, MD; Cesare R. Sirtori, PhD, MD.

E. Grossi Paoletti Center, Department of Pharmacological Sciences, University of Milan, Via Balzaretti, 9, Milan, Italy.

Running head: A method to improve varicose veins diameter determination.

Address for Reprints

Dr. Damiano Baldassarre

E. Grossi Paoletti Center

Department of Pharmacological Sciences

University of Milan

Via Balzaretti, 9,

20133, Milan, Italy.

E-mail : damiano.baldassarre@unimi.it

Phone: +39 02 6471730

Fax: +39 02 6470594

Abstract:

Purpose: The feasibility and reproducibility of a new ultrasonic method for the direct assessment of maximal varicose vein diameter (VVD) was evaluated. A study was also performed to demonstrate the capacity of the method to detect changes in venous diameter induced by a pharmacological treatment.

Subjects and Methods: Patients with varicose vein disease were recruited. A method that allows the precise positioning of patient and transducer and to perform scans in a gel-bath was developed. Maximal VVD was recorded both in the standing and supine positions. The intra-assay reproducibility was determined by replicate scans made within 15 minutes in both positions. The inter-observer variability was assessed by comparing VVDs measured during the first phase baseline examination with those obtained during baseline examinations in the second phase of the study.

Results: The error in reproducibility of VVD determinations was 5.3%, when diameters were evaluated in the standing position and 6.4%, when assessed in the supine position. The intra-method agreement was high, with a bias between readings of 0.06±0.18 mm and of -0.02±0.19 mm, respectively, in standing and supine positions. Correlation coefficients were better than 0.99 in both positions. The method appears to be sensitive enough to detect small changes in VVDs induced by treatments.

Conclusions: The proposed technique provides a tool of potential valid use in the detection and in vivo monitoring of VVD changes in patients with varicose vein disease. The method offers an innovative approach to obtain a quantitative assessment of varicose vein progression and of treatment effects, thus providing a basis for epidemiological surveys.

Key words: B-Mode Ultrasonography, Varicose veins diameter, Reproducibility, Essaven gel.

Introduction

Human venous disease of the lower extremities is a condition affecting millions of people in the world. Its manifestations may be associated with more serious underlying problems undetectable by visual inspection. Apart from the cosmetic nuisance, varicose vein disease results in a number of uncomfortable symptoms which may progress, if untreated, to cutaneous pigmentation, dermatitis, ulcerations, haemorrhages, or superficial thrombophlebitis.[Johnson 97] Although uncomplicated cases of the disease are more common, venous disease should not be taken lightly. Steps to retard disease expression and progression should be implemented whenever possible. In addition, the high incidence of acute and chronic disease of the venous system[Johnson 97, Muller-Lisse 98] requires the application of reliable, non invasive, low-cost methods both for diagnosis and follow-up after therapy.

Until now, goals of non–invasive vascular diagnosis of the venous system of the lower limbs were: 1) to evaluate the venous system during deambulation at baseline, after surgery or after using elastic stockings,[vettorello 94] 2) to get detailed information on the localization of valvular dysfunctions as the basis of any reflux pathology[Thibault 92, evans 99] and, 3) to identify and quantify venous flux and reflux during walking.[Vettorello 1994] Although clinically important, these parameters allow only the assessment of gross changes due to the disease such as, i.e., the appearance of a new reflux due to valvular dysfunction, and do not allow the assessment of minor venous changes that do not affect venous flux and reflux.

In recent years, a number of new technologies have been made available for the non-invasive monitoring of the evolution of varicose veins disease.[Muller-Lisse 98; Ghiringhelli L 92] Among these, a new technique evaluating varicose vein diameter (VVD)

may prove useful to easily follow even the minor evolution of the venous disease. However, difficulty in performing diameter measurements with a high degree of accuracy and reproducibility have so far prevented general use of these techniques in the clinic and in angiology research. The major factor that influences reproducibility of VVD evaluation is the repeated identification of the same venous ectasy in successive determinations. In the present study, the accuracy and reproducibility of a new method for VVD assessment was evaluated and quantified.

Essaven gel (EG) is a naturally derived herbal compound indicated for the local treatment of venous microcirculatory alterations of the limb such as varicose veins and chronic venous insufficiency (CVI).[Belcaro 2001] Active ingredients of EG are sodium heparin, aescinate and essential phospholipids. Since there are studies showing that EG can cause an improvement in venous tone[Annoni 79] and in venous disease,[Grossmann 1991] a double blind crossover placebo controlled study was also carried out in order to evaluate the value of the proposed treatment on VVD changes in a group of patients with varicose vein disease.

Patients and methods

36 patients (11 males and 25 females; age from 31 to 67 years) with a diagnosis of varicose vein disease entered the study. A written informed consent was obtained from all subjects and the study was approved by the Institutional Review Board. The subjects were recruited with the unique criteria that they had a measurable VVD.

Measurements were made in a temperature controlled room at 24±2°C, after 15 minutes of acclimatization.

Exclusion criteria were: a) incompetence of deep venous circles of lower extremities as determined by the Perthes' test,[kim 00] b) no administration of systemic or local drugs with trophic action (i.e. anti-edematous or analgesic agents) during the 30 days preceding the study, c) known hypersensitivity to EG, d) presence of other pathologies, especially of the skin, that could interfere with drug application or with the evaluation of treatment, e) poor treatment compliance.

At each visit the subjects' VVD was assessed in the standing and supine positions. In order to assess the intra- and inter-assay reproducibility, all the examinations were performed by the same sonographer (D.B) and followed exactly the same scan protocol. Three patients performed the baseline assessment but did not complete the trial for reasons not connected to the study. These patients were considered for the intra-assay reproducibility studies but their data were not included in the pharmacological study. The remaining 33 patients completed the trial without any serious adverse events; they remained clinically stable during the study, and did not change any concomitant drug therapy. Compliance in these 33 patients was 100% as assessed by counting of tubes returned.

An ESAOTE AU4 ultrasonograph, configured with a 10-13 MHz linear array probe which maintains an axial resolution of about 0.2 mm was used to image VVDs. This type of ultrasonic transducer focalizes images in a range of depth from 2.5 to 3 cm. Thus, if used as such, it does not allow to image very superficial vessels such as subcutaneous veins. In order to solve this problem the probe was assembled with an appropriate spacer (figure 1), which allows to separate the probe from the skin by 2-2.5 cm, interposing a pipe of rubber filled with water. In addition, since veins may easily collapse changing their diameter even with a very light skin

compression, the ultrasonic scans were performed in a gel-bath, carefully avoiding any contact between the spacer and the patient's skin (figure 1, right panel and figure 2, bottom panels). This spacer was appropriately modified with two plastic rings, thus imposing a fixed distance between the spacer and the skin (figure 1).

The subcutaneous varicose veins' anatomy is composed of a series of messy and not easily recognizable ectasies (figure 3, right panel). Thus, in order to improve accuracy and reproducibility of measurements of the diameters of ectasies, a specific equipment which allows to identify, at each visit, exactly the same ectasy measured in the first examination was developed (figure 2, top panels). This new methodology consists of a series of external reference guides allowing the precise positioning of patient and transducer as in the previous examination. Specifically, the equipment consists of a small platform adjustable in height with a precision of 1 mm (figure 2, left panels). This platform is used to support the probe which, in turn, was assembled with the spacer. The platform allows to study the patient in the standing position, also allowing a circumferential scan of the area of interest, thus accurately avoiding unintentional vertical movements of the transducer. The platform also allows to draw a horizontal line on the patient's skin necessary for the positioning of a second vertical platform for precise probe positioning on the leg when the patient is in the supine position (figure 2, right panels).

During the first scanning, the position of the feet with respect to the platform is recorded by tracing feet perimeters on an individual paper sheet (figure 2, top and left panel). The height of the horizontal platform is adjusted according to the position of the ectasy and then recorded. The probe is positioned on the platform and approached to the skin, carefully avoiding any compression. When a selected ectasy is imaged, the probe position on the platform is designated by specific

coordinates. In addition, images of the ectasies chosen for diameter measurements are printed for comparison with images obtained in the following visits (example in figure 3, right panel). Traced footprints, height of the platform and probe position as well as printed images guided the operator in the search for the same ectasy during the following scans. When measurements in the standing position are completed the patient takes the supine position. The horizontal line drawn on the skin during the standing examination is used for positioning of the vertical platform for the supine examination (figure 2, right panels). Once positioned, the vertical platform helps the operator in the search of the same ectasy visualized in the standing position. Also these images, visualized for venous diameter measurements in the supine position, are printed and stored for visual comparison with images obtained at the following visits.

After 15 minutes of rest, in the sitting position, measurements of ectasies in the standing and supine position are repeated for the assessment of intra-assay reproducibility. The complete procedure is generally carried out in less than 40 minutes.

In order to obtain a higher accuracy, the VVD of each imaged ectasy was obtained by averaging values of at least three randomly chosen frames. The individual subject's mean VVD values were then calculated averaging values from all visualized ecstasies.

Essaven gel administration

In order to assess the method capacity to detect VVD changes induced by a pharmacological treatment, a double-blind, crossover study, was performed. To this aim, after the baseline visit, patients with varicose vein disease were randomly

allocated either to therapy with Essaven Gel (EG) (AVENTIS PHARMA S.p.A. Italy) or to placebo. After a treatment period of 4 weeks, each patient was switched to the respective alternate treatment option for another 4 weeks. EG was administered 3 times daily in a thin film, evenly distributed over the area of interest. Patients were instructed to standardize gel applications as follows: a cylinder of 3 cm of gel (about 0.6 g of compound) was carefully measured in length and applied to the area of interest. A superficial standard massage was made using two fingers for 5 minutes in circulatory motions stimulating absorption. After the baseline investigation, patients were monitored again after one month of treatment. Treatment was repeated with a cross-over design after a wash-out period of two weeks. The operator was unaware of the contents of the gel tube. Sealed envelopes were opened at the end of the evaluation of all subjects and data entry. The randomization process was controlled by an external Clinical Research Organisation.

Intra- and inter-assay variability

Intra- and inter-assay repeatability in VVD determination have been investigated. In order to estimate intra-assay variability, subjects underwent the ultrasonic VVD examination twice, 15 minutes apart. For the analysis, data of replicate scans performed in the two baseline visits of the cross-over study have been pooled and a total of 72 replicate scans analyzed.

Inter-assay variability was evaluated by comparing VVD values obtained averaging measurements of the two replicate scans obtained during the baseline examination of the first phase with those obtained during the second baseline examination of the crossover phase performed after 15 days of wash out. Thus a total of 36 duplicate

values were analyzed. Measurements and calculations of the average diameter of all ectasies considered were carried out, on line, by an independent blind investigator.

Statistical analyses

Means and SD values were used as descriptive measures of normally distributed variables. Error bars on the figures represent ± SD. The intra- and inter-assay comparisons were evaluated by estimating the consistent bias between measurements, as recommended by Bland and Altman.[Bland and Altman Lancet. 1986] The coefficient of repeatability was calculated according to the British Standards Institution,[British standards institution 1979] and corresponds to 2SD of the relative difference between replicate measurements. The response to EG administration was analyzed by ANOVA for repeated-measures. The crossover treatment trial was analyzed according to the recommendations of Hills and Armitage[Hills Br J Clin Pharmacol. 1979] for crossover trials.

Results

Intra-assay repeatability of VVD measurements: initial vs 15 minutes replicate values

The intra-assay comparison of VVD values between the initial and replicate scan is shown in figure 4. Relative differences in VVD values remained constant as the VVD increased from 1.4 mm to 7.8 mm in the standing position (figure 4, left panel) and from 0.8 mm to 6.8 mm in the supine position (figure 4, right panel). Although there was some variability in the measurements of VVD, the intra-assay agreement was high, with a bias between measurements of 0.06±0.18 mm, with limits of

agreement ranging from -0.29 to 0.41 mm in the standing position and of -0.02±0.19 mm and limits of agreement ranging from -0.39 to 0.36 mm in the supine position. The intra-assay mean absolute difference was 0.14±0.11 mm (range: 0.00 to 0.57 mm), with a correlation coefficient of 0.99 ($p<0.0001$; figure 5, left panel), the coefficient of repeatability being 0.37 mm in the standing position. In the supine position the mean absolute difference was 0.14±0.12 mm (range: 0.00 to 0.51 mm), with a correlation coefficient of 0.99 ($p<0.0001$; figure 5, right panel) and a coefficient of repeatability of 0.37 mm.

Inter-assay repeatability of VVD measurements: comparison between baseline values of the two phases of the pharmacological study

The inter-assay comparison of VVD values between the baseline of the first and the second phase of the clinical study are shown in figure 6. As in the intra-assay comparison, relative differences in VVDs remained constant as the diameters of ectasies increased from the lowest to the highest diameter. Although also in this case there was some variability in VVD measurements, the inter-method agreement was similar to that observed in the intra-assay assessment, with a bias between measurements of 0.06±0.34 mm, with limits of agreement ranging from -0.61 to 0.73 mm in the standing position (Figure 6, left panel) and of 0.07±0.40 mm, with limits of agreement ranging from -0.72 to 0.86 mm in the supine position (Figure 6, right panel). The inter-assay mean absolute difference was 0.21±0.26 mm (range: 0.00 to 1.29 mm), the correlation coefficient 0.98 ($p<0.001$; figure 7, left panel) and the coefficient of repeatability 0.67 mm in the standing position. In the supine position the mean absolute difference was 0.26±0.30 mm (range: 0.01 to 1.13 mm),

the correlation coefficient 0.97 ($p<0.0001$; figure 7, right panel) and the coefficient of repeatability 0.37 mm.

Evaluation of the method ability in detecting VVD changes induced by EG treatment

No significant differences were found in any baseline clinical characteristic between patients allocated either to EG first (n=18) or to placebo first (n=18); (data not shown).

No statistically significant EG variations on standing or supine VVD were observed either in the first phase or in the second cross-over phase of the study. Since one of the methodological errors that often occurs in this type of studies is the recruitment of patients not strictly comparable for the degree of venous dilatation[(Cornu-Thenard Phlebologie 1992)] analyses was repeated in more comparable patients obtained by the exclusion of the patients in the lowest tertile of baseline VVD.

Changes in VVDs before and after treatment obtained in these more homogeneous (and probably more treatment sensitive) patients are reported in figure 8. Although again not statistically significant, treatment with EG induced, on average, a reduction in standing VVD in both phases of the cross-over study; while the placebo did not. Indeed, while in the placebo group mean increases in VVD of about 0.01 mm were observed both in the first and in the second phase of the cross-over study, a reduction of VVD of about 0.03 mm in the first phase and of 0.09 mm in the second phase was observed in patients treated with EG. VVDs in the supine position and supine/standing VVD ratios were again unaffected by EG treatment.

Discussion

This study demonstrates an accurate and precise method for the imaging of veins and venous ectasies in patients with varicose vein disease. The high tortuosity of varicose veins, the lack of clear points of reference, and the high collapsibility of subcutaneous vessels when the probe is positioned on the skin, makes standard ultrasound methods poorly reproducible and not applicable for the study of varicose vein disease in clinical research. We succeeded in bypassing the above mentioned problems and benefited from the specific tools described in this study. To the best of our knowledge this is the first study evaluating the reproducibility of VVD measurements and, as such, comparison of results with those found by others was difficult.[cornu-Thenard 92, Jeanneret 99,]

On the basis of our experience, variability of VVD measurements is mainly determined by sonographer's subjectivity in image collection and by biological differences between subjects (in patients with highly tortuous ectasies, measurements may be less accurate). Since biological differences between subjects cannot be influenced, it is important to reduce, whenever possible, the effect of other factors determining variability.

In the present study a) combining the probe with an appropriate spacer which allows to image very superficial vessels b) performing scans carefully avoiding any contact between the spacer and the patient's skin, and c) using specific equipment for guiding the operator in patient and probe positioning, we were able to avert biases easily occurring upon repeated measurements.

The ability of the proposed method to assess VVD changes is supported by its capacity to detect very small changes induced by EG treatment. Data in figure 8, indeed, make it clearly evident, that the method is sensitive enough to detect, at least in the standing position, VVD changes induced by this pharmacological

treatment.[Sirtori 2001] Standing VVDs were, in fact, consistently lower after treatment than at baseline, even if differences did not reach statistical significance. Because of the lack of statistical significance, likely due to small sample size, this finding must be viewed with caution; however, the fact that the effects on standing VVD were evident in both phases of the cross-over suggests a low probability that results may have been obtained only by chance.

In conclusion, our results show the possibility of measuring VVD with high accuracy and precision, thus allowing to propose this method, as a reliable technique for VVD assessment in clinical trials and/or as suitable for short and long-term follow-up of patients with varicose vein disease. Such a systematic follow-up will identify possible associations between early alterations and the subsequent development of clinical conditions. Finally, changes in vein diameters induced by pharmacological treatments could be accurately monitored by this technology.

References

Annoni F, Mauri A, Marincola F, Resele LF. Venotonic activity of escin on the human saphenous vein. Arzneimittelforschung 1979;29(4):672-675.

Belcaro G, Nicolaides AN, Geroulakos G, et al. Essaven gel. Review of experimental and clinical data. Angiology 2001;52:S1-4.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-310.

Boivin P, Cornu-Thenard A, Charpak Y. Pregnancy-induced changes in lower extremity superficial veins: an ultrasound scan study. J Vasc Surg 2000;32:570-574.

British standards institution. Precision of test methods I: Guide for the determination and reproducibility for a standard test method (BS 5497, part 1). London: BSI, 1979.

Coleridge-Smith PD. Venous ulcer. Br J Surg 1994;81:1404-1405.

Cornu-Thenard A, Boivin P, Garde C, Sentou Y. Evaluation of the results of the curative treatment of varices using 3 scoring systems: clinical, Doppler and echographic. Phlebologie 1992;45(4):389-399.

Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Comm Health 1999;53:148-153.

Evans CJ, Fowkes FGR, Hajivassiliou CA, et al. Epidemiology of varicose veins: a review . Int Angiol 1994;13:263-270.

Ghiringhelli L. Instrumental diagnosis of varicose veins. Ann Ital Chir 1992;63:417-422.

Grossmann K. Die medikamentöse therapie der chronischen venenerkrankungen. Vasomed aktuell 1991;5:21-32.

Hertzberg BS, Kliewer MA, DeLong DM, et al. Sonographic estimates of vein size in the lower extremities: subjective assessment compared with direct measurement. J Clin Ultrasound 1998;26(3):113-117.

Hills M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8:7–20.

Jeanneret C, Labs KH, Aschwanden M, Bollinger A, Hoffmann U, Jager K. Physiological reflux and venous diameter change in the proximal lower limb veins during a standardised Valsalva manoeuvre. Eur J Vasc Endovasc Surg 1999;17(5):398-403.

Johnson MT. Treatment and prevention of varicose veins. J Vasc Nurs 1997;15(3):97-103.

Kim J, Richards S, Kent PJ. Clinical examination of varicose veins: a validation study. Ann R Coll Surg Engl 2000;82(3):171-175.

Leifeld K, Ranft J, Kucharczik A, et al. Imaging real-time sonography (B-scan) of peripheral veins-possibilities for use with reference to secondary prevention. Vasa Suppl 1991;33:257-258.

Muller-Lisse UL, Muller-Lisse GU, Holzknecht N, Reiser M. Ultrasonography of veins. Radiologe 1998;38:560-569.

Niebes P. Vessel wall modification in venous pathology. Application to the study of phlebotonic drugs. Int Angiol 1996;15:88-92.

Sirtori CR. Aescin: pharmacology, pharmacokinetics and therapeutic profile. Pharmacol Res 2001;44(3):183-193.

Sohn C, Karl C, Schonlau H. Comparative studies of the venous system of the arm and leg before and after delivery. Z Geburtshilfe Perinatol 1987;191(6):219-224.

Thibault PK, Lewis WA. Recurrent varicose veins. Part 1: Evaluation utilizing duplex venous imaging. J Dermatol Surg Oncol 1992;18(7):618-624.

Vettorello GF, Gasbarro V, Mascoli F, Navarra G, Occhionorelli S, Rubbini M, Cerreta G, Pozza E, Donini I. "Simulated walking" in the duplex evaluation of the venous system. The clinical and instrumental correlations. Minerva Cardioangiol. 1994;42(12):559-567.

Legends to figures

Figure 1. In the left panel is represented the spacer's transducer which allow to outdistance the probe from the skin of 2-2.5 cm interposing a pipe of rubber filled with water. The spacer is also assembled with the two rings allowing ultrasonic scans in a gel-bath without contact between the spacer and the patient's skin. In the right panel the spacer is assembled with the transducer.

Figure 2. External reference guide which allows to identify, at each visit, exactly the same ectasy measured during the first examination (see text). The platform also permits to draw an horizontal line on the patient's skin necessary for the positioning of a vertical platform (right panels) which allow the precise probe positioning on the leg when the patient is in supine position.

Figure 3. Typical image of a subcutaneous saphenous veins of a control subject (left panel) and of saphenous veins ectasies (right panel) as assessed by B-mode ultrasonography.

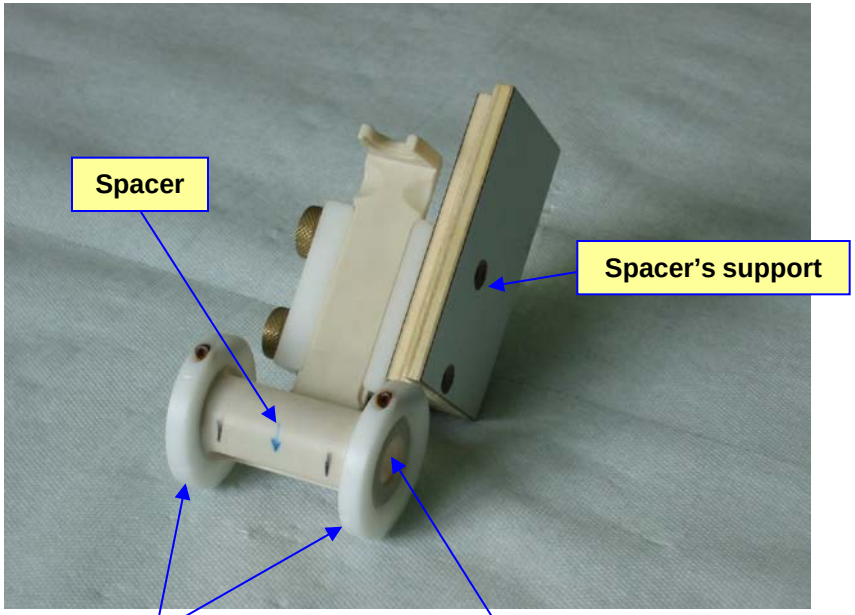
Figure 4. Intra-assay repeatability of varicose veins diameter (VVD) determination in the standing position (left panel) and the supine position (right panel). Scatterplots show the differences between the first and second scanning of the VVD measurements plotted against their mean. The mean difference (dashed line) and the limits of agreement (continuous line) are also indicated.

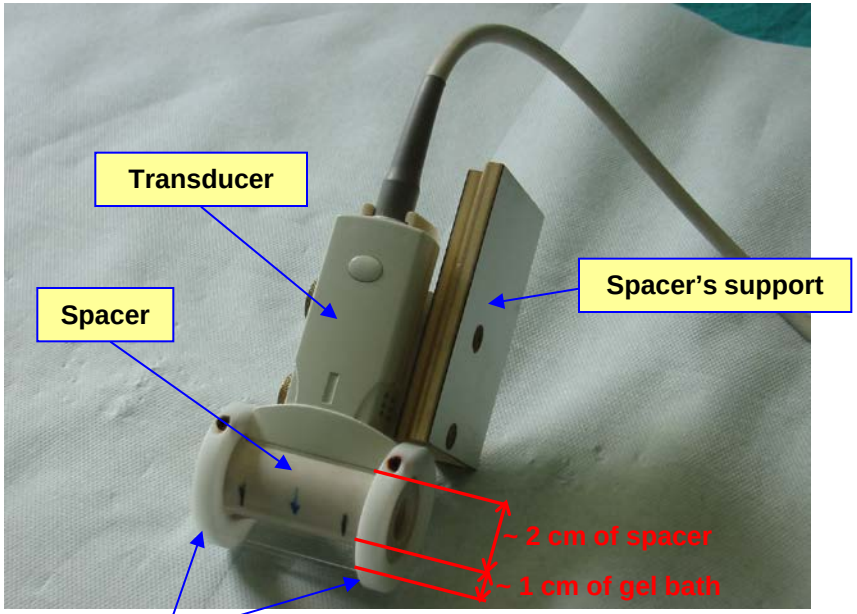
Figure 5. Intra-assay relationship between scan 1 and scan 2 for VVD measurements obtained in the standing (left panel) or in the supine position (right panel).

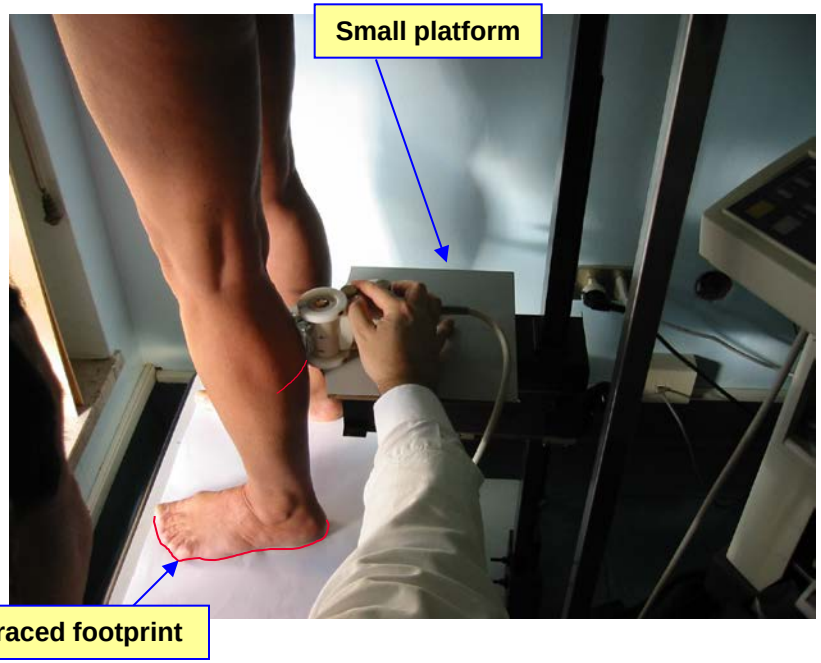
Figure 6. Inter-assay repeatability of varicose veins diameter (VVD) determination in the standing position (left panel) and the supine position (right panel).

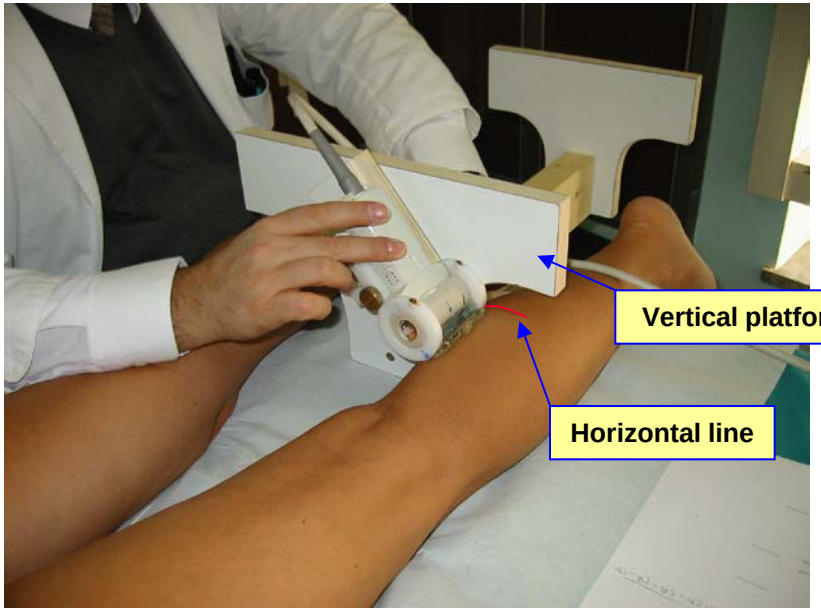
Figure 7. Inter-assay relationship between scan 1 and scan 2 for VVD measurements obtained in the standing (left panel) or in the supine position (right panel).

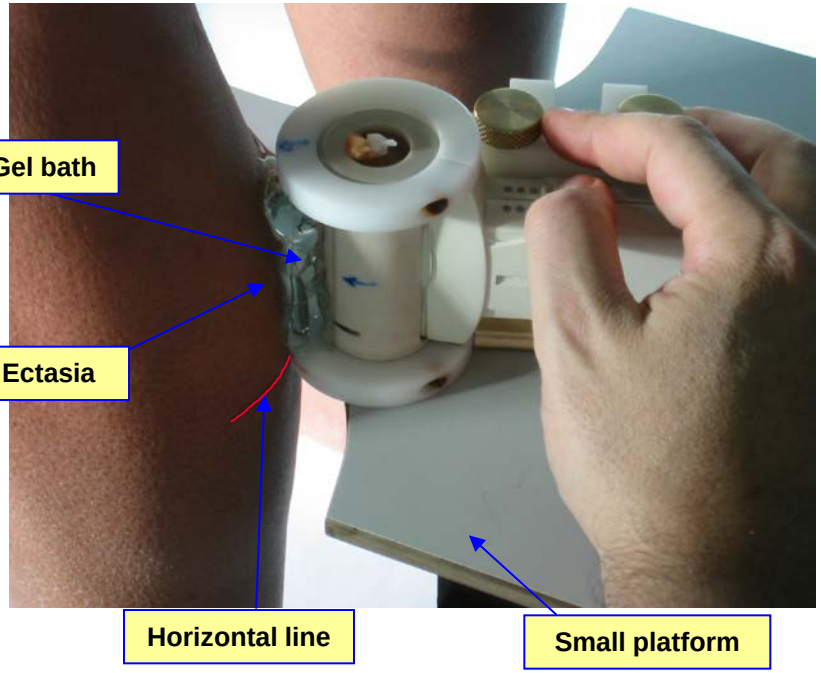
Figure 8. VVD changes induced by Essaven gel in a cross over design after exclusion of patients in the first tertile of baseline VVD. Although not statistically significant, in both phases of the cross-over study the treatment seems to reduce the standing VVD in the Essaven gel treated group but not in the placebo treated group.

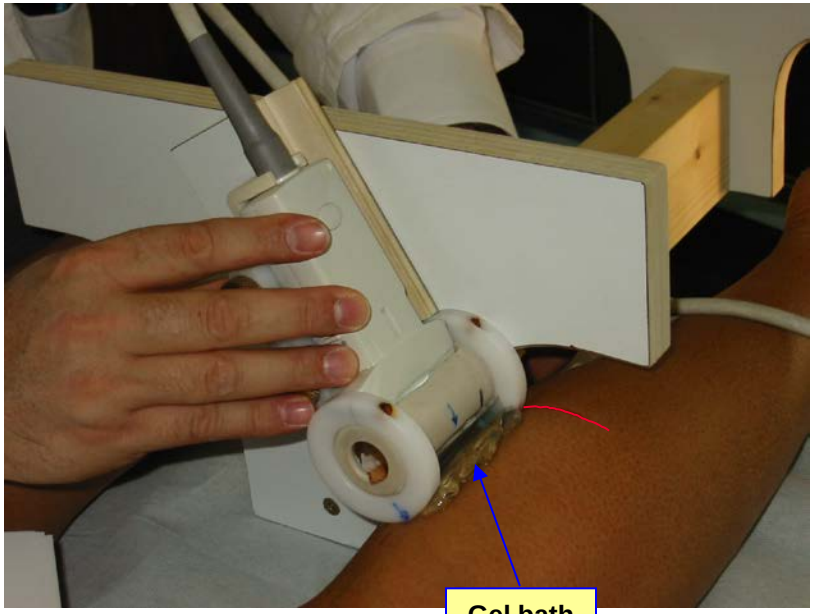

Spacer
Spacer's support
Plastic rings
Pipe of rubber

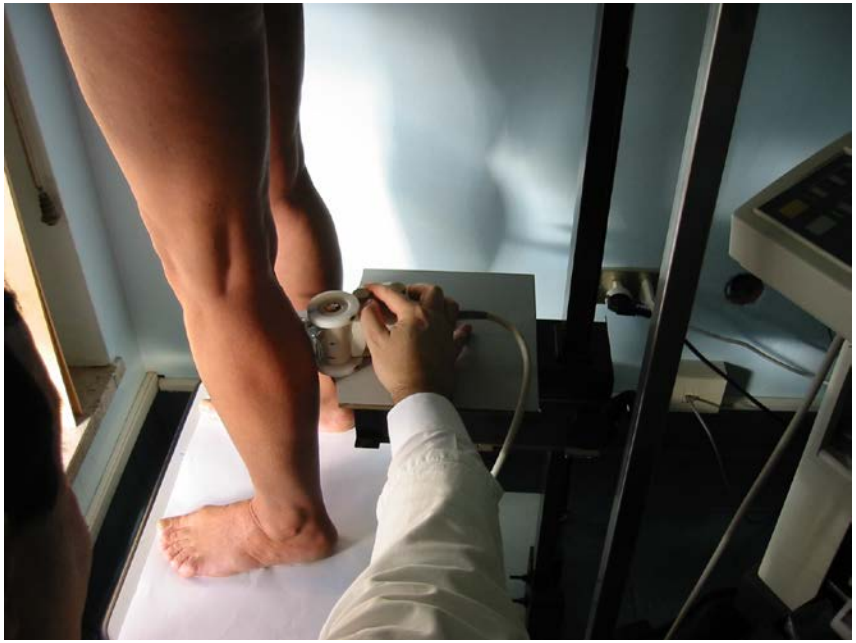

Transducer
Spacer's support
Spacer
~ 2 cm of spacer
~ 1 cm of gel bath
Plastic rings

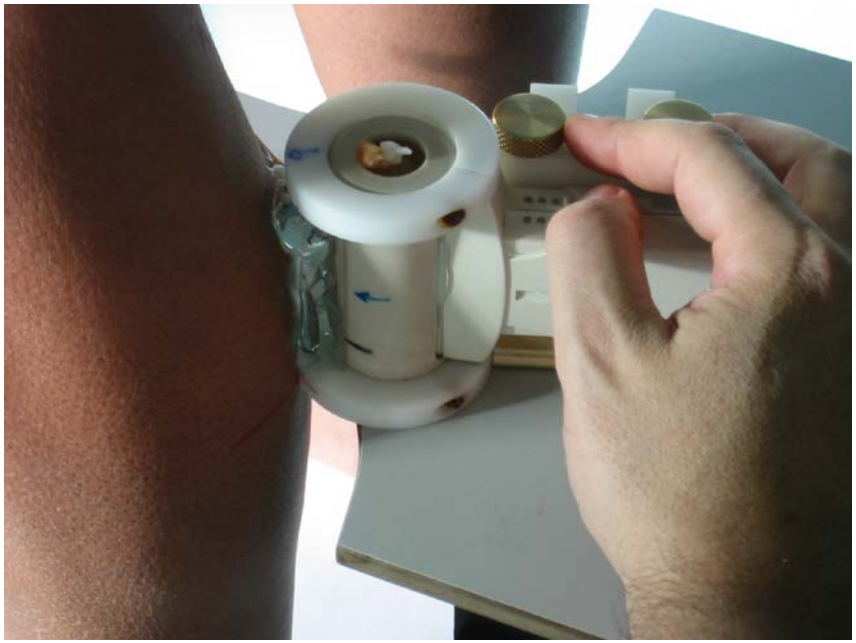

Small platform
Traced footprint

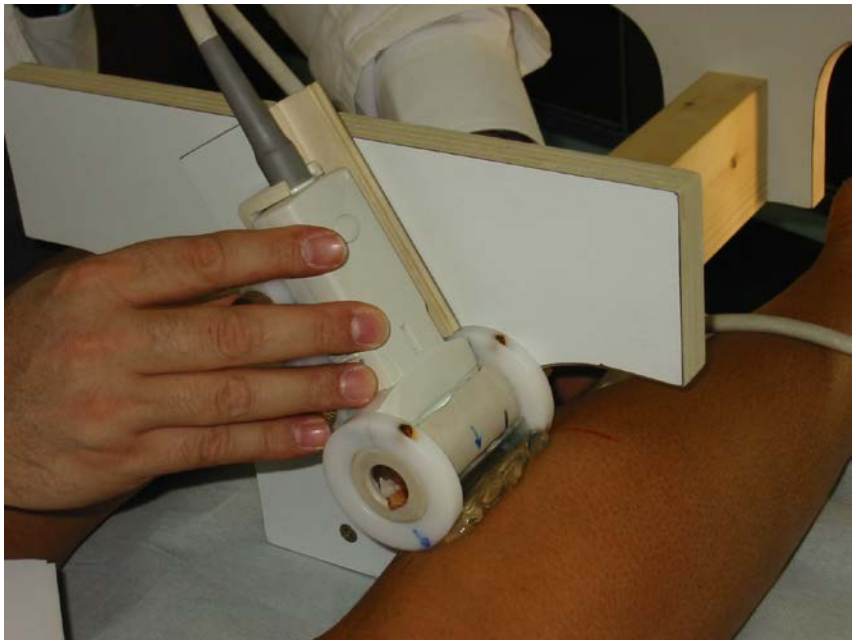

Vertical platform
Horizontal line

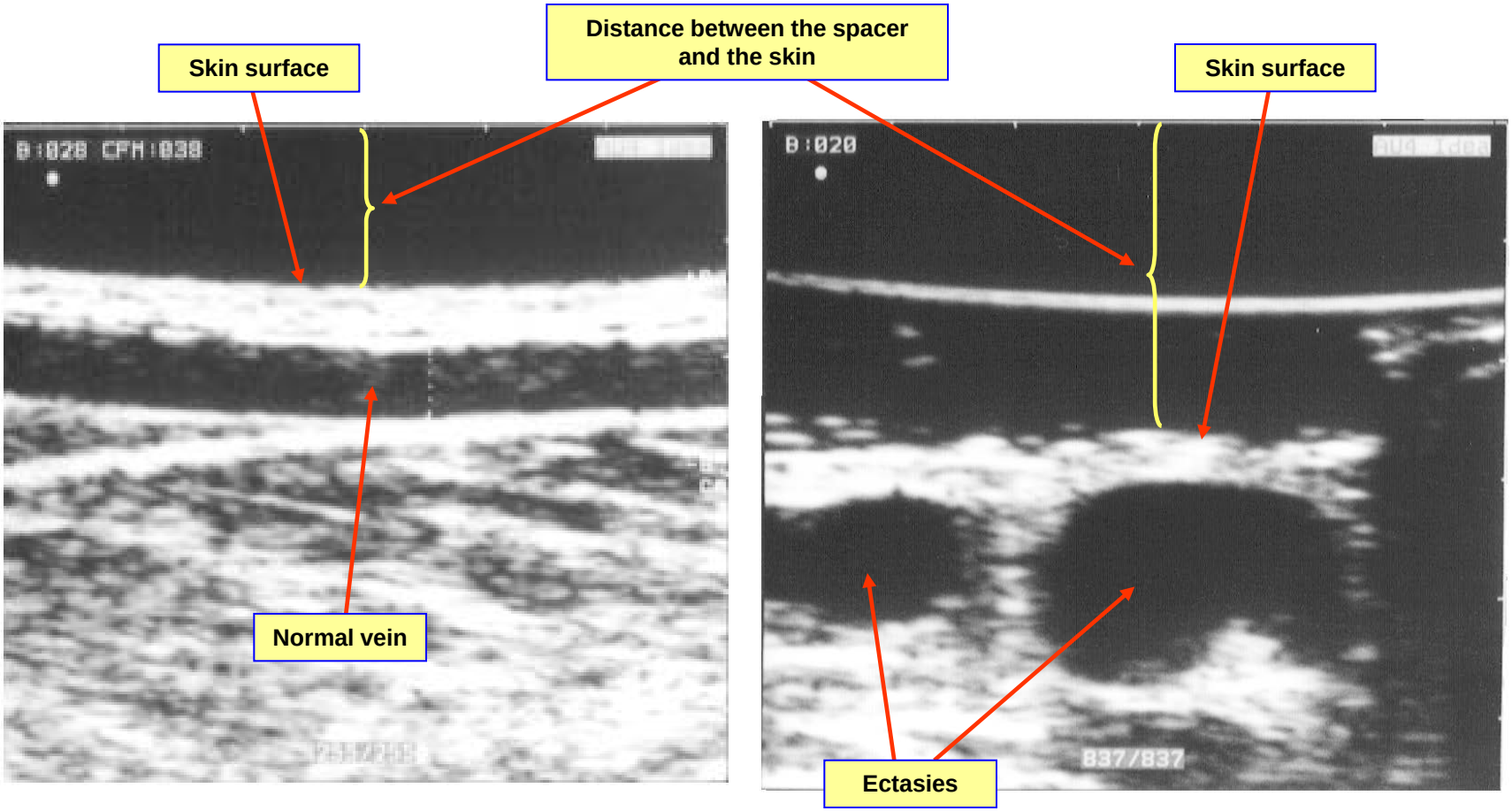

Gel bath
Ectasia
Horizontal line
Small platform

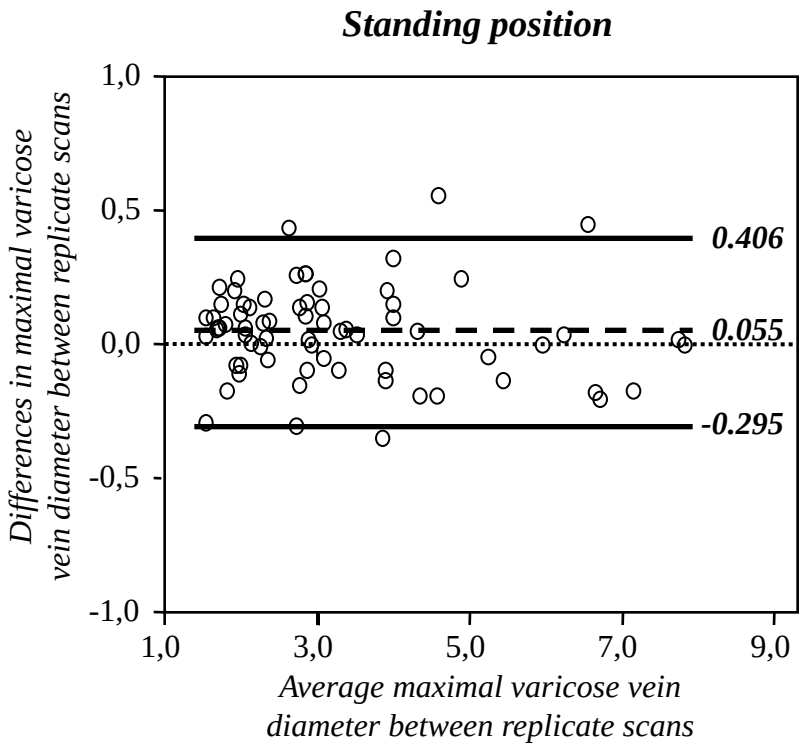

Gel bath

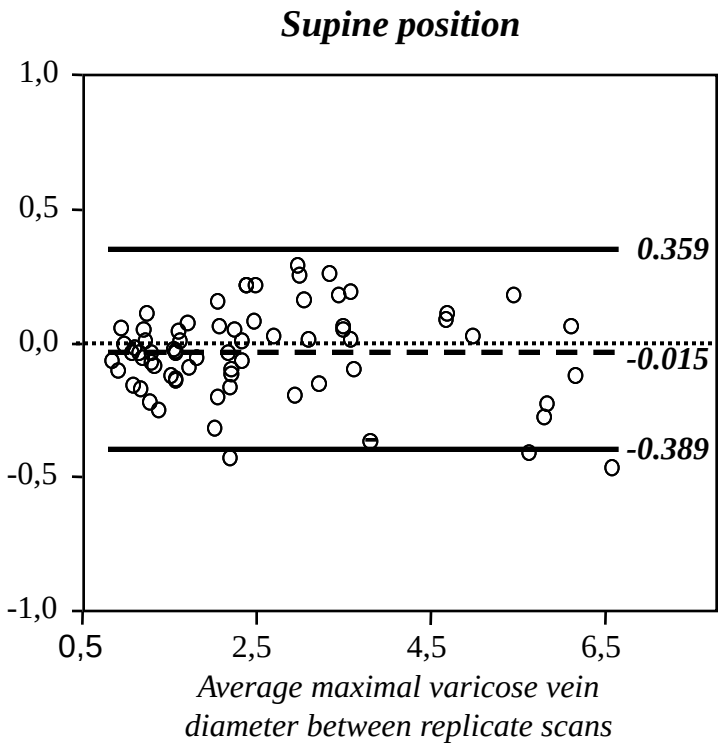


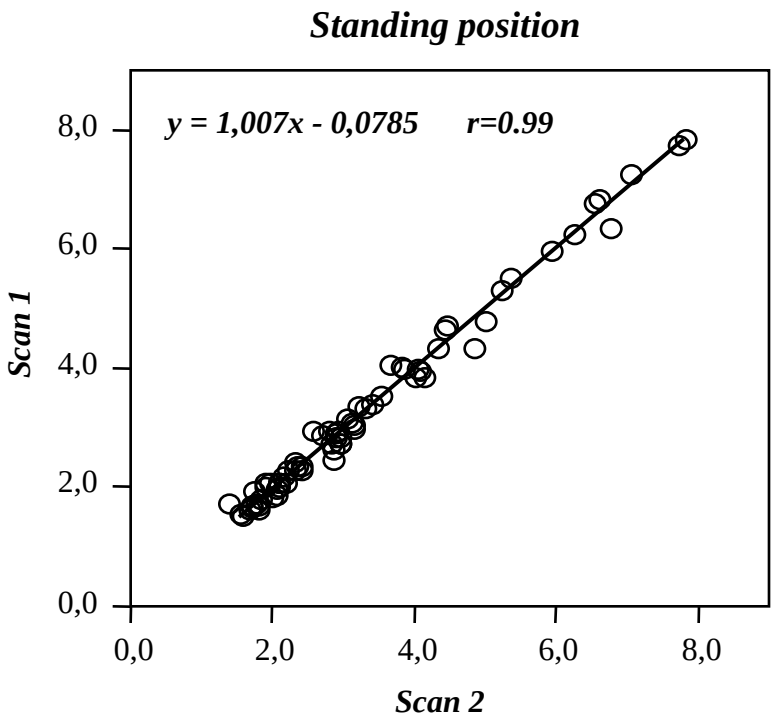


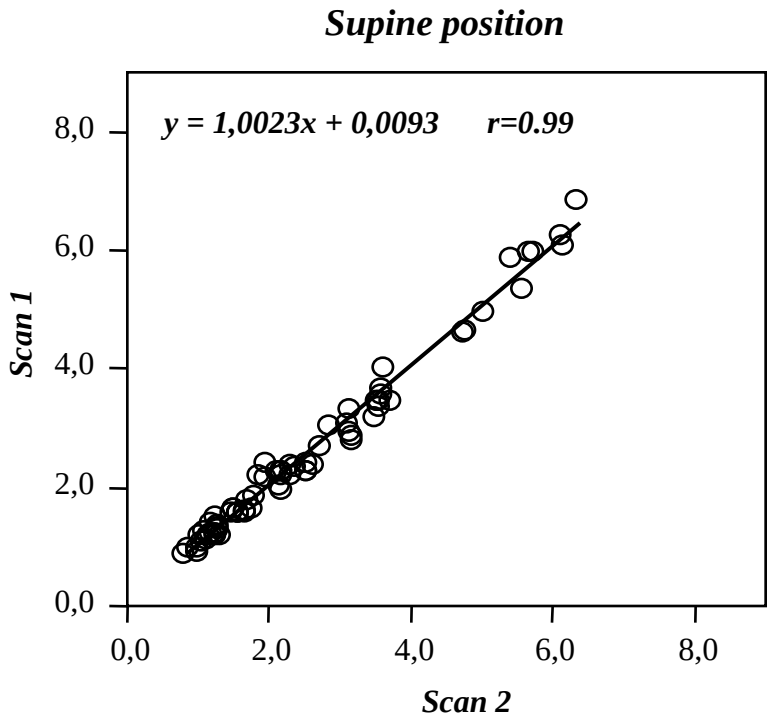


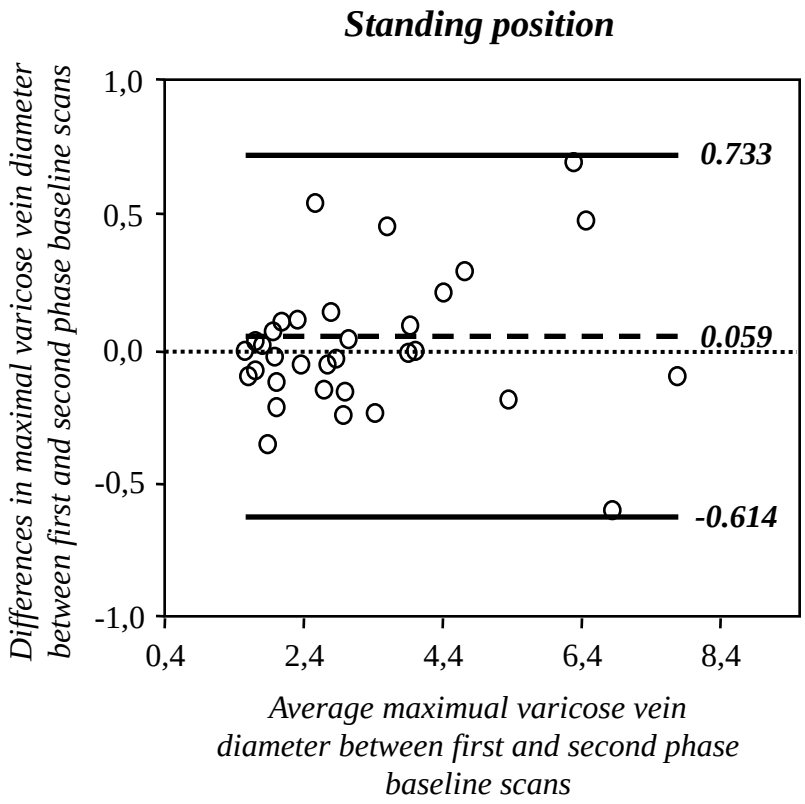

Skin surface
Distance between the spacer and the skin
Skin surface
Normal vein
Ectasies

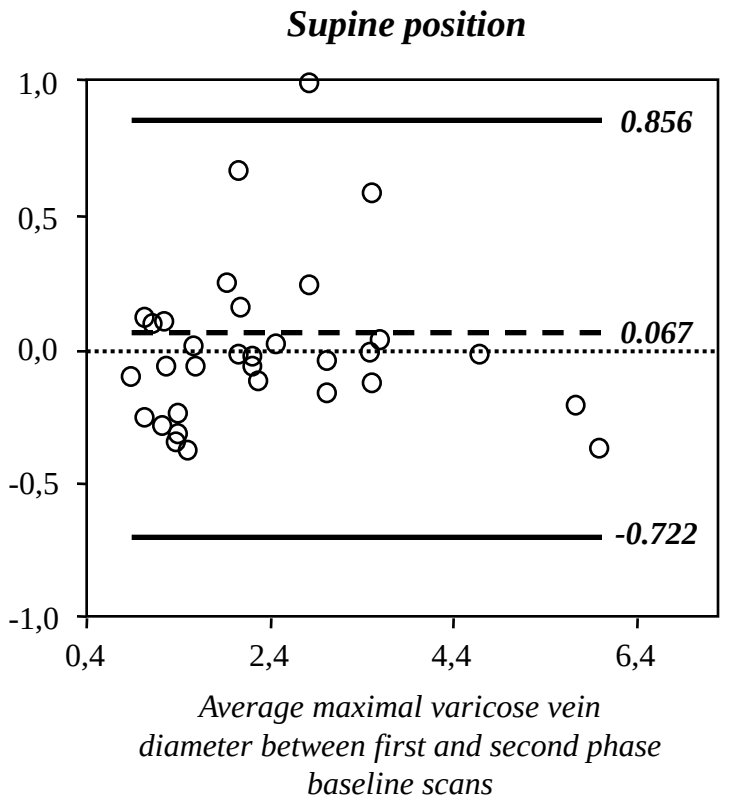

Standing position
Differences in maximal varicose vein diameter between replicate scans
1,0
0,5
0,0
-0,5
-1,0
0.406
0.055
-0.295
1,0
3,0
5,0
7,0
9,0
Average maximal varicose vein diameter between replicate scans

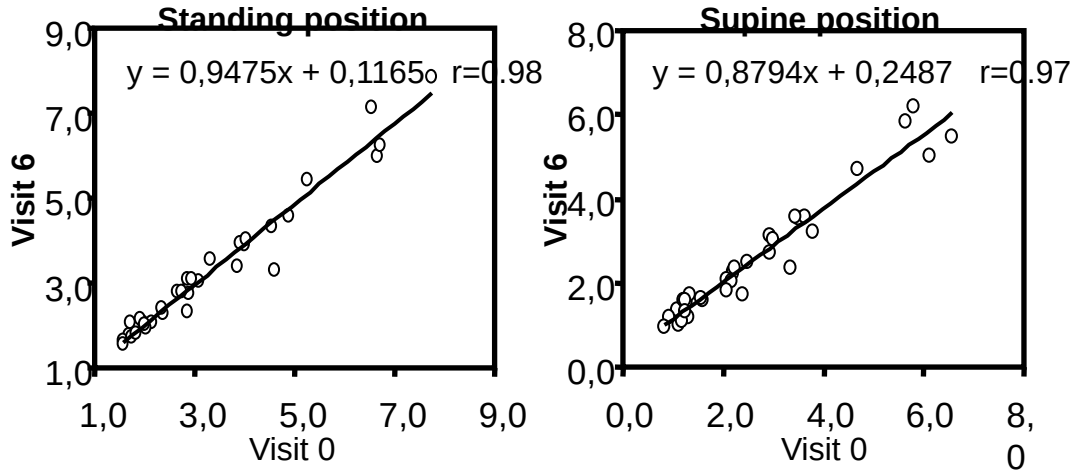

Supine position
1,0
0,5
0,0
-0,5
-1,0
0.359
-0.015
-0.389
0,5
2,5
4,5
6,5
Average maximal varicose vein diameter between replicate scans

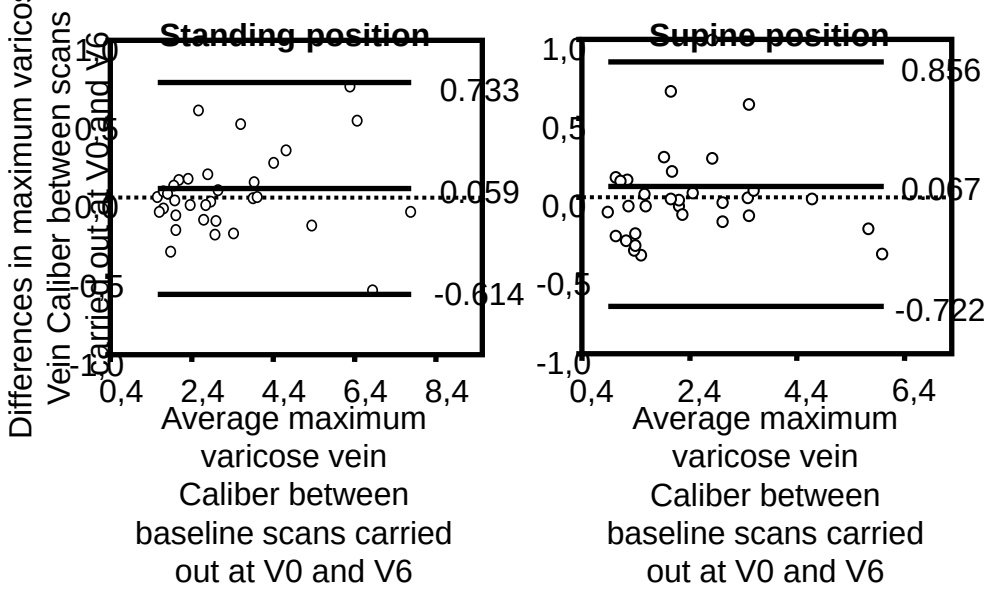

Standing position
y = 1,007x - 0,0785 r=0.99
Scan 1
Scan 2
0,0
2,0
4,0
6,0
8,0

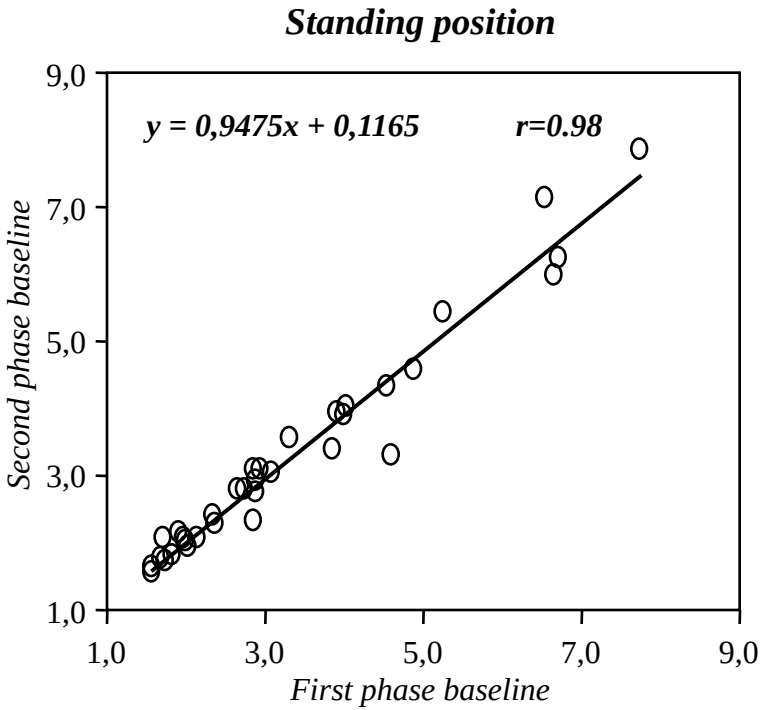

Supine position
y = 1,0023x + 0,0093 r=0.99
Scan 1
Scan 2
0,0
2,0
4,0
6,0
8,0

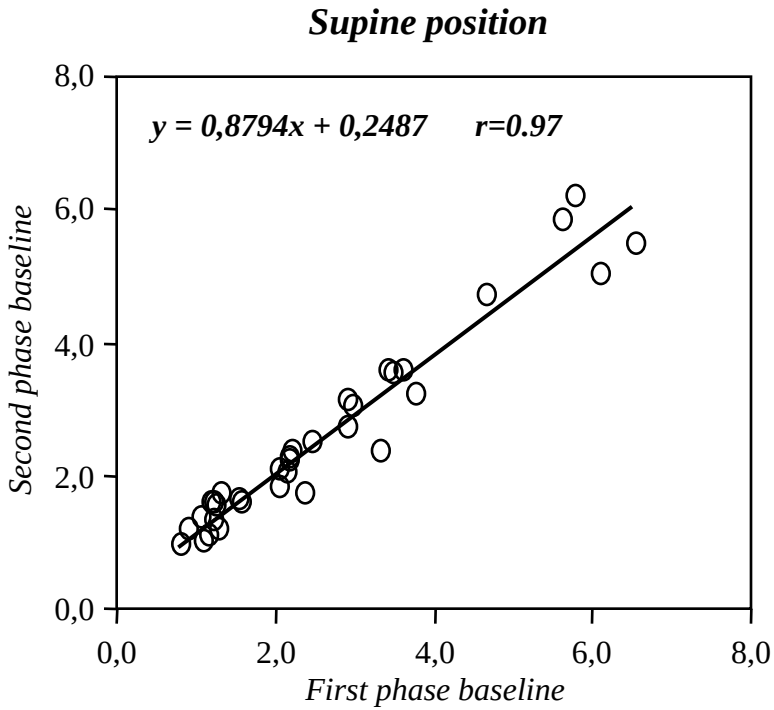

Standing position
Differences in maximal varicose vein diameter between first and second phase baseline scans
1,0
0,5
0,0
-0,5
-1,0
0,4
2,4
4,4
6,4
8,4
0.733
0.059
-0.614
Average maximual varicose vein diameter between first and second phase baseline scans

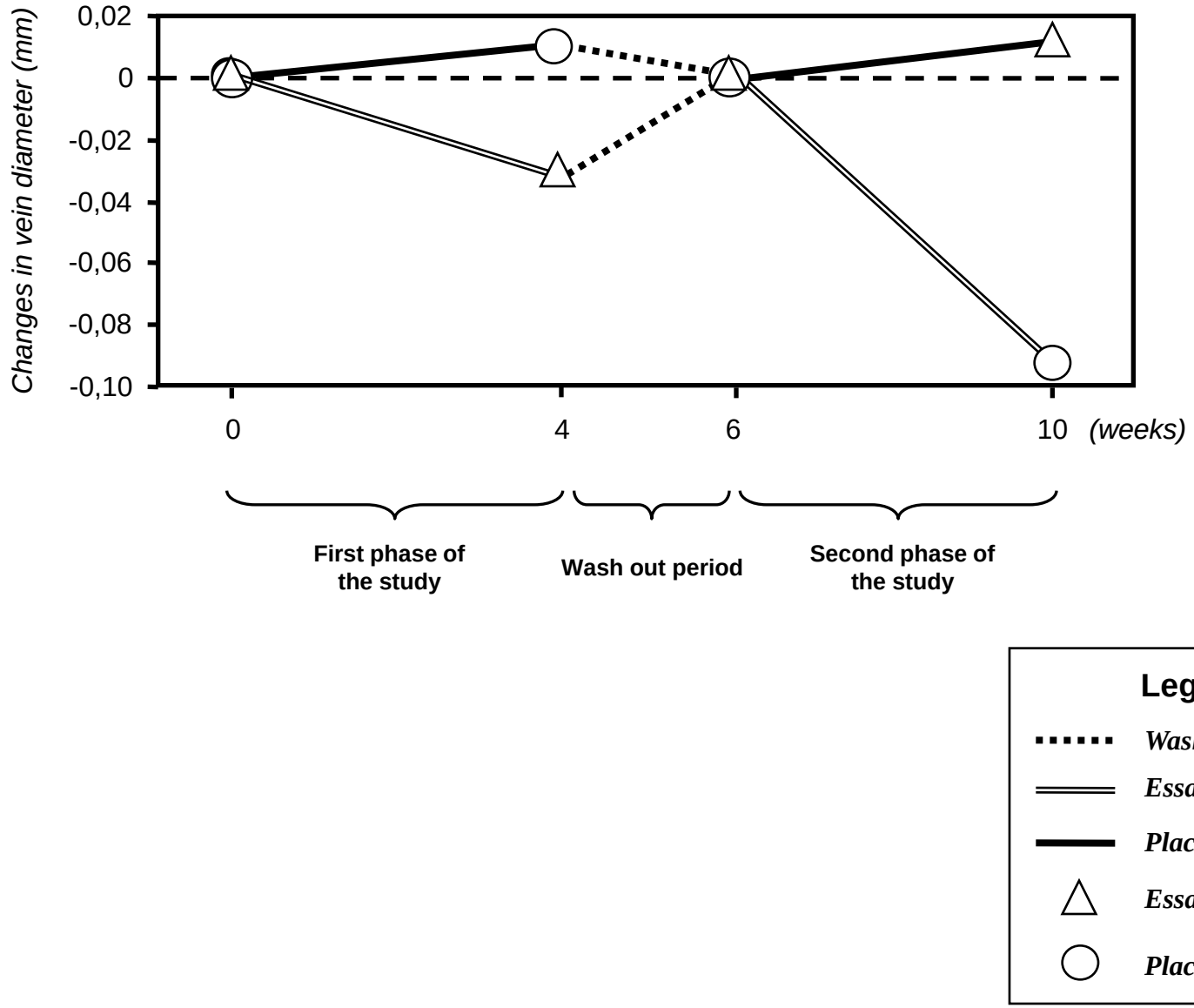

Supine position
1,0
0,5
0,0
-0,5
-1,0
0,4
2,4
4,4
6,4
0.856
0.067
-0.722
Average maximal varicose vein diameter between first and second phase baseline scans


Standing position
y = 0,9475x + 0,1165
r=0.98
Visit 6
Visit 0
9,0
7,0
5,0
3,0
1,0
1,0
3,0
5,0
7,0
9,0
Supine position
y = 0,8794x + 0,2487
r=0.97
Visit 6
Visit 0
8,0
6,0
4,0
2,0
0,0
0,0
2,0
4,0
6,0
8,0


Standing position
Supine position
Differences in maximum varicose Vein Caliber between scans carried out at V0 and V6
0.733
0.059
-0.614
0.856
0.067
-0.722
1,0
0,5
0,0
-0,5
-1,0
0,4
2,4
4,4
6,4
8,4
Average maximum varicose vein Caliber between baseline scans carried out at V0 and V6


Standing position
y = 0,9475x + 0,1165
r=0.98
Second phase baseline
First phase baseline
9,0
7,0
5,0
3,0
1,0
1,0
3,0
5,0
7,0
9,0


Supine position
y = 0,8794x + 0,2487
r=0.97
Second phase baseline
First phase baseline
8,0
6,0
4,0
2,0
0,0
0,0
2,0
4,0
6,0
8,0


Changes in vein diameter (mm)
0,02
0
-0,02
-0,04
-0,06
-0,08
-0,10
0
4
6
10
(weeks)
First phase of the study
Wash out period
Second phase of the study
Legend
Wash out period
Essaven
Placebo
Essaven-Placebo group
Placebo-Essaven group