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Venous Reflux and Venous Distensibility in Varicose and Healthy Veins

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Objectives. *The aim of this study was to analyse venous diameter changes and venous reflux parameters, assessed during a standardised Valsalva manoeuvre in healthy subjects and in patients with varicose veins.*
Methods. *Measurements were carried out in 444 vein segments, (96 legs of 48 healthy volunteers, 52 legs of 35 patients with varicose veins). The common femoral vein (CVF), the femoral vein (FV) and the great saphenous vein (GSV) were investigated. The parameters of reflux and the relative venous diameter change (VD diff %) were measured simultaneously during a standardised Valsalva manoeuvre.*
Results. *Venous diameter changes during Valsalva manoeuvre (VD diff) were significantly greater in the GSV and in the deep veins of varicose patients compared to healthy subjects. The median (Interquartile range) of VD max in the CFV was: 13.1 (3.5) mm and 11.2 (3.4) mm ($p = 0.0002$, Mann-Whitney - U test), in the FV 7.8 (2.7) mm and 6.9 (2.0) mm ($p = 0.01$, Mann-Whitney), in the GSV: 7.3 (3.7) mm and 4.2 (1.1) mm ($p < 0.0001$, Mann-Whitney) for the varicose and healthy veins respectively. Good correlation was seen for the retrograde peak reflux velocity (PRV) and VD diff % in varicose veins ($r = 0.71$ (0.57 − 0.81) $p < 0.0001$, Mann-Whitney).*
Conclusion. *Relative venous diameter - changes during a standardised Valsalva manoeuvre are significantly larger in the deep and superficial veins of varicose vein patients compared with healthy veins, the increased distensibility correlates with venous reflux parameters in varicose vein patients.*

Keywords: Venous reflux; Venous diameter changes; Varicose veins; Venous distensibility; Valsalva manoeuvre.

Introduction

Duplex ultrasonography has become the method of choice to investigate morphology and haemodynamic properties of varicose veins. Confirmation of venous incompetence has primarily been based on extent and duration of retrograde flow during standardised manoeuvres.[1,2] Suggested cut-off values for the duration of venous reflux range from 0.5 to 2 s.[3–8]

Veins distend greatly in response to pressure or volume flow changes as can be observed analysing venous wall motion.[9] Venous diameter changes during the rise of intravenous pressure may determine the duration and flow volume of reflux either by the extent of venous wall motion and/or by modifying venous valve function.[10] The widely used compression manoeuvre described by van Bemmelen does not provide conclusive testing of venous diameter changes, as it is only applicable in standing position.[2] The standardised Valsalva method has the advantage of reliable testing in both, the supine and standing positions.[11] Duplex ultrasonography allows simultaneous assessment of venous diameter changes over time in addition to venous flow.

Previous publications have not sought to correlate venous wall motion and venous reflux. The aim of this study was to investigate a possible correlation between venous reflux and venous diameter changes during a standardised Valsalva manoeuvre assessed by duplex ultrasonography in healthy subjects and in patients with varicose veins. We hypothesised that varicose veins are larger and more distensible than healthy veins.

Materials and Methods

Healthy subjects

Ninety-six legs of 48 healthy volunteers with a median age of 35.2 (range 20–76) years, including 23 female

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and 25 male, were investigated. All subjects were free of varicose veins (clinical class according to the CEAP classification = 0).[12] Median body mass index (BMI) was 22.0 kg/m^2 (16.8 − 32.0). Of the 48 healthy volunteers, 20 had at least one family member suffering from varicose veins.

Patients with varicose veins

Fifty-two legs of 35 patients (24 female, 11 male) with an incompetent sapheno - femoral junction (reflux time > 0.5 s) and an incompetent GSV in the thigh. Patients were included in they had at least a grade C_2 CEAP clinical classification[12] (C_2: 36 legs, C_3: 11 legs, C_4: 9 legs, C_5: 1 leg. The median age was 43.4 (range 21 − 73) years. The patients had a median BMI of 25 kg/m^2 (17.6 − 30.8). Thirty-one patients had family members with varicose veins.

Clinical investigation

The patients and the control subjects were investigated in the supine position after 10 minutes of rest. The room temperature was kept between 21° and 23° C. Clinical data recorded included family history, personal history, measurement of height and weight as well as assessment of the clinical and anatomic scores according to the CEAP classification.[12] Patients with a history of lung disease, symptomatic arterial occlusive disease and a history of deep vein thrombosis were excluded. All volunteers gave their informed consent for inclusion in this study.

Duplex ultrasonography and Valsalva manoeuvre

Duplex ultrasonography was performed with an ATL HDI 3500 ultrasound imaging system (Philips, Bothell, WA, USA). All measurements were made by the same investigator (CJ). A linear array probe (10−5 MHz) was placed in the groin in the sagittal plane, moving from the femoral artery medially to the common femoral vein (CFV), the femoral vein (FV) and the great saphenous vein (GSV). The Doppler insonation angle was set to 60°, the Doppler sample volume size was adjusted to insonate the entire vessel. If detectable, venous valves were noted if present in the CFV.. The measurements were carried out one cm below to the sapheno-femoral junction in the GSV and the CFV, and one cm below to the femoral junction in the FV. The diameter measurements were made between the inside walls of all veins. The venous diameters were measured whilst volunteers breathed normally and during the standardised Valsalva manoeuvre. The Valsalva manoeuvre was elicited by a forceful expiration into a tube, allowing measurement of the airways pressure by a manometer. A transducer (Trantec, Model 60-800, American Edward's Laboratories, USA) was used to allow the expiratory pressure to be displayed on the duplex screen. A pressure of 30 mmHg had to be established within 0.3 s and maintained for a period of at least 3 s.[1] The following parameters of reflux were measured during the investigation using the software of the duplex ultrasound machine: the retrograde peak reflux velocity (PRV cm/s), the reflux time (RT s) and the time average mean velocity (TAV cm/s). The flow volume (FVOL ml/s) and the absolute displaced volume (ADVOL ml) were calculated using the following formulas: FVOL = area × TAV (ml/s) and ADVOL = FVOL × RT (ml).[6] The venous diameter changes (in mm) were assessed and documented simultaneously with the reflux measurements during the Valsalva manoeuvre. Baseline venous diameter was taken during normal breathing (VD min). The maximal diameter during Valsalva manoeuvre (VD max) was defined using the cineloop and choosing the largest diameter during the increased expiratory pressure phase. To calculate the relative diameter changes in %, the diameter difference was divided by the baseline diameter.

Three measurements were made in each vein and an average of these was used for further statistical analyses. The investigations were recorded on videotape as well as on prints of still images.

Statistics

All limbs were analysed as an independent unit. Statistical analysis was calculated using the Stat View software package version 5.0 for Mac OS 9 (Stat View Software by Abacus C., Berkley, California) and Graphpad Prism version 4 for Mac OS X (Graphpad Software, San Diego, California).

As some venous distensibility variables and reflux values were not normally distributed, data were expressed as median with interquartile range (IQR), that is, the interval between the first and third quartiles. However, sample size calculation was performed on VD max of the common femoral vein after confirming normal distribution using D'Agostino and Pearson omnibus normality test. Sample size was estimated at 50 in each group to detect a difference between means of VD max of 1.9 (patients vs controls) with a significance level (alpha) of 0.05 (two-tailed) and a 95% power assuming a standard deviation (SD) of 2.6 (based on previous published data).[1]

Table 1. Median and interquartile range (IQR) of venous diameter (VD min) in mm during normal breathing at baseline and during Valsalva manouevre (VD max), absolute venous diameter change (VD diff) and relative venous diameter change during Valsalva manoeuvre in % of the venous diameter at baseline (VD %) in control subjects and in patients with varicose veins, investigated in the supine position

Vein segments parameters	Healthy subjects ($n = 96$ legs)	Varicose vein patients ($n = 52$ legs)	p
CFV VD min	8.4 (3.0)	9.7 (3.0)	0.004
FV VD min	5.9 (1.8)	6.0 (1.8)	0.4
GSV VD min	3.5 (0.93)	5.3 (2.8)	<0.0001
CFV VD max	11.2 (3.4)	13.1 (3.5)	0.0002
FV VD max	6.9 (2.0)	7.8 (2.7)	0.01
GSV VD max	4.2 (1.1)	7.3 (3.7)	<0.0001
CFV VD diff	2.3 (1.9)	3.1 (2.4)	0.03
FV VD diff	1.1 (0.9)	1.6 (1.5)	0.002
GSV VD diff	0.57 (0.47)	1.5 (1.5)	<0.0001
CFV VD %	0.27 (0.23)	0.30 (0.31)	0.4
FV VD %	0.19 (0.15)	0.27 (0.26)	0.005
GSV VD %	0.15 (0.15)	0.29 (0.26)	<0.0001

Common femoral vein (CFV), femoral vein (FV) great saphenous vein (GSV) Mann-Whitney U test.

Sample size calculation was performed using Graphpad Prism 4.0b and StatMate 2.0a.

Comparison between two groups was done by the non-parametric, unpaired Mann-Whitney-U test. Spearman correlation coefficients were calculated for association between independent, different parameters. A probability level of <0.05 was considered significant.

Results

Vein diameters in healthy subjects and varicose vein patients

The median and interquartile range (IQR) of venous diameters in healthy and varicose veins are displayed in Table 1. Except for the baseline - diameter in the FV, the venous diameters were significantly larger in patients compared to healthy veins (Table 1). The absolute difference defined as:

$$VD\ diff = VD\ max - VD\ min$$

and the relative venous diameter changes defined as:

$$VD\% = (VD\ max - VD\ min)/VD\ min \times 100$$

were significantly different in the venous disease and control groups. The only exception to this was for the relative diameter change in the CFV. The p values are given for the differences of each parameter between the healthy and varicose veins.

The impact of the body mass index (BMI) on venous diameter measurements is shown in Table 2. A cut off point of 22.5 kg/m^2 was used for analysis.[1] In healthy subjects BMI had no significant influence on venous diameters. In varicose vein patients VD min in the CFV and GSV as well as the VD max in the GSV were larger in individuals with higher BMI. This had no impact on venous diameter change measurements (VD %).

Except for the FV, no significant difference for absolute and relative diameter changes was seen between the left and the right leg in either varicose vein patients or in healthy subjects, as shown in Table 3.

Reflux parameters in healthy subjects and varicose vein patients

As shown in Table 4, reflux time (RT) and peak reflux velocity (PRV) in the proximal leg veins of varicose patients were significantly longer and higher, whereas FVOL and ADVOL in the CFV and the FV were equal in healthy and varicose veins. Venous valves were detectable in the CFV of 19 limbs.

Table 2. Median (IQR) of venous diameter changes in mm and in % in healthy subjects as well as in patients with varicose veins with a body mass index (BM) > 22.5 kg/m^2 and 22.5 kg/m^2, respectively

Vein segments parameters	Healthy subjects		p	Varicose vein patients		p
	BMI ≤ 22.5	BMI > 22.5		BMI ≤ 22.5	BMI > 22.5	
CFV VD min	8.1 (2.5)	9.1 (3.3)	0.1	8.3 (2.3)	10.4 (2.8)	0.02
FV VD min	5.6 (1.6)	6.1 (2.0)	0.3	5.9 (1.0)	6.0 (2.1)	0.9
GSV VD min	3.3 (0.83)	3.7 (0.86)	0.1	4.9 (1.4)	5.8 (3.2)	0.008
CFV VD max	10.6 (2.8)	11.7 (4.5)	0.08	10.8 (2.9)	13.2 (2.7)	0.07
FV VD max	6.8 (1.6)	7.3 (2.0)	0.1	7.3 (1.4)	8.1 (2.9)	0.4
GSV VD max	3.9 (0.98)	4.4 (1.3)	0.1	5.5 (2.6)	7.4 (3.7)	0.03
CFV VD diff	2.3 (2.2)	2.1 (1.7)	0.9	2.8 (1.4)	3.1 (2.6)	0.4
FV VD diff	1.0 (0.82)	1.2 (1.0)	0.3	0.87 (0.97)	1.8 (1.3)	0.1
GSV VD diff	0.56 (0.43)	0.56 (0.56)	0.7	1.5 (1.8)	1.5 (1.2)	0.5
CFV VD %	0.29 (0.27)	0.24 (0.18)	0.9	0.33 (0.25)	0.27 (0.32)	0.4
FV VD %	0.19 (0.13)	0.20 (0.16)	0.3	0.15 (0.23)	0.29 (0.22)	0.1
GSV VD %	0.15 (0.15)	0.16 (0.16)	0.7	0.36 (0.34)	0.28 (0.23)	0.5

P values for comparison, assessed with the Mann-Whitney U test.

Table 3. Venous diameter changes in healthy and varicose veins, right and left leg

Vein segments parameters	Healthy subjects		p	Varicose vein patients		p
	Right leg	Left leg		Right leg	Left leg	
CFV VD diff	2.5 (1.9)	2.5 (2.4)	0.33	2.9 (2.7)	3.1 (2.5)	0.94
FV VD diff	1.5 (1.2)	1.1 (0.88)	0.01	2.0 (1.6)	1.4 (1.2)	0.02
GSV VD diff	0.83 (0.83)	0.75 (0.86)	0.63	1.2 (1.1)	1.8 (1.8)	0.3
CFV VD %	0.30 (0.23)	0.24 (0.32)	0.22	0.32 (0.24)	0.30 (0.34)	0.69
FV VD %	0.23 (0.23)	0.19 (0.17)	0.02	0.34 (0.24)	0.24 (0.25)	0.07
GSV VD %	0.19 (0.21)	0.21 (0.18)	0.51	0.29 (0.25)	0.29 (0.23)	0.55

Median (IQR) of the venous diameter change during Valsalva manoeuvre (VD diff) in mm, venous diameter change in % of the baseline diameter (VD %), in the common femoral vein (CFV), the femoral vein (FV), the great saphenous vein (GSV), p values for comparison, Mann-Whitney U test.

Venous diameter changes and reflux parameters

Correlation coefficients of VD diff and reflux parameters are shown in Table 5. Best correlation was found between venous diameter change and PRV as well as with ADVOL, FVOL and TAV. Relative venous diameter changes expressed in percentage of the baseline diameter correlated better in varicose veins compared to healthy veins. Figs. 1 and 2 show the relation of PRV in cm/s and the relative venous diameter changes in % of the baseline diameter in the GSV of varicose vein patients and of healthy subjects.

Discussion

Compared to control subjects, the deep vein diameter in varicose vein patients increases significantly during a standardised Valsalva manoeuvre. Investigated under the same conditions, venous reflux parameters and venous diameter increase do correlate in the deep and superficial proximal lower limb veins. The best correlation was seen with the peak reflux velocity, the flow volume, the absolute displaced volume and the time average mean velocity in varicose veins. Body mass index and except for the FV, the side of the limb (right or left) had little or no influence on venous diameter changes.

Table 4. Median (IQR) of venous reflux parameters in healthy and varicose veins in the supine position

Vein segments parameters	Healthy subjects	Varicose vein patients	p
CFV RT	0.37 (0.46)	0.99 (1.0)	<0.0001
FV RT	0.17 (0.14)	0.26 (0.26)	<0.0001
GSV RT	0.16 (0.1)	3.5 (2.2)	<0.0001
CFV PRV	16.6 (12-5)	30.2 (26.6)	0.005
FV PRV	9.6 (6.4)	11.7 (10.3)	0.03
GSV PRV	7.9 (5.1)	21.3 (29.0)	<0.0001
CFV TAV	4.0 (5.3)	4.9 (5.1)	0.5
FV TAV	2.3 (2.2)	1.9 (1.5)	0.8
GSV TAV	1.4 (1.6)	3.6 (2.5)	<0.0001
CFV FVOL	4.3 (10.7)	6.5 (7.5)	0.6
FV FVOL	0.84 (1.3)	0.69 (1.5)	0.8
GSV FVOL	0.25 (0.34)	1.4 (2.4)	<0.0001
CFV ADVOL	4.1 (12.7)	5.9 (18.1)	0.3
FV ADVOL	0.17 (0.51)	0.26 (0.61)	0.8
GSV ADVOL	0.07 (0.06)	7.3 (13.4)	<0.0001

Reflux time (RT) in s, peak reflux velocity (PRV) in cm/s, time average mean velocity (TAV) cm/s, flow volume (FVOL) ml/s, absolute displaced volume in ml (ADVOL), common femoral vein (CFV), femoral vein (FV), great saphenous vein (GSV), p values for comparison, Mann-Whitney U test.

The commonly used method of venous reflux testing, the distal compression test described by van Bemmelen only works in the standing position.[1,3,13,14] The Valsalva manoeuvre can be used in both the supine and standing positions. This is an excellent tool providing information about venous wall motion during a defined intravenous pressure rise, assuming the procedure is done in a standardised manner. We developed a tube system, which allows us to monitor the expiratory pressure established by the volunteer under investigation.[1] Limited use of the method is seen in patients with obstructive airways disease. The assumption that the increase of intra abdominal pressure as a result of increased expiratory pressure results in raised intravenous pressure has not been confirmed. However we were able to show venous reflux in healthy and varicose vein patients with every Valsalva manoeuvre and with small intra-individual variability, which makes it very likely that a Valsava manoeuvre results in a rise of intravenous pressure. However as has been shown previously,[1] competent valves make the method reliable only in proximal vein segments with just one competent valve above the area investigated. Therefore more distally located vein segments were not included in the study. As shown in an earlier publication, the proximal leg veins are still circular in the supine position during normal breathing as well as during a Valsalva manoeuvre[15] and the diameter in transverse section corresponds well to the one assessed in the sagittal plane. In consequence venous diameters measured in the supine position are reliable parameters for the assessment of the vessel area. Distensibility on the other hand is defined as the relative volume change during a change of pressure (distensibility $= ((2 \times \partial d)/d)/\partial p))$.[16] As

Table 5. Relationship (spearman correlation r) between reflux parameters and relative venous diameter changes in the CFV, the FV and in the GSV, both in healthy subjects as well as in patients with varicose veins

Vein segments parameters	Healthy subjects r (CI)	*p*	Varicose vein patients r (CI)	*p*
CFV RT	0.35 (0.16−0.51)	0.0004	0.52 (0.33−0.67)	0.0001
FV RT	0.23 (0.03−0.41)	0.007	0.14 (−0.10−0.36)	0.2
GSV RT	0.33 (0.14−0.46)	0.001	0.35 (0.13−0.44)	0.003
CFV PRV	0.61 (0.46−0.72)	<0.0001	0.51 (0.32−0.67)	0.0004
FV PRV	0.23 (0.02−0.41)	0.03	0.57 (0.38−0.71)	<0.0001
GSV PRV	0.16 (−0.05−0.35)	0.1	0.71 (0.57−0.81)	<0.0001
CFV TAV	0.19 (−0.19−0.53)	0.3	0.56 (0.29−0.74)	0.0002
FV TAV	0.54 (0.21−0.76)	0.003	0.46 (0.17−0.67)	0.003
GSV TAV	0.11 (−0.27−0.47)	0.6	0.48 (0.19−0.69)	0.002
CFV FVOL	0.41 (0.05−0.68)	0.03	0.69 (0.49−0.83)	<0.0001
FV FVOL	0.75 (0.53−0.87)	<0.0001	0.69 (0.49−0.83)	<0.0001
GSV FVOL	0.57 (0.25−0.78)	0.001	0.73 (0.54−0.85)	<0.0001
CFV ADVol	0.59 (0.29−0.79)	0.0006	0.45 (0.15−0.67)	0.004
FV ADVol	0.73 (0.49−0.87)	<0.0001	0.58 (0.32−0.76)	<0.0001
GSV ADVol	0.54 (0.21−0.76)	0.003	0.73 (0.53−0.85)	<0.0001

Absolute venous diameter changes (VD diff in mm and %) and parameters of venous reflux (RT in s, PRV in cm/s, FVOL in ml/s and ADVOL in ml) *p* values for Z-test, spearman correlation coefficient r (CI = confidence interval).

we standardised the Valsalva manoeuvre with a defined pressure rise (30 mmHg), the relative diameter change may be considered as a parameter of venous distensibility.[17,18]

A limitation of the study is the assessment of the maximum diameter during the Valsalva manoeuvre. The diameter during reflux may be subject to change. However the pressure established by the controls and patients was constant over time, we therefore assume the maximum diameter is unchanged during the Valsalva manoeuvre. Zamboni *et al.* found a linear relationship between venous pressure and venous diameters.[19] This correlation was seen above a pressure value of 20 mmHg. In our study the pressure used was 30 mmHg. We can assume that the amount of venous reflux depends on the venous pressure, which explains the good correlation of PRV and the relative diameter change (venous distensibility) in our investigation. This is also in agreement with Neglen *et al.*, who showed that PRV is a better parameter describing the magnitude of venous incompetence than reflux duration.[6] We consider PRV to be the best parameter to correlate with venous wall distensibility in varicose vein patients.

Additionally to increased venous reflux, Vasdekis *et al.* also found increased venous diameters in varicose veins.[20] We found increased absolute and relative venous diameter changes in the proximal superficial and deep veins of the lower limb, with the exception of the relative diameter change in the CFV. A possible explanation of this finding is, that the varicose CFV diameter starts at a higher baseline. In consequence

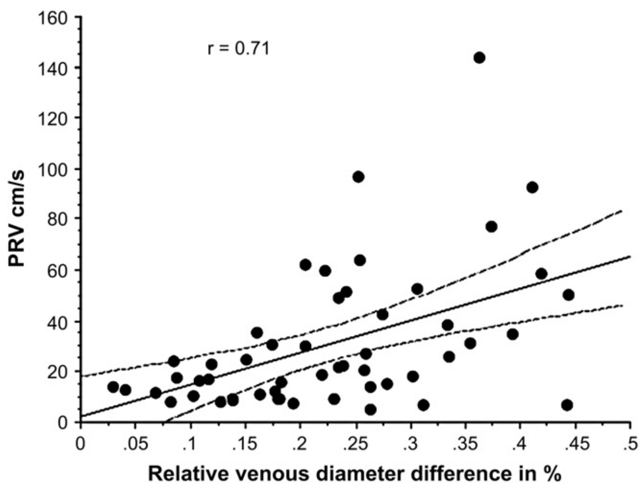

Fig. 1. Relation of peak reflux velocity (PRV) in cm/s to relative venous diameter change in the great saphenous vein of patients with varicose veins.

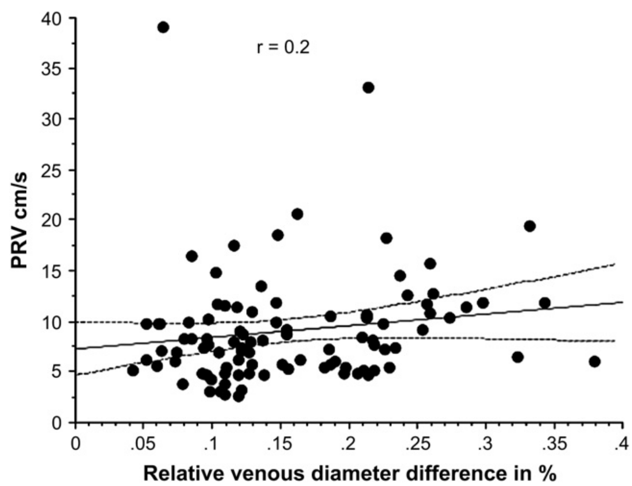

Fig. 2. Relation of peak reflux velocity (PRV) in cm/s to relative venous diameter change in the great saphenous vein of healthy subjects.

the relative diameter increase as a percentage of the baseline diameter is not significantly larger compared to the corresponding healthy veins. The absolute diameter change, however is larger.

Venous valve insertion sites (increased number of collagen fibres) in addition to the larger amount of surrounding tissue may influence wall distensibility in this particular vein segment.

As already published by Labropoulos and other authors,[6,21–24] venous reflux parameters assessed by duplex sonography correspond well with the C class of CEAP classification. Evaluation of this feature of venous disease was not an aim of our study, so we did not include enough vein segments in different CEAP classes to have enough statistical power to test this relationship.

Changes of the biophysical properties of the venous wall (elastic fibre degradation) as shown by Wali *et al.* and Kockx *et al.*[25–27] may be the reason for increased distensibility. It will be interesting to quantify the ultra structural changes of the vein wall and relate this to impaired wall motion. Impaired wall motion such as increased venous distensibility may be reversible as shown by Ahmad *et al.* He found that the deep vein diameter decreased after superficial vein ablation.[28] The investigation of venous wall distensibility could also be a tool for follow up measurements of wall remodelling processes.

Further investigations should also address the issue of distensibility measurements in more distally located incompetent vein segments and in varicose veins. The different behaviour of wall sections at different distances from the valve leaflet origin might give us further insights in the pathophysiology of this vessel wall disease.

Conclusion

In patients with an incompetent SFJ and GSV, the venous distensibility and the reflux parameters increase significantly in the deep veins as assessed by a standardised Valsalve manoeuvre compared with control subjects. The reflux parameter PRV correlates best with the venous diameter changes. Further studies should address the issue of venous distensibility measurements in more distal incompetent venous segments.

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