Original Article

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DOI:
10.4103/VIT.VIT_3_20

Noninvasive measurement of lower limb outflow resistance and implications for stenting

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Abstract:

AIMS: Stenting to relieve iliac vein obstruction is now practical and safe. However, the rates of ulcer healing, pain, and edema relief are 76%, 52%, and 42% respectively. In addition, a high ulcer recurrence (up to 86%) has been reported. Currently, patient selection depends on symptoms, imaging methods, and intravascular ultrasound (IVUS) for the assessment of iliac vein stenosis without consideration of the collateral circulation. The aim of this article is to present the results of a noninvasive method of measuring lower limb outflow resistance (LOR) and also to test the hypothesis that LOR is extremely variable in limbs with iliac obstruction and that some patients with iliac stenosis may have a LOR close to that of normal limbs as a result of a well-developed collateral circulation.

MATERIALS AND METHODS: LOR was measured at different venous pressures from 60 to 25 mmHg using air-plethysmography in 15 limbs without and 15 limbs with iliac vein obstruction. Reflux in ml/sec (venous filling index [VFI]) and venous clinical severity score (VCSS) were also measured in all limbs.

RESULTS: The LOR at 25 mmHg (LOR_{25}) was found to be the most discriminating measurement between the two groups. The area under the receiver operating characteristic curve was 0.973 (95% confidence interval [CI] 0.923–1.000). The range of LOR_{25} in limbs without obstruction was 0.0043–0.038 mmHg/ml/min and 0.0170–0.330 mmHg/ml/min in limbs with obstruction. By plotting VFI against LOR_{25}, a subgroup of limbs was identified with iliac obstruction that had a high VCSS (5–12) and a near-normal LOR_{25} (0.050 mmHg/ml/min) presumably as a result of a well-developed collateral circulation but a high VFI in the range of 5–14 ml/s. Another subgroup of limbs with iliac obstruction and a high VCSS (5–18) had a high LOR_{25} (0.100–0.330 mmHg/ml/min) presumably from a poorly developed collateral circulation.

CONCLUSION: The noninvasive measurement of LOR_{25} provides a quantitative estimation of overall lower LOR. It can indicate which limbs are compensated by the development of a good collateral circulation and which are not. The combination of LOR_{25} with VFI enables the clinician to determine the relative contribution of reflux and obstruction in individual limbs. A low LOR_{25} in the presence of severe iliac stenosis or occlusion is an indication of a well-developed collateral circulation and suggests that stenting would provide little benefit if any. However, this hypothesis needs to be verified by future prospective studies.

Keywords:

Lower limb outflow resistance, noninvasive measurement, implications for stenting

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Submitted: 10-Dec-2019
Revised: 22-Dec-2019
Accepted: 24-Dec-2019
Published: 25-Feb-2020

Introduction

The measurement of leg volume changes and volume flow (Q) such as reflux in absolute units, ml, and ml/s, respectively, using air-plethysmograph (ACI) became possible when the instrument was calibrated in the 1980s.[1] By combining air-plethysmographic volume outflow changes with simultaneous venous pressure

How to cite this article: Nicolaides A, Maleti O, Lugli M, Guerzoni S. Noninvasive measurement of lower limb outflow resistance and implications for stenting. Vasc Invest Ther 2019;2:88-94.

changes via a needle in a vein in the foot, it became possible to measure limb outflow resistance (LOR) in the 1990s.[2-5] At that time, the measurement of outflow resistance provided a quantitative measure of outflow obstruction and contributed to a better understanding of the hemodynamic mechanisms of obstruction in patients with the postthrombotic syndrome (PTS), but in the absence of a practical method to treat obstruction, the method remained a research tool.

Stenting to relieve iliac vein obstruction is now practical and safe as shown by two recent systematic reviews and meta-analyses.[6,7] However, in these reviews, the primary, assisted primary, and secondary patency rates were 68%, 82%, and 86% at 36 months, respectively; also, the rates of ulcer healing, pain, and edema relief were 76%, 52%, and 42% respectively. In addition, a high ulcer recurrence (up to 86%) has been reported.[8,9]

Failure to relieve symptoms and heal ulcers after stenting a severe iliac stenosis can be attributed to the presence of venous reflux which is invariably present in patients with PTS or an insignificant contribution of the stent to lowering LOR because it is already near normal due to a well-developed collateral circulation.

Ultrasound examination can determine the presence or absence and anatomic extent of reflux and obstruction but does not provide quantitative measurements of the severity of either. Quantitative measurements of reflux in ml/s and obstruction in terms of LOR in mmHg/ml/min (the latter includes iliac vein and pelvic collaterals) may be helpful in determining which of the two is the most predominant and in deciding whether to stent, deal with reflux, or correct both.

A drawback of the method of measuring outflow resistance as already published[2-5] had been the cannulation of a vein that was necessary to obtain pressure measurements. However, the method has been modified so that it is now noninvasive. The aim of this article is to present this noninvasive method of measuring lower LOR and also to test the hypothesis that LOR is extremely variable in both normal limbs and limbs with iliac stenosis and that some patients with iliac stenosis may have a LOR close to that of normal limbs as a result of a well-developed collateral circulation.

Materials and Methods

Patient selection and investigation

Lower LOR was measured in 16 limbs of 16 patients who presented with symptomatic varicose veins (CEAP Clinical Class C1 or C2) and 14 limbs of 14 patients with edema, skin changes, or ulceration (CEAP Clinical Class C3–C6). They were selected from the pool of patients being investigated in the vascular laboratoty so that 15 had iliac vein obstruction and 15 had no evidence of obstruction.

Duplex scanning confirmed the presence of patent deep veins with competent valves without any evidence of outflow obstruction in 15 of the 16 patients in CEAP Class C1 and C2. There was iliac stenosis in one patient although there was no history of deep-vein thrombosis.

Duplex scanning confirmed the presence of axial reflux in the deep veins with the presence of residual old (echogenic) thrombus and severe (>70%) iliac vein obstruction in the 14 patients in the CEAP C3–C6 classes. The presence of iliac vein stenosis or occlusion was confirmed with computed tomography–venography or conventional venography.

The venous clinical severity score (VCSS) was calculated for all patients.

Air-plethysmography was performed to measure reflux (venous filling index [VFI])[1] and LOR as described below. This was part of the routine investigation of patients' assessment.

Patients were investigated in two different vascular laboratories. Patients number 1–18 were studied in Cyprus and the rest 19–30 in Modena. Two different air-plethysmographic systems were used: the APG® from ACI Medical, LIC, San Marcos, California, USA (info@acimedical.com) in the Cyprus laboratory and the air-plethysmographic equipment from Angioflow Microlab, Padova, Italy, in the Modena laboratory.

Measurement of reflux (Venous Filling Index) and limb outflow resistance

Measurement of reflux

The air chamber of the air-plethysmograph was placed around the calf. The chamber extended from the ankle to the knee. The air-plethysmograph was calibrated by injecting 100 ml of air in the air chamber. This provided a means of expressing volume changes of the calf in ml.[1] The 100 ml used for calibration was then removed. A 10 cm wide cuff was placed proximally on the thigh [Figure 1].

The leg was elevated to 30° to empty the veins. When a plateau was reached, the patient was asked to stand up with the weight on the opposite leg while steadying himself by holding on an orthopedic frame until the volume increase reached a new plateau. The difference between the two plateaus represented the functional venous volume (FVV). The VFI was the average rate of reflux and was calculated by dividing the 90% FVV by the time taken for this level to be reached in seconds. It was expressed in ml/s.

Determination of pressure/volume relationship for the leg being examined (low recording speed)

The proximal thigh cuff was used to calibrate the leg being studied in terms of pressure and volume. The leg was elevated at 30° with the foot resting on a block and the proximal thigh cuff inflated to 80 mmHg [Figure 1]. When a plateau was reached, the cuff was deflated in steps of 10 mmHg, starting from the pressure of 80 mmHg and ending at the pressure of 10 mmHg. At each step, 1–2 min was required for a new plateau to be defined. For each plateau, corresponding calf volume measurements in ml were obtained (the distance of plateau from the baseline) [Figure 2]. Using these measurements, a pressure/volume curve could be constructed which was specific for the leg being examined [Figure 3a].

Recording of outflow curve (high-speed paper)

The thigh cuff was again inflated to 80 mmHg, and when a plateau was reached, it was deflated suddenly providing a volume outflow curve [Figure 3b]. This was repeated twice so that three outflow curves were available. Curves with small motion artifacts were accepted [Figure 2].

Calculation of limb outflow resistance

Tangents at 0.2 s interval points on the outflow curve provided flow values in ml/min [Figure 3b]. Pressures corresponding to these points were obtained from the pressure/volume curve [Figure 3a]. LOR at every point was calculated by the equation: resistance = pressure/flow. Resistance measurements at pressures of ≤20 mmHg were ignored.

Statistical methods

Initially, a resistance curve was obtained for every limb by plotting the resistance (LOR) obtained at different pressures [Figure 4a and b].

Subsequently, boxplots were constructed for the LOR at different pressures (60, 50, 40, 30, and 25 mmHg) for the limbs without and with iliac obstruction [Figure 5a-c].

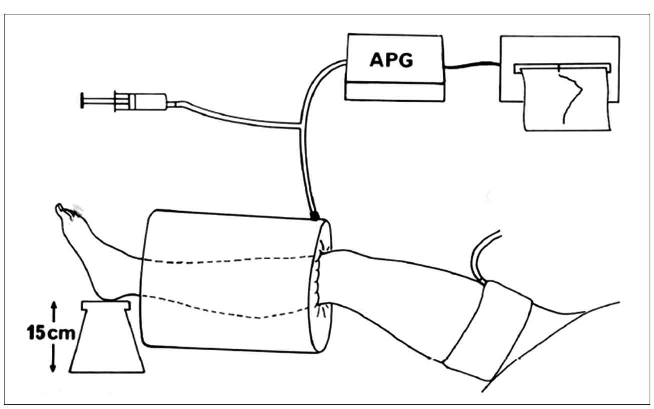

Figure 1: Position of limb with air-plethysmograph leg chamber and proximal thigh cuff during measurements of limb outflow resistance

The areas under the receiver operating characteristic (ROC) curves for identifying patients with iliac stenosis from the LOR were obtained for LOR_{60}, LOR_{50}, LOR_{40}, LOR_{30}, and LOR_{25}.

Scattergrams were obtained by plotting VFI against LOR_{25} to demonstrate the relationship of these measurements with the presence or absence of iliac stenosis and VCSS [Figure 6].

Finally, a multivariable linear regression analysis was performed with VCSS as the dependent variable and with VFI and LOR_{25} as the explanatory variables [Table 1]. Using the regression equation obtained, the predicted VCSS was calculated using the values of VFI and LOR_{25}. A plot of VCSS against the predicted VCSS was constructed, and the correlation coefficient (r) between the two was obtained to demonstrate the strength of the prediction [Figure 7].

Results

The presence of iliac stenosis, CEAP class, VCSS and and overall lower limb reflux (VFI) for the 30 patients studied are shown in Table 2.

Figure 4a shows resistance curves at different pressures in five limbs without iliac stenosis and Figure 4b shows the resistance curves from five patients with iliac stenosis (only five curves from each group are shown for the sake of clarity). The increasing resistance at the low pressures of 30 mmHg and 25 mmHg is clearly shown.

The boxplots [Figure 5a-c] show the decreasing overlap of LOR measurements between limbs with iliac stenosis and those without obtained at decreasing pressures of 60, 40, and 25 mmHg. The area under the ROC curve for identifying patients with iliac stenosis from the LOR was 0.850 (95% confidence interval [CI]: 0.664–1.00) at the pressure of 60 mmHg, 0.842 (95% CI: 0.647–1.00) at the pressure of 50 mmHg, 0.942 (95% CI: 0.830–1.0) at the pressure of 40 mmHg, 0.958 (95% CI: 0.869–1.00) at

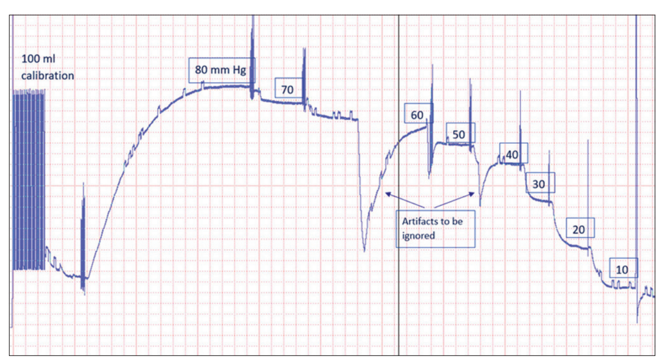

Figure 2: Air-plethysmographic recording of 100 ml calibration, initial plateau at 80 mmHg and stepwise deflation of thigh cuff. For each plateau the volume is obtained from the distance between the plateau and the baseline

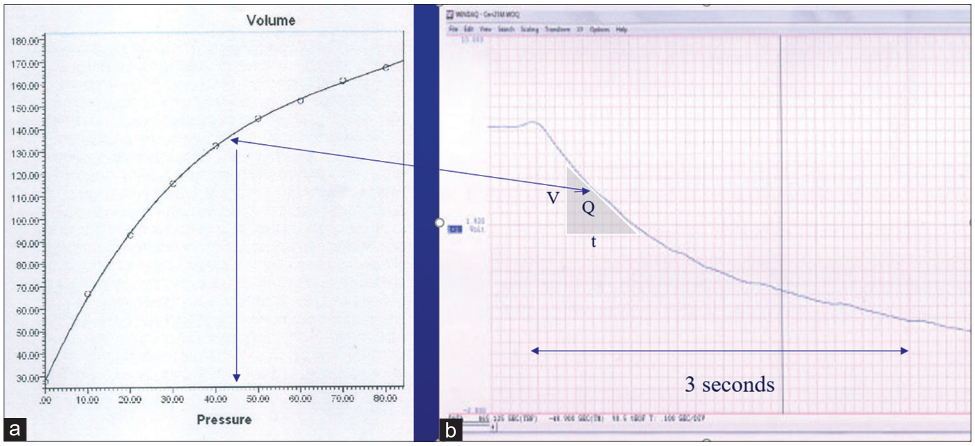

Figure 3: (a) Pressure/volume relationship of the leg examined using measurements of pressure and volume from Figure 2. This curve is specific for the leg examined. (b) Outflow curve used to measure flow from tangent at any point. For any volume point on this curve the corresponding pressure can be obtained from the pressure/volume curve in Figure 3a

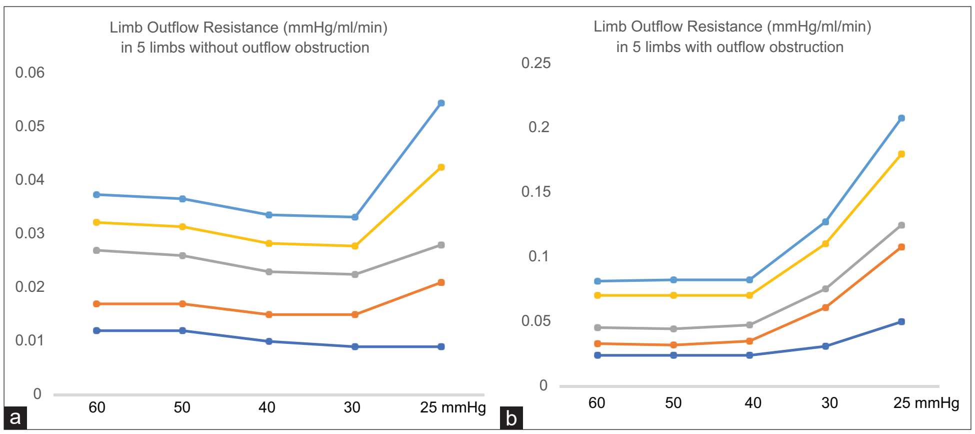

Figure 4: (a) Limb outflow resistance at different pressures in five limbs without and (b) with iliac stenosis

the pressure of 30 mmHg, and 0.973 (95% CI: 0.923–1.0) at the pressure of 25 mmHg.

In the 30 limbs studied, the lowest LOR recorded at a pressure of 25 mmHg (LOR_{25}) was 0.0043 mmHg/ml/s and the highest 0.330 mmHg/ml/s which represents an increase of 77 times. The mean LOR_{25} was 0.014 ± 0.009 mmHg/ml/min in the limbs without obstruction and 0.111 ± 0.099 mmHg/ml/min in the limbs with obstruction ($P < 0.0001$). The range of LOR_{25} in the limbs without obstruction was 0.0043–0.038 mmHg/ml/min and 0.0170–0.330 mmHg/ml/min in limbs with obstruction.

The mean VFI was 2.64 ± 1.57 ml/s in the limbs without obstruction and 7.97 ± 3.47 ml/s in the limbs with obstruction ($P < 0.0001$). The range of VFI in the limbs without obstruction was 0.72–5.20 ml/s and 3.80–15.13 ml/s in limbs with obstruction.

Figure 6a is a scattergram of reflux (VFI) against LOR_{25}, showing the large range of measurements in the patients without (blue) and patients with iliac stenosis (red). In 9 of the 15 limbs with stenosis (red dots in a dotted parallelogram in Figure 6a), the LOR is close to 0.05 mmHg/ml/min, suggesting that the stenosis is of mild hemodynamic significance. Figure 6b is the same scattergram showing the VCSS for each limb.

Table 1: Results of multivariable linear regression analysis with VCSS as the dependent variable and with VFI and LOR_{25} as explanatory variables

Variables	B Coefficients	*t*	*P*
VFI	0.577	2.802	0.009
LOR25	21.95	2.403	0.023
Constant	1.265	1.099	0.282

Regression equation: VCSS=1.265 + (VFI x 0.577) + (LOR25 x 21.9)

In a multivariable linear regression analysis with VCSS as the dependent variable and with VFI and LOR_{25} as the explanatory variables, both VFI and LOR_{25} were independent predictors of VCSS [Table 1]. By substituting VFI and LOR_{25} in the regression equation shown in Table 1, the predicted VCSS was calculated for every patient. Figure 7 is a scatterplot of the VCSS against the predicted VCSS showing the regression line and the correlation ($r = 0.710$; $P < 0.0001$) between them.

Discussion

The results of this study show that both the overall lower limb reflux (VFI) and LOR can be obtained noninvasively using air-plethysmography. They also show that LOR is not the same at different pressures. It increases with decreasing pressure, especially in patients with iliac obstruction [Figure 4]. This is presumably the result of vein diameter reduction at pressures lower than 40 mmHg. At pressures lower than 25 mmHg, the resistance curves shown in Figure 4 become almost vertical and make the resistance difficult to measure. This is because at pressures lower than 25 mmHg, the slope of the plethysmographic outflow curve is very small [Figure 3b].

The results also demonstrate that the most discriminant LOR value is the one at 25 mmHg (LOR_{25}) [Figure 5a-c]. This is also shown by the high area under the ROC curve

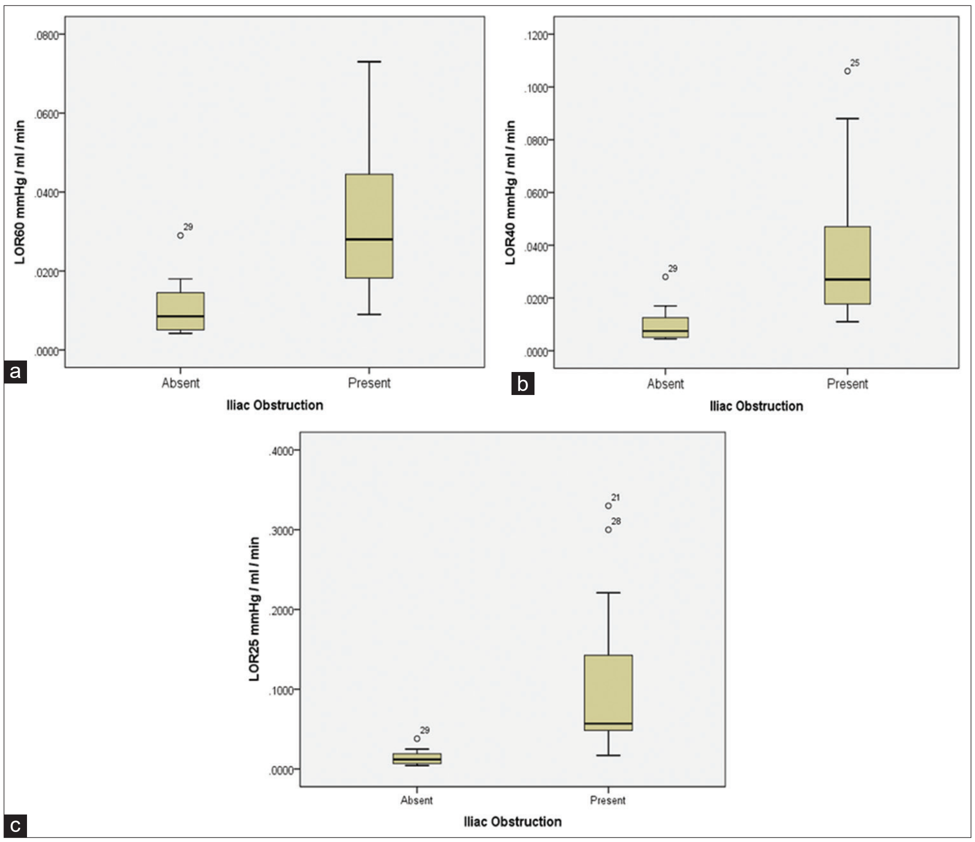

Figure 5: (a-c) Boxplots showing the decreasing overlap of limb outflow resistance measurements between limbs without (*n* = 15) and those with iliac stenosis (*n* = 15). (a) Limb outflow resistance measured at 60 mmHg; (b) limb outflow resistance measured at 40 mmHg and (c) limb outflow resistance measured at 25 mmHg

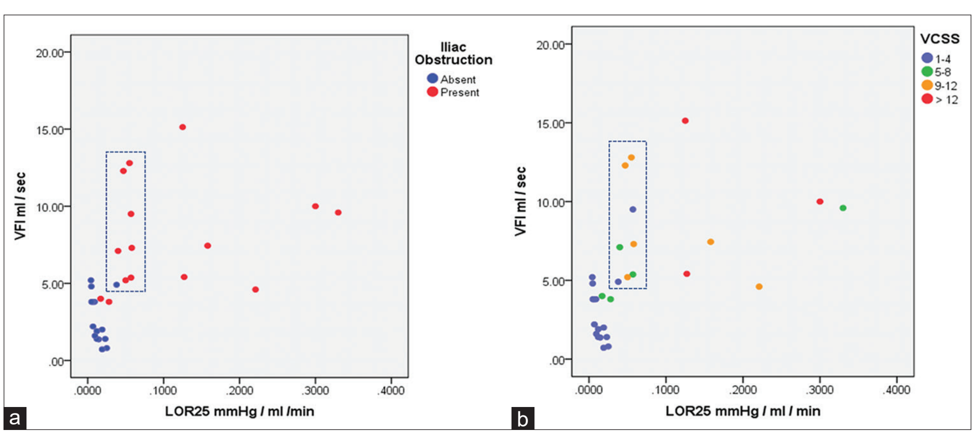

Figure 6: (a) Scattergram showing the range of VFI and limb outflow resistance LOR_{25} readings in the 15 limbs without iliac obstruction (blue) and 15 limbs with iliac obstruction (red) studied. (b) The same scattergram showing the venous clinical severity score. Dotted-line parallelogram includes limbs with severe reflux and a borderline limb outflow resistance

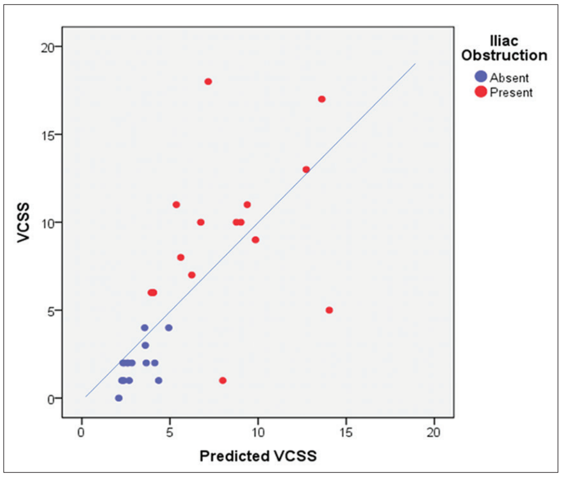

Figure 7: Venous clinical severity score plotted against the predicted venous clinical severity score as calculated from the venous filling index and limb outflow resistance 25 using the equation obtained from the multivariable regression as shown in Table 2. The regression line is also shown (Pearson correlation coefficient $r = 0.710$; $P < 0.0001$)

of 0.973 (95% CI 0.923–1.0) for the detection of iliac obstruction by LOR_{25}.

Reflux, obstruction, or both contribute to the development of a high VCSS. However, until now, it was impossible to determine the relative hemodynamic contribution of each in the development of symptoms or signs. The plot of VFI against LOR_{25} is one way of visually determining the relative contribution of each parameter [Figure 6]. It appears that limbs with VFI <5 ml/s and LOR_{25} < 0.05 mmHg/ml/min have a VCSS of <4. In limbs with iliac obstruction, there is a wide range of LOR_{25} from 0.017 to 0.33 [Figure 6] irrespective of the VCSS. In fact, Figure 6 shows that a subgroup of patients with iliac obstruction (limbs enclosed in dotted rectangular) have LOR_{25} close to 0.05 mmHg/ml/min which is borderline abnormal and two limbs that have LOR_{25} in the normal range. Our new hypothesis is that limbs in this subgroup are the ones that if stented would show little improvement. These limbs have a high VCSS because of high reflux (VFI >5 ml/s) and are more likely to benefit from the valve or neovalve reconstruction.[10] In contrast, limbs with LOR_{25} > 0.100 mmHg/ml/min are the ones likely to have a poor collateral circulation and are more likely to benefit from stenting. This hypothesis needs to be tested in prospective studies.

Finally, VFI and LOR25 are independent predictors of VCSS. The predicted VCSS which is calculated from the values of VFI and LOR_{25} is highly correlated with the actual VCSS ($r = 0.710$; $P < 0.0001$) [Figure 7]. These results confirm our previous finding using the invasive method of measuring LOR.[5]

A limitation of the study is that it is based on a relatively small number of patients. The findings need to be validated in a larger series. Another limitation is that the duration of the reflux or obstruction has not been considered. It is well known that skin changes become worse with time, even in the presence of low-grade reflux. In the absence of any consideration or correction for the duration the pathology was present, the correlation found between the VCSS and predicted VCSS calculated from VFI and LOR_{25} is remarkable.

Table 2: The presence of iliac stenosis, CEAP clinical class, venous clinical severity score (VCSS) and lower limb reflux in terms of venous filling index (VFI) in the 30 limbs studied with air-plethysmography

Patient Number	Iliac Stenosis	CEAP Clinical Class	VCSS	VFI ml/sec
1	No	2	2	3.8
2	No	2	2	1.9
3	No	2	1	2.2
4	No	2	1	1.4
5	No	2	2	1.4
6	No	2	2	1.6
7	No	2	2	1.4
8	No	2	2	4.8
9	No	2	1	5.2
10	No	2	3	3.8
11	No	2	4	3.8
12	No	2	2	2.0
13	Yes	6	11	5.2
14	Yes	5	10	7.3
15	Yes	3	6	4.0
16	Yes	3	9	12.8
17	Yes	6	6	3.8
18	Yes	3	8	5.4
19	No	1	1	0.8
20	Yes	5	11	12.3
21	Yes	3	5	9.6
22	No	1	0	0.7
23	Yes	4	7	7.1
24	Yes	5	13	15.1
25	Yes	4	18	5.4
26	Yes	2	1	9.5
27	Yes	4	10	7.4
28	Yes	6	17	10.0
29	No	2	4	4.9
30	Yes	5	10	4.6

Conclusion

The noninvasive measurement of LOR_{25}, which is a measurement that accounts for the effect of both iliac lesions and the collateral venous development, provides a quantitative measurement of overall lower LOR. It can indicate which limbs are compensated by the development of a good collateral circulation and which are not. The combination of LOR_{25} with VFI enables the clinician to determine the relative contribution of reflux and obstruction in individual limbs. A low LOR_{25} in the presence of severe iliac stenosis or occlusion is an indication of a well-developed collateral circulation and suggests that stenting would provide little benefit if any. However, this hypothesis needs to be verified by future prospective studies. Such studies should include measurements of VFI and LOR_{25} before and after stenting followed by correlation of these hemodynamic parameters with clinical outcomes so that eventually we can refine the indications for stenting.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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