Photoplethysmographic Venous Refilling Times Following Ultrasound Guided Foam Sclerotherapy for Symptomatic Superficial Venous Reflux: Relationship with Clinical Outcomes

K.A.L. Darvalla a,b,*, R.C. Sam b, G.R. Bate a, D.J. Adam a, S.H. Silverman b, A.W. Bradbury a

a Birmingham University, Department of Vascular Surgery, Heart of England NHS Trust, Birmingham, UK
b Department of Vascular Surgery, City Hospital, Birmingham, UK

Submitted 15 July 2009; accepted 23 February 2010
Available online 1 April 2010

Abstract
Introduction: Digital photoplethysmography (PPG) provides an inexpensive, reproducible, quantitative, non-invasive assessment of lower limb venous function.
Aim: To examine the relationship between venous refilling time (VRT) and severity of venous disease, and also between changes in VRT and symptomatic improvement after ultrasound guided foam sclerotherapy (UGFS) for symptomatic superficial venous reflux (SVR).
Methods: Prior to and 6 months after UGFS, 246 patients (317 limbs) completed a symptom questionnaire, underwent duplex ultrasonography and clinical assessment, and VRT measurement by digital PPG. Health related quality of life (HRQL) questionnaires were also completed.
Results: Median VRT improved from 11 to 31 s (P < 0.0005, Wilcoxon Signed Ranks). Abnormal VRT (<20 s) correlated well with the presence of SVR on duplex (sensitivity 75%, specificity 94%). Pre-treatment there was a significant relationship between reducing VRT and increasing CEAP clinical grade (P < 0.0005, χ²), extent of SVR on duplex (P < 0.0005) and a non-significant relationship with overall increasing symptom severity (P = 0.097). Relief of all symptoms was more likely when there was normalisation of VRT after treatment (80% vs. 65%, P = 0.003, Spearman’s rank). Pre-treatment VRT correlated with both generic physical (r = 0.428, P = 0.002) and disease-specific (r = −0.413, P = 0.003, Spearman’s rank) HRQL.
Conclusions: UGFS for SVR improves VRT measured by digital PPG and that improvement correlates with symptom relief.

© 2010 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.
Introduction

Although population based studies have reported a poor correlation between lower limb symptoms and the presence and severity of lower limb venous disease,1,2 numerous groups, including our own, have shown that the surgical treatment of superficial venous reflux (SVR) improves symptoms, generic and disease-specific health related quality of life (HRQL),3-7 as well as venous hemodynamics as measured by digital photoplethysmography (PPG).8 However, outcomes following non-surgical treatments for SVR, and the relationships between changes in venous refilling time (VRT) and relief of physical symptoms, are not well defined. The aim of the present study, therefore, was to examine for the first time the relationship between VRT and severity of venous disease, and also the relationship between changes in VRT and symptomatic improvement after ultrasound guided foam sclerotherapy (UGFS) for symptomatic SVR.

Methods

Local ethics committee approval and written informed consent from each patient included in the study was obtained. Prior to and 6 months after UGFS for symptomatic isolated SVR, 246 consecutive patients (317 limbs) completed a symptom questionnaire and underwent CEP grading,9 duplex ultrasonography (DUS), and measurement of VRT by digital PPG. Limbs with deep venous reflux were excluded. The asymptomatic, contralateral limbs of 47 patients were also examined. Patients undergoing unilateral treatment also completed generic (SF12) and disease-specific (Aberdeen Varicose Vein Symptom Severity Score [AVSS]) HRQL questionnaires.

Duplex ultrasound examination

All examinations were performed in a standard manner by one of the authors (GB). Patients were examined standing with their weight on the contralateral limb and the leg to be examined slightly bent with the heel on the floor to relax the calf muscle while maintaining stability, with a Sonosite Micromaxx (Sonosite Ltd, Hitchin, Herts, UK) using a 10MHz transducer. The following venous segments were insonated: proximal and distal superficial femoral vein; above and below knee popliteal vein; saphenofemoral and sapheno-popliteal junctions, the whole length of the great saphenous vein (GSV) and the small saphenous vein (SSV). All veins were assessed for patency and compressibility. Reflux was induced with a manual calf squeeze and was defined as reverse flow of greater than 0.5 s. To grade the extent of reflux according to duplex scanning, we determined the presence of reflux in 4 superficial venous segments: GSV in the thigh, GSV below the knee, SSV, and anterior accessory saphenous vein (AASV), giving a score of 0–4 refluxing venous segments.

Photoplethysmography

Quantitative digital PPG (Huntleigh Dopplex® Vascular Assist, Huntleigh Healthcare, UK) was used to measure post-exercise VRT in the sitting position as previously described.10 The PPG probe was attached to the skin using a double-sided sticky pad, 10cm above the medial malleolus and 1–2 cm posterior to the subcutaneous border of the tibia. Any areas of scarring, prominent varicosities, or pigmentation were avoided. With the patient remaining still, the computer automatically calibrated the signal, and once a stable baseline was achieved the exercise was commenced using an inbuilt metronome. Patients completed 10 dorsi- and plantar-flexions over a 15 s period and were then asked to rest as motionless as possible. The ejection of blood from the skin and the subsequent refilling curve are displayed visually and the computer calculates the RT (seconds) from the curve up to a maximum of 45 s. VRT was measured twice in each limb 2–5 min apart, and the mean of the two measurements used. Normal VRT was defined as ≥20 s. VRT measurement was repeated in each treated limb 6 months after UGFS.

Symptom questionnaire

Patients were asked to complete a symptom questionnaire based upon the Edinburgh Vein Study1,2 one week before and six months after UGFS treatment regarding the presence of pain, itching, tingling, cramp, restless legs, feeling of swelling and heaviness. Possible responses in terms of symptom improvement were "none at all", "a little", "quite a bit", "a lot" and "an awful lot". For the purposes of analysis, only "quite a bit", "a lot", and "an awful lot" were considered symptomatic improvement.

HRQL questionnaires

Patients undergoing unilateral UGFS completed generic (Physical Component Summary score [PCS] of the Short Form [SF]-12) and disease-specific (AVSS) HRQL instruments before and six months after treatment.3,11-14 A lower PCS signifies worse general physical HRQL and the mean PCS of the general population is set at 50. A higher AVSS signifies more symptomatic lower limb venous disease.

Treatment details

UGFS was performed on an outpatient basis using foam prepared by the Tessari technique (two, 2 ml syringes connected with a 3-way tap and a 5 μl filter) and comprising one part 3% sodium tetradecyl sulphate. Fibrovein®, STD Pharmaceuticals, Hereford, UK) and three parts air. Venous trunks to be treated were marked with the patient in the standing position, and these were cannulated directly under ultrasound guidance with the patient supine. Following UGFS, compression was applied to the treated limb by means of Pehahaft® (Hartmann, Germany) bandage over Velband® (Johnson & Johnson Medical, Ascot, Berkshire, UK) applied along the length of treated vein, held in place with Medipore (3M) adhesive tape. A thigh-length Class II compression stocking was applied over the bandaging. This remained in place for 10 days, after which time the bandaging was removed and the class II stocking worn for a further 14 days. Success of treatment was reviewed at one month and further injections undertaken as judged necessary. Around 10–15% of limbs require a second treatment.
Statistical analysis

Non-parametric methods within Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Chicago, IL, USA) were used. Chi-squared test was used to compare the proportions of limbs with each symptom according to whether VRT was normal or abnormal prior to treatment, and also whether individual symptoms were more likely to improve in those limbs in which VRT normalised after treatment. Chi-squared test for trend was used to examine the relationship between pre-treatment VRT and both CEAP clinical grade and the extent of SVR measured by DUS. Mann–Whitney U test was used to examine the difference in median VRT by clinical severity and also extent of SVR. Wilcoxon signed ranks test was used to determine intra-person improvement in VRT following UGFS. Spearman’s rank correlation was used to assess the relationship between VRT and SF12 PCS and AVSS, and also between the change in these values between 0 and 6 months.

Results

Demographics, CEAP clinical grade, treatment data and the numbers available for analysis in each part of the analysis are shown in Table 1.

All limbs had primary venous disease (Ep) in association with superficial venous reflux only (Ap) without obstruction (Pp). Reflux was not present in any of the 47 CEAP C0 and C1 limbs.

Relationship between VRT, duplex findings and clinical severity

For all 364 examined limbs, the presence of SVR on duplex ultrasound examination was compared with the VRT, defined as normal (≤20 s) or abnormal (<20 s), to determine the sensitivity and specificity of digital PPG-derived VRT in detecting SVR. Abnormal VRT correlated well with the presence of SVR on duplex (sensitivity 75% [95% CI 70–80%], specificity 94% [95% CI 82–98%]). An abnormal VRT was 12.5 times more likely to be obtained in a limb with reflux.

Fig. 1 shows the relationship between median VRT and the clinical severity of disease as defined by CEAP clinical grade. Prior to treatment there was a significant relationship between reducing (worse) median VRT and increasing CEAP clinical grade (P < 0.0005, χ² trend test). Mann–Whitney U (MWU) test was also used to compare median VRT excluding those asymptomatic (C0/C1) limbs without reflux. Limbs were grouped according to whether they were uncomplicated (C2 and C3; n = 225) or had skin complications of venous disease (C4, C5 and C6; n = 92). Median VRT was significantly worse (P < 0.0005, MWU) in those limbs with complicated VV (median 9.0 s, interquartile range [IQR] 6.0–14.0 s) compared with those with uncomplicated VV (median 15.0 s, IQR 9.0–23.8 s).

Fig. 2 shows the relationship between median VRT and extent of SVR defined by the number of refluxing segments seen on DUS in all 364 examined limbs. Prior to treatment there was a significant relationship between reducing VRT and the extent of SVR on DUS (P < 0.0005, χ² trend test). MWU test was also used to compare the median VRT excluding those asymptomatic (C0/C1) limbs without reflux. Limbs were grouped according to whether they had 1–2 (n = 300) or 3–4 (n = 17) refluxing segments. There was no difference in median VRT between the two groups; median VRT 12.0 s in both groups.

Data on lower limb symptoms and pre-treatment VRT was available for 247 limbs. The number of lower limb symptoms (1–7) in each limb was compared with whether

<table>
<thead>
<tr>
<th>Table 1 Demographic data and full CEAP classification.</th>
<th>All patientsa</th>
<th>Pre-treatment symptom analysis</th>
<th>Symptom improvement analysis</th>
<th>HRQL improvement analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>246</td>
<td>198</td>
<td>84</td>
<td>50</td>
</tr>
<tr>
<td>Limbs</td>
<td>364</td>
<td>247</td>
<td>101</td>
<td>50</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- median (range)</td>
<td>56 (19–86)</td>
<td>58 (22–86)</td>
<td>60 (29–86)</td>
<td>58 (29–79)</td>
</tr>
<tr>
<td>Male sex</td>
<td>95 (39)</td>
<td>81 (41)</td>
<td>24 (29)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>CEAP clinical grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- C0</td>
<td>35 (–)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- C1</td>
<td>12 (–)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- C2</td>
<td>191 (60)</td>
<td>140 (57)</td>
<td>50 (50)</td>
<td>24 (48)</td>
</tr>
<tr>
<td>- C3</td>
<td>34 (11)</td>
<td>25 (10)</td>
<td>18 (18)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>- C4</td>
<td>63 (20)</td>
<td>56 (23)</td>
<td>21 (21)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>- C5</td>
<td>15 (5)</td>
<td>14 (6)</td>
<td>5 (5)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>- C6</td>
<td>14 (4)</td>
<td>12 (5)</td>
<td>7 (7)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>77 (21)</td>
<td>53 (21)</td>
<td>20 (20)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>GSV reflux</td>
<td>313 (86)</td>
<td>215 (87)</td>
<td>83 (82)</td>
<td>38 (76)</td>
</tr>
</tbody>
</table>

a Percentages shown for CEAP clinical grade, recurrent disease and GSV reflux are for 317 symptomatic limbs only (C0 and C1 limbs excluded).
the VRT in that limb was normal or abnormal. An abnormal VRT became more common as the number of symptoms present increased: 28 of 41 limbs (68%) with 1 or 2 symptoms only had an abnormal VRT, compared to 45 of 54 limbs (83%) with all 7 symptoms, but this did not reach statistical significance ($P = 0.097$, $\chi^2$ trend test).

The percentage of limbs with each symptom according to normal or abnormal VRT is shown in Fig. 3. Only itching (74% vs. 60%, $P = 0.034$, $\chi^2$ test) and a feeling of swelling (75% vs. 45%, $P < 0.0005$, $\chi^2$ test) were significantly more common in limbs with abnormal VRT.

### Relationship between improvements in VRT and symptoms after UGFS

There was a significant improvement in median (IQR) VRT after UGFS ($n = 101$, median 11 [8–18] vs. 31 [20–44] seconds, $P < 0.0005$, Wilcoxon signed ranks test).

Limbs that showed no change in VRT (abnormal, $n = 23$, or normal, $n = 17$, pre- and post-treatment) are compared with those that normalised their VRT in Fig. 4. Relief of all symptoms was significantly more likely when there was normalisation of a previously abnormal VRT (80% vs. 65%, $P < 0.0005$, $\chi^2$ test). Each lower limb symptom showed more improvement in the limbs that also showed improvement in VRT from abnormal to normal. Looking at individual symptoms, this attained statistical significance for itching (87% vs. 64%, $P = 0.021$, $\chi^2$ test), but not for pain ($P = 0.54$), tingling ($P = 0.13$), cramp ($P = 0.18$), restless legs ($P = 0.16$), feeling of swelling ($P = 0.28$), or heaviness ($P = 0.062$).

### Relationship between improvements in VRT and HRQL

In the subgroup of 50 patients who also completed HRQL questionnaires (SF12 and AVSS), pre-treatment VRT showed significant correlation with both SF12 PCS ($r = 0.43$, $P = 0.002$, $P < .0005$).
Spearman’s rank) and AVSS ($r = 0.41$, $P = 0.03$, Spearman’s rank) (Figs. 5 and 6). The same relationships were present after 6 months but the association was weaker and did not reach significance (PCS: $r = 0.28$, $P = 0.05$; AVSS: $r = -0.19$, $P = 0.18$; Spearman’s rank). There was no significant correlation between change in VRT between 0 and 6 months, and change in either PCS or AVSS between 0 and 6 months.

**Discussion**

The main findings of the current study are that VRT measured by digital PPG correlates well with clinical severity of venous disease, and also with lower limb symptoms and HRQL. However, patients in CEAP clinical stages C3–C6 showed similar venous refilling times. VRT improved significantly following UGFS and was associated with an improvement in lower limb symptoms, particularly itching and heaviness.

Direct ambulatory venous pressure (AVP) measurement is believed to give the best overall assessment of lower limb venous function, but it is invasive and thus unsuitable for routine clinical use. Air plethysmography gives accurate and reproducible information and is non-invasive but the test is time-consuming and relies on bulky equipment. VRT measured by PPG correlates well with direct pressure measurements.

Kulkarni et al. found significant improvements in median VRT in patients undergoing superficial venous surgery as part of their treatment for chronic venous ulceration (CEAP C5 or 6). Interestingly, they also found that the patients who had ulcer recurrence had no such improvement in VRT, concluding that a low VRT after surgery predicts ulcer recurrence. The measurement of VRT using a tourniquet has previously been shown to predict haemodynamic improvement after saphenous surgery, and Gohel et al. found the same to be true for healing rates and recurrence rates of chronic venous ulceration in patients undergoing superficial venous surgery.

The current study provides evidence that the significant improvement in VRT observed after UGFS also translates to an improvement in lower limb venous symptoms. This lends some support to the suggestion by Beraldo et al. that PPG be used as an initial screening test to give objective evidence of venous dysfunction and thus identify those most likely to benefit from intervention. Thus, we have found that limbs with a normal VRT prior to treatment are less likely to have symptoms, and that those symptoms are less likely to improve following treatment. The poor response rate to the HRQL questionnaires and repeat VRT measurements at 6 months is a weakness of the study. Unilateral procedures were performed in 128 patients, yet complete data were available for only 50. However, it can be seen in Table 1 that these 50 differed little in terms of demographics, CEAP clinical grade and treatment data from the whole cohort.

In conclusion, VRT measured by digital PPG is a simple, non-invasive and reproducible test of venous function that correlates well with clinical severity of venous disease and helps predict symptomatic improvement following intervention for superficial venous reflux.

**Conflict of Interest/Funding**

None.

**References**


Ware JE, Kosinski M, Keller SD. How to score the SF-12 physical and mental health summary scales. 4th ed. Lincoln (RI): QualityMetric Inc; 2002.


