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Quantifying saphenous reflux

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Background: **Quantification of reflux is desirable in advanced chronic venous disease as clinical features are based on its adverse impact on ambulatory venous pressure (AMVP). Prior clinical observation suggests that reflux in a saphenous vein >5 mm is likely significant. On the basis of normal calf pump mechanics, we hypothesized that a reflux volume ≥30 mL was necessary to upset pump equilibrium.**

Methods: **Venous laboratory data in 119 limbs with isolated saphenous reflux were analyzed. Reflux volume was calculated by duplex ultrasound (area × velocity × duration). The relationship of reflux volume to saphenous size, calf pump function (air plethysmography, AMVP), flow resistance (Poiseuille equation), and clinical severity were examined.**

Results: **Saphenous size had a bimodal relationship to reflux volume. Reflux volume of ≥30 mL occurred mostly (97% of limbs) with saphenous size of ≥5.5 mm, but 51% of saphenous veins >5.5 mm had reflux volumes <30 mL. This is because saphenous veins invariably carried less than their maximum reflux potential indicated by their size (Poiseuille equation). Variable additional focal resistance across refluxive valve cusps and narrower re-entry perforators is not taken into account when only saphenous truncal size is used for resistance calculation. Furthermore, the association of AMVP with reflux was found not to be based on a set (≥30 mL) threshold but was variable, depending on existing calf pump mechanics, compensatory in some (12% of limbs) and aggravating reflux effects in others (26%). Calf pump abnormalities were found in 70% of refluxive limbs and in 44% (n = 16) of contralateral limbs without any reflux. Reflux volume was significantly higher overall in limbs with ulcer (C6), but the range overlapped with lesser clinical classes. Seven of 14 limbs with active ulcers had reflux volume >30 mL; six of seven limbs with active ulcers and reflux volume of <30 mL had calf pump abnormalities that would be poorly tolerant of reflux even at these smaller volumes.**

Conclusions: **Saphenous size alone cannot be used as an indicator of significant reflux. More than two thirds of the limbs with isolated saphenous reflux have calf pump abnormalities, which also occurred without reflux in the opposite limb—a novel finding. This means that in addition to quantification of reflux volume, calf pump assessment such as with air plethysmography and AMVP is desirable in clinical classes 3 and higher for proper assessment. (J Vasc Surg: Venous and Lym Dis 2015;3:8-17.)**

In the last decade, reflux-mediated microvascular injury has emerged as the central pathologic change of chronic venous disease.[1-3] At least two distinct pathophysiologic stages in the evolution of overt disease appear to be involved: (1) an initial venous dilation from shear stress-induced release of nitrous oxide and cytokines and (2) the later appearance of venous hypertension due to progressive increase in reflux and calf pump dysfunction that perpetuates shear stress-mediated injury.[4,5] The initial vasodilation may be reversible in early stages of the disease by saphenous ablation.[6] In CEAP classes 3 to 6 disease, clinical severity correlates with ambulatory venous hypertension.[7] Any benefit of saphenous ablation in this setting will depend on the quantity of reflux load eliminated from the calf pump to reduce ambulatory venous pressure (AMVP).

There have been several attempts to quantify reflux by many different technologies. Indirect methods such as photoplethysmography and air plethysmography (APG) gauge reflux by measuring refill time (after emptying) of a relatively small area of the superficial venous network and the whole calf, respectively. The photoplethysmography technique is prone to large changes in monitored capacitance from thermal and other influences. Because refilling depends on many such variables, including arterial inflow and reflux from elsewhere, these indices are considered only qualitative or at best semiquantitative indices of global reflux.[8-14] For quantifying reflux in individual vessels, a direct measurement with duplex ultrasound is preferable.[10,15] Clinical correlation with CEAP classes has been poor with both direct and indirect indices of reflux. Some authors have combined or modified these techniques in an attempt at better clinical correlation with some success.[10,16]

Duplex ultrasound can measure several components of reflux, such as vessel size, velocity, and duration as well as the reflux volume. There have been several attempts to use one or the other of these components as a surrogate for overall reflux severity to simplify the metrics. Reflux duration at a specific valve site can be reproducibly measured if standardized distal compression with pneumatic cuffs to elicit reflux is used.[17] Initial hopes of a quantitative role for valve closure times pioneered by van

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Table I. CEAP clinical class of diseased limbs with isolated superficial reflux

CEAP clinical class	*N = 119*
0-1	8
2	19
3	30
4	38
5	2
6	20
No data	2

Bemmelen et al were not realized, and the measure is only qualitative.[17,18] Reflux duration now survives as a useful threshold to define reflux.[19] The size of the saphenous vein has been used as an index of reflux severity with fair correlation to clinical severity as well as to plethysmographic parameters.[20-22] A significant correlation between APG measures of reflux and size of refluxing veins at the knee as well as diameter of veins below the knee (weak to moderate, respectively) has been shown.[23] Our initial objective in this retrospective analysis was to relate reflux volume to saphenous size in the expectation that reflux volume will be more accurate. As the analysis progressed, it became clear that saphenous size had a bimodal correlation to reflux volume, and reflux volume in turn affected AMVP variably, depending on prevailing calf pump mechanics that could either buffer or magnify the effect of reflux. The aim of this study was to present the parameters of this complex calf pump pathophysiology.

METHODS

Patients. A total of 119 limbs with *isolated* reflux in the greater saphenous vein (reflux in no other venous segment) during an 11-year period were analyzed. All patients with an adequate data set (APG, AMVP) were included. Patients with combined superficial and deep reflux have been excluded to simplify analysis. The CEAP clinical classification of the study participants is shown in Table I.

AMVP measurement. AMVP was measured by standard technique through a needle in a dorsal foot vein. Measured parameters are percentage drop and venous filling time (VFT). Fig 1 illustrates the pressure dynamics that occur. Although it is referred to as a calf pump, it includes both superficial and deep compartments with a 10% to 20% and 80% to 90% volume split, respectively.[24] When the calf pump contracts, simultaneous ejection occurs in both the great saphenous vein and the deep veins, lowering the pressure in both. The major pressure drop in the saphenous vein occurs during the first step.[25] During calf diastole, reflux occurs through the saphenous vein, refilling both compartments through perforators until they are full.[26,27] The numerous (≈150) perforators, many with bidirectional flow, ensure pressure equivalence between the superficial and deep veins when filling is completed (Pascal law).[28-30] When forward flow resumes, pressure differences due to local flow conditions in the valved system may be present.[31,32]

VFT is a more sensitive parameter than percentage drop as it is more often associated with reflux and C6 disease, has a better resolution, and reflects not only the initial pressure drop but also the calf pump elastance component during pressure recovery.[14] VFT is preferentially used in this analysis.

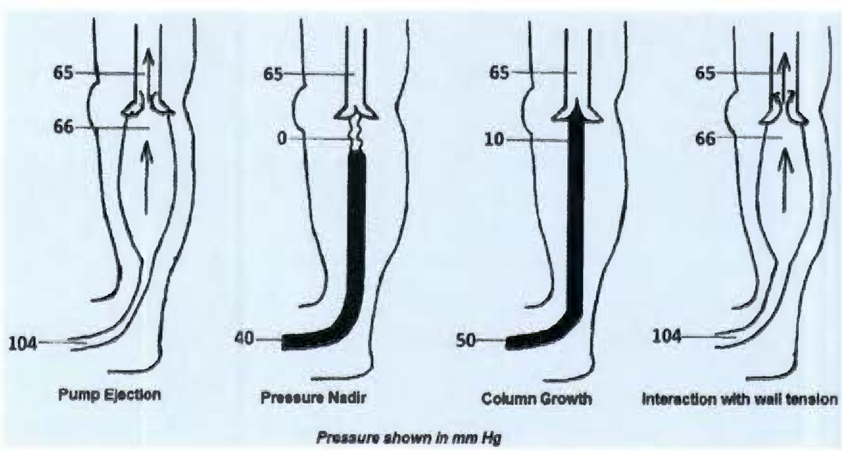

Fig 1. Pressure changes in the calf pump. The resting pressure of ≈104 mm Hg at the foot level declines to 40 mm Hg with ejection. Note the fully distended state of the calf pump veins before ejection. After ejection, the popliteal valve closes, the veins below collapse, and the pressure at the top of the residual venous column is zero. The pressure above the closed popliteal valve is ≈65 mm Hg. The calf pump begins to fill with inflow from the arterial side. As the blood column grows and touches the popliteal valve, the infrapopliteal veins are full but not stretched; the pressure will be relatively low within the calf pump (≈10 mm Hg) at this stage, and the popliteal valve will continue to remain closed. Continued arterial inflow slowly distends the calf pump veins. This "stretching" of the venous wall is necessary to create enough pressure (>65 mm Hg) adequate to open the popliteal valve and to restore flow.

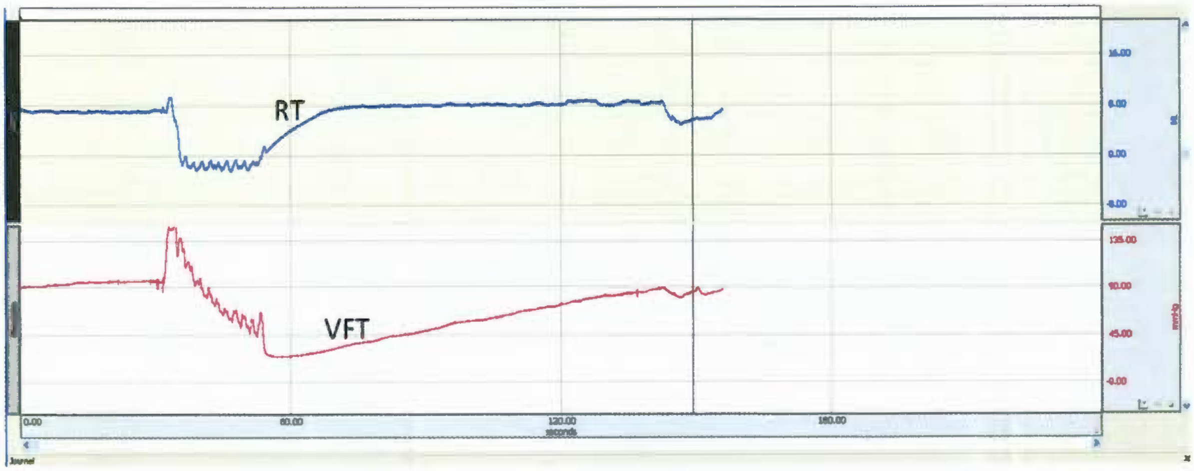

Fig 2. Simultaneous calf volume (air plethysmography [APG], *blue*) and pressure (ambulatory venous pressure [AMVP], *red*) recordings with calf exercise. The calf volume recovers rapidly in a fraction of the time (recovery time [*RT*]) compared with the time for pressure recovery (venous filling time [*VFT*]). The difference is due to stretching of the venous wall required to recover the high resting pressures. The ratio between RT and VFT could be used as an index of calf pump elastance in the stretching mode. Note that calf volume recovery is complete when the ambulatory pressure gradient is the highest. Significant reflux is not possible after calf volume recovery is complete.

APG. The technique described by Christopoulos and Nicolaides was used.[33]

AMVP and erect portions of the APG study [ejection volume (EV), ejection fraction (EF), residual volume (RV), and residual volume fraction (RVF)] were simultaneously acquired with a single calf exercise maneuver after recumbent portions of the APG study [venous volume (VV) and venous filling index (VFI_{90})] were completed.

Compliance index. After calf pump action, APG volume recovery takes place sooner than ambulatory pressure recovery (Fig 2).[34,35] The difference between volume recovery time (RT) and VFT represents the phase when calf volume interacts with vein wall tension and therefore is an index of calf vein wall compliance during the stretching portion of the bimodal compliance curve. Compliance index (CI) is calculated as follows: CI = (VFT − RT)/VFT; it is expressed as a percentage.

Arterial inflow. Arterial inflow into the calf pump was calculated (mL/s) from venous occlusion plethysmography by APG to monitor calf volume changes.[36]

Duplex measurement of reflux. Saphenous reflux was measured 2 cm distal to the saphenofemoral junction (cephalad to any runoff into branches) in the standing subject with rapid inflation/deflation cuffs with defined sizes and inflation pressures around the calf as described by Masuda et al.[37,38] This standardized technique is highly reproducible and eliminates the variability that may be found with manual compression techniques to elicit reflux. Pressure drop during pneumatic cuff calf emptying is similar to that of active calf exercise.[30] Sampling gate was set to correspond to the color flow channel. Vessel diameter was measured; time-averaged velocity and duration were provided by the machine (LOGIQ 9; GE, Fairfield, Conn). Reflux duration >10 seconds was recorded as 10 seconds because of machine presets in 38 limbs (35%). Significant reflux can occur only during calf volume RT but not after the calf pump is full. On the basis of this, a retrospective correction was made in these 38 limbs by inserting the actual RT (APG) instead of the machine-limited (10 seconds) reflux duration. Because the volume recovery curve at the end is steep (Fig 2), it is reasonable to assume that the reflux velocity was the same in the adjusted extension of duration as before; that is, error in reflux volume calculation is likely to be minor and in any case understates the discrepancy between saphenous size and reflux volume (see later).

Volume of reflux (mL/per calf refill) was calculated from these parameters (vessel area (πr^2) × time-averaged reflux velocity × duration).

Maximum reflux potential. The maximum reflux potential of an avalvular saphenous vein of a given size can be estimated from Poiseuille's law : $F = \Delta P \times \pi\ r^4/8\ L\ n$. "Normal" saphenous length and AMVP gradient are assumed. Reflux velocity and duration do not enter the equation. The measured saphenous radius (fourth power) is the dominant factor. Other constants used in the calculation were viscosity (n = 0.04 poise), mean ambulatory pressure drop (ΔP) of 71 mm Hg, and 50 cm for length of the saphenous vein (L) from groin to 5 cm below the knee (likely site of re-entry perforator). The last two were average values obtained in normal volunteers in our laboratory. Because F is reflux rate (mL/s), it was multiplied by 10 seconds (mean reflux duration in the data set) for proper comparison with actual measured reflux volume.

Hydraulic diameter of imputed reflux channel. Reverse flow in the saphenous vein encounters resistance three to eight times higher than forward flow despite incompetent valves.[34] This is probably due to valve cusps protruding across the reflux stream and the smaller caliber of re-entry perforators (resistance $\approx 1/\pi r^4$). In individual limbs, pressure drop may be less than the normal average. As a result, actual reflux seldom equals the maximum reflux potential based on saphenous lumen size and average pressure gradient. It is useful to compute the hydraulic diameter (HD) of the imputed reflux channel for comparison/correlation with actual saphenous size. This can be calculated from Poiseuille's equation ($F = \Delta P \times \pi r^4/8\ L\ n$) in individual limbs by inserting the measured volumetric reflux rate (mL/s) for F, measured ambulatory pressure drop (ΔP), assumed length ($l = 50$ cm), and viscosity ($n = 0.04$ poise) in the formula. This yields a solution for *r*, and the HD is twice the value. It will be strongly influenced by the narrowest diameter in the real reflux stream at either the valve or re-entry perforator level. The calculated reflux channel is not physical but imputed as it aggregates both the diffuse and focal areas of resistance in actual flow and distributes it into a calculated channel of uniform caliber and resistance ($1/\pi r^4$). The extent of disparity between actual saphenous size and the imputed reflux channel is a measure of the error that occurs when saphenous size is used as an index of reflux severity.

Statistics. Descriptive statistics, specifically the median and range, were computed to summarize the data. Because data were not normally distributed, a two-sided nonparametric Wilcoxon rank sum test was conducted to test differences between groups. Spearman rank correlation coefficient (ρ) was computed to measure the correlation between variables, and the χ^2 test was used to test differences in proportions. In comparing test limbs with normal limbs, the 95% confidence interval (mean $\pm$ two standard deviations) from the normal limbs was calculated. For some analyses, sample sizes differ because of missing data as a result of a patient's inability to perform clinical tests or technical reasons. Statistical significance was defined as a *P* value < .05. All analyses were performed with Prism software (Prism Software Corporation, Irvine, Calif) and SAS version 9.3 (SAS Institute, Cary, NC).

Institutional Review Board approval was obtained in acquiring data from normal limbs. Venous test data were anonymously extracted from past records of patient consented investigations.

RESULTS

Measured volumetric reflux. Duplex-measured median (range) time-averaged velocity, duration, and diameter were 7 (1-40) cm/s, 10 (1-24) seconds, and 0.6 (0.2-1.53) cm, respectively. Diameter has an exponential influence (πr^2) in calculating refluxing volume. Actual measured reflux in individual limbs is plotted in Fig 3. A *horizontal green line* marks the 30-mL reflux mark. This is approximately half of the average calf EV and is empirically chosen (see later) as likely to have an impact on calf function. All except three of the limbs (5 mm, 5 mm, and 5.2 mm, respectively) with a volumetric reflux of ≥30 mL had a diameter of 5.5 mm (*vertical green line*) or more. However, the reverse is not true. *Fig 3 suggests that reflux in most limbs (94% in this series) with saphenous vein <5.5 mm in size will be limited to <30 mL, but reflux in larger saphenous veins (>5.5 mm) may be greater or lesser (49% and 51%, respectively, in this sample) than the 30-mL threshold* (P *< .0001).*

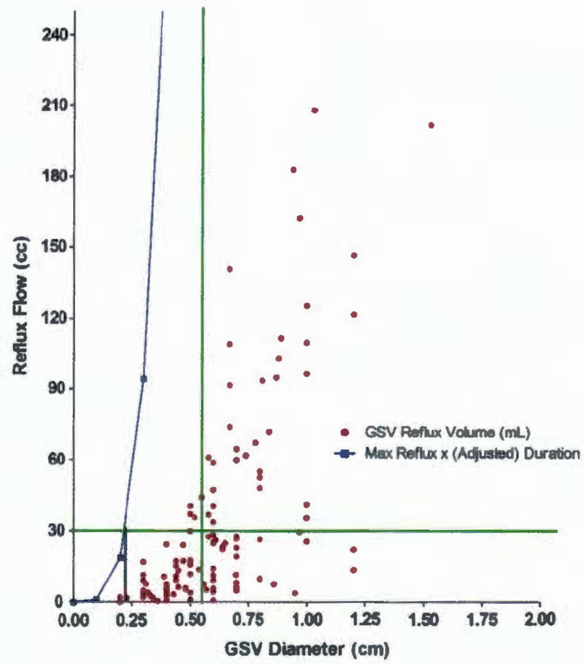

Fig 3. Relationship of measured reflux volume and saphenous size. All except three limbs (0.5 cm, 0.5 cm, and 0.52 cm, respectively) with a saphenous diameter <0.55 cm had reflux volumes of 30 mL or less. However, the reverse was not true; roughly half the limbs with saphenous diameter ≥5.5 mm had measured reflux volumes <30 mL and the other half >30 mL. Maximum reflux potential of various saphenous sizes is shown as a line (*blue*). Actual measured reflux volume was much less than the maximum potential. See text for explanation. *GSV,* Great saphenous vein.

The overall correlation between size and reflux volume in the entire subset ($n = 119$) was $r = 0.69$. Saphenous size ≥5.5 mm, reflux velocity, or duration could not be used alone clinically as an index of reflux severity ($r = 0.5$, 0.83, and 0.30, respectively, vs reflux volume ≥30).

Maximum reflux potential. The projected reflux potential from Poiseuille's law for various saphenous sizes is also shown in Fig 3. Actual volumetric reflux for a given saphenous size is much less than reflux potential for reasons stated earlier. A maximum reflux potential of 30 mL is reached when the saphenous vein is 2.3 mm in diameter (shown by a line intercept), much smaller than the observed (5.5 mm).

HD of imputed reflux channel. Fig 4 shows the HD of the imputed reflux channel and the actual diameter of refluxing saphenous veins (x-axis) plotted against flow. The imputed HD is much smaller than the actual saphenous diameter (HD median, 0.37 cm; great saphenous vein median, 0.6 cm; *P* < .0001), emphasizing the importance of reflux channel bottlenecks through remnant valve cusps and re-entry perforators that are likely narrower than the saphenous vein.

The calf pump. Calf pump parameters in normal limbs from volunteers, the refluxive limb, and the contralateral

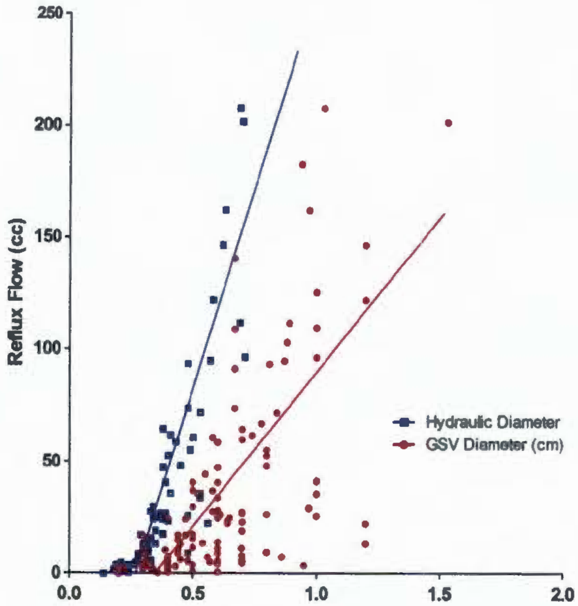

Fig 4. Hydraulic diameter (HD) of the reflux channel (*blue*) and actual diameter of the saphenous vein (*red*). The diameter is shown on the *x-axis* and reflux volume on the *y-axis*. The volume scale represents the rate of reflux volume (mL/s) for the HD and total measured volume for actual diameter. The HD is a virtual rendering of the reflux channel. This artifice aggregates many of the variables of reflux into a single comparator (HD) to gauge severity (see text). *GSV,* Great saphenous vein.

asymptomatic limb (without reflux) are shown in Table II. Significant deviations from normal limbs (means outside the 95% confidence interval) along with incidence rates (percentage abnormal) are also shown. Among 103 contralateral limbs in the subset, 84% had reflux and were excluded for this compilation. Summaries for the remaining 16 limbs without contralateral reflux by calf pump are shown.

One or more calf pump abnormalities, either compensatory or worsening the effect of reflux, were present in 70% of diseased limbs with reflux and 44% of contralateral limbs without reflux.

Measured reflux volume had no significant correlation to any of the calf pump parameters (EV, EF, RV, RVF). In the contralateral limb, VV and EV were decreased such that RVF remained normal. In the diseased limb with reflux, EV was significantly ***increased*** even though VV trended lower (normal EV median, 53.8 mL; diseased median, 66.5 mL; $P = .03$). The increase in EV appears to be a compensatory mechanism to buffer reflux and to keep the RVF normal. Compliance was significantly less in diseased limbs with reflux (normal median, 74%; diseased median, 63.5%; $P = .02$).

Measured reflux volume had a low correlation with VFI_{90} ($\rho = 0.42$) and with VFT ($\rho = -0.26$), probably because these measures are influenced not only by reflux but also by one or more of the other types of calf pump dysfunction, such as capacitance (VV), compliance, and EF.[14] VFT was significantly worse ($P < .0001$) when measured reflux volume was >30 mL (median VFT, 14) compared with lesser volumetric reflux of <30 mL (VFT median, 21.5). VFT was unaffected when saphenous reflux was confined to above the knee in comparison to reflux both above and below the knee (proximal-only median, 22.5; proximal and distal median, 15; $P = .07$), suggesting that the thigh segment of saphenous reflux is the key component.

VFT plotted against the corresponding measured reflux volume for the refluxive limbs is shown in Fig 5. The overall low correlation is apparent. However, if the limbs are segregated according to a threshold reflux volume of 30 mL (***vertical line*** in Fig 5) and VFT of 20 seconds (***horizontal line***), a less chaotic picture emerges. Of the limbs, 62% (41 of 66) have a concordant VFT, ie, the limbs above the reflux threshold have shortened VFT (***lower right quadrant***) and the limbs with <30 mL reflux (***upper left quadrant***) have normal VFT (≥20 seconds). The other 25 limbs (38%) have discordant VFT (ie, opposite to

Table II. Air plethysmography (APG) and ambulatory venous pressure (AMVP) parameters in normal, diseased, and contralateral limbs without reflux

	Normal (n = 21)	*Diseased limb (n = 109)*		*Contralateral limbs without reflux (n = 16)*	
Calf pump	*Mean ± SD*	*Mean ± SD*	*% Abnormal*[a]	*Mean ± SD*	*% Abnormal*[a]
VV	109 ± 35	88 ± 51[b]	26	80 ± 29[b]	7
EV	50 ± 19	75 ± 44[b]	39	34 ± 20[b]	13
EF	46 ± 13	51 ± 24	23	42 ± 19	20
RV	42 ± 22	34 ± 30[b]	7	28 ± 20[b]	0
RT	17 ± 8	11 ± 5[b]	0	13 ± 6	0
RVF	39 ± 11	39 ± 20	26	36 ± 20	27
VFT	71 ± 27	27 ± 20[c]	26	41 ± 22[b]	25
CI	73 ± 15	58 ± 25[b]	26	51 ± 28	33
% Total abnormal limbs			70		44

CI, Compliance index; *EF,* ejection fraction; *EV,* ejection volume; *RT,* refilling time; *RV,* residual volume *RVF,* residual volume fraction; *SD,* standard deviation; *VFT,* venous filling time; *VV,* venous volume.

P values based on Wilcoxon rank sum test.

[a]Based on 95% confidence interval for normal limbs.

[b]Denotes $P < .05$.

[c]Denotes $P < .0001$.

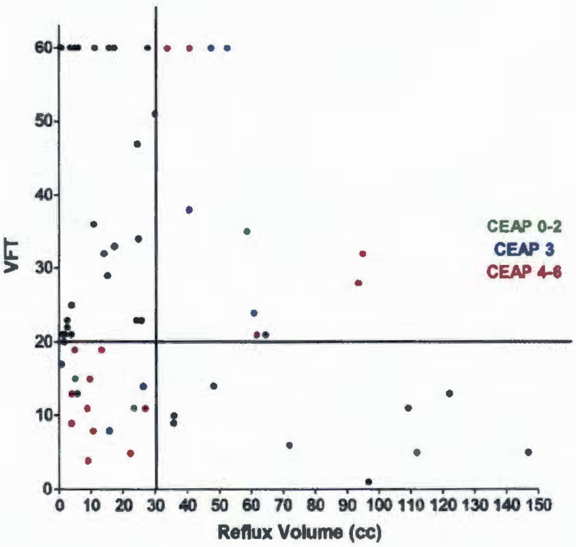

Fig 5. Relationship between measured reflux volume and venous filling time (*VFT*) of ambulatory venous pressure (AMVP). The data set is divided into four rectangles on the basis of intersecting lines marking the 30-mL reflux volume and 20-second VFT, which is considered normal. Limbs (62%) in the *outer rectangles* along the *x-axis* and *y-axis* have concordant VFT, ie, normal VFT if the reflux volume is <30 mL and abnormal VFT when reflux volume exceeds this threshold; 12% of limbs above the VFT line have normal VFT despite reflux volume exceeding the 30-mL threshold; 26% of limbs (innermost rectangle on *x-y intersection*) have abnormally shortened VFT despite a relatively small volume of reflux <30 mL. CEAP clinical classes 0 to 2 are shown in *green*, class 3 is shown in *blue*, and classes 4 to 6 are shown in *red*. The discordant VFT in the last two groups is due to identifiable reflux buffering mechanisms and intrinsic calf pump abnormalities, respectively, in many of the limbs (see text).

expected as explained before), apparently because of reflux buffering mechanisms in the calf pump or more often because of associated intrinsic calf pump abnormalities. We examined APG data in individual limbs for evidence of such buffering or calf pump abnormalities (Table III). Of eight of 25 limbs with volumetric reflux >30 mL with normal VFT, buffering mechanisms were found in six limbs. Among 17 of 25 limbs with volumetric reflux of <30 mL that nevertheless had short VFT, nine had poor calf mechanics likely aggravating reflux effects. Obstruction was not investigated in this study and could have been a factor in the eight limbs with no detectable APG abnormalities.

Reflux surrogates. A number of surrogate measures of reflux other than saphenous diameter were investigated for correlation with volumetric reflux >30 mL. These are presented in Table IV. Peak velocity as well as the product of peak velocity and diameter had a stronger correlation with volumetric reflux >30 mL than diameter alone. However, even this level of correlation will not be useful for clinical decision making.

Clinical correlation. Median reflux volume trended higher, although it was not statistically significant ($P = .17$), in C6 (median, 26.8 mL) compared with C0 to C5 clinical class (median, 17.3 mL) limbs with wide overlap, suggesting that measurement of volumetric reflux alone even in this severe C6 clinical subset will be of limited value in deciding suitability for saphenous ablation (Fig 6).

We examined individual APG and AMVP data (both concordant and discordant) in 14 limbs with active ulcer. Seven of 14 limbs had reflux volume >30 mL, and the other seven had reflux volume <30 mL. All in the group with reflux volume >30 mL had shortened VFT with the exception of one limb, which had normal VFT with calf pump buffering. All limbs in the group with reflux volume <30 mL had shortened VFT but with subnormal calf mechanics except one limb, which had normal VFT and normal mechanics (?obstruction).

DISCUSSION

The key findings of this analysis are (1) saphenous size, reflux velocity, and its duration individually are unreliable measures of reflux volume, and actual measurement of

Table III. Discordant[a] ambulatory venous pressure (AMVP) venous filling time (*VFT*) with reflux volume >30 mL and <30 mL

		Reflux >30 mL, normal VFT	
CEAP class	*n = 8*	*Calf pump buffering mechanisms*[b] *(n = 6)*	*No abnormality (n = 2)*
0-2	1	1 limb: ↑ EF, ↑ EV, and ↓ arterial inflow	0
3	4	1 limb: ↑ EF, ↓ RVF, and ↓ arterial inflow; 1 limb: ↑ EF	2
4-6	3	2 limbs: ↑ EF, ↑ EV, and ↓ RVF; 1 limb: ↑ VV and ↑ EV	0
		Reflux <30 mL, short VFT	
CEAP class	*n = 17*	*Subnormal calf pump parameters*[b] *(n = 9)*	*No abnormality (n = 8)*
0-2	2	1 limb: ↓ compliance	1
3	4	1 limb: ↓ VV and ↑RVF	3
4-6	11	4 limbs: ↓ compliance; 2 limbs: ↓ VV; 1 limb: ↑ RVF	4

EF, Ejection fraction; *EV*, ejection volume; *RVF*, residual volume fraction; *VV*, venous volume.
[a]Reflux volumes ≥30 mL and ≤30 mL with normal and abnormal VFTs, respectively, which are opposite of what is expected.
[b]Calf pump values outside of the 95% confidence interval for normal limbs were considered abnormal for this subset analysis.

Table IV. Correlation of reflux surrogates to measured volumetric reflux >30 mL

	Measured reflux volume (>30 mL)
GSV diameter ≥ 0.55 cm	0.5
Peak velocity, cm/s	0.65
VFI_{90}	0.4
Peak velocity × GSV diameter	0.6

GSV, Great saphenous vein; *VFI,* venous filling index.

reflux volume is necessary; (2) the impact of reflux volume on AMVP is likely to be variable, depending on calf pump mechanics that may buffer or magnify the effect of the reflux load; and (3) calf pump abnormalities may be present in limbs with or without reflux.

Our analysis indicates that the best quantification of saphenous reflux is actual measurement of reflux volume. The size of the saphenous trunk and the velocity of reflux and its duration can vary widely for any given reflux volume, rendering them poor surrogates. The poor relationship of truncal size to reflux volume probably arises from the fact that other focal areas of high resistance damp reflux in addition to saphenous size. This results in the difference between the HD of the imputed reflux channel and the actual diameter. The size and number of re-entry perforators and their combined conductance (Fig 7) are probably more restrictive than the actual size of the refluxive saphenous vein in volume loading of the calf pump. It is likely to be the reason that actual reflux is much less than the maximum possible based on saphenous size. Anatomic studies have established that on an average, ≈80 to 150 perforators are present in the limb. Even this large number can be restrictive of reflux because resistance increases by the fourth power inversely with size as shown in Fig 7. Furthermore, most perforators connect to the posterior arch vein, not the main saphenous trunk. Most perforators are 1 mm or smaller, beyond detection by current duplex instrumentation on routine examination.[39]

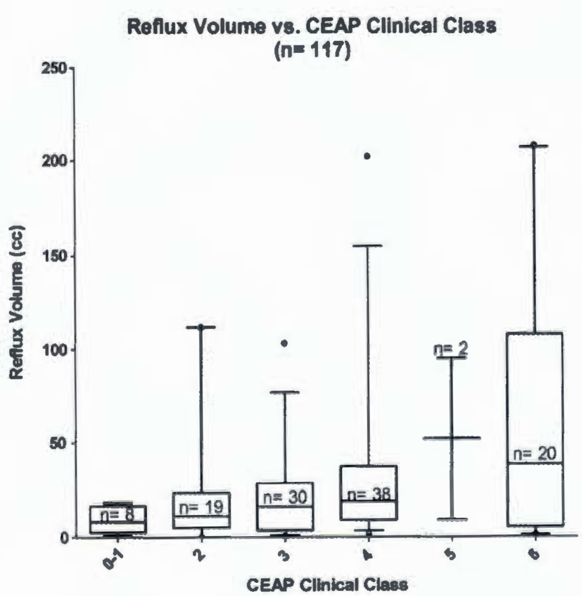

Fig 6. Measured reflux volume vs CEAP clinical class. There is no significant difference in median reflux in the various CEAP categories.

The HD provides average flow resistance to reflux ($1/\pi r^4$); and reflux volume per second (rate of reflux) can be calculated if the ambulatory pressure gradient (same as ambulatory pressure drop) is also known. A large-caliber saphenous vein will have a slower reflux velocity than in a smaller saphenous vein but with the same reflux volume (and HD), hence the poor correlation of reflux velocity to reflux volume.

The poor correlation of reflux duration to reflux volume arises from the fact that a saphenous vein with a faster rate of reflux of short duration can have the same reflux volume as a limb with a slower rate of reflux with longer duration. Reflux duration is controlled by calf pump refilling time with some possible exceptions (see later).

It is a common misconception that saphenous reflux restores column pressure immediately, defeating column segmentation by the calf pump. Reflux in motion does not transmit column pressure. This can be shown in a simple experimental model of calf pump.[35] If column pressure is restored at the start of the reflux, there will be no pressure differential and the reflux will come to a stop. The pressure head at the top is dissipated by viscous flow resistance equaling exactly the ΔP prevailing at the moment between the top and bottom of the refluxing column. The AMVP curve at the foot level will mirror the gradual restoration of column pressure with saphenous reflux. Most authorities associate reflux duration with pressure recovery in the calf.[26,27,31,32,40,41] Most of the reflux will take place during volume recovery at a time when ambulatory pressure is low because of the nonlinear relationship. The mean reflux duration in this sample (10 seconds) closely approximates volume RT (11 seconds). In several limbs, reflux duration was very short, <2 seconds, suggesting that reflux duration can be shorter than RT in some cases. Explanations include less nonlinear pressure-volume relationship in post-thrombotic veins, arresting reflux before full calf volume recovery; reflux in high-resistance saphenous veins (narrow HD) that falls below detectable levels by duplex ultrasound (<3 cm/s) as the mean calf pressure rises; closure of refluxive valves as the segment below fills due to valve station mechanics before full calf volume recovery; and reflux into isolated pockets of varices without connection to the calf pump that were emptied by the pneumatic cuff. None of these explanations have been studied in detail and remain speculative.

When saphenous reflux is present along with deep reflux, the saphenous reflux will be truncated in duration and volume because of premature filling of the calf pump from coexisting deep reflux. In such cases, measurement of volumetric saphenous reflux cannot reliably predict the utility of saphenous ablation to improve symptoms. Prior

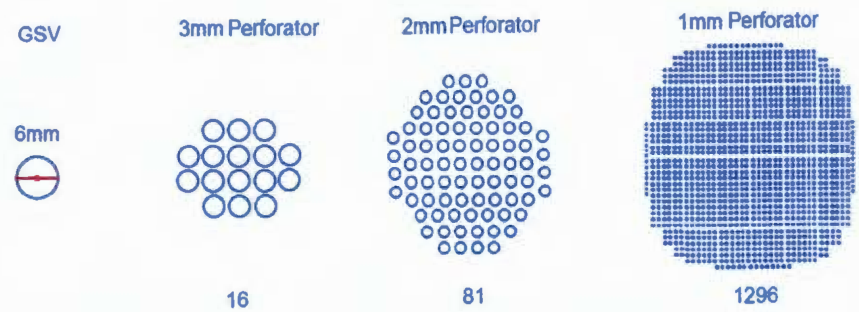

Fig 7. Relative conductance of saphenous vein and perforators of various sizes. Average size of the saphenous vein is 4 to 5 mm and that of a perforator is 1 to 2 mm, with larger sizes when reflux is present. Because conductance is based on the fourth power of the radius, this disparity in size results in an enormous difference in conductance. The number of perforators of various sizes required to equal the conductance of a 6-mm saphenous vein is shown under each cartoon. See text. *GSV,* Great saphenous vein.

attempts to use a tourniquet to eliminate saphenous reflux for assessment have been shown to be faulty.[42,43] Direct compression with a duplex probe may be more reliable.

Calf pump mechanics. Normal EV is ≈ 50 mL, and an absolute volume reflux of 30 mL (60% of EV) will shorten calf refill time (RT) roughly by the same percentage if all other calf parameters are normal and compensatory mechanisms do not occur (often they do). Lesser refluxing volumes (<30 mL) may cause ambulatory venous hypertension if certain calf pump parameters are abnormal and buffering mechanisms are absent. The reflux volume threshold in this setting is likely to be variable and has to be tested in individual limbs by saphenous occlusion maneuvers.

Mechanisms that buffer reflux at the calf pump as well as abnormalities that degrade calf pump function are shown in Fig 8.[14] The calf pump has a muscle component that provides contractile power and a venous component that provides capacitance (VV), compliance, and ejection as primary inputs. Interaction between these can result in secondary abnormal metrics such as EF and RVF. A mix of these mechanisms, sometimes working against each other, is often present. The net effect on calf function will be reflected in AMVP (VFT). Reflux is extrinsic to the calf pump mechanism and is the major factor that short-circuits calf pump efficiency. Increasing EV appears to be a prime compensatory mechanism, and clinical deterioration may not occur until this mechanism too is exhausted.[44,45] Arterial inflow may be increased in some cases of chronic venous insufficiency and arteriovenous malformations.[14,34,46] Arterial inflow falls with standing (venoarteriolar reflux) and increases with exercise. We

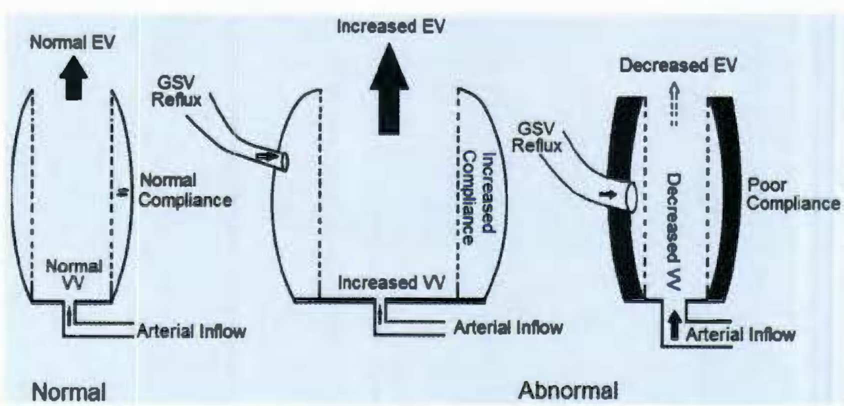

Fig 8. A cartoon (not to scale) of calf pump mechanics, normal and abnormal. Reflux is extrinsic to the calf pump mechanism itself and is a major cause of its decompensation. The calf pump has a venous (bladder) component and a muscle component. Normal function is dependent on adequate priming (capacitance or venous volume [*VV*]), normal compliance, and normal ejection volume (*EV*) as shown on the *left panel.* Reflux can be buffered if the EV and compliance are increased. Increased VV can buffer reflux if EV is simultaneously increased; it can worsen the effects of reflux if EV is unchanged (*middle panel*). Most abnormalities of the calf pump involve the venous bladder component with decreased capacitance, ejection, compliance, or a combination (*right panel*). Ejection fraction (EF) and residual volume fraction (RVF) are secondary metrics of calf pump function based on interaction between primary functional parameters (VV, EV, compliance). Arterial inflow can be a source of calf pump dysfunction in some cases. See text. *GSV,* Great saphenous vein.

assume (unproven) that the recumbent arterial inflow measured herein will reflect, in some measure, erect flows.

A novel finding in this analysis was the presence of calf pump abnormality in opposite limbs of patients without reflux, suggesting that it can occur with or without reflux.

Study limitations. The study is retrospective, and reflux data were collected from only one site for reasons mentioned earlier. An error, likely minor but of unknown precise dimension, was introduced when reflux duration times were assigned in some limbs to overcome machine presets. No conclusion about selection of patients for saphenous ablation can be drawn from this study as neither saphenous compression nor postoperative data (only about half the limbs underwent ablation) were analyzed to limit the scope and length of the manuscript.

CONCLUSIONS

Diagnostic assessment in modern clinical practice has devolved into use of duplex alone, often in qualitative mode, defined by duration of reflux exceeding a set threshold. This study suggests that volumetric measurement is clearly better but is inadequate in and of itself. It is not the given volume of reflux but how it interacts with the calf pump that sets the clinical picture as suggested previously by Araki et al.[44] As many as 70% of limbs with saphenous reflux had calf pump abnormalities in this series. Threshold reflux volumes that would be injurious in this setting are unknown but probably vary with severity of calf pump abnormality. A proper clinical assessment will therefore require calf pump assessment in addition to duplex ultrasound (preferably with digital saphenous compression), at least in C4 to C6 limbs, as suggested by several authors.[23,38,44,45]

AUTHOR CONTRIBUTIONS

Conception and design: SR
Analysis and interpretation: SR
Data collection: SR, MW
Writing the article: SR, MW, TJ
Critical revision of the article: SR
Final approval of the article: SR
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Obtained funding: Not applicable
Overall responsibility: SR

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