Ambulatory venous pressure, air plethysmography, and the role of calf venous pump in chronic venous disease

Seshadri Raju, MD, FACS, Jordan Knepper, MD, MSc, Corbin May, MS, Alexander Knight, BS, Nicholas Pace, MS, *and* Arjun Jayaraj, MD, FACS, *Jackson, Miss*

ABSTRACT

Background: Ambulatory venous pressure (AMVP) records pressure dynamics with calf exercise. Air plethysmography (APG) measures related volume detail. APG has been suggested as a noninvasive surrogate for AMVP. We examine the correlations between APG and AMVP parameters and the role of "calf pump failure" in chronic venous disease (CVD).

Methods: A total of 8456 limbs in 4610 patients investigated for CVD during a 20-year period were analyzed. APG and AMVP data were available in 4599 limbs for calculation of Pearson correlation coefficient; 1347 of these limbs had significant iliac vein stenosis, proven by intravascular ultrasound. Venn diagrams are used to explore overlapping incidence of APG and AMVP abnormalities.

Results: APG calf volume and reflux (venous volume, venous filling index) showed progressively significant deterioration with advancing Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) clinical class, anatomic extent of reflux (superficial, deep, perforator), and reflux severity (axial reflux, segmental score). Notably, calf ejection volume increased in a nearly linear fashion ($R = 0.71$) to venous volume such that residual volume fraction (RVF) remained normal even in the worst of these categories. AMVP too progressively deteriorated with clinical disease and reflux severity. Venous filling time was the key parameter as the pressure drop alone was abnormal in only 4% of the limbs analyzed. There was no correlation between RVF and AMVP ($R = 0.22$) or between AMVP and many other APG parameters. Venn distribution showed only minor overlap (30%) between AMVP and key APG abnormalities overall, but the overlap increases from 40% to 70% in advanced clinical and reflux categories. AMVP was rarely abnormal (7%) when APG was normal. Median AMVP was normal in calf pump failure categories, however defined (subnormal ejection fraction, RVF, or both). Median AMVP is normal in venous obstruction without reflux, while AMVP abnormalities are associated three to seven times more with reflux than with obstruction.

Conclusions: APG (venous filling index) is a useful index of reflux. Calf pump ejection is a powerful and plastic compensatory mechanism, and calf pump failure is rare. Ambulatory venous hypertension is dominantly associated with reflux and less with obstruction. AMVP too worsens with clinical and reflux severity categories. However, there is little correlation between APG and AMVP parameters as APG measures volume and AMVP measures pressure, each in its own domain, and the volume-pressure curve is nonlinear. AMVP may be omitted in routine clinical testing if APG is normal, as the yield (7%) will be very low. AMVP reflects venous hypertension, the end stage in CVD. AMVP should be used to identify such cases when APG is abnormal. (J Vasc Surg: Venous and Lym Dis 2019;7:428-40.)

Keywords: Ambulatory venous pressure; Air plethysmography; Calf pump failure

Ambulatory venous pressure (AMVP) is considered the "gold standard" of functional venous tests. It is a global measure of calf pump function, integrating its many components—foot pump, ankle joint motion, calf muscles, capacitance and compliance of contained venous network, and outflow obstruction. It is, however, invasive and has fallen out of use in clinical practice. Christopoulos et al[1] described a clinical tool using air plethysmography (APG) to measure various aspects of calf pump function. It is commercially available and is currently the functional test most commonly used. A noteworthy claim made by the original authors of APG is that residual volume fraction (RVF) measured by the device faithfully reflects AMVP with nearly linear correlation ($n = 89$; $r = 0.83$), since confirmed by others.[2,3] This was intriguing as translation of volume into pressure is through the volume-pressure curve, which is known to be nonlinear and varies with underlying disease.[4]

The aim of this study was to explore the relationship between APG and AMVP in a large cohort of chronic venous disease (CVD) patients. The analysis also examines the concept of "calf pump failure" in this context.

METHODS

Contemporaneously acquired electronic medical record venous laboratory test data of 8456 limbs in 4610 patients with CVD symptoms seen from 1995 to 2016 were analyzed. Included in the analysis are 1347

From The Rane Center at St. Dominic Hospital.

Author conflict of interest: S.R. holds U.S. patents in intravascular ultrasound diagnostics and venous stent design and receives stock/royalty from Veniti.

Correspondence: Seshadri Raju, MD, FACS, The Rane Center at St. Dominic Hospital, 971 Lakeland Dr, Ste 401 East Tower, Jackson, MS 39216 (e-mail: rajumd@earthlink.net).

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limbs from the same group with intravascular ultrasound (IVUS)-proven iliac vein stenosis. Duplex ultrasound data were available in 8456 limbs, APG data in 7910, and AMVP data in 4766; both AMVP and APG data (plus duplex ultrasound) were available in 4599 limbs. AMVP was available in fewer limbs than APG because of patient refusal, low indication (Clinical, Etiology, Anatomy, and Pathophysiology [CEAP] clinical class 0-2 limbs without reflux), and failed or unavailable access (CEAP clinical class ≥3). Total number values displayed in individual tables vary slightly from these number values because of missing data in individual tests.

APG

A commercially available instrument (ACI Medical, San Marcos, Calif) with standard protocol described by Christopoulos was used. The following parameters were obtained: venous volume (VV), venous filling index (VFI $_{90}$), ejection volume (EV), ejection fraction (EF), residual volume (RV), RVF, and calf volume recovery time (RT). RT can be calculated from the APG tracing as described previously.[5]

AMVP

Pressures were measured by a needle in the dorsal foot vein through a high-frequency transducer (Biopac Systems, Goleta, Calif) mounted at the foot level. Pressure tracings were acquired using digital software (Biopac Systems). Resting pressure was obtained in the erect position with weight bearing on the opposite limb. AMVP was recorded with 10 tiptoe movements. The pressure nadir represented postexercise pressure, also referred to as AMVP. Ambulatory pressure drop (% drop) was calculated as (Pressure drop/Base) × 100. The time in seconds (venous filling time [VFT]) for pressure recovery to baseline was recorded.[6-8]

APG and AMVP were typically performed simultaneously (Fig 1).

Duplex ultrasound

Patients were examined in the erect position with automated inflation-deflation cuffs to elicit reflux. A color duplex ultrasound machine (Logiq 9; GE Healthcare, Wauwatosa, Wisc) was used per standard protocol. Reflux was defined as reverse flow >1 second in duration for both the deep and superficial veins, which has been in place in our laboratory since 1995. The definition for superficial reflux in the recent Society for Vascular Surgery/American Venous Forum guidelines is shorter for superficial, perforator, and deep femoral reflux (>500 milliseconds).

A reflux segment score was determined on the basis of the number of refluxive vein segments: 1 point each for great saphenous vein, small saphenous vein, perforator, femoral vein, profunda, popliteal vein, and posterior tibial vein. With this grading, 0 is no reflux; with a score of 7, all the segments are refluxive. This scoring system has been shown to correlate with clinical severity.[7] Reflux severity analysis also included the Kistner classification using duplex ultrasound.[6,9]

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective cohort study
- **Key Findings:** In 4599 limbs with chronic venous disease, air plethysmography (APG) and ambulatory venous pressure (AMVP) parameters showed progressive deterioration across Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) clinical classes, with little correlation between APG and AMVP. AMVP was rarely positive if APG was negative, whereas both were positive in 40% to 70% with higher clinical or reflux categories.
- **Take Home Message:** AMVP can probably be omitted in routine clinical testing if APG is normal, but AMVP is a better reflection of underlying venous hypertension in advanced chronic venous disease and can be used to identify venous hypertension when APG is abnormal.

IVUS

The technique of IVUS diagnostics in iliac venous stenosis has been described in detail elsewhere.[10,11]

Statistics

Initial analysis. Multiple comparisons between APG and AMVP parameters were obtained using Pearson correlation coefficient (R). Two-tailed unpaired t-test and analysis of variance were used for statistical comparison of variables as appropriate. A commercially available software program (GraphPad Prism; GraphPad Software Inc, La Jolla, Calif) was used. Data for all test parameters are analyzed and displayed as a continuous variable; when median value crosses normal thresholds, it is so noted.

Multiple regression analysis. RV and AMVP data were analyzed using SPSS 12.1 (Softonic, Barcelona, Spain). Given the large amount of data known about patients' venous status, propensity matching was used with visible venous disease as the marker. Prediction of CEAP clinical class was the outcome parameter. Right legs were used as the derivation cohort and left legs as the validation cohort; identity linkers were removed to increase validity. The models were tested for goodness of fit. A P value of $<.5$ was considered significant.

Venn distribution diagrams of selected parameters were constructed using R, an open source statistical computing and graphic software (R Foundation for Statistical Computing, Vienna, Austria).

Informed consent

Informed consent for the various tests was obtained. Institutional Review Board permission was granted for publication of this deidentified retrospective analysis.

Fig 1. Air plethysmography (APG) and ambulatory venous pressure (AMVP) tests can be performed simultaneously as the tiptoe calf exercise maneuver is the same.

Table I. Demographics of 4610 patients (8456 limbs) investigated for chronic venous disease (CVD)

Male:female	1:2
Age, years, median (range)	65 (15-116)
Left:right	1:1
CEAP clinical class, right (n = 3947)	0-2: 18%
	3: 59%
	4-6: 23%
CEAP clinical class, left (n = 3263)	0-2: 14%
	3: 63%
	4-6: 23%
Body mass index, kg/m^2, median (range)	32 (16-75)

CEAP, Clinical, Etiology, Anatomy, and Pathophysiology.

RESULTS

The demographics and CEAP clinical classification of the cohort of patients are shown in Table I.

Reflux distribution

The incidence of superficial, deep, and perforator reflux and of combinations is shown in Table II. Of the investigated limbs, 67% had reflux in various combinations; 33% of the limbs had no reflux.

APG and AMVP parameters are presented in this order: CEAP clinical class (Tables III and IV), anatomic system involvement (Table V), and reflux segment and axial scores (Table VI-VIII). Intratest and intertest comparisons are then provided, followed last by data pertaining to calf pump failure.

APG. Median APG parameters per CEAP clinical class are shown in Table III, and the AMVP parameters are shown in Table IV. The first column shows threshold normal values used as a benchmark for comparisons; these are commonly used nominal values from the literature.

There is steady deterioration in key APG and AMVP parameters across CEAP clinical classes. A general trend in most parameters is apparent, with values reaching statistical significance along the way. Calf volume (VV) trended higher and calf RT trended lower. The reflux parameter (VFI_{90}) trended higher. The EV trended higher, keeping EF at normal or nearly normal levels. RV and RVF remained well within normal limits. RV was significantly less in CEAP class 3 (swelling). The overall trend is one of worsening reflux (VFI_{90}) and related parameters (VV and RT), with a compensatory increase in calf pump ejection keeping RVF within normal limits.

This general pattern of worsening APG parameters related to reflux (VV, VFI_{90}, and RT) with normal or nearly normal EF and normal RVF can be seen in all high-reflux categories in Tables V, VI, and VIII showing anatomic

Table II. Anatomic distribution of reflux[a] in limbs investigated for chronic venous disease (CVD)

Reflux location	Total limbs (N = 8456), No. (%)
No reflux	2745 (33)
Reflux	5711 (67)
Superficial only	3616 (63)
Deep only	2324 (40)
Perforator isolated	621 (11)
Superficial and deep	1459 (25)
Superficial, deep, and perforator	288 (5)

[a]Reflux was defined as reverse flow >1 second in duration for both the deep and superficial veins.

Table III. Air plethysmography (*APG*) parameters in Clinical, Etiology, Anatomy, and Pathophysiology (*CEAP*) clinical classes

APG parameters (normal values)	CEAP class 0-2 (n = 1105)	CEAP class 3 (n = 4045)	CEAP class 4 (n = 974)	CEAP class 5-6[a] (n = 465)
VV	90 (0-325)	87 (0-447)*	103 (0-240)***	100 (0-373)**
VFI_{90} (2.2 mL/s)	1.3 (0-18.2)	1.3 (0-21)	2.1 (0-21)***	2.7 (0-21)***
EV	43 (0-188)	43 (0-214)	54 (0-270)***	50 (0-194)**
EF (>50%)	48.6 (0-89.7)	51.3 (0-89.8)***	53 (0-89)***	48 (0-89)
RV	31.4 (0-188)	28 (0-250)***	32.6 (0-208)	36.6 (0-249)
RVF (<50%)	35 (0-87)	32 (0-89)***	32 (0-88)**	36 (0-89)
RT, seconds	11 (0-117)	11 (0-86)	10 (0-45)	9 (0-100)***

EF, Ejection fraction; *EV*, ejection volume; *RT*, recovery time; *RV*, residual volume; *RVF*, residual volume fraction; *VFI_{90}*, venous filling index; *VV*, venous volume.
Values are presented as median (range).
P vs CEAP classes 0-2: **P* ≤ .05, ***P* ≤ .01, ****P* ≤ .001.
[a]CEAP classes 5 and 6 were significantly worse than CEAP class 4 in VFI_{90} ($P \leq .001$), EF ($P \leq .001$), and RT ($P \leq .001$). CEAP classes 5 and 6 were significantly worse than CEAP class 3 in VV ($P \leq .001$), VFI_{90} ($P \leq .001$), and RT ($P \leq .001$) and better in EV ($P \leq .01$), RV ($P \leq .001$), and RVF ($P \leq .05$).

distribution of reflux, reflux segment score, and Kistner axial reflux grades, respectively.

AMVP. Median AMVP (% drop/VFT) detail per CEAP clinical class is shown in Table IV. VFT is borderline normal in CEAP clinical class 4 and is significantly shortened in classes 5 and 6. The % drop also trended lower across CEAP clinical classes even though the median value was in the normal range (>50%) in all CEAP clinical classes. Note that both VFT and % drop were quantitatively worse in CEAP clinical classes 5 and 6 than in CEAP class 3 or class 4, that is, AMVP deterioration was progressive across all CEAP clinical classes and did not stall with CEAP 3 as in the report of Welkie et al.[3]

Median values for VFT and % drop for anatomic reflux distribution, segment score, and Kistner severity classifications are shown in Tables V, VII, and VIII, respectively. VFT trends lower in high-reflux categories and is in the abnormal range in multisystem reflux in Table V, segmental score 3 and higher in Table VII, and Kistner grades 1 through 3 in Table VIII. The % drop also trends worse in high-reflux categories but remains within normal range in all of these categories with the sole exception of segmental score 6 and 7 in Table VII.

Venn distributions. AMVP abnormalities were overwhelmingly associated with reflux in CVD limbs (Fig 2); 67% of CVD limbs had reflux and 33% did not. The overall incidence of abnormal AMVP was 1682 of 4599 or 37% in CVD limbs (n = 4599); 74% of AMVP abnormalities occurred in refluxive limbs. It was less common (24%) for AMVP to be abnormal in the absence of reflux. Overall, the incidence of abnormal AMVP without reflux occurred in only 9% of limbs.

Venn distribution of AMVP and key APG abnormalities (VFI_{90}, EF, and RVF) is shown in Fig 3. APG abnormality occurred in more than two-thirds of CVD limbs and was about twice as frequent as AMVP abnormality; the abnormal test results overlapped in only 30%. In 23%, neither test result was positive; 81% of limbs with abnormal AMVP were associated with APG abnormalities. AMVP abnormalities occurred in only 7% of limbs in the absence of APG abnormalities. The overlap between APG and AMVP abnormalities progressively increases with increasing clinical and reflux severity: from 42% in CEAP clinic classes 4 to 6 to 66% in reflux segment score 4 to 7.

In CVD, 67% of limbs have normal VFT and normal % drop. Abnormal VFT is seen in 33% and abnormal % drop in only 11% (Fig 4). Only 4% of limbs with normal VFT had an abnormal % drop. Therefore, it is rare for % drop to be abnormal if VFT is normal.

Table IV. Ambulatory venous pressure (*AMVP*) parameters in Clinical, Etiology, Anatomy, and Pathophysiology (*CEAP*) clinical classes

AMVP (normal values)	CEAP class 0-2 (n = 462)	CEAP class 3 (n = 2387)	CEAP class 4 (n = 606)	CEAP class 5-6[a] (n = 270)
% Drop (>50%)	74 (18-94)	76 (5-98)*	71 (4-95)**	63 (15-95)****
VFT (>20 seconds)	40 (15-141)***	40 (19-274)	20 (0-127)***	11 (0-84)***

VFT, Venous filling time.
Values are presented as median (range).
P vs CEAP classes 0-2: **P* ≤.05, ***P* ≤ .01, ****P* ≤ .001, *****P* ≤ .0001.
[a]CEAP classes 5 and 6 were significantly worse than CEAP classes 3 and 4 in % drop ($P \leq .001$) and VFT ($P \leq .001$). CEAP classes 5 and 6 were significantly different from CEAP class 3 in % drop ($P \leq .001$) and VFT ($P \leq .001$).

Table V. Air plethysmography (*APG*) and ambulatory venous pressure (*AMVP*) parameters according to anatomic distribution of reflux

APG parameters (normal values)	Superficial reflux only (n = 3434)	Deep reflux only (n = 2197)	Superficial and deep reflux (n = 1379)[a]	Superficial, deep, and perforator reflux (n = 269)[b]
VV	101 (0-373)	101 (0-388)	106 (0-370)*	126.5 (0-330)***
VFI_{90} (2.2 mL/s)	2.2 (0-21.1)	2.3 (0-21.1)	2.7 (0-21.1)***	3.8 (0-15.7)***
EV	49 (0-270)	49 (0-270)	52 (0-270)	58 (0-174)***
EF (>50%)	49 (0-89.8)	49 (0-89.8)	48 (0-89.8)	47 (0-89.6)
RV	35 (0-250)	33 (0-337)	37 (0-209)	48 (0-186)***
RVF (<50%)	36 (0-89)	35 (0-89)	37 (0-89)	41 (0-88)**
RT, seconds	10 (0-185)	9 (0-185)	9 (0-185)***	8 (0-28)***
AMVP (normal values)	**Superficial reflux only (n = 2007)**	**Deep reflux only (n = 1348)**	**Superficial and deep reflux (n = 868)[a]**	**Superficial, deep, and perforator reflux (n = 188)[b]**
VFT (>20 seconds)	21 (0-185)	18 (0-185)	15 (0-185)***	9 (0-99)***
% Drop (>50%)	70 (4-98)	67 (6-98)	65 (6-98)****	58 (18-94)****

EF, Ejection fraction; *EV,* ejection volume; *RT,* recovery time; *RV,* residual volume; *RVF,* residual volume fraction; *VFI_{90},* venous filling index; *VFT,* venous filling time; *VV,* venous volume.
Values are presented as median (range).
*$P \leq .05$, **$P \leq .01$, ***$P \leq .001$, ****$P \leq .001$.
[a]Compared with superficial reflux only.
[b]Compared with deep reflux only.

Venous obstruction

Among the 1347 limbs with IVUS-proven obstruction, associated reflux was present in 949 limbs (70%). The remaining 398 limbs (30%) had pure obstruction without reflux as shown in Table IX.

APG. All APG parameters are normal in obstruction without reflux. Significant APG abnormalities along the pattern described in previous refluxive groups are seen in combined obstruction and reflux.

AMVP. VFT and % drop are normal in the nonrefluxive group and significantly worse in the refluxive group. Median VFT was below normal threshold in the refluxive group, but % drop was in the normal range, similar to the pattern seen earlier in other refluxive groups.

Fig 5 shows Venn distribution of AMVP abnormalities in venous obstruction. AMVP abnormalities were overwhelmingly (87%) associated with reflux in the obstructive limbs. The incidence of AMVP abnormalities in pure obstruction (no reflux) was only 13%.

It appears that AMVP abnormalities are overwhelmingly associated with reflux, not obstruction.

Intratest correlations

APG. EV had a significantly strong correlation to VV ($R = 0.71$; Fig 6). Note that EV increases up to three to four times normal in response to greater capacitance (preload). VV had a moderate correlation to VFI_{90} ($R = 0.53$). RT was poorly correlated to VV ($r = 0.05$) or VFI_{90} ($r = 0.06$).

Table VI. Air plethysmography (*APG*) parameters according to reflux segmental scores

APG parameters (normal values)	Segmental score: 0 (n = 2536)	1 (n = 2623)	2 (n = 1373)	3 (n = 693)	4 (n = 402)	5 (n = 166)	6 and 7 (n = 85)
VV	79 (0-447)	90 (0-331)***	99 (0-388)***	104 (0-351)***	111 (0-319)***	120.5 (11-262)***	134 (30-248)***
VFI_{90} (2.2 mL/s)	1 (0-101)	1.4 (0-21.1)***	2 (0-16.6)***	2.3 (0-21.1)***	3.1 (0-20.5)***	4 (0.45-14)***	4.3 (0.9-13.9)***
EV	40 (0-214)	45 (0-248)***	49 (0-203)***	49 (0-200)***	52 (0-159)***	59 (3-270)***	48 (8-124)*
EF (>50%)	53 (0-89.9)	51 (0-89.9) NS	49 (0-89.9)**	49 (0-89.9)**	47 (0-87.8)***	48 (8.5-87.5) NS	44 (0-97)**
RV	21 (0-250)	27 (0-197)***	32 (0-337)***	35 (0-194)***	39 (0-187)***	42 (0-162)***	45 (0-151)***
RVF (<50%)	28 (0-89)	33 (0-89)***	35 (0-88)***	37 (0-89)***	38 (0-89)***	40 (0-84)***	45 (0-85)***
RT, seconds	12 (0-117)	10 (0-86)***	10 (0-185)***	9 (0-53)***	8 (0-71)***	7 (2-42)***	7 (1-15)***

EF, Ejection fraction; *EV,* ejection volume; *NS,* not significant; *RT,* recovery time; *RV,* residual volume; *RVF,* residual volume fraction; *VFI_{90},* venous filling index; *VV,* venous volume.
Values are presented as median (range).
*$P \leq .05$, **$P \leq .01$, ***$P \leq .001$ (segmental score 1-7 vs segmental score 0).

Table VII. Ambulatory venous pressure (*AMVP*) parameters according to reflux segmental scores

	Segmental score						
AMVP (normal values)	0 (n = 1428)	1 (n = 1439)	2 (n = 796)	3 (n = 441)	4 (n = 256)	5 (n = 105)	6 and 7 (n = 60)
VFT (>20 seconds)	52 (0-274)	36 (0-155)***	24 (0-141)***	19 (0-185)***	12 (0-99)***	10 (0-65)***	6 (0 -79)***
% Drop (>50%)	79 (10-98)	76 (7-98)****	72 (4-98)****	69 (6-95)****	58 (11-95)****	61 (16-93)****	44 (17-95)****

VFT, Venous filling time.
Values are presented as median (range).
***$P \leq .001$, ****$P \leq .0001$ (segmental score 1-7 vs segmental score 0).

AMVP. There was moderate correlation between % drop and VFT ($r = 0.48$).

Correlation between AMVP and APG

There was no correlation between RVF ($R = 0.22$) and AMVP (postexercise pressure; Fig 7) or between RVF and VFT ($R = 0.11$). This lack of correlation between RVF and the two AMVP parameters persisted in all CEAP clinical classes ($R < 0.33$). There was also no correlation between RVF and the two AMVP parameters (% drop, VFT) when only limbs with abnormal RVF and AMVP (RVF <50% and % drop of <50% or VFT of <20 seconds) were analyzed (data not shown). Table X shows lack of significant correlation between several pairs of APG and AMVP analogues. Notably, there was no correlation between VFI_{90} and VFT or % drop. These APG and AMVP parameters are known to reflect reflux severity within their own frame of scale.

Multiple regression analysis

Volume and pressure terms in multivariate analysis are shown in (Fig 8).

RVF has a relatively minor influence on postexercise venous pressure (pressure nadir). RVF distribution was skewed toward higher CEAP clinical classes (3, 4, 5, and 6) with >80% existing in these groups. In the model of prediction, RVF was significant only in C6 with a *P* value of .03. The AMVP model showed statistically significant prediction in C2 through C6 with only one N_O not being reliably predicted, with all *P* values <.05 in other subclasses. The model confirmed the dominant contribution of pressure term over volume in predicting C3 to C6.

No APG parameter could be found as a useful filter to select limbs for the AMVP test with a good chance of being abnormal. Only 42% of limbs (n = 648) had abnormal AMVP with a VFI_{90} >3 seconds. Only 7% of limbs had abnormal AMVP in the presence of normal APG. This means that AMVP requiring a needle stick can be optionally omitted if the APG results are normal. Higher clinical and reflux classes with an abnormal APG are more likely to yield an abnormal AMVP.

Calf pump failure

The definition of calf pump failure has varied in the literature, some focusing on EF and others on RVF.[12-14] The incidence breakdown of four APG groups based on EF and RVF combination abnormalities among CEAP clinical class and reflux classifications is shown in Table XI. No clear pattern is visible. An

Table VIII. Air plethysmography (*APG*) and ambulatory venous pressure (*AMVP*) parameters according to Kistner's reflux grade classification[a]

APG (normal values)	Grade 0 (n = 5631)	Grade 1 (n = 245)	Grade 2 (n = 632)	Grade 3 (n = 239)
VV	87 (0-447)	112.5 (0-322)***	109 (15-388)***	109 (11-284)***
VFI_{90} (2.2 mL/s)	1.3 (0-101)	2.2 (0-15)***	3 (0-20)***	3.7 (0-14)***
EV	43 (0-214)	53 (0-156)***	49 (2-185)***	51 (4-163)*
EF (>50%)	51 (0-89)	44 (0-89)**	48 (0-89)***	46 (0-89)***
RV	27 (0-250)	42 (0-189)***	39 (0-337)***	42 (0-150)***
RVF (<50%)	31 (0-89)	39 (0-89)***	38 (0-89)***	40 (0-89)***
RT, seconds	11 (0-185)	10 (0-26)***	8 (1-81)***	7 (1-23)***
AMVP (normal values)	**Grade 0 (n = 3157)**	**Grade 1 (n = 139)**	**Grade 2 (n = 415)**	**Grade 3 (n = 172)**
% Drop (>50%)	77 (4-98)	65 (15-98)****	64 (6-95)****	56 (11-95)****
VFT (>20 seconds)	40 (0-274)	16 (0-120)***	17 (0-120)***	9 (0-79)***

EF, Ejection fraction; *EV*, ejection volume; *RT*, recovery time; *RV*, residual volume; *RVF*, residual volume fraction; VFI_{90}, venous filling index; *VFT*, venous filling time; *VV*, venous volume.
Values are presented as median (range).
*$P \leq .05$, **$P \leq .01$, ***$P \leq .001$, ****$P \leq .0001$ (grade 0 vs 1, 2, 3).
[a]Grade 0, no reflux; grade 1, reflux to the thigh; grade 2, reflux below knee; grade 3, reflux to ankle.

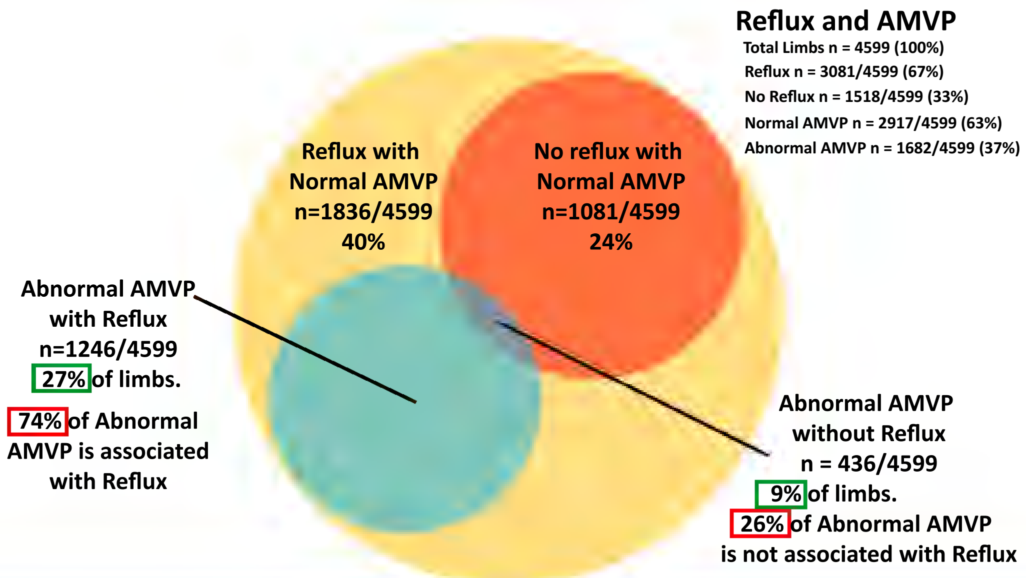

Fig 2. Distribution of reflux and ambulatory venous pressure (*AMVP*) abnormalities. Reflux was present in 67% of the limbs; AMVP was abnormal in 37% of the limbs. AMVP abnormalities are mostly associated with reflux (74%) in chronic venous disease (CVD) limbs; 24% of limbs with abnormal AMVP had no reflux. Overall, abnormal AMVP without reflux occurred in only 9% of limbs.

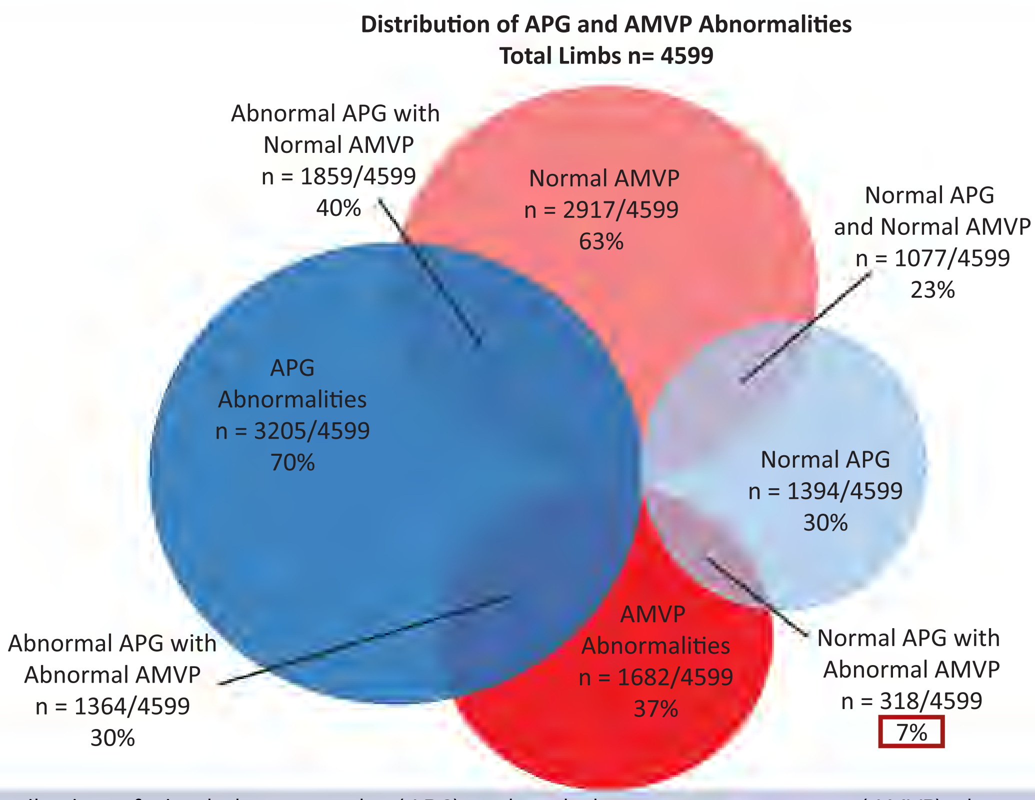

Fig 3. Distribution of air plethysmography (*APG*) and ambulatory venous pressure (*AMVP*) abnormalities in chronic venous disease (CVD) limbs. APG was considered abnormal if one or more of the three key APG parameters was abnormal: venous filling index (VFI_{90}) >2.3 mL/s; ejection fraction (EF) <50%, or residual volume fraction (RVF) >50%. APG was abnormal in 70% and AMVP in 37% of limbs, with an overlap of 30% when both test results were abnormal. Note: 23% of the limbs had no abnormality by either test. AMVP was abnormal in the absence of APG abnormalities in only 7% of the limbs. One may choose to avoid the AMVP test in clinical practice if APG is normal. In 1364 of 1682 (81%) limbs, AMVP abnormality was associated with APG abnormalities.

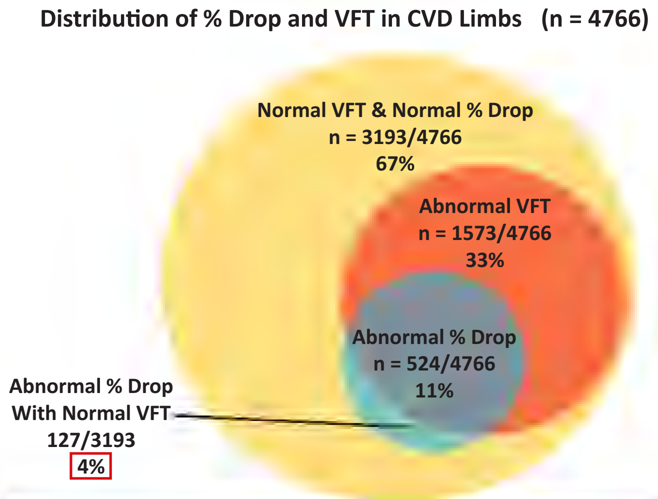

Fig 4. Relative distribution of % drop and venous filling time (*VFT*) in the ambulatory venous pressure (AMVP) test is shown. Both parameters were normal in 67% of tested limbs. VFT was abnormal in 33% and % drop in 11% of the limbs. Only 4% of limbs with normal VFT had abnormal % drop.

isolated RVF abnormality (group 2) is very rare (≈3%). Combined RVF and EF abnormalities (group 4) occurred significantly more often (≈25%) in high-reflux categories.

AMVP values among the four groups of calf pump function as defined before are shown in Table XII. The % drop and VFT are within the normal range in all groups, despite being statistically worse in groups 3 and 4 compared with group 1 (normal EF and RVF). The incidence of AMVP abnormalities (VFT or % drop)

Table IX. Air plethysmography (*APG*) and ambulatory venous pressure (*AMVP*) parameters in obstructed limbs with and without venous reflux

APG (normal values)	No reflux (n = 398; 30%)	Reflux (n = 949; 70%)
VV	75 (0-193)	94 (0-388)***
VFI_{90} (2.2 mL/s)	1.1 (0-6)	2.3 (0-21)***
EV	40 (0-169)	47 (0-186)***
EF (>50%)	54 (8-90)	49 (1-89)***
RV	16 (0-124)	28 (0-337)***
RVF (<50%)	26 (0-83)	36 (0-88)***
RT, seconds	12 (0-45)	10 (0-89)***
AMVP (normal values)	**No reflux (n = 258)**	**Reflux (n = 653)**
% Drop (>50%)	80 (34-97)	69 (4-97)****
VFT (>20s)	38 (0-165)	18 (0-132)***

EF, Ejection fraction; *EV*, ejection volume; *RT*, recovery time; *RV*, residual volume; *RVF*, residual volume fraction; *VFI_{90}*, venous filling index; *VFT*, venous filling time; *VV*, venous volume.
Values are presented as median (range).
***$P \leq .001$, ****$P \leq .0001$ (no reflux vs reflux).

was 11%, 19%, and 10% in groups 2, 3, and 4, respectively. Thus, calf pump failure defined by subnormal EF, RVF, or both does not appear to be reflected in AMVP abnormalities except in a small fraction. AMVP abnormalities are multifactorial, not exclusive to pump failure.[8]

DISCUSSION

The pathologic mechanism of CVD can be reflux, obstruction, or often a combination. The interrelationship between reflux and obstruction is not clear.[15] Pure obstruction without reflux occurs in about 30% of limbs in this and other series.[16] The incidence of iliac vein stenosis may be as high as 70% in the general and CVD populations.[16-18] The importance of obstruction in CVD was not appreciated until recently.[19,20] Currently, there are no reliable functional tests to assess obstruction; diagnosis has relied on imaging modalities. Much of the clinical and research focus in the past two centuries has been on the reflux component. Duplex ultrasound is routinely used, APG less often, and AMVP only rarely in the clinical setting. AMVP is arguably the more important test, as venous hypertension is at the core of CVD and clinical manifestations.

Duplex ultrasound. Duplex ultrasound is qualitative, and several attempts to devise a quantitative scheme have not been totally satisfactory.[21-23] The Kistner classification or a modification based on caudal extent of reflux in the limb by duplex ultrasound is used most often.[6,9] The disadvantage is that only deep reflux is assessed, and the resolution is skewed toward the higher reflux categories. Several authors add a superficial reflux component to this classification.[21,24] The segmental score system allows weight to a greater number of refluxive segments and offers a broader range of reflux gradations that parallel APG and AMVP gradations (Tables VI and VII).

APG. APG has been evaluated by multiple authors in CVD.[7,25-29] It appears to yield a reproducible measure of reflux (VFI_{90}), whereas other parameters have been less consistent for clinical assessment. The usefulness of VFI_{90} in assessing reflux severity is confirmed in this study. EV and EF reflect single ejection from standstill and reflux is not a factor. RVF integrates the end effects of multiple ejections with reflux return of a fraction of each ejected aliquot. The RV plus reflux volume added after cessation of the last calf pump determines RVF. It is therefore more valuable in clinical assessment of the limb. VV and RT, parameters related to calf capacitance, may also be useful in identifying severe disease as shown in this study, but threshold values are not established. Normalizing these parameters by relating them to calf volume as originally described by Christopoulos et al[1] may be a way to standardize these parameters.

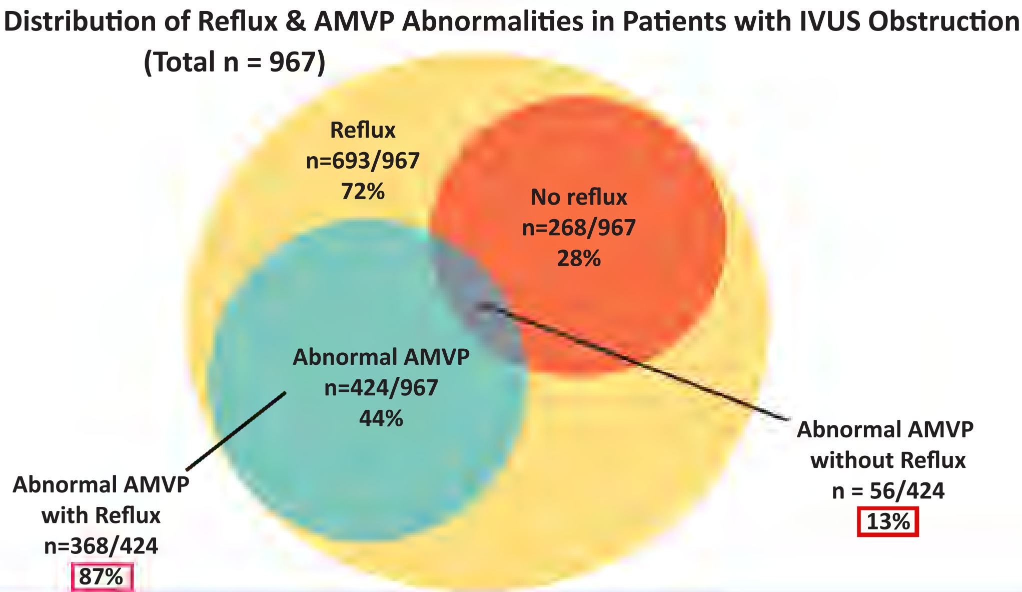

Fig 5. In limbs with intravascular ultrasound (*IVUS*)-proven obstruction, 72% had reflux and 28% did not. Abnormal ambulatory venous pressure (*AMVP*; % drop or venous filling time [VFT]) was present in 44% of the obstructed limbs. The overwhelming majority (87%) occurred in association with reflux in obstructed limbs. The incidence of AMVP abnormalities was low (13%) in obstructed limbs without reflux.

Calf venous pump. The calf pump appears to respond to reflux with passive and active compensatory mechanisms.[5] A passive mechanism is the increase in VV that has the effect of reducing volumetric reflux into a smaller fraction of pump capacitance. An increase in VV results in a nearly linear increase in EV (Fig 6). This active compensatory mechanism has the net effect of keeping EF and RVF at normal or nearly normal levels despite an increase in calf volume due to reflux. Examination of Fig 6 shows that a threefold increase in calf volume is met with a parallel increase in EV. In this respect, the calf pump resembles the heart, which is able to adjust its output for even a threefold increase in inflow, keeping the EF within normal range. Such an adaptable compensatory mechanism is a powerful one, more so than the passive mechanism. Others have documented this feature as well.[12,27]

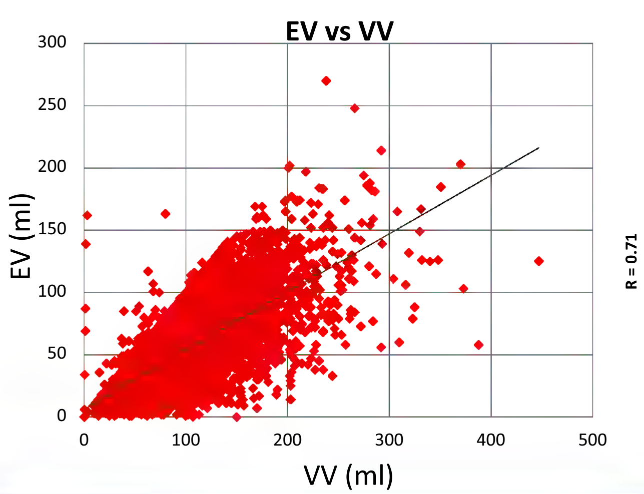

Fig 6. Correlation between ejection volume (*EV*) and venous volume (*VV*) in 7877 chronic venous disease (CVD) limbs ($R = 0.71$). The calf pump appears adaptable to pump a wide range of volumes presented to it. In the illustration, EV ranges up to 150 mL, or three times normal (50 mL). The higher the calf VV, the higher the EV, with good linear correlation.

Calf pump failure is frequently cited in the literature as a cause of CVD and a neurogenic etiology has been suggested as a contributory cause.[30,31] In this analysis, the incidence of calf pump failure (↓EF and RVF) was low or negligible even in advanced clinical and reflux severity categories, a finding previously reported by Criado et al.[32] Furthermore, calf pump failure, however defined, does not correlate with ambulatory venous hypertension. There is documented support for calf pump failure (EF, RVF) in a subset of ulcerated limbs with ankle joint or neuropathic calf muscle dysfunction.[12,30,33,34] These subsets were not specifically identified in this analysis; they are appropriate subjects for future research. One can conclude that calf pump function improves in compensation to reflux load and in the majority of CVD patients; calf pump failure is rare unless the muscle or the ankle joint is directly restricted.

AMVP. AMVP, particularly VFT, also mirrors reflux and clinical severity but is abnormal in only about 30% of the CVD population compared with APG abnormalities (70%). The % drop is abnormal in even a smaller fraction of the CVD population (11%) but may represent the most

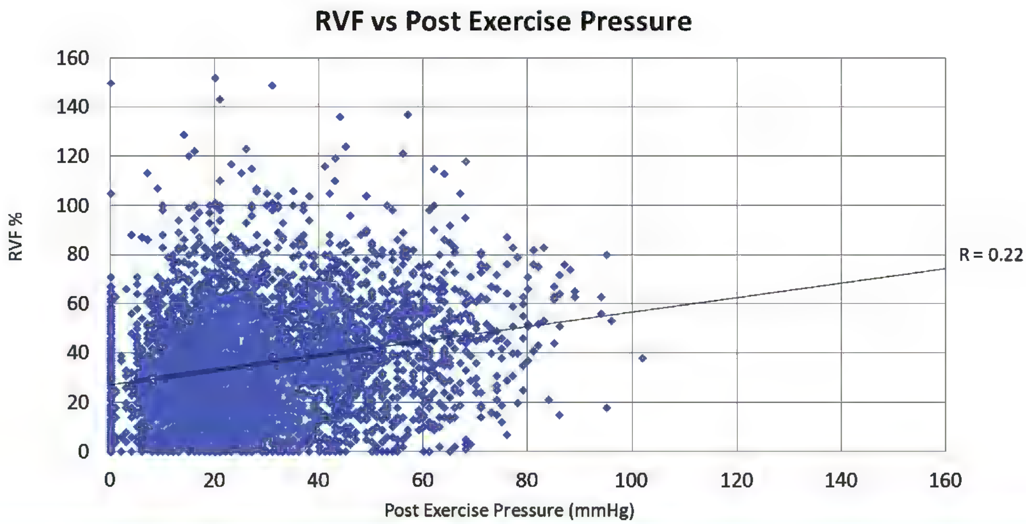

Fig 7. There is poor correlation between residual volume fraction (*RVF*) and postexercise pressure in 7877 chronic venous disease (CVD) limbs ($R = 0.22$). This is due to the nonlinear relationship between volume and pressure in veins. Air plethysmography (APG) and ambulatory venous pressure (AMVP) tests each measure different parameters in different domains. APG and AMVP abnormalities also appear to occur in different populations of CVD limbs. See text.

severe clinical and reflux grades, as shown in this study. The calf pump is able to power through outflow obstruction to keep AMVP normal, but overcoming reflux after each contraction appears to be less successful. AMVP was overwhelmingly associated with reflux in this report. Median AMVP is in the normal range in CVD limbs without reflux. Abnormal incidence in Venn distribution was low (26%) vs incidence with reflux (74%; Fig 2). There is peripheral venous hypertension in venous obstruction, but the pressure elevation is muffled in the AMVP test because of the large added gravity component and the pumping efficiency of the calf muscles. Elevated venous pressures are more noticeable in supine pressure measurement (unpublished data).

Table X. Correlations (*R* value) between air plethysmography (*APG*) and ambulatory venous pressure (*AMVP*) parameters

APG and AMVP parameters	*R* value
VV vs base pressure	0.22
VFI_{90} vs VFT	0.3
EV vs % drop	0.1
EF vs VFT	0.09
RT vs VFT	0.31
RVF vs % drop	0.24
VFI_{90} vs % drop	0.2
VV vs VFT	0.14
RVF vs VFT	0.11
RVF vs AMVP	0.22

EF, Ejection fraction; *EV*, ejection volume; *RT*, recovery time; *RVF*, residual volume fraction; *VFI_{90}*, venous filling index; *VFT*, venous filling time; *VV*, venous volume.

Lack of correlation between APG and AMVP. There is little correlation between APG and AMVP parameters in this large series. Venn distributions involve different subsets with an overlap of only 30%. The two techniques operate in different anatomic and functional domains (Fig 9). There was no correlation between RVF and postexercise pressure, contrary to other reports.[2,3,35] APG measures volume and AMVP measures pressure, each with a different scale. Relationship between the two in

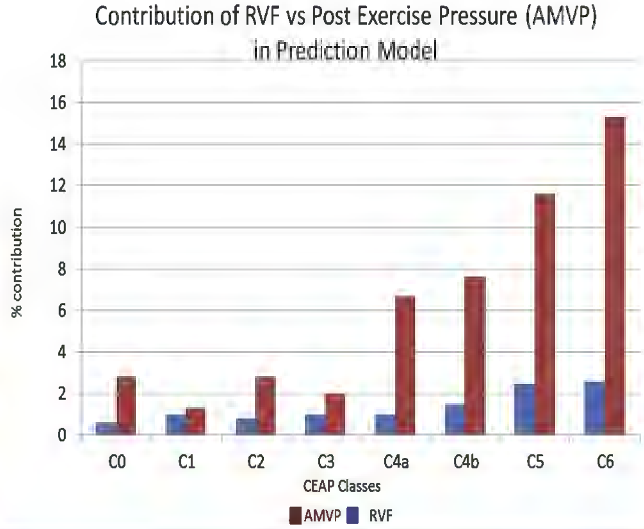

Fig 8. Multiple regression model incorporating residual volume fraction (*RVF*) and postexercise pressure (ambulatory venous pressure [*AMVP*]). Postexercise pressure has a significant contribution (vs RVF) to Clinical, Etiology, Anatomy, and Pathophysiology (*CEAP*) clinical class presentation. The contribution of RVF is minor. See text.

Table XI. Incidence of calf pump failure according to Clinical, Etiology, Anatomy, and Pathophysiology (*CEAP*) clinical class, anatomic distribution of reflux, segmental score, and Kistner class

	CEAP classes 0-2	CEAP class 3	CEAP classes 4-6[a]	Superficial reflux	Deep reflux	Superficial and deep reflux[b]	Superficial, deep, and perforator reflux[c]	Segmental score 0-3	Segmental score 4-7[d]	Kistner class 0 and 1	Kistner class 2 and 3[e]
Total in class/reflux category	1052	3723	1294	3221	2049	1293	252	6619	610	6297	904
Group 1: Normal EF and RVF	462 (44)	1874 (50)	662 (51)	1420 (44)	889 (43)	540 (42)	89 (35)	3271 (49)	233 (38)	2752 (43)	342 (37)
Group 2: Normal EF and abnormal RVF	23 (2)	46 (1) NS	23 (2) NS	89 (3)	50 (2)	42 (3) NS	13 (5)**	120 (2)	19 (3) NS	97 (2)	26 (2) NS
Group 3: Normal RVF and abnormal EF	295 (28)	968 (26)*	251 (19)*	815 (25)	536 (26)	324 (25) NS	55 (22) NS	1714 (26)	149 (24) NS	1456 (23)	222 (24%) NS
Group 4: Abnormal EF and RVF	226 (21)	700 (19) NS	293 (23) NS	731 (23)	474 (23)	318 (25) NS	73 (29)*	1119 (17)	169 (27)***	976 (15)	207 (22)***

EF, Ejection fraction; *NS,* not significant; *RVF,* residual volume fraction.
Values are reported as number of limbs (%).
Normal EF is ≥50%; normal RVF is ≤50%; abnormal EF is <50%; abnormal RVF is >50%.
**P* ≤ .05, ***P* ≤ .01, ****P* ≤ .001.
[a]CEAP classes 4-6 vs class 3 and classes 0-2.
[b]Compared with superficial reflux only.
[c]Compared with deep reflux only.
[d]Compared with segmental score 0-3.
[e]Compared with Kistner class 0-1.

nonthrombotic and post-thrombotic limbs is likely to be different, as noted by Wilkie et al in their series.[3] The discordance between this and other series is likely to be due to a different mix of thrombotic and nonthrombotic limbs and sample size.

Venous obstruction. Median AMVP is in the normal range in IVUS-proven obstruction. The overall incidence of abnormal AMVP was only 44%. The incidence (Venn) of abnormal AMVP in pure obstruction without reflux was only 13% vs 87% in obstruction with reflux. APG was normal as well unless reflux was associated with obstruction. Others have noted that standard APG has little role in diagnosis of outflow obstruction.[36] Lattimer et al[37] have described a novel APG technique to assess obstruction. This technique is being evaluated in many centers.

Clinical recommendations. APG is a good screening test as APG abnormalities are present in 75% to 90% of patients with advanced CVD clinical features or reflux severity. It provides a useful quantitative measure of reflux severity (VFI_{90}) that may be used also to monitor correctional outcome.[30,38] Other APG parameters can be used to understand compensatory mechanisms that occur in response to reflux in individual limbs. A normal APG test result would suggest either a nonvenous cause of symptoms or venous obstruction without reflux, which occurs in about 30% of limbs with May-Thurner syndrome.[16]

If APG is normal, the AMVP test may be avoided as the yield is low (7%). Both APG and AMVP tests have a good yield in limbs of higher clinical and reflux severity categories. However, AMVP abnormality represents the end stage of CVD. When APG is abnormal, an AMVP test is recommended to identify such limbs with end-stage disease.

Table XII. Ambulatory venous pressure (*AMVP*) and abnormal incidence (Venn) in calf pump failure

AMVP parameter (normal values)	Group 1: Normal EF and RVF (n = 1992)	Group 2: Normal EF and abnormal RVF (n = 80)	Group 3: Normal RVF and abnormal EF (n = 1083)	Group 4: Abnormal EF and RVF (n = 865)
% Drop (>50%)	77 (19-97)	76 (9-95)*	74 (12-98)****	67 (4-96)****
VFT (>20 seconds)	35 (0-274)	25.5 (0-120)	36 (0-145)	21 (0-155)***
Venn abnormal incidence	0%	11%	19%	10%

EF, Ejection fraction; *RVF,* residual volume fraction; *VFT,* venous filling time.
Values are presented as median (range).
Normal EF is ≥50%; normal RVF is ≤50%; abnormal EF is <50%; abnormal RVF is >50%.
**P* ≤ .05, ****P* ≤ .001, *****P* ≤ .0001 (group 1 vs groups 3 and 4).

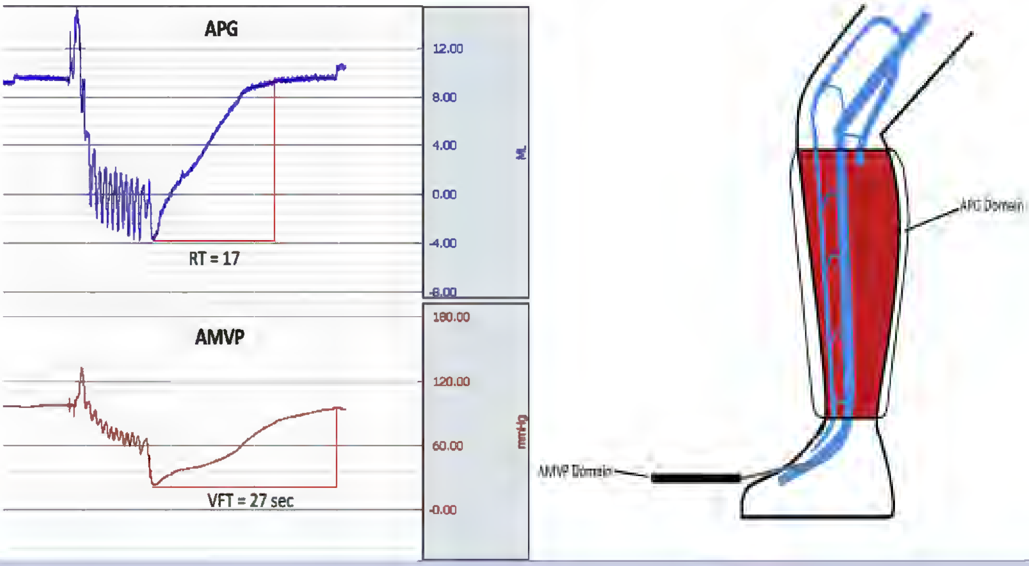

Fig 9. Air plethysmography (*APG*) measures volume-related parameters in the calf, whereas ambulatory venous pressure (*AMVP*) measures pressure-related parameters in the axial flow channel (*right*). The flow channel volume is <5% of the calf volume. The calf volume, though larger, refills faster (recovery time [*RT*]) before refill of the axial flow channel is complete (venous filling time [*VFT*]) as shown on the *left*. The two tests (APG and AMVP) operate in different anatomic and hemodynamic domains. The volume-pressure curve is necessarily an intermediary between the two. Note also that abnormalities in the two tests have different distribution in Venn diagrams. See text.

CONCLUSIONS

There is progressive deterioration of APG and AMVP parameters across CEAP clinical classes and reflux severity categories. APG provides a useful measure of reflux and compensatory mechanisms in response to reflux. The main compensatory mechanism is the powerful calf pump. Calf pump failure caused by reflux is rare. There is little correlation between APG and AMVP parameters as they measure different paraments and affect different subsets of the CVD population. AMVP is rarely positive if APG is negative. Both test results are positive in 40% to 70% of limbs in higher clinical and reflux categories. An AMVP abnormality indicates end-stage disease, and AMVP should be performed in these categories if APG is abnormal. Ambulatory venous hypertension is overwhelmingly associated with reflux but much less with obstruction.

AUTHOR CONTRIBUTIONS

Conception and design: SR, JK
Analysis and interpretation: SR, JK, CM, AK, NP, AJ
Data collection: SR, JK, CM, AK, NP
Writing the article: SR, JK, CM, AK, NP
Critical revision of the article: SR, AJ
Final approval of the article: SR, JK, CM, AK, NP, AJ
Statistical analysis: SR, JK, CM, AK, NP
Obtained funding: SR
Overall responsibility: SR
SR and JK contributed equally to this article and share co-first authorship.

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