Peripheral venous hypertension in chronic venous disease

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ABSTRACT

Background: Microvascular venous hypertension has emerged as a central feature of chronic venous disease (CVD). Yet, the incidence and severity of peripheral venous hypertension in the clinical setting have not been reported. This is an observational study of venous hypertension in the lower limb of a large cohort of patients with suspected CVD referred to a single referral center during a 16-year period.

Methods: Clinical and venous laboratory test data for 8868 limbs of 5792 patients with CVD symptoms seen from 1999 to 2015 were analyzed. Subset A limbs had a mix of obstruction/reflux or neither (n = 4132). These are limbs in which duplex ultrasound reflux (yes/no) status is known. The incidence and severity of obstruction in these limbs are unknown as tests of obstruction were not routinely performed. Subset B limbs had central obstruction (n = 159). These are limbs with intravascular ultrasound-proven stenosis in the iliac veins that was corrected by stent placement. Reflux was assessed by duplex ultrasound and air plethysmography (venous filling index [VFI_{90}]). Pressure measurements included supine venous pressure, erect venous pressure, and ambulatory venous pressure (AMVP). Pressure measurements are categorized according to Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) clinical class, reflux and obstruction with Venn distributions of prevalence.

Results: All pressures (supine, erect, and ambulatory) trended worse in higher CEAP clinical classes. Supine foot venous pressures were elevated in 70% and 76% of subsets A and B, respectively. A positive association between elevated supine pressures and reflux could not be shown in this study. Supine foot venous pressure did not worsen with increasing reflux in the two subsets, but erect foot venous pressure did. Elevated supine pressures were associated with obstruction in subset B. AMVP worsened in most higher reflux categories. Ambulatory venous hypertension was dominantly associated (Venn distribution) with reflux, less commonly with obstruction.

Conclusions: Supine venous hypertension is associated with obstruction and does not worsen with reflux. In contrast, erect foot venous pressure worsens in severe reflux categories. Ambulatory venous hypertension worsens in higher CEAP clinical classes. It worsens with increasing reflux. AMVP is dominantly associated (Venn distribution) with reflux, not obstruction. (J Vasc Surg: Venous and Lym Dis 2019;7:706-14.)

Keywords: Venous pressure; Reflux; Obstruction; Venoarteriolar reflux

Peripheral venous hypertension has emerged as a central feature of chronic venous disease (CVD). Yet, its prevalence and severity in the CVD population are unknown. Elevated venous pressures may result from reflux, obstruction, or a combination and less commonly from high arterial inflow. Venous obstruction of clinical consequence occurs in two forms in the CVD limb: central obstruction of thrombotic or nonthrombotic etiology commonly occurring in the iliac veins; and peripheral venous obstruction, usually of post-thrombotic etiology that results in caliber reduction of infrainguinal veins. There have been no definitive studies to examine the relative occurrence of venous hypertension in these various pathologic processes.

Venous pressure in the lower limb is usually measured in three different ways: supine resting pressure; erect resting pressure; and ambulatory venous pressure (AMVP). Each of these pressures is modulated in vivo by different mechanisms. Intra-abdominal pressure modifies venous pressure in the abdomen and in the limbs.[1,2] The negative pressure in the thorax has an influence on supine venous pressure as well as on erect venous pressure. In the erect position, a large gravity component is added to resting venous pressure.[2] This is offset to a certain extent by a reduction in arterial flow (venoarteriolar reflux or Bayliss phenomenon) in the erect position.[3,4] Valve reflux worsens AMVP parameters.[5] It has been assumed that venous obstruction worsens AMVP parameters. There are several early reports of elevated venous pressure (peripheral or femoral) in post-thrombotic limbs with combined obstruction/reflux that worsened on exercise. The sample size in these series was small, obstruction and reflux were not precisely graded, and

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

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the exercise protocol varied widely.[6-10] Presence of ambulatory venous hypertension in chronic venous obstruction using a standardized protocol has not been definitively established.

The aim of this study was to describe the incidence and severity of peripheral venous hypertension (supine, erect, and ambulatory) in a large unselected population of CVD patients categorized according to Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) clinical class and reflux severity and in a selected subset with intravascular ultrasound (IVUS)-proven iliac vein central (iliac vein) obstruction.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study of prospectively collected data
- **Key Findings:** Peripheral venous pressure was elevated in 70% of 4132 limbs with symptomatic chronic venous disease and in 76% of 159 limbs with intravascular ultrasound-proven iliac venous obstruction. Supine venous pressure did not worsen with reflux, but erect resting and ambulatory venous pressures did.
- **Take Home Message:** Venous obstruction is associated with elevated supine pressures in chronic venous disease limbs, whereas reflux is associated with elevated erect resting and ambulatory venous pressures.

METHODS

This is a retrospective observational study of data prospectively entered into an electronic medical record system. Patients referred to a single referral center with a diagnosis of CVD during a 16-year period (1999-2015) were analyzed. Clinical and laboratory findings were evaluated per a standardized venous template by four attending surgeons over the duration. Laboratory data were obtained and interpreted in an accredited venous laboratory under the supervision of the first author (S.R.).

Patients

Contemporaneously acquired electronic medical record venous laboratory test data for 8868 limbs of 5792 patients with CVD symptoms seen from 1999 to 2015 were analyzed. Duplex ultrasound data were available for all 8868 limbs, and venous pressure and air plethysmography data were available for 4132 limbs of 3655 patients. Only symptomatic limbs in terms of side (right, left, or both) were analyzed; 1905 (41%) limbs were left sided, and 1273 (28%) limbs were right sided. Bilateral symptomatic limbs (n = 954 [21%]) were present in 477 patients (12%). These limbs were assigned to the appropriate side.

The sample was analyzed in two subsets based on objective presence of reflux and obstruction. In subset A limbs (mix of obstruction/reflux or neither; n = 4132), duplex ultrasound reflux (yes/no) status is known. The incidence and severity of obstruction in these limbs are unknown as tests of obstruction were not routinely performed. Subset B limbs (central obstruction; n = 159) were drawn from subset A and were subsequently shown to have IVUS-proven iliac vein stenosis that was corrected by stent placement in the years 2013 to 2015. Roughly three-fourths of these limbs had associated reflux and one-fourth had pure obstruction without reflux. Preoperative pressure measurements are the target for this analysis.

All limbs that had a clinical and duplex ultrasound examination are included. Some limbs (≈10% estimated) had superficial interventions elsewhere before presentation to our clinic; duplex ultrasound and pressure data obtained in our clinic at presentation are included. Patients with suspected arterial disease underwent ankle and arm pressure measurement. Those with an ankle-arm index <0.8 were excluded.

Informed consent from patients for the procedures and Institutional Review Board permission for retrospective analysis and publication of this study were obtained.

Clinical assessment

All limbs were categorized according to CEAP clinical class, ranging from no visible disease (C0) to open ulcer (C6).

Venous laboratory tests

Technical details of the various test procedures have been described at length elsewhere.[11,12]

Reflux. A color duplex ultrasound machine (Logiq 9; GE Healthcare, Wauwatosa, Wisc) was used per standard protocol. Patients were examined in the erect position with automated inflation/deflation cuffs to elicit reflux. Reverse flow >1 second was considered reflux for deep and superficial veins. These thresholds have been in use in our laboratory since 1995. The Society for Vascular Surgery guideline shortening reflux threshold to 0.5 second for superficial veins was not implemented in this analysis.

A *reflux segment score* was determined on the basis of the number of refluxive vein segments; 1 point each was assigned for great saphenous vein, small saphenous vein, perforator, femoral vein, deep femoral vein, popliteal vein, and posterior tibial vein. With this grading, a score of 0 indicates no reflux; a score of 7 signifies that all the segments are refluxive. This scoring system has been shown to correlate with clinical severity and appears to be superior to other methods of grading reflux.[11,13]

Air plethysmography. A commercially available instrument (ACI Medical, San Marcos, Calif) with standard protocol described by Christopoulos was used.[14] The reflux parameter of venous filling index (VFI_{90}) is of interest in this analysis. A VFI_{90} <2.3 is considered normal; a value ≥2.3 is considered to indicate reflux in this study.

Supine venous pressure, erect venous pressure, and AMVP. Pressures were measured by a needle in the dorsal foot vein through a high-frequency transducer mounted at the foot level. Pressure tracings were acquired using digital software (Biopac Systems, Goleta, Calif). Supine pressure was recorded in the recumbent position; erect venous pressure was recorded in the standing position with weight bearing on the opposite limb. AMVP was recorded with 10 tiptoe movements. The pressure nadir reached at the end of the tiptoe exercise represented postexercise pressure. AMVP drop (% drop) was calculated: (Pressure drop/Base) × 100. Venous filling time (VFT) in seconds for pressure recovery back to baseline was recorded. A narrow ankle cuff to isolate the role of superficial reflux as described by Hosoi et al[15] was not used in this study.

Normal values for various pressure parameters as derived from common acceptance in the literature are as follows: supine venous pressure is 5 to 10 mm Hg; normal erect venous pressure in a person of average height is 80 to 100 mm Hg.[1,2,16,17] A supine foot pressure ≥11 mm Hg and an erect foot pressure ≥100 mm Hg are considered venous hypertension in this analysis. A % drop of >50% and a VFT >20 seconds are considered normal.[12,16,18] The normal values are indicated in most tables for ready reference.

IVUS and iliac vein stenting

The indications, technique, and outcome of iliac vein stenting have been described in detail previously.[19] The use of IVUS for the diagnosis of iliac vein stenosis and stent placement has been described elsewhere.[20,21] It has been shown that the caliber of the iliac vein segments measured by IVUS planimetry approximates normal vein caliber to maintain normal peripheral venous pressure. These caliber values for common iliac vein, external iliac vein, and common femoral vein are 200, 150, and 125 mm^2, respectively.[21] The median IVUS stenosis of limbs in subset B was 58%.

Statistics

Descriptive statistics such as median (range) and frequencies (percentages) were used to summarize continuous and categorical data, respectively. All analyses for subset A were stratified by left and right limb because measurements were obtained from either limb in the majority and both limbs of patients with bilateral symptoms.

The Mann-Whitney test and Kruskal-Wallis test were used to compare ordinal or continuous data in the presence of two and three categories, respectively. The χ^2 test was used to compare differences among proportions. The Wilcoxon signed rank test was used to compare data before and after stenting. All analyses were performed with commercial software (Prism Corporation, Irvine, Calif). Number values for individual analyses may vary because of missing data. These are reflected in number values shown in individual analysis.

The four pressure parameters related to clinical and reflux variables are presented in a series of tables. Each pressure parameter has a normal range and a threshold reference value that is considered abnormal when breached (higher than threshold value for supine and erect pressures; lower than threshold value for % drop and VFT). These normal reference values are shown in the first column of most tables. An improving or deteriorating trend within the normal range is shown in blue and red color fonts, respectively. When the value has breached the threshold, it is shown in a red box. Both measures are important in relational analysis.

RESULTS

Demographics of the subsets are shown in Table I. Median age was similar. Women were twice as common as men. The ratio of left and right sides was 1:1 in the large subset A but 2:1 in the smaller subset B. CEAP clinical classes 3 and 4 to 6 were higher in subset B. Reflux segment score was similar.

Subset A

CEAP clinical class categories. Supine venous pressure was elevated in 70% (≥11 mm Hg) of all diseased limbs (right or left), and 30% were in the normal range (<11 mm Hg). The highest supine venous pressure recorded in the entire data set was 24 mm Hg.

Table II shows venous pressures in different CEAP clinical class categories in subset A with left and right limb detail. Right and left limbs trended similarly; median values were identical or close to each other with an occasional exception when sample size was small.

Median supine pressures are elevated (≥11 mm Hg) in all CEAP clinical classes including CEAP clinical classes

Table I. Patients' characteristics

Demographics	Subset A	Subset B
No.	4132	159
Age, years	59 (14-101)	59 (27-86)
Male to female ratio	1:2 (1232:2206)	1:2 (101:53)
Left to right ratio	1:1	2:1
CEAP clinical class		
0-2	327 (8)	8 (5)[a]
3	1571 (38)	108 (68)
4-6	591 (14)	39 (25)
Reflux segment scores		
0	1207 (29)	38 (24)
1-3	2510 (61)	101 (64)
4-5	366 (9)	15 (9)
6-7	49 (1)	5 (3)

CEAP, Clinical, Etiology, Anatomy, and Pathophysiology.
Categorical variables are presented as number (%). Continuous variables are presented as median (range).
[a]With venous pain.

Table II. Venous pressures in different Clinical, Etiology, Anatomy, and Pathophysiology (*CEAP*) clinical classes in subset A

Type of pressure (normal value)	CEAP clinical class 0-2 (n = 327)	CEAP clinical class 3 (n = 1571)	CEAP clinical class 4-6 (n = 591)
Supine foot pressure (<11 mm Hg)			
Left	***12*** (4-24)	***15*** (4-24)[a]	***17*** (5-24)[a]
Right	***14*** (4-24)	***15*** (5-24)[a]	***15*** (5-24)[b]
Erect foot pressure (<100 mm Hg)			
Left	93 (68-111)	**96** (57-133)[a]	***101*** (73-120)[a]
Right	95 (54-128)	**97** (50-124)[c]	***101*** (79-123)[a]
% Drop (>50%)			
Left	75 (31-92)	*76* (21-98)	**72** (13-96)
Right	76 (35-97)	*77* (6-98)	**69** (12-98)[a]
VFT (>20 seconds)			
Left	45 (6-141)	*47* (6-145)	***19*** (3-105)[a]
Right	43 (2-140)	**39** (1-155)	***14*** (1-78)[a]

VFT, Venous filling time.
Values are presented as median (range). An increase in supine and erect foot venous pressure is worse, but an increase in % drop and VFT is an improvement. Worsening and improving median values are shown in *bold* and *italic* numbers, respectively. Median values breaching normal threshold are shown in a *bold italic.*
[a] $P \leq .001$ compared with CEAP clinical class 0-2, Kruskal-Wallis nonparametric test.
[b] $P \leq .05$.
[c] $P \leq .01$.

0 to 2. Median supine pressures trend significantly worse in higher CEAP clinical classes. Other median pressure parameters (erect and ambulatory) also trend significantly worse with higher clinical classes; erect venous pressure and VFT in CEAP clinical classes 4 to 6 fall below normal threshold values.

Reflux severity categories. Venous pressures according to anatomic system (superficial, deep, perforator) reflux involvement are shown in Table III. Venous pressures according to segmental reflux score are shown in Table IV, and venous pressures according to air plethysmography reflux grading (VFI_{90}) are shown in Table V.

A common pattern is observed with increasing reflux severity. Supine foot venous pressure is elevated above normal (≥11 mm Hg) in all reflux categories, but worsening with increasing reflux severity is *not* seen. In contrast, erect venous pressure shows a worsening trend, falling into abnormal territory in some categories with increasing

Table III. Venous pressures according to anatomic distribution of reflux in subset A

Type of pressure (normal value)	No reflux (n = 1207)	Superficial reflux only (n = 1929)	Deep reflux only (n = 1489)	Superficial and deep reflux (n = 944)	Superficial, deep, and perforator reflux (n = 209)
Supine foot pressure (<11 mm Hg)					
Left	***14*** (4-24)	*13* (4-24)	***14*** (4-24)	***14*** (4-24)	***14*** (4-22)
Right	***14*** (4-24)	*13* (4-24)[a]	*13* (4-24)[a]	*13* (4-24)[a]	*12* (4-24)[a]
Erect foot pressure (<100 mm Hg)					
Left	93 (54-120)	**96** (73-133)[a]	**97** (73-123)[a]	**97** (75-133)[a]	**97** (76-113)[b]
Right	95 (60-124)	**96** (55-128)	**97** (73-123)[a]	**97** (76-123)[a]	**98** (80-121)[b]
% Drop (>50%)					
Left	80 (18-98)	**73** (13-98)[a]	**71** (23-98)[a]	**71** (24-97)[a]	**69** (24-96)[b]
Right	79 (12-98)	**71** (6-98)[a]	**71** (6-98)[a]	**68** (6-98)[a]	**65** (13-98)[a]
VFT (>20 seconds)					
Left	58 (6-165)	**26** (3-143)[a]	**22** (3-120)[a]	**20** (3-120)[a]	***14*** (3-102)[a]
Right	60 (4-140)	***19*** (1-144)[a]	***18*** (1-120)[a]	***15*** (1-120)[a]	***10*** (1-109)[a]

VFT, Venous filling time.
Values are presented as median (range). An increase in supine and erect foot venous pressure is worse, but an increase in % drop and VFT is an improvement. Worsening and improving median values are shown in *bold* and *italic* numbers, respectively. Median values breaching normal threshold are shown in a *bold italic.*
[a] $P \leq .001$ compared with no reflux, Kruskal-Wallis nonparametric test.
[b] $P \leq .01$.

Table IV. Venous pressures according to reflux segmental scores in subset A

Type of pressure (normal value)	Segmental score						
	0 (n = 1207)	1 (n = 1268)	2 (n = 750)	3 (n = 492)	4 (n = 255)	5 (n = 111)	6 and 7 (n = 49)
Supine foot pressure (<11 mm Hg)							
Left	***14*** (4-24)	***14*** (4-24)	***14*** (4-24)	*13* (4-24)	***14*** (4-24)	***17*** (4-24)	***15*** (4-22)
Right	***15*** (4-24)	*14* (4-24)	*13* (4-24)[a]	*13* (4-24)[b]	*13* (4-24)	*14* (4-22)	*14* (4-23)
Erect foot pressure (<100 mm Hg)							
Left	93 (73-120)	**95** (73-122[c]	**97** (73-120)[a]	**97** (76-122)[a]	**98** (81-133)[a]	**96** (83-120)[b]	**98** (84-111)
Right	95 (73-124)	**96** (74-128)	**96** (73-117)	**98** (76-121)	**98** (81-121)	***101*** (88-123)[a]	**99** (86-121)
% Drop (>50%)							
Left	80 (18-98)	**76** (21-98)[a]	**74** (13-98)[a]	**71** (23-96)[a]	**70** (27-96)[a]	**62** (24-92)[a]	**55** (38-95)[a]
Right	79 (12-98)	**78** (8-98)	**75** (22-98)[c]	**68** (6-95)[a]	**61** (15-98)[a]	**65** (21-93)[a]	***50*** (19-84)[a]
VFT (>20 seconds)							
Left	58 (6-165)	**39** (6-141)[a]	**27** (6-141)[a]	**20** (3-120)[a]	***17*** (3-120)[a]	***14*** (5-62)[a]	***11*** (6-102)[a]
Right	60 (4-140)	**37** (0-155)[a]	**22** (1-144)[a]	***19*** (2-113)[a]	***11*** (1-120)[a]	***9*** (1-109)[a]	***6*** (0-35)[a]

VFT, Venous filling time.
Values are presented as median (range). An increase in supine and erect foot venous pressure is worse, but an increase in % drop and VFT is an improvement. Worsening and improving median values are shown in *bold* and *italic* numbers, respectively. Median values breaching normal threshold are shown in a *bold italic.*
[a] $P \leq .001$ compared with no reflux, Kruskal-Wallis nonparametric test.
[b] $P \leq .05$.
[c] $P \leq .01$.

severity of reflux. AMVP parameters also trend worse with increasing reflux. VFT is abnormal (<20 seconds) in many severe reflux categories, whereas % drop is within normal range of >50% in most reflux categories.

Venous pressure details of the entire subset A split into no reflux and reflux groups are shown in Table VI. Supine venous pressures are elevated (≥11 mm Hg) in both reflux and no reflux groups with some exceptions. In contrast, erect foot venous pressure was significantly worse in the refluxive group; % drop and VFT were also worse in the reflux group within normal threshold range.

Subset B: central obstruction

In this subset, 76% of limbs had elevated (>11 mm Hg) supine venous pressures. Supine, erect, and ambulatory pressures in subset B (with IVUS-proven iliac vein

Table V. Venous pressures according to air plethysmography reflux severity in subset A

Type of pressure (normal value)	$VFI_{90} \leq 2.2$ (n = 2745)	$VFI_{90} = 2.3\text{-}5$ (n = 1015)	$VFI_{90} = 5.1\text{-}7$ (n = 188)	$VFI_{90} > 7$ (n = 143)
Supine foot pressure (<11 mm Hg)				
Left	***13*** (4-24)	***14*** (4-24)[a]	***14*** (4-24)	**14** (4-22)
Right	***14*** (4-24)	***14*** (4-24)	***14*** (4-24)	*12* (4-24)
Erect foot pressure (<100 mm Hg)				
Left	94 (73-122)	**98** (66-122)[b]	***101*** (80-133)[b]	**99** (73-116)[b]
Right	95 (73-124)	**99** (75-128)[b]	***101*** (81-123)[b]	***100*** (73-119)[b]
% Drop (>50%)				
Left	78 (18-98)	**72** (27-96)[b]	**69** (13-96)[b]	**65** (24-87)[b]
Right	78 (6-98)	**72** (12-98)[b]	**64** (13-98)[b]	**67** (19-98)[b]
VFT (>20 seconds)				
Left	50 (6-165)	***19*** (3-128)[b]	***16*** (3-97)[b]	***12*** (6-99)[b]
Right	45 (1-155)	***17*** (1-117)[b]	***7*** (1-65)[b]	***9*** (1-100)[b]

VFI, Venous filling index; *VFT,* venous filling time.
Values are presented as median (range). An increase in supine and erect foot venous pressure is worse, but an increase in % drop and VFT is an improvement. Worsening and improving median values are shown in *bold* and *italic* numbers, respectively. Median values breaching normal threshold are shown in a *bold italic.*
[a] $P \leq .05$.
[b] $P \leq .001$ compared with $VFI_{90} \leq 2.2$: Kruskal-Wallis nonparametric test.

Table VI. Venous pressures in reflux vs no reflux in subset A

Type of pressure (normal value)	Subset A	
	No reflux (n = 1207)	Reflux (n = 2925)
Supine foot pressure (<11 mm Hg)		
Left	***14*** (4-24)	***14*** (4-24)
Right	***15*** (4-24)	*13* (4-24)[a]
Erect foot pressure (<100 mm Hg)		
Left	93 (54-120)	**96** (54-133)[a]
Right	95 (60-124)	**97** (50-128)[b]
VFT (>20 seconds)		
Left	58 (6-165)	**29** (3-143)[a]
Right	60 (4-140)	**23** (1-155)[a]
% Drop (>50%)		
Left	80 (18-98)	**74** (13-98)[a]
Right	79 (12-98)	**74** (6-98)[a]

VFT, Venous filling time.
Values are presented as median (range). An increase in supine and erect foot venous pressure is worse, but an increase in % drop and VFT is an improvement. Worsening and improving median values are shown in *bold* and *italic* numbers, respectively. Median values breaching normal threshold are shown in a *bold italic*.
[a] $P \leq .0001$ compared with no reflux, Mann-Whitney test.
[b] $P \leq .01$.

Table VII. Venous pressures with and without reflux in subset B with intravascular ultrasound (IVUS)-proven iliac vein stenosis

Type of pressure (normal value)	Obstruction without reflux (n = 38)	Obstruction plus reflux (n = 121)
Supine foot pressure (<11 mm Hg)		
Left	***15*** (7-21)	***15*** (7-24)
Right	***17*** (11-22)	*13* (7-24)
Erect foot pressure (<100 mm Hg)		
Left	96 (83-110)	***101*** (70-120)[a]
Right	97 (80-103)	***100*** (80-116)
% Drop (>50%)		
Left	80 (38-94)	**73** (27-94)[b]
Right	71 (63-80)	**68** (17-92)
VFT (>20 seconds)		
Left	48 (0-60)	**23** (4-60)[a]
Right	60 (17-60)	**24** (0-60)[b]

VFT, Venous filling time.
Values are presented as median (range). An increase in supine and erect foot venous pressure is worse, but an increase in % drop and VFT is an improvement. Worsening and improving median values are shown in *bold* and *italic* numbers, respectively. Median values breaching normal threshold are shown in a *bold italic*.
[a] $P \leq .01$ compared with no reflux, Mann-Whitney test.
[b] $P \leq .05$.

stenosis) sorted according to associated reflux are shown in Table VII. Supine pressure were elevated (≥11 mm Hg) in the presence of central obstruction, with no significant difference between limbs with and without associated reflux. In contrast, erect foot pressures worsened in left limbs with associated reflux ($P = .01$), breaching normal thresholds. Erect foot pressure in the right limb trended worse with reflux (P = NS), approaching abnormal threshold. AMVP parameters (% drop, VFT) are normal in iliac vein obstruction, worsening significantly with associated reflux, but did not reach abnormal levels.

Venn distributions

The preceding tables show median pressure values. Prevalence *distribution* (Venn) of pressure abnormalities further supplements the interpretation of median pressure variations in the various groups.

Venn distribution of reflux, obstruction, and the four pressure parameters in subsets A and B is shown in Table VIII. Distribution of abnormal supine pressures is significantly less in refluxive limbs. In contrast, prevalence distribution of abnormal erect supine pressures and AMVPs is significantly more in refluxive limbs. This corresponds to severity (median values) of pressure parameters presented in earlier tables The incidence of AMVP abnormalities is dominantly associated with reflux, not obstruction.

Summary of key results

The following conclusions can be drawn on the basis of both severity (median values) of pressure derangements and their incidence (Venn) distributions.

- Elevated supine venous pressures are associated with central venous obstruction.
- An association between reflux severity and elevated supine pressures was *not* shown in this study. Elevated supine pressures did not worsen with higher CEAP clinical classes or with increasing reflux.
- In contrast, elevated erect venous pressures are associated with higher CEAP clinical classes and higher reflux categories.
- Ambulatory venous hypertension is predominantly associated with reflux, not obstruction.

DISCUSSION

The findings described herein are novel and conflict with prevailing notions.

Supine venous pressure. Microvascular inflammatory damage appears to be the root cause of pathologic changes in the lower limb characteristic of CVD. There is strong experimental evidence for microvascular hypertension associated with reflux.[22,23] However, a clear association between reflux and venous hypertension in foot veins beyond venules has not been shown previously and was not evident in this study.

Table VIII. Prevalence distribution (Venn) of venous hypertension in refluxive and nonrefluxive limbs

	Total No. (refluxive + nonrefluxive)	Prevalence in refluxive limbs	Prevalence in nonrefluxive limbs
Subset A			
Elevated supine foot pressure (≥11 mm Hg)	2779	1933 (69)	846 (73)[a]
Elevated erect pressure (≥100 mm Hg)	1331	1006 (37)[b]	325 (29)
Ambulatory venous hypertension			
% drop ≤50% or VFT ≤20 seconds	1044	888 (39)[b]	156 (15)
Subset B			
Elevated supine foot pressure (≥11 mm Hg)	121 (80)	89 (76)	32 (91)[a]
Elevated erect pressure (≥100 mm Hg)	69 (49)	53 (53)[c]	10 (28)
Ambulatory venous hypertension			
% drop ≤50% or VFT ≤20 seconds	73 (26)	67 (32)[b]	6 (8)

VFT, Venous filling time.
Data are presented as number (%); missing data in nonrefluxive limbs.
[a] $P \leq .05$.
[b] $P \leq .0001$ comparing differences among proportions using χ^2 test.
[c] $P \leq .01$.

Elevated supine pressure was present in about two-thirds of CVD limbs in this large series (subsets A and B).

Supine venous pressure was elevated in many subgroups of the large subset A. The exact incidence of central or peripheral obstruction in this subset is unknown as relevant investigations were not routinely performed in these limbs. However, we suspect that the incidence was substantial, explaining the elevated supine pressure. This is based on reported prevalence of obstruction in 50% to 75% in several series in the general population as well as in CVD limbs.[24-29] Combined obstruction/reflux is the most common disease in primary as well as in post-thrombotic limbs, as was the case in this series.[19,24,26,30] Reflux severity was not associated with elevated supine venous pressure in this analysis (subsets A and B) as shown in Table VI and VII.

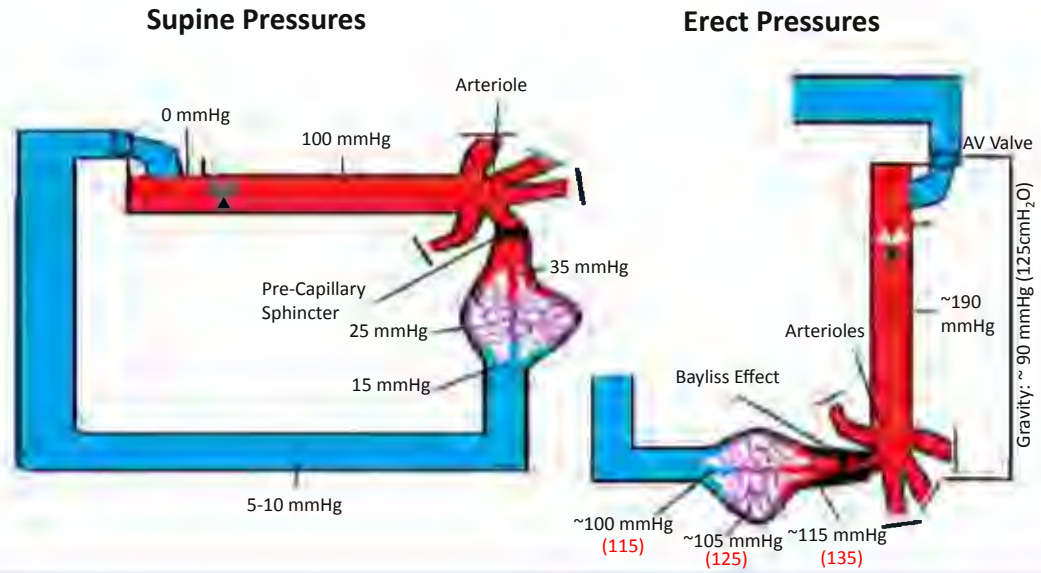

Fig. Postural changes in venous pressure. *Left,* Supine pressures are shown. Arterial pressure of 100 mm Hg degrades to ~35 mm Hg at the arteriolar-capillary level because of the resistance of precapillary sphincters. *Right,* In the erect position, the gravity component of ~90 mm Hg (variable on the patient's height) is added to supine pressure levels at the arterial, microcirculatory, and venous levels. Note that arterial pressure nearly doubles. Uncorrected, this may lead to dangerous imbalances in the Starling exchange at the capillary level. There is compensatory vasoconstriction of the arterioles and the precapillary sphincters (Bayliss effect or venoarteriolar reflex). This reduces perfusion pressures by ~20 mm Hg than uncorrected pressures, shown in *red in parentheses.* Note that there is no such compensatory reduction on the venous side of the circulation (see text). *AV,* Atrioventricular.

In subset B, 25% of limbs with IVUS-proven iliac vein stenosis had supine pressures of <11 mm Hg. The threshold of 11 mm Hg for normal supine pressures used in this analysis is somewhat arbitrary. The "critical" supine pressure threshold that upsets homeostasis is probably a range rather than a fixed number. A number of factors, such as collaterals, compliance changes, and lymphatic insufficiency, may influence the critical threshold.[2,9] Whether supine pressure is a reliable hemodynamic metric in venous stenting is unknown. Supine venous pressure as a hemodynamic parameter in iliac vein stenosis remains to be explored further.

We have previously shown that about a third of patients with CVD symptoms have central obstruction without reflux.[26] This was the case in 25% of limbs in subset B in this series.

Erect venous pressure. Erect venous pressure is the sum of supine pressure plus a fixed gravity component related to the patient's height.[1,2,16,31] Erect venous pressure worsened with increasing severity of reflux in this study, whereas supine pressure showed no such rising trend. This is incongruous because the gravity component related to height is unlikely to be different in groups with reflux compared with those without reflux. We hypothesize that the elevated pressures are due to inhibition of the Bayliss phenomenon or venoarteriolar reflex in CVD limbs, which is illustrated in the Fig. There is evidence for such inhibition in CVD limbs.[14,32-36]

AMVP. AMVP has long been known to be associated with reflux. It is known to worsen with severity of reflux and CEAP clinical class categories.[16] It is widely assumed that AMVP is associated with obstruction as well. An earlier study using venographic obstruction suggested otherwise.[37] In this analysis, abnormal AMVP was predominantly linked with reflux and only infrequently with IVUS-proven obstruction. The explanation is that the powerful calf pump mechanism can surge through obstruction but is vulnerable to the load of recurrent reflux volume after each contraction.[13,15,38]

We used % drop and VFT, the traditional markers for AMVP assessment, in this study. VFT is more sensitive than % drop.[13,18] O'Donnell et al[39] pointed out as early as 1979 that systolic peak pressures with calf contraction may be more important than the pressure nadir with calf exercise, a view that has been endorsed by an expert panel.[16] Hosoi et al[15] have constructed a mathematical hemodynamic model that appears to validate this hypothesis. Such an analysis was not used in this study.

CONCLUSIONS

Venous hypertension is present in approximately two-thirds of patients with CVD. An association between reflux severity and venous hypertension was not able to be shown in this study. Supine venous pressure does not worsen with reflux, but erect venous pressure does. This may be due to a muted postural vasoconstrictor response in CVD limbs. Ambulatory venous hypertension is dominantly associated with reflux and much less frequently with obstruction.

AUTHOR CONTRIBUTIONS

Conception and design: SR
Analysis and interpretation: SR, AK, LL, NP, TJ
Data collection: SR, AK, LL, NP, TJ
Writing the article: SR, AK, LL, NP, TJ
Critical revision of the article: SR, TJ
Final approval of the article: SR, AK, LL, NP, TJ
Statistical analysis: SR, AK, LL, TJ
Obtained funding: SR
Overall responsibility: SR

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