VENOUS RETURN REVIEW

Ambulatory venous pressure: new concepts

S Raju[1]

[1]The Rane Center, Suite #401 971, Lakeland Dr., Jackson MS 39216

submitted: Jan 27, 2021, accepted: Mar 24, 2021, EPub Ahead of Print: Jul 13, 2021
Conflict of interest: None

DOI: 10.24019/jtavr.105 - Corresponding author:Prof. Seshadri Raju,

Abstract

Background: The importance of the calf pump (the 'peripheral heart') in the lower limb venous circulation is well known. The ambulatory venous pressure (AMVP) is generally considered the quintessential functional test of calf pump function. However, much controversy exists on the basic hemodynamics of AMVP as well as its measurement. Recent work has helped to revise/clarify many of these controversies. Results from experimental simulations are used to illustrate key hemodynamic concepts.

A multicameral model of calf pump: Arnoldi popularized the notion that deep venous pressures can be monitored by inserting a needle in the dorsal foot vein (unicameral model). It has been shown recently that ambulatory venous pressures in the deep system is different from that in the dorsal foot vein and also the saphenous vein. AMVP profile in the three valved systems are different from each other (multicameral model). AMVP is traditionally monitored via % drop and also Venous refill time (VFT). Analysis of a large cohort of patients shows that VFT is more sensitive. % drop can be omitted as it is rare for it to be abnormal without concurrent abnormal VFT. AMVP is normal in venous obstruction, contradicting common belief. Ambulatory venous hypertension is a specific property of reflux, not obstruction. Supine venous pressure is elevated in obstruction but not reflux despite the suspected role of microvascular hypertension in reflux pathology.

Role of calf capacitance & compliance: While severe reflux can shorten VFT, reduced calf capacitance and compliance are more important as can be shown in experimental set ups and clinical analysis.

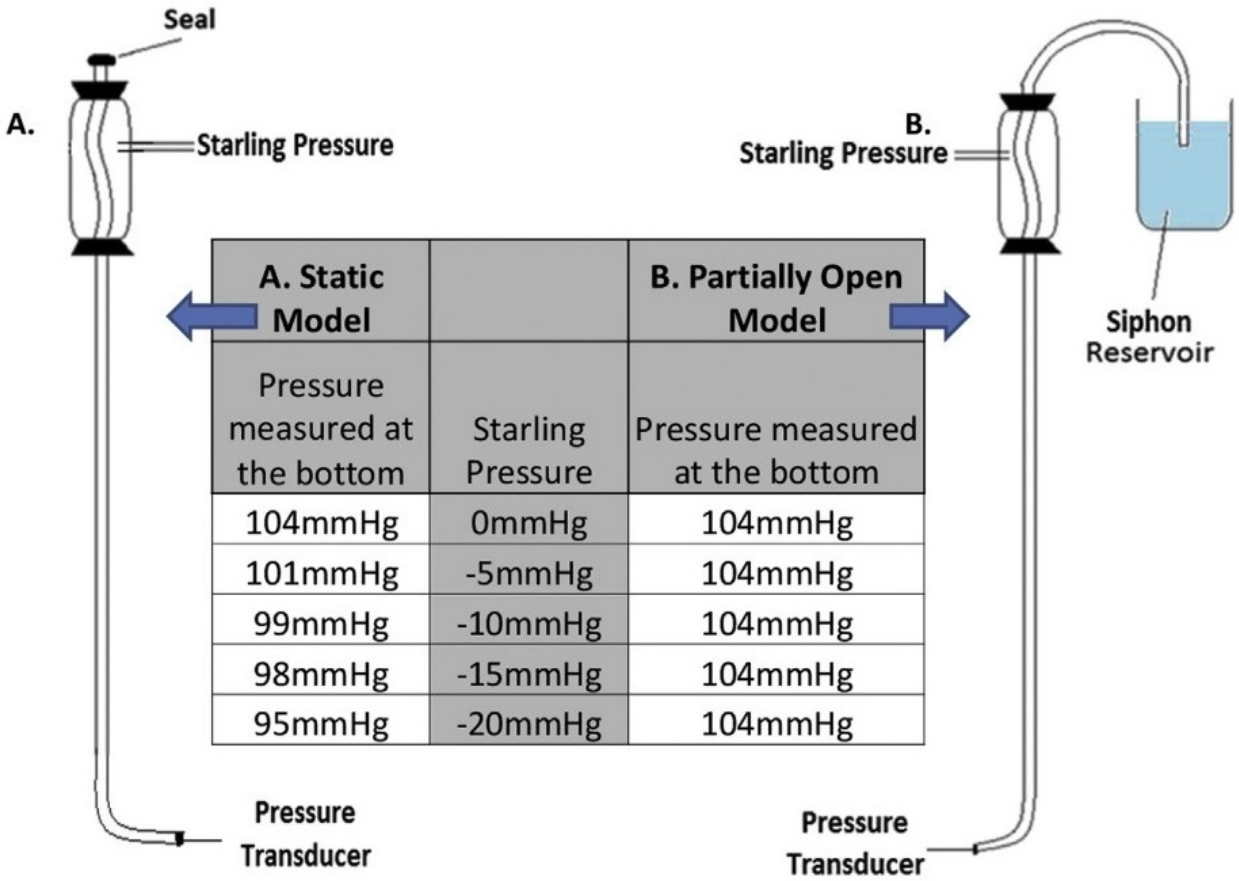
Calf Pump failure: Like the heart, the calf pump can eject all the inflow presented to it (up to 3X normal). Thus the popular concept of 'calf pump failure' from reflux overload has little concrete evidence to support it.

Column segmentation: It is commonly assumed that valve closure results in column segmentation. It can be shown in experimental settings that collapse of the venous segment below the valve closure is necessary for column segmentation. Furthermore a reconstruction of the events surrounding column restoration makes it clear that a closed valve above the calf pump cannot reopen with the hydrostatic pressure of the restored column height below the closed valve alone. Much higher pressures generated by inflow interacting with wall tension of the infra-valvular segment is necessary to reopen the closed valve and restore flow. AMVP does not reach resting levels in experimental models till wall tension is restored to resting levels. A full blown reflux through an open valve will not transmit column pressure when the calf pump is partially collapsed.

A non-invasive replacement for AMVP: Prevailing clinical practice and recent guidelines emphasize duration of reflux at the proximal saphenous, femoral and popliteal valves for assessment of reflux severity. It has been shown that these proximal valves play no significant role in column segmentation. A group of valves in the posterior tibial vein and the great saphenous vein near the ankle are the critical players in column interruption duration (CID). CID can be measured non-invasively by duplex after calf ejection by pressurized cuffs.

Conclusion: AMVP has declined in clinical use as duplex identification of reflux in proximal valves has become common practice. More useful information can be obtained by using Duplex to measure CID.

Keywords Ambulatory venous pressure, column segmentation, calf pump, reflux, venous pressure.



A. Static Model		B. Partially Open Model
Pressure measured at the bottom	Starling Pressure	Pressure measured at the bottom
104mmHg	0mmHg	104mmHg
101mmHg	-5mmHg	104mmHg
99mmHg	-10mmHg	104mmHg
98mmHg	-15mmHg	104mmHg
95mmHg	-20mmHg	104mmHg

*Figure 1A&B - Static and dynamic models in foot venous pressure. Simulating the effect of negative chest pressure on the measured venous pressure of the foot. Negative pressure applied to the Starling resistor near the top in a closed static model (**A**) significantly lowers foot venous pressure from resting levels (up to 9 mmHg). This is consistent with the current concept but does not correctly explain in vivo pressure discrepancy. With the siphon arrangement (**B**), the space created in the Penrose by the negative Starling pressure is quickly filled from the siphon. Pressure at the bottom remains unchanged, showing that the negative pressure theory is not valid. (Reprinted from Eur. J. Vasc. Endovasc. Surg. 2016;51(2):275-284, with permission from Elsevier)*

Introduction

The evolution of man to assume the erect posture from our mammalian ancestors strains venous return from the lower limbs. The adaptation of the calf pump mechanism (the peripheral heart) to normalize venous return in the erect posture is imperfect- still a work in progress in evolutionary terms. Chronic venous disease (CVD) is a result of this as yet incomplete postural evolution. Early studies on calf pump function had to rely on primitive diagnostic tools. Duplex imaging and electronic pressure transducers had not arrived yet. It is surprising that much of the early framework of calf pump function laid out by the pioneers still holds in aggregate if not in details.

The protocol for ambulatory pressure measurement was standardized by Nicolaides and Zukowski in 1985[1]. The patient was asked to do ten tip-toe stands while holding on to a sturdy frame. Venous pressure changes were monitored through a needle inserted into the dorsal foot vein. 'Ambulatory venous pressure' (AMVP) was expressed as % pressure drop from resting levels (% drop) and venous refill time (VFT) for pressure recovery back to resting levels. A % drop of ~50% and VFT ~20 sec. is considered normal. A basic assumption was that there was rapid pressure equilibration between the superficial and deep venous systems that was reflected in the dorsal foot venous pressure (unicameral model). The concept was never fully validated clinically at a time when deep venous cannulation was considered risky.

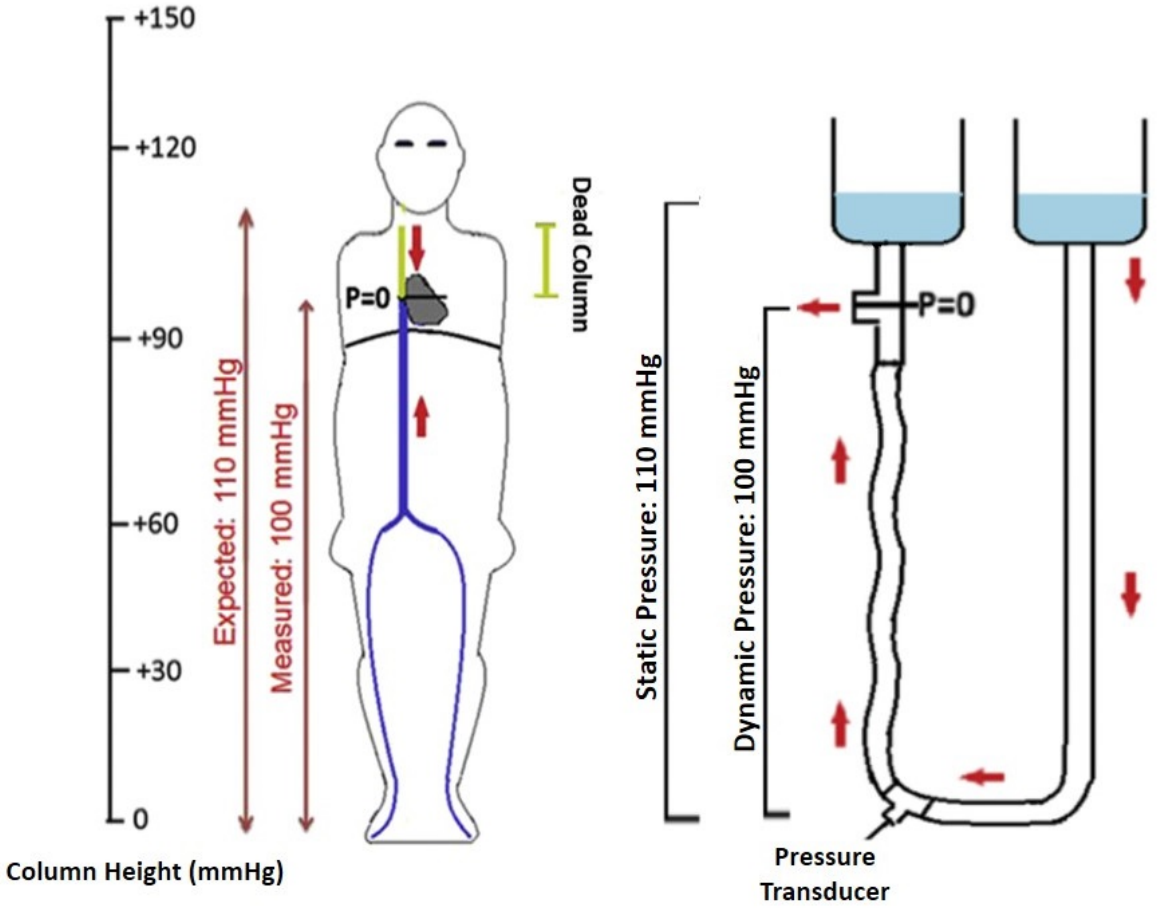


Figure 2 - The flow in the superior vena cava is downward while the flow in the inferior vena cava is in the opposite direction as shown in the left. The pressure read at the foot level is about 10 mm Hg less ("Dead column") than the combined column height above and below the heart. A flow model representing these opposing flows is shown on the right. The pressure read at the bottom of the 'U' is the same as the column height below the 'T'. The pressure of the column above the 'T' flowing in the opposite direction does not register at the bottom because hydrostatic column continuity is not present (See Text). (Reprinted from Eur. J. Vasc. Endovasc. Surg. 2016;51(2):275-284, with permission from Elsevier)

Calf Pump Modelling

The fluid dynamics of ambulatory venous pressure changes are complex. Mechanical simulation has helped to clarify basic features.

A solution to an old mystery

An incongruency between theory and observation in AMVP measurement was recognized early: the resting venous pressure at the foot level in the erect individual was ~7 mm Hg *less* than the hydrostatic pressure calculated from venous column height. It was postulated that the negative pleural pressure of similar magnitude was responsible, offsetting part of the column pressure. Such a mechanism can be shown to occur in experimental models where the venous column is enclosed in a tightly sealed closed system (Figure 1A)[2]. The human venous system with highly compliant walls and a dynamic flow of ~100 cc/sec. is a quasi-open system resembling the model shown in Fig. 1B.

Any vacuum created by external negative pressure will be transient and quickly filled by the fast moving circulation and wall movement. Thus the negative pressure theory is unlikely. A more likely explanation for the discrepant erect venous pressure measurement is shown in Fig. 2. The venous column is not stationary or even unidirectional in flow. The flow in the superior vena cava is downward while the flow in the inferior vena cava is in the opposite direction.

The pressure read at the foot level is about 10 mm Hg less ("Dead column") than the combined column height above and below the heart. A flow model representing these opposing flows is shown on the right. The pressure read at the bottom of the 'U' is the same as the column height below the 'T'. Column pressure above the 'T' flowing in the opposite direction does not register i.e. hydrostatic column continuity is not present.

Reflux and column pressure

Figure 3A illustrates reflux through a fully open mechanical valve into Penrose tubing below representing the tibial valve and the calf pump[3]. Column pressure fails to fully register at the bottom of the set up while reflux is in motion. The column pressure is mostly dissipated in overcoming viscous resistance of reflux flow. I.e., *reflux in motion will not fully transmit column pressure*. It is well known that thin walled tubes will not support column pressure in the collapsed state. More of the column pressure is registered as the Penrose fills and reflux flow slows (Fig. 3B). The full column pressure is recorded when the Penrose is full and reflux flow had ceased even though the valve is still wide open (Fig. 3C). If the valve is fully closed at this juncture, there is no observable reduction in the pressure at the bottom of the set up (Fig. 3D).

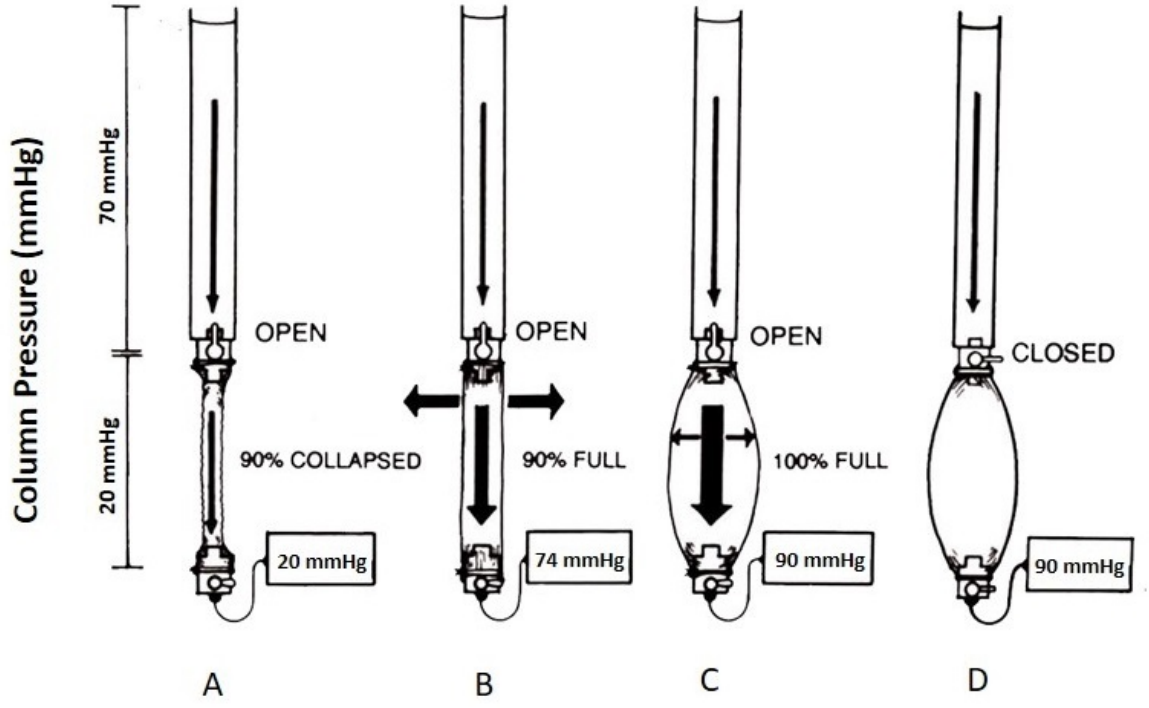


*Figure 3 - Diagram illustrates influence of tube collapse on dampening restoration of hydrostatic column pressure after ejection. (**A**) A 60 mm Hg hydrostatic column is present above a refluxive valve, which is open. Only 20 mm Hg is recorded at bottom of Penrose tube, which is 90% empty and collapsed. Most hydrostatic pressure is dissipated from viscous flow resistance in filling collapsible tube. Thus hydrostatic column is functionally broken even though there is physical continuity of fluid column through the refluxive valve. (**B**) As filling of Penrose tube progresses, more hydrostatic pressure head is recorded at bottom of Penrose. When Penrose tube is 90% full, 74 mm Hg is recorded at bottom of Penrose tube. (**C**) When Penrose tube is 100% full and distended, hydrostatic column pressure is fully restored; pressure reading of 90 mm Hg is now obtained at bottom of Penrose tube. (**D**) If the valve is closed at this point, the pressure at the bottom will continue to read 90 mm Hg even though the column is now physically segmented by the closed valve. This is because 'stressed' volume is trapped below the closed valve. Unstressed column height in the Penrose is only ~20 mm Hg. The excess pressure generated by 'stressing' the calf pump volume is an important component of calf pump mechanics.*

The column height in the Penrose below the closed valve is only 25 cm equal to 18.4 mm Hg. The recorded pressure at the bottom is far higher because it represents the compliance pressure of the volume within the distended Penrose. This volume consists of unstressed volume (~70%) filling the Penrose up to the stretching point plus an additional stressed volume (~30%) accumulated as the Penrose distends under the hydrostatic load of the fluid column above. Thus valve closure by itself is not enough to segment the column and reduce column pressure; collapse of the infra-valvular segment with disgorgement of stressed and unstressed volumes is necessary for column segmentation. When the tibial valve closes after calf ejection, this process occurs in reverse when the segmented venous column reconstitutes as shown in Fig. 4A-D. The column will grow in height with continuing arterial 'inflow' touching the popliteal valve some seconds later. But the pressure at the top of the unstressed column is zero, not enough to open the closed valve under high pressures above. With continuing inflow, the column begins to be stressed as it distends the vein, ultimately generating the high pressures necessary to open the tibial valve.

The stressed and unstressed venous volumes are related to the *bending* and *stretching* compliance regimens. The *Tube law* relates the lumen geometries of the bimodal regimen with its transmural pressure (Fig. 5)[4].

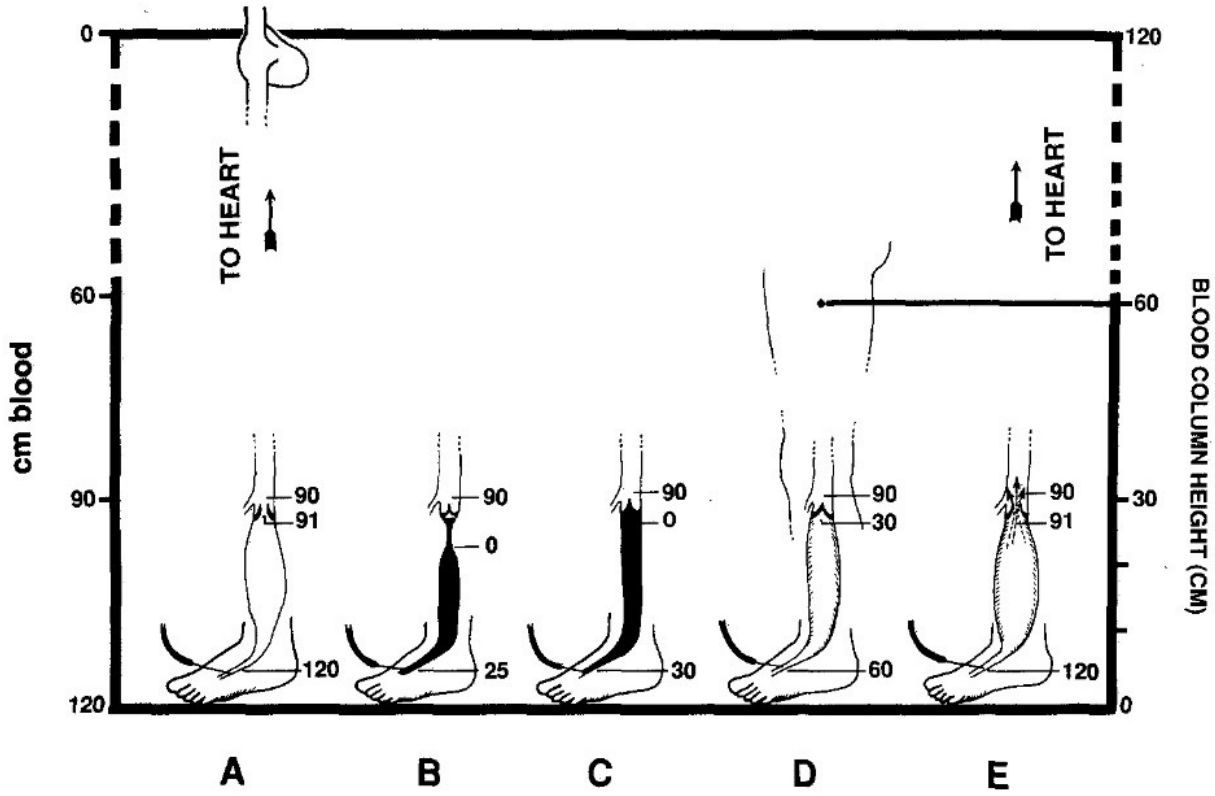


*Figure 4 - Scheme of nominal pressure relationships related to tibial valve closure. (**A**) During resting flow the pressure immediately above and below the tibial valve is 90 and 91 mm Hg, respectively. (**B**) After ejection, the tibial valve closes under the pressure of 90 mm Hg. The pressure below the valve is zero at the top of the residual column. (**C**) Even when the column grows from arterial inflow to touch the valve, the pressure will be zero at the top of the column, not enough to open the valve. (**D**) The high pressure necessary to open the valve is provided by continued arterial inflow into the closed segment. (**E**) Continued inflow "stresses" the volume further raising the pressure to 91 mm Hg opening the valve and restoring flow. (Reprinted from J. Vasc. Surg. 1993;17(3):459-469, with permission from Elsevier)*

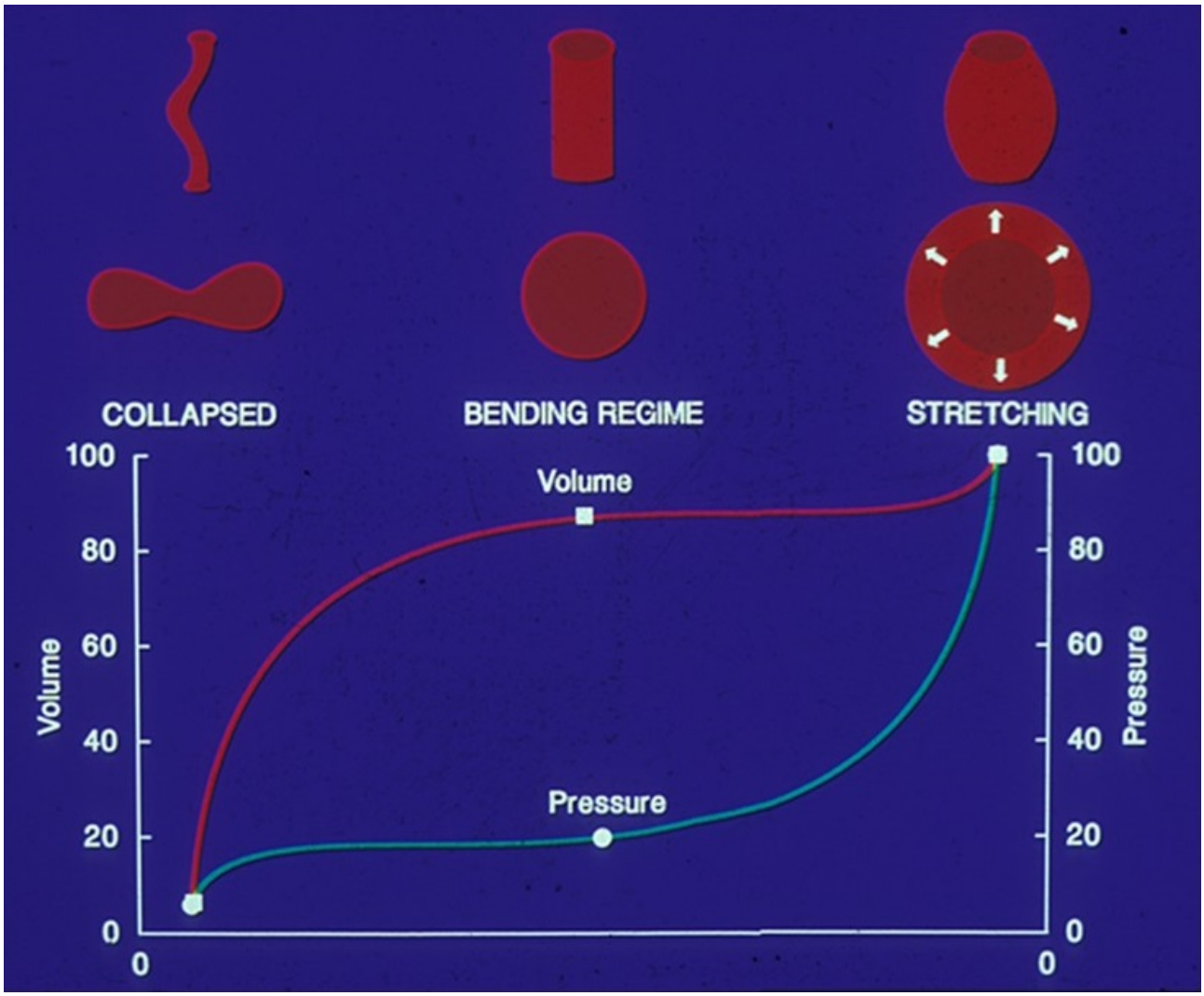


Figure 5 - Veins are collapsible tubes and there is an asynchronous pressure/volume relationship. Most of the volume filling (up to ~80%) occurs initially under low pressure. The pressure goes up only when the tube stretches stressing the volume inside. Thus the terminal high pressure is produced by ~20% volume addition at the end. (Reprinted from Journal of Endovascular Therapy. 1998;5(1):42-51, with permission from SAGE)

It is clear from the foregoing that the mechanics of column segmentation involves not only the valve but also the venous segment below as shown in Fig. 6A. Column segmentation is initiated by valve closure but the process is completed only when the infra-valvular segment collapses. Continued valve closure is necessary to maintain its collapsed state during the recovery period. The infra-valvular segment also plays an important buffer function (‘pedestrian shocks’!) in moderating rapid pressure swings due to reflux (from cough, Valsalva for example) or calf ejection. Intramuscular pressures as high as 250 mm Hg have been recorded during calf muscle contractions. The buffer function is a property of vertically oriented collapsible tubes (Fig. 6B). The self levelling mechanism is most efficient when the tube is in the bending regimen. Some degree of pressure buffering may be retained even in the stretching regimen if the tube (vein) wall retains adequate compliance.

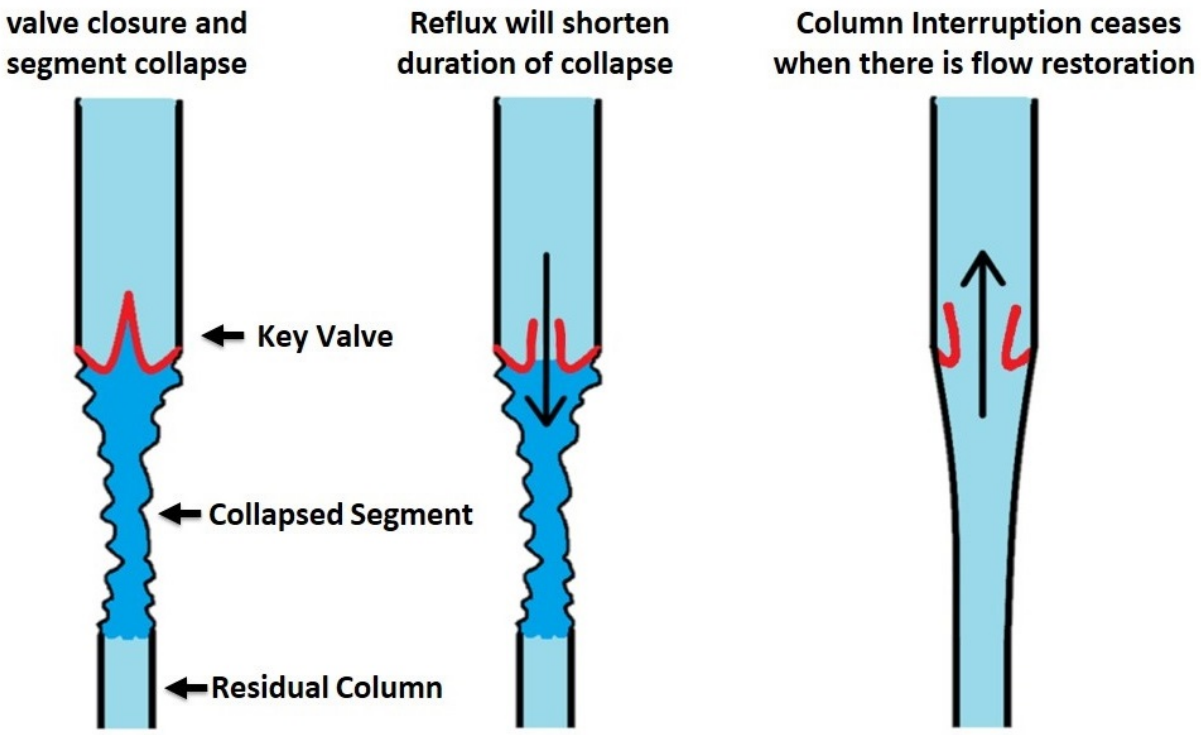


Figure 6A - Valve closure by itself does not lead to pressure reduction. The post ejection collapse of the infra valvular segment is responsible for column segmentation and the resulting pressure reduction (see also Fig. 3) Reflux will shorten duration of collapse but the low pressure nadir may not change. Column interruption ceases when there is flow restoration. This can be monitored by Duplex or pressure restoration in infra valvular segment(s). Column segmentation is more efficient when it occurs in the lower part of the leg as the residual column will be shorter and the pressure lower compared to segmentation higher up in the limb.

The flow mechanics of the infra-valvular *conduit* have been studied in mechanical models utilizing Penrose as well as less compliant materials such as Polyethylene or PTFE as conduits[4,5]. Post ejection pressure and recovery time (model analogues for post-exercise pressure and venous filling time of AMVP test) were monitored. Post ejection pressure remained constant for a wide range of ejection fractions and reflux settings (Fig. 7) when the Penrose remained in the bending regimen (EF>40%) but recovery time became shorter with smaller ejection fractions and increased reflux (data not shown). If the Penrose is substituted with less compliant tubing such as PTFE of same physical dimensions, post ejection pressure paradoxically becomes lower but recovery time also becomes much shorter (Fig. 8) due to a very limited stretching regimen. Reducing the capacitance of normally compliant tubes also results reduced recovery times. The compliance or stressed volume of poorly compliant conduits is just a fraction of Latex by an order of magnitude. The Penrose can buffer sudden increase in transmural pressure even in the stretching regimen more effectively than less compliant tubes. The relative importance of reflux vs conduit compliance is best illustrated in a 2 segment model shown in Fig. 9[5]. It consists of two segments, the upper one functioning as a pump for ejection. Ejection occurs through a graduated valve which can be set up for varying degrees of reflux back into the pump. The lower segment functions as a conduit. It is separated from the upper pump by a *competent* valve with low (< 1 mm Hg) opening pressure. When the upper pump ejects, a favorable gradient is created for the lower conduit to flow into the upper segment (Fig. 9). Reflux into the pump will shorten the duration of favorable gradient resulting in incomplete ejection from the segment below. This arrangement more closely aligns with venous flow in vivo. Penrose and PTFE segments were used in varying pump/conduit combinations to simulate normal and stiff (poorly compliant) post-thrombotic veins respectively. The recovery time in the conduit for the various pump/conduit combinations is shown as a bar graph in Fig. 9. Stiffness (poor compliance) is a dominant factor in shortened recovery times even in the absence of reflux.

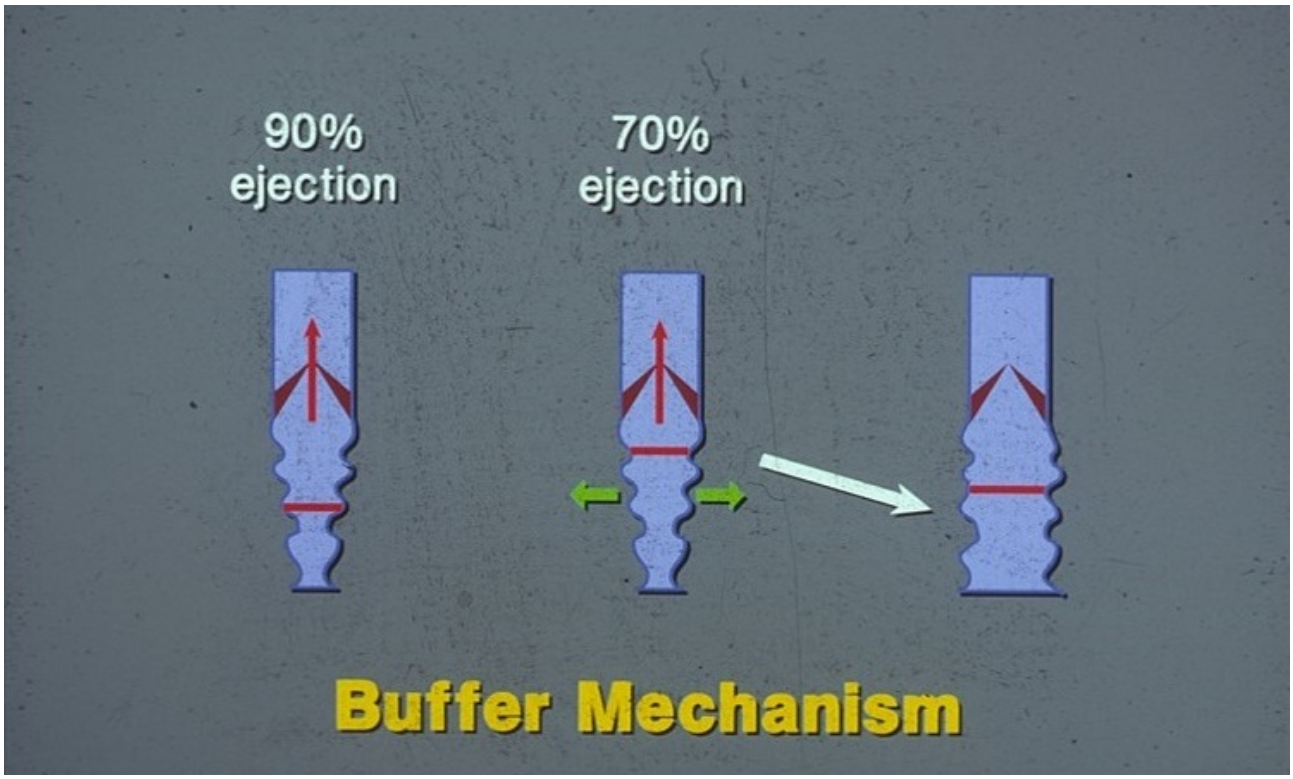


Figure 6B - The buffer mechanism of tube collapse which tends to compensate for poor ejection or even mild to moderate reflux. Very little energy is required to expand a collapsed tube. The transient high residual fluid column from poor ejection or reflux will expand the tube in the bending regimen quickly, restoring low residual column height and pressure. (Reprinted from Journal of Endovascular Therapy. 1998;5(1):42-51, with permission from SAGE)

Clinical Correlation

AMVP was intended to measure the effect of reflux on calf pump function. Over time, reflux pathology and ambulatory venous hypertension became almost synonyms and other causes of ambulatory hypertension are seldom considered. There are many other potential causes of ambulatory venous hypertension as described in the modelling experiments described above.

In a clinical analysis of 373 consecutive limbs with ambulatory venous hypertension, six of the experimentally suggested factors were found to be causative:

- 1. Reflux
- 2. Increased arterial inflow
- 3. Reduced venous capacitance
- 4. Poor calf ejection or increased residual volume fraction
- 5. Poor calf venous compliance and
- 6. A combination of these[6].

Quantification of these pathologies was made possible by simultaneous AMVP measurement and air-plethysmography (with measurement of arterial inflow). Multiple regression analysis was used to model ambulatory venous hypertension. Regression analysis showed that reflux, though present in 97%, was a dominant factor in ambulatory venous hypertension in only 57% of limbs; other listed factors were dominant in the rest. 91% of the limbs had at least 2 of the listed factors and 57% at least 3. A multifactorial etiology for ambulatory venous hypertension rather than any single factor in a particular patient is more likely (Fig. 10)[7]. Increased arterial inflow has been attributed to vascular invasion of the venous thrombus and its evolution. It can be concluded that reflux has to be quantitatively significant to produce ambulatory venous hypertension. Ambulatory venous hypertension is associated with worsening CEAP clinical class, multisystem involvement in reflux, high grade reflux segmental score, VFI_{90} (APG) and Kistner axial grading[8].

In a large analysis of 4599 limbs with CVD referred to our tertiary center, Duplex reflux was present in 67% of the limbs which was associated with ambulatory venous hypertension in 27%; in 9% of the limbs no reflux was found despite presence of ambulatory venous

hypertension[8]. When ambulatory venous hypertension is present, VFT alone is shortened in ~96% (about a third with abnormal % drop). Abnormal % drop with normal VFT occurs in only ~4% of the limbs (Fig.11)

- It appears that AMVP technique can be simplified by relying only on VFT and omitting the % drop parameter without much clinical penalty.

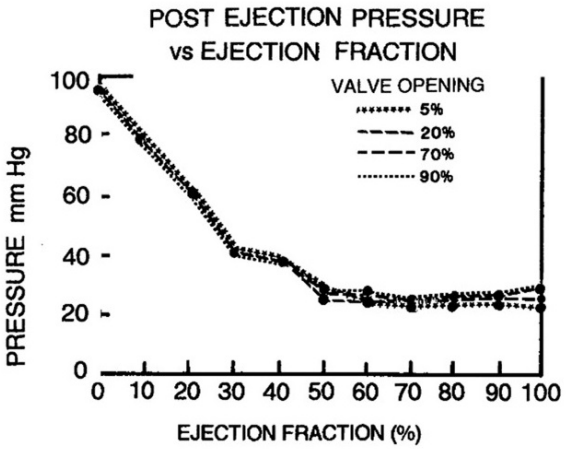


Figure 7 - An ejection fraction >~40% will place the tube in the bending (collapsed) regimen. This will result in a flat post ejection pressure curve for all ejection fractions >~40%. (Reprinted from Journal of Endovascular Therapy. 1998;5(1):42-51, with permission from SAGE)

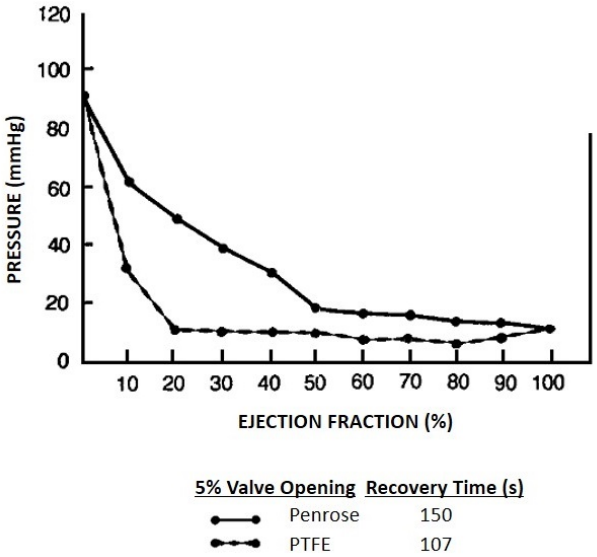


Figure 8 - Compliance and tube collapse. Post ejection pressure is paradoxically lower with the PTFE tube than latex Penrose. However the recovery time becomes shorter than latex Penrose. (Reprinted from Journal of Endovascular Therapy. 1998;5(1):42-51, with permission from SAGE)

Unexpected AMVP Findings

- The association of microvascular hypertension with reflux is experimentally well established. However in an analysis of 4132 limbs with CVD symptoms, elevated supine venous pressure was *not* associated with reflux[9].
- Prevalence of ambulatory venous hypertension was analyzed in 967 limbs with IVUS proven obstruction. Combined obstruction and reflux was present in 693 (72%) limbs and the remaining 268 (28%) limbs had no reflux. Ambulatory venous hypertension was overwhelmingly (87%) associated with limbs with obstruction+ reflux. Only 13% of non-refluxive limbs with pure IVUS obstruction had ambulatory venous hypertension[8].

Calf pump failure

The concept of calf pump failure from chronic reflux overload is a popular concept. Ejected volume (EV) was plotted against resting venous volume (VV) from APG measurements in 7877 limbs with CVD symptoms[8]. VV progressively increases with increasing severity of reflux. EV increases (up to 3X normal) in parallel (r=0.71) to keep the ejection fraction normal (Fig. 12). This appears to be a compensatory phenomenon in CVD to maintain normal calf pump pressures.

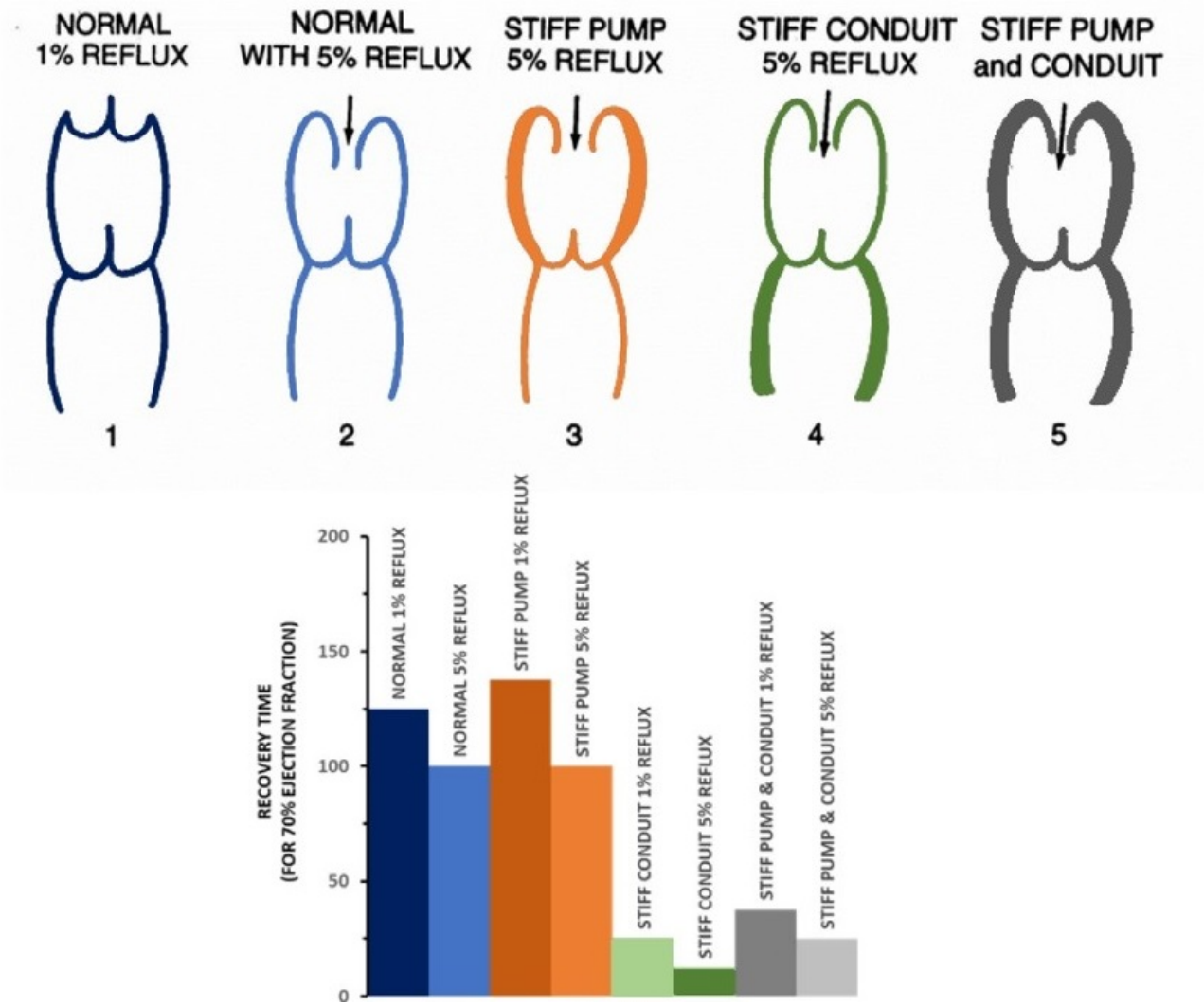


Figure 9 - A 2 segment 2 valve setup using combinations of Penrose and PTFE for the pump and conduit. The upper valve is adjustable for reflux. The valve separating the pump and conduit is a competent membranous valve with low opening pressure. The recovery time is more severely shortened by a stiff conduit than a refluxive pump. (See text.)

Nicolaides has pointed out that the deleterious effect of severe reflux is cumulative[10]. A single calf ejection typically lasts 3-4 seconds. Mild to moderate reflux (<50% ejection fraction) typically occurring over a much longer duration is easily cleared without residual by one or more calf contractions. Reflux volume clearance will be incomplete if large volume of reflux occurs over a shorter duration overwhelming the functional efficiency (~70%) of the calf pump. In that case, part of the reflux volume will accumulate after each calf contraction, leading to ambulatory venous hypertension. In contrast, the calf muscles are able to pump adequately against the fixed resistance of pure obstruction without reflux to maintain normal ambulatory venous pressure.

The relative roles of ejection fraction and residual volume fraction in calf pump 'failure' is unclear[8].

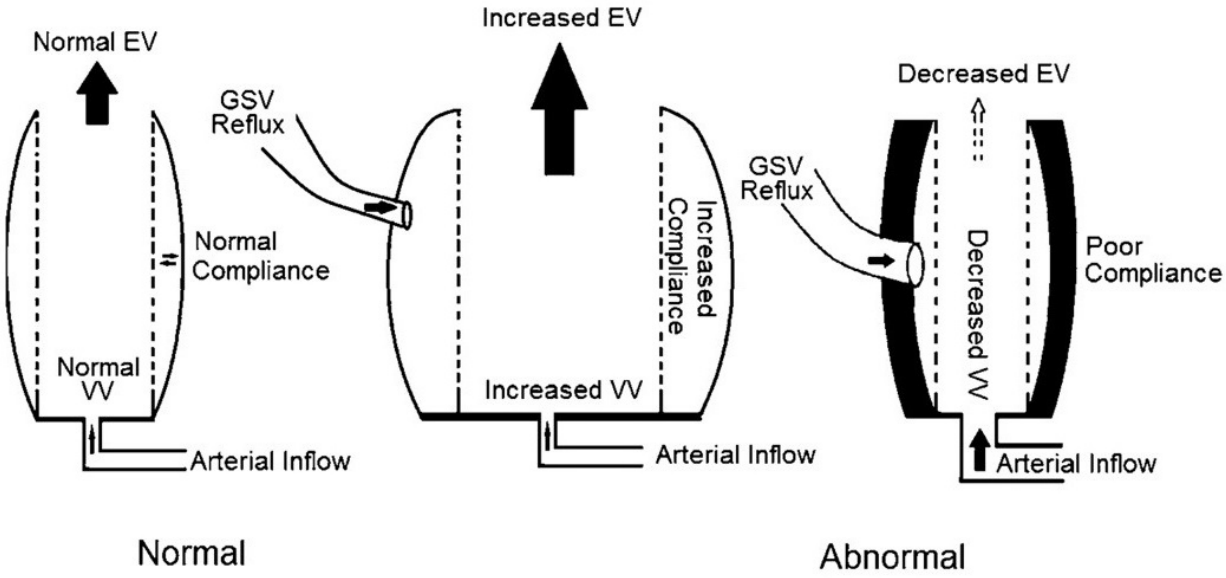


Figure 10 - Calf-pump mechanics (normal and abnormal). Increased VV with increased EV can buffer reflux keeping the post ejection pressure normal. Poor compliance, decreased VV, decreased EV or increased arterial Inflow can decrease VFT and magnify even low level reflux. (See text.) (Reprinted from J. Vasc. Surg. Venous. Lymphat. Disord. 2015;3(1):8-17, with permission from Elsevier)

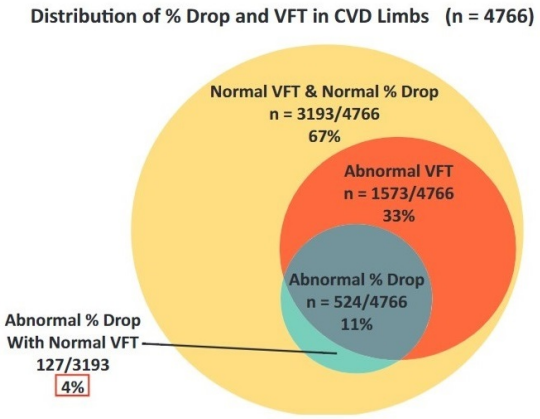


Figure 11 - Relative distribution of % drop and venous filling time (VFT) in the ambulatory venous pressure (AMVP) test is shown. Both parameters were normal in 67% of tested limbs. VFT was abnormal in 33% and % drop in 11% of the limbs. Only 4% of limbs with normal VFT had abnormal % drop. (See text.) (Reprinted from J. Vasc. Surg. Venous. Lymphat. Disord. 2019;7(3);428-440, with permission from Elsevier)

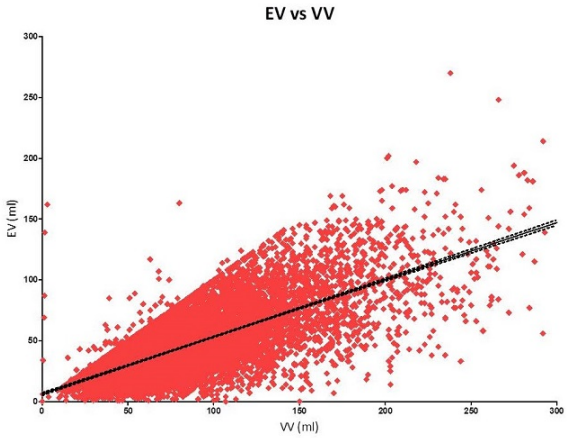


Figure 12 - Ejection volume (EV) and venous volume (VV) in 7877 limbs with chronic venous disease (R=0.71). EV and VV show a good linear correlation, indicating the effective compensation of the calf pump to a wide array of volumes. Also shown are 95% confidence bands calculated with standard errors (the confidence band is the area that has 95% chance of containing the true regression line). (Modified and reprinted from J. Vasc. Surg. Venous. Lymphat. Disord. 2019;7(3);428-440, with permission from Elsevier)

Limitations of AMVP

The original premise of the AMVP test that the dorsal foot venous pressure reflects deep venous pressure appears not to be correct. The superficial system, the deep system and the dorsal foot vein are valved compartments. Equilibration between the compartments lags, particularly during the diastolic phase of calf contraction[8,11,12].

Simultaneous recording of pressures in the three compartments clearly shows different pressure profiles. Some patients are unable to tolerate the required

venipuncture in the foot and access may be difficult in others. The AMVP test may be denied in as many as ~30% or more.

Air-plethysmography (APG) provides a reliable non-invasive estimate of reflux via the VFI_{90} parameter. There is little correlation between APG and AMVP parameters because the former monitors volume and the latter pressure; the compliance curve is known to be non-linear[8].

A non-invasive replacement for AMVP

The concept that calf pump contraction facilitates column interruption, thereby reducing venous pressure in the gaiter region is fundamentally sound. It is also true that valve reflux truncates this beneficial mechanism though the details as currently perceived is not correct. Current focus is on the large 'gateway' valves at the outflow of femoral, popliteal and saphenous veins. A lot of emphasis is placed on the duration of reflux at these gateway valves. It could be said that we are "looking for reflux in all the wrong places" in a word play on a popular lyric. These gateway valves remain closed only for a few seconds following calf contraction. Column segmentation is produced by valves in the tibial veins and the distal saphenous vein in the ankle region that remain closed for up to 20 seconds or more during calf diastole[13]. The duration of their closure can be measured by monitoring resumption of forward flow in these critical veins via duplex (Fig. 13). Given the numerous conceptual and technical problems associated with AMVP, duplex measurement of column interruption duration (CID) appears to be a superior option.

Peripheral Venous Pressure

Supine venous pressure in the lower limb is elevated in two thirds of limbs with proven obstruction[9]. Non-invasive measurement of limb venous pressure may be a useful test in patients with obstructive symptoms. Bartolo and colleagues have laid the framework for such a technique using Doppler[14].

Figure 13 - Measurement of column interruption duration (CID). The patient is examined in full weight-bearing erect position, remaining motionless while holding on to a rigid support. An automated quick inflation/deflation cuff is applied to the upper calf. Calf ejection is produced by cuff inflation to 110 mm Hg followed by deflation. One of the posterior tibial veins below the cuff is monitored after cuff deflation. The duration of reappearance of flow (B flow or color flow) represents CID for the tibial vein. The CID for the great saphenous vein (GSV) is similarly determined via duplex probe focused on the vein immediately below the cuff. (See text.) (Reprinted from J. Vasc. Surg. Venous. Lymphat. Disord. 2020;8(1):127-136, with permission from Elsevier)

References

1) Nicolaides AN, Zukowski AJ. The value of dynamic venous pressure measurements. World journal of surgery. 1986;10(6):919-24.

2) Raju S, Varney E, Flowers W, Cruse G. Effect of External Positive and Negative Pressure on Venous Flow in an Experimental Model. Eur. J. Vasc. Endovasc. Surg. 2016;51(2):275-84.

3) Raju S, Fredericks R, Lishman P, Neglen P, Morano J. Observations on the calf venous pump mechanism: determinants of postexercise pressure. Journal of vascular surgery. 1993;17(3):459-69.

4) Raju S, Green AB, Fredericks RK, Neglen PN, Hudson CA, Koenig K. Tube collapse and valve closure in ambulatory venous pressure regulation: studies with a mechanical model. Journal of endovascular therapy. 1998;5(1):42-51.

5) Raju S, Hudson CA, Fredericks R, Neglen P, Greene AB, Meydrech EF. Studies in calf venous pump function utilizing a two-valve experimental model. European journal of vascular and endovascular surgery: the official journal of the European Society for Vascular Surgery. 1999;17(6):521-32.

6) Raju S, Neglen P, Carr-White PA, Fredericks R, Devidas M. Ambulatory venous hypertension: component analysis in 373 limbs. Vascular and endovascular surgery. 1999;33:257-67.

7) Raju S WJM, and Jones T. Quantifying saphenous reflux. J. Vasc. Surg. Venous. Lymphat. Disord. 2015;3:8-17.

8) Raju S, Knepper J, May C, Knight A, Pace N, Jayaraj A. Ambulatory venous pressure, air plethysmography, and the role of

calf venous pump in chronic venous disease. J. Vasc. Surg. Venous. Lymphat. Disord. 2019;7(3):428-40.

9) Raju S, Knight A, Lamanilao L, Pace N, Jones T. Peripheral venous hypertension in chronic venous disease. J. Vasc. Surg. Venous. Lymphat. Disord. 2019;7(5):706-14.

10) Hosoi Y, Zukowski A, Kakkos SK, Nicolaides AN. Ambulatory venous pressure measurements: new parameters derived from a mathematic hemodynamic model. Journal of vascular surgery. 2002;36(1):137-42.

11) Neglén P, S R. Ambulatory Venous Pressure Revisited. Journal of Vascular Surgery. 2000;31(6):1206-13.

12) Neglén P, S R. Differences in pressures of the popliteal, long saphenous, and dorsal foot veins. Journal of Vascular Surgery. 2000;32(5):894-901.

13) Raju S, Walker W, May C. Measurement of ambulatory venous pressure and column interruption duration in normal volunteers. J. Vasc. Surg. Venous. Lymphat. Disord. 2020;8(1):127-36.

14) Bartolo M, Antignani PL, Di Folca A, Pittorini L, Todini AR. Mesure de la pression veineuse avec le Doppler: standardisation de la méthode [Measuring Venous pressure with Doppler: Standardization of method]. Phlebologie. 1984 Jan-Mar;37(1):97-101. French. PMID: 6718510.