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Venous Tone and Stressed Blood Volume in Heart Failure: JACC Review Topic of the Week

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Abstract

Elevation in cardiac filling pressures is the hallmark of acute and chronic heart failure (HF). A number of pathological processes contribute to the elevation in cardiac filling pressures, including myocardial dysfunction and primary volume overload. In this review, we discuss the important role of the venous system and the concepts of *stressed blood volume* (SBV) and *unstressed blood volume* (UBV). We review how regulation of venous tone modifies the distribution of blood between these two functional compartments, the physical distribution of blood between the pulmonary and systemic circulations, and how these relate to hemodynamic abnormalities observed in HF. Finally, we review recently applied methods to estimating SBV and how they are being applied to results of clinical studies to provide new insights into resting and exercise hemodynamics and therapeutics for HF.

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Tweet: The functional concept of stressed and unstressed blood volume is fundamental to cardiovascular function. The venous system and its regulation of stressed blood volume in HF has been largely ignored. We review the above and its relationship with therapeutic effects of drugs/devices

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Condensed Abstract

In this review, we discuss the important role of the venous system and the concepts of *stressed blood volume* (SBV) and *unstressed blood volume* (UBV). We review how regulation of venous tone modifies the distribution of blood between these two functional compartments, the physical distribution of blood between the pulmonary and systemic circulations, and how these relate to hemodynamic abnormalities observed in HF. Finally, we review recently applied methods to estimating SBV and how they are being applied to results of clinical studies to provide new insights into resting and exercise hemodynamics and therapeutics for HF.

Keywords

Volume regulation; venous tone; exercise; heart failure; stressed blood volume; unstressed blood volume

Introduction

Despite decades of investigation, the mechanisms responsible for elevated cardiac filling pressures in patients with heart failure (HF) with preserved or reduced ejection fraction at rest, during exertion and during episodes of decompensation are not fully explained. Cardiac factors such as reduced inotropic reserve, blunted chronotropic reserve, impaired diastolic function and pericardial restraint have been implicated, particularly to explain abnormal exertional hemodynamics (1). Derangements in the vascular system, such as blunted vasodilatory responses, increased pulmonary arterial resistance, and decreased pulmonary arterial compliance, are also recognized. The discussion concerning such vascular effects has focused on the systemic arterial circulation because of the well-recognized relationship between cardiac afterload and cardiac performance (2), driving the belief that ventricular-vascular mismatch (or uncoupling) contributes to hemodynamic abnormalities in HF.

However, the venous system has received very little attention despite its primary role in determining cardiac filling pressures and regulating cardiac output (CO)(3). In this review, we discuss the role of the venous system and the concepts of *stressed blood volume* (SBV) and *unstressed blood volume* (UBV). We discuss how regulation of venous tone modifies the distribution of blood between these two functional compartments. Finally, we touch on recently developed methods for estimating SBV and how they are being applied to results of clinical studies to provide new insights into resting and exercise hemodynamics and HF therapeutics (Central Illustration).

General Considerations

Veins are not merely a conduit for the return of blood to the heart, but also serve as a functional blood reservoir. Veins contain around 70% of the total blood volume (TBV) in comparison to only ~30% contained in arteries (4). Furthermore, the highly-vascularized organs of the splanchnic compartment, such as liver, spleen, and intestines, contain approximately 20–30% of the TBV (5). Veins are more compliant than arteries (>20:1) and like arteries, have a smooth muscle layer with dense autonomic innervation.

Splanchnic vessels receive more adrenergic innervation than central and peripheral vessels (6). Furthermore, the innervation is higher in the splanchnic veins than in the splanchnic arteries (7). Thus, the splanchnic venous compartment is the main site of venous capacity in animals (4) and humans (8). A basic understanding of the concepts of UBV and SBV is fundamental to understanding how regulation of venous tone exerts potent control of ventricular filling pressures and CO in health and disease. A summary of key terms and their definitions used throughout this review are outlined in Supplemental Table 1.

Basic Concepts

TBV of the body is functionally divided into two pools: $UBV+SBV=TBV$. Despite the central role of SBV and UBV in regulating cardiac performance, direct measurement of these parameters requires invasive methods. Specifically, quantification of SBV and UBV requires repeated measurements of mean circulatory filling pressures (MCFPs) over a range of TBVs. MCFP is the intravascular pressure when the heart is stopped, and pressures equilibrate throughout the circulation.

In practice, estimation of UBV and SBV starts with the measurement of TBV, often done using an indicator-dilution technique that involves injecting a known quantity of an indicator (e.g., Evans-blue dye which binds to albumin (9), or I^{131} -radiolabeled albumin (10)) that distributes throughout the intravascular space. After injection of a known quantity of the indicator, either an equilibrium concentration (in the case of Evans-blue) or the time course of decay (in the case of I^{131}) is measured, which is converted to total plasma volume (TPV) (9,10). TBV is then obtained from $TPV/(1-hematocrit)$. Next, MCFP must be measured at more than one TBV, which is achieved by infusing or withdrawing a known quantity of blood (Figure 1A/B).

The relationship between MCFP and TBV is nonlinear, such that a significant amount of intravascular volume is required before there is any significant rise of MCFP. In shown in Figure 1A, MCFP does not rise until TBV is more than 2L and does not exceed 2.5 mmHg until TBV is nearly 4L. Furthermore, once flow in the circulatory system begins, for a given MCFP, central venous pressure (CVP) decreases, and mean arterial pressure (MAP) increases (Figure 1C).

UBV is defined as the volume required to fill the vasculature before there is any significant rise of MCFP. The portion of TBV in excess of UBV is the SBV. Under normal conditions, $UBV \sim 4/5^{\text{th}}$ of TBV and only $\sim 1/5^{\text{th}}$ is SBV. Importantly, the distinction between SBV and UBV is functional, and does not suggest physically isolated volumes.

Guyton and colleagues have taught that insights into cardiovascular performance are obtained by plotting “Starling curves” on the same axes as “venous return curves” (Figure 2). A “Starling curve” is a plot of CO as a function of CVP at a given ventricular contractility, heart rate and systemic vascular resistance: CO increases with increases of CVP, a manifestation of the Frank-Starling Law of the heart. A “venous return curve” shows the rate of blood return to the right atrium as function of CVP (i.e., the plot obtained by swapping the axes of Figure 1C): increases of CVP result in decreased venous return. The

venous return curve intersects the volume axis (i.e., when flow equals 0) when CVP reaches MCFP. Since CO must equal venous return in steady-state conditions, the intersection between the Starling curve and the venous return curve defines the CVP and CO for a given state (solid red dot in Figure 2). With this construct, it is easy to appreciate how MCFP is a key regulator of cardiac performance.

Regulation of SBV and MCFP

With fixed vascular tone, MCFP and SBV trend in parallel (Figure 1A/B). For example, as blood is infused (increased TBV) or withdrawn (decreased TBV), SBV and MCFP increase and decrease, respectively, since UBV is constant. Conceptually, this reflects the clinical course for patients with HF: filling pressures rise as fluid accumulates in early stages of an exacerbation and fall with diuresis.

However, regulation of venous tone offers a potent means of modifying SBV in the setting of constant TBV. Experimental studies demonstrate that with sympathetic activation and vasoconstrictive pharmacologic agents, the MCFP-TBV relationship shifts leftwards towards lower volumes with the steep portion of the curve shifting in roughly parallel manner (Figure 3)(11). Thus, increased venous tone decreases UBV with complementary increase of SBV, while compliance ($\Delta V / \Delta P$ in the typical working range of pressures) remains relatively constant. The example of Figure 3 depicts an $\sim 0.75L$ shift of the MCFP-TBV relationship, which results in a 75% increase of SBV (from 1.00 to 1.75L) but only an 18.8% reduction of UBV (from 4.00 to 3.25L); this shift resulted in a large, 12.5mmHg increase of MCFP. Thus, relatively small changes in venous tone can achieve large changes of MCFP. In contrast to the effects of increased sympathetic tone, sympathetic blockade and venodilators (e.g., pharmacological sympatholytics or nitrates) shift the MCFP-TBV curve rightward, increasing UBV and decreasing SBV.

In the setting of acute blood loss, the UBV can functionally serve as a reservoir for autotransfusion into the SBV pool. Controlled hemorrhage experiments in humans show that over a large range, every milliliter of blood removed from the body is “replaced” by $\frac{1}{2}$ milliliter of blood by splanchnic venoconstriction (12). Furthermore, up to 10–12% of blood volume loss is tolerated without changes in blood pressure, heart rate or CVP.

Physical exercise is a major cardiovascular stressor that requires augmentation of CO to meet the increased metabolic needs of working muscles. In healthy adults, exercise steepens the slope of the Frank-Starling curve due to increased cardiac contractility, increased heart rate, and decreased systemic vascular resistance. Yet, the modulation of CO with exercise is more strongly determined by cardiac preload augmentation via increased SBV. Upright exercise in humans has been associated with a 23% reduction in splanchnic blood volume (liver 18%, kidney 24%, spleen 46%) and a 30% reduction of leg blood volume, the latter also being mediated by the effects of the muscle pump (4,13). Since leg blood volume is a third of splanchnic blood volume, the majority of recruited blood volume originates from the abdominal compartment (4,13). In comparison, with light supine exercise, the reduction of splanchnic blood volume has been estimated to be $\sim 34\%$ (14). Because the cardiovascular

circulation is a closed system, the decrease in venous capacity during exercise increases blood volume in the heart and lungs by ~38% (13).

Catecholamines (endogenous or exogenous) act as the primary mediator of splanchnic vascular tone (15), largely via alpha adrenergic receptors. Endogenous release of norepinephrine makes up more than 40% of the total body norepinephrine spillover (16). Naturally, (patho)physiological increases in catecholamine release will lead to decreased splanchnic vascular capacitance and increases in eSBV such as can occur with acute decompensated heart failure, cardiac dysfunction (e.g., cardiogenic shock), hypoxia (sleep apnea), physical stress (exercise) or emotional stress.

In addition to pharmacologic and physiological stimuli, preclinical and human studies have shown that direct stimulation of the splanchnic nerve increases SBV and increases CVP, PA pressures and CO (17). The changes were shown to be driven by translocation of blood from the splanchnic compartment, which occurred within seconds of stimulation onset and subsided within minutes after the stimulation ended. While these regulatory mechanisms evolved to enhance the odds of survival and ability to exercise, sympathetic modulation of venous tone can contribute unfavorably in the setting of acute and chronic HF.

Studying the venous system in humans

Sympathetic and pharmacologic regulation of vascular compliance and capacity has been investigated extensively for both the systemic (18) and pulmonary circulation (19). Such experiments have involved either: 1) single or dual heart bypass preparations with external blood reservoirs; or 2) radio-labeled blood cell scintigraphy during volume infusion and withdrawal maneuvers. There are few comparable experiments in humans largely because the required methods are highly invasive and/or cumbersome to execute.

Magder and DeVarenes quantified SBV in patients undergoing hypothermic circulatory arrest during cardiac surgery (20). Similar to experiments in animals, cardiac surgery patients are connected to a cardiopulmonary bypass system with a reservoir, and MCFP can be reduced to 0 mmHg. Accordingly, the amount of blood that translocates to the external reservoir at the point when filling pressure reaches 0 mmHg is the SBV. SBV averaged 1290 ± 296 mL, or 20.2 ± 1.0 mL/kg, which amounted to ~30% of predicted TBV. Similarly, Mass et al. measured MCFP, SBV, and vascular compliance in 15 intubated postoperative patients (21). These patients were subjected to a sequence of breath-hold, volume infusions and withdrawals, and arm stop-flow maneuvers while measuring CO and arterial and venous pressures. They found that SBV was 1265 ± 541 mL, an average of 28.5% of predicted TBV and systemic vascular compliance was 0.97 ± 0.49 mL·mmHg⁻¹·kg⁻¹, which was similar to values reported in normal animals (4,11).

There are also other less invasive techniques. Venous occlusion plethysmography can index flow and segmental blood volume in arms and legs and assess the effects of vasoactive drugs (22). The application of a tight tourniquet to the proximal portion of a limb interrupts venous outflow but does not obstruct arterial inflow. A venous cannula is used to measure pressure. Plethysmography simultaneously estimates changes in limb volume over time.

Plotting measured pressure versus estimated limb volume yields a venous pressure-volume relationship. This technique is limited to the exploration of limb physiology, which may or may not be reflective of the splanchnic bed or lungs.

Radionuclide plethysmography (radio-labeled albumin or red blood cells) images the blood pool of a region of interest. This technique can estimate acute changes of regional blood volume and vascular capacity (23). For example, radionuclide plethysmography has been used to assess splanchnic capacity humans (8,13) with and without cardiovascular disease, at rest and with exercise (13). This technique is time consuming and technically challenging, limited by the use of radioactive material, and the fact that it measures relative (not absolute) volumes in a region of interest. These factors have limited widespread adoption and resulted in the lack of recent investigations into SBV. New approaches are reviewed in greater detail in the Supplemental Figure 1–7.

Evidence for the role of stressed blood volume in heart failure

Increased RV and LV filling pressures (i.e., central and pulmonary venous pressures) at rest, and more so during exercise, are key hallmarks of HF and are believed to be important determinants of exercise intolerance (24). One paradigm explaining elevation in cardiac filling pressures in HF is abnormal LV and RV function leading to increased diastolic pressures, which transmit backwards to the pulmonary and systemic venous circulation. Others relate filling pressure elevation to blood and plasma volume expansion due to renal sodium retention. However, accumulating evidence suggests these paradigms do not fully explain the hemodynamic alterations in HF, as both cardiac dysfunction and blood volume expansion each only partially explain the increase in filling pressures (25) (Supplemental Figure 8). Accumulating evidence indicates that hemodynamic abnormalities in HF are also strongly driven by decreased splanchnic venous capacity and increased SBV which, in turn, is mediated by neurohormonal activation (26,27).

Investigations in animal models of acute and chronic HF confirm a reduction in venous capacity. Acute HF induced by cardiac ischemia in canines reduced splanchnic vascular volume by displacing the splanchnic venous pressure–volume relation to the left without a significant change in compliance (Supplemental Figure 9)(28). Redistribution of splanchnic volume occurred despite an increase in portal venous pressures, mostly due to active vasoconstriction rather than passive mechanisms of volume recruitment in the setting of neurohormonal hyperactivation (29). Baroreflex mediated venoconstriction accounted for about 80% of the increase in LV end-diastolic pressure, while LV dysfunction itself only accounted for 20% (28,30). SBV-increase has also been observed in chronic HF. In multiple animal models of HF, total vascular capacity was reduced, in some cases ~50% (31).

A recent study using these techniques provided new insights into the role of venous capacitance and distribution of blood volume between the SBV and UBV in humans (32). As compared to controls, patients with HFpEF displayed an 11% higher TBV, but more striking 81% higher SBV, with a greater proportion of TBV as SBV (44% vs. 30%, $p < 0.0001$, Figure 4A), suggesting reduced venous capacitance in HFpEF at rest. During exercise, there was a greater absolute increase in SBV in patients with HFpEF compared

to controls. Despite higher SBV at rest and with exercise, the ability to augment CO was depressed, indicating that in HFpEF, the heart is operating on the plateau of the Frank-Starling curve, where increases in SBV are not translated to increases in tissue perfusion (Figure 4B). This study identified a greater role for abnormalities in venous capacitance with excess body fat. SBV correlated with the body mass index (Figure 4C), but the increase in SBV could not be fully explained by adipose-associated volume expansion because the ratio of SBV/TBV also increased linearly with increasing body mass. These data identify a new mechanism that may predispose patients with obesity to develop HFpEF, and suggest that patients with the obese phenotype may be better-positioned to respond favorably to therapies targeting SBV (32).

Finally, the role of SBV in cardiogenic shock has also been investigated with focus on the difference between shock due to acute myocardial infarction (AMI-CS) or due to decompensated chronic heart failure (HF-CS)(33). While SBV was similarly elevated in these two subgroups, patients with HF-CS shock who died had a significantly higher SBV than those who survived.

To date there are no data to suggest that venous physiology in patients with HF depends on ejection fractions (EF) or other factors related to specific HF phenotypes. Compared to controls, we have seen similar increases in eSBV in patients with HFrEF, HFpEF and PH-HFpEF (Supplemental Figure 8). More specifically, eSBV is greater in HF than in controls and increases by a greater amount during exercise than in controls. Interestingly, the percent of TBV residing in the stressed component is greater in HF than in normals, and this does not seem to depend on the EF phenotype.

In contrast, while eSBV increases with TBV in obesity, eSBV expressed as a percent of TBV also increases with the body mass index (BMI), indicating fundamental difference related to excess body fat (32). However, obesity appears to have a similar impact on venous physiology and volume distribution in people with and without HF. Patients with greater abnormalities in RV-PA coupling display higher eSBV in cross sectional analysis, but the direction of causality remains unclear (32). Whether the influence of venous tone modulation on hemodynamics or clinical outcomes will depend on EF or other factors (e.g., RV dysfunction with or without pulmonary hypertension) is unknown at this time. However, as with lack of differential adverse events with pharmacologic vasodilator therapy, early experience with splanchnic nerve denervation has not uncovered any such concerns in patients with common forms of HFpEF (34). These considerations would be of more concern for patients with infiltrative cardiac diseases, such as amyloid, with severe diastolic dysfunction characterized by small RV and/or LV chambers and leftward-shifted end-diastolic pressure-volume relationships (35).

Stressed blood volume as a target in heart failure

Despite a strong evidence base and proposed importance of SBV several decades ago (36), the role of venous tone and SBV as a potential target for therapeutics has remained speculative due to lack of evidence until very recently. We now review different therapies whose action appear, in part, to be mediated by venodilation and reductions of SBV.

Guideline directed medical therapy (GDMT)

Several pharmacologic agents which are components of GDMT for HFrEF such as sympatholytics (alpha/beta-blockers), renin-angiotensin-aldosterone system blockers (i.e., angiotensin-converting enzyme inhibitors, aldosterone inhibitors, etc.) and sodium-glucose linked transporter 2 inhibitors (SGLT2i) have proven benefits on neurohormonal balance. Further, there is evidence these drugs reduce (e)SBV in HF (28,37). To what degree SBV changes contribute to the observed clinical benefits with these drugs is unclear.

NO donors

As noted above, nitroglycerine and NO donors with preferential effects on venous capacity are well known to reduced cardiac filling pressures. As shown in the preclinical study depicted in Supplemental Figure 9A, this is at least partially mediated by venodilation. Indeed, drugs like nitroglycerin (primary venodilator) and nitroprusside (mixed arterial-venodilator) are commonly used to treat acute decompensated HF. Among Black patients with NYHA-class III/IV HFrEF, treatment with fixed dose isosorbide dinitrate plus hydralazine was associated with reductions in all-cause death and time-to-first HF hospitalization, with improvement in quality-of-life scores (38). A different nitrate, isosorbide mononitrate, failed to improve activity levels or 6-minute walk distance in HFpEF (39). The reasons for the neutral response are not clear but may relate to excessive and tonic venodilation in a patient population characterized by labile blood pressure swings due to ventricular-vascular stiffening (2). Inorganic nitrite provides more targeted NO provision with less effect at rest because conversion from nitrite is facilitated during conditions of exercise including venous hypoxia and acidosis. In this light, a number of placebo-controlled studies have revealed marked reductions in right and left heart filling pressures with nitrite during exercise, consistent with reductions in SBV (40). While one trial did not demonstrate an improvement in exercise capacity with nitrite (41), this may relate to the inhaled drug delivery route, and multiple trials are ongoing.

Splanchnic Nerve Modulation

The splanchnic sympathetic nerves innervate the highly vascularized organs of the abdomen. The concept of splanchnic nerve blockade emerged following the observation that significant hemodynamic effects of splanchnic nerve stimulation in healthy animals and humans (17) and the observation in HF of acute or chronic SBV increase resulting in acute rises in cardiac filling pressures (42). Temporary splanchnic nerve modulation in patients hospitalized for decompensated HF or chronic ambulatory HF resulted in a reduction in right and left sided filling pressures (43–46). A reduction in resting and exercise induced pressure elevations was primarily explained by a reduction in SBV following splanchnic nerve blockade (Figure 5A)(44). Similar effects on filling pressures have recently been reported with surgical ablation of the splanchnic nerve (47); percutaneous approaches to achieving the same effects are currently under investigation (48).

Milrinone

A recent study explored the impact of acute intravenous milrinone on exercise hemodynamics in patients with HFpEF (49). The original hypothesis for choosing milrinone

was that its pulmonary and systemic arterial vasodilator effects and inotropic effects (on the right ventricles) would act to reduce CVP and PCWP while permitting greater exercise-induced increases of cardiac output. Indeed, milrinone was shown to increase heart rate, LV contractility and to reduce SVR. Unexpectedly, however, analysis showed that estimated SBV was also decreased by milrinone (Figure 5B). Furthermore, while the changes of heart rate, contractility and SVR were the main contributors to increased exercise-induced CO, the reduction of SBV appeared most responsible for reductions of CVP and PCWP (50). Venodilatory effects of milrinone may be mediated by activating ATP-dependent potassium channels of venous smooth muscles causing muscle relaxation (51). Venodilatory effects of increased cAMP and subsequent PKA activation by milrinone should also be considered.

Levosimendan

Similar to the study of milrinone described above, levosimendan was studied in view of its pulmonary and systemic arterial vasodilator effects and inotropic effects (on left and right ventricles) in patients with pulmonary hypertension associated with HFpEF(52). In contrast to milrinone which showed effects on multiple parameters, a 24-hour levosimendan infusion decreased resting and exercise CVP and PCWP in the absence of evidence of pulmonary or arterial dilatatory effects and without increase in cardiac output (Figure 5C). Similar results were obtained following 6, weekly levosimendan infusion which, by echocardiography, also showed no detectable improvement of LV or RV contractility. Rather, analysis showed that, in comparison to placebo, the hemodynamic effects at rest and in response to passive leg raise were due to a reduction in estimated SBV (Figure 5D)(53). Though not widely appreciated, levosimendan has venodilatory effects that are mediated through activation of ATP-dependent potassium channels (54).

Summary and Conclusions

The role of venous system tone and its regulation of SBV in HF has been largely ignored and, until recently, has not been exploited as a therapeutic target. While direct and repeated measurements of SBV and venous tone are difficult in the clinical setting, especially during exercise or in response to therapies, analytical approaches have recently been developed and indirectly validated for this purpose. These methods have provided new insights into the pathophysiology of HF. Additionally, several recent studies have suggested a primary role of venodilation and reductions of SBV in explaining reductions of CVP and PCWP. All told, the evidence suggests that venodilation may be a viable target for HF for reducing resting and exercise cardiac filling pressures. It will be important to determine whether hemodynamic effects will translate into improvements of symptoms, exercise tolerance and mortality. Use of existing techniques and development of novel ways to investigate the venous system are needed. Future studies should consider the impact of the impact of drug- and device-based therapies on the venous system and the potential impact on SBV and UBV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

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Abbreviations:

HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
CVP	Central venous pressure
MCFP	Mean circulatory filling pressure
MPFP	Mean pulmonary filling pressure
MSFP	Mean systemic filling pressure
SBV	Stressed blood volume
PCWP	pulmonary capillary wedge pressure
TBV	Total blood volume
UBV	Unstressed blood volume

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Highlights:

- Venous tone regulates the distribution of blood volume between stressed and unstressed compartments.
- This distribution in turn influences pressures in the pulmonary and systemic circulations, contributing to hemodynamic abnormalities in heart failure
- Venodilation and reduction of stressed blood volume underlie the therapeutic effects of many of the drugs and devices used for management of heart failure.

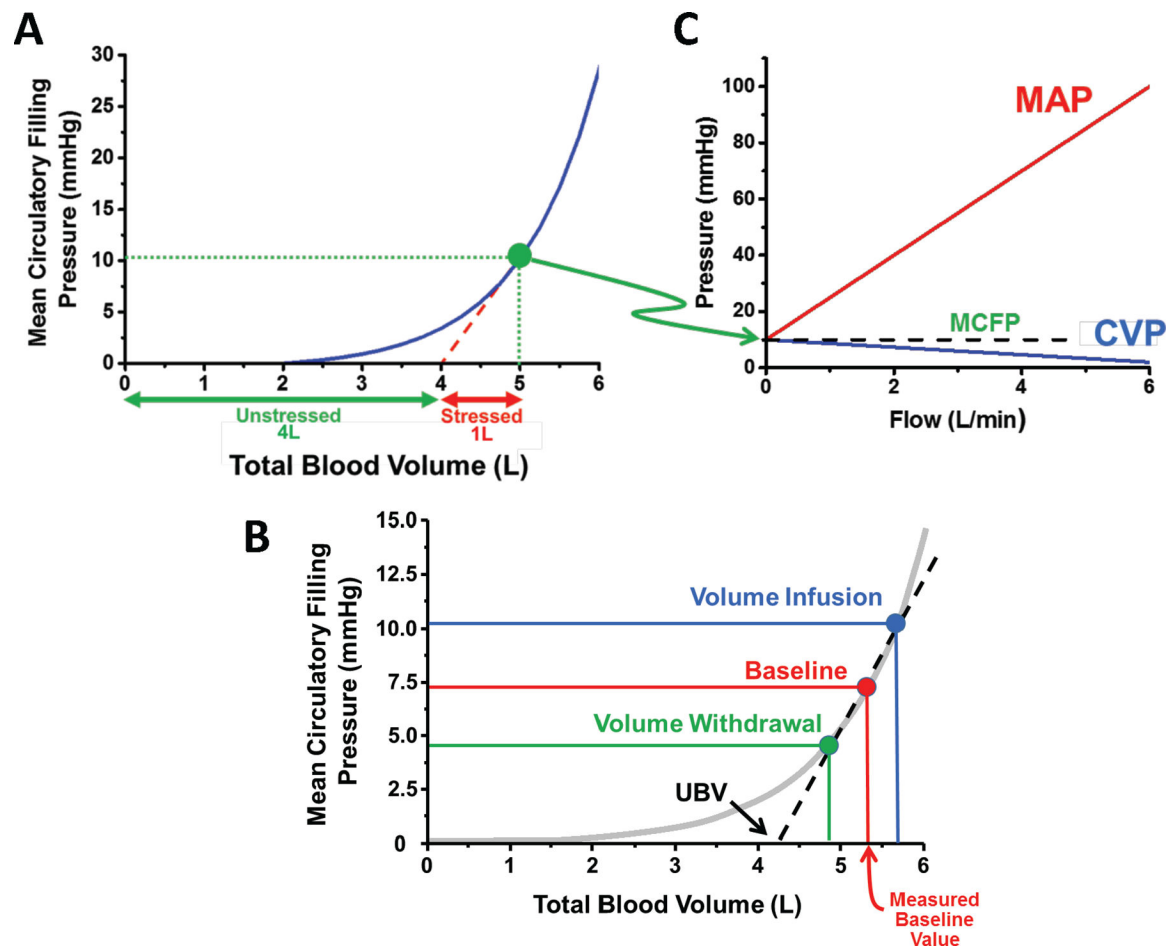


Figure 1. Interrelationship of stressed and unstressed blood volume.

A. The sum of unstressed (UBV) and stressed blood volume is the total blood volume. The relationship between mean circulatory filling pressure (MCFP) and total blood volume is non-linear. UBV is estimated from the volume axis intercept of the linearly extrapolated MCFP-total blood volume relationship measured over a limited range of volumes (red dotted line). B. The impact of volume infusion vs withdrawal on the stressed and UBV are shown. C. MCFP is the equilibration pressure throughout the circulation when there is no blood flow. Once flow starts, for a given MCFP, central venous pressure (CVP) decreases, and mean arterial pressure (MAP) increases.

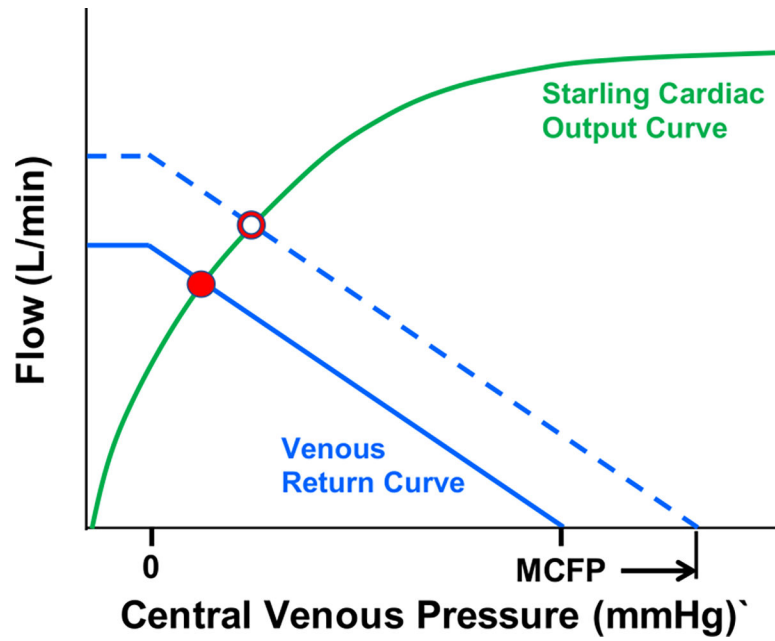


Figure 2. Interrelationship between Starling cardiac output curve and venous return curve. The intersection between the Starling curve and the venous return curve determines the cardiac output (solid red dot). The venous return curve intersects the central venous pressure axis at the mean circulatory filling pressure (MCFP). An increase of MCFP shifts the venous return curve rightward in parallel manner and intersects the Starling-curve at a higher value of cardiac output (open red dot).

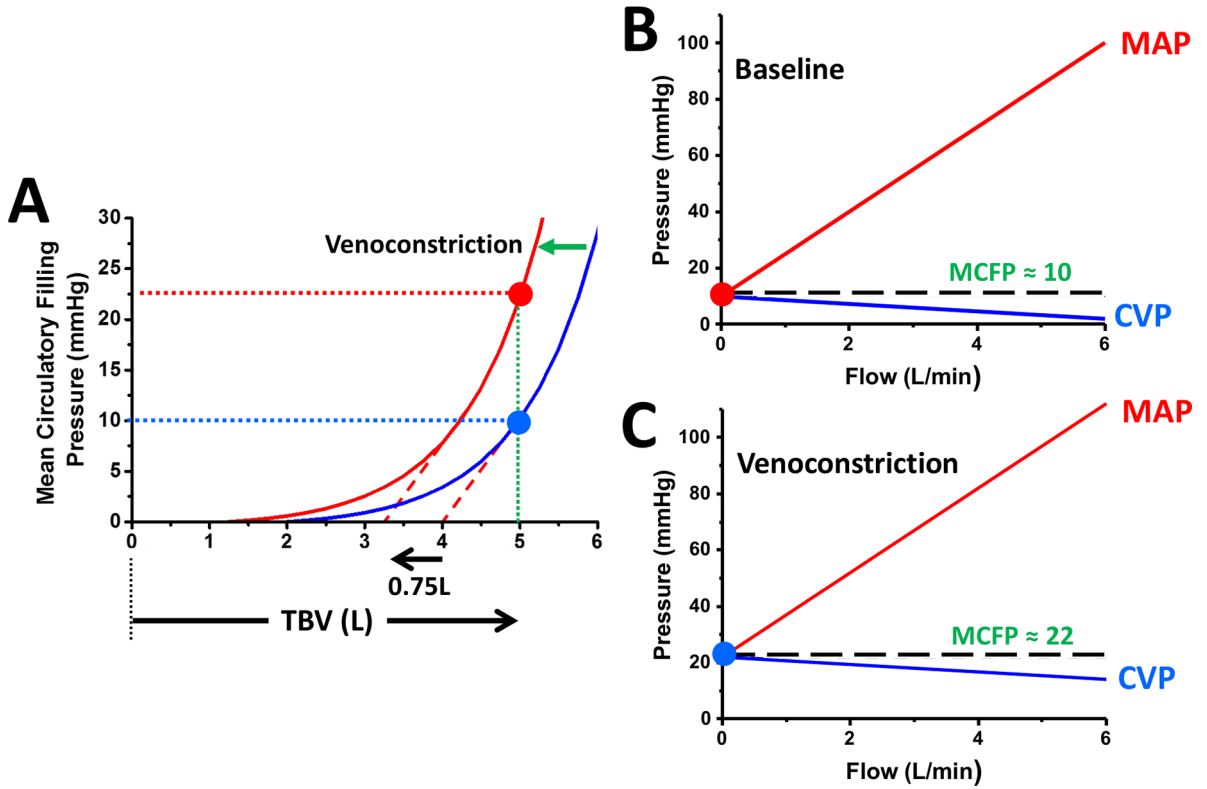


Figure 3. Effects of venoconstriction on stressed and unstressed blood volume.

A. Effect of venoconstriction (e.g., via sympathetic hyperactivation) on the relationship between mean circulatory filling pressures (MCFP), blood volume. A 0.75L increase of stressed blood volume (SBV) resulted in an increase of MCFP from 10 to 23mmHg. B. The relationship between cardiac output (CO), mean arterial pressure (MAP) and central venous pressure (CVP). When CO is 0, MAP and CVP equilibrate at the MCFP. As CO is increased, MAP increases and CVP decreases. C. In the vasoconstricted case, despite constant total blood volume (TBV), MCFP is increased and both MAP and CVP are higher at any given CO compared to the baseline state.

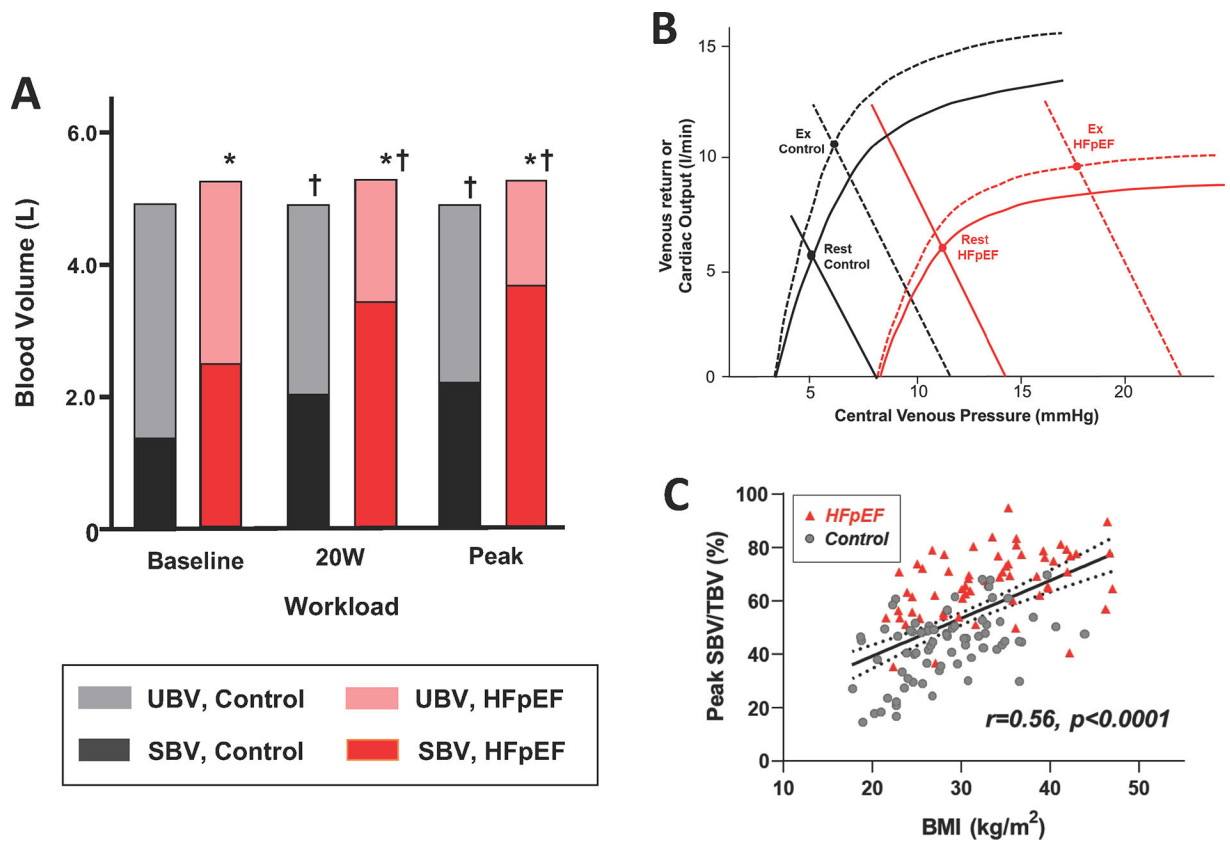


Figure 4. Stressed and unstressed volume in HFpEF, obesity phenotype.

A. Comparison of total blood volume, stressed blood volume (SBV) and unstressed blood volume (UBV) at rest and during exercise in controls and patients with HFpEF. B.

Explanation of why, despite a greater increase of SBV during exercise in HFpEF patients, they have a markedly blunted increase of cardiac output. C. Relationship between percent of blood ascribed to SBV as a function of body mass index (BMI). Adapted from (32).

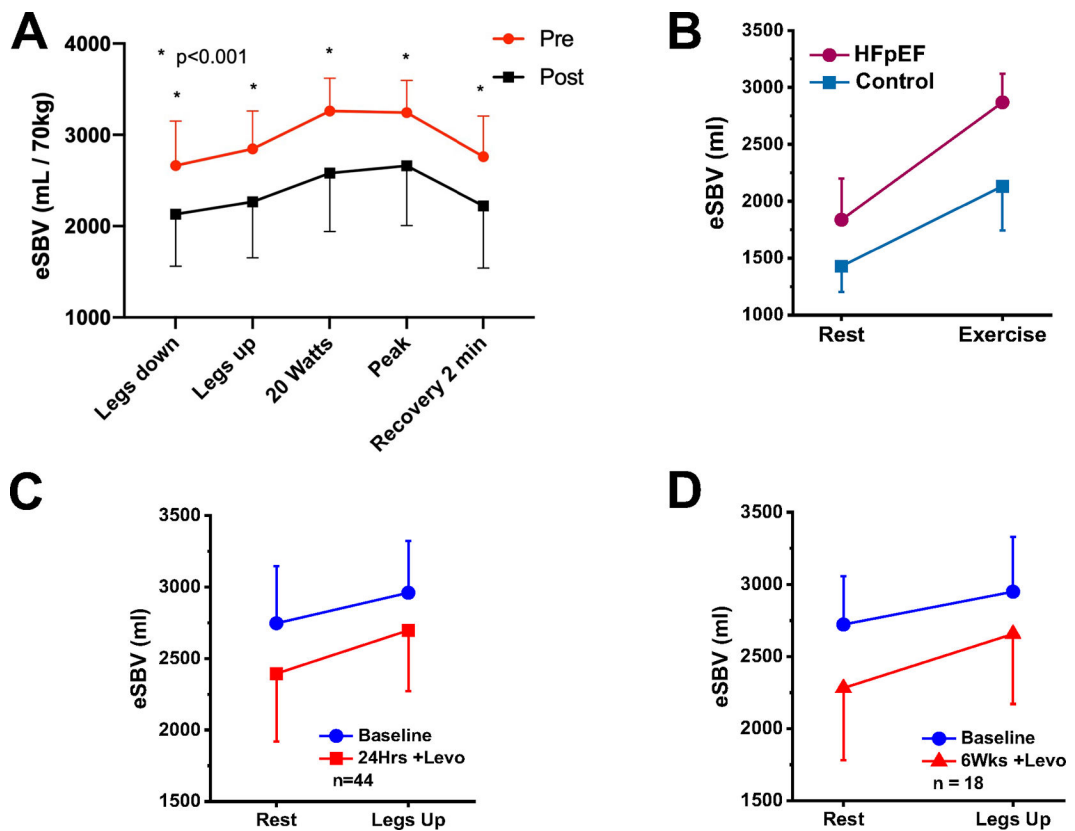
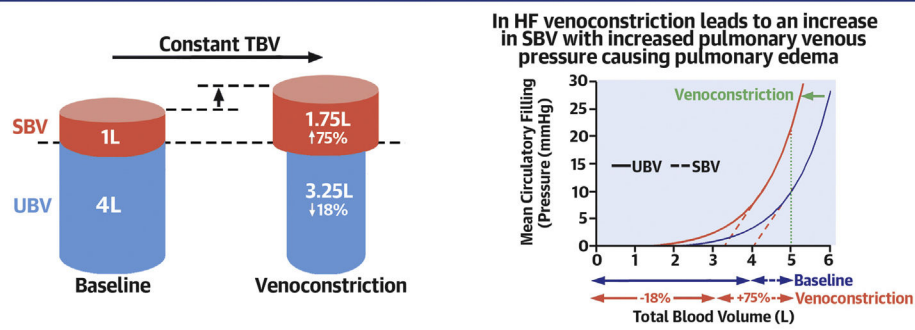


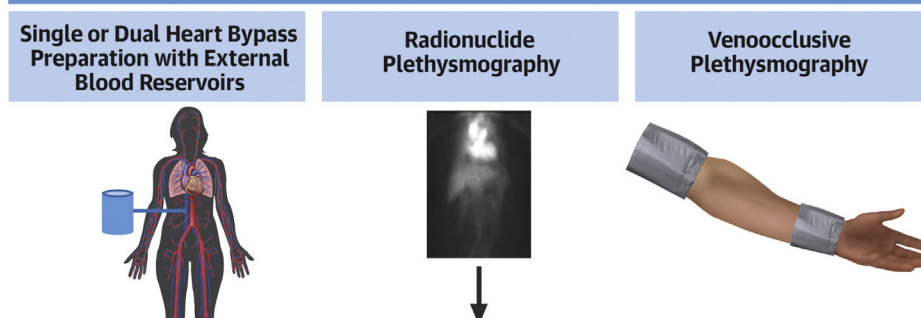
Figure 5. Impact of therapeutic interventions on estimated stressed blood volume.

A: Estimated stressed blood volume (eSBV) and effects of splanchnic nerve blockade in ambulatory heart failure. *indicates an adjusted $p < 0.001$ for a pairwise comparison with the pre-SNB value. Abbreviations: HF-heart failure, eSBV-estimated stressed blood volume, SNB-splanchnic nerve block. B: Impact of acute intravenous milrinone on estimated exercise hemodynamics in patients with heart failure and preserved ejection fraction (HFpEF). C. Effect of a 24 hours levosimendan infusion on eSBV at rest and with leg elevation. D. Effect of weekly levosimendan infusion on eSBV at rest and with leg elevation at 6 weeks.

Venous Tone and Stressed Blood Volume (SBV): Assessment and Effects in Heart Failure



Methods to Determine SBV



Disadvantages: Invasive, Complex, Repeated Measurements over Wide Range of Volumes, etc.

Modeling

- Allows for readily available assessment of SBV/UBV
- Assessment of individual variable contribution

Effects of Therapies Mediating Venodilatation and Reduction of SBV (GDMT, NO Donors, Splanchnic Nerve Modulation, Milrinone, Levosimendan)

Central Illustration: Venous Tone and Stressed Blood Volume.
 Venous tone and stressed blood volume regulation and measurement
 Abbreviations: SBV–stressed blood volume, UBV–unstressed blood volume