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JACC REVIEW TOPIC OF THE WEEK

Venous Tone and Stressed Blood Volume in Heart Failure

JACC Review Topic of the Week

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ABSTRACT

A number of pathologic processes contribute to the elevation in cardiac filling pressures in heart failure (HF), 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 and unstressed blood volume. We review how regulation of venous tone modifies the distribution of blood between these 2 functional compartments, the physical distribution of blood between the pulmonary and systemic circulations, and how these relate to the hemodynamic abnormalities observed in HF. Finally, we review recently applied methods for estimating stressed blood volume and how they are being applied to the results of clinical studies to provide new insights into resting and exercise hemodynamics and therapeutics for HF.
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Despite decades of investigation, the mechanisms responsible for elevated cardiac filling pressures in patients with heart failure (HF) with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) 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

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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 the reduction of stressed blood volume underlie the therapeutic effects of many of the drugs and devices used for the management of heart failure.

(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 the regulation of venous tone modifies the distribution of blood between these 2 functional compartments. Finally, we touch on recently developed methods for estimating SBV and how they are being applied to the 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 they also serve as a functional blood reservoir. Veins contain approximately 70% of the total blood volume (TBV) in comparison to only approximately 30% contained in arteries.[4] Furthermore, the highly vascularized organs of the splanchnic compartment, such as the 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 the key terms and definitions used throughout this review is outlined in Supplemental Table 1.

BASIC CONCEPTS

TBV of the body is functionally divided into 2 pools: UBV + SBV = TBV. Despite the central role of SBV and UBV in regulating cardiac performance, the direct measurement of these parameters requires invasive methods. Specifically, the 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, the 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 (eg, 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 and is converted to total plasma volume.[9,10] TBV is then obtained from the following: (total plasma volume) / (1 - hematocrit). Next, MCFP must be measured at >1 TBV, which is achieved by infusing or withdrawing a known quantity of blood (**Figures 1A and 1B**).

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. As shown in **Figure 1A**, MCFP does not rise until TBV is >2 L, and it does not exceed 2.5 mm Hg until TBV is nearly 4 L. Furthermore, once flow in the circulatory system begins, for a given MCFP, the central venous pressure (CVP) decreases, and the mean arterial pressure increases (**Figure 1C**).

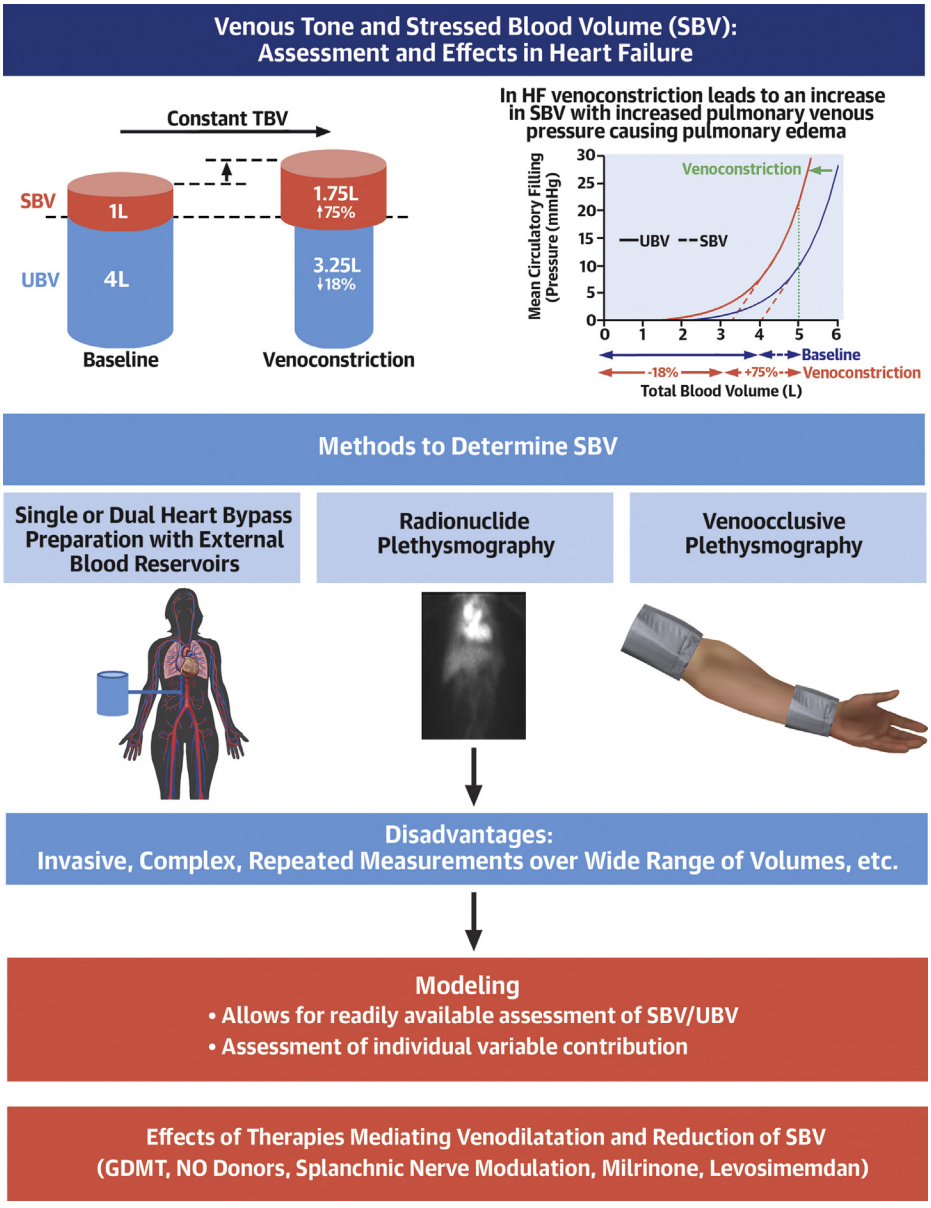
UBV is defined as the volume required to fill the vasculature before there is any significant rise of MCFP. In practice, the TBV-MCFP relationship is considered to be linear in the normal working range, so that UBV is estimated as the volume axis intercept extrapolated from the linear portion of the curve (**Figure 1A**). The portion of TBV in excess of UBV is the SBV. Under normal conditions, UBV is approximately four-fifths of the TBV, and only approximately one-fifth 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

ABBREVIATIONS AND ACRONYMS

CO = cardiac output
CVP = central venous pressure
eSBV = estimated stressed blood volume
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
LV = left ventricular
MCFP = mean circulatory filling pressure
PCWP = pulmonary capillary wedge pressure
RV = right ventricular
SBV = stressed blood volume
TBV = total blood volume
UBV = unstressed blood volume

CENTRAL ILLUSTRATION Venous Tone and Stressed Blood Volume



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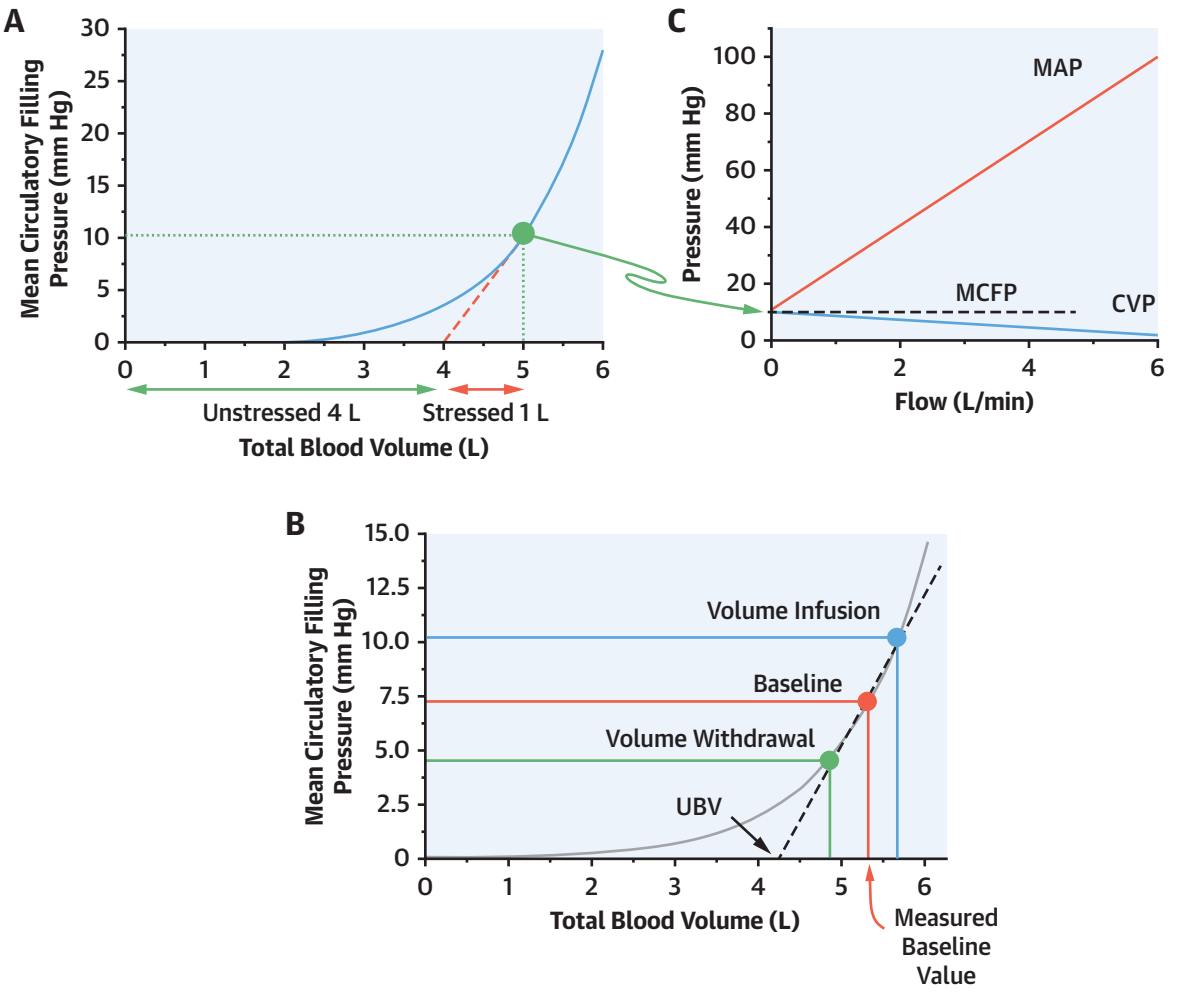
Venous tone and stressed blood volume regulation and measurement. SBV = stressed blood volume; GDMT = guideline-directed medical therapy; HF = heart failure; NO = nitric oxide; UBV = unstressed blood volume.

"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 (ie, 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 (ie, when flow equals 0) when CVP reaches MCFP. Because CO must equal venous return in steady-state conditions, the intersection between the Starling curve and the venous return curve defines the CVP

FIGURE 1 Interrelationship of Stressed and Unstressed Blood Volume



(A) The sum of UBV and stressed blood volume is the total blood volume. The relationship between MCFP and total blood volume is nonlinear. 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 blood volume 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, CVP decreases, and mean arterial pressure increases. CVP = central venous pressure; MAP = mean arterial pressure; MCFP = mean circulatory filling pressure; UBV = unstressed blood volume.

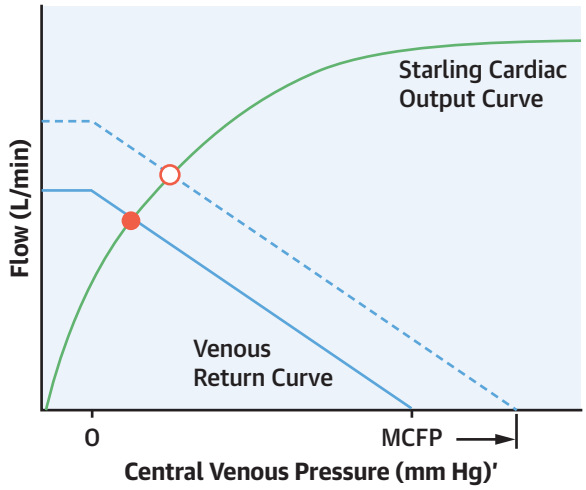
and CO for a given state (solid red dot in Figure 2). With this construct, it is easy to appreciate how MCFP is a key regulator of cardiac performance.

REGULATION OF SBV AND MCFP

With fixed vascular tone, MCFP and SBV trend in parallel (Figures 1A and 1B). For example, as blood is infused (increased TBV) or withdrawn (decreased TBV), SBV and MCFP increase and decrease, respectively, because 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 leftward toward lower volumes, with the steep portion of the curve shifting in a roughly parallel manner (Figure 3).[11] Thus, increased venous tone decreases UBV with a complementary increase of SBV, and compliance ($\Delta V/\Delta P$ in the typical working

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 MCFP. An increase of MCFP shifts the venous return curve rightward in a parallel manner and intersects the Starling curve at a higher value of cardiac output **(open red dot)**. MCFP = mean circulatory filling pressure.

range of pressures) remains relatively constant. The example of Figure 3 depicts an approximately 0.75-L shift of the MCFP-TBV relationship, which results in a 75% increase of SBV (from 1.00 to 1.75 L) but only an 18.8% reduction of UBV (from 4.00 to 3.25 L); this shift resulted in a large, 12.5-mm Hg 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 (eg, pharmacologic 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 0.5 mL 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 because of increased cardiac contractility, increased heart rate, and decreased systemic vascular resistance. However, 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] Because 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 approximately 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 approximately 38%.[13]

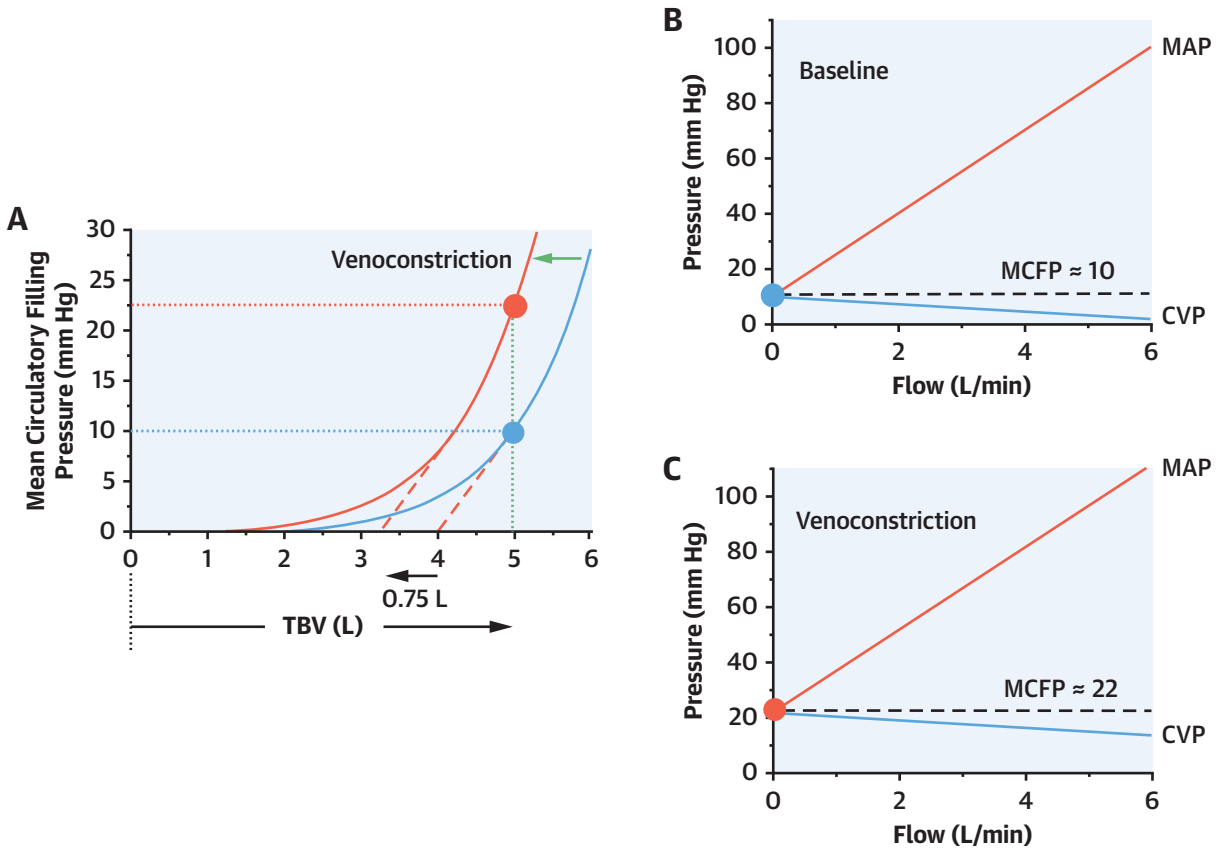
Catecholamines (endogenous or exogenous) act as the primary mediator of splanchnic vascular tone,[15] largely via alpha adrenergic receptors. Endogenous release of norepinephrine makes up >40% of the total body norepinephrine spillover.[16] Naturally, (patho) physiologic increases in catecholamine release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

In addition to pharmacologic and physiologic stimuli, preclinical and human studies have shown that direct stimulation of the splanchnic nerve increases SBV and increases CVP, pulmonary artery pressures, and CO.[17] The changes were shown to be driven by the translocation of blood from the splanchnic compartment, which occurred within seconds of stimulation onset and subsided within minutes after the stimulation ended. Although these regulatory mechanisms presumably 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 have 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) radiolabeled blood cell scintigraphy during volume infusion and withdrawal maneuvers. There are few

FIGURE 3 Effects of Venoconstriction on Stressed and Unstressed Blood Volume



(A) Effect of venoconstriction (eg, via sympathetic hyperactivation) on the relationship between MCFP and blood volume. A 0.75-L increase of stressed blood volume resulted in an increase of MCFP from 10-23 mm Hg. **(B)** The relationship between cardiac output, MAP, and CVP. When cardiac output is 0, MAP and CVP equilibrate at the MCFP. As cardiac output is increased, MAP increases and CVP decreases. **(C)** In the vasoconstricted case, despite constant TBV, MCFP is increased, and both MAP and CVP are higher at any given cardiac output compared to the baseline state. TBV = total blood volume; other abbreviations as in Figure 1.

comparable experiments in humans, largely because the required methods are highly invasive and/or cumbersome to execute.

Magder and De Varennes 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 mm Hg. Accordingly, the amount of blood that translocates to the external reservoir at the point when the filling pressure reaches 0 mm Hg is the SBV. SBV averaged 1,290 ± 296 mL, or 20.2 ± 1.0 mL/kg, which amounted to approximately 30% of predicted TBV. Similarly, Mass et al[21] measured MCFP, SBV, and vascular compliance in 15 intubated postoperative patients. These patients were subjected to a sequence of breath hold, volume infusions and withdrawals, and arm stop-flow maneuvers while CO and arterial and venous pressures were measured. Mass et al found that SBV was 1,265 ± 541 mL, an average of 28.5% of the predicted TBV, and that systemic vascular compliance was 0.97 ± 0.49 mL·mm Hg^{-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 vs 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 in humans[8,13] with and without cardiovascular disease, at rest and with exercise.[13] This technique is time consuming and technically challenging, and it is 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 have resulted in the lack of recent investigations into SBV. New approaches are reviewed in greater detail in Supplemental Figures 1 to 7.

EVIDENCE FOR THE ROLE OF SBV IN HF

Increased right ventricular (RV) and left ventricular (LV) filling pressures (ie, 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 the elevation in cardiac filling pressures in HF is abnormal LV and RV function leading to increased diastolic pressures, which transmit backward to the pulmonary and systemic venous circulation. Others relate filling pressure elevation to blood and plasma volume expansion attributable to renal sodium retention. However, accumulating evidence suggests these paradigms do not fully explain the hemodynamic alterations in HF, because 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]

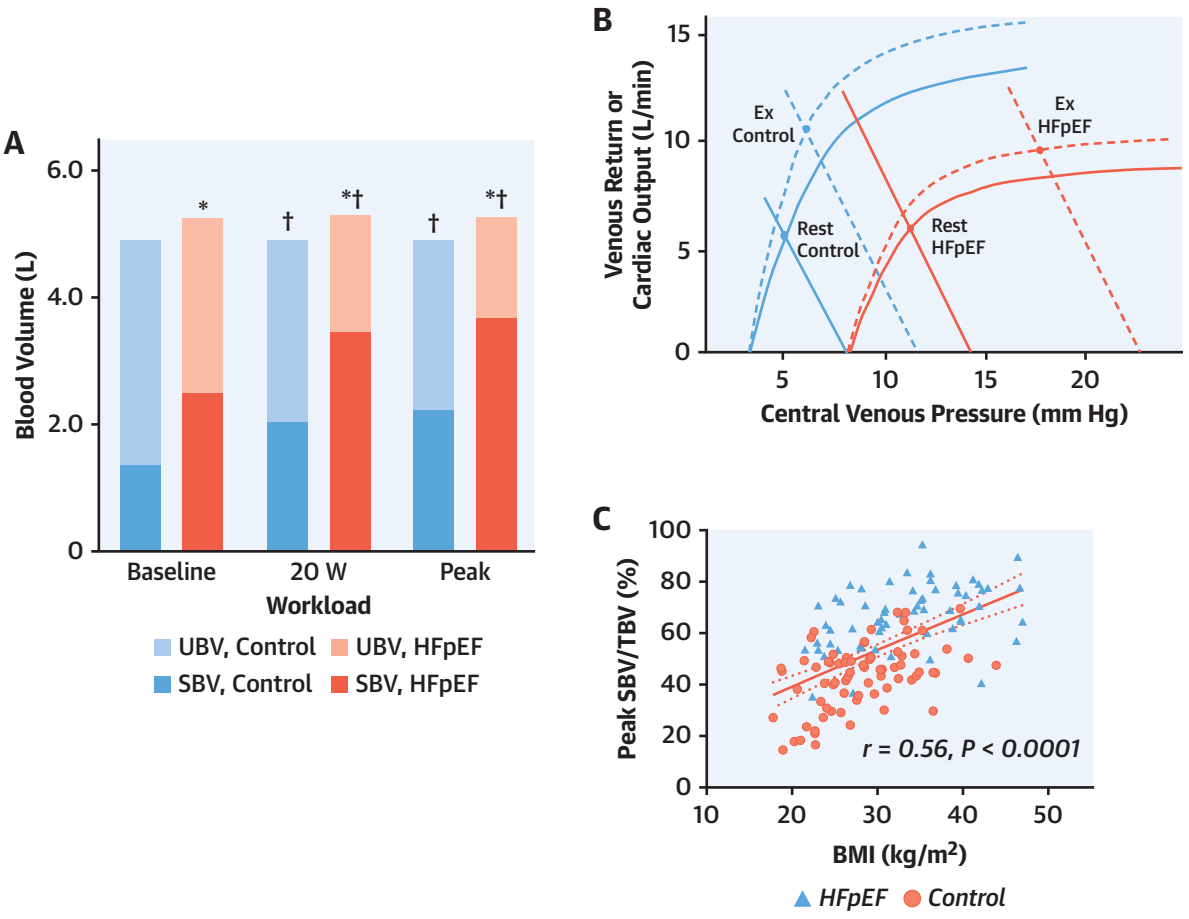
Investigations in animal models of acute and chronic HF confirm a reduction in venous capacity. Acute HF induced by cardiac ischemia in canines reduced splanchnic vascular volume by displacing the splanchnic venous pressure-volume relation to the left without a significant change in compliance (Supplemental Figure 9).[28] Redistribution of splanchnic volume occurred despite an increase in portal venous pressures, mostly because of active vasoconstriction rather than passive mechanisms of volume recruitment in the setting of neurohormonal hyperactivation.[29] Baroreflex-mediated venoconstriction accounted for approximately 80% of the increase in LV end-diastolic pressure, whereas LV dysfunction itself accounted for only 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 by approximately 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 control individuals, patients with HFpEF displayed an 11% higher TBV but a 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 control individuals. 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] However, obesity appears to have a similar impact on venous physiology and volume distribution in people with and without HF.

Finally, the role of SBV in cardiogenic shock has also been investigated with focus on the difference between shock attributable to acute myocardial infarction or to decompensated chronic HF.[33] Although SBV was similarly elevated in these 2 subgroups, patients with shock caused by decompensated chronic HF 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 or other factors related to specific HF phenotypes. Compared to control individuals, we have seen similar increases in eSBV in patients with HFrEF, HFpEF, and pulmonary hypertension-HFpEF (Supplemental Figure 8). More specifically, eSBV is greater in HF than in control individuals and increases by a greater amount during exercise than in

FIGURE 4 Stressed and Unstressed Volume in HFpEF, Obesity Phenotype



(A) Comparison of TBV, SBV, and UBV at rest and during exercise in control individuals 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 the percentage of blood ascribed to SBV as a function of BMI. Adapted with permission from Sorimachi et al.[32] BMI = body mass index; Ex = exercise; HFpEF = heart failure with preserved ejection fraction; SBV = stressed blood volume; TBV = total blood volume; UVB = unstressed blood volume.

control individuals. Interestingly, the percentage of TBV residing in the stressed component is greater in HF than in healthy individuals, and this does not seem to depend on the HF phenotype. Whether the influence of therapeutic venous tone modulation on hemodynamics or clinical outcomes will depend on the ejection fraction or other factors (eg, RV dysfunction with or without pulmonary hypertension) is unknown at this time.

SBV AS A TARGET IN HF

Despite a strong evidence base and the proposed importance of SBV several decades ago,[34] the role of venous tone and SBV as a potential target for therapeutics has remained speculative because of a lack of evidence until very recently. We now review different therapies whose actions appear, in part, to be mediated by venodilation and reductions of SBV.

GUIDELINE-DIRECTED MEDICAL THERAPY. Several pharmacologic agents that are components of guideline-directed medical therapy for HFrEF, such as sympatholytics (alpha/beta-blockers), renin-angiotensin-aldosterone system blockers (ie, angiotensin-converting enzyme inhibitors, aldosterone inhibitors, and so on), and sodium-glucose transporter-2 inhibitors, have proven benefits on neurohormonal balance. Furthermore, there is evidence that these drugs reduce (e)SBV in HF.[28,35] To what degree SBV changes contribute to the observed clinical benefits with these drugs is unclear.

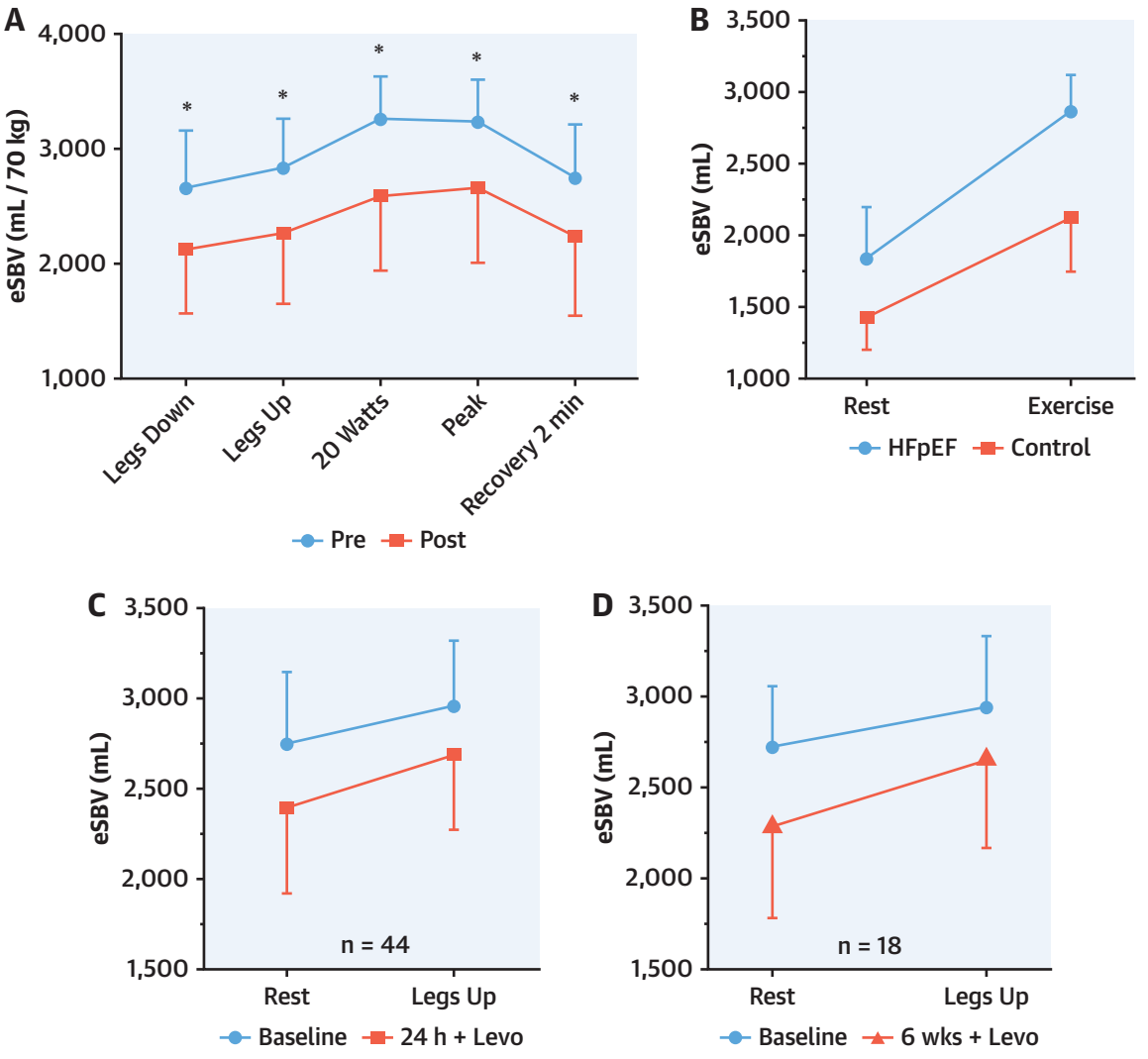
NITRIC OXIDE DONORS. Nitroglycerine and nitric oxide donors with preferential effects on venous capacity are well known to reduce cardiac filling pressures. As shown in the preclinical study depicted in Supplemental Figure 9A, this is at least partially mediated by venodilation. Indeed, drugs like nitroglycerin (primary venodilator) and nitroprusside (mixed arterial-venodilator) are commonly used to treat acute decompensated HF. Among Black patients with New York Heart Association functional 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.[36] A different nitrate, isosorbide mononitrate, failed to improve activity levels or 6-minute walk distance in HFpEF.[37] 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 attributable to ventricular-vascular stiffening.[2] Inorganic nitrite provides more targeted nitric oxide 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.[38] Although one trial did not demonstrate an improvement in exercise capacity with nitrite,[39] 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 of 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.[40] 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.[41-44] A reduction in resting and exercise-induced pressure elevations was primarily explained by a reduction in SBV following splanchnic nerve blockade (**Figure 5A**).[42] Similar effects on filling pressures have recently been reported with surgical ablation of the splanchnic nerve[45]; percutaneous approaches to achieving the same effects are currently under investigation.[46] Despite variable efficacy of pharmacologic vasodilator therapy in HFpEF, early experience with splanchnic nerve denervation has not uncovered such concerns in patients with common forms of HFpEF.[47] 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.[37,48]

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 pulmonary capillary wedge pressure (PCWP) while permitting greater exercise-induced increases of CO. Indeed, milrinone was shown to increase heart rate and 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 adenosine triphosphate-dependent potassium channels of venous smooth muscles, causing muscle relaxation.[51] Venodilatory effects of increased cyclic adenosine monophosphate and subsequent protein kinase A activation by milrinone should also be considered.

LEVOSIMENDAN. Similar to the study of milrinone described, levosimendan was studied in view of its pulmonary and systemic arterial vasodilator effects and inotropic effects (on the 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 dilatory effects and without increase in CO (**Figure 5C**). Similar results were obtained following 6 weekly levosimendan infusions, which, by echocardiography, also showed no detectible 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 attributable to a reduction in estimated SBV (**Figure 5D**).[53] Although not widely appreciated, levosimendan has venodilatory effects that are also mediated through the activation of ATP-dependent potassium channels.[54]

FIGURE 5 **Impact of Therapeutic Interventions on eSBV**



(A) eSBV and effects of splanchnic nerve blockade in ambulatory heart failure. *An adjusted $P < 0.001$ for a pairwise comparison with the pre-splanchnic nerve block value. **(B)** Impact of acute intravenous milrinone on estimated exercise hemodynamics in patients with HFpEF. **(C)** Effect of a 24-hour 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. eSBV = estimated stressed blood volume; HFpEF = heart failure and preserved ejection fraction; Levo = levosimendan.

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. Although direct and repeated measurements of SBV and venous tone are difficult in the clinical setting, especially during exercise or in response to therapies, analytic 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 drug- and device-based therapies on the venous system and the potential impact on SBV and UBV.

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APPENDIX For supplemental figures and a table, please see the online version of this paper.