

Role of Volume Redistribution in the Congestion of Heart Failure

Marat Fudim, MD; Adrian F. Hernandez, MD; G. Michael Felker, MD

In Heart Failure: Congestion Does Not Equal Volume Overload

Most of the current heart failure (HF) prevention or management programs assume that cardiovascular decompensations are primarily driven by volume overload that result in cardiopulmonary congestion. Subsequently, a centerpiece of HF therapies is decongestion of the cardiovascular system. Diuretic drug therapies are known to improve HF symptoms, but more aggressive volume removal strategies such as ultrafiltration have not been proven effective in HF.^{1,2} Current strategies for longitudinal HF management often focus on some form of postdischarge surveillance that targets outpatient weight and volume status trends.

Home or remote monitoring efforts commonly rely on daily weight measurements where an acute change in weight would result in a change in medical therapy. The sensitivity of such weight changes prior to hospitalizations were found to be very low (9%), whereas the specificity of such changes is high (97%).³ Notably, many patients do not experience a change in weight before a hospitalization for acute decompensated heart failure (ADHF). In fact, $\approx 50\%$ of patients gain an insignificant amount of weight (<2 pounds or <2 kg based on the study) in the days preceding a hospitalization.^{3,4} Similarly, in the post-hoc analysis of the ADHF patients in the ASCEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure), 26% of patients showed no weight loss (-1 kg \leq change <1 kg) and 8% actually experienced weight gain (≥ 1 kg) during the hospitalization.⁵ Importantly, in the evaluation of intracardiac filling pressures in an ambulatory setting, recent studies found that in ADHF, right- and left-sided pressures generally start to increase before any notable weight changes take place preceding an

admission (Figure 1).^{6,7} Thus, an increase in right and left heart filling pressures occurs in many cases in the absence of weight gain or total body volume increase.^{8,9} Supportive evidence is provided by body volume analysis using the iodohippurate sodium I 131-labeled human serum albumin indicator–dilution technique. Using this technology, studies found that patients admitted for HF in many cases (34%) were either normovolemic or hypovolemic¹⁰ with often normal plasma volume.¹¹ The heterogeneity of clinical presentation suggests the presence of a complementary mechanism to explain increased filling pressures and subsequent ADHF despite a lack of fluid retention. A potential contributing mechanism could be blood volume redistribution between different vascular compartments in the human body. We explore the physiology and rationale for this concept below.

Blood Distribution in the Human Body

Blood makes up about 5% of the water in the human body. Most of the blood is held by capacitance vessels, which are generally considered to be veins. Consequently, the venous system contains $\approx 70\%$ of total blood volume and is roughly 30 times more compliant to store blood than the arterial system.¹² The high vascular compliance allows veins to adapt to changes in the blood volume more easily. Blood vessels with a great compliance are able to store large amounts of blood and are called capacitance vessels. However, capacitance vessels do not simply store blood, but are actively involved in the regulation of the preload to the heart and cardiac output via active constrictions of the vessels (vascular capacitance). Interestingly, the venous system does not contribute to the vascular capacitance equally. The veins of the abdomen, otherwise referred to as splanchnic veins, are considerably more compliant than veins of the extremities and skin.¹³ Unlike many other organs, the visceral organs are marked by a relatively large volume of blood in comparison to the tissue volume. Because of the low vascular resistance and high capacitance, the splanchnic system receives $\approx 25\%$ of the cardiac output and the splanchnic veins contain anywhere from 20% to 50% of the total blood volume,^{14,15} with approximately the following distribution across splanchnic organs: liver 14%; spleen 12%; intestines and stomach about 10%.¹⁶

From the Division of Cardiology, Department of Internal Medicine, Duke University Hospital, Durham, NC (M.F., A.F.H., G.M.F.); Duke Cardiovascular Research Institute, Durham, NC (A.F.H., G.M.F.).

Correspondence to: Marat Fudim, MD, Division of Cardiology, Duke University, Durham, NC. E-mail: marat.fudim@duke.edu

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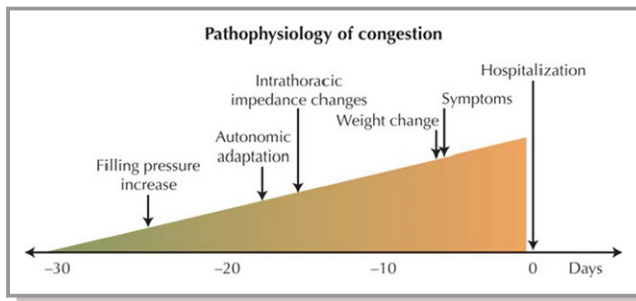


Figure 1. A simplified understanding of heart failure pathophysiology that includes changes in filling pressures using hemodynamic monitoring devices, autonomic adaptation measuring heart rate variability, and alterations in intrathoracic fluid content using thoracic impedance. Reproduced with permission from Adamson.⁷

Because of its unique properties, the splanchnic vascular compartment serves as the major blood reservoir (“venous reservoir” or “unstressed volume”) that can take up or release, actively and passively, the major part of any change in circulating blood volume. The “effective circulatory volume”

or “stressed volume” refers to a physiologically, but not anatomically separate compartment (Figure 2, Central Compartment illustration), which consists of blood that is present mainly in the arterial system and in nonsplanchnic venous vessels. The “effective circulatory volume” is one of the main determinants of preload to the heart.^{17,18}

Regulation of Splanchnic Blood Volume

Changes in the blood volume of venous capacitance vessels can be induced via a passive or active mechanism. Passive is the result of transmural pressure changes. Active is the result of a change in the level of contraction of vascular smooth muscle. An example of passive recruitment relevant to HF is “bendopnea,” which refers to a symptom of dyspnea when bending forward.¹⁹ One of the main determinants of active recruitment is the sympathetic nervous activity (SNA), which causes venoconstriction through epinephrine and norepinephrine, thereby reducing splanchnic capacitance and recruiting effective circulatory volume. Here cardiopulmonary

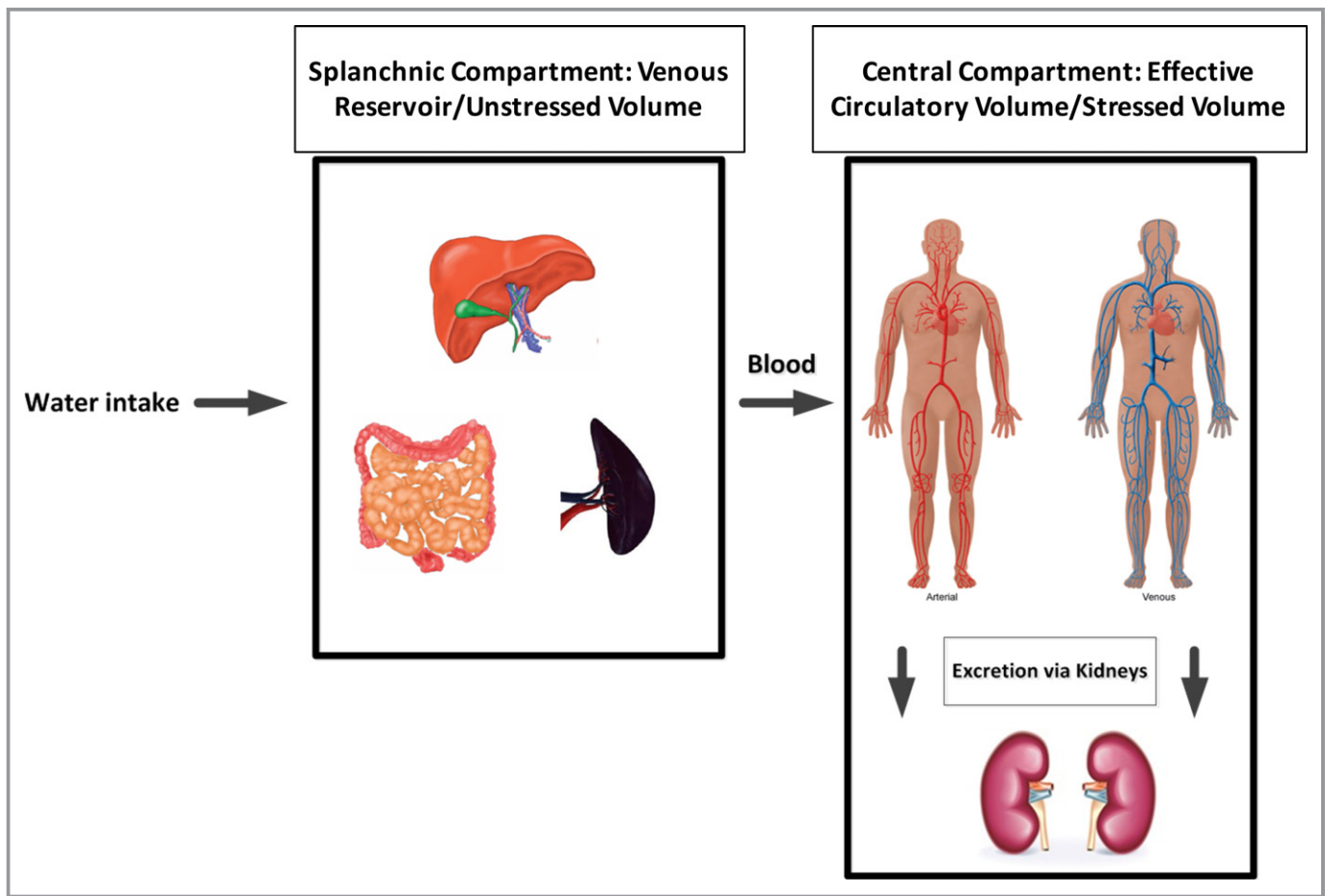


Figure 2. (Central Illustration): Illustrated is the 2-compartment model of the human blood pool. The splanchnic compartment (left) serves as the venous reservoir/unstressed volume. To the right is the central compartment that contributes to the effective circulation/stressed volume and regulates volume content via the kidneys.

and arterial baroreflexes appear to play a key role in regulation of SNA,²⁰ where a reduction in vascular or cardiac filling pressures is sensed by baroreceptors and as part of a reflex loop increases the sympathetic tone to recruit blood from the splanchnic and peripheral compartment to the heart. The strong interrelationship between venous vascular tone and the sympathetic nervous system can be explained by a large number of adrenergic receptors on the splanchnic vasculature,¹² with a 5 times higher density of adrenergic terminals on veins than arteries.²¹ The consequence is a more pronounced venous vasomotor response in the splanchnic system compared with other vascular regions.

The sympathetic nervous system controls the splanchnic compartment via branches from the sympathetic thoracic ganglia (T6 through T11) that converge in the celiac plexus and innervate the splanchnic vasculature.^{22,23} When the SNA decreases, the vascular compliance increases, and, subsequently, splanchnic reservoir volume increases. On the other hand, sympathoadrenal stimulation translocates blood volume from the splanchnic reservoir to the central circulation. In animal experiments, targeted splanchnic nerve stimulation can lead to a recruitment of up to 80% of the splanchnic volume, which, despite adrenalectomy,²² results in a blood shift of >20% of the total body blood volume.^{24,25} In a human case study, the stimulation of the nerves resulted in an increase in preload (50%) and cardiac output (200%) within 2 minutes.²⁶ Exercise, orthostasis, and hemorrhage are 3 classic examples of an increased demand or a sudden reduction in effective circulatory volume/preload that require rapid recruitment of the unstressed volume via splanchnic bed vasoconstriction.^{12,27}

Splanchnic Capacitance in HF

In HF, a state of neurohormonal activation, the splanchnic vascular compartment is at the center of volume dysregulation in acute and chronic HF. Current strategies of ADHF management and prevention have focused on the classical paradigm that salt and fluid retention is the culprit of intravascular fluid expansion and cardiac decompensation. However, the concept of disrupted intravascular fluid distribution might play a significant role in the process of chronic HF and/or ADHF even in the absence of increases of total body salt and water¹⁷ (Figure 3).

There appear to be 3 primary mechanisms by which the splanchnic vascular compartment contributes to the inappropriate volume handling in patients with HF:

1. Passive: Impaired storage capacity of the splanchnic vascular bed that reduces its ability to buffer extra fluid.
2. Active: Increases in sympathetic tone move fluid out of the splanchnic compartment into the effective circulation that

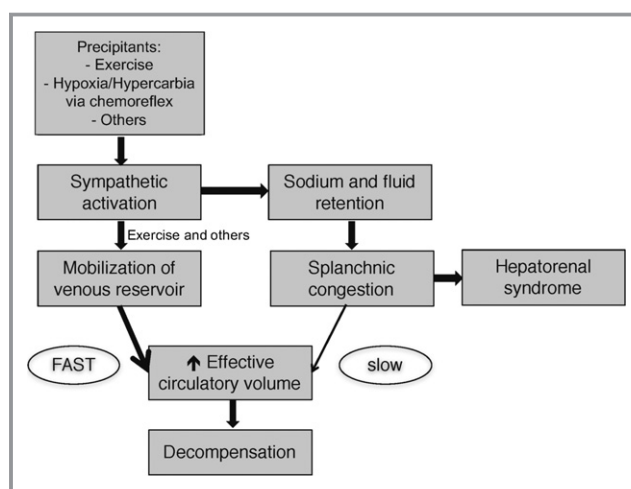


Figure 3. The proposed mechanism of progression from chronic compensated to acute heart failure is summarized in this figure. Sodium retention and fluid expansion result in an increase of unstressed volume and subsequent splanchnic congestion. This process is slow and takes days to weeks. The fast component often observed in the few days before decompensation is driven by autonomic imbalance with overactivity of the sympathetic nervous system. This results in an intercompartmental fluid shift into the central circulation with a subsequent accelerated increase in central filling pressures. Rapid fluid mobilization also occurs with activity and can explain exercise limitations experienced by heart failure patients. Adapted with permission from Fallick et al.¹⁷ Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer.

results in increased cardiac preload and extravascular edema.

3. Cardiorenal/Hepatorenal: Direct interactions between the splanchnic vascular compartment with the kidneys that result in inappropriate fluid retention.

Experimental Evidence

Theoretical modeling by Burkhoff and Tyberg in the 1990s suggested that acute left ventricular dysfunction with associated decrease in cardiac output and increase in peripheral vascular resistance alone cannot explain the rise in pulmonary vascular pressures.²⁸ Evidence suggested that an additional change in venous capacity with associated central volume distribution is a major contributor to the increase in pulmonary venous pressures.^{28–30} Next, the contribution of the splanchnic vascular bed to the diminished vascular capacitance in HF was tested in animal models of HF. Cardiac failure induced by rapid right ventricular pacing in dogs resulted in a profound reduction in total vascular capacitance or in other words a reduction in the body's blood storage capacity. Given a more or less stable blood volume over time,

the circulatory filling pressures increased.³¹ These profound effects on total vascular capacitance over several weeks caused enormous changes in cardiac loading conditions. Consequently, decompensation of the HF model following volume loading has been linked to a shift of blood from the splanchnic vascular compartment (unstressed volume) to the central compartment (stressed volume) rather than a primary increase in the stressed volume (for example, by an external fluid bolus).³²

Barnes and colleagues provide further evidence for the role of the splanchnic vascular bed as a major contributor to deleterious fluid shifts observed in ADHF. In this study, changes in cardiac output and mean right atrial pressure were evoked at different circulating blood volumes by stimulation of the splanchnic sympathetic nerves. With high circulating volumes, infusion of more volume did not consistently alter output or aortic pressure, but splanchnic nerve stimulation increased peripheral resistance and aortic pressure and commonly evoked a rise in left ventricular stroke volume.²² The study by Barnes and colleagues suggests that constriction of the splanchnic vasculature is more effective in raising cardiac filling pressures than external volume loading alone and thus emphasizes the potential contribution of the splanchnic vascular compartment to cardiac decompensation.

Clinical Evidence for Impaired Splanchnic Capacitance

It is important to note that, because of a lack of simple techniques to study the distribution of intravascular blood volume and measure regional sympathetic tone, there have not been definitive studies to prove the concept of intercompartmental fluid shifts as a mechanism of ADHF in humans.

In one of the few relevant studies, Rapaport and colleagues studied patients with HF and found that, on one side, the splanchnic blood flow was decreased and, on the other side, the splanchnic blood volume was actually elevated when compared with healthy controls.³³ These results are not surprising given high right-sided filling pressures and abdominal congestion, which in some patients is the predominant sign of right-sided HF. However, it can be speculated that the incremental splanchnic capacity (“remaining storage space”) in HF patients is limited when compared with healthy individuals (Figure 4).

While peripheral vascular capacitance is unchanged in HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) compared with controls,³⁴ the splanchnic vascular capacitance has not been explored in different HF states. The baroreflex normally restrains fluid from shifting away from the splanchnic reservoir by providing a sympatho-inhibitory influence to this vascular bed.³⁵ The decreased baroreflex function in HF³⁶ inhibits the body's

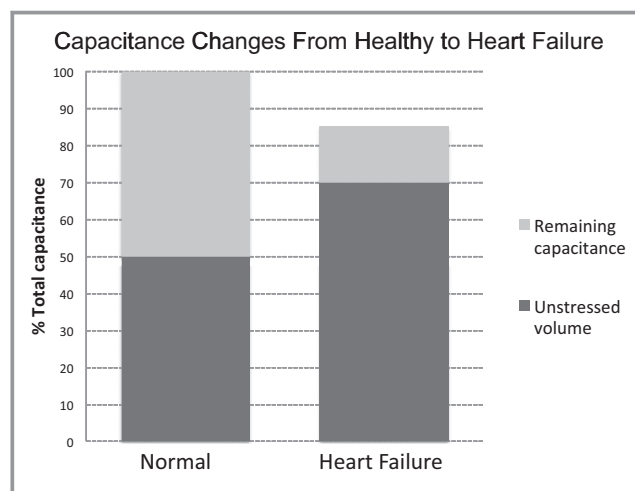


Figure 4. This graphic illustrates the hypothesized variation in splanchnic vascular compliance between healthy and disease states. Heart failure is signified by a decrease in total vascular capacitance of the splanchnic compartment. The remaining storage capacity of the splanchnic compartment depends on the body's volume-loading condition.

function to buffer eventual rises of effective circulatory volume in chronic, but especially acute disease states.³⁷ Logically, a reduced buffer function (“passive”) of the main storage compartment predisposes the body to decompensate (“overflow”) in the setting of total body fluid volume increase (oral or intravenous fluid intake).

The splanchnic vascular compartment may play a particularly important role in patients with HFpEF. Patients with HFpEF are especially sensitive to volume overload in the setting of exercise, and a striking increase in left atrial pressure often occurs transiently and is rapidly resolved by intravascular volume reduction.^{38,39} For example, a passive leg raise in HFpEF patients during a right heart catheterization causes significant increases in wedge pressures that only continue to climb with exercise.⁴⁰ Such increases in wedge pressure indicate the significance of even small changes in cardiac preload. Although the pathophysiology of HFpEF was initially thought to be caused by left ventricular diastolic dysfunction, recent studies have suggested more complex involvement of multiple abnormalities.⁴¹ The diagnosis of HFpEF in many patients at rest would be missed if the diagnosis merely relied on resting clinical, echocardiographic, or even invasive hemodynamic measurements.⁴² A subset of HFpEF patients experience significant exercise-related symptoms without evidence of congestion at rest, which suggests a noncompliant cardiopulmonary system as well as a potentially inappropriate volume distribution. With exercise-induced sympatho-activation, blood is redirected away from the splanchnic compartment and actively moved out of the abdomen into the central vascular compartment such as the heart and lungs.⁴³ Taken together, the active and passive

contribution of the splanchnic vascular compartment can significantly contribute to cardiopulmonary congestion with exercise.

Increased chemosensitivity to hypoxia and hypercarbia could be a mechanism of acute and chronic sympathetic stimulation with subsequent decrease in splanchnic vascular capacitance (Figure 1).⁴⁴ Patients with HF have an increased sensitivity of the peripheral chemoreceptors,^{45,46} leading to exaggerated responses in respiratory drive and sympathetically mediated blood pressure increases to hypoxic stimulation.^{47,48} Moreover, peripheral chemoreceptor hypersensitivity was found to be an independent predictor of mortality in patients with HF.⁴⁹ Activation of the chemoreflex drives activates SNA and further impairs baroreflex function in HF patients,^{50–52} which consequently drives the volume intolerance of patients with HF and especially HFpEF.⁵³ Patients with obstructive or central sleep apnea are at an especially high risk of chemoreceptor-mediated SNA increases, given frequent hypoxic and hypercarbic exposure.⁵⁴

Splanchnic Compartment: The Link Between HF and Cardiorenal Syndrome

Venous congestion has been found to be the most important hemodynamic factor driving worsening renal function in patients presenting with ADHF.^{55,56} A number of mechanisms have been implicated in its development: (1) Global activation of the sympathetic nervous system causes renal vasoconstriction; and (2) Worsening of glomerular filtration rate.⁵⁷ This effect, combined with the direct effects of elevated venous pressure on the kidney, leads to diuretic resistance and further elevation of filling pressures.⁵⁸

Moreover, there is evidence that chronic splanchnic congestion by itself can result in renal dysfunction and concomitant diuretic resistance. Local reflex systems such as stretch receptors in the venous wall of the portal vein function as a link between the splanchnic compartment and the kidneys. This local reflex may be involved in an excitatory response to the renal sympathetic nerves, leading to renal vasoconstriction during the portal vein distension (hepatorenal reflex).⁵⁹ The interaction between liver/spleen and kidneys is complex and implies the presence of osmo-, chemo-, and baroreceptors in the liver that sense specific stimuli and react to them through neural-mediated circuits that directly affect the kidneys and their function.^{60,61} Receptor activation results in an increase of sympathetic nervous tone and sodium and water absorption through the kidney. In our opinion, the potentially important role of this reflex for the mechanism of congestion in HF has not received adequate attention.

In animal studies, splanchnic congestion activates hepatic and splenic baroreceptors and, in response, increases the

sympathetic efferent nerve activity to the kidneys and cardiopulmonary region. Activation of the hepatic and splenic mechanoreceptors is associated with increases in renal vasoconstriction, renin release, and tubular sodium and water reabsorption or decreases in glomerular filtration rate and renal blood flow.⁶² Conversely, interruption of the afferent or efferent reflex arm abolishes the hepatorenal or splenorenal reflex,^{62,63} as seen with section of the anterior hepatic nerves, which eliminated the reflex increase in renal efferent nerve activity.

The hepatorenal/splenorenal becomes significant in 2 different forms of splanchnic congestion: HF and hepatorenal syndrome. In HF that is characterized by abdominal congestion and increased portal pressures, distension of splanchnic mechanoreceptors leads to the above-described activation of the hepatorenal and splenorenal reflex with inadvertent sodium and volume retention. Interruption of the reflex arc and offloading those receptors have been shown to eliminate this reflex. A percutaneous nerve block of the lumbar nerves in the clinical setting of hepatorenal syndrome improved renal function with increased urine output.⁶⁴ Notably, the pathology in liver cirrhosis is comparable in the component of portal hypertension and splanchnic congestion.

Diagnostic and Therapeutic Approaches

The complexity in studying volume shifts explains the lack of attention to the contribution of the splanchnic compartment and intercompartmental fluid shifts to the pathophysiology of HF. Biomarkers such as natriuretic peptides and routine physical exam evaluation using vascular congestion (jugular venous distension), extravascular volume (lower extremity edema and ascites), and change in body weight correlate poorly with total body volume state^{65–67} and provide little information on the distribution of intravascular volume between the central and splanchnic vascular compartment. Potentially useful diagnostic tools to measure intercompartmental fluid shifts include radionuclide plethysmography, which allows measurements of the splanchnic blood pool over time.⁶⁸ However, the technical requirements of this procedure make it unsuitable for clinical practice. Furthermore, bioimpedance⁶⁹ and bioelectrance⁷⁰ can provide a less complicated, but yet less accurate estimation of intercompartmental fluid shifts. The bioimpedance and bioelectrance technologies are based on the assumption that human tissue is an inhomogeneous electrical conductor. The properties of electrical current traveling through tissue differ with changes in blood/fluid content; however, the technologies are limited by their inability to discriminate intravascular from extravascular volume.

A very simple diagnostic tool to assess splanchnic vascular capacitance is orthostatic stress. The key component that

leads to a drop in preload with orthostasis is a passive blood volume shift into the veins of the abdomen and pelvis more so than peripheral blood vessels (arms and legs).⁷¹ The hemodynamic response to tilt-table testing in chronic HF is atypical; that is, there was no significant peripheral pooling in the upright posture.⁷² Better tolerance of orthostatic stress in HF patients can be explained by higher filling volumes and decreased splanchnic capacity, which prevents a drop in cardiac preload. In HF patients, decongestion with diuretics⁷³ or blood removal⁷⁴ results in orthostatic hypotension they previously did not have. Simplified, this means the presence of orthostatic symptoms in a patient with HF suggests normal to high splanchnic (and peripheral) capacitance, whereas a lack of orthostatic symptoms implies the opposite.

A comprehensive approach to the treatment of HF should include a careful assessment of volume status. As we have outlined, ADHF can, in a significant amount of cases, be a problem of volume redistribution instead or in addition to external volume. The challenge that arises is how to reverse the volume shift and direct volume into the splanchnic compartment away from the central compartment and/or decongest both compartments without removing too much volume, thus risking renal dysfunction (Figure 5).

Medications to Increase Splanchnic Vascular Capacitance

Drugs such as angiotensin-converting enzyme inhibitors and nitrates have an established role in the treatment of HFrEF. Interestingly, both agents were shown to increase splanchnic capacitance.^{75,76} Cody and colleagues showed that acute and chronic captopril challenge reestablished orthostatic symptoms in HF with a tilt test.⁷⁷ Captopril caused a drop in preload, pulmonary pressures, wedge pressure, and cardiac index. These results could not be explained by a change in systemic vascular resistance (as it actually went up), but likely were caused by an acute reduction in preload.

It can be speculated that some of the observed effects of angiotensin-converting enzyme inhibitors, nitrates, and ganglionic blockers such as trimethaphan⁷⁸ could stem from an increase in vascular capacitance with a redistribution of blood into the venous reservoir, thereby lowering the left ventricular end diastolic pressure. These effects could be acute or chronic. However, arterial vasodilatory drugs such as hydralazine did not show an effect on splanchnic vascular capacitance.⁷⁶ To what extent the splanchnic vasodilatory mechanism of a drug reflects its effect on HF morbidity and mortality requires further evaluation. Splanchnic vasodilation could also be achieved via a reduction in sympathetic nervous tone with drugs such as the adrenergic receptor blockers. β -Blockers such as metoprolol and carvedilol have an established benefit in HFrEF patients,⁷⁹ but it remains unclear

whether global reduction of SNA using adrenergic receptor blockers is sufficient to modify the local SNA in the splanchnic compartment and favorably modify the vascular capacitance. Systemic as opposed to targeted sympathetic blockade might result in the expected splanchnic vasodilatory effect at a potentially high cost of systemic blood pressure reduction and exaggerated negative inotropy, which have been linked to poor clinical outcomes in patients with HF.^{80,81}

Autonomic Modulation

Autonomic modulation presents an attractive option for the treatment of the described pathomechanism for HF and cardiorenal syndrome. Conceptually, the reduction of splanchnic sympathetic tone may result in an increase in splanchnic vascular capacitance. For patients with HFpEF, more so than HFrEF, an increase in vascular capacitance could improve dyspnea and capacity to exercise. Furthermore, the expected benefits of unloading the central venous and arterial system could lessen the incidence and severity of acute decompensations. This concept has been explored in healthy mongrel dogs, where abdominal sympathetic denervation via the celiac plexus increased splanchnic capacitance.⁸² Unfortunately, human and animal data are not available for the HF space. Thus, this area holds interesting promise, but requires significantly more work.

Besides a direct modulation of the splanchnic vascular tone, targeted therapies could modify the detrimental influence of the chemoreflex and the impaired baroreflex on the autonomic tone and their role as triggers for HF decompensation. Therapies targeting the carotid body (location of the peripheral chemoreflex)⁸³ and the baroreflex⁸⁴ are currently under investigation with some initially promising results on outcomes in HF patients. Furthermore, the experimental therapy for renal denervation targets the reflex loops between the kidneys and the central nervous system that appear to contribute to the autonomic imbalance. Despite some early positive results, the intervention failed to meet the set expectations.^{85,86} Nevertheless, the evaluation of autonomic modulation is ongoing and holds promise for the treatment of hepatorenal and splenorenal syndrome in the HF setting.

Volume Reduction Therapies

Since the splanchnic and central vascular compartments are connected, selective offloading is not possible. Despite a lack of clear benefit of ultrafiltration over diuretic strategies, ultrafiltration has the ability to provide quicker and higher volume decongestion.^{1,2,87} Ultrafiltration removes intravascular volume and can provide rapid and partial decompression of the renal and splanchnic vasculature,⁸⁸ which in return

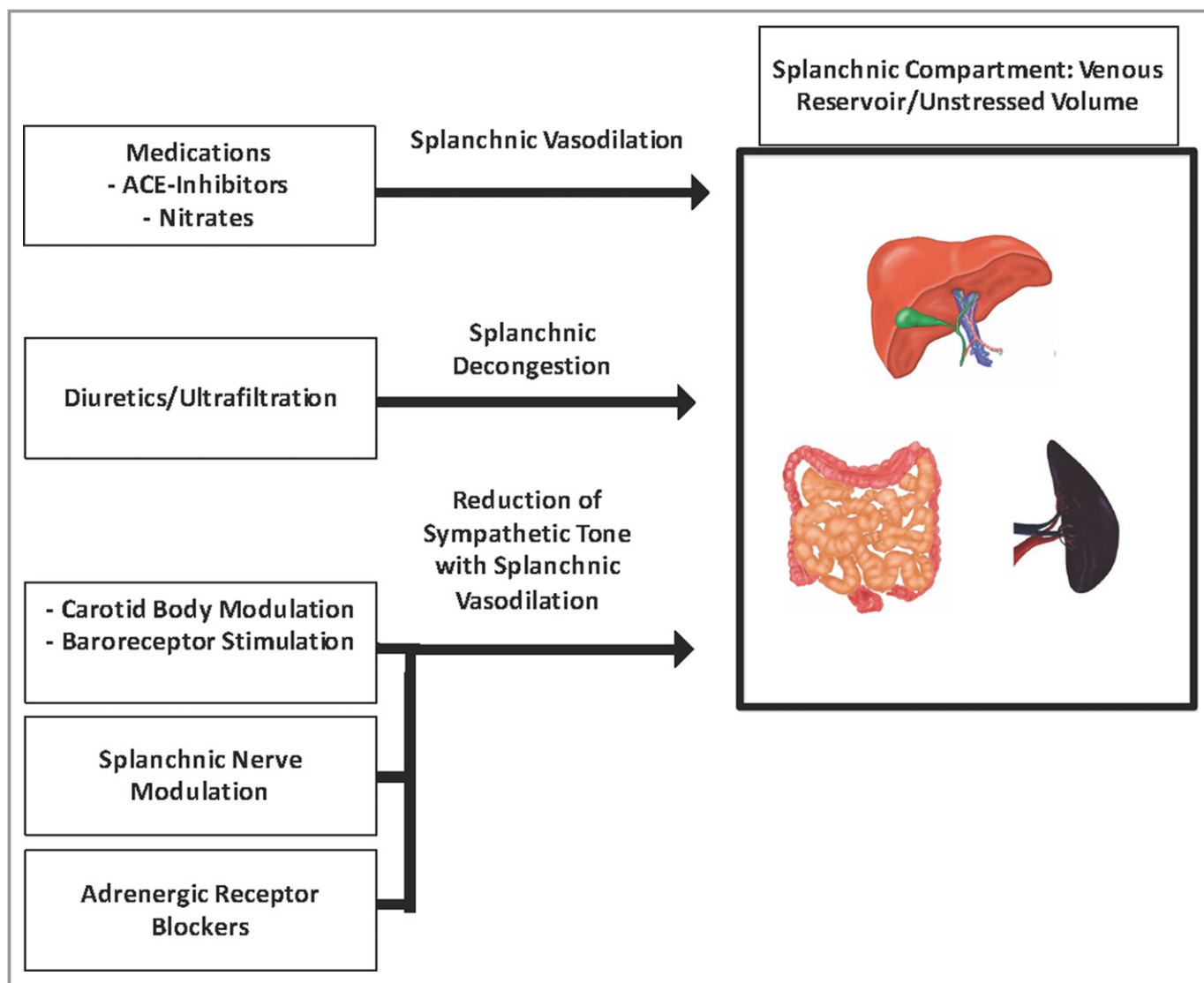


Figure 5. In heart failure, the splanchnic vascular compartment has a decreased vascular storage capacitance. Illustrated are different therapeutic approaches to increase the splanchnic vascular capacitance and allow blood redistribution into the splanchnic compartment. ACE indicates angiotensin-converting enzyme.

offloads portal mechanoreceptors and inhibits the hepatorenal and splenorenal reflex.⁸⁹ The positive effect of rapid intravascular decongestion was demonstrated in a study by Marenzi and colleagues,⁹⁰ where ultrafiltration produced a 5-fold increase in diuresis in ADHF admission with oliguria. This increase could occur even though the output of the heart remained unchanged. In contrast, patients without congestion but with normal urine output and controls did not respond with comparable improvement in diuresis. The UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) and AVOID-HF (Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure) trials showed that ultrafiltration resulted in more weight, net fluid loss, and favorable outcomes compared with usual care.^{2,87} Because of

concerns about a possible renal impairment from the CARRESS (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trial, this therapy is currently only the second choice.¹ We speculate that the reported association of ultrafiltration with renal side effects is attributable to overaggressive volume removal. Ultrafiltration is possibly more harmful in cases where volume shift is the predominant cause of decompensation rather than an increase in total body fluid volume, since the forceful removal of intravascular volume can lead to vascular underfilling with insufficient time for re-equilibration with the extravascular space. This question requires further exploration in future studies.

While our review focuses on the role of intravascular fluid compartments for HF, the extravascular volume of the abdominal cavity is of direct relevance to the discussed

topic. A large amount of ascites is uncommonly encountered in patients with HF but suggests a high portal pressure. Increased intra-abdominal pressure (intra-abdominal pressure ≥ 12 mm Hg) has been clearly associated with organ dysfunction, especially renal dysfunction⁹¹ and conceivably results in an increased splanchnic vascular tone with stimulation of hepatic and splenic baroreceptors that play an integral role in the hepatorenal reflex. Mullens and colleagues demonstrated that HF-impaired renal function is observed with only small rises in intra-abdominal pressure, in the range of 8 to 12 mm Hg.⁹² In contrast, a reduction of ascites via decongestive therapy (possibly also paracentesis) improves renal function,^{88,92} suggesting that decongestive therapies need to target not only the intravascular but also the extravascular fluid compartment.

Conclusions

In this review we discussed the concept of a compartment model of intravascular volume distribution and its role in chronic and acute HF. Special attention is paid to the splanchnic vascular compartment and its regulation by the autonomic nervous system. We describe how a decreased vascular capacitance and intercompartmental fluid shift can predispose HF exacerbations regardless of the total body fluid status. This concept is complementary to the established concept of sodium and fluid retention as the main drivers of cardiovascular decompensation. Future studies should focus on confirming the proposed physiology in HF patients and try to identify patients at risk for intercompartmental volume redistribution as a leading component of HF decompensation. Finally, there is a need for more clinically relevant and applicable methods to measure fluid distribution so it can be readily applied in the clinical and research arena.

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