Sympathetically Mediated Changes in Capacitance
Redistribution of the Venous Reservoir as a Cause of Decompensation

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“...to be accepted as a paradigm, a theory must seem better than its competitors, but it need not, and in fact never does, explain all the facts with which it can be confronted.”
—Thomas Kuhn, *The Structure of Scientific Revolutions*

**Heard on Rounds**
“A 57-year-old patient with a history of heart failure states that she began experiencing worsening shortness of breath 4 days prior to admission, with lower extremity edema developing 1 day prior to admission. She is compliant with her medications, though has had similar admissions previously. She states that her weight at home increased by “a couple of pounds” 2 days ago and that she increased her diuretic dose but her symptoms worsened. She says that she generally adheres to her low salt diet, but admits to eating pretzels 5 days ago. The physical examination showed BP 136/84, HR 94, weight 3 lbs above baseline, elevated JVP, basilar rales, and 1+ pedal edema.”

As the intern finishes the presentation, the Senior expresses surprise that the patient’s weight had increased only 3 pounds, and comments about salt and volume overload leading to acute decompensated heart failure (ADHF). The Attending adds that recent data reveal that many patients presenting with ADHF have minimal or no weight gain, but that there is no clear mechanism to explain this phenomenon. They set in place plans for diuresis, increasing vasodilators, and further patient education.

On the surface, there is nothing remarkable about this case, and the usual approaches to treat this entity have remained remarkably consistent since the advent of loop diuretics over 50 years ago: salt restriction, patient education, uptitration of medications if not already at optimal doses, and diuresis. However, approximately 1 in 4 such patients are readmitted to the hospital within 30 days,1 and the disease continues to progress. It is clear that removing fluid often does not create a long-lasting respite, though unclear exactly why. In this article, we present a novel hypothesis to explain the phenomenon of ADHF without weight gain and why these mechanisms also may be operative in many patients who do present with weight gain.

**Current Paradigm of ADHF**
The American College of Cardiology/American Heart Association (ACC/AHA) guidelines cite 3 profiles of patients presenting with ADHF: volume overload, low cardiac output, and a combination of fluid overload and shock.2 The guidelines further recommend that “…the following common potential precipitating factors for acute HF be identified as recognition of these comorbidities is critical to guide therapy: acute coronary syndromes/coronary ischemia, severe hypertension, atrial and ventricular arrhythmias, infections, pulmonary emboli, renal failure, and medical or dietary noncompliance.” However, when no evidence for these precipitants are found, there appears to be little else to explain the decompensation, so patient noncompliance often ends up being invoked even in the absence of any hard evidence. We offer a potential (and we believe likely) explanation for the phenomenon of decompensation in the absence of weight gain: we hypothesize that an autonomically mediated shift between total extracellular fluid volume and effective circulating blood volume explains the development of congestion in many patients with decompensated HF.

**Increased Volume Is Neither Necessary Nor Sufficient to Cause Congestion**
Early stages of congestion in ADHF often occur in the absence of significant changes in body weight.3 Chaudhry showed that a weight gain of 2 pounds or more occurs in only 46% of patients presenting with ADHF.4 Multiple studies have been conducted using a variety of implantable hemodynamic monitors in patients with HF to measure changes in cardiac filling pressures in the outpatient setting, including COMPASS-HF, HOMEOSTASIS, and most recently, the CHAMPION trial.5–7 A consistent finding from these trials is that weight gain does not occur in many patients before a HF-related event,8 and when it occurs, does so after changes in filling pressure rather than preceding it, as would be expected if increases in total body sodium and water were the driving force.

In COMPASS-HF, 33% of patients had clinical heart failure with minimal or no change in weight, clearly arguing against the concept that sodium and water retention caused the increases in filling pressure. This suggests instead that shifts between total extracellular fluid volume and effective circulating volume underlie the development of ADHF. Despite the absence of changes in body weight, pulmonary arterial pressures were noted...
to begin rising an average of 3 weeks before an HF-related event. The pulmonary artery pressure increased even more rapidly in the week before such an event in patients with both preserved and reduced systolic function HF.8

In the CHAMPION trial, monitoring of pulmonary pressures and acting on elevations of pressure resulted in significantly fewer hospitalizations, an effect that was attributable to clinical management informed by changes in filling pressures. Although weight changes were not reported, the authors did note that changes in outpatient medications in the treatment group occurred at a higher rate over the 6-month study period compared with the control group. Length of stay for hospitalization in the treatment group was also lower, suggesting that treating changes in pulmonary pressures before the traditional predictors of dyspnea, leg swelling, and weight gain moderates the magnitude of an episode of decompensation.

In addition to the fact that total body volume changes often do not occur before clinical congestion, dyspnea is a useful but insensitive metric of pulmonary pressures or volume status. The UNLOAD trial showed that ultrafiltration resulted in more weight and net fluid loss compared with usual care.9 Although dyspnea at 48 hours improved in most patients regardless of treatment group, no correlation was identified between dyspnea score and either weight change or net fluid loss. A similar dissociation was seen in EVEREST, in which tolvaptan administration resulted in more weight loss in patients with ADHF but no difference in dyspnea,10 though a post hoc analysis suggested that tolvaptan was associated with a greater improvement in dyspnea compared with placebo at 12 hours and an association between the improvement in dyspnea with the absolute amount of weight loss in the first 24 hours.11 Finally, intrathoracic impedance was recently found to be more sensitive than weight gain in predicting heart failure events.12 These findings illustrate the complexity in correlating symptoms, filling pressures, and redistribution of intravascular volume, as well as potentially the multiplicity of mechanisms which may contribute. However, they do suggest that changes in total volume are not the only important factor in dyspnea improvement. Indeed, a long history of titration of treatments targeted against elevated filling pressures grew for the failure of symptoms (besides orthopnea13) or physical examination to correlate with filling pressure. It should be noted that there was little a priori expectation that this should be the case, as the symptom of dyspnea captures changes in the work of breathing due to changes in airway resistance and lung stiffness, interstitial and alveolar water content, dynamic changes in dead space, and sympathetically mediated changes in ventilation.14 Thus, dyspnea is not a dependable metric of circulating blood volume.

The Venous System and Its Regulation

Both veins and arteries are innervated heavily with adrenergic receptors. On the arterial side, this occurs predominantly at the level of the resistance vessels. It is well known that the sympathetic nervous system (SNS) plays a major role in determining systemic vascular resistance and in mediating short-term changes of vascular resistance, predominantly through activation and deactivation of cardiopulmonary and arterial baroreflexes,15,16 as well as through changes in circulating norepinephrine. Less well appreciated is the critical role played by autonomic regulatory mechanisms governing the venous system, particularly venous compliance. The venous system contains approximately 70% of total blood volume and is roughly 30 times more compliant than the arterial system.17 Splanchnic veins are considerably more compliant than veins of the extremities. Large numbers of α1 and α2 adrenergic receptors are present in splanchnic veins, making them highly sensitive to stimulation by the SNS.17 Compared with arteries, veins contain more than 5 times the density of adrenergic terminals, which are distributed throughout the media as opposed to being localized around the adventitial medial border in arteries.18 These anatomic findings translate to physiological responses, since studies have shown that the magnitude of vasomotor responses induced by nerve stimulation is greater in veins compared with arteries.19 The implication of this is that for a given sympathetic stimulus, the veins respond to a much greater degree than the arteries, and this response is predominantly a reduction in capacitance.

Splanchnic veins and venules account for most of the active capacitance responses in the circulation. The SNS regulates both the resistance and compliance of these vessels. In an elegant study examining the role of the SNS and splanchnic venous capacitance in rats with salt-sensitive hypertension, King randomized rats to either celiac ganglionectomy (to cause splanchnic sympathetic denervation) or sham surgery in rats fed a high salt diet and infused for 14 days with angiotensin II.20 Increased capacitance caused by the inhibition of sympathetic outflow to the veins from the celiac ganglionectomy prevented the angiotensin II–induced hypertension. Mean circulatory filling pressure increased in the sham salt-fed rats, an effect that was nullified in the angiotensin II infused salt-fed rats after celiac ganglionectomy. Thus, prevention of sympathetic activation of the splanchnic venous circulation prevented the hypertension mediated by fluid shifts from the venous reservoir to the conduit veins and arterial system.

Distribution of Blood Volume: Venous Reservoir Versus Effective Circulatory Volume

The term “venous reservoir” (or “unstressed volume”21) refers to the blood volume that resides mainly in the splanchnic vessels that does not contribute to the effective circulating volume but can be recruited with activation of the SNS (including reflexes), drugs, or hormones.22 The term “effective circulatory volume” (or “stressed volume”21) refers to blood that is present mainly in the arterial system and in nonsplanchnic venous vessels and is one of the main determinants of venous return. It is approximately equal to the difference between total blood volume in the body minus volume in the venous reservoir.

A New Mechanism for Decompensation: Inability of the Venous Reservoir to Buffer Changes in Effective Circulatory Volume

1. Recruitment of Venous Reservoir Leading to Decompensation in Left Ventricular Dysfunction

In the normal resting state, venous compliance allows for distribution of volume that optimizes cardiac and renal function. A decrease in capacitance of the venous reservoir corresponds to an almost instantaneous increased preload in the stimulated state. In patients with cardiac dysfunction, this
sympathetically stimulated reduction in venous capacitance would serve to shift volume out of the splanchnic vessels and increase effective circulating blood volume, leading to increases in preload in the absence of any changes in total circulating blood volume or total body (intracellular plus extracellular) volume. This theoretical framework is supported by a set of classic experiments dating back to the 1960s in which Guyton showed that reductions in vascular capacitance could amplify significantly the hemodynamic effects of sodium and water retention.23,24 Burkhoff and Tyberg first proposed the idea that volume shifts might be important in acute HF.25 In a computer model of time-varying elastance, they showed that pulmonary venous pressures do not increase substantially in the presence of simulated left ventricular dysfunction unless venous capacitance decreases, probably mediated by the SNS. A more recent computational model challenged their work and instead suggested that acute left ventricular dysfunction can lead to elevated pulmonary pressures even without volume shifts, though in the setting of a higher initial effective circulatory volume.26

Peripheral venous capacitance appears to be normal in HF27,28 and amplified by bradykinin in patients receiving angiotensin-converting enzyme inhibitors.29 However, less is known about the function of splanchnic veins in HF, which account for a much greater proportion of the total capacitance in the venous system and therefore contribute more importantly to intravascular volume shifts.

2. Evidence for the Dysfunctional Venous Reservoir
Sympathetic activation of the splanchnic capacitance veins rapidly increases effective circulatory volume by translocating the splanchnic venous reservoir to the effective circulatory volume. This change in distribution of volume can occur rapidly and dramatically, “auto-transfusing” up to 800 mL of blood within seconds.21 We postulate that sympathetic activation and splanchnic venous alterations can alone explain the seeming paradox of congestion without weight gain. This new approach assigns sympathetic activation of the venous capacitance vessels in the setting of left ventricular dysfunction as the major driving source of elevated filling pressures.

Adamson and colleagues30 evaluated changes in heart rate variability (an indication of parasympathetic and sympathetic control) through an implanted monitor in patients with HF. They found that reduced heart rate variability was a leading indicator of destabilization and that it occurred a median of 16 days before hospitalization for ADHF at around the same time as pulmonary pressures begin to rise. This reduction in heart rate variability (and presumably parasympathetic tone) suggests a concomitant increase in sympathetic activity associated with the increases in filling pressures. Although increases in cardiac filling pressures normally would tend to inhibit sympathetic outflow and return the effective circulatory volume to a healthier preload, these inhibitory mechanisms do not function normally in HF.32–36 allowing sympathetic activation to progress unchecked. This creates a chronic state of increased sympathetic drive leading to sustained elevations in filling pressures. Elevations in pulmonary pressures may even promote this sympato-excitatory state through activation of pulmonary afferents.37

In a recent analysis of the COMPASS-HF study, Zile and colleagues found that estimated pulmonary artery diastolic pressure fluctuated markedly during the day.38 These fluctuations appear to be sympathetically mediated because they can occur in response to assumption of upright posture or exercise, and many of these do not lead to HF-related events. We propose that when the fluctuations occur in the context of a compliant venous reservoir, they do not result in an HF-related event. However, when an acute fluctuation occurs in the setting of a venous reservoir that is already compromised by progressive sympathoexcitation, it can lead to the development of an acute HF event.

These mechanisms are depicted in Figure 1. A relatively minor precipitant causes a small increase in sympathetic activity. This increase in SNS activity causes a reduction in venous compliance, which leads to mobilization of fluid from the venous capacitance vessels to the effective circulatory volume, culminating in the syndrome of congestion. Three points are particularly important about these pathways. First, these are self-amplifying mechanisms, because (as noted above) reductions in vascular capacitance amplify significantly the hemodynamic effects of sodium and water retention. Second, multiple iterations along this pathway occur completely in the absence of any change in weight. Third, sympatho-excitation promotes a state of sodium retention that contributes to the decompensation.

The more conventional concepts leading to congestion are shown on the right, with renal and dietary mechanisms leading to sodium and water retention causing increased effective circulatory volume, mechanisms that occur relatively slowly, over a period of days to weeks. Depicted on the left are the dynamic processes that can occur rapidly and involve a relatively minor increase in sympathetic outflow acting on the splanchnic reservoir of blood resulting in a shift of volume from the capacitance vessels into the systemic circulation, increasing effective circulatory volume and causing congestion.

3. Negative Effects on the Kidney
In addition to the effects of both circulating and neuronally released norepinephrine on the heart, SNS effects on the
kidney probably are an important part of the progression from chronic to acute HF. Activation of the SNS causes renal vasoconstriction and worsening of glomerular filtration rate.40 This effect combined with the direct effects of elevated venous pressure on the kidney41 leads to diuretic resistance and further elevation of filling pressures. Mullens and colleagues showed that elevated filling pressures were the only hemodynamic measurement that correlated with worsening renal dysfunction during treatment for ADHF,42 and driving central venous pressure below 8 mm Hg correlated with improvements in renal function. Neither cardiac index nor pulmonary capillary wedge pressure correlated with worsening renal function, suggesting that arterial vasoconstriction, decreased stroke volume, and net increases in sodium and fluid were insufficient to cause the decreased renal function. The mechanism we describe is consistent with this finding because SNS effects on venous capacitance and sodium handling by the kidney would increase effective circulating blood volume and increase filling pressure, but need not be accompanied by a decreased cardiac index.

4. The Role of Fluid and Sodium Retention
Despite the absence of weight gain in many patients with ADHF, some do present with net increases in volume. We propose that shifts from the venous reservoir to the effective circulatory blood volume may be operative in these patients as well, and present a hypothetical case to illustrate why moderate increases in sodium and water appear to be insufficient to explain the development of ADHF. As depicted in Figure 2, total body water normally comprises ~60% of total weight.43 Thus, a 70-kg person has roughly 42 L of total body water, of which intravascular fluid comprises only 3.5 L. Let us assume that a patient has gained 10% of total body water, or 4.2 L. In the absence of changes in oncotic pressure, this fluid will be distributed approximately equally throughout total body water, resulting in a net gain of only 350 mL in the intravascular compartment. Because 70% of intravascular fluid resides in the venous system (mostly in the splanchnic vessels), that leaves only 105 mL contributing to effective circulating blood volume. Thus, even in the presence of weight gain comprising 10% of total body water, it is unlikely that a 105 mL increase would be enough to increase filling pressure and cause decompensation, especially because nearly 8 times this amount can be translocated within seconds from the venous reservoir.

5. The Unmasking of Venous Capacitance as a Mechanism Leading to Decompensation
Treatment of chronic HF has resulted in marked improvements in the natural history of the disease process. The most impressive treatments have targeted activated neurohumoral systems and remodeling processes, including inhibitors of the renin-angiotensin-aldosterone system and SNS,44–47 selective vasodilators,48 and device-based therapies.49 Despite these advances, hospitalizations for ADHF remain common. Although previously described mechanisms remain operative, we postulate that the inability of the vascular system to stabilize changes in circulatory volume has been unmasked because other mechanisms have been rendered less active in part by the effectiveness of current optimal HF therapy. Although neurohormonal blockers attenuate the mechanisms caused by β-adrenergic, angiotensin II, and aldosterone activation50,51 (and decrease the likelihood of hospitalization), relatively small perturbations continue to act on other vascular mechanisms and cause the events leading to decompensation.

Early in the development of cardiac dysfunction, these processes are protected by cardiac reflexes that remain responsive enough to buffer the effects of elevating filling pressures by activating the arterial and venous circulation to respond to changes in volume.52 Continued loss of baroreflex reactivity and possibly alterations in their set point could lead to a larger and therefore inadequate and less responsive loop gain. In the normal state, activation of cardiac baroreflexes leads to prompt inhibition of sympathetic outflow. However, in HF, a maximal stimulus to cardiopulmonary baroreflexes fails to inhibit sympathetic outflow.54 Additionally, high pressures in the pulmonary artery stimulate sympatoexcitatory reflexes, which could further exacerbate these abnormal mechanisms in a “feedforward” manner.57 Although angiotensin-converting enzyme inhibitors can attenuate these abnormal mechanisms and improve sympathoinhibitory responses, they do not prevent these abnormalities entirely. Treatment with enalapril fails to prevent impaired cardiopulmonary baroreflex control in dogs with pacing-induced HF.53 Thus, this “unmasking” of abnormal reflexes and distribution of volume may occur primarily in the setting of neurohormonal blockade.

Future Directions: Early Detection
Detection of shifts from the venous reservoir to the effective circulating blood volume involves unique challenges.
Changes in weight clearly are insufficient to detect such shifts. This was demonstrated pointedly in a recent clinical trial of remote telemonitoring in which accurate measurements of daily weights with medical support 24 hours a day failed to either reduce mortality or decrease hospitalizations for HF.54 As noted already, these changes can occur rapidly, so it seems unlikely that intermittent measuring of cardiac or pulmonary pressures alone would suffice to adequately measure shifts within intravascular fluid compartments.

Measurements of compliance of the venous reservoir are challenging because currently they are available only in research settings. Although methodology has been developed to detect alterations in regional water distribution, it is not available in the continuous ambulatory setting. Perhaps a combination of pressure monitoring and regional volume measurements, especially in response to a stimulus such as upright posture, might prove to be the most valuable in measuring changes in compliance of the venous reservoir preceding decompensation.

**Future Directions: Potential Treatment Options**

Treatment options to protect against—or treat—shifts between intravascular volume compartments must take into account mechanisms responsible for these shifts. Adrenergic blockade to block the effect of SNS stimulation on the splanchnic vasculature would appear to offer the most important protection and treatment against such shifts, and the efficacy of adrenergic blockade in decreasing hospitalizations for ADHF would support this concept. However, β-blockers do not protect completely against surges in adrenergic traffic, especially at doses used in common clinical practice. Furthermore, because adrenergic blockers are competitive antagonists, surges in SNS activity can overcome the effect of these antagonists. Thus, additional therapies are needed to protect against (or treat) these shifts in volume.

**Bed Rest**

Upright posture activates the SNS, reduces renal blood flow, and increases splanchnic vascular resistance.57 Bed rest augments the effects of diuretics and produces considerably more weight loss compared with being supine only at night.59 Bed rest also provides beneficial hemodynamics effects in HF consisting of reductions in filling pressures and systemic vascular resistance and an increase in cardiac index, especially during the first 24 hours.60 We speculate that these effects are mediated principally through the sympathoinhibitory effects of recumbency. However, continuous bed rest has been largely abandoned in all but the sickest patients due to concerns regarding the effects of inactivity on muscle wasting.61 Revisiting the use of bed rest may be useful and would have few side effects if used judiciously.

**Additional Robust Adrenergic Blockage**

Before episodes of decompensation, heart rate variability decreases secondary to vagal withdrawal and the continued effects of sympathetic excitation despite the use of β-blockers. This can be explained by 2 mechanisms: (1) β-blockade acts through competitive inhibition at the level of the receptor and can be overwhelmed by an outpouring of sympathetic activation, and (2) increasing venous resistance is largely unaffected by β-blockade due to the predominance of α receptors controlling splanchnic venous tone. This may in part explain the advantage of carvedilol over metoprolol tartrate seen in the COMET trial, though hospitalizations were similar between groups. Efforts at further blunting the effects of chronic adrenergic stimulation could be beneficial, including treatment of conditions such as sleep apnea and anemia that stimulate sympathetic outflow. Although β-blockade is still considered contraindicated in the setting of acute decompensation, perhaps judicious use of combined α- and β-blockade could be considered in the future, even in the setting of ADHF.

**Diuretic Sparing Regimens**

Loop diuretics cause release of renin from the macula densa in the kidney, leading to increases in angiotensin II and aldosterone, both of which have deleterious effects in HF. Less well-recognized is the fact that renin and angiotensin II levels are normal even in patients presenting with ADHF but rise in response to administration of diuretics. Increases in angiotensin II lead to heightened sympathetic activity, so activation of the renin-angiotensin system by diuretics also may lead to mobilization of the venous reservoir regardless of volume status. Thus, it is possible that the use of diuretics may actually promote further episodes of decompensation and that strategies to redistribute blood volume back to the venous reservoir without activating the renin-angiotensin system and/or SNS would theoretically be more advantageous than the use of diuretics. Because diuretic use also has been linked to reductions in glomerular filtration rate and development of the cardiorenal syndrome, there are multiple reasons why alternate strategies such as ultrafiltration or aquaresis, using vasopressin antagonists might be advantageous, especially those that tend to blunt further activation of renin-angiotensin system and SNS.

**Vagal Stimulation**

Heart failure is accompanied by autonomic imbalance consisting of excess SNS activity and a withdrawal of parasympathetic tone. Parasympathetic effects occur through both direct and indirect mechanisms mediated in part by sympatholysis. Vagal stimulation has been shown to be beneficial in animal models of heart failure and has started to be explored in early clinical trials in patients. We speculate that the sympatholytic effects of vagal stimulation might protect against sympathetically mediated shifts in volume and possibly decrease the occurrence of decompensation.

**Renal Nerve Denervation**

Denervation of renal nerves has been shown to lead to decreases in sympathetic outflow, probably as the result of interruption of afferent fibers that contribute to sympathetic activation. Techniques have now been developed to perform this procedure in humans and have been shown to lead to marked reductions in blood pressure in resistant hypertension caused by reductions in SNS activity. It is possible that this approach may be beneficial in preventing either the chronic or acute changes in SNS activity leading to redistribution of volume and compensated HF.

**Summary and Conclusions**

Mechanisms that have been proposed previously as leading to ADHF continue to be important in the differential diagnosis
of ADHF. In this article, we have described a mechanism that explains the phenomenon of congestion without weight gain: the presence of a compromised venous reservoir unable to buffer shifts of fluid leading to increases in effective circulatory volume and to decompensated heart failure. Additional studies are needed to understand the fundamental pathophysiology of this phenomenon and to determine whether its occurrence depends on increased stimulation of α and/or β receptors. Understanding how abnormalities in baroreflexes or changes caused by ineffective loop gain between veins, arteries, and baroreflexes result in higher filling pressures also will help to clarify the deleterious consequences to the venous reservoir and to the patient.

Disclosures
Dr Sobotka is an employee of Medtronic Inc and former Chief Medical Officer of Ardian Inc (Symplicity Catheter System, renal denervation). Dr Dunlap received research grants from Medtronic Inc/Ardian Inc (Symplicity Catheter System renal denervation) and BioControl Medical Inc (CardioFit System, vagal stimulation); he is a member of the Consultant/Advisory Board, has received honoraria, and serves on the Speakers’ Bureau for Otsuka Pharmaceuticals Inc. Drs Dunlap and Sobotka were involved in the Symplicity HTN-1 study and served as members of the writing committee for the report.

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**Key Words:** autonomic nervous system • blood volume • heart failure • splanchnic circulation • veins • fluid shifts • sympathetic
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