

Assessment and Management of Volume Overload and Congestion in Chronic Heart Failure: Can Measuring Blood Volume Provide New Insights?

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Key Words

Blood volume quantitation · Chronic heart failure · Hemodynamic congestion · Symptomatic clinical congestion · Volume overload congestion

Abstract

Background: Volume overload and fluid congestion remain primary clinical challenges in the assessment and management of patients with chronic heart failure (HF). **Summary:** The pathophysiology of volume regulation is complex, and the simple concept of passive intravascular fluid accumulation is not adequate. The dynamics of interstitial and intravascular fluid compartment interactions and fluid redistribution from venous splanchnic beds to the central pulmonary circulation need to be taken into account in strategies of volume management. Clinical bedside evaluations and right heart hemodynamic assessments can alert of changes in volume status, but only the quantitative measurement of total blood volume can help identify the heterogeneity in plasma volume and red blood cell mass that are features of volume overload in chronic HF. The quantitative assessment of intravascular volume is an effective tool to help guide individualized, appropriate therapy. **Key Message:** Not all volume overload is the same, and the measurement of intravascular volume identifies heterogeneity to guide tailored therapy.

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Introduction

The features of chronic heart failure (HF) reflect a syndrome characterized by the renal retention of sodium and water with resulting intravascular and interstitial fluid volume expansion and redistribution. The kidney acts as an early responder to the myocardial dysfunction and the resulting arterial underfilling with a reduction in effective circulating blood volume (BV) [1, 2]. This response occurs in conjunction with baroreceptor activation and neurohormonal stimulation, which further promote renal sodium and water retention. While an initial sympathetic-driven vasoconstriction maintains organ perfusion pressure in the short term, a more gradual accumulation of extracellular/interstitial compartment fluid also occurs, which supports a compensatory expansion of intravascular plasma volume (PV). The expansion of the interstitial fluid compartment with an associated increase in interstitial tissue pressure thus provides a mechanistic basis for sustaining the compensatory expansion of intravascular volume over time.

Given that only 30–40% of total BV normally resides in the arterial circulation [3, 4], and even less in the presence of systolic HF with relative arterial underfilling, considerable overall volume expansion is required to maintain effective tissue perfusion dynamics. While this pro-

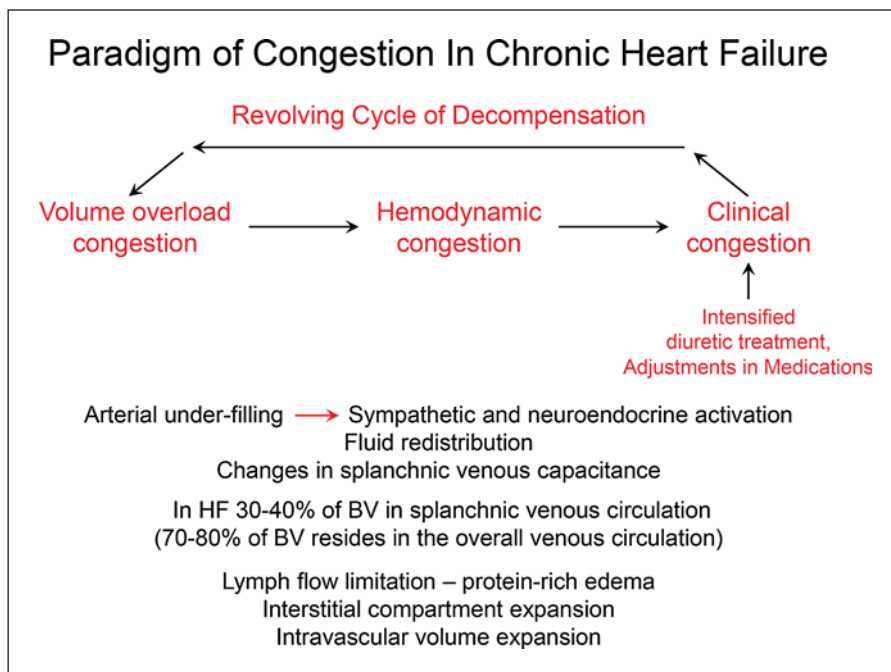


Fig. 1. Paradigm of recurring symptomatic clinical volume overload and congestion in chronic HF.

cess occurs initially as compensatory mechanisms to maintain effective circulating BV, over time, they become detrimental with the development of pathologic inappropriate BV and interstitial fluid expansion contributing to volume overload and organ congestion. Volume overload leads to hemodynamic congestion with increased central filling pressures and the eventual development of symptomatic clinical congestion. The latter may be slowly progressive and delayed in presentation, but once it develops in chronic HF, marked fluid retention has often already occurred and, depending on the volume capacity of the interstitial compartment, can reflect multi-liter fluid excess. This chronic volume excess is often only marginally mitigated with standard diuretic and vasodilator therapies [5]. As a result, a cycle of decompensation (acute on chronic) provoking a clinical response of aggressive short-term diuretic treatment of congestive symptoms occurs, which is then followed by the gradual recurrence of fluid accumulation and/or fluid redistribution, which in turn promotes another cycle of decompensation (fig. 1).

Chronic HF has many complexities, and among the questions that arise is the basic one of what degree of PV expansion and interstitial fluid accumulation contributes to a favorable compensated state in chronic HF, and conversely, what degree becomes detrimental with refractory volume overload contributing to recurrent cycles of con-

gestion and negative myocardial and vascular remodeling over time? These are issues yet to be addressed in the pathophysiology of HF, along with the potential for the excess intravascular and interstitial fluid to be targets in strategies for early therapeutic interventions and the prevention of HF progression.

Intravascular and Interstitial Volume Overload and Clinical Congestion

Total BV normally accounts for 6–7% of lean body weight and 11–12% of total body fluids [3]. The importance of an adequate BV in maintaining normal organ perfusion is well recognized, and several early studies by Warren et al. [6, 7] and others have demonstrated the importance of the role of the interstitial fluid compartment in supporting the maintenance of a normal intravascular volume. Shifts in the distribution of body fluid between the interstitial and intravascular fluid compartments as a function of transcapillary oncotic and hydrostatic disequilibria have been recognized since the early work of Darrow and Yannet [8] which evolved from the even earlier observations by Starling [9] who described the transcapillary exchange of fluid from the interstitial space as a principal mechanism for PV restoration. The balance of Starling forces across the capillary wall normally estab-

lishes an equilibrium resulting in stable no net movement of fluid in steady-state conditions. However, the decrease in capillary hydrostatic pressure as occurs in HF with impaired cardiac output dictates the net movement of interstitial fluid into the intravascular space in an attempt to restore effective circulating BV and maintain normal organ perfusion. This reserve capacity of the interstitial fluid compartment, therefore, provides a compensatory mechanism to support PV expansion in HF patients, but the heterogeneity in how this mechanism plays out, from patient to patient, due to multiple confounding influences (differences in systemic systolic blood pressure, opposing oncotic forces, changes in capillary permeability, lymphatic drainage, degree of neurohormonal activation, and intrinsic renal function, among others) is significant and, therefore, makes the extent of BV expansion highly variable and the degree of benefit (compensatory PV expansion) or detriment (pathophysiologic PV expansion) difficult to determine without a quantitative method of intravascular volume assessment. The physiologic PV expansion that contributes to maintaining an overall normal total BV as occurs, for example, with blood loss hemorrhage is a compensatory mechanism, while an excess in PV expansion that contributes to greater than normal total BV (e.g. volume overload in HF) is pathologic and potentially has long-term detrimental consequences.

Because increases or decreases in the volume of the interstitial fluid compartment contribute to corresponding changes in PV, their mutual regulation is closely aligned. Studies by Anand et al. [10] in untreated symptomatic HF patients with reduced ventricular ejection fraction, using indicator-dilution techniques to quantitate fluid volumes, demonstrated that the volumes of the interstitial and intravascular compartments expanded proportionately (33–35% above normal volumes). This occurs at least in part due to neurohormonal mechanisms stimulating increased renal sodium and water retention. The extent of interstitial volume expansion and, therefore, BV expansion has also been shown to be related to the severity of HF by NYHA functional class as reported in studies by Gibson and Evans [11] decades earlier, where the average BV excess (above expected normal volume) was >20%, while in class IV HF, there was an average deviation of +55% above normal BV. Marked heterogeneity in BV expansion has also been demonstrated with contemporary methods [5, 12–13]. Variability in volume expansion and response to diuretic therapy reflects the influence of multiple recognized factors (e.g. systemic blood pressure, plasma protein concentrations, intrinsic renal function, the extent of neurohormonal activation, and the

impact of medical therapies, particularly vasodilator therapies). Another often unconsidered factor is the variability in the capacitance or distensibility of the interstitial fluid compartment to accumulate fluid and expand over time. Normally, the interstitium is a low-compliance compartment, and a reduction in the capacity to expand (less tissue stretching) would be expected to be reflected in greater PV expansion (more net forces driving fluid into the vascular space) in the setting of increased fluid retention. With chronic HF, however, the interstitial compartment appears to develop into a high-compliance reservoir and, therefore, has an increased capacity to contain excess fluid volume. It has also been demonstrated that it is difficult to effectively reduce interstitial fluid accumulation to, in turn, control BV expansion in patients with chronic HF even when clinical findings of volume overload such as peripheral edema or dyspnea are no longer present [5, 12].

Normally, the fluid capacity of the interstitial compartment is approximately 3–4 times that of the intravascular compartment with the volume of interstitial fluid being a fairly direct determinant of the volume of the intravascular compartment. In the setting of chronic HF, however, there is a reduction in capillary hydrostatic pressure due to reduced effective circulating BV and systemic blood pressure, which then favors the movement of fluid across the capillary wall from the interstitial space into the intravascular compartment as a compensatory mechanism. There is also an alteration in capillary endothelial permeability in HF, which in association with reduced plasma oncotic pressure (loss of plasma proteins, mainly albumin) promotes a loss of fluid from the intravascular compartment into the interstitial space. These dynamic forces establish a new equilibrium which impacts the maintenance of adequate tissue perfusion pressures. The net accumulation of interstitial fluid, therefore, provides a means by which increasing tissue pressure supports the development of an expanded PV. Intravascular PV is thus functionally the part of the overall extracellular fluid compartment, which is determined to a large extent by the fluid capacity and tissue pressure of the interstitial compartment. When adequate intravascular plasma protein concentrations are present, this contributes to holding fluid volume within the intravascular compartment. These factors in turn, sometimes acutely, promote elevation in central venous and cardiac filling pressures, leading to hemodynamic congestion which precedes the development of clinical congestion. A marked expansion in the interstitial compartment volume is thus one of the most persistent and significant re-

sponses to systolic HF and, depending on the volume compliance of the interstitial compartment, may exceed the normal 3–4:1 interstitial to PV ratio by several fold to a point where this fluid compartment may no longer be adequately responsive to standard diuretic therapy and, as a result, refractory volume overload develops over time.

Assessment of Congestion and Fluid Volume Overload

Physical signs and symptoms of the clinical assessment of volume status such as the presence or absence of elevated jugular venous pressure, orthopnea, lower extremity edema, +S3, and hepatojugular reflux lack sensitivity and specificity [14–16]; however, they often point to a need for further assessment. Similarly, while the use of biomarkers such as the natriuretic peptides (e.g. elevated blood concentrations of BNP and NT-proBNP) has been shown to be beneficial in aiding diagnosis, assessing prognosis, and correlation with NYHA class in HF patients, their utility to estimate and monitor changes in volume status has not been supported. In studies by James et al. [17], Androne et al. [12], and Miller W. [author's data, 2016] (total BV vs. NT-proBNP, $r = 0.316$, $p = 0.031$, $n = 50$), no clinically meaningful associations between quantitated BV and BNP or NT-proBNP levels were identified.

Right heart catheter hemodynamic pressure measurements (central venous pressure and pulmonary capillary wedge pressure) are also commonly used to interpret and guide management of intravascular volume status in acutely ill patients. While a statistically significant correlation was reported by Androne et al. [12] in chronic HF patients undergoing pretransplant evaluations ($r = 0.69$, $p = 0.01$, $n = 17$), central pressure measurements, like the other surrogate markers of volume status, have more frequently been shown to be an unreliable (discordant pre- to posttreatment) [17] or a very poor correlate to measured intravascular volume [18–21]. Thus, while commonly employed in the critical care setting for the assessment of volume status, right heart hemodynamic parameters provide helpful pressure-related information but are not the equivalent of volume data and, therefore, lack reliability for informing decisions regarding true volume status and management, including fluid resuscitation or fluid reduction. Right heart hemodynamic data, thus, have a complementary role by identifying the transition from steady-state volume overload congestion to he-

modynamic congestion, but central pressures do not reliably inform the extent of intravascular volume expansion or contraction.

More direct methods of volume determination developed with the introduction and advancement of the indicator dilution method permit quantitation of BV in vivo. Initially, this was done by the calculation of the dilution volume of injected plasma dyes or labeled red blood cells. The dye method was introduced in 1915 [22] using vital red and blue dyes. Gibson and Evans [23] (1937) described the use of one of the early and often used dyes, T-1824, more commonly known as Evans Blue dye. Later came indocyanine, also known as Fox green (1957), which like the other dyes binds to plasma proteins, mostly albumin [24]. Other plasma labels include the radioactive tracer iodine-131 used in radioiodinated serum albumin techniques [25]. To account for sufficient mixing of the marker to occur and correct for losses from the circulation during the mixing period, the extrapolation method was advanced by Erlanger [26] (1921) and developed by Gibson and Evans [23]. Multiple samples are taken over a predetermined time period (e.g. 5-min intervals over 30 min), and the log values are linearly plotted. Back extrapolation to time zero then gives the value for the initial concentration required to calculate the overall intravascular compartment volume.

Contemporary quantitative analysis of total BV also utilizes the indicator-dilution principle; however, the technique now uses a standardized computer-based and clinically available method to administer low-dose iodinated labeled albumin (iodine-131, 5–30 μCi) intravenously. The technique requires about an hour to complete and has been validated clinically [5, 12, 27–31] and in research analyses [32, 33]. The radiolabeled albumin is injected intravenously, and from the contralateral forearm venous catheter, 4-ml blood samples are collected at time 0 (preinjection) and 12, 18, 24, 30, and 36 min postinjection. Plasma radioactivity of each sample is measured in duplicate in a semi-automated computerized counter (FDA-approved 1998, BVA-100 Blood Volume Analyzer, Daxor Corp., New York, N.Y., USA). By extrapolation of the radioactivity to time zero, PV can be measured. Total BV is quantitated using the measured PV and the patient's peripheral venous hematocrit. Each patient's peripheral hematocrit is normalized to a mean body hematocrit adjusting for trapped plasma and for what the patient's hematocrit would be if the PV was expanded or contracted consistent with a normal total BV. Reference normal expected total BV values are calculated

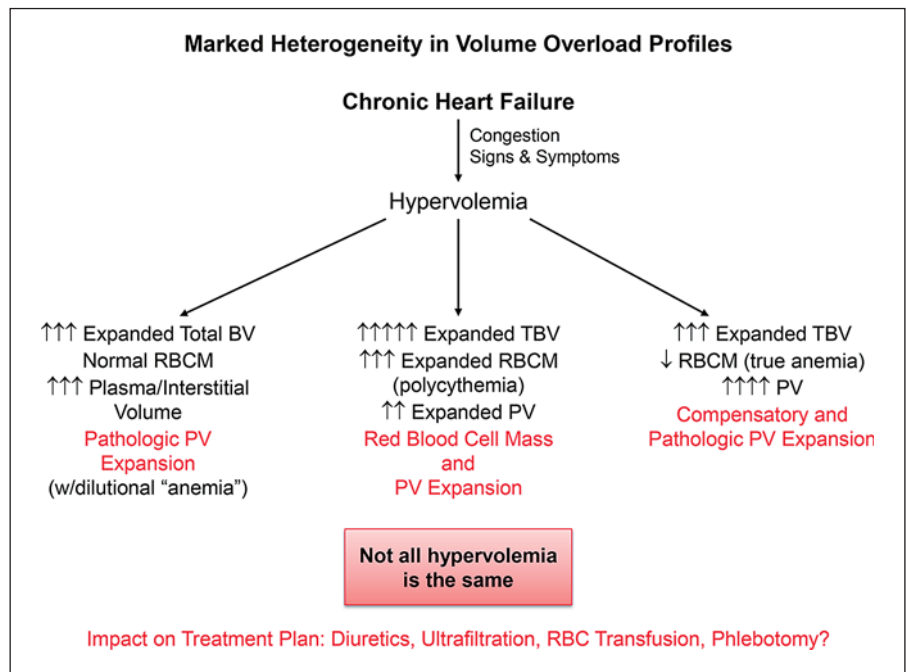


Fig. 2. Not all volume overload is the same from patient to patient. Quantitative BV analysis identifies multiple PV and RBCM profiles which impact the approach to treatment.

using the percent deviation from normal body weight method with values derived from measurements determined from extensive life insurance tables for age, gender, weight, and height [23, 33]. This technique has been validated against the technically difficult and time-intensive double-labeled technique of chromium-tagged red blood cells and plasma albumin 1–125 (considered the gold standard) with the comparator volumes being within 1% of one another [32, 34]. Normal total BV by this technique is defined as measured volumes within $\pm 8\%$ of the expected normal volume for each individual patient and red blood cell mass (RBCM) and PV as measured volumes within $\pm 10\%$ of expected normal volumes. This reflects approximately 3 standard deviations from the expected normal value and assures that measured values lying beyond these parameters are not in a normal range for the individual subject. Mild to moderate total BV expansion is considered $>8\%$ ($>10\%$ for RBCM and PV) to $<25\%$, and severe expansion as $\geq 25\%$ of the expected normal volume. Intravascular volumes are reported as absolute values and as a percentage of normal expected volume either as within the normal range, as a deficit (–), or an excess (+). This technique requires steady-state conditions, so its use in patients who are hemodynamically unstable or undergoing acute volume transitions may not be optimal. Otherwise, by this technique BV quantitation has an intraindividual reproducibility of

within $\pm 2.5\%$. This methodology, when employed in clinically appropriate settings, can provide a tool to quantitatively identify PV and RBCM profiles in the individual HF patient and, thereby, aid in guiding tailored volume management therapy.

Summary

Volume overload with the development of hemodynamic and clinical congestion is a highly complex pathophysiologic process afflicting patients with acute and chronic HF. The renal retention of sodium and water is an early response mechanism contributing to fluid accumulation, but redistribution of fluid mainly from the abdominal venous reservoir secondary to changes in venous capacitance to the central cardiopulmonary vascular beds is also a significant factor in the development of acute and subacute symptom progression and clinical congestion. Multiple factors, thus, contribute to the accumulation and redistribution of body fluid with the expansion over time of the interstitial and intravascular compartments, often ultimately leading to refractory volume overload and organ congestion. Clinical signs and symptoms and right heart hemodynamics can be helpful in alerting of a change in volume status; however, the quantitative measurement of total BV in the individual patient can best be

used to identify the specific volume profiles and guide the management strategy needed to treat the volume status in this diverse population of high-risk patients. The elements of volume overload vary from patient to patient and, therefore, the treatment must vary (fig. 2).

Conflict of Interest Statement

The author has no conflicts of interest to disclose.

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