

Fluid Volume Overload and Congestion in Heart Failure Time to Reconsider Pathophysiology and How Volume Is Assessed

Wayne L. Miller, MD, PhD

Abstract—Volume regulation, assessment, and management remain basic issues in patients with heart failure. The discussion presented here is directed at opening a reassessment of the pathophysiology of congestion in congestive heart failure and the methods by which we determine volume overload status. Peer-reviewed historical and contemporary literatures are reviewed. Volume overload and fluid congestion remain primary issues for patients with chronic heart failure. The pathophysiology is complex, and the simple concept of intravascular fluid accumulation is not adequate. The dynamics of interstitial and intravascular fluid compartment interactions and fluid redistribution from venous splanchnic beds to central pulmonary circulation need to be taken into account in strategies of volume management. Clinical bedside evaluations and right heart hemodynamic assessments can alert clinicians 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 patients with chronic heart failure and help guide individualized, appropriate therapy—not all volume overload is the same. (*Circ Heart Fail.* 2016;9:e002922. DOI: 10.1161/CIRCHEARTFAILURE.115.002922.)

Key Words: blood volume quantification ■ chronic heart failure ■ volume overload

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 resulting arterial underfilling with 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. Although an initial sympathetic-driven vasoconstriction maintains organ perfusion pressure in the short-term, a more gradual accumulation of interstitial compartment fluid also occurs which supports a compensatory expansion of intravascular plasma volume (PV). The expansion of the interstitial fluid compartment with associated increase in interstitial tissue pressure, thus, provides a mechanistic basis for sustaining the compensatory expansion of intravascular volume over time (Figure 1).

Given that only 30% to 40% of total BV normally resides in the arterial circulation,^{3,4} and even less in the presence of systolic HF, considerable overall volume expansion is required to maintain effective tissue perfusion dynamics. Although this process occurs initially as compensatory mechanisms to maintain effective circulating BV, over time they become detrimental with the development of pathological 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 multiliter 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) stimulating a response of aggressive short-term diuretic treatment of congestive symptoms occurs, which is then followed by the gradual recurrence of fluid accumulation and fluid redistribution, which in turn promotes another cycle of decompensation—so-called frequent flyer syndrome (Figure 2).

The story of 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 congestion and negative myocardial and vascular remodeling over time? These issues also relate to more compensated New York Heart Association class I and II HF patients—do they remain compensated because they maintain an appropriate degree of intravascular and interstitial volume expansion or do they maintain a normal intravascular volume until some event or duration of HF pushes them into decompensation? These are issues yet

Received December 28, 2015; accepted May 12, 2016.

From the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

Correspondence to Wayne L. Miller, MD, PhD, 200 First St, SW, Rochester, MN 55905. E-mail miller.wayne@mayo.edu

© 2016 American Heart Association, Inc.

Circ Heart Fail is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.115.002922

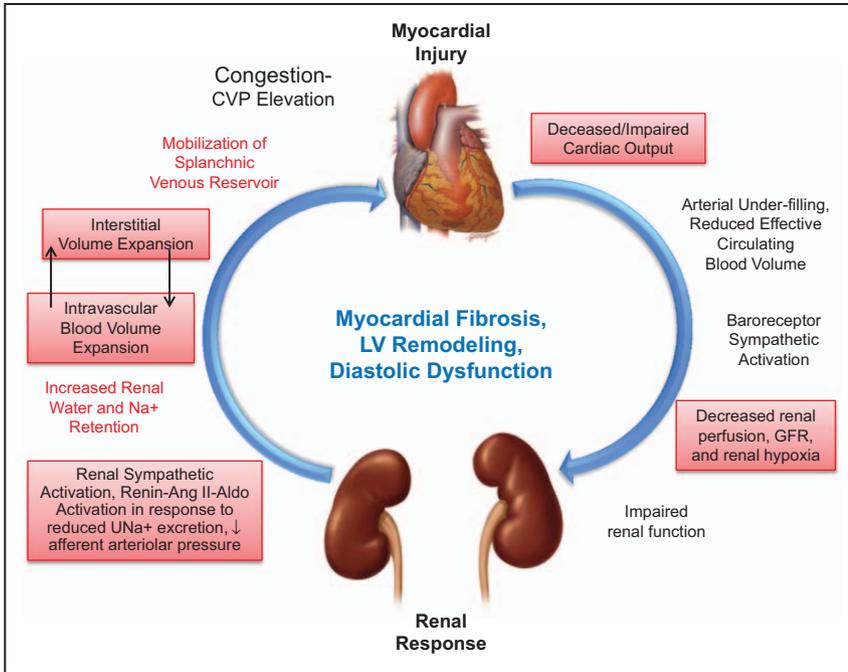


Figure 1. Cardio-renal interactions in volume expansion and congestion in chronic heart failure. GFR indicates glomerular filtration rate.

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. These, among other issues, remain poorly understood and can only be highlighted in this discussion. The intent, therefore, of this review is to reassess concepts relating to the pathophysiology of volume overload and congestion in chronic HF and to reconsider our understanding of how these processes develop and how we might more effectively and objectively determine volume status and intervene in a more informed manner for our patients.

Role of the Interstitial Fluid Compartment in Intravascular Volume Overload and Congestion

Total BV normally accounts for 6% to 7% of lean body weight and 11% to 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 interstitial fluid compartment in supporting the maintenance

of a normal intravascular volume. Shifts in the distribution of body fluid between the interstitial and the intravascular fluid compartments as a function of transcapillary oncotic and hydrostatic disequilibria have been recognized because the early work of Darrow and Yannet,⁸ which evolved from the even earlier observations by Starling⁹ 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 establishes 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 patients with HF, but the heterogeneity in how this mechanism plays out, patient to patient, because of multiple confounding influences (differences in systemic

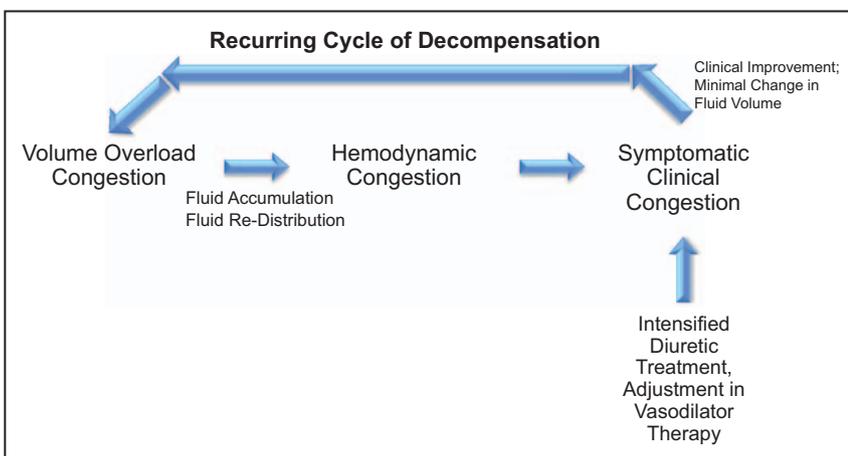


Figure 2. Concept of recurring symptomatic clinical volume overload and congestion in chronic heart failure.

systolic blood pressure, opposing oncotic forces, changes in capillary permeability, lymphatic drainage, degree of neurohormonal activation, and intrinsic renal function, among others) is highly variable and, therefore, makes the extent of BV expansion highly variable and the degree of benefit (compensatory PV expansion) or detriment (pathophysiological PV expansion) difficult to determine without a quantitative method of volume assessment. The physiological PV expansion that contributes to maintaining an overall normal total BV as occurs, for example, with blood loss hemorrhage is a compensatory mechanism, whereas an excess in PV expansion that contributes to greater than normal total BV (eg, volume overload in HF) is pathological 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 al¹⁰ in untreated symptomatic HF patients with reduced ventricular ejection fraction (31±4%) 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 because of 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 New York Heart Association functional class as reported in studies by Gibson and Evans¹¹ decades earlier, where the average BV excess (above expected normal volume) was greater than +20% and in class IV HF an average deviation of +55% above normal BV. Marked heterogeneity in BV expansion has also been demonstrated with contemporary methods (Figure 3).^{5,12} Variability in volume expansion and response to diuretic therapy reflects the influence of multiple recognized factors (eg, systemic blood pressure, plasma protein concentrations, intrinsic renal function, the extent of neurohormonal activation, the impact of medical therapies, and 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 seems to develop into a high compliance and, therefore, the 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} This persistence in intravascular volume overload despite diuretic intervention was also demonstrated in the insightful studies by Seymour et al,¹³ where measured intravascular volume was decreased with diuresis by 1.2 L or ≈25% by volume; however, despite a marked decrease in overall body fluid by a mean reduction of 12.7 L, the measured extracellular fluid volume remained +50% expanded above normal volume.

Normally, the fluid capacity of the interstitial compartment is ≈3× to 4× 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 because of 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 affects 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 responses to systolic HF, and depending on the volume compliance of the interstitial compartment may exceed the normal 3 to 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.

To a large extent, as goes the volume of the interstitial fluid compartment, so goes the volume of the intravascular compartment and, therefore, total BV. The interstitial fluid compartment may expand over months, perhaps even years, after myocardial injury and, depending on the capacity of the interstitial space, underpins the expansion of intravascular volume and volume overload congestion providing a pathophysiological basis for the development of hemodynamic congestion and then symptomatic clinical congestion often with relapsing cycles of decompensation (Figure 4).

Contribution of Intravascular Fluid Redistribution to Hemodynamic and Clinical Congestion in Chronic HF

Our understanding of the pathophysiology of volume overload and the concepts of fluid accumulation and fluid redistribution as prime mechanisms for the development of clinical congestive events in acute on chronic decompensated HF remains debated and incompletely understood.^{1,14–16} The concept of sympathetically mediated venous fluid volume redistribution principally from the splanchnic venous reservoir through changes in venous capacitance as a mechanism for the precipitation of acute (on chronic) HF events is comprehensively discussed by Tyberg¹⁷ and Fallick et al.¹⁸ The concept of fluid redistribution suggests that multiple confounding factors (eg,

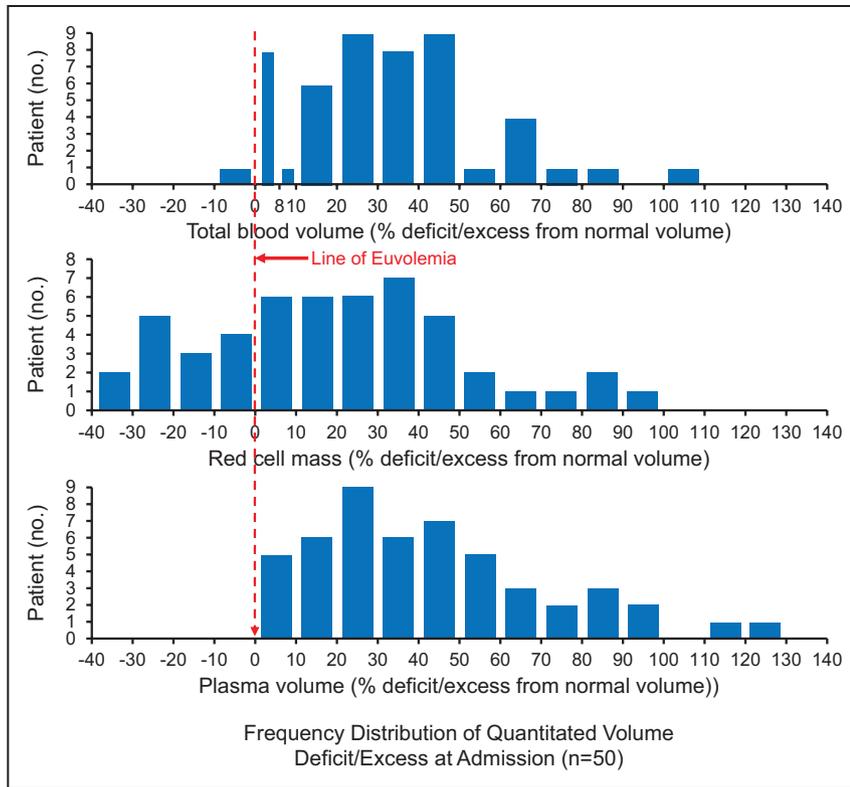


Figure 3. Frequency distribution of measured total blood volume, red blood cell mass, and plasma volume at hospital admission in patients with decompensated chronic heart failure. Percent deviation from normal expected volumes.

traumatic events, myocardial ischemia, hypertensive episodes, changes in medication regimen, worsening renal function, and increased neurohormonal-sympathetic activation) could provoke increases in venous tone (decreased venous capacitance), which in the setting of existing intravascular volume overload could precipitate rapid redistribution of fluid from a peripheral venous reservoir (eg, splanchnic venous bed) to the central cardiopulmonary circulation. This along with fluid shifts from the interstitial compartment would elevate central venous and ventricular filling pressures with the result of producing transudation of fluid into the pulmonary alveolar space and the development of worsening dyspnea and symptomatic clinical congestion. This could result in the acute translocation of as much as 1 L of fluid without a net change in body weight. Here, vasodilator therapy would be more appropriate than aggressive diuretic intervention.

Although it is recognized that hemodynamic congestion can precede symptomatic cardiopulmonary congestion by several days and that clinical congestion can resolve even in the presence of ongoing hemodynamic congestion, a basic driving mechanism remains the persistent volume overload of the intravascular and the interstitial compartments. It may be postulated that if such volume overload could be prevented from developing then the ability of venous capacitance system to buffer fluid redistribution would be preserved, which could translate into fewer episodes of acute decompensation and, therefore, potentially fewer rehospitalizations. Thus, the ability to quantitatively assess and serially monitor total BV in the early stages of HF would permit fluid management to be emphasized and acted on before potentially nonreversible interstitial and intravascular volume expansion occurs.

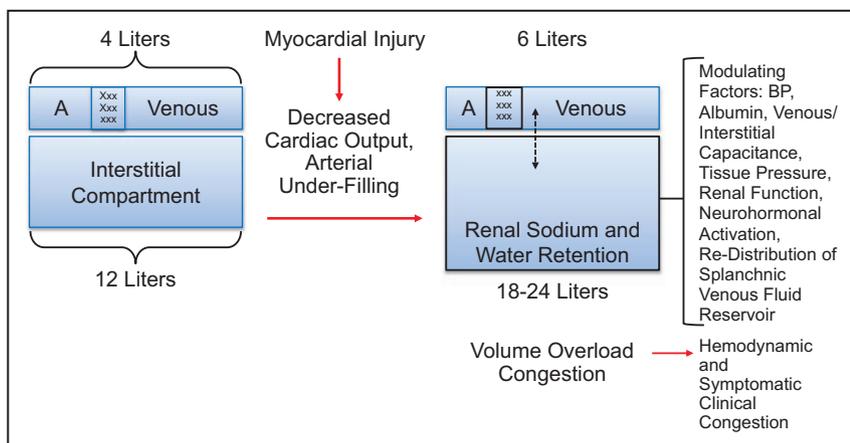


Figure 4. Paradigm of interstitial and intravascular volume expansion in chronic heart failure. BP indicates blood pressure; and CO, cardiac output.

Not All Volume Overload Is the Same: Contribution of Red Blood Cell Mass

Clinically, volume overload is most often considered to solely reflect PV expansion. The contribution of red blood cell mass (RBCM) to volume overload is generally not considered a significant issue. Marked variability in RBCM profiles, however, has been reported in patients hospitalized for volume overload HF (Figure 5).¹⁹ Although RBC polycythemia has been identified in patients with chronic HF, the observation that this is more common than expected is not well recognized particularly when presenting peripheral hemoglobin or hematocrit levels are low secondary to PV dilution, suggesting that anemia is present. Thus, not only do a large number of patients with chronic HF develop significant PV expansion many also develop an often unrecognized excess in RBCM as a significant contributing factor to overall intravascular volume congestion. RBC polycythemia, however, should not be considered an unexpected response to low cardiac output, hypoxemic tissue perfusion, impaired oxygen exchange, and persistent acidotic tissue conditions in the setting of chronic HF. Related to this is that the standard approach for treatment of volume overload is intravenous diuretic therapy, which is used in most clinical strategies but would not be expected to normalize intravascular volume and may, in the setting of underlying RBCM polycythemia, potentially contribute to an increased thrombotic risk and increased blood viscosity–related myocardial work.^{20,21} Thus, quantitative data on RBCM and PV status can inform this circumstance before inappropriate therapy is initiated. The consequences of long-term RBCM polycythemia in patients with chronic HF, however, needs further study.

It is also important to note that low peripheral hemoglobin concentrations are commonly reported in patients with chronic HF and are considered to reflect the presence of anemia of chronic disease and renal dysfunction. However, a primary pathophysiologic derangement of HF is the expansion of

the PV and, therefore, it becomes difficult to accurately differentiate true anemia from dilution-related anemia or even the presence of excess RBCM (polycythemia) based on peripheral hemoglobin or hematocrit measurements alone.^{22–24} Although the importance of a low hemoglobin and its causes in chronic HF should not be underestimated in terms of outcome implications,²⁵ the concept of pseudoanemia secondary to PV excess and even with RBCM polycythemia has been under-recognized. As a result, in the clinical setting of volume overload chronic HF, the complex of true anemia, pseudoanemia, and RBCM polycythemia with PV expansion and the relation to peripheral venous hemoglobin values has gone, with a few exceptions,^{12,26} largely unreported and with it the implications for volume management. Profiles of RBCM deficits (true anemia), as well as, PV expansion dilution-related pseudoanemia, both presenting with low peripheral hemoglobin concentrations are also common. As a result, the reliance on peripheral venous hemoglobin concentration can be a misleading index of RBCM and overall intravascular volume status. The interpretation of hemoglobin concentrations, therefore, needs to take into account quantitative data of both RBCM and PV. Low hemoglobin may reflect true anemia with associated RBCM deficit or it may reflect a relative dilution-related anemia with compensatory and often additional pathological PV expansion producing total blood volume excess. The implications are significant not only in furthering our understanding of the pathophysiology of HF but also for determining the most effective intervention strategies for patient outcomes. Such a differentiation was shown to be important by Borovka et al²⁷ in identifying responders and nonresponders to erythropoietin therapy. Patients with true anemia identified by quantitative BV analysis responded to therapy, whereas patients with dilution-related anemia from pathological PV expansion in the setting of normal RBCM did not respond. Thus, it would seem that a goal of volume management to treat a balance of RBCM and PV could translate into better outcomes.

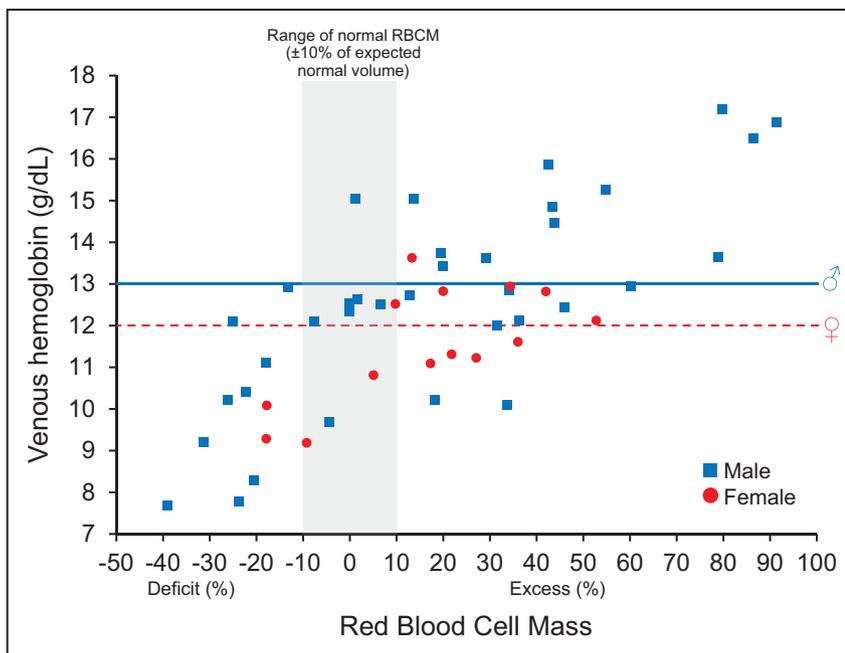


Figure 5. Mismatch of measured red blood cell mass (RBCM) and peripheral venous hemoglobin concentration in patients with decompensated chronic heart failure. Percent deviation of RBCM from normal expected volume with hemoglobin measured at hospital admission (n=50). Horizontal lines define World Health Organization cut points for normal hemoglobin concentrations (<13 g/dL for males [solid line] and <12 g/dL for females [broken line]). Hemoglobin values can be misleading when used to predict intravascular volume and red cell status.

Therefore, of clinical relevance to volume management is recognizing that marked heterogeneity exists in the composition of intravascular volume expansion, and that a significant component of the volume expansion can frequently be contributed by RBCM excess, as well as, pathological PV expansion. In such patients, 1 or 2 unit therapeutic whole-blood phlebotomy may be most appropriate albeit somewhat of an anachronistic concept in current HF practice. Some patients will also demonstrate PV expansion with a normal overall total blood volume, where true anemia (RBCM deficit) is present and RBC transfusion with limited diuretic therapy would be a more appropriate intervention, rather than aggressive diuresis which could be detrimental. Therefore, the ability to quantify RBCM and PV can be useful in guiding effective therapy and determining the most appropriate course for a tailored volume management strategy (Figure 6).

Assessment of Congestion and Extracellular Fluid Volume Overload: Historical and Contemporary Methodology

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,²⁸⁻³⁰ however, they often point to a need for further evaluation. Similarly, although the use of biomarkers such as the natriuretic peptides (eg, elevated blood concentrations of BNP and NT-proBNP) has been shown to be beneficial in aiding diagnosis, assessing prognosis, and correlation with New York Heart Association class in patients with HF, their use to estimate and monitor changes in volume status has not been supported. In the studies by James et al,³¹ Androne et al,¹² and 2016 W. Miller (BV versus Nterminal-proBNP, $r=0.316$, $P=0.031$, $n=50$, unpublished data), no clinically meaningful association between quantitated BV and BNP or Nterminal-proBNP levels was 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. Although a statistically significant correlation was reported by

Androne et al¹² in patients with chronic HF undergoing pre-transplant 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 post-treatment)³¹ or a poor correlate to measured intravascular volume (Figure 7).³²⁻³⁵ Thus, although commonly used in the critical care setting for the assessment of volume status, right heart hemodynamic parameters provide helpful pressure-related information, they are not the equivalent of volume data and, therefore, lack reliability for informing decisions about true volume status and management, including fluid resuscitation or fluid reduction. Right heart hemodynamic data, thus, serve a complementary role by identifying the transition from steady-state volume overload congestion to hemodynamic congestion but central pressures do not reliably inform the extent of intravascular volume expansion or contraction.

The concept of the quantitative measurement of BV in the assessment of volume status is accredited to Valentin (ca. 1838) and involved the quantitation of the fall in concentration of blood solids or red blood cells (hemoglobin concentration) produced as the result of the infusion of a known volume of fluid. The circulating BV was then estimated from the dilution of the total blood solids. The majority of indirect methods in use are based on the dilution of a known amount of an intrinsic marker such as plasma albumin, red blood cells, or an appropriate test substance introduced into the circulatory system. Although peripheral venous hemoglobin concentration and hematocrit and changes in these parameters have been used to estimate changes in intravascular volume status^{25,36} with prognostic benefit, the absolute values show poor correlation with measured total BV in patients with chronic HF.¹⁹ Recognizing the transcapillary fluid shifts that occur between interstitial and intravascular compartments with chronic HF makes this discrepancy not unexpected.

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

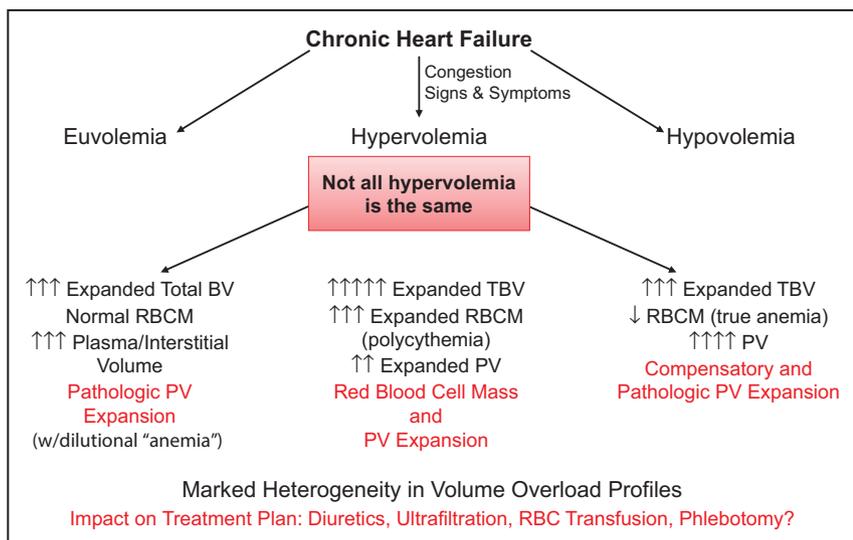


Figure 6. Not all hypervolemia is the same: quantitative blood volume (BV) analysis identifies multiple plasma volume (PV) and red blood mass (RBCM) profiles, which affects approach to treatment. UF indicates ultrafiltration.

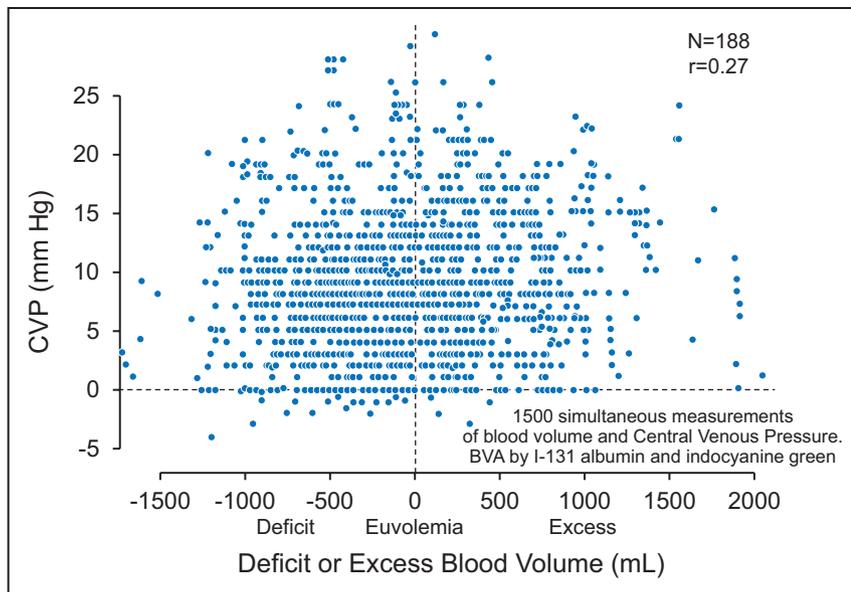


Figure 7. Lack of correlation between central venous pressure and measured total blood volume. Pressure is not volume. Reprinted from Shippy et al³³ with permission of the publisher. Copyright ©1984, Wolters Kluwer Health.

introduced in 1915³⁷ using Vital red and blue dyes. Gibson and Evans³⁸ described the use of one of the early and often used dyes, T-1824, more commonly known as Evans Blue dye. Later came indocyanine (Fox) green (1957), which like the other dyes binds to plasma proteins, mostly albumin.³⁹ Other plasma labels include the radioactive tracer I-131 used in radioiodinated serum albumin techniques.⁴⁰ The basic principle of the indicator–dilution technique is derived from the following premise: a known quantity (q) of a given substance is dissolved in the unknown volume (V) of a fluid compartment and the concentration (C) is then measured. If the quantity and the volume of the injected substance are known, then the unknown volume of the fluid compartment can be calculated ($V=q/C$). Two requirements must be met if the true volume of the compartment is to be calculated: (1) the value of q must be known at the time C is measured and (2) the value measured for C must be equal to the mean concentration for the entire fluid compartment being monitored. This second requirement is not easily met when nonpermanent labels are used. After an adequate period of mixing within the vascular compartment, unknown amounts of the label may be lost from the circulation resulting in the invalidation of the first requirement. The labeled RBC methods (carbon monoxide, radiophosphorus P-32, and radiochromium Cr-51 tagged RBCs) have a theoretical advantage in that the tagged cells do not leak from the intravascular space. Also, if measurements are taken too close to the time of injection, errors from inadequate mixing can arise. Thus, to allow sufficient mixing to occur and yet correct for losses from the circulation during the mixing period, the extrapolation method was suggested by Erlanger⁴¹ and developed by Gibson and Evans.³⁸ Multiple samples are taken during a predetermined time period (eg, 5-minute intervals over 30 minutes), and the log values are linearly plotted. Back extrapolation to time zero then gives the value for the initial concentration (C) required to calculate the overall intravascular compartment volume. The validity of this technique depends on the assumption that the calculated slope of the disappearance curve correctly estimates a constant removal rate of the label after mixing is complete.

This requirement is met by current methodology. More detailed reviews of the historical and technical aspects of BV determination can be found elsewhere.^{42–45}

Contemporary quantitative analysis of total BV also uses the indicator–dilution principle; however, the technique now uses a standardized computer-based and clinically available method to administer low dose iodinated labeled albumin (I-131, 5–30 micro Curies) intravenously. The technique requires about an hour to complete and has been validated clinically^{5,12,22,26,46–48} and in research analyses.^{48,49} The radiolabeled albumin is injected intravenously and from the contralateral forearm venous catheter 4-mL blood samples are collected at time 0 (preinjection), 12, 18, 24, 30, and 36 minutes post injection. Plasma radioactivity of each sample is measured in duplicate in a semiautomated computerized counter (Food and Drug Association–approved 1998, BVA-100 Blood Volume Analyzer, Daxor Corp, New York, NY). By extrapolation 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 were expanded or contracted consistent to a normal total BV. Reference normal expected total BV values are calculated using the percent deviation from normal body weight method with values derived from measurements determined from extensive life insurance tables for age, sex, weight, and height.^{46,49} 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 to 125 (considered the gold standard) with the comparator volumes being within 1% of one another.^{50,51} Normal total BV by this technique is defined as measured volumes within $\pm 8\%$ of the expected normal volume for each individual patient and RBCM and PV as measured volumes within $\pm 10\%$ of expected normal volumes. This reflects ≈ 3 SDs 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 blood volume expansion is considered >8% (>10% for RBCM and PV) to <25%, and severe as ≥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 is limited. Otherwise, by this technique BV quantitation has an intraindividual reproducibility of ±2.5%. Although this methodology is not necessary for all patients with HF, when used in clinically appropriate settings, it provides a tool to quantitatively identify PV and RBCM profiles in the individual 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. Multiple factors contribute to the accumulation and redistribution of body fluid with the expansion over time of the interstitial and intravascular compartments often ultimately leading to volume overload and organ congestion. The renal retention of sodium and water is an early response mechanism contributing to fluid accumulation, but redistribution of fluid mainly from 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. Clinical signs and symptoms and right heart hemodynamics can be helpful in alerting 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.

Disclosures

None.

References

- Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med.* 1990;113:155–159. doi:10.7326/0003-4819-113-2-155.
- Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol.* 2008;52:1527–1539. doi: 10.1016/j.jacc.2008.07.051.
- Walker RH ed. *Technical Manual of the American Association of Blood Banks.* 10th ed. Arlington, VA: American Association of Blood Banks; 1990:650.
- Rothe CF. Reflex control of veins and vascular capacitance. *Physiol Rev.* 1983;63:1281–1342.
- Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. *JACC Heart Fail.* 2014;2:298–305. doi: 10.1016/j.jchf.2014.02.007.
- Warren JV, Merrill AJ, Stead EA. The role of the extracellular fluid in the maintenance of a normal plasma volume. *J Clin Invest.* 1943;22:635–641. doi: 10.1172/JCI101435.
- Warren JV, Stead EA. Fluid dynamics in chronic congestive heart failure. *Arch Intern Med* 1944; 73:138–147. doi: 10.1001/archinte.1944.00210140028004.
- Darrow DC, Yannet H. The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte. *J Clin Invest.* 1935;14:266–275. doi: 10.1172/JCI100674.
- Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol.* 1896;19:312–326. doi: 10.1113/jphysiol.1896.sp000596.
- Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation.* 1989;80:299–305. doi: 10.1161/01.CIR.80.2.299.
- Gibson JG, Evans WA. Clinical studies of the blood volume III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. *J Clin Invest.* 1937;16:851–858. doi: 10.1172/JCI100911.
- Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. *Am J Cardiol.* 2004;93:1254–1259. doi: 10.1016/j.amjcard.2004.01.070.
- Seymour WB, Pritchard WH, Longley LP, Hayman JM. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein, and kidney function during cardiac failure and after improvement. *J Clin Invest.* 1942;21:229–240. doi: 10.1172/JCI101294.
- Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghide M. Fluid overload in acute heart failure—re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail.* 2008;10:165–169. doi: 10.1016/j.ejheart.2008.01.007.
- Metra M, Dei Cas L, Bristow MR. The pathophysiology of acute heart failure—it is a lot about fluid accumulation. *Am Heart J.* 2008;155:1–5. doi: 10.1016/j.ahj.2007.10.011.
- Gheorghide M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *Am J Med.* 2006;119(12 suppl 1):S3–S10. doi: 10.1016/j.amjmed.2006.09.011.
- Tyberg JV. How changes in venous capacitance modulate cardiac output. *Pflugers Arch.* 2002;445:10–17. doi: 10.1007/s00424-002-0922-x.
- Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. *Circ Heart Fail.* 2011;4:669–675. doi: 10.1161/CIRCHEARTFAILURE.111.961789.
- Miller WL, Mullan BP. Peripheral venous hemoglobin and red blood cell mass mismatch in volume overload systolic heart failure: implications for patient management. *J Cardiovasc Transl Res.* 2015;8:404–410. doi: 10.1007/s12265-015-9650-4.
- Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J.* 2004;25:1021–1028. doi: 10.1016/j.ehj.2004.04.023.
- Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease—the Framingham study: a 34-year follow-up. *Am Heart J.* 1994;127:674–682.
- Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. *Circulation.* 2003;107:226–229. doi: 10.1161/01.CIR.0000052623.16194.80.
- Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low versus preserved left ventricular ejection fractions. *Am J Cardiol.* 2008;102:1069–1072. doi: 10.1016/j.amjcard.2008.05.058.
- Hong N, Youn JC, Oh J, Lee HS, Park S, Choi D, Kang SM. Prognostic value of new-onset anemia as a marker of hemodilution in patients with acute decompensated heart failure and severe renal dysfunction. *J Cardiol.* 2014;64:43–48. doi: 10.1016/j.jjcc.2013.11.007.
- van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol.* 2013;61:1973–1981. doi: 10.1016/j.jacc.2012.12.050.
- Adlbrecht C, Kommata S, Hülsmann M, Szekeres T, Bieglmayer C, Strunk G, Karanikas G, Berger R, Mörtl D, Kletter K, Maurer G, Lang IM, Pacher R. Chronic heart failure leads to an expanded plasma volume and pseudoanaemia, but does not lead to a reduction in the body's red cell volume. *Eur Heart J.* 2008;29:2343–2350. doi: 10.1093/eurheartj/ehn359.
- Borovka M, Teruya S, Alvarez J, Helmke S, Maurer MS. Differences in blood volume components between hyporesponders and responders to erythropoietin alfa: the heart failure with preserved ejection fraction

- (HFPEF) anemia trial. *J Card Fail.* 2013;19:685–691. doi: 10.1016/j.cardfail.2013.08.508.
28. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA.* 1989;261:884–888. doi: 10.1001/jama.1989.03420060100040.
 29. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, Myerberg RJ. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med.* 1991;90:353–359.
 30. Stein JH, Neumann A, Marcus RH. Comparison of estimates of right atrial pressure by physical examination and echocardiography in patients with congestive heart failure and reasons for discrepancies. *Am J Cardiol.* 1997;80:1615–1618. doi: 10.1016/S0002-9149(97)00776-5.
 31. James KB, Troughton RW, Feldschuh J, Soltis D, Thomas D, Fouad-Tarazi F. Blood volume and brain natriuretic peptide in congestive heart failure: A pilot study. *Am Heart J* 2005; 150:984.e1–984.e6. doi: 10.1016/j.ahj.2005.07.031.
 32. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest.* 2008;134:172–178. doi: 10.1378/chest.07-2331.
 33. Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med.* 1984;12:107–112.
 34. Oohashi S, Endoh H. Does central venous pressure or pulmonary capillary wedge pressure reflect the status of circulating blood volume in patients after extended transthoracic esophagectomy? *J Anesth.* 2005;19:21–25. doi: 10.1007/s00540-004-0282-0.
 35. Küntschler MV, Germann G, Hartmann B. Correlations between cardiac output, stroke volume, central venous pressure, intra-abdominal pressure and total circulating blood volume in resuscitation of major burns. *Resuscitation.* 2006;70:37–43. doi: 10.1016/j.resuscitation.2005.12.001.
 36. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol.* 2013;62:516–524. doi: 10.1016/j.jacc.2013.05.027.
 37. Keith NM, Rountree LG, Geraghty JT. A method for the determination of plasma and blood volume. *Arch Intern Med.* 1915;16:547–576.
 38. Gibson JG, Evans WA. Clinical studies of the blood volume. I. Clinical application of a method employing the azo dye “Evans Blue” and the spectrophotometer. *J Clin Invest.* 1937;16:301–316. doi: 10.1172/JCI100859.
 39. Fox IJ, Brooker LG, Heseltine DW, Essex HE, Wood EH. A tricarbo-cyanine dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation. *Proc Staff Meet Mayo Clin.* 1957;32:478–484.
 40. Fine J, Seligman AM. Traumatic shock: IV. A study of the problem of the “Lost Plasma” in hemorrhagic shock by the use of radioactive plasma protein. *J Clin Invest.* 1943;22:285–303. doi: 10.1172/JCI101395.
 41. Erlanger J. Blood volume and its regulation. *Physiol Rev.* 1921: 1:177–207.
 42. Gregersen MI, Rawson RA. Blood volume. *Physiol Rev.* 1959;39:307–342.
 43. Lawson HF. The volume of blood – a critical examination of methods for its measurement. In: Hamilton WF and Dow P, eds. *Handbook of Physiology. Circulation.* Washington, DC:23–49.
 44. Shoemaker WC. The nature of the problem. In: Kugelmass, ed. *Shock, Chemistry, Physiology, and Therapy.* Springfield, IL: CC Thomas; 1967:3–13.
 45. Gauer OH, Henry JP, Behn C. The regulation of extracellular fluid volume. *Annu Rev Physiol.* 1970;32:547–595. doi: 10.1146/annurev.ph.32.030170.002555.
 46. Feldschuh J. Blood volume measurements in hypertensive disease. In: Larah JH, Brenner BM, eds. *Hypertension: Pathology, Diagnosis, and Management.* New York: NY: Raven Press; 1990.
 47. Katz SD. Blood volume assessment in the diagnosis and treatment of chronic heart failure. *Am J Med. Sci.* 2007;334:47–52. doi: 10.1097/MAJ.0b013e3180ca8c41.
 48. Van PY, Riha GM, Cho SD, Underwood SJ, Hamilton GJ, Anderson R, Ham LB, Schreiber MA. Blood volume analysis can distinguish true anemia from hemodilution in critically ill patients. *J Trauma.* 2011;70:646–651. doi: 10.1097/TA.0b013e31820d5f48.
 49. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation.* 1977;56(4 pt 1):605–612.
 50. Dworkin HJ, Premo M, Dees S. Comparison of red cell and whole blood volume as performed using both chromium-51-tagged red cells and iodine-125-tagged albumin and using I-131-tagged albumin and extrapolated red cell volume. *Am J Med. Sci.* 2007;334:37–40. doi: 10.1097/MAJ.0b013e3180986276.
 51. Fairbanks VF, Klee GG, Wiseman GA, Hoyer JD, Tefferi A, Pettitt RM, Silverstein MN. Measurement of blood volume and red cell mass: re-examination of ⁵¹Cr and ¹²⁵I methods. *Blood Cells Mol Dis.* 1996;22:169–86. doi: 10.1006/bcmd.1996.0024.