Understanding the Heterogeneity in Volume Overload and Fluid Distribution in Decompensated Heart Failure Is Key to Optimal Volume Management
Role for Blood Volume Quantitation

Wayne L. Miller, MD, PHD,* Brian P. Mullan, MD†

Rochester, Minnesota

Objectives   This study sought to quantitate total blood volume (TBV) in patients hospitalized for decompensated chronic heart failure (DCHF) and to determine the extent of volume overload, and the magnitude and distribution of blood volume and body water changes following diuretic therapy.

Background   The accurate assessment and management of volume overload in patients with DCHF remains problematic.

Methods   TBV was measured by a radiolabeled-albumin dilution technique with intravascular volume, pre-to-post–diuretic therapy, evaluated at hospital admission and at discharge. Change in body weight in relation to quantitated TBV was used to determine interstitial volume contribution to total fluid loss.

Results   Twenty-six patients were prospectively evaluated. Two patients had normal TBV at admission. Twenty-four patients were hypervolemic with TBV (7.4 ± 1.6 liters) increased by +39 ± 22% (range, +9.5% to +107%) above the expected normal volume. With diuresis, TBV decreased marginally (+30 ± 16%). Body weight declined by 6.9 ± 5.2 kg, and fluid intake/fluid output was a net negative 8.4 ± 5.2 liters. Interstitial compartment fluid loss was calculated at 6.2 ± 4.0 liters, accounting for 85 ± 15% of the total fluid reduction.

Conclusions   TBV analysis demonstrated a wide range in the extent of intravascular overload. Dismissal measurements revealed marginally reduced intravascular volume post-diuretic therapy despite large reductions in body weight. Mobilization of interstitial fluid to the intravascular compartment with diuresis accounted for this disparity. Intravascular volume, however, remained increased at dismissal. The extent, composition, and distribution of volume overload are highly variable in DCHF, and this variability needs to be taken into account in the approach to individualized therapy. TBV quantitation, particularly serial measurements, can facilitate informed volume management with respect to a goal of treating to euvolemia.   (J Am Coll Cardiol HF 2014;2:298–305) © 2014 by the American College of Cardiology Foundation

Volume overload and abnormal fluid distribution are front-line features in the syndrome of decompensated chronic heart failure (DCHF) (1–4). The accurate clinical assessment of volume status, particularly in determining euvolemia in the context of diuretic therapy, remains a significant challenge. Also, the dynamics and clinical significance of the heterogeneity in volume overload and fluid distribution are yet to be evaluated. Surrogate markers, such as the presence or absence of elevated jugular venous pressure (JVP), dyspnea, peripheral edema, S3, or hepatojugular reflux are commonly used and are considered the mainstays of the clinical evaluation of a patient's volume status. However, these markers lack

sensitivity and reliability (5,6). Accordingly, we sought to assess intravascular volume by direct measurement in patients admitted to the hospital for DCHF with clinically determined volume overload. The aims of the study were to measure total blood volume (TBV), red cell volume (RCV), and plasma volume (PV) at hospital admission and repeating these measurements at hospital discharge after standard-of-care diuretic

therapy. A primary goal was to determine the source, quantity, and variability of fluid removed with respect to intravascular and interstitial compartment volumes, and the relative completeness of diuretic therapy in achieving euvolemia. Our study hypothesis was that patients hospitalized for clinically determined volume overload would demonstrate not only hypervolemia, but also significant heterogeneity in the extent and distribution of volume overload. Furthermore, we hypothesized that serial TBV measurements would demonstrate persistent hypervolemia, despite typical duration and intensity of diuretic intervention.

Methods

Study group. Nonconsecutive patients admitted to the hospital for symptomatic DCHF (New York Heart Association functional classes III to IVa) and clinically determined volume overload were evaluated prospectively. Quantitated TBV measurements were obtained before diuresis therapy was initiated by the primary care service. In a portion of these patients, TBV was also measured on the day of hospital discharge. Patients who required urgent intensive care management were not included in this study because of logistic issues in carrying out volume measurements and the priority of other interventions. All patients received standard oral HF medical therapy, including beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and oral diuretics at the time of admission and throughout the hospital stay; the exception was the transition from oral to intravenous diuretic in the majority of patients. Patient inclusion criteria were: 1) age >18 years; 2) patients identified with DCHF (reduced or preserved left ventricular ejection fraction [LVEF]) and diagnosed clinically with volume overload by the admitting outpatient clinic cardiologist or emergency department evaluation; 3) ischemic or nonischemic etiology of HF; and 4) LVEF measured within 6 months before study enrollment. Exclusion criteria were: 1) chronic kidney disease requiring hemodialysis; 2) known renal artery stenosis disease; and 3) women who were pregnant. All patients except 3 received intravenous loop diuretic therapy (furosemide) at 10 to 20 mg/h for an average of 5 ± 2 days. The remaining 3 patients received oral furosemide equivalent of 80 to 160 mg/day for the same period on the basis of multiples of the outpatient oral regimen.

Changes pre-to-post–diuretic therapy in quantitated TBV by serial measurements and the commonly monitored clinical parameter of volume assessment (first morning post-void body weight changes) were used to determine the relative contributions of intravascular and interstitial fluid to overall total body fluid loss in response to diuretic therapy. The change in body weight over the short duration of this study was assumed to reflect change in total body water. Total body fluid removed (i.e., change in body weight in liters) minus the change in TBV equals the fluid removed from the interstitial compartment. The study was approved by the Mayo Foundation Institutional Review Board as required by Minnesota Statute 144.335/CFR 21 (Part 50).

Quantitation of intravascular volume. TBV, RCV, and PV quantitation analyses were performed in the Mayo Clinical Nuclear Medicine Laboratory using standard procedures to administer low-dose iodinated I-131–labeled albumin intravenously (Volumex, Daxor Corporation, New York, New York). This is a validated and standardized clinically available technique using the indicator-dilutional principle. The radiolabeled albumin is injected, and from a contralateral forearm, venous catheter 6-ml blood samples are collected at time 0 (pre-injection), and at 12, 18, 24, 30, and 36 min post-injection. Hematocrit is determined from each sample, and the plasma radioactivity of each sample is measured (in duplicate) in a semi-automated counter (Food and Drug Administration approved BVA-100 Blood Volume Analyzer, Daxor Corporation). By extrapolating the radioactivity from the samples to time 0, TBV can be derived. Each patient's peripheral hematocrit was "normalized" for what the patient's hematocrit would be if the PV were expanded or contracted to maintain a normal TBV. The TBV values were adjusted for age, sex, weight, and height using a published formula to calculate normal volumes as derived from >100,000 measurements of height and weight from Metropolitan Life tables (7). Normal TBV was defined pre-hoc as measured volumes within ±8% of the expected normal volume for that individual patient. Mild to moderate volume expansion was considered >8% to <25%, and severe as ≥25% of the expected normal volume. This permitted the determination of hyper-, hypo-, or euvolemia status, which was reported as an absolute value and as a percentage (excess or deficit) of the normal value. The coefficient of variation of the analytic technique is <3.5% (8). This technique is recommended for quantitative assessment of TBV by the International Committee for Standardization in Hematology for its precision and reproducibility (9). It has also been validated against the technically difficult and time-intensive, double-labeled technique of chromium tagged red cells and albumin 1-125 (considered the gold standard), with the published results demonstrating results within 1% of each other (10). The feasibility of the described TBV-PV quantitation technique has been well validated clinically (9,11–14) and in research analyses (7,9,10). TBV analysis can be repeated at 24 h due to the low background I-131 activity. The TBV measurement technique has an accuracy of ±2.5%.

Statistical analysis. Baseline continuous variable characteristic data are reported as mean ± SD or median with

Abbreviations and Acronyms

BP = blood pressure

DCHF = decompensated chronic heart failure

I/Os = fluid intake/ fluid output

JVP = jugular venous pressure

LVEF = left ventricular ejection fraction

PV = plasma volume

RCV = red cell volume

TBV = total blood volume

Table 1	Baseline Clinical and Demographic Characteristics of Patients Hospitalized for Decompensated Chronic Heart Failure (Total Cohort N = 26)
Age, yrs	73 ± 9
Male	18
Etiology of heart failure	
Ischemic	15
Nonischemic	11
Systolic blood pressure, mm Hg	120 ± 18
Body mass index, kg/m^2	35 ± 9
Left ventricular ejection fraction, %	38 ± 18
Length of hospital stay, days	6.0 ± 2.4
Diabetes, n	12
Hypertension, n	20
Coronary artery disease, no	18
Atrial fibrillation, n	11
NT-proBNP, pg/ml	4,886 (2,522, 12,361)
Albumin, g/dl	3.7 ± 0.3
K+, mEq/l	4.4 ± 0.5
Na+, mEq/l	139 ± 4.3
sCr, mg/dl	1.8 ± 0.9
BUN, mg/dl	44 ± 23
Hemoglobin, g/dl	12.2 ± 2.2
Hematocrit, %	38 ± 6.2
Plasma glucose, mg/dl	111 ± 24
Symptoms/signs, % of patients	
Dyspnea on exertion/orthopnea	100%
Fluid weight gain	86%
Increasing fatigue	88%
Lower extremity edema	79%
Hepatojugular reflux	62%
Jugular venous distension	90%

Values are mean ± SD, percent or number of patients in a category, or median (25th, 75th percentile confidence limits).

BUN = blood urea nitrogen; K = potassium; Na = sodium; NT-proBNP = N-terminal pro–B-type natriuretic peptide; sCr = serum creatine.

interquartile range for non-normally distributed data. Categorical variables are reported as frequency (percentage) or number in the category. Hospital admission and discharge TBV quantifications are reported as absolute volumes in liters and percent of calculated normal expected volumes. Wilcoxon signed-rank tests were used for comparing pre- and post-treatment measures in the same individuals with significance defined as $p < 0.05$. Simple linear regression analysis was used to examine predictive associations between individual variables. Controlling for multiple comparisons was not performed. Statistical analyses were performed using SAS version 9 statistical software (SAS Institute, Cary, North Carolina) and JMP 8 (SAS Institute).
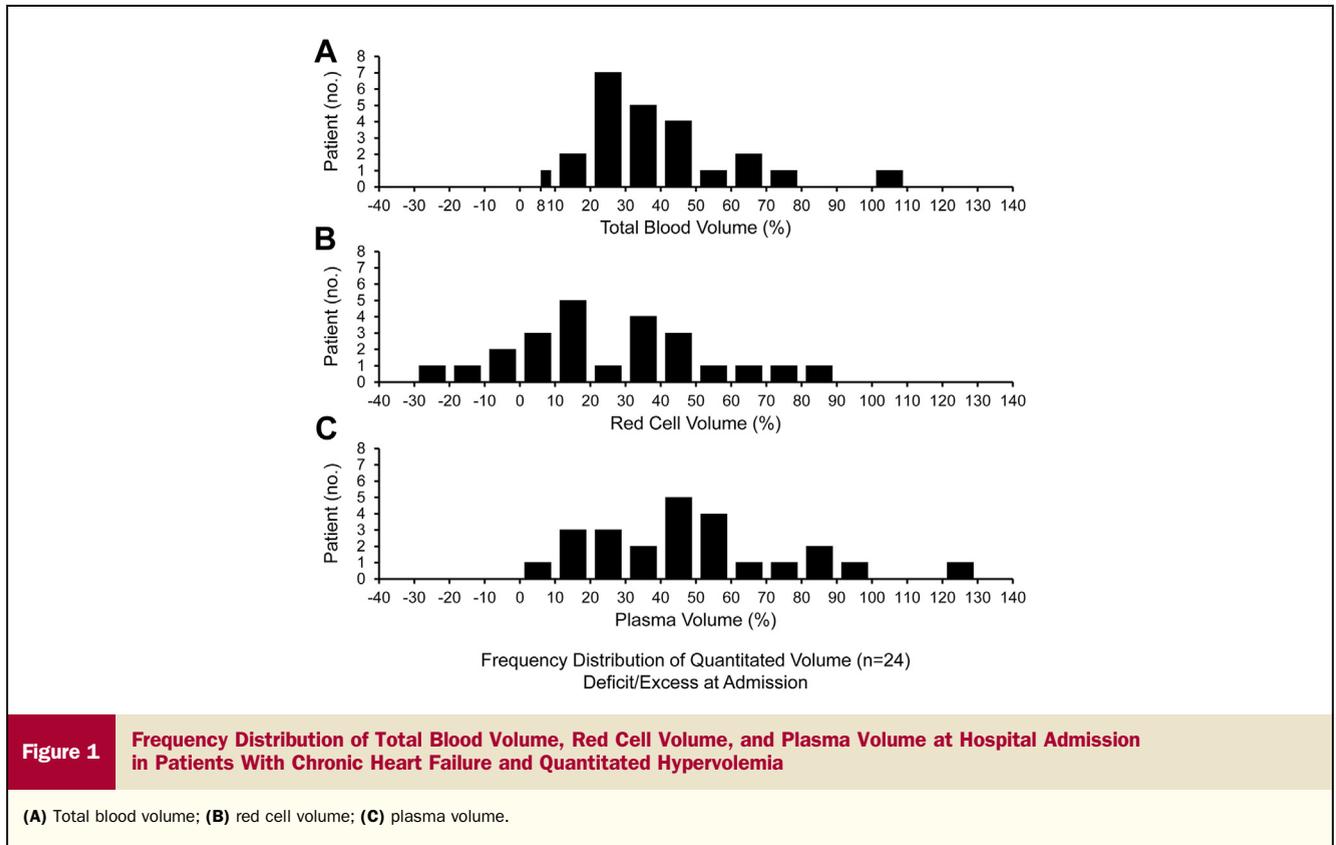
Results

The study cohort consisted of 26 Caucasian patients admitted to St Mary's Hospital, Mayo Clinic, Rochester, Minnesota, for DCHF, who were considered to require aggressive diuresis by the primary hospital service for symptomatic volume overload, and who also met inclusion and/or exclusion criteria. The principal admitting concerns expressed by the patients were worsening exertion dyspnea-orthopnea and fluid weight gain over the previous 10 days to 2 weeks. The clinical characteristics and demographic characteristics for this cohort are shown in Table 1. Of the 26 patients included in this study, all had TBV analysis performed at admission, and of this group, 17 patients also had TBV quantitated at hospital discharge. Two of the 26 patients were, by pre-hoc definition (total BV expansion ≤8%), euvolemic at admission, with a mean deviation from normal expected TBV value of +4 ± 5%; 24 patients were hypervolemic with a mean deviation from the normal expected TBV value of +39 ± 22%, reflecting a 2.1 ± 1.2 liter intravascular volume excess (Table 2). The frequencies of volume distribution (TBV, RCV, and PV) for the patients with hypervolemia at admission are shown in Figures 1A to 1C, respectively. No patients demonstrated volume contraction hypovolemia at admission.

Of the 2 patients who were euvolemic at admission, 1 patient was anemic, with an adjusted hematocrit for normal TBV of 35% (unadjusted peripheral hematocrit of 32%). This patient demonstrated a reduction in RCV (−22%) from normal expected volume with a compensatory expansion of PV by +28% to maintain an overall normal TBV. Of the 24 patients with hypervolemia at admission, 3 patients demonstrated true anemia (reduced RCV −21.3 ± 2.5% and hematocrit <38% after adjustment for normal TBV) with combined compensatory and pathologic PV expansion (mean deviation from normal PV value +53.2 ± 8.9%). Three patients demonstrated hemodilution-related anemia with normal quantitated RCV but pathological PV expansion (mean deviation from normal PV value +55.1 ± 19.6%). The remaining patients (n = 18) demonstrated dilution-related "anemia," or more appropriately, pseudo-anemia in the context of combined RCV expansion (mean deviation from normal range +38.5 ± 20.5%) and disproportional pathological PV expansion (mean deviation from normal range +52.6 ± 30.4%). No clinical features or laboratory findings distinguished these subgroups from the cohort as a whole. The

Table 2	Blood Volume Analysis of Hypervolemic Patients With Decompensated Chronic Heart Failure at Hospital Admission (N = 24)		
Variables	Total Blood Volume	Red Blood Cell Volume	Plasma Volume
Measure volume, liters	7.4 ± 1.6 (5.0 to 11.9)	2.6 ± 0.8 (1.4 to 4.7)	4.8 ± 1.0 (2.9 to 7.8)
Expected normal volume, liters	5.3 ± 0.7 (3.8 to 6.5)	2.1 ± 0.3 (1.4 to 2.7)	3.2 ± 0.4 (2.5 to 3.9)
Volume deviation from expected normal volume, %	+39 ± 22% (+9.5 to +107%)	+25 ± 27% (−24 to +65%)	+49 ± 28% (+13 to +128%)

Values are mean ± SD with range of values in parentheses.

Figure 1 **Frequency Distribution of Total Blood Volume, Red Cell Volume, and Plasma Volume at Hospital Admission in Patients With Chronic Heart Failure and Quantitated Hypervolemia**

(A) Total blood volume; **(B)** red cell volume; **(C)** plasma volume.

range of hypervolemia as demonstrated by quantitated TBV and PV was extensive, reflecting the marked heterogeneity in the patterns of volume expansion in these 24 DCHF patients (TBV: +9.5% to +107%; RCV: −24% to +70%; PV: +13% to + 128% from expected normal volumes).

Changes in volume and fluid distribution in response to diuretic therapy. Admission and dismissal characteristics of the 17 patients who had TBV quantitated both at hospital admission and at discharge are shown in Table 3. Collective changes in TBV, RCV, and PV with diuretic therapy are shown in Table 4. Intravascular volume was increased in these patients at admission, with an average TBV excess of +40 ± 27% and PV increase of +49 ± 32%. The heterogeneity, as reflected in the frequency distributions of the quantitated TBV and PV at admission, is shown in Figures 2A and 3A, respectively.

With diuresis intervention, relatively minor changes in the quantitated TBV were demonstrated at discharge, with a mean of less than 1 liter of net fluid reduced from the intravascular compartment during the hospital stay (Table 4) (p = 0.214). The relatively minor quantitated intravascular volume change was, however, in the setting of large reductions in body weight (−6.9 ± 5.2 kg) and net negative fluid intake/fluid output (I/Os) (−8.4 ± 5.2 liters) during this same period. The change in body weight (kilograms) over the short duration of this study was assumed to be equivalent to changes in total body water

(liters). Thus, the change in observed body weight in liters less the reduction in TBV reflected fluid loss from the interstitial compartment occurring as a result of transcapillary refill of the intravascular compartment. The

Table 3 **Clinical Features of Hypervolemic Patients With Hospital Admission and Discharge Quantitated Blood Volume Analyses (N = 17)**

Variables	Values
Age, yrs	74 ± 10
Male	13
Body mass index, kg/m^2	34 ± 8
Left ventricular ejection fraction, %	34 ± 16
Length of hospital stay, days	6.4 ± 1.9
Change in weight, kg	−6.9 ± 5.2
Net fluid intake/fluid output, liters	−8.4 ± 5.2

	Admission	Discharge
Systolic blood pressure, mm Hg	122 ± 17	116 ± 16
Albumin, g/dl	3.6 ± 0.3	3.5 ± 0.4
Na+, mEq/l	138 ± 5	139 ± 4
K+, mEq/l	4.3 ± 0.4	4.0 ± 0.4
sCr, mg/dl	2.0 ± 1.1	2.0 ± 1.2
BUN, mg/dl	50 ± 27	52 ± 23
Hemoglobin, g/dl	12.6 ± 2.4	12.8 ± 2.2
Hematocrit, %	40 ± 6.8	39 ± 6.3
Normalized hematocrit, %	55 ± 14	52 ± 12
Plasma glucose, mg/dl	113 ± 22	117 ± 28

Values are mean ± SD or n.
Abbreviations as in Table 1.

Table 4	Quantitated Volume Changes Admission to Discharge in Response to Diuretic Therapy in Hypervolemic Patients (N = 17)		
Variables	**Total Blood Volume**	**Red Cell Volume**	**Plasma Volume**
Admission volume, liters	7.4 ± 1.6 (4.6 to 11.9)	2.6 ± 0.9 (1.5 to 4.7)	4.7 ± 1.2 (2.7 to 7.8)
Dismissal volume, liters	6.7 ± 1.3* (4.9 to 8.9)	2.4 ± 0.7* (1.3 to 4.4)	4.3 ± 0.8* (3.0 to 5.9)
Net volume change, liters	−0.7 ± 1.1 (+0.5 to −3.9)	-0.2 ± 0.3 (+0.5 to −0.8)	−0.5 ± 0.8 (+0.3 to −3.1)
Expected volume, liters	5.3 ± 0.8 (3.8 to 6.5)	2.1 ± 0.4 (1.4 to 2.7)	3.2 ± 0.4 (2.5 to 3.9)
Volume deviation from normal: admission, %	+40 ± 27 (+9 to +106)	+25 ± 20 (-24 to +70)	+49 ± 32 (+5 to +128)
Volume deviation from normal: dismissal, %	+30 ± 16 (+9 to +51)	+21 ± 20 (−21 to +69)	+38 ± 18 (+12 to +77)

Values are mean ± SD and range of values in parentheses. Interstitial transcapillary refill volume (TCRV) = 6.2 ± 4.0 liters (TCRV = Change in body weight [in liters] minus change in total blood volume [in liters]) Percent of total body fluid volume loss derived from the interstitial space = 85 ± 15%. *p > 0.05, nonsignificant difference with admission values.

calculated volume (interstitial fluid removed = body weight change [in liters] − TBV change [liters]) was 6.2 ± 4.0 liters, reflecting 85 ± 15% of the overall fluid loss being derived from the interstitial compartment. However, even with this diuretic-induced fluid loss, the quantitated TBV and PV at hospital discharge compared with volumes at admission remained persistently increased by +30 ± 16% and +38 ± 18%, respectively. This reflected a persistent TBV hypervolemia of 1.5 ± 0.9 liters and PV of 1.2 ± 0.6 liters. The heterogeneity in the distribution of the quantitated TBV and PV at dismissal is shown in Figures 2B and 3B, respectively. Individual patient data on TBV at hospital admission and at discharge are shown in Figure 4A, with the corresponding patient's net total body fluid loss shown in Figure 4B.

No significant associations of length of hospital stay with change in TBV (r = 0.394, p = 0.119) or with change in body weight (r = 0.407, p = 0.105) were

demonstrated. Also, no predictive associations among hemoglobin or hematocrit with admission TBV (r = 0.161, p = 0.433; r = 0.103, p = 0.616, respectively), hemoglobin or hematocrit with discharge TBV (r = 0.162, p = 0.496; r = 0.184, p = 0.438, respectively), or changes in hemoglobin or hematocrit with change in TBV (pre-to-post–diuretic therapy) (r = 0.181, p = 0.486; r = 0.171, p = 0.511, respectively) were demonstrated. At discharge, all patients described some degree of subjective improvement (even resolution) in reported admission symptoms (exertion dyspnea-orthopnea, lower extremity edema, fluid weight gain), but such symptom changes were not reflected in the objective findings of ongoing fluid retention as demonstrated in this cohort. Elevated JVP and hepatojugular reflux were still present in approximately 50% and 70%, respectively, of patients when reported at discharge. This discrepancy was likely a basis for early recurrence of symptoms post-discharge and repeat hospital stays.
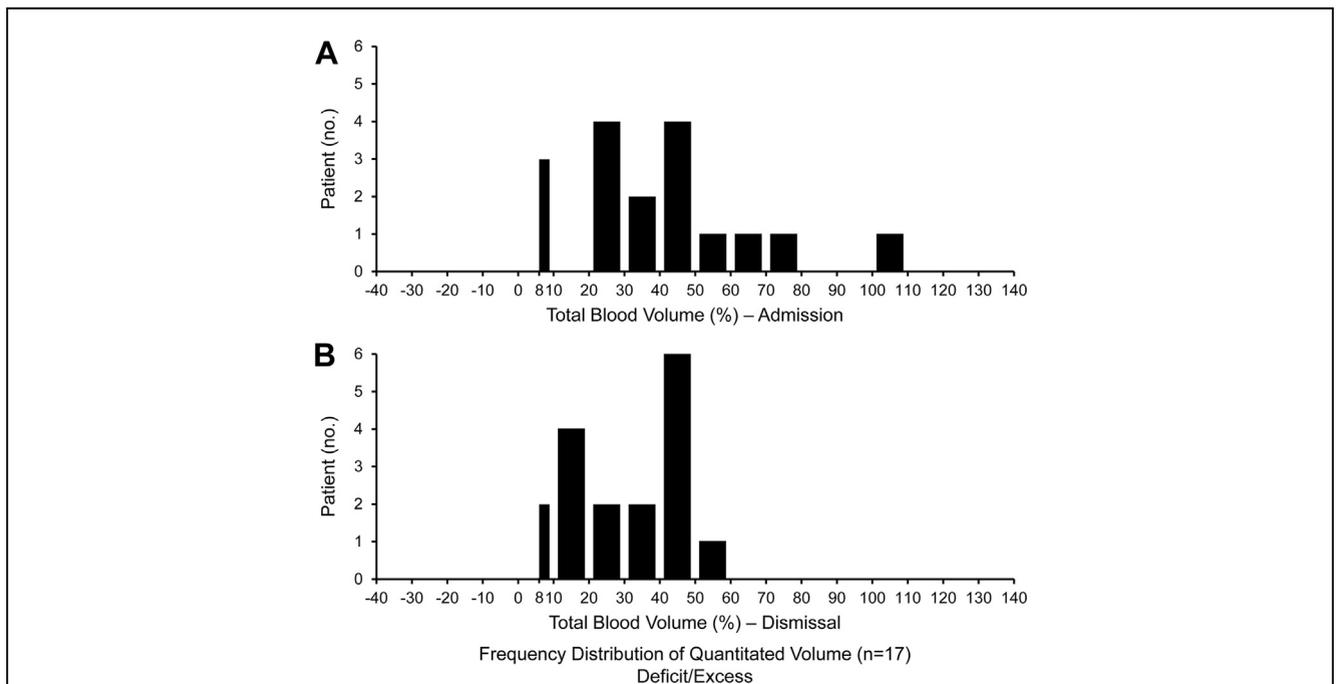

Figure 2   Frequency Distribution of Total Blood Volume in Hypervolemic Patients With Paired Admission and Discharge Volume Analyses

(A) Paired admission; **(B)** discharge volume analyses.

Figure 3   Frequency Distribution of Plasma Volume in Hypervolemic Patients With Paired Admission and Discharge Volume Analyses

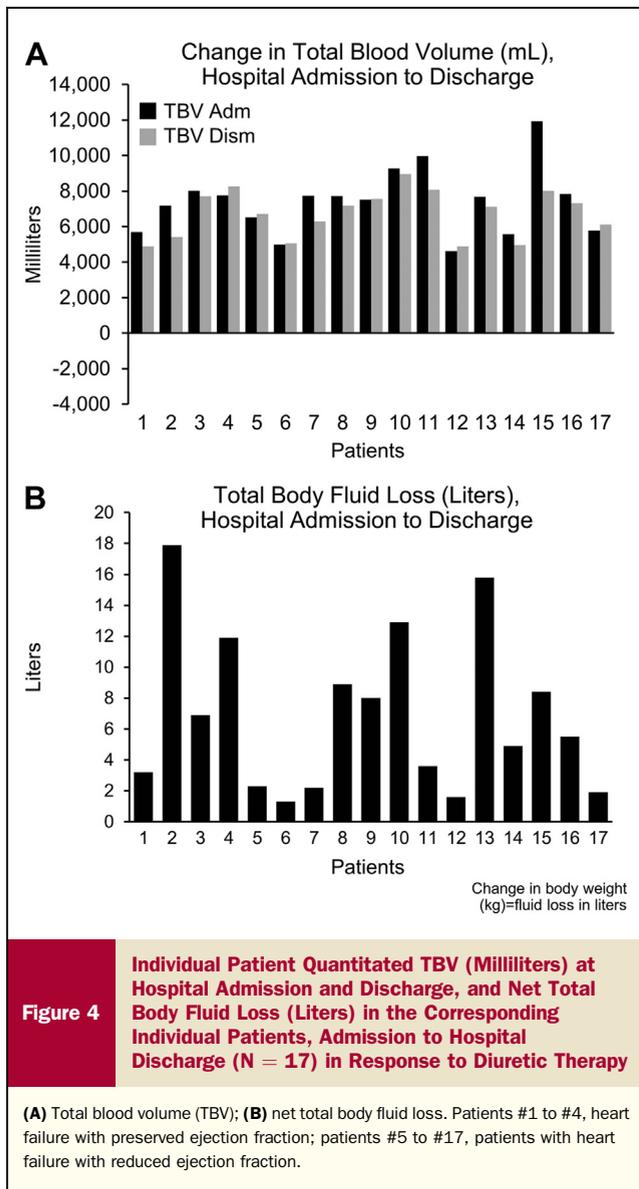**(A)** Paired admission; **(B)** discharge volume analyses.
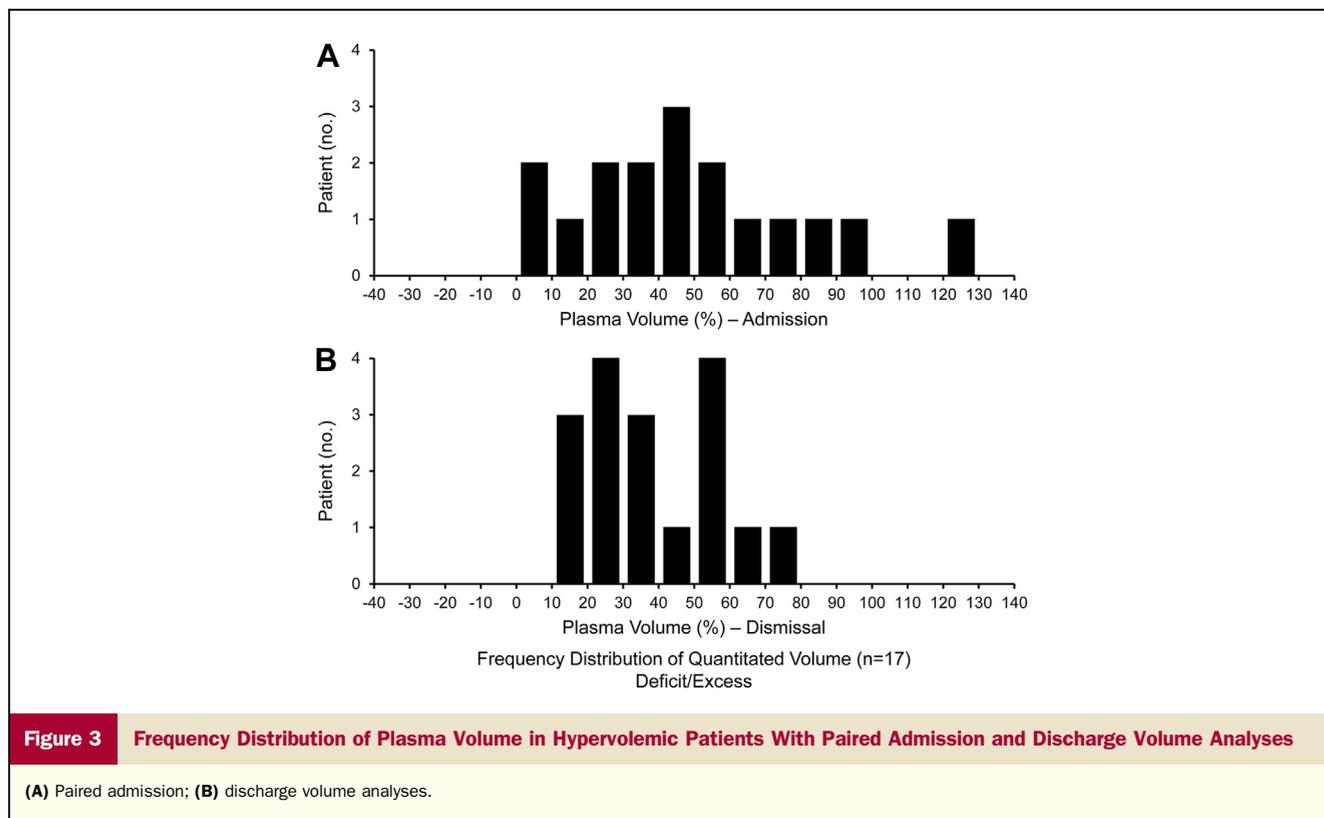
Discussion

The findings of this study, using quantitated analysis of TBV, demonstrate marked heterogeneity in the extent of intravascular volume overload (range of 10% to more than 100% volume increase) in patients hospitalized for DCHF and clinically suspected hypervolemia. Our data also demonstrate, for the first time, that the major component of volume loss with diuretic therapy is derived from the interstitial space (approximately 85% in this cohort) and not from the intravascular compartment, and that despite large reductions in body weight and high net negative I/Os, intravascular volume remains persistently overloaded (+30%) at hospital discharge.

The interplay of multiple confounding factors (hemoglobin concentration [anemia, polycythemia], oncotic pressures [low albumin concentration], systemic hypotension, diuretic and vasodilator therapies, and intrinsic renal function) influences fluid distribution with differential interstitial and intravascular volume expansion. Although it is recognized that volume expansion may be compensatory for reduced cardiac output, arterial underfilling, and hypotension, it can also be excessive and detrimental. The marked heterogeneity in excess volume expansion and the dispersion of the fluid removed, as shown in our study, are not commonly considered factors in a comprehensive volume management strategy. It is clinically important to recognize that the preponderance of the fluid removed is from the chronic expansion of the interstitial compartment, with mobilization of this fluid into the intravascular space during diuretic therapy. Although a reduction in intravascular volume with diuretic therapy was demonstrated, this was a relatively small component of the overall change compared with that of the fluid shifted from the interstitial compartment. It is notable that despite the large volume shift and volume loss with diuretic therapy, the intravascular space still remained significantly expanded at hospital discharge. This identifies DCHF patients as not achieving euvolemia although commonly used clinical parameters of weight change and net I/Os suggested that significant intravascular volume reduction had been achieved.

The heterogeneity observed in this analysis emphasizes the importance of recognizing that changes in TBV and PV need to be interpreted with respect to the red blood cell mass. Using the World Health Organization criterion for defining anemia by hemoglobin concentration (<13 g/dl for men and <12 g/dl for women), 14 of the 26 patients (54%) would be categorized as anemic at hospital admission. However, it is important to differentiate true anemia with appropriate homeostatic expansion of PV from pathological PV expansion related to neuroendocrine activation of sodium and water retention mechanisms by the kidney, which results in extracellular volume expansion over time and the development of hemodilution-related "anemia." It is often less appreciated that TBV expansion can also develop as a result

A   Change in Total Blood Volume (mL), Hospital Admission to Discharge

B   Total Body Fluid Loss (Liters), Hospital Admission to Discharge

Change in body weight (kg)=fluid loss in liters

Figure 4   **Individual Patient Quantitated TBV (Milliliters) at Hospital Admission and Discharge, and Net Total Body Fluid Loss (Liters) in the Corresponding Individual Patients, Admission to Hospital Discharge (N = 17) in Response to Diuretic Therapy**

(A) Total blood volume (TBV); (B) net total body fluid loss. Patients #1 to #4, heart failure with preserved ejection fraction; patients #5 to #17, patients with heart failure with reduced ejection fraction.

of compensatory tissue hypoxemia-driven red cell mass expansion (polycythemia) and by pathological PV expansion, as demonstrated in our study. Hence, there is a value in quantitating the components of TBV (RCV and PV) to sort out and appropriately manage the heterogeneities associated with fluid overload. This concept is also supported by a recent report (15) that assessed the response to erythropoietin therapy in patients with heart failure with preserved ejection fraction who had reduced hemoglobin; quantitative analysis of TBV demonstrated that responders had true RCV deficit anemia with compensatory PV expansion, whereas non-responders had dilution-related pseudo-anemia with no RCV deficit, but did have pathological PV expansion.

The treatment of hospitalized DCHF patients with a prime focus on diuresis may not always be optimal. Some patients, as shown in this study, are euvolemic at the time of admission despite a clinical assessment that suggests volume overload. Aggressive diuretic therapy in such patients could contribute to intravascular volume contraction and end-organ impairment. Other patients, as also shown in this analysis, demonstrate compensatory PV expansion in the presence of true anemia, but have an overall normal TBV. Transfusion with gentle diuresis would be a more appropriate intervention than aggressive diuresis, which could be detrimental (11). Systemic hypotension noted in our cohort (13 of 26 patients at admission had systolic blood pressure [BP] of <115 mm Hg, and 11 of 17 patients had lower BP at discharge than systolic BP at admission) in relation to impaired myocardial function, vasodilator medications, and ongoing diuresis is a plausible contributing factor to renal hypoperfusion, pre-renal azotemia, and impaired diuretic response, and therefore, persistent hypervolemia at discharge.

The importance of hypervolemia as a powerful marker of risk in chronic HF has been linked to poor outcomes (4,16,17), and the American College of Cardiology Foundation/American Heart Association practice guidelines recommend not discharging patients until euvolemia has been achieved (18). The accurate assessment of hypervolemia or even euvolemia, however, remains a difficult issue even for the experienced clinician. The assessment of volume status using clinical markers such as elevated JVP, lower extremity edema, or S3 remains inadequate. Hemoconcentration, identified by increases in hemoglobin, hematocrit, or plasma albumin as reflections of reduction in intravascular volume, has also been suggested as a means of assessing change in volume status (19–21). These surrogates, however, lack sensitivity and specificity (5,6), and therefore, could contribute to a false interpretation of a patient's true volume status. Even asymptomatic patients with chronic HF and no clinically recognized volume overload have been shown to be hypervolemic, as shown in the study by Androne et al. (14), in which quantitated TBV analysis was undertaken in 43 ambulatory patients with heart failure with reduced ejection fraction. The presence of hypervolemia was associated with poor long-term survival compared with euvolemic patients.

The findings of our study in symptomatic HF patients reveal a significant variability in the extent and pattern of hypervolemia that cannot be confidently identified by clinical assessment alone. Therefore, the ability to directly quantitate intravascular volume can be a useful tool in guiding effective volume management and determining the most appropriate course of diuretic therapy (i.e., more diuresis, less diuresis, or when not to initiate diuretic therapy). Also, given the worsening HF epidemic and the high frequency of repeat hospital stays in HF patients (22,23), a relevant question is: Would knowing the TBV status help to effectively guide restoration to a compensated state of HF, and would this, in turn, favorably affect repeat hospital stay rates and long-term mortality? Whether longer length of hospital stays to achieve euvolemia in DCHF patients can be justified is not clear at present, but a hypothesis that longer lengths of stay with individualized quantitated TBV-guided

management would be compensated by reductions in 30-day repeat hospital stay rates and better long-term outcomes merits study. The present findings conceptually support the development of a randomized clinical trial of TBV analysis-guided versus standard clinically guided volume management in DCHF patients to assess long- and short-term outcomes.

Study limitations and strengths. Although the present study represents a small series of DCHF patients that limits broad inference, each patient underwent a comprehensive quantitated volume assessment, and the findings constitute important proof of concept of the heterogeneity in volume expansion, composition, and distribution of fluid overload in HF. The confounding factors of systemic hypotension, reduced oncotic pressures (hypoalbuminemia), anemia, and impaired renal function also influence volume distribution and response to diuretic therapy. Due to the small number of patients in this cohort, these factors could not be adequately evaluated. The interstitial fluid contribution to the volume loss with diuretic therapy is a calculated volume, and no direct measurement of total interstitial fluid is available at present to permit a quantitative assessment.

Conclusions

The quantitation of TBV in patients with DCHF demonstrates that significant heterogeneity exists in the extent, composition, and distribution of volume overload and that vigorous diuretic therapy may only marginally affect intravascular volume status at discharge despite large reductions in fluid-associated body weight. The transcapillary mobilization of expanded interstitial space fluid into the intravascular compartment accounts for this disparity and identifies the major contribution to fluid loss with diuresis. The quantitative measurement of TBV, RCV, and PV, particularly serial measurements, in individual DCHF patients thus permits an informed pathophysiological-based understanding of the complexity of volume overload, and provides a direct measure to guide tailored volume management.

Reprints and correspondence: Dr. Wayne L. Miller, Mayo Clinic, Division of Cardiovascular Diseases, 200 First Street, SW, Gonda Building 5S130, Rochester, Minnesota 55905. E-mail: miller.wayne@mayo.edu.

REFERENCES

1. Francis GS, Goldsmith SR, Levine B, Olivari MT, Cohn JA. The neurohormonal axis in congestive heart failure. Ann Intern Med 1984; 101:370–7.
2. Hamilton RW, Buckalew WM Jr. Sodium, water, and congestive heart failure. Ann Intern Med 1984;100:902–3.
3. Cody RJ, Covit AB, Schaer GL, Laragh JH, Sealey JE, Feldschuh J. Sodium and water balance in chronic congestive heart failure. J Clin Invest 1986;77:1441–52.
4. Ghali JK, Tam SW. The critical link of hypervolemia and hyponatremia in heart failure and the potential role of arginine vasopressin antagonists. J Cardiac Fail 2010;16:419–31.
5. Chakko S, Woska D, Martinez H, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med 1991;90: 353–9.
6. Butman SM, Ewy GA, Standen JR, Kern KB, Hahn E. Bedside cardiovascular examination in patients with severe chronic heart failure: importance of rest or inducible jugular venous distension. J Am Coll Cardiol 1993;22:968–74.
7. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. Circulation 1977;56:605–12.
8. Feldschuh J. Blood volume measurements in hypertensive disease. In: Larah JH, Brenner BM, editors. Hypertension: Pathology, Diagnosis, and Management. New York, NY: Raven Press, 1990;339–47.
9. Fairbanks VF, Klee GG, Wiseman GA, et al. Measurement of blood volume and red cell mass: re-examination of 51Cr and 125I methods. Blood Cells Mol Dis 1996;22:169–86.
10. Dworkin HJ, Premo M, Dees S. Comparison of red cell volume 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.
11. Androne A, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. Circulation 2003;107:226–9.
12. Katz SD. Blood volume assessment in the diagnosis and treatment of chronic heart failure. Am J Med Sci 2007;334:47–52.
13. Van PY, Riha GM, Cho SD, et al. Blood volume analysis can distinguish true anemia from hemodilution in critically ill patients. J Trauma 2011;70:646–51.
14. 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;93:1254–9.
15. Borovka M, Teruya S, Alvarez, 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 Cardiac Fail 2013;19:685–91.
16. Bonfils PK, Damgaard M, Taskiran M, Goetze JP, Norsk P, Gadsboll N. Impact of diuretic treatment and sodium intake on plasma volume in patients with compensated systolic heart failure. Eur J Heart Fail 2010;12:995–1001.
17. Davila DF, Nunez TJ, Oderman R, Mazzei de Davila CA. Mechanisms of neurohormonal activation in chronic congestive heart failure: pathophysiology and therapeutic implications. Int J Cardiol 2005;101: 343–6.
18. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure in adults. J Am Coll Cardiol 2013;62:1495–539 [full-text, J Am Coll Cardiol 2013;62: e147–239].
19. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265–72.
20. Van der Meer P, Postmus D, Ponikowski P, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol 2013;61:1973–81.
21. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WHW. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival. J Am Coll Cardiol 2013;62:516–24.
22. Butler J, Kalogeropoulos A. Worsening heart failure hospitalization epidemic. J Am Coll Cardiol 2008;52:435–7.
23. Ross JS, Chen J, Lin Z, et al. Recent national trends in readmission rates after heart failure hospitalization. Circ Heart Fail 2010;3: 97–103.