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# Understanding the Heterogeneity in Volume Overload and Fluid Distribution in Decompensated Heart Failure Is Key to Optimal Volume Management

## Role for Blood Volume Quantitation

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**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

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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.

**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

## 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 prehoc 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