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Volume Overload Profiles in Patients With Preserved and Reduced Ejection Fraction Chronic Heart Failure

Are There Differences? A Pilot Study

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ABSTRACT

OBJECTIVES This study aimed to characterize volume profiles and their differences in heart failure (HF) patients with preserved (HFpEF) and reduced (HFrEF) ventricular systolic function.

BACKGROUND The extent and distribution of volume overload and the associated implications for volume management have not been studied in decompensated HFpEF compared with HFrEF.

METHODS Total blood volume (TBV) was quantitated using a standardized computer-based radiolabeled albumin dilution technique.

RESULTS Twenty HFpEF and 35 HFrEF patients were evaluated at hospital admission. TBV was expanded by 27 ± 21% (range -5.2% to 77%; $p = 0.002$) and 37 ± 25% (0% to 107%; $p < 0.001$), respectively, above normal volumes. Red cell mass (RBCM) was expanded in HFrEF (24 ± 31%; $p = 0.004$) but within normal limits in HFpEF (8 ± 34%; $p = 0.660$) with, however, large variability in both groups. RBCM excess was more prominent in HFrEF (63% vs. 45%) than the RBCM deficit in HFpEF (35% vs.14%). With diuresis, TBV decreased to 25 ± 20% ($p = 0.029$) in HFrEF but was not changed in HFpEF (18 ± 20% [$p = 0.173$]). Body weight declined 6.6 ± 4.4 kg in HFrEF and 10.5 ± 8.3 kg ($p = 0.026$) in HFpEF. Interstitial fluid losses accounted for 85 ± 13% (HFrEF) and 93 ± 6% (HFpEF) ($p = 0.012$) of total volume removed.

CONCLUSIONS TBV profiles differ between HFpEF and HFrEF patients with DCHF. Quantitated volume analysis revealed both significant RBCM (polycythemia) and plasma volume excess in HFrEF, whereas a higher RBCM deficit (true anemia) was demonstrated in HFpEF. Diuresis produced only a modest reduction in intravascular volumes with persistent hypervolemia in both groups at discharge, but overall more total body fluid was lost in HFpEF. These profile differences have implications for individualizing volume management. (J Am Coll Cardiol HF 2016;4:453–9)
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The accurate clinical assessment of overall volume status, and particularly the composition and distribution of volume overload, historically and currently remains a significant issue in patients hospitalized with decompensated chronic heart failure (DCHF) (1–5). Although we and others have described the marked heterogeneity in the extent and distribution (intravascular and interstitial) of volume overload in patients with DCHF (6,7), it is as yet unclear if the profiles of volume overload, and, therefore, the implications for volume management, differ substantially in patients with HF with preserved left ventricular ejection fraction (HFpEF) relative to those from reduced ejection fraction (HFrEF). Accordingly, we sought to assess intravascular volume by direct quantitative measurement in

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ABBREVIATIONS AND ACRONYMS

DCHF = decompensated chronic heart failure

ED = emergency department

HFpEF = heart failure with preserved ejection fraction

HFREF = heart failure with reduced ejection fraction

PV = plasma volume

RBCM = red blood cell mass

TBV = total blood volume

patients with HFpEF and HFrEF who were admitted to the hospital for DCHF with clinically assessed volume overload. The aims of the study were to quantitate total blood volume (TBV), red blood cell mass (RBCM), and plasma volume (PV) at hospital admission and determine if differences exist in the intravascular volume profiles with regard to extent and composition of fluid

SEE PAGE 460

overload and how diuretic therapy affected these volume profiles. Our study hypothesis was that patients hospitalized for clinically determined volume overload with HFpEF would demonstrate more normal range intravascular volume (euvolemia) than HFrEF and that hypervolemia (attributable to greater RBCM and PV expansion) would be more prevalent in patients with HFrEF. Further, we hypothesize that serial TBV measurements would demonstrate more persistent hypervolemia in the HFrEF phenotype despite standard-of-care diuretic therapy intervention in both subgroups.

METHODS

STUDY GROUP. Symptomatic New York Heart Association functional class III to IVa patients with clinically determined volume overload (DCHF) by an outpatient clinic cardiologist or emergency department (ED) physician, admitted to a cardiology hospital service, and met study criteria were analyzed. TBV was measured in all study patients before the initiation of scheduled diuretic therapy as ordered by the primary care service. Four patients who were admitted from the ED received a single 20-mg intravenous bolus of furosemide while in transit from the ED to their hospital rooms. TBV was also measured before hospital discharge. Patients requiring intensive care management such as need for intravenous positive inotrope therapy or other invasive therapies were not included in this analysis. All patients were receiving standard oral HF medical therapy including beta-blockers, converting enzyme inhibitor or angiotensin receptor blockers, and oral diuretics at the time of admission. Patient inclusion criteria were: 1) age >18 years; 2) patients identified with DCHF, HFrEF (EF <50%), HFpEF (preserved left ventricular EF [LVEF] ≥50%), and diagnosed clinically with volume overload by the admitting outpatient clinic cardiologist or ED 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) females who were pregnant. All patients except 4 received intravenous loop diuretic therapy (furosemide) at 10 to 20 mg/h for an average of 5 ± 2 days. The 4 patients (3 HFrEF, 1 HFpEF) who did not receive intravenous diuretic therapy received oral furosemide or equivalent at 80 to 160 mg per day for the same period.

Changes in quantitated TBV by serial measurements (admission and predischarge) and first morning postvoid and preprandial body weight changes were used to determine the relative contributions of intravascular and interstitial fluids to overall total body fluid loss in response to diuretic therapy. The change in body weight over the course of the hospitalization was assumed to reflect change in total body water content. The calculation for the total fluid removed from the interstitial compartment was the total body fluid removed as reflected in the change in body weight in liters less the change in TBV. 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, RBCM, and PV quantitation analyses using the radiotracer indicator-dilution method were undertaken in the Mayo Clinical Nuclear Medicine Laboratory using standardized computer-based procedure to administer low dose (micro-Ci) iodinated I-131-labeled albumin intravenously (Volumex, Daxor Corp., New York, New York). The radiolabeled albumin was injected, and from a contralateral forearm venous catheter 4-ml blood samples were collected at time 0 (preinjection), 12, 18, 24, 30, and 36 min postinjection. Hematocrit was determined from each sample, and plasma radioactivity of each sample was measured (in duplicate) in a semiautomated counter system (BVA-100 Blood Volume Analyzer, Daxor Corp.). By extrapolating the radioactivity from the samples to time 0, TBV can be measured with the use of whole body hematocrit to determine RBCM. Expected normal reference volumes for the individual patient are also incorporated into the computer analysis (8,9). Normal TBV was defined pre hoc as measured volumes within ±8% of the expected normal volume for the individual patient. Mild to moderate volume expansion was considered >8% to <25%, and severe as ≥25% above the expected normal volumes. Volumes are reported as an absolute values and as a percentage excess (+) or deficit (-) of expected normal value. This technique has been recommended for the quantitative assessment

of TBV by the International Committee for Standardization in Hematology for its precision and reproducibility (9,10) and has also been validated against the double-label technique of chromium tagged red cells and albumin 1-125 with the published results demonstrating results within 1% (11). The feasibility of the TBV quantitation technique, which requires about 1 h for completion and has an intra-individual reproducibility of ±2.5%, has been validated clinically and in research analyses (8–15).

STATISTICAL ANALYSIS. Baseline continuous variable characteristic data are reported as mean SD or median with interquartile range for nonnormally distributed data. Categorical variables are reported as frequency (percentage) or number in the category. Wilcoxon signed-rank tests were used for comparing pre- and post-diuretic treatment measures in the same individuals with significance defined as $p < 0.05$. Intergroup differences were analyzed using nonpaired Student *t* testing. Controlling for multiple comparisons was not undertaken. Renal function was determined by calculation of the estimated glomerular filtration rate (ml·min·1.73 m^2) using the Modification of Diet in Renal Disease equation (16). Statistical analyses were performed using SAS, version 9, statistical software (SAS Institute, Cary, North Carolina) and JMP 8.

RESULTS

The study cohort consisted of 55 patients (35 with HFrEF; 20 patients with HFpEF) admitted to hospital for DCHF and considered to require diuresis by the primary hospital service for symptomatic volume overload and who also met inclusion/exclusion criteria. The principal admitting complaints expressed by the patients were worsening exertion dyspnea, orthopnea, and fluid weight gain over the previous 1 to 2 weeks. The clinical characteristics and demographics for the cohort by HFpEF and HFrEF subgroup are shown in Table 1. Patients with HFpEF had higher systolic blood pressure, morbid obesity by body mass index, and lower plasma N-terminal pro-B-type natriuretic peptide and hemoglobin levels than patients with HFrEF.

Overall volume analysis data are shown in Table 2. Four patients in the HFpEF group (20%) and 5 patients in the HFrEF group (14%) demonstrated normal TBV (within ±8% of the normal expected volumes) at admission. No patients in either group were hypovolemic at admission. Hypervolemia (TBV >8% of expected volume) was observed in the remaining patients in both groups at admission: HFpEF, 7.2 ± 1.5 l (34 ± 19%; range 11% to 77% above expected normal; $p = 0.003$) and HFrEF, 7.8 ± 2.0 l, 43 ± 23% (range 9.5% to 107% above expected normal; $p < 0.001$). In those patients with TBV hypervolemia, PV was expanded (HFpEF 4.9 ± 1.1 l [44 ± 25%]; range 6.5 to 80%) and HFrEF 5.0 ± 1.4 l (53 ± 30%; range 8.5% to 128% above expected normal) in the majority of patients in both groups (94% and 97%, respectively).

Overall, RBCM was expanded in HFrEF (26 ± 31%; $p = 0.004$) but was within normal range in HFpEF (8.0 ± 34%; $p = 0.660$), although there was large variability in both groups. Although one-fifth of patients in each group had a normal RBCM at admission, true anemia with both low peripheral hemoglobin and RBCM deficit was more prominent in HFpEF (35% vs. 14%) and RBCM excess (polycythemia) in HFrEF (63% vs. 45%). In contrast to the quantitative volume data, peripheral venous hemoglobin concentrations would have identified 65% of HFpEF and 60% of HFrEF patients as being anemic by World

TABLE 1 Baseline Clinical and Demographic Characteristics of Patients Hospitalized for Decompensated Chronic Heart Failure

	HFrEF (n = 35)	HFpEF (n = 20)	Intergroup Comparison p Value
Age, yrs	69 ± 14	67 ± 12	0.478
Female/male	5/30	11/9	
Etiology of heart failure			
Ischemic	n = 16	n = 8	
Nonischemic	n = 19	n = 12	
Systolic blood pressure, mm Hg	115 ± 17	129 ± 16	0.004
Body mass index, kg/m^2	33 ± 8	44 ± 8	< 0.001
Left ventricular ejection fraction, %	27 ± 9	61 ± 5	< 0.001
Diabetes, %	32	65	
Hypertension, %	57	75	
Coronary artery disease, %	68	45	
Atrial fibrillation, %	42	65	
NT-proBNP, pg/ml	9,103 (3,647–11,574)	2,313 (989–4,088)	0.020
Albumin, g/dl	3.7 ± 0.4	3.6 ± 0.5	0.778
Potassium, mEq/l	4.4 ± 0.5	4.2 ± 0.5	0.159
Sodium, mEq/l	140 ± 3.2	139 ± 5.2	0.464
eGFR, ml·min·1.72 m^2	50.2 ± 23.9	49.4 ± 23.4	0.454
Serum creatinine, mg/dl	1.8 ± 0.9	1.6 ± 0.9	0.431
BUN, mg/dl	42 ± 23	39 ± 21	0.794
Hemoglobin, g/dl	12.6 ± 2.1	11.3 ± 2.3	0.037
Hematocrit, %	39.1 ± 5.7	36.2 ± 7.8	0.119
Normalized hematocrit, %	54.2 ± 14.4	46.1 ± 14.6	0.051
Plasma glucose, mg/dl	115 ± 36	140 ± 64	0.068

Values are mean ± SD. N-terminal pro-B-type natriuretic peptide expressed as median with 25th to 75th percentile confidence limits and percent or number of patients in a category.

BUN = blood urea nitrogen; eGFR= estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

TABLE 2 Measured Blood Volume Analysis at Admission in HFpEF and HFrEF Patients Hospitalized for Clinically Determined Volume Overload

	Total Blood Volume			Red Cell Mass			Plasma Volume		
	HFpEF	HFrEF	p Value	HFpEF	HFrEF	p Value	HFpEF	HFrEF	p Value
Measured admission volume, l	7.0 ± 1.4 (5.0–10.1)	7.6 ± 2.0 (4.6–14.5)	0.241	2.3 ± 0.84 (1.4–5.1)	2.7 ± 0.90 (1.5–5.1)	0.110	4.7 ± 1.1 (3.2–7.9)	4.8 ± 1.4 (2.7–9.4)	0.785
Expected normal volume, l	5.4 ± 1.6 (1.2–8.8) p = 0.002*	5.5 ± 0.96 (3.8–8.5) p < 0.001*	0.773	2.2 ± 0.56 (1.2–3.6) p = 0.660*	2.2 ± 0.43 (1.4–3.5) p = 0.004*	1.000	3.4 ± 0.71 (2.1–5.3) p < 0.001*	3.3 ± 0.54 (2.5–5.1) p < 0.001*	0.559
Volume excess (+)/deficit (−) from expected normal volume, %	+27 ± 21 (−5.2 to +77%)	+37 ± 25 (0 to +107%)	0.112	+8 ± 34 (−39.3 to +92%)	+24 ± 31 (−28 to +87%)	0.073	+38 ± 25 (+6.5 to +80%)	+47 ± 31 (0 to +128%)	0.289

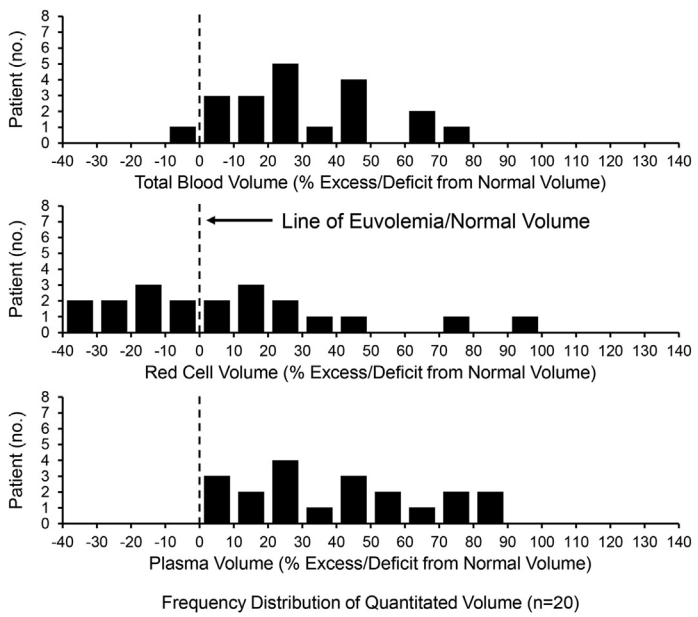
Values are mean ± SD (minimum and maximum range). *Measured vs. expected volumes. HFpEF (≥50%), n = 20; HFrEF (<50%), n = 35.
Abbreviations as in Table 1.

Health Organization gender-adjusted criteria (17). The marked heterogeneity in volume profiles for patients with HFpEF and HFrEF is reflected in the frequency distributions of quantitated TBV, RBCM, and PV at admission as shown for the cohort in Figures 1 and 2, respectively.

Changes in volume status and fluid distribution in response to diuretic therapy are shown in Table 3. With diuresis, discharge TBV modestly decreased from 27 ± 21% to 18 ± 20% expanded in HFpEF (p = 0.173) and from 37 ± 25% to 25 ± 20% (p = 0.03) expanded in HFrEF. TBV, therefore, remained significantly expanded at discharge in both groups despite intensive diuretic therapy. PV was decreased to 34 ± 22% (p = 0.047) expanded in HFrEF but in HFpEF the reduction to 28 ± 24% expansion was not significant (p = 0.205). RBCM was not significantly changed from admission in either group.

Body weight declined 10.5 ± 8.3 kg in the HFpEF group and 6.6 ± 4.4 kg in the HFrEF group (p = 0.026). This change in body weight (in kilograms) over the short duration of hospitalization was considered to be equivalent to the change in total body fluid in liters. Thus, the change in observed body weight in liters less the reduction in TBV reflects fluid loss from the interstitial compartment occurring as a result of transcapillary refill of the intravascular compartment. The calculated volume (interstitial fluid removed = body weight change [in liters] minus TBV change [in liters]) was 12.2 ± 10.7 l in HFpEF and 6.4 ± 4.9 L in HFrEF, thus accounting for 93 ± 6% and 85 ± 13% (p = 0.012), respectively, of the total body fluid loss being derived from the interstitial compartment during diuretic therapy. Net total fluid loss was greater in patients with HFpEF with comparable diuretic intensity of therapy and length of hospital stay for both groups. Nonetheless, even with this diuretic-induced fluid loss, the quantitated TBV (intravascular volume) at hospital discharge compared with volumes at admission still remained significantly expanded with large patient-to-patient variability (Table 3).

FIGURE 1 Intravascular Volume Overload in HFpEF



Frequency distribution of total blood volume, red blood cell mass, and plasma volume at hospital admission in patients with chronic HFpEF. HFpEF = heart failure with preserved ejection fraction.

DISCUSSION

The findings of this study, using quantitated TBV analysis, demonstrate that patients with HFpEF and

HFrEF who are hospitalized for DCHF with clinically suspected volume overload have markedly different fluid volume and fluid distribution profiles. Although there is large heterogeneity in intravascular volume both in patients with HFpEF (range -5% to 60%) and HFrEF (range 0% to 107%), the intravascular and interstitial distributions of volume excess and response to diuretic intervention differ between these 2 HF phenotypes. The clinical features in this cohort that seem to distinguish HFpEF from HFrEF patients are overall less intravascular volume expansion, more interstitial fluid congestion, morbid obesity, more diabetes and hypertension, and more true anemia. Whether these reflect features of an obesity-related cardiomyopathy phenotype of HFpEF or different pathophysiology is yet to be explored. Our data from this perspective are hypothesis generating.

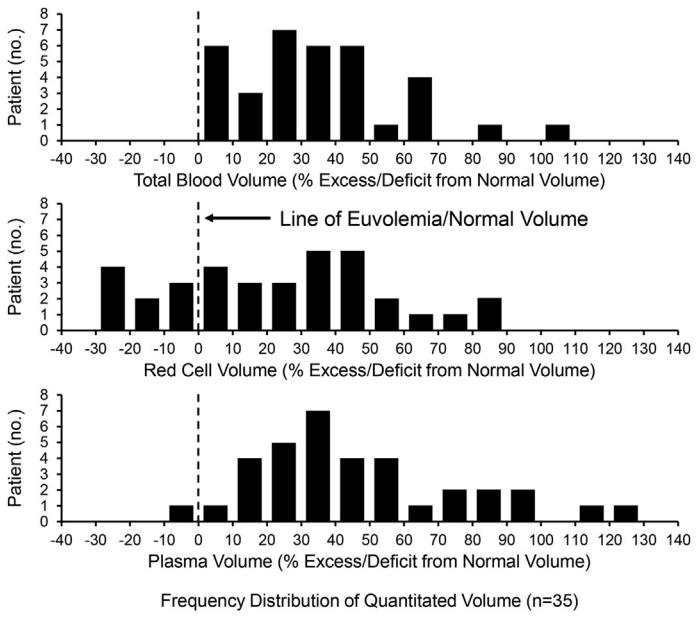
Quantitated volume analysis also reveals that RBCM excess (polycythemia) is more common in HFrEF (63% vs. 45%), while patients with HFpEF tend to demonstrate more RBCM deficit (true anemia) (35% vs. 14%). This observation was also noted by Abramov et al. (18), but in a cohort of stable ambulatory outpatients with chronic HF. Their data showed a higher incidence of RBCM deficit in patients with HFpEF, but with much higher prevalence (88% in HFpEF and 59% in HFrEF, $p = 0.04$) than observed in our cohort of DCHF patients.

Slightly more patients with HFpEF demonstrated euvolemia at admission, and the hypervolemic HFpEF patients revealed a lesser extent of intravascular volume expansion than HFrEF patients. In response to diuretic therapy, patients in our study with HFrEF revealed a greater reduction in intravascular volume but overall appeared to lose less total body fluid compared with HFpEF patients where the majority of body fluid loss was derived from the interstitial compartment with the intravascular volume excess not significantly reduced. Thus, volume overload in HFpEF appears more attributable to fluid overload of the interstitial compartment, and it appears this fluid is more readily mobilized than in patients with HFrEF. These findings would be consistent with reduced venous capacitance and lower arterial compliance (19), contributing to a greater extravascular distribution of volume excess in patients with HFpEF relative to HFrEF. How these compartments should most effectively interact to maintain appropriate circulating arterial volume in chronic HF patients is an important issue for study.

The finding of this study that patients with HFrEF and HFpEF distribute excess fluid volume differently both in terms of PV and RBCM has implications for an effective and safe approach to volume management. Measuring and, therefore, knowing intravascular volume in patients with HFpEF can prevent overly aggressive diuretic therapy that could outstrip the transcapillary refill rate and contribute to intravascular volume contraction and potential end-organ impairment. In both groups, however, despite large reductions in body weight and high net negative fluid intakes/outputs secondary to diuretic therapy, intravascular volumes remained expanded at the time of hospital discharge, albeit to a lesser extent in the HFpEF subgroup.

The heterogeneity in volume distributions observed in this analysis also emphasizes the importance of recognizing that changes in TBV and PV need to be interpreted with respect to the RBCM. It is important to differentiate true anemia with appropriate compensatory PV expansion from pathologic PV expansion related to greater activation of sodium and water retention mechanisms by the kidney resulting in excess PV expansion and the development of dilution-related pseudo-anemia. Thus, there is a value in quantitating all the components of TBV (RBCM and PV) to differentiate the different volume profiles associated with fluid overload.

FIGURE 2 Intravascular Volume Overload in HFrEF



Frequency distribution of total blood volume, red blood cell mass, and plasma volume at hospital admission in patients with chronic HFrEF. HFrEF = heart failure with reduced ejection fraction.

TABLE 3 Blood Volume Analysis Pre- and Post-Diuresis in HFpEF and HFrEF Patients Hospitalized for Clinically Determined Volume Overload

	HFpEF	HFrEF	p Value
Change in measured TBV admission to discharge, l	−0.670 ± 0.688 (−1.7 to +0.500 l)	−0.727 ± 0.945 (−3.9 to +0.341 l)	0.814
TBV excess (+)/deficit (−) from normal expected volume at discharge (post-diuresis), %	+18 ± 20% (0–57%) p = 0.173*	+25 ± 20% (−5.4 to +70%) p = 0.029*	0.217
Length of hospital stay, days	6.1 ± 2.6 (3–10)	5.3 ± 1.9 (3–9)	0.196
Net I/O, l	−12.2 ± 10.0 (−6 to −46 l)	−7.8 ± 5.2 (−7 to −21 l)	0.036
Change in body weight admission to discharge, kg	−10.5 ± 8.3 (−4 to −55 kg)	−6.6 ± 4.4 (−3 to −19 kg)	0.026
Interstitial transcapillary refill volume, l (change in body weight in l minus change in TBV)	12.2 ± 10.7 (3–34 l)	6.4 ± 4.9 (2–18 l)	0.008
Body fluid loss derived from the interstitial compartment with diuresis, %	93 ± 6% (81–99%)	85 ± 13% (63–99%)	0.012

Values are mean ± SD (minimum and maximum range of values). *Comparison of admission to discharge (post-diuresis) percent TBV excess. HFpEF (≥50%), n = 20; HFrEF (<50%), n = 35.

Abbreviations: I/O = fluid intake/output; TBV = total blood volume; other abbreviations as in Table 1.

Although it is recognized that the interplay of multiple confounding factors (endothelial dysfunction with changes in capillary permeability, altered capillary oncotic and tissue pressures [Starling forces, systemic hypotension, diuretic and vasodilator therapies, and intrinsic renal function]) (20,21) influence the distribution of fluid overload between the interstitial and intravascular compartments, our findings suggest that the preservation of a normal LVEF and higher systolic blood pressure may also play a role. Better cardiac output and arterial filling with higher systemic blood pressure, probable better tissue perfusion, and less venous congestion may contribute to maintaining a lesser degree of intravascular volume expansion than observed with HFrEF. The marked heterogeneity, however, in the extent of volume expansion and the distribution of fluid removed in both patients with HFpEF and HFrEF as shown in our study is not commonly taken into account in a comprehensive strategy of volume management. The findings of this study also beg the question (hypothesis generating) as to what is the appropriate intravascular volume or overall body fluid volume to be achieved in the long-term management of chronic HFrEF and HFpEF patients. Treatment to true intravascular euvolemia may not be the proper clinical target, especially in patients with HFrEF. Some degree of intravascular volume expansion is probably necessary to maintain effective arterial filling and organ perfusion, but how much becomes too much needs to be determined. Clinical assessment, right heart hemodynamic measures, or parameters such as changes in body weight and net fluid intake/fluid outputs alone will not provide the answer but in combination with a quantitative assessment of TBV will provide an opportunity to address these issues.

STUDY LIMITATIONS. Although the focus on DCHF patients limits generalization of the findings to other HF stages, the comprehensive quantitated volume assessment provides new data describing composition and distribution differences in fluid overload in HFpEF and HFrEF. How significant these differences are in terms of clinical outcomes and implications for implementation of volume management strategies requires further study. The interstitial fluid contribution to overall volume loss is a derived volume because no direct quantitative measurement technique of total interstitial fluid that has clinical utility is available at present. In the statistical analyses, correction for multiple comparisons was not undertaken, which may increase the possibility of a type 1 error; however, there are no findings that this contributed to an overestimation of significance in these data.

CONCLUSIONS

Patients with HFpEF and HFrEF demonstrated substantially different intravascular volume profiles and distribution of fluid overload. Quantitated volume analysis revealed both significant RBCM (polycythemia) and PV expansion in HFrEF, whereas patients with HFpEF demonstrated more true anemia with compensatory PV expansion. In response to diuretic therapy, patients with HFrEF revealed a greater reduction in intravascular volume but overall appear to mobilize less total body fluid compared with HFpEF in which the majority of body fluid loss was derived from the interstitial compartment with the intravascular volume overload remaining unchanged. Both phenotypes, however, show persistent intravascular volume excess at hospital discharge despite intravenous diuretic therapy and significant weight reduction. These differences have implications for the approach to volume management. TBV quantitation, particularly serial measurements, can therefore help guide individualized therapy in HFpEF and HFrEF patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The markedly different intravascular volume profiles including RBCM excess (polycythemia) and RBCM deficit (true anemia) with PV expansion, and varied distribution of fluid overload in patients with HFpEF versus HFrEF should be identified before a plan of management is implemented. These differences have clinically significant implications for how best to establish a treatment regimen in the individual patient and avoid possible detrimental consequences.

TRANSLATIONAL OUTLOOK: The measurement of TBV provides a means to objectively assess the volume status of HF patients. The significance of the marked differences in degree of volume overload in terms of PV expansion and RBCM among patients with HFpEF and HFrEF needs further study. One issue is identifying whether the marked heterogeneity in volume expansion has clinical implications in terms of development of cardiorenal syndrome. Analysis of these differences in extent of TBV expansion and the development of congestion may point toward clinical targets that may allow more tailored therapy in the individual patient and better outcomes, particularly with regard to readmission rates.

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