

# Relation of Unrecognized Hypervolemia in Chronic Heart Failure to Clinical Status, Hemodynamics, and Patient Outcomes

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Clinically unrecognized intravascular volume overload may contribute to worsening symptoms and disease progression in patients with chronic heart failure (CHF). The present study was undertaken to prospectively compare measured blood volume status (determined by radiolabeled albumin technique) with clinical and hemodynamic characteristics and patient outcomes in 43 nonedematous ambulatory patients with CHF. Blood volume analysis demonstrated that 2 subjects (5%) were hypovolemic (mean deviation from normal values  $-20 \pm 6\%$ ), 13 subjects (30%) were normovolemic (mean deviation from normal values  $-1 \pm 1\%$ ), and 28 subjects (65%) were hypervolemic (mean deviation from normal values  $+30 \pm 3\%$ ). Physical findings of congestion were infrequent and not associated with blood volume status. Increased blood volume was associated with increased pulmonary capillary wedge pressure ( $p =$

0.01) and greatly increased risk of death or urgent cardiac transplantation during a median follow-up of 719 days (1-year event rate 39% vs 0%,  $p < 0.01$  by log-rank test). Systolic blood pressure was significantly lower in hypervolemic patients than in those with normovolemia or hypovolemia ( $107 \pm 2$  vs  $119 \pm 2$  mm Hg,  $p = 0.008$ ), and hypotension was independently associated with increased risk of hypervolemia in multivariate analysis (odds ratio 2.64 for a 10-mm Hg decrease in systolic blood pressure, 95% confidence interval 1.13 to 6.19,  $p = 0.025$ ). These findings demonstrate that clinically unrecognized hypervolemia is frequently present in nonedematous patients with CHF and is associated with increased cardiac filling pressures and worse patient outcomes. ©2004 by Excerpta Medica, Inc.

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Intravascular volume can be directly measured noninvasively with isotopic tracer and dye dilution techniques.<sup>1</sup> Previous reports of blood volume measurements with chronic heart failure (CHF) were conducted in small study populations without a detailed description of physical examination findings and background medical therapy.<sup>2-6</sup> Based on the findings of previous hemodynamic studies,<sup>7-10</sup> we hypothesized that clinically unrecognized increases in blood volume may be common, even in nonedematous patients with CHF. The present study was undertaken to noninvasively measure blood volume after iodine-125 albumin injection in ambulatory nonedematous patients with CHF. Our goal was to quantify blood volume derangements and to compare measured blood volume status with clinical and hemodynamic characteristics of heart failure.

## METHODS

**Study group:** Forty-three consecutive nonedematous ambulatory patients with CHF were studied. Sub-

jects between 21 and 80 years of age with CHF for  $>3$  months' duration, with stable New York Heart Association class II to IV symptoms for  $>2$  months, and left ventricular ejection fraction  $\leq 35\%$  were eligible for the study. Criteria for exclusion were acute decompensated heart failure, severe renal dysfunction (serum creatine  $>2.5$  mg/dl or history of nephrotic syndrome), severe hepatic dysfunction (serum liver enzymes  $>3$  times the upper limits of normal or history of cirrhosis), pregnancy, history of thyroid disease, and patients with known history of allergy to iodine or iodinated products. Background cardiac medications included stable doses of diuretics, digoxin, renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and/or angiotensin receptor antagonists), and/or  $\beta$ -adrenergic receptor antagonists for  $>2$  months before the study. The protocol was approved by the institutional review board at Columbia Presbyterian Medical Center. All subjects gave written informed consent before participation.

**Blood volume analysis:** Blood volume was determined after intravenous administration of iodine-131-labeled albumin as previously described.<sup>1,11,12</sup> After obtaining a baseline sample of 5 ml of venous blood as a control for background radiation, 10 to 25  $\mu$ Ci of iodine-131-labeled albumin (Volumex, Daxor Corp., New York City, New York) was injected into a peripheral vein from a specialized prefilled flow chamber designed to ensure  $>99.8\%$  delivery of the radio-

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isotope dose. Five milliliters of venous blood were collected from an indwelling catheter placed in a forearm vein of the contralateral arm at 12, 18, 24, 30, and 36 minutes after isotope injection. Spun hematocrit was determined from each sample and plasma radioactivity of each sample was measured in a semiautomated counter (BVA-100 Blood Volume Analyzer, Daxor Corp.). Plasma volume was determined as the zero-time volume of distribution of the radiolabeled albumin obtained by semilogarithmic extrapolation of values measured from the 5 samples.<sup>1,11</sup> Blood volume and red blood cell volumes were calculated from the plasma volume measurement, and the measured hematocrit corrected for trapped plasma and mean body hematocrit and then compared with normal values for age, gender, height, and weight based on the ideal weight system.<sup>11,13,14</sup> The coefficient of variance for this analytic technique is <3.5%.<sup>11,15</sup> Normovolemia was prospectively defined as a measured blood volume within  $\pm 8\%$  of the predicted normal value.<sup>11</sup>

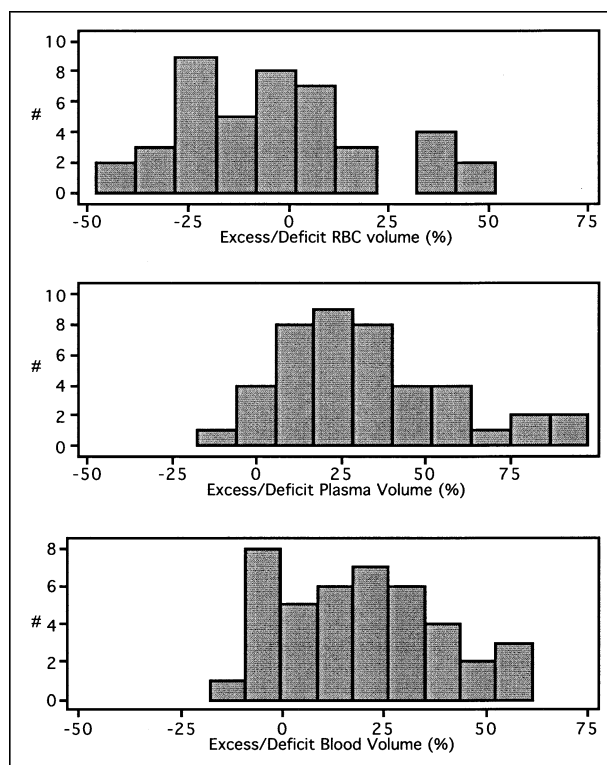
**Clinical assessment of volume status:** The clinical volume status was assessed immediately before blood volume analysis. Blood pressure and heart rate were measured with an automated cuff device with patients in the supine position (Dinamapp, Critikon, Tampa, Florida). Jugular venous pressure was assessed in a seated position and was considered elevated if venous pressure waves were visible above the clavicle. Presence or absence of elevated jugular venous pressure, inspiratory rales, S3 gallops, and hepatomegaly were recorded as dichotomous variables. Clinical hypervolemia was defined empirically as the presence of  $\geq 1$  physical finding of congestion (elevated jugular venous pressure, rales, or hepatomegaly) and the presence of  $\geq 1$  congestive symptom (orthopnea, paroxysmal nocturnal dyspnea, abdominal bloating, nocturia).

**Patient outcomes determination:** Patient outcomes as of April 1, 2003 (death or urgent cardiac transplantation, nonurgent cardiac transplantation, or no event) were determined for all patients by direct contact with the patient or their family or physician.

**Hemodynamic measurements:** Seventeen subjects who were undergoing outpatient cardiac transplantation evaluations had elective outpatient right-sided cardiac catheterization performed for assessment of pulmonary vascular resistance on the same day as blood volume analysis with standard clinical techniques. The catheter tip position was confirmed by fluoroscopy and hemodynamic monitoring. A mean pulmonary capillary wedge pressure of  $\geq 15$  mm Hg was used as the clinically derived criterion to infer hypervolemia.

**Plasma brain natriuretic peptide measurements:** In 18 subjects, plasma brain natriuretic peptide was measured with a calibrated automated quantitative fluorescent sandwich immunoassay device (Biosite Diagnostic, San Diego California).<sup>16</sup>

**Statistical analysis:** All values are presented as means  $\pm$  SEM. Clinical characteristics of subjects grouped by blood volume status (hypervolemia vs normovolemia or hypovolemia) were compared with Student's *t* test for unpaired observations, chi-square



**FIGURE 1.** Frequency distribution (number of subjects) of red blood cell (RBC) volume (top panel), plasma volume (middle panel), and blood volume (bottom panel) in 43 patients with CHF.

analysis, or Fisher's exact test as appropriate (Stata software version 8.0, College Station, Texas). Diuretic dose and brain natriuretic peptide levels were not normally distributed, so the natural log transformation or nonparametric testing was used in statistical analyses. Multivariate logistic regression models were explored to identify clinical predictors of hypervolemia. Age, gender, and New York Heart Association class were included in all models. Other variables with univariate *p* values  $\leq 0.20$  were added in stepwise fashion and retained in the model if the adjusted *p* value was  $\leq 0.20$ . The Hosmer-Lemeshow goodness-of-fit statistic was used to test model assumptions. Survival data were analyzed by the Kaplan-Meier method and stratified log-rank tests. Observations for patients with elective cardiac transplantation were censored at the time of surgery. For all analyses, a *p* value  $< 0.05$  was considered statistically significant.

## RESULTS

**Blood volume analysis:** Blood volume analysis demonstrated that 2 subjects (5%) were hypovolemic (mean deviation from normal blood volume values  $-20 \pm 6\%$ ), 13 subjects (30%) were normovolemic (mean deviation from normal blood volume values  $-1 \pm 1\%$ ), and 28 subjects (65%) were hypervolemic (mean deviation from normal blood volume values  $+30 \pm 3\%$ ). The increased blood volume was largely attributable to an expanded plasma volume component (Figure 1). Patients with hypervolemia had signifi-

	All Subjects (n = 43)	Normovolemia/hypovolemia (n = 15)	Hypervolemia (n = 28)	p Value*
Age (yrs)	57 ± 2	55 ± 2	58 ± 2	0.37
Men	79%	67%	83%	0.14
Body mass index (kg/m <sup>2</sup> )	27 ± 1	28.2 ± 2.0	26.5 ± 1.9	0.35
Etiology of cardiomyopathy				0.66
Ischemic	51%	47%	54%	
Nonischemic	49%	53%	46%	
Left ventricular ejection fraction (%)	24 ± 1	28 ± 2	22 ± 1	0.02
New York Heart Association class				0.33
II	28%	33%	25%	
III	53%	60%	50%	
IV	19%	7%	25%	
Hematocrit (%)	36 ± 1	34 ± 1	36 ± 1	0.16
Serum sodium (mEq/L)	135 ± 1	135 ± 1	134 ± 1	0.52
Serum creatine (mg/dl)	1.5 ± 0.1	1.3 ± 0.2	1.5 ± 0.1	0.25
Blood urea nitrogen (mg/dl)	35 ± 3	28 ± 4	39 ± 4	0.08
Glomerular filtration rate (ml/min) <sup>†</sup>	76 ± 7	90 ± 15	68 ± 7	0.13
Serum albumin (g/dl)	4.2 ± 0.1	4.3 ± 0.1	4.1 ± 0.1	0.38
Loop diuretics	91%	100%	86%	0.12
Digoxin	81%	93%	75%	0.14
Renin-angiotensin system inhibitors	81%	80%	82%	0.85
β blockers	67%	87%	57%	0.049
Loop diuretic dose (mg/day) <sup>‡</sup>	118 ± 113	149 ± 35	102 ± 18	0.20

\*The p values are for comparison of normovolemic/hypovolemic subjects versus hypervolemic subjects.  
<sup>†</sup>Glomerular filtration rate estimated from serum creatine measurement adjusted for age and gender as previously described.<sup>28</sup>  
<sup>‡</sup>Loop diuretic dose calculated in furosemide equivalents with conversion factors: 1 mg of bumetanide = 40 mg of furosemide, and 1 mg of torsemide = 2 mg of furosemide.

	All Subjects (n = 43)	Normovolemia/Hypovolemia (n = 15)	Hypervolemia (n = 28)	p Value*
Heart rate (min <sup>-1</sup> )	73 ± 2	70 ± 3	75 ± 5	0.22
Systolic blood pressure (mm Hg)	111 ± 2	119 ± 2	107 ± 2	0.008
Diastolic blood pressure (mm Hg)	66 ± 1	67 ± 2	66 ± 1	0.58
Mean arterial pressure (mm Hg)	81 ± 1	84 ± 3	80 ± 2	0.09
Increased jugular venous pressure	30%	20%	36%	0.29
Rales	9%	7%	11%	0.66
S3 gallop	91%	87%	93%	0.51
Hepatomegaly	12%	13%	11%	0.80
Clinical hypervolemia	40%	33%	44%	0.54

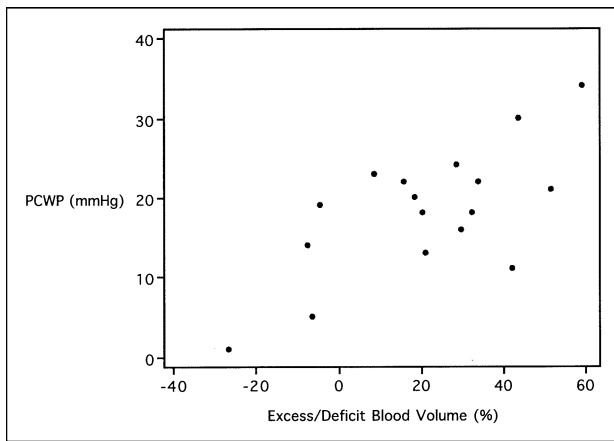
\*The p values are for comparison of normovolemic/hypovolemic subjects versus hypervolemic subjects.

cantly lower ejection fraction and were significantly less likely to receive β-adrenergic receptor blockade therapy than the other subjects (Table 1).

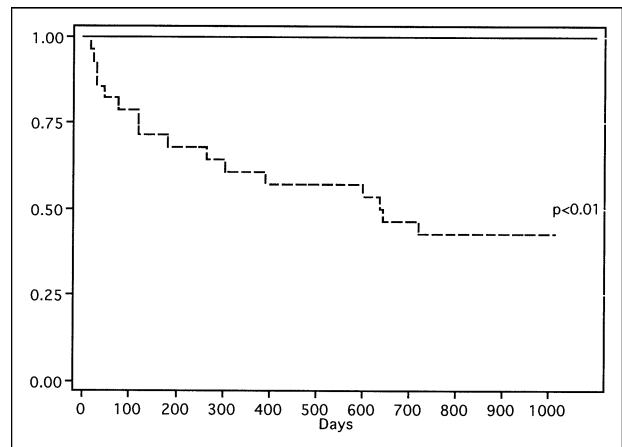
**Clinical assessment:** Congestive signs (increased jugular venous pressure, rales, and hepatomegaly) were infrequently detected by physical examination and were not significantly associated with blood volume status (Table 2). A S3 gallop was a frequent finding but was not associated with volume status, as determined by blood volume analysis (Table 2). Systolic blood pressure was significantly lower in hypervolemic subjects than in other subjects. Clinical assessment and measured blood volume analysis were concordant in 22 of 43 patients (51%, both normovolemic [n = 10], both hypervolemic [n = 12]). Sensitivity and specificity of clinical assessment for the diagnosis of hypervolemia were 0.43 and 0.67, respectively.

**Hemodynamic correlates:** Outpatient elective right-sided cardiac catheterization was performed in 17

subjects as part of a cardiac transplantation evaluation. Subjects who underwent right-sided cardiac catheterization were in a more severe New York Heart Association functional class than other subjects (p = 0.04) but otherwise had clinical characteristics that did not differ from the remaining study participants. In these 17 patients, blood volume analysis revealed hypovolemia in 1 subject (6%), normovolemia in 3 subjects (18%), and hypervolemia in 13 subjects (76%) (p = 0.34 vs subjects without right-sided cardiac catheterization). Pulmonary capillary wedge pressure was significantly higher in hypervolemic subjects than in other subjects (21 ± 2 vs 10 ± 4 mm Hg, p < 0.01) and was significantly correlated with measured blood volume (r = 0.69, p = 0.01; Figure 2). Pulmonary capillary wedge pressure was ≥ 15 mm Hg in 11 of 13 subjects with hypervolemia and in 1 of 4 subjects with normovolemia or hypovolemia. Sensitivity and specificity of pulmonary capillary wedge pressure ≥ 15



**FIGURE 2.** Blood volume (percent deviation from normal values) versus pulmonary capillary wedge pressure (PCWP, in mm Hg) in 17 patients with CHF.



**FIGURE 3.** Kaplan-Meier plot of proportion of patients with hypervolemia surviving without urgent transplantation over time (dashed line) and in patients with normovolemia or hypovolemia (solid line).

mm Hg for the diagnosis of hypervolemia were 0.85 and 0.75, respectively.

**Brain natriuretic peptide measurements:** Plasma brain natriuretic peptide measurements were performed in the last 18 subjects enrolled, 5 normovolemic subjects (28%) and 13 hypervolemic subjects (72%) ( $p = 0.41$  vs subjects without brain natriuretic peptide measurements). Mean plasma brain natriuretic peptide was  $549 \pm 121$  pg/ml. Plasma brain natriuretic peptide levels tended to be higher in hypervolemic subjects than in other subjects ( $654 \pm 138$  vs  $275 \pm 191$  pg/ml,  $p = 0.067$  by Wilcoxon signed-rank test) and tended to be positively associated with blood volume (Spearman's rank correlation  $\rho = 0.39$ ,  $p = 0.11$ ). Brain natriuretic peptide levels were  $\geq 100$  pg/ml in 2 of 5 normovolemic subjects and in 11 of 13 hypervolemic subjects. Sensitivity and specificity of brain natriuretic peptide levels  $\geq 100$  pg/ml for the diagnosis of hypervolemia were 0.85 and 0.60, respectively.

**Clinical outcomes:** During a median follow-up of 719 days, 16 subjects died ( $n = 8$ ) or underwent urgent cardiac transplantation ( $n = 8$ ), and 3 patients underwent elective cardiac transplantation. Blood volume analysis demonstrated hypervolemia in all 16 subjects with death or urgent transplantation. Risk of death or urgent transplantation was significantly greater among patients with hypervolemia than among patients with normovolemia or hypovolemia (1-year event rate 39% vs 0%,  $p < 0.01$  by log-rank test; Figure 3). Hypervolemia remained significantly associated with increased risk of death or urgent transplantation when adjusting for age, left ventricular ejection fraction, and New York Heart Association functional class ( $p < 0.04$  by stratified log-rank test). In a secondary analysis in which all transplantation patients were censored at the time of surgery, hypervolemia remained significantly associated with increased risk of death ( $p = 0.02$  by log-rank test).

**Clinical predictors of hypervolemia:** In multivariate logistic regression models, increased systolic blood pressure and treatment with  $\beta$ -adrenergic receptor

**TABLE 3** Estimates of Risk of Hypervolemia as Determined by Blood Volume Analysis for Clinical Variables in Multivariate Logistic Regression Models

	OR	95% CI	p Value
Systolic blood pressure (mm Hg)	0.91	0.83–0.99	0.025
$\beta$ blockers	0.02	0.01–0.66	0.029
Loop diuretic dose (mg/d)*	0.22	0.04–1.22	0.083
Left ventricular ejection fraction	0.92	0.82–1.04	0.18
New York Heart Association	4.24	0.62–29.1	0.14
Gender	0.43	0.01–13.5	0.63
Age (yrs)	1.00	0.91–1.10	0.97

\*Odds ratio (OR) is based on natural log transformation of diuretic dose data.  
CI = confidence interval.

blockers were the only significant independent predictors of reduced risk of hypervolemia (Table 3). Based on the model parameters, a 10-mm Hg decrease in systolic blood pressure was associated with an estimated 2.64-fold increased risk for hypervolemia (odds ratio 2.64, 95% confidence interval 1.13 to 6.19). Higher doses of loop diuretics were associated with decreased risk of hypervolemia with borderline statistical significance.

## DISCUSSION

The present findings demonstrate that blood volume, as determined by the radiolabeled albumin technique, is frequently increased in nonedematous patients with CHF and is associated with increased cardiac filling pressures and worse patient outcomes. Physical examination did not accurately predict hypervolemia in these subjects.

This report had a larger study population and more comprehensive clinical characterization than previous studies on blood volume analysis in CHF and is the first to report patient outcomes. Previous small studies evaluating blood volume alterations in patients with CHF have reported mixed findings. Anand and colleagues<sup>17</sup> reported a 34% increase in blood volume in

6 patients with untreated CHF compared with healthy controls. Although these patients had clinical evidence of fluid overload (as evidenced by peripheral edema, elevated jugular venous pressure, and ascites) and had never received diuretic treatment for heart failure, the degree of volume overload was only slightly greater than that observed in the present study population of treated nonedematous subjects. In previous studies of treated patients with CHF, blood volume expansion ranging from 12% to 23% has been reported.<sup>2-4</sup> In contrast to our findings and other previous reports, Feigenbaum and colleagues<sup>5</sup> reported a 23% reduction in blood volume in 12 patients with CHF compared with normal control subjects. Details of physical examination findings and diuretic regimens were not reported in these previous studies. The discrepancy between our findings and those reported by Feigenbaum et al<sup>5</sup> may be in part related to clinical differences in the study populations, differences in techniques for measuring blood volume, and/or differences in the norms used to interpret blood volume status.<sup>1,18</sup> The radiolabeled albumin technique used in the present study is recommended for quantitative assessment of blood volume by the International Committee for Standardization in Hematology for its excellent precision and reproducibility compared with alternate methods.<sup>1,15</sup> Our measured blood volume data are internally consistent, because hypervolemia was significantly associated with increased pulmonary capillary wedge pressure and worse clinical outcomes.

The dissociation between hypervolemia as determined by blood volume analysis and physical findings of congestion in our study population is in accord with previous clinical and hemodynamic studies.<sup>7-10,19</sup> In 50 patients with CHF, Stevenson and Perloff<sup>9</sup> reported that physical signs of congestion were absent in 42% of patients with measured pulmonary capillary wedge pressure  $\geq 22$  mm Hg. Butman and colleagues<sup>19</sup> detected pulmonary rales in only 24% of patients with pulmonary capillary wedge pressure  $\geq 18$  mm Hg. In a series of 52 patients with CHF referred for cardiac transplantation evaluation, radiographic pulmonary congestion was absent in 53% and 39% of patients with pulmonary capillary wedge pressures of 16 to 29 mm Hg and  $\geq 30$  mm Hg, respectively.<sup>10</sup> Pulmonary vascular and lymphatic factors may protect against alveolar edema in response to chronic elevations in pulmonary venous pressure.<sup>20</sup> An S3 gallop was a frequent finding in our study group with advanced CHF, but, in agreement with previous studies, was not closely linked to measured volume status.<sup>9,10,21</sup> Estimation of jugular venous pressure by physical examination has not been closely correlated to hemodynamic measurements in previous studies and was not associated with measured volume status in the present study.<sup>22</sup>

Our finding of worse clinical outcomes in patients with hypervolemia as determined by blood volume analysis is consistent with previous studies demonstrating that increased volume overload, as assessed by physical findings, hemodynamic findings, or brain natriuretic peptide levels, is associated with increased

mortality risk in heart failure.<sup>23-25</sup> Volume overload may directly contribute to poor outcomes by augmenting ventricular remodeling or may be a surrogate marker of more severe ventricular dysfunction and/or neurohormonal activation.

The clinical implications of these findings are uncertain because this study did not address the practicality of implementation of blood volume measurements in clinical practice settings. The subjects in this study were recruited from a tertiary referral heart failure and heart transplantation center and may not be representative of subjects with heart failure in community settings. However, clinically unrecognized hypervolemia was frequently present, even in our less severely ill patients with New York Heart Association class II symptoms. Inaccurate assessment of physical findings and consequent misclassification of clinical volume status have been previously described and may have contributed to our findings.<sup>21-23</sup> One of the most useful clinical signs of volume overload—hepatojugular reflux—was not assessed in our subjects. Because blood volume measurements were assessed in a single point in time, the effects of medical therapy on blood volume cannot be determined from this study.<sup>26,27</sup>

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