Blood Volume Assessment in the Diagnosis and Treatment of Chronic Heart Failure

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ABSTRACT: Symptoms of intravascular volume overload and increased cardiac filling pressures in the systemic and pulmonary venous circulations are among the most common complaints in patients with chronic heart failure (CHF). The clinical utility of physical examination for estimation of intravascular volume status in patients with CHF is limited due to poor specificity and sensitivity of most signs of congestion. Direct measurement of blood volume with radioisotope techniques is FDA-approved and has been shown to be closely associated with invasive measurements of cardiac filling pressures in patients with CHF. Unrecognized volume overload is common in CHF patients and is associated with adverse clinical outcomes. Additional work is needed to determine the clinical utility of serial blood volume measurements in the management of patients with CHF. **KEY INDEXING TERMS:** Blood volume; Heart failure; Diagnostic testing; Radioisotope. **[Am J Med Sci 2007;334(1):47–52.]**

Increased intravascular volume in heart failure results from a complex interaction of hemodynamic and neurohormonal factors that induce renal sodium and water retention in response to decreased cardiac output and renal hypoperfusion.[1,2] In chronic heart failure (CHF), clinical assessment of intravascular volume status may be confounded by compensatory mechanisms that mask physical findings of congestion.[3–7] In a clinical series of 50 CHF patients, physical signs of congestion including rales, elevated jugular venous pressure, and edema were not detected in 18 of 43 patients with documents elevation of pulmonary capillary wedge pressure ≥22 mm Hg.[5] Radiographic evidence of congestion is also frequently absent in CHF patients with documented high pulmonary capillary wedge pressures.[7] Inaccurate clinical assessment of volume status may lead to inappropriate diuretic use with adverse consequences.[8] Pulmonary capillary wedge pressure (PCWP) and plasma brain natriuretic peptide (BNP) have been used as surrogate markers of volume status, but neither is an exact indicator of measured blood volume, and PCWP requires invasive catheterization.

Intravascular volume can be directly measured noninvasively with isotopic tracer and dye dilution techniques.[9] This review summarizes reports of direct blood volume measurement in patients with heart failure.

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Historical Studies of Blood Volume and the Pathogenesis of Edema

Early studies, several of which are summarized in Table 1,[10–13] examined the pathogenesis of edema formation in heart failure. The majority of studies demonstrated increased blood volume in decompensated heart failure patients, a finding that supports the modern concept that edema formation in chronic heart failure is dependent on renal retention of sodium and water in response to renal hypoperfusion (forward failure), rather than a primary increase in cardiac filling pressures causing transudation to the extravascular space and secondary renal retention of sodium to maintain intravascular homeostasis (backward failure).[1,14]

Findings from dye dilution techniques showed a correlation between symptomatic heart failure and increased volume and between treatment to a compensated state and reduction in volume. Results from radioisotopically tagged red cells showed greater overlap between heart failure and control populations and did not show a clear correlation between improvement of symptoms and reduction in blood volume. Subsequent studies using simultaneous measurement of red cell and plasma volume[15] found a similar discrepancy and suggested changes in the ratio of whole body to venous hematocrit as a factor in these differences. Plasma volume measurement was concluded to be the more accurate method.

Interpretation of these historical studies was limited by the absence of well-established norms. Blood volume is known to vary according to the subject gender, age, and body habitus. Variability in these factors, as well as the underlying cardiac disease all

Table 1. Summary of Historical Studies on Blood Volume in Heart Failure

Authors	Subjects	Method of Blood Volume Measurement	Normal Range	Results
Brown and Rowntree (1925)	50 normal subjects; 2 subjects with mitral insufficiency and severe lower extremity edema; 1 subject with hypertension, ischemic heart disease, and extreme obesity	Congo red dye	104–114 mL/kg	2 CHF subjects had blood volumes above normal range before and after treatment. Subject with ischemic heart disease had blood volume below normal range, but obesity recognized as a factor.
Gibson and Evans (1937)	99 subjects with cardiac disease in 5 groups ranked according to CHF symptoms	Evans Blue dye	Normal values based on height	Subjects with obvious symptoms of heart failure had increased blood volumes; treatment of 13 patients to a compensated state associated with decrease in blood volumes.
Prentice et al (1951)	27 patients with CHF	P^{32}-labeled red blood cells	Males: 56–81 mL/kg Female: 48–80 mL/kg	Increased blood volume present in 15/27 patients. No significant associations between blood volume and central venous pressure or circulation time. No consistent pattern in recovery to compensated state and decrease in blood volume.
Gunton and Paul (1955)	102 patients with heart failure; 107 control subjects	P^{32}-labeled red blood cells	Comparison with controls	Mean blood volume increased in heart failure subjects, but there overlap between the groups in nearly 50% of the heart failure subjects. Distributions of blood volume measurements in heart failure subjects with and without overt signs of congestion did not differ. In the subgroup with decompensated heart failure, recovery back to compensated state associated with decrease in blood volume and increase in hematocrit.
Reilly et al (1954)	56 cardiac disease patients and 89 control subjects	Cr^{51}-labeled red blood cells	Comparison with controls	Blood volume increased over control values only in the subgroup of cardiac patients with overt signs of right sided congestion.

contribute to the wide range of values reported in these studies and limits interpretation of the findings. It is also difficult to translate these findings to more recent clinical situations, because the subjects were not characterized with respect to ejection fraction and the treatment approaches available at the time were vastly different from current guidelines.

Seminal studies by Feldschuh and Enson[16] in the 1970s advanced the diagnostic utility of blood volume measurement with the establishment of accurate normal values for the radiolabeled albumin technique based on deviation from ideal body weight. These investigators measured blood volume with radiolabeled albumin in 160 normal subjects (80 men and 80 women) across of wide range of heights and weights. When compared with estimation of normal values based on height alone, or body surface area, estimation based on the percent deviation from ideal body weights (derived from Metropolitan Life table of ideal body weight) was associated with the smallest error when compared with measured values. Establishment of reliable normal values for blood volume increases the potential utility of this measurement in clinical heart failure studies.

Neurohormonal Activation and Blood Volume

In 1982, Fouad and colleagues[17] found that introduction of ACE inhibition in 19 patients with New York Heart Association Class III and IV CHF led to a reduction in body weight and a significant increase in plasma volume, suggesting shifts of fluid from extravascular to the intravascular space, likely due to venodilation.

In a carefully controlled study of 10 subjects with compensated CHF, Cody and colleagues[18] found that

in comparison with a low-sodium diet (10 mEq sodium/d), a high sodium diet (100 mEq sodium/day) was associated with a 2 kg weight gain and suppression of activation of the sympathetic nervous and renin-angiotensin systems. An increase in blood volume (5062 ± 430 mL on 10 mEq/d and 5296 ± 418 on 100 mEq/d) was not statistically significant, but the power of the study was limited by the small sample size. These findings indicate that the renin-angiotensin system regulates distribution of excess sodium and water between the intravascular and extravascular space.

Anand and colleagues[19] compared 8 untreated subjects with decompensated heart failure with normal control subjects and found that heart failure subjects had increased plasma renin activity, increased blood levels of aldosterone, norepinephrine, aldosterone, atrial natriuretic peptide, and a 22% increase in blood volume. These findings extend those of Cody and colleagues and demonstrate that neurohormonal activation occurs in decompensated heart failure even in the absence of diuretic therapy or sodium restriction.

The interaction between cardiac output, neurohormonal activation, and blood volume was further investigated in the unique setting of left ventricular assist device (LVAD) support in patients with severe decompensated heart failure.[20] Implantation of LVAD increased cardiac index and decreased plasma renin activity and blood levels of aldosterone, arginine vasopressin, and atrial natriuretic peptide. Plasma volume decreased from 123 ± 20% of normal before LVAD support to 115 ± 14% of normal after 8 weeks.

Like the earlier studies, these findings extended understanding of the pathophysiology of heart failure, but extrapolation to clinical assessment of patients is limited, as little information on patient clinical status was provided.

Blood Volume and Clinical Status

Several studies have examined blood volume measurement with an emphasis on clinical characterization of patients.

Anand and colleagues[21] measured plasma volume with radiolabeled albumin in 13 subjects with CHF optimally treated with furosemide (mean dose, 131 mg/d) and amiloride (mean dose, 16 mg/d). Patients were not treated with angiotensin converting enzyme inhibitors or other vasodilators. Physical findings of congestion were not reported in this study, but mean measured pulmonary capillary wedge pressure was 18 mm Hg. When compared with 10 healthy historical control subjects, the mean plasma volume did not differ between groups (CHF, 47 mL/kg vs control subjects, 44 mL/kg). However, several of the heart failure subjects did appear to have persistently high plasma volume when compared with the normal range, although a specific analysis to determine if these values were outside of the normal range was not reported. Mean values of total body water and extracellular volume were also similar in the two groups. This study indicates that clinically adjusted high dose diuretic use was associated with return to normal plasma volume in the majority of CHF subjects.

Androne and colleagues[22] measured blood volume with radiolabeled albumin in 43 nonedematous subjects with stable CHF. These patients were treated with diuretics, angiotensin converting enzyme inhibitors and β-adrenergic receptor blockers. The mean dose of furosemide was 118 mg/d. Two subjects (5%) were hypovolemic (mean blood volume, 53 ± 5 mL/kg; mean deviation from normal values, –20 ± 6%), 13 (30%) were normovolemic (mean blood volume, 59 ± 2 mL/kg; mean deviation from normal, –1 ± 1%), and 28 subjects (65%) were hypervolemic (mean blood volume, 82 ± 2 mL/kg; mean deviation from normal, +30 ± 3%). Clinical assessment of volume status by experienced cardiologists was correct only 51% of the time. Increased blood volume was significantly associated with increased pulmonary capillary wedge pressure ($r = 0.69$, $P = 0.01$), but not brain natriuretic peptide levels (rho = 0.39, $P = 0.11$). Increased blood volume was associated with markedly increased risk of death or urgent cardiac transplantation during a median follow-up period of 719 days. The 1-year event rate was 39% vs. 0%, $P < 0.01$ by log rank test, and the 2-year event rate was 55% vs 0%.[22] This cross-sectional study demonstrated a strong link between blood volume status and prognosis among clinically similar CHF patients. These findings contrast those of Anand and colleagues as summarized above in a cohort of CHF patients receiving comparable high dose diuretic treatment as the only therapy for CHF. It is possible that the use of vasodilator agents may alter the relationship between clinical assessment of volume status and measured blood volume.

James and colleagues[23] reported on blood volume determined by radiolabeled albumin, cardiac filling pressures, and brain natriuretic peptide levels in a study of 10 hospitalized patients with decompensated CHF. Baseline blood volume was increased above normal by 29 ± 19% and was associated with pulmonary artery diastolic pressure ($r = 0.61$). In response to treatment, decreases in blood volume were associated with decreases in central venous pressure ($r = 0.71$). There was no apparent association between brain natriuretic peptide levels and measured blood volume before or after treatment. The authors suggested that improvement in acute heart failure as a result of treatment may have been more quickly indicated by improvement (decrease) in blood volume, while improvement in BNP may occur over a longer time lag.

Feigenbaum and colleagues measured blood volume with Evans blue dye in 12 subjects with treated

CHF.[24] All patients were receiving diuretic agents, but physical signs of congestion were not described for the study sample. In contrast to other reports, blood volume was decreased in subjects with CHF when compared with 7 normal control subjects (58.5 ± 12.3 vs 70.8 ± 12.6 mL/kg, $P < 0.05$). These findings may be attributable to the use of Evans blue dye rather than radiolabeled albumin, the use of a small control group for determination of normal values with relative obesity in the CHF group, or unspecified clinical differences in the study sample or treatment strategy, particularly with regard to diuretic use.

The recently published ESCAPE study examined outcomes after treatment based on pulmonary capillary wedge pressure (PCWP), a highly invasive surrogate measurement for blood volume, as compared to outcomes after treatment based on clinical assessment alone.[25] Treatment incorporating PCWP endpoints was associated with increased anticipated adverse events (most arising from the pulmonary artery catheterization procedure), had no effect on six-month mortality, and was associated with short-term improvement in quality of life but no significant difference in quality of life after 6 months. The authors suggest that the lack of precisely defined treatment strategies for achieving PCWP goals may have contributed to unclear results. Another factor may be that since PCWP is not a direct measurement of blood volume, abnormal intravascular volumes may have been present even when PCWP goals were achieved. Additionally, as the amount of time after PCWP measurement increased, ongoing treatment became increasingly based on ongoing clinical assessment. The short-term improvement immediately after PCWP measurement may be related to a short-term difference in assessment and treatment that converged over the following months. Because PCWP is highly invasive, it is not feasible to make repeated measurements in ambulatory patients. Direct blood volume measurement can be performed more frequently in a wider range of patient populations; studies of outcomes based on blood volume endpoints may provide clearer results.

Clinical Recommendations

Although the majority of studies report increased blood volume on average in patients with CHF, it is important to note that almost all studies reported a wide range of blood volumes, with a substantial minority of patients demonstrating normal and subnormal blood volumes. Accurate assessment of volume status in heart failure patients is clinically important since unrecognized and untreated volume overload may contribute to ongoing congestive symptoms and overdiuresis to hypovolemia can compromise renal perfusion. The study by Androne and colleagues, consistent with previous reports based on hemodynamic measurements, emphasizes the limitations of physical assessment in the diagnosis of volume overload. Although the clinical goals for treatment of volume overload are primarily directed at symptomatic relief, untreated volume overload may also contribute to progression of ventricular remodeling in CHF patients. Chronic volume overload in experimental aortocaval fistula is associated with progressive left ventricular dilatation and myocardial dysfunction.[26] Chronic volume overload due to aortic or mitral regurgitation is associated with ventricular dilatation and eventually heart failure in the absence of timely surgical repair.[27] Prospective trials are needed to determine whether volume overload in heart failure directly contributes to disease progression, or is merely a reflection of the severity of underlying ventricular dysfunction.

Until further clinical trial information is available, routine use of blood volume measurement in the assessment of all CHF patients is not recommended. Blood volume measurement may be used as a noninvasive adjunct to clinical assessment to clarify volume status in symptomatic patients who no longer manifest rales or edema. Blood volume measurement with tagged red cells or radiolabeled albumin is available at many hospitals. The radiolabeled albumin technique used in recent studies by Androne and colleagues and James and colleagues is recommended for noninvasive blood volume measurement, as normal values for this technique are firmly established and included in the report (BVA-100, Daxor Corp, New York).[16] This device provides an accurate measurement of blood volume in 90 minutes and has been found to be equivalent to the more time-consuming techniques previously recommended by the International Committee for Standardization in Haematology.[9,28]

Future Directions

The American College of Cardiology/American Heart Association guidelines for diagnosing and treating heart failure[31] recommend assessing volume status in all heart failure patients and specifically establishing euvolemia in patients with refractory end-stage heart failure. Androne and colleagues found a strong link between volume status and mortality in ambulatory, nonedematous heart failure patients. These findings are consistent with previous hemodynamic studies and provide data in support of the ACC/AHA guidelines. The ESCAPE trial had ambiguous results with regard to treating to PCWP endpoints, but the limitations of the study make extrapolation to blood volume endpoints of limited value. Additional controlled prospective studies are needed to test the hypothesis that routine direct measurement of blood volume will be associated

with improved clinical outcomes in patients with chronic heart failure. To test this hypothesis in a prospective trial, eligible patients with chronic heart failure without clinical signs of congestion would all undergo serial blood volume analysis, but a randomization process would release the results of the blood volume measurement to only half of the physicians providing care for the patients. Therapy would be algorithmically driven to achieve blood volume within the normal range with prospective determination of clinical outcomes (all-cause hospitalization and mortality) and safety (blood pressure and biomarkers of renal function).

Thoracic impedance measurements provide an indirect measurement of thoracic fluid content.[29] In pilot study of 34 heart failure patients with recorded thoracic impedance data derived from an implanted device, a decrease in thoracic impedance (consistent with increase thoracic fluid content) was predictive of subsequent hospitalization in heart failure.[30] In a larger pilot study of 212 heart failure patients with repeated measures of thoracic impedance with an external electrode device at 2-week intervals over 26 weeks, a decrease in thoracic impedance was an independent predictor of risk for adverse clinical outcomes.[31] Thoracic impedance measurements may be altered by adiposity, muscularity, height, intrinsic lung characteristics, electrode placement and skin preparation for electrodes.[31] Due to inter- and intra-subject variability in measurements related to these factors, the clinical utility of impedance measurements is dependent on observations of relative change over time within subjects. Direct blood volume measurement offers complementary information that could improve the clinical utility of thoracic impedance measurements. It is possible that normovolemia determined by direct blood volume measurement could be used to "calibrate" the thoracic impedance measurement as the normal baseline and improve clinical decision making based on subsequent thoracic impedance measurements. Additional studies are needed to determine the relationship between direct measurements of blood volume and thoracic impedance in patients with heart failure.

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