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