Unrecognized Volume Overload in Congestive Heart Failure

a report by
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A recent study reported the clinical characteristics and outcomes of 43 non-edematous ambulatory patients with congestive heart failure, in whom clinical volume status was categorized by a direct measurement of blood volume by a radioisotope technique.[1] Despite on-going treatment with high doses of loop diuretics and few physical signs of congestion, 65% of the subjects in this cohort were found to have large increases in blood volume. Those patients that were classified as hypervolemic (>8% above the predicted normal blood volume) had a mortality rate of 39% within one year, and a 55% mortality rate within two years versus a 0% mortality rate for those patients who were classified as normovolemic or hypovolemic.

Since more than 4.5 million Americans have been diagnosed with heart failure, and nearly 550,000 new cases are diagnosed annually,[2] it is important to consider the potential contribution of direct blood volume measurement in enhancing diagnosis, treatment, and prognostic assessment of heart failure patients.

Heart failure is a clinical syndrome rather than a specific disease state. Progressive changes in left ventricular structure and peripheral arteriolar structure and function that occur in response to various sources of myocellular stress and/or injury reduce cardiac output reserve and aerobic capacity. Renal hypoperfusion secondary to reduced cardiac output is commonly associated with sodium and water retention (increased plasma volume) and consequent congestive signs and symptoms. Co-morbid conditions, such as hypertension, renal disease, diabetes, and coronary artery disease (CAD) also contribute to progression of disease and heterogeneity in clinical presentations.

Blood Volume Measurement Technique

Although derangements in blood volume are integral in the pathophysiology of heart failure, until recently direct measurement of blood volume has not been feasible for routine clinical practice. Radioisotopic blood volume measurement is considered the gold standard for assessment of blood volume.[3] However, until recently, radioisotopic measurement of blood volume has been difficult and time-consuming, requiring as much as four to six hours to complete. As a result, clinical blood volume status has been routinely estimated using a combination of findings from clinical history, physical examination, and proxy tests such as the hematocrit, hemoglobin, plasma brain natriuretic peptide levels, and azotemia.

Clinical assessment of blood volume, however, is frequently inadequate. In a recent study of heart failure patients, clincical assessment of a patient's volume status (normovolemic, hypovolemic, or hypervolemic) by a board-certified internist with specialty heart failure training was correct only 51% of the time.[1] In this study, measurement of pulmonary capillary wedge pressure was more accurate than clinical assessment (82% accurate), but is highly invasive. Plasma brain natriuretic peptide measurements were also more accurate than clinical assessment, but only correctly identified blood volume status in 72% of cases.

A recently available US Food and Drug Administration (FDA)-approved semi-automated instrument enables radioisotopic blood volume measurement to be performed within one and a half hours or less with a 98% accuracy. The test requires intravenous injection of a small amount of radiolabeled albumin and collection of six serial venous blood specimens over a 40-minute period. The samples are analyzed by semi-logarithmic plot to calculate the volume of distribution of albumin (plasma volume) and corrected hematocrit measurements are used to calculate red blood cell volume and total blood volume (red blood cell volume plus plasma volume). The results are adjusted for factors known to affect blood volume

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(body habitus, age, and gender) and displayed in both absolute and normalized values.

This non-invasive method of blood volume measurement provides accurate and clinically accessible blood volume measurements for application in research and clinical settings.

Heterogeneity of Blood Volume in Heart Failure

The classic blood volume abnormality in heart failure is expansion of the plasma volume. Plasma expansion occurs in conjunction with increased vasoconstriction when the renin angiotensin aldosterone (RAA) system and other neurohormonal mechanisms are activated in response to decreased renal perfusion. The pharmacological treatment of heart failure or co-morbid conditions in heart failure patients may further alter blood volume, at times in divergent ways. Diuretics reduce plasma volume, while long-term vasodilation with organic nitrates and other vasodilators can lead to an increase in blood volume. Nesiritide produces both vasodilation and mild diuresis and thus may have mixed effects on blood volume. The interactions of blood volume alterations resulting from heart failure, co-morbid conditions, and the treatment of these conditions can lead to a variety of sometimes unexpected blood volume changes in heart failure patients. One study of clinically stable heart failure patients receiving pharmacotherapy found that the patients tended to have contracted plasma and whole blood volumes compared with healthy controls.[4] A study of heart failure patients with no peripheral edema found a mixture of hypervolemic, normovolemic, and hypovolemic patients, with the majority of patients being hypervolemic.[1] Interestingly, the degree of volume overload in these treated non-edematous patients was comparable with another population of newly diagnosed decompensated heart failure patients who had never received treatment.

Anemia is also common in heart failure. Depending on the clinical characteristics of the patient population and the diagnostic criteria for anemia, the incidence has been found to be anywhere from 10% to over 50%.[5,6] Anemia is more common in women than in men and is more prevalent in individuals with more severe heart failure.[6,7] Current diagnosis of anemia is typically based on hemoglobin or hematocrit measurement and thus does not differentiate between true anemia and pseudoanemia resulting from hemodilution (increased plasma volume). A recent study utilizing radioisotope blood volume measurements in anemic heart failure patients demonstrated that pseudoanemia secondary to hemodilution is a common cause of anemia in this patient population.[7]

Blood Volume in Relation to the Diagnosis, Treatment, and Prognosis of Heart Failure

In non-edematous heart failure patients, hypervolemia determined by radioisotope blood volume analysis was associated with a significantly increased risk of mortality or urgent cardiac transplantation when adjusting for other known prognostic markers.[1]

In patients with pulmonary hypertension, increased plasma volume in association with advanced right-sided heart failure was associated with increased mortality.[8] Anemia has been associated with increased mortality risk in a number of heart failure populations.[9,6,10,11] In anemic heart failure patients, pseudoanemia secondary to hemodilution has been found to be associated with greater mortality risk than true anemia.[7]

Because of the heterogeneity of blood volume status

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among heart failure patients related to the underlying pathophysiology, co-morbid conditions, and treatments, blood volume measurement may prove useful for optimization of medical management in heart failure. Measuring blood volume in an individual patient could theoretically enable physicians to determine precisely which medications are needed to restore a normovolemic state. For example, while a non-edematous heart failure patient with an expanded plasma volume determined by radioisotope blood volume analysis might benefit from more aggressive diuretic therapy, another non-edematous patient with decreased blood volume may be at risk of hypotension unless the diuretic dose is decreased or discontinued entirely. The use of high doses of diuretics in patients who had developed diuretic resistance was found to be associated with increased mortality,[12] possibly indicating that overdiuresis with consequent hypovolemia may occur in some patients.

hypervolemia is associated with increased mortality risk. Anemia is increasingly recognized as a prognostic marker of poor outcome in heart failure. Although true anemia and pseudoanemia are rarely differentiated in reported studies or clinical practice, pseudoanemia secondary to plasma volume expansion may be an important cause of increased mortality risk in anemic heart failure patients. The incorporation of blood volume measurement into the diagnosis of heart failure and anemia may provide important information about a patient's prognosis and may assist in the optimization of medical therapy. Radioisotopic blood volume measurement is currently the most accurate non-invasive method for determining blood volume.

Further study is warranted to determine whether adjustments in therapy to normalize blood volume in heart failure patients improves outcomes. Additional studies on the relationships between blood volume and

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More subtle interactions may occur between blood volume and vasoactive drugs, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, organic nitrates, or nesiritide. Because heart failure patients' regulatory mechanisms are already impaired, patients tend to be highly sensitive to changes in blood volume. Administration of vasodilator drugs to patients with hypovolemia may lead to arterial hypotension. Further study of the interactions between blood volume status and side-effects (specifically hypotension) from vasoactive drugs may help determine optimum medications and dosages, and limit side-effects. Blood volume measurement over longer periods of time may help elucidate longer-term effects of vasoactive drugs on volume, perfusion, and clinical outcomes. Prospective clinical trials are needed to determine whether incorporation of blood volume measurements in clinical decision-making is associated with improved patient clinical status and outcomes.

Conclusion

Many heart failure patients without overt signs of congestion have expanded blood volume. Unrecognized various medications may provide information leading to improved diagnostic precision and streamlined strategies for optimization of medical therapy. ■

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