

## Blood Volume Analysis Coupled with Ultrafiltration in the Management of Congestive Heart Failure—Guided Therapy to Achieve Euvolemia

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### Abstract

Abnormal regulation of intravascular volume plays a key role in the pathophysiology of heart failure. Expert consensus guidelines recommend treating volume-overloaded heart failure patients with lifestyle modifications and diuretics to return them to a euvolemic (normovolemic) state. The diagnosis of volume overload can be imprecise, as previous studies have shown that signs of congestion detected by physical examination and chest radiography are inaccurate markers of fluid excess. The most direct and accurate method available for determination of intravascular volume status is radioisotopic measurement using the indicator dilution method. This technique can be applied to clinical decision-making in heart failure patients and may be used to more precisely guide fluid removal by ultrafiltration such that patients are restored to euvolemia with minimal risk.

### Keywords

Ultrafiltration, hypervolemia, euvolemia/normovolemia, blood volume, congestion, heart failure, diuretics, hematocrit, anemia, BVA-100

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### Volume Overload in Heart Failure

The burden of heart failure (HF) remains formidable in the US, with nearly one million annual hospital admissions and frequent outpatient visits to a variety of care providers.<sup>1</sup> While HF outcomes have improved modestly over the past several decades, many patients still struggle to maintain a satisfactory quality of life.<sup>2</sup> Implantable cardioverter-defibrillators have reduced the risk for sudden cardiac death. Thus, more patients experience progressive ventricular dysfunction and are at higher risk for episodes of fluid retention. In fact, fluid retention is the primary presenting symptom in roughly 90% of the one million annual hospitalizations for HF.<sup>3</sup>

Diuretics are the most commonly prescribed medical therapy for hospitalized HF patients.<sup>3</sup> Diuretics are prescribed out of necessity, although they are associated with worse outcomes in both inpatient and outpatient settings.<sup>4</sup> It is a major challenge to determine when an HF patient has achieved euvolemia (normovolemia) and to adjust diuretic therapy appropriately. Recently published guidelines from the American College of Cardiology (ACC), the American Heart Association (AHA), the Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC) recommend regular volume assessment of HF patients coupled with therapy aimed at achieving euvolemia.<sup>1,5,6</sup>

Salt and water retention in HF is due, in part, to neurohormonal activation of the renin-angiotensin-aldosterone system (RAAS) and

increased vasopressin levels. Suboptimal patient adherence to and compliance with medical therapy and dietary restrictions also contribute to volume overload.<sup>7</sup> Almost 25% of discharged HF patients are re-hospitalized within 30 days, many for recurrent volume overload.<sup>8</sup> Inadequate correction of hypervolemia at the initial admission may account for some of this elevated risk, while poor patient compliance and suboptimal co-ordination of care at discharge likely explain the remaining residual risk.<sup>9–12</sup>

What is lacking in the routine care of the HF patient is a more systematic approach to guide fluid management therapy by helping clinicians to determine when patients have achieved normovolemia. This article will highlight this unmet need and explore the use of quantitative blood volume analysis (BVA) as a tool to guide management of volume overload in HF patients.

### Pharmacological Management of Volume Overload in Heart Failure

Loop diuretics are the first-line therapy for volume management of HF. These agents produce rapid, albeit hypotonic, natriuresis and diuresis, which can decrease lung congestion, dyspnea, and the peripheral stigmata of volume overload (e.g. edema). Nevertheless, there is little evidence from controlled trials to support their use. In fact, evidence suggests that diuretics are not benign medications, as patients managed with diuretics experience increased mortality, elevated risk for

renal dysfunction, and electrolyte abnormalities that may precipitate dysrhythmias and greater neurohormonal activation.<sup>13-15</sup> Moreover, prolonged use of diuretics may lead to a state of diuretic resistance where, despite ongoing diuretic therapy, a patient fails to achieve or maintain normovolemia. It is estimated that up to 35% of HF patients experience diuretic resistance.<sup>16-18</sup> Many of these diuretic-resistant patients will require hospitalization and/or intravenous diuretics or ultrafiltration to treat their ongoing fluid overload.

## Direct Fluid Removal to Manage Volume Overload in Heart Failure

Direct fluid removal is a common form of treatment for volume overload. Phlebotomy was once considered the method of choice for reducing congestion, although in recent times it has primarily been used for patients with both red cell and plasma volume expansion. By contrast, ultrafiltration (UF) removes isotonic plasma water while retaining higher-molecular-weight particles such as red blood cells (RBCs) and plasma proteins. Thus, UF depletes plasma volume without altering the red cell volume and may therefore hemoconcentrate patients with elevated baseline red cell volumes.

## Clinical Studies Show Ultrafiltration Provides Benefits Compared with Diuretic Therapy

Several studies have shown the benefits of UF in managing volume overload in HF patients.<sup>19-22</sup> Agostoni et al. evaluated outcomes in 16 New York Heart Association (NYHA) class II and III HF patients treated with diuretics compared with ultrafiltration. While all patients showed initial symptomatic improvement, only those treated with UF showed sustained clinical improvement throughout a three-month period. By contrast, diuretic-treated patients showed positive water balance, elevated ventricular filling pressures, and recurrence of lung congestion in the same time-frame. Additional work by Agostoni et al. evaluated the neurohormonal impact of UF compared with diuretics for comparable quantities of fluid removal. Only UF produced sustained reductions in plasma renin, norepinephrine, and aldosterone.<sup>19</sup> Moreover, diuretic-treated patients who ceased therapy regained all of their lost weight within one week, while UF-treated patients sustained their weight reductions for at least three months.

Sheppard et al. evaluated the use of intermittent UF in 19 outpatients with refractory congestive HF (CHF).<sup>23</sup> Patients were given intermittent UF for at least one year, and the results for each patient were compared with those from the year prior to initiation of UF therapy. The initiation of UF correlated with striking reductions in the number of patients considered inotrope-dependent (86.4 versus 36.8%;  $p < 0.005$ ) and the number of hospitalizations (2.6 versus 0.3;  $p < 0.005$ ), and correlated with a significant improvement in the NYHA functional class (from 4 to 3.1;  $p < 0.005$ ).

The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated HF (UNLOAD) trial was the first to randomize hospitalized volume-overloaded HF patients to either intravenous (IV) diuretic therapy or UF.<sup>24</sup> Inclusion criteria mandated at least two signs of fluid overload on physical examination. Significantly more fluid was removed with UF compared with either intermittent or bolus IV diuretics in the trial. Dyspnea was initially improved to a similar extent

using either diuretics or UF at 48 hours. However, at 90 days, the UF group showed significantly fewer HF re-hospitalizations, fewer re-hospitalization days, and fewer unscheduled emergency department visits compared with the diuretic-treated group. It was hypothesized that the increased salt removal achieved by UF was largely responsible for the dramatic reduction in re-hospitalizations. In many cases, the diuretic dose was lowered when UF-treated patients resumed diuretics in the outpatient setting, consistent with improved diuretic sensitivity.

## Blood Volume Measurement

Regardless of the method of volume removal employed, clinicians struggle to identify when a patient has achieved euvoolemia. In many cases, the physician's efforts to fully resolve congestive signs and symptoms lead to overdiuresis and hypovolemia, with an accompanying deterioration in renal function that delays hospital discharge. Clinical criteria such as resolution of edema and dyspnea, interval improvement in chest radiographic images, and reductions in brain natriuretic peptide (BNP) levels are often used as surrogate measures to estimate changes in volume status, despite findings that show that these surrogates lack sensitivity.<sup>25,26</sup> Androne et al. published a study in which direct blood volume analysis was used to determine the intravascular fluid status of 43 HF patients. It was observed that clinical assessment by experienced HF physicians and measured blood volumes were concordant in only 51% of cases.<sup>27</sup> More importantly, the patients identified as hypervolemic by blood volume analysis exhibited substantially higher mortality rates. Clearly, clinical findings alone are not sufficient to identify those patients at higher risk for adverse events.<sup>27</sup>

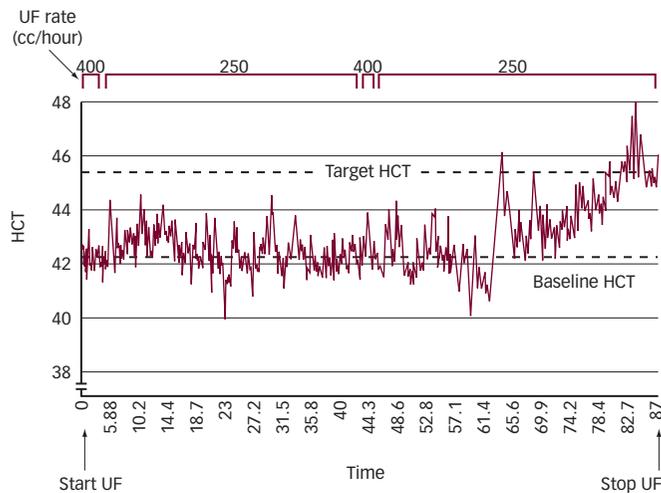
Radioisotopic blood volume analysis provides a direct measure of intravascular volume status. A commercially available semi-automated system (BVA-100; Daxor Corporation, New York) currently in use provides a highly accurate quantification of total blood volume, RBC volume, and plasma volume.<sup>28</sup> Blood volume is measured by the indicator dilution technique, in which a known volume of radioactive tracer is injected into a patient's unknown intravascular volume.<sup>29</sup> Blood volume results are automatically compared with predicted normal values based on the patient's deviation from ideal weight, and categorized according to the severity of their volume derangements.<sup>30</sup>

## Potential Use of Blood Volume Measurement to Guide Fluid Removal in Volume-overloaded Heart Failure Patients

Reliance on surrogate measures to guide UF may lead to an inappropriate degree of fluid removal. Patients with residual hypervolemia have been shown to experience higher rates of adverse outcomes,<sup>31</sup> including an increased risk for early re-hospitalization. In attempting to resolve congestion, caution must be exercised to avoid excessive fluid removal that may produce hypotension, worsening renal function, and intolerance to HF therapies with proven mortality benefits, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and beta blockers. Thus, there is a strong need to identify which patients may benefit from UF and which may actually be harmed.

Intravascular plasma volume remains stable throughout the early phase of a UF treatment session<sup>32</sup> as rates of plasma refill from the

**Figure 1: Realtime Hematocrit Monitoring During Ultrafiltration Therapy**



Time is represented on the x-axis and hematocrit (HCT) data on the y-axis. The baseline and target HCT, which are derived from blood volume analysis, are represented by dashed lines. As ultrafiltration (UF) progresses and the plasma refill rate falls below the UF rate, HCT begins to rise. In response, the UF rate is gradually reduced in a step-wise fashion and ultimately stopped once the target HCT has been achieved.

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interstitium match the rate of fluid removal by UF. This minimizes the risk of hypotension and declining renal function. This equilibrium state persists until the plasma refill rate declines due to equalization of the intravascular and extravascular oncotic and hydrostatic pressures. Hematocrit (HCT) is defined as (RBC volume/total blood volume) x 100. Assuming a constant RBC mass, HCT will increase as the plasma volume is decreased by UF, provided that the UF fluid removal rate exceeds the plasma refill rate. This permits use of the 'normalized HCT,' which is calculated as baseline peripheral HCT corrected for the expected 'normal' intravascular volume, as a target to indicate when euvoolemia has been achieved. Therefore, by using realtime, in-line HCT measurement technology attached to the withdrawal limb of the veno-venous circuit during UF, volume removal can be precisely quantified and titrated so as to avoid excessive plasma reduction (see Figure 1).<sup>33</sup>

Indeed, this approach is under active investigation in the Treating to Euvoolemia by Clinical Assessment and Measured Blood Volume during Ultrafiltration (TEAM-UF) clinical study. The objective of this study is to examine whether the 'normalized HCT,' derived from blood volume analysis, can be used to provide realtime guidance of UF in hospitalized HF patients. The safety and efficacy of this approach compared with UF guided solely by clinical findings will be evaluated prospectively with the hope of demonstrating improved patient outcomes.

## Blood Volume Measurement Distinguishes True Anemia from Hemodilution in Heart Failure Patients

Anemia is frequently observed in CHF patients and is associated with a poor prognosis. However, it is clinically challenging to distinguish those HF patients whose reduced HCT is the result of an expansion in plasma volume rather than a reduction in RBC mass. One study showed that patients with hemodilution exhibited worse survival than patients with true anemia, suggesting that volume overload contributes to poor outcomes in anemic HF patients.<sup>34</sup> Blood volume analysis provides a unique quantitative method to distinguish HF patients with true anemia versus hemodilution so that they can be treated appropriately.

Those HF patients who are shown to exhibit true anemia can be optimally managed by an anemia work-up, followed by erythropoietin (EPO) therapy or RBC transfusions, if needed. By contrast, HF patients who are shown to be hemodiluted with preserved RBC mass can be spared transfusion and EPO therapies in favor of plasma volume reduction through UF or diuresis. Without the ability to quantify RBC mass using the blood volume analysis technique, there is a theoretical risk of increased blood viscosity with UF as plasma volume is reduced while RBC mass is increased.<sup>35</sup> In practice, if the normalized HCT derived from the blood volume analysis is >45%, UF therapy is tailored to ensure that patients do not exceed this HCT threshold during the course of therapy to avoid potential complications such as hypercoagulability or thrombosis.

## Conclusions

HF decompensation is routinely associated with intravascular volume expansion and signs of clinical congestion such as dyspnea and edema. Restoration of euvoolemia is of paramount importance to ensure optimal outcomes and quality of life in this fragile patient population. Surrogate measures and signs of renal dysfunction are commonly used to guide diuretic therapy, despite the lack of sensitivity and reliability of these methods. Ultrafiltration provides another well-established method of removing volume from HF patients, and is frequently used in patients who have exhibited diuretic resistance. The reduced risk of re-hospitalization observed in UF-treated HF patients demonstrates the potential benefit of this approach compared with conventional diuretics.

Blood volume analysis provides a tool to precisely quantify intravascular volume status and to discriminate between patients with true versus dilutional anemia. The use of baseline and normalized HCT data derived from blood volume analysis, coupled with the realtime tracking of HCT throughout UF, may offer a promising approach to precisely identify when a volume-overloaded HF patient has achieved euvoolemia. This approach is under active investigation and may represent a new paradigm to ensure the best possible outcomes and to reduce the tremendous morbidity associated with HF. ■

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