

# Diagnosis and Management of Fluid Overload in Heart Failure and Cardio-Renal Syndrome: The “5B” Approach

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**Summary:** Cardio-Renal syndrome may occur as a result of either primarily renal or cardiac dysfunction. This complex interaction requires a tailored approach to manage the underlying pathophysiology while optimizing the patient's symptoms and thus providing the best outcomes. Patients often are admitted to the hospital for signs and symptoms of congestion and fluid overload is the most frequent cause of subsequent re-admission. Fluid management is of paramount importance in the strategy of treatment for heart failure patients. Adequate fluid status should be obtained but a target value should be set according to objective indicators and biomarkers. Once the fluid excess is identified, a careful prescription of fluid removal by diuretics or extracorporeal therapies must be made. While delivering these therapies, adequate monitoring should be performed to prevent unwanted effects such as worsening of renal function or other complications. There is a very narrow window of optimal hydration for heart failure patients. Overhydration can result in myocardial stretching and potential decompensation. Inappropriate dehydration or relative reduction of circulating blood volume may result in distant organ damage caused by inadequate perfusion. We suggest consideration of the “5B” approach. This stands for balance of fluids (reflected by body weight), blood pressure, biomarkers, bioimpedance vector analysis, and blood volume. Addressing these parameters ensures that the most important issues affecting symptoms and outcomes are addressed. Furthermore, the patient is receiving the best possible care while avoiding unwanted side effects of the treatment.

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Fluid overload is a common result of cardiovascular disease (especially heart failure) and kidney disease. When the heart and kidney present a combined dysfunction such as in the case of cardio-renal syndromes (CRS), overhydration is almost the rule.<sup>1,2</sup> The diagnosis, objective quantification, and management of this problem is integral in attempting to improve clinical outcomes, including mortality and quality of life. Many clinical conditions lead to fluid overload, including decompensated heart failure and acute kidney injury (AKI) after the use of contrast media, the administration

of nephrotoxic drugs (eg, amphotericin B), drugs associated with precipitation of crystals (eg, methotrexate, acyclovir), or shock caused by cardiogenic, septic, or traumatic causes. Adequate fluid status should be obtained but a target value should be set according to objective indicators and biomarkers. Once the fluid excess is identified, a careful prescription of fluid removal by diuretics or extracorporeal therapies must be made. While delivering these therapies, adequate monitoring should be performed to prevent unwanted effects such as worsening of renal function or other complications. Thus, the clinical challenge becomes the use of all currently available methods for objective measurement to determine the patient's volume status.

The term CRS is used to include the vast array of interrelated derangements between the heart and kidney, and to stress the bidirectional nature of their interactions. Generally, CRS are defined as pathophysiologic disorders of either organ system, in which acute or chronic dysfunction of one may induce acute or chronic dysfunction of the other.<sup>3</sup> CRS can be categorized into 5 subtypes that reflect the pathophysiology, time frame, and nature of concomitant cardiac and renal dysfunction (Table 1). CRS are therefore typical conditions in which fluid overload may occur and may require specific diagnosis and management. The various types of CRS may present with different signs and symptoms but fluid overload represents one of the common pathways toward hospitalization and bad outcomes.

For CRS type 1, the hemodynamic mechanisms induced by heart failure represent the etiologic events lead-

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**Table 1.** CRS

General definition	Pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other
CRS type I (acute CRS)	Abrupt worsening of cardiac function leading to AKI
CRS type II (chronic CRS)	Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)	Abrupt worsening of renal function causing acute cardiac disorders
CRS type IV (chronic renocardiac syndrome)	Chronic kidney disease contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)	Systemic condition (eg, diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

ing to sodium and water retention (Fig. 1). They basically can be summarized into two main aspects: the arterial underfilling and the venous congestion. Important compensatory mechanisms occurring in response to hemodynamic alterations can be divided into two phases: vasoconstriction or vasodilation (Fig. 2). In the first, activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), vasopressin, and endothelin result in decreased water and sodium excretion and, depending on the degree of renal functional impairment, increased urine concentration. To compensate for such condition, vasodilation occurs via natriuretic peptide (NP) release, activation of the kinin-kallikrein system, secretion of vasodilatory prostaglandins, and expression of endothelial relaxation factor, thus increasing water and sodium excretion. However, this second phase may be inadequate to counter the initial vasoconstrictor effects, and disease progression may occur. In most cases, inappropriate water retention also is caused by a nonosmotic release of arginine-vasopressin that, in heart failure, worsens vasoconstriction via the stimulation of V1 receptors and dramatically increases the back-transport of water in the distal tubule via the stimulation of V2 receptors and aquaporin activation.

When cardiac disease (or heart failure) results in renal hypoperfusion, renal medullary ischemia is the consequence. Initially functional, it ultimately results in tissue damage. Further hypoperfusion and sustained tubuloglomerular feedback often will sustain the hemodynamic effect. In such clinical situations, the important objective is the maintenance of renal blood flow. This may be accomplished by acting on cardiac output, thus maintaining intravascular volume and renal perfusion pressure. There is a very narrow window of optimal hydration in such conditions. Overhydration can result in myocardial stretching and potential decompensation. Inappropriate dehydration or relative reduction of circulating blood

volume may result in distant organ damage caused by inadequate perfusion. Renal function may be affected by both situations.

Efficient management of cardiac output requires optimization of heart rate, rhythm, preload, afterload, myocardial contractility, and, if required, surgical intervention in the instance of anatomic instability. Left ventricular assist devices are considered when these approaches fail.

Ultimately, knowledge of the degree of cardiac output is vital because there is no scientific case for fluid administration when the cardiac output exceeds 2.5 L/min/m<sup>2</sup> in patients not receiving inotropes. Particularly when sepsis is present, if the cardiac output is high and the patient is hypotensive, vasopressors, rather than fluids, are required irrespective of central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), or right ventricular end diastolic volume levels. Thus, in sepsis, vasopressors, such as norepinephrine (and dobutamine), are required to maintain renal perfusion even if the cardiac output is normal or high. If heart failure is present either with preserved left ventricular function or decreased ejection fraction, abnormal cardiac output and altered hemodynamics may result in oliguria and inappropriate water retention and diuretics and/or extracorporeal ultrafiltration must be considered.

In other words, fluids may be either required or removed in conjunction with other therapeutic strategies. In heart failure, most patients present with overhydration and the main strategy is to remove fluid and obtain the target hydration status in the absence of hemodynamic perturbation and worsening of renal failure.

## 5Bs

In the clinical routine, physicians are challenged by the unstable hemodynamics of the patient even in the presence of fluid overload and congestion. Strategies to achieve optimal hydration often include diuretic therapy or ultrafiltration even though a precise target for fluid status is missing. Thus, a comprehensive approach to fluid management is required: the following are five aspects of the approach to fluid overload in the context of CRS, a mnemonic termed the *5Bs* (Table 2).

### Balance of Fluids

There is a large body of evidence suggesting that fluid overload is a dangerous situation.<sup>4</sup> In several studies a clear association between fluid balance and clinical outcome was shown. In a prospective cohort of 113 patients with acute respiratory distress syndrome (ARDS) evaluated for up to 14 days after intubation patients who lost 3 kg or more weight had a much higher survival rate than those who gained 3 kg or more weight (67% and 0%, respectively, on day 14) and these patients showed a lower daily/cumulative fluid balance.<sup>5</sup> In a retrospective analysis of 89 patients with acute lung injury (ALI)/ARDS who had pulmonary artery catheters and extravas-

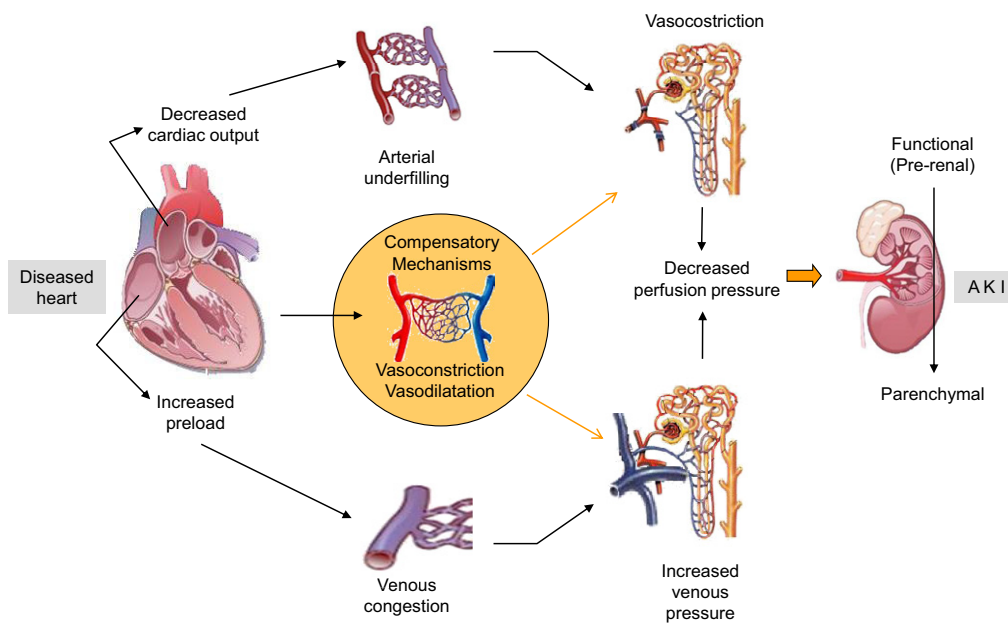


Figure 1. BNP consensus guidelines.

cular lung water greater than 7 mL/kg, mortality (74% versus 50%), duration of days on a ventilator, intensive care unit (ICU) stay, and hospital stay all were lower in patients who had gained less than 1 L over 36 hours into the study.<sup>6</sup> The Program to Improve Care in Acute Renal Disease (PICARD) data on 618 patients with AKI (396 required dialysis) revealed that the adjusted odds ratio for death with percent with fluid overload (%FO) greater than 10% at dialysis initiation was 2.07 (95% confidence

interval [CI], 1.27-3.37). At dialysis cessation those patients who were still in fluid overload (FO) with a %FO greater than 10% had an adjusted odds ratio of death of 2.52 (95% CI, 1.55-4.08).<sup>7</sup> In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, which was a large multicenter European observational study in critically ill patients, in patients with acute renal failure the mean daily fluid balance was significantly more positive among nonsurvivors than among survivors ( $0.98 \pm 1.5$  versus

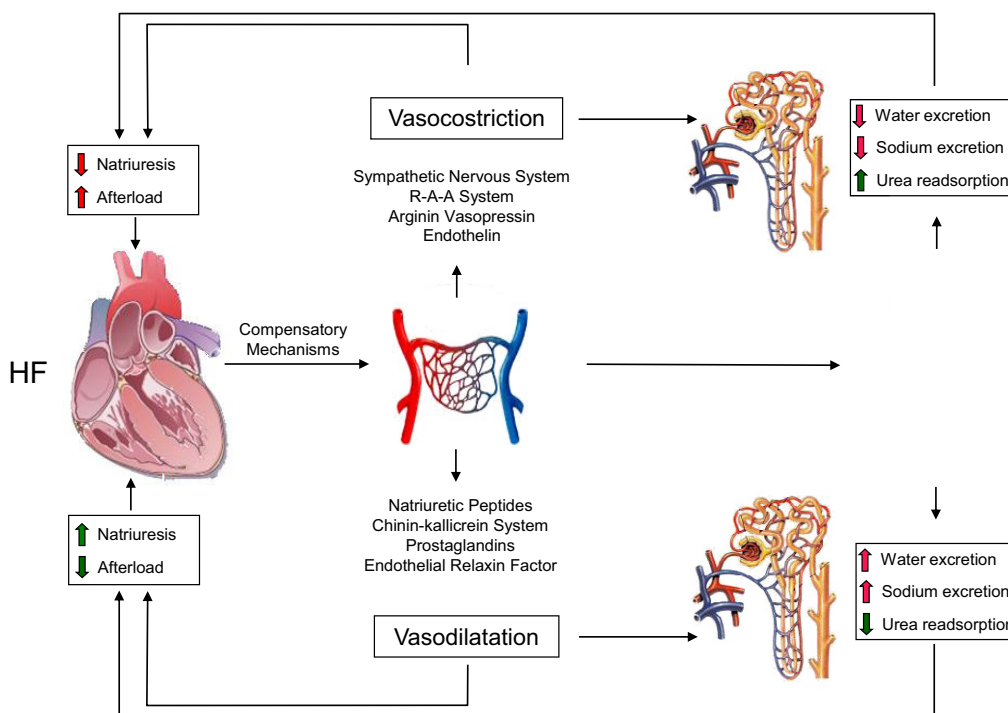


Figure 2. Hemodynamic mechanisms activated in CRS type 1.

**Table 2.** Overhydration and Congestion: Management With the 5 Bs

Balance of fluids
Blood pressure
Biomarkers
Bioimpedance
Blood volume

0.15 ± 1.06 L/24 h;  $P < .001$ ). Among oliguric patients and patients treated with renal replacement therapy (RRT), the mean daily balance was significantly more positive (0.62 ± 1.33 versus 0.27 ± 1.23 L/24 h;  $P < .001$ , and 0.60 ± 1.5 versus 0.39 ± 1.21 L/24 h;  $P < .001$ ) and 60-day mortality rates were significantly higher (39.6% versus 32.1%;  $P < .01$ , and 49.5% versus 31.2%;  $P < .01$ ). In patients in whom treatment with RRT was started early in the course of ICU admission, the median length of ICU stay was significantly shorter (6.1 versus 12.2 d;  $P < .001$ ) and 60-day mortality was significantly lower (44.8% versus 64.6%;  $P < .01$ ).<sup>8</sup> The ARDS trial randomized 1,000 patients to conservative and liberal fluid strategies. The mean (± standard error [SE]) cumulative fluid balance during the first 7 days was -136 ± 491 mL in the conservative-strategy group and 6,992 ± 502 mL in the liberal-strategy group ( $P < .001$ ). The patients on conservative fluid strategy showed an improved gas exchange and improved ventilator- and ICU-free days.<sup>9</sup> In surgical patients, a randomized controlled trial in 172 elective colorectal surgery patients evaluated restrictive (aimed to maintain preoperative weight) versus standard perioperative fluid strategy. The restrictive strategy was associated with lower cardiopulmonary and tissue healing complications and with no mortality as compared with four deaths in the standard fluid strategy group.<sup>10</sup> More recently, review of fluid balance in the 778 patients enrolled in the Vasopressin in Septic Shock Trial found a significant increase in cumulative fluid balance in these patients from +4.2 L at 12 hours to +11 L at 4 days. This positive fluid balance at 12 hours and 4 days was associated with a significant increase in mortality after correcting for age and severity of illness.<sup>11</sup>

Similar results have been shown in the pediatric AKI population. Goldstein et al<sup>12</sup> examined outcomes of 21 children receiving continuous veno-venous hemofiltration (CVVH)/D using Pediatric Risk of Mortality scores to control for severity of illness. The degree of FO in survivors (16.4% ± 13.8%) was significantly lower than in nonsurvivors (34.0% ± 21.0%). These findings were reiterated by the same investigators<sup>13</sup> in a retrospective analysis of 116 patients with multi-organ dysfunction syndrome (MODS) receiving RRT. A retrospective review of 77 children found that children with a high FO (>10%) at continuous renal replacement therapy initiation were at 3.02 times greater risk of mortality than those with low or no FO (95% CI, 1.50-6.10;  $P = .002$ ).<sup>14</sup>

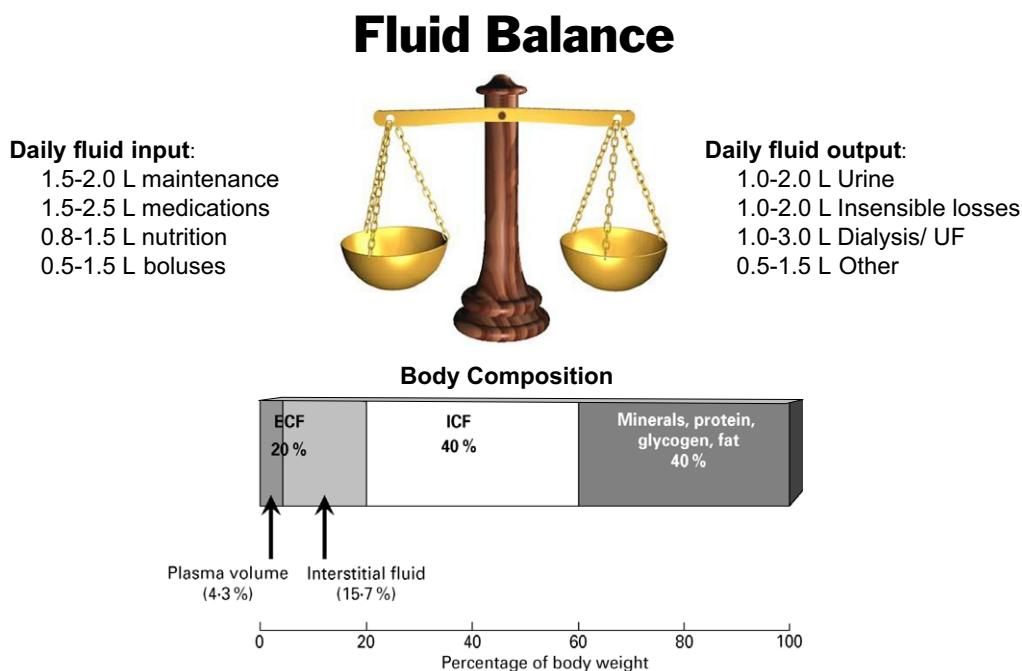
Another retrospective review of 297 pediatric patients from across 13 US centers suggested a 3% increase in mortality for every 1% increase in severity of fluid overload at initiation of dialysis.<sup>15</sup>

Recently, Grams et al<sup>16</sup> attempted to elucidate the association between FO, diuretic dose, and short-term mortality after AKI in critically ill patients. They evaluated 306 patients who developed AKI in the first 2 days of the Fluid and Catheter Treatment Trial (FACTT). Of these, 137 patients were in the fluid-liberal arm and 169 patients were in the fluid-conservative arm. A positive fluid balance after AKI was associated strongly with mortality. Post-AKI diuretic therapy was associated with 60-day patient survival in FACTT patients with ALI but this was not significant after correction for post-AKI fluid balance. Moreover, this protective association between furosemide dose and mortality was significant only in women, the fluid-conservative arm, and patients with oliguria during the first 7 study days. The investigators speculated that this positive effect may have been mediated by fluid balance.<sup>16</sup> Prowle et al<sup>17</sup> searched the PubMed electronic reference database to identify clinical studies examining fluid balance or therapy in critically ill adult patients. They found no studies examining restrictive fluid strategies in the ICU that showed a clinically significant worsening of renal function with fluid restriction. The FACTT trial reported a decrease in requirement of RRT in the conservative fluid arm group despite the fact that these patients had ALI and were on mechanical ventilation with high positive end-expiratory pressures. Similarly, Vidal et al<sup>18</sup> showed that patients with less positive FO and normal intra-abdominal pressures had fewer organ failures and shorter ICU stays.

The consequences of fluid overload are largely a result of tissue edema. Depending on the organ, this tissue edema may result in impaired oxygenation and metabolite diffusion, distorted tissue architecture, obstruction of capillary blood flow and lymphatic drainage, and disturbed cell-cell interactions that may then contribute to progressive organ dysfunction.<sup>17</sup> In fact, in heart failure (HF), data from the Acute Decompensated Heart Failure Registry database have reported the incidence of HF with preserved left ventricular systolic function to be as high as 50.4% in patients with decompensated HF.<sup>19</sup> Previous studies in HF have shown an association between central venous pressure, right atrial pressure, and renal function.<sup>20-22</sup> This may be related to distention of venules surrounding the distal tubules, back transmission of the right atrial pressure to the renal veins and interstitium, and development of increased intra-abdominal pressure.

Thus, although fluid status analysis requires great attention for the earlier-mentioned reasons, correct understanding of the problem of fluid balance requires a clear set of definitions.<sup>23</sup> First, fluid balance normally is defined by the daily difference in all intakes and outputs; this generally does not include insensible losses, it may not correlate with weight, although it should include





**Figure 3.** Compensatory mechanisms in HF.

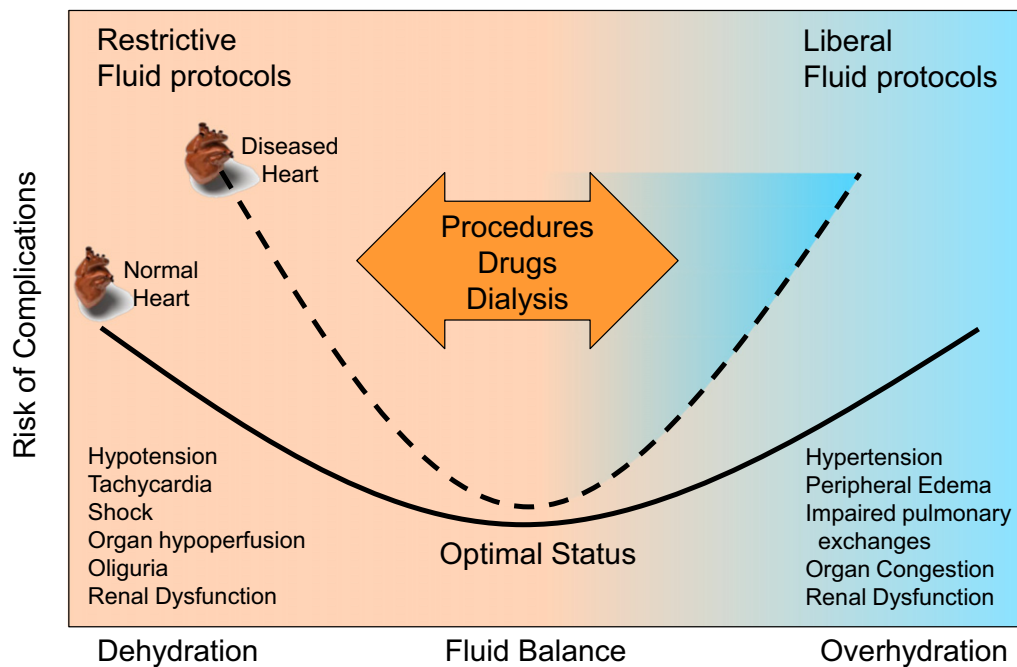
dialysis fluid removal (if the patient is on RRT). Second, cumulative fluid balance is defined by the sum of fluid accumulation over a set period of time. This parameter is more important and relevant to assess change over time, the amount and duration of key parameters associated with outcome, and, finally, the response to treatment. Third, fluid overload is represented by the cumulative fluid balance expressed as a percentage of body weight at baseline (hospital admission). A cut-off value of 10% has been associated with increased mortality.

Body volume and fluid composition must be considered in conjunction with all the inputs and outputs from the body (Fig. 3). Assessment of volume status requires knowledge of all subdivisions of total body water, particularly the intravascular compartment (arterial, venous, and capillary) and the interstitial compartment. Composition of the body fluid (ie, total osmolality), the concentration of specific electrolytes, and the acid-base status also must be known. When patients first present, clinical examination of the jugular venous pressure in particular may help discriminate between fluid overload and hypovolemia. Blood pressure, while lying down and standing if possible, hepatic enlargement, the observation of pulmonary rales or pleural effusion, and examination for peripheral edema are useful physical signs. Urinary excretion rate, its osmolality, sodium concentration, and microscopic examination may help to differentiate dehydration and AKI in the oliguric patient. Invasive monitoring including central venous pressure, pulmonary arterial pressure, cardiac output, volume responsiveness, and use of echocardiography and bioimpedance contribute diagnostic information. Although a chest radiograph is useful to exclude various pathologies, and may be

diagnostic in severe presentations, overall it is a blunt tool with poor sensitivity and specificity, and is even less reliable when a portable technique is used.

Whatever the initial estimate of volume is, in the patient with potential or recognized AKI, continued knowledge of fluid balance is essential to successful fluid management. An accurate measure of body weight is an excellent starting point. A major benefit of the ICU environment is the ability to obtain reasonably accurate estimates of fluid balance. Challenges in obtaining vital information are obvious, even in the best circumstances. Much balance information may be available only in a research environment (examples include fluid loss by respiration, insensible loss, and fecal electrolyte excretion). In the critically ill patient, accurate measurement of oral, intravenous, and fluid intake during extracorporeal therapy is countered by insensible losses, and those from the gastrointestinal tract and wound drainage are required but seldom obtained. Further, volume administration often is mismanaged by the use of a routine intravenous line in which the combination of maintenance fluids, fluids for drug administration, nutritional requirements, and therapeutic or diagnostic boluses may amount to large daily volumes. Although urinary excretion usually can be measured accurately, all other fluid losses are subject to gross error. Balance often may be replaced by estimates of body fluid compartments. This also is difficult because much excess fluid may be in noncommunicating pools (third spacing, not directly related to the circulation). New methods of assessing tissue hydration may be useful in this context.

In Figure 4, a schematized fluid balance domain is depicted. If fluid optimization is reached, this must be main-

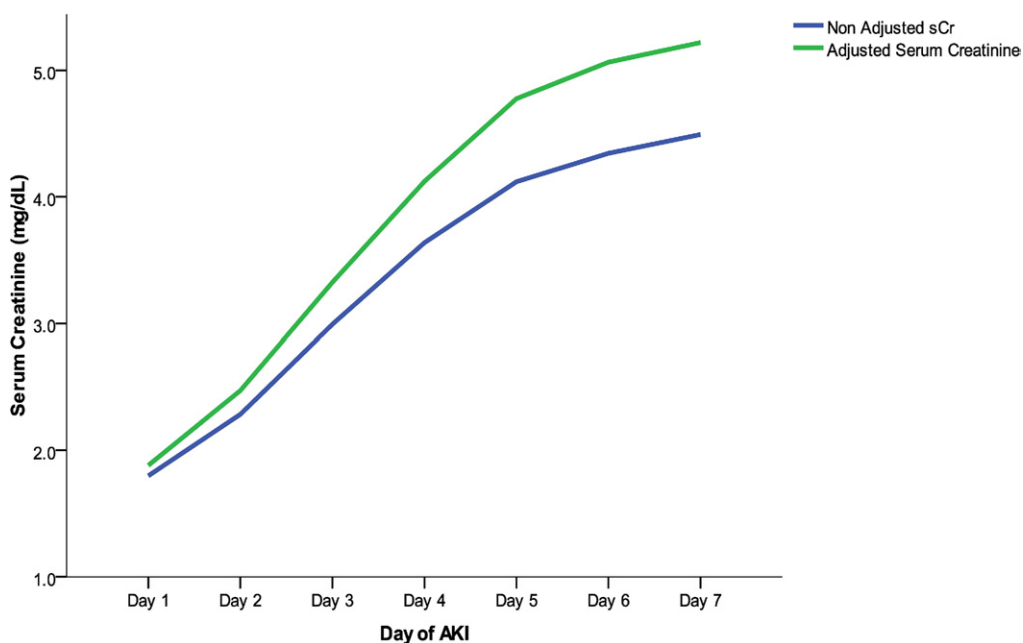


**Figure 4.** Components of fluid balance calculation and fluid distribution in the body.

tained through fluid balance optimization. Considering all the factors described in [Figure 3](#), fluid-restrictive protocols may lead to potential dehydration and the risk for complications such as hypotension, shock, and renal dysfunction increase. On the contrary, fluid-liberal protocols may induce various degrees of overhydration with consequent peripheral and pulmonary edema, congestion, and renal dysfunction. Although the healthy subject presents a certain degree of tolerance and compliance to fluid balance shifts, individ-

uals with heart failure have a narrower window of tolerance, presenting significant complications even in the presence of small deviations from optimal fluid balance. Fluid overload also may contribute to underestimation of the severity of AKI as depicted in [Figure 5](#).<sup>24,25</sup>

In practice, the approach to fluid balance is to do no harm while maintaining perfusion. In many instances a gradual reduction in administered fluid volumes is appropriate, coupled with careful observation of vital signs.



**Figure 5.** Delicate balance between dehydration and overhydration. The effects are different in a normal individual and in a patient with a diseased heart. In the latter, the window of optimal fluid status is narrower.

The use of diuretics to test renal responsiveness requires that the patient is at least normally hydrated. With decreasing blood pressures in the septic patient, it may be difficult to have confidence in the volume assessment. As a consequence, large volumes often are administered quickly. Although achieving a positive balance, this carries the potential for harm. Alternatively, excessive use of diuretics is associated with worsening renal function, as shown by creatinine increases in HF patients, with little clinical improvement.<sup>1</sup> The UNLOAD trial<sup>2</sup> compared diuretic use with ultrafiltration in the management of HF. Ultrafiltration resulted in greater weight loss and an initial, but not later, increase in serum creatinine level and fewer hospital re-admissions. These data suggest that ultrafiltration results in more effective fluid removal and improvement in cardiac function. Importantly, ultrafiltration can be controlled more tightly than the use of diuretics. The latter has the defect of intermittent stimulation of the sympathetic nervous system, whereas the more controllable use of ultrafiltration is shown to have less of this effect.

Although evidence that diuretics actually improve chronic mortality is poor, any increase in urine production clearly facilitates fluid management. Although registry data have shown that earlier diuretic use decreases mortality in severe acute decompensated heart failure,<sup>26</sup> it also reports a relationship between increased loop diuretic dosing and mortality.<sup>27</sup> Felker et al<sup>1</sup> clearly showed in patients with decompensated HF that use of boluses or continuous infusions of diuretics at high diuretic doses did not improve outcomes. In CRS type 1, the use of diuretics at inappropriate doses or frequencies, even in the less acutely ill patient, can cause sympathetic stimulation and RAAS activation that results in decreased cardiac and renal perfusion, and concomitant increases in sodium reabsorption. With the sicker patient, the hemodynamic effects of diuretics may precipitate acute cardiac ischemic insult and AKI.

The value of prompt action to replace fluid based on central venous pressure and oxygen control has been emphasized. However, fluid overload in the oliguric patient can occur easily with consequent endothelial damage and added cardiac risk. In the absence of diuretic responsiveness, techniques available for fluid removal are ultrafiltration, hemofiltration, hemodialysis, and hemodiafiltration. These all can be used intermittently, and the first two continuously. What are the special indications? Continuous slow ultrafiltration and hemofiltration permit the dissociation of water and salt removal by varying the combination of different removal and replacement fluids. Intermittent hemodialysis, with inappropriate choices of dialysate electrolyte concentrations or ultrafiltration rates, can result in blood volume reduction, hypotension, and, paradoxically, sodium loading. The response to fluid removal is dependent on the rate of removal, blood volume refilling into the vascular space, cardiovascular compensation, and the initial state of body

hydration. Potential errors in the estimation of fluid balance can be from negligible to catastrophic.<sup>28</sup>

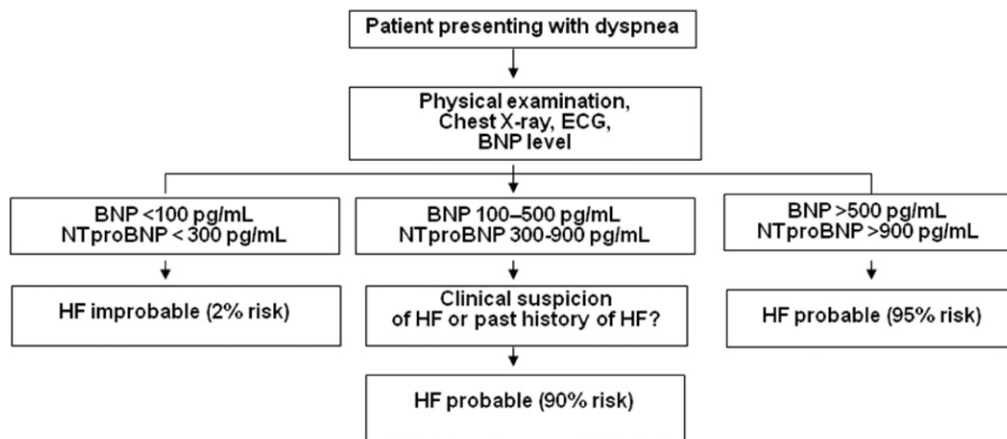
An interesting approach to potential errors with the use of continuous RRT machines is the prevention of a fluid balance error by specific software blocking the treatment after a certain number of alarm overrides. Most machines continue treatment after multiple over-ridings of the fluid balance alarm, thus creating the risk of severe injury. By analyzing the times taken for alarm occurrence, and the threshold value for fluid balance error after the alarm has been overridden, changes in software now prevent the accumulated error to exceed 200 to 250 mL before the treatment automatically is stopped.<sup>28</sup>

### Blood Pressure

Blood pressure, as a measure of volume status, is a poor and late changing indicator. Because pressure and perfusion are linked in the physiologic range, a myriad of compensatory responses hold blood pressure constant, despite wide fluctuations in volume status. Further, the consequences of administered medications further obscure the relationship, as does the impact of co-existing underlying pathologies. Thus, although an isolated blood pressure measurement in the expected range does not exclude the possibility of volume perturbations, an abnormal blood pressure measurement suggests that the patient's volume status is significantly disturbed, and of a severity of sufficient magnitude to overwhelm endogenous counterbalances. Based on these considerations, our second "B" in the fluid management strategy is blood pressure.

Orthostatic vital signs combine dynamic gravity induced changes in pulse and blood pressure that occur as a consequence of volume movement resulting from postural change. Easily obtained, rapidly performed, commonly used, and noninvasive significant changes are defined as a blood pressure decrease in excess of 10 mm Hg, or a heart rate increase exceeding 20 beats per minute. Unfortunately, the results do not withstand scientific validation. In a prospective study of 132 euvolemic patients, using the standard definition of a significant change, 43% would have been considered "positive."<sup>29</sup> In another study of 502 hospitalized geriatric patients with orthostatic vital signs obtained three times daily, 68% had significant changes documented daily.<sup>30</sup> Conversely, in a systematic review evaluating blood loss, the most helpful findings were postural dizziness to the extent that it prevented upright vital signs, or a postural pulse increase exceeding 30 beats per minute. Unfortunately, the sensitivity for moderate blood loss with either of these predictors was only 22%. Only when blood loss exceeded 1 L did the sensitivity and specificity improve to 97% and 98%, respectively.<sup>31</sup> Blood pressure and hemodynamic response in general is a precious parameter to consider when procedures or ultrafiltration is performed. A typical perturbation induced by fluid removal is a reduction in systolic blood pressure: this might

# BNP Consensus Guidelines



Adapted from Silver MA et al. *Congest Heart Fail.* 2004;10(5 suppl 3):1–30.

**Figure 6.** Fluid overload leads to underestimation of severity of AKI. ECG, electrocardiogram. Reprinted with permission from Macedo et al.<sup>24</sup>

be caused by a sudden decrease in circulating blood volume (owing to rapid fluid removal) or by a significant decrease in the extracellular fluid volume owing to excessive and prolonged negative fluid balance.

Hypotension is a typical sign of sepsis often reaching severe levels of abnormality in septic shock. In this case, blood pressure might be restored only if the original cause of sepsis is removed. Nevertheless, in the mean time, fluid resuscitation is a common approach.<sup>32</sup> Once fluid has been administered and titrated in boluses to achieve a cardiac index higher than 2.5 L/m in the absence of inotropes, further fluid administration is useless and vasopressors are required. Contrary to common belief, the use of norepinephrine in septic patients increases organ and specifically renal perfusion pressure, ameliorating renal function and diuresis. Thus, as a main message we can recommend that in the presence of low-pressure states, three cornerstones of hemodynamics should be considered: volume (effective versus overall), cardiac output, and vascular tone. Each of them requires specific attention and adequate therapy.

## Biomarkers

There are many contenders for diagnostic and prognostic biomarker indicators of acute and chronic injury occurring in CRS type 1. The most frequently used HF markers are the NPs. Knowledge of the B-type NP (BNP) level, a hormone produced by the myocardium in response to pressure or volume stress, can assist in differentiating HF from other causes of dyspnea.<sup>33</sup> NPs initially are synthesized as the precursor protein, pro-BNP, which then is cleaved by the enzyme corin into the inactive metabolite N-terminal proBNP (NT-proBNP) and the biologically active BNP that causes both vasodilation and natriuresis.

NPs can be measured clinically. If increased (>900

NT-proBNP, or >400 pg/mL BNP), early treatment may be considered because the positive predictive value for acute heart failure is in the range of 90%. Alternatively, a low NP level (<300 NT-proBNP, or 100 BNP pg/mL) suggests an alternative diagnosis because the negative predictive values approximate 90%. Levels between the paired cut-off points define a gray zone (300-900 for NT-proBNP, and 100-400 pg/mL for BNP) in which diagnostic certainty is unclear and additional testing is suggested (Fig. 6).<sup>34</sup>

NPs have several limitations. Because any myocardial stress (eg, myocardial infarction) may cause elevated NPs, it is important to consider the clinical scenario when interpreting results. Furthermore, non-HF increases of NPs occur with renal insufficiency, where levels increase in proportion to the severity of renal injury.<sup>35,36,37</sup> Some researchers have suggested the BNP cut-off point for HF should be doubled in the setting of renal insufficiency. Finally, another NP confounder is obesity, in which an inverse relationship between levels and body mass exists.<sup>38</sup> It has been suggested that if the body mass index (BMI) is greater than 35, the measured BNP should be doubled to improve the sensitivity for HF.

The clinical impact of BNP testing has been evaluated in the 1,586-patient prospective Breathing Not Properly study,<sup>39</sup> which found the accuracy of clinical judgment without BNP was 74%, improving to 81.5% if BNP results also were considered. Similar findings have been shown with NT-proBNP.<sup>40</sup>

Besides diagnostic utility, BNP has prognostic ability to identify patients with a HF mortality risk. In a 50,000-patient analysis of the Acute Decompensated Heart Failure Registry, an increased BNP was associated with a marked increase in acute mortality.<sup>41</sup> Acute mortality was 6% in patients with a BNP in the highest quartile at



presentation (BNP > 1,730 pg/mL), versus 2.2% in those in the lowest quartile (BNP < 430 pg/mL).

Kidney injury biomarkers have been clearly divided into those useful as indicators of the diagnosis of AKI, with cell damage, and for the diagnosis of cell death (serum creatinine and blood urea nitrogen increase). Unfortunately, blood urea nitrogen and creatinine are extremely late indicators of renal injury. Neutrophil gelatinase-associated lipocalin (NGAL), combined with BNP, is probably the indicator for which there is the most evidence of successful use in the diagnosis of acute CRS type 1. NGAL is a member of the lipocalin protein family. Normally produced by kidney tubule cells, it is secreted into the urine and serum at low levels. However, the synthesis of NGAL increases dramatically after ischemic, septic, or toxic injury of the kidneys.<sup>42-48</sup>

Evidence from experimental and human studies have indicated that urinary NGAL is derived from increased synthesis and release from the distal nephron as a rapid response to AKI, previously referred to as *acute renal failure*.<sup>45-48</sup> The use of NGAL as a novel serum or urine biomarker of AKI has been studied in post-cardiac surgery,<sup>46</sup> cardiac catheterization, after contrast-induced nephropathy,<sup>47</sup> hemolytic uremic syndrome, and kidney transplantation,<sup>46,49-53</sup> chronic kidney disease secondary to autoimmune disease,<sup>54</sup> and polycystic and proteinuric diseases.<sup>55-57</sup> In these areas, NGAL has been shown to be a useful, sensitive, specific, noninvasive, and highly predictive biomarker for AKI.

BNP might provide early evidence of fluid overload, followed by NGAL indicating renal damage. Both measurements can be performed at the bedside, using point-of-care equipment.

In the 5B approach, biomarkers represent a cornerstone for the diagnosis of HF contributing to the evaluation of the wet and dry condition of the patient. At the same time, the evaluation of AKI biomarkers may help to identify patients at risk for AKI or patients in whom AKI can be diagnosed much earlier than usual. The combination of BNP and NGAL represents the most advanced diagnostic panel to identify even mild forms of CRS type 1. NGAL may in fact increase well before creatinine increases in patients hospitalized for HF and fluid overload. The possible renal insult generated by inappropriate management of fluid overload by diuretics or ultrafiltration can be detected in the very early phases, allowing modification of the therapeutic approach and thus preventing further damage.

### Bioimpedance

Bioimpedance vector analysis (BIVA) is a noninvasive bedside volume assessment technique that can be performed within minutes. BIVA is based on the electrical principle that the body is a circuit with a given resistance (opposition of current flow through intracellular and extracellular solutions) and reactance (the capacitance of cells to store energy). With BIVA, total body water may

be measured by placing a pair of electrodes on the dorsum of the wrist and ipsilateral ankle, and then applying a 50-kHz current to the body. BIVA is displayed graphically so that relative hydration is depicted as vector length. Shorter vectors are associated with volume overload, whereas longer vectors equate to volume depletion (Fig. 7).

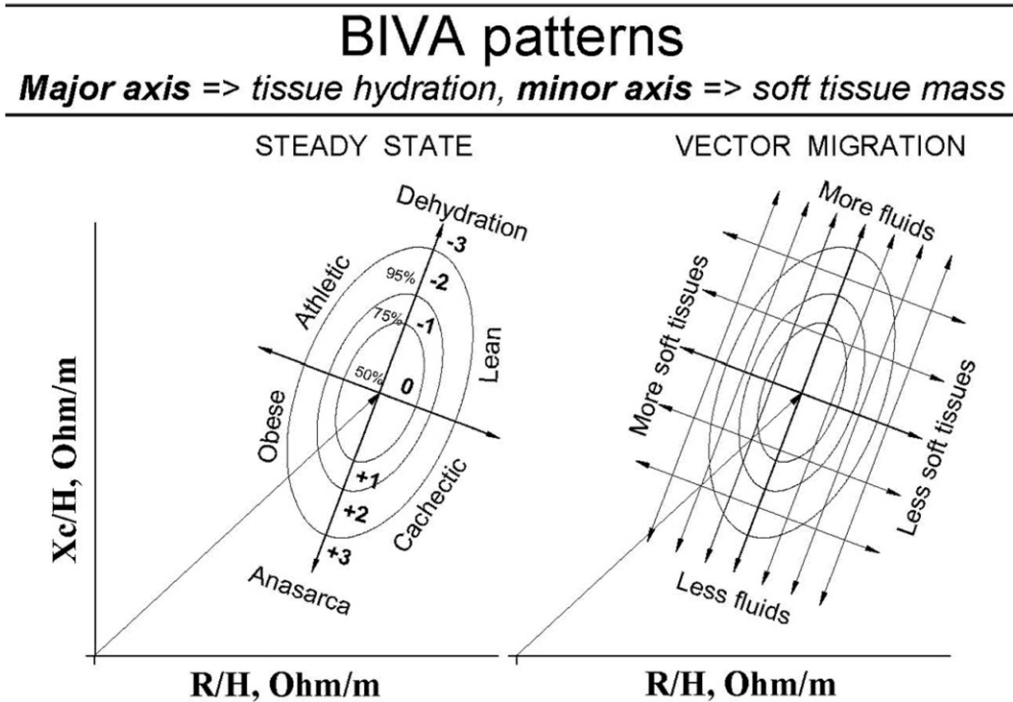
BIVA is an excellent indicator of total body water. Reports have indicated it has a strong correlation with the gold standard volume assessment technique of deuterium dilution ( $r > 0.99$ ).<sup>58</sup> Clinically, BIVA has been used to determine both volume depletion<sup>59</sup> and volume overload in HF,<sup>60</sup> kidney failure,<sup>61</sup> and liver disease.<sup>62</sup> It is superior for diagnosing volume overload as compared with anthropometric measurements, for which it has a sensitivity of 88% and a specificity of 87% for detecting edema.<sup>63</sup> Further, BIVA is able to identify volume-overloaded states in diverse populations. In 217 renal patients, BIVA accurately differentiated edematous and normovolemic populations.<sup>64</sup>

BIVA is not confounded by obesity, a common challenge for volume assessment. In 540 obese (BMI > 31 kg/m<sup>2</sup>), 726 nonobese (BMI < 31 kg/m<sup>2</sup>), and 50 edematous renal patients, BIVA was 91% accurate for discriminating between edematous and obese patients.<sup>65</sup> Subsequent caloric restriction for 1 month found no vector change, but volume removal was associated with vector lengthening. Ultimately, in critical care environments, where rapid accurate and objective results are needed, BIVA's ease and speed may provide opportunities for improved patient care.

Clinically, BIVA has been used to diagnose and guide therapy. In one study, BIVA determined the adequacy of ultrafiltration in more than 3,000 hemodialysis patients.<sup>66</sup> Short vector lengths corresponded to greater soft-tissue hydration (less adequate ultrafiltration). Defining a vector length of 300 to 350 ohm/m as the referent category, the risk of death was approximately 50% and 180% higher for those with inadequate volume removal as reflected by a BIVA vector length of 200 to 250 and less than 200 ohm/m, respectively.

Combining BIVA with a NP may provide both biomarker and physical evidence concerning fluid overload. One prospective study evaluated the diagnostic value of the use of both BIVA and BNP measurements in 292 dyspneic patients.<sup>67</sup> Regression analysis found that whole-body BIVA was a strong predictor of ADHF (Area Under the Receiver Operating Characteristic curve (AUROC), 0.934; SE, 0.016), with similar accuracy to BNP (AUROC, 0.970; SE, 0.008). The most accurate volume status determination was by the combination of BIVA and BNP (AUROC, 0.989; SE, 0.005), for which the combined accuracy exceeded either BNP or BIVA alone.

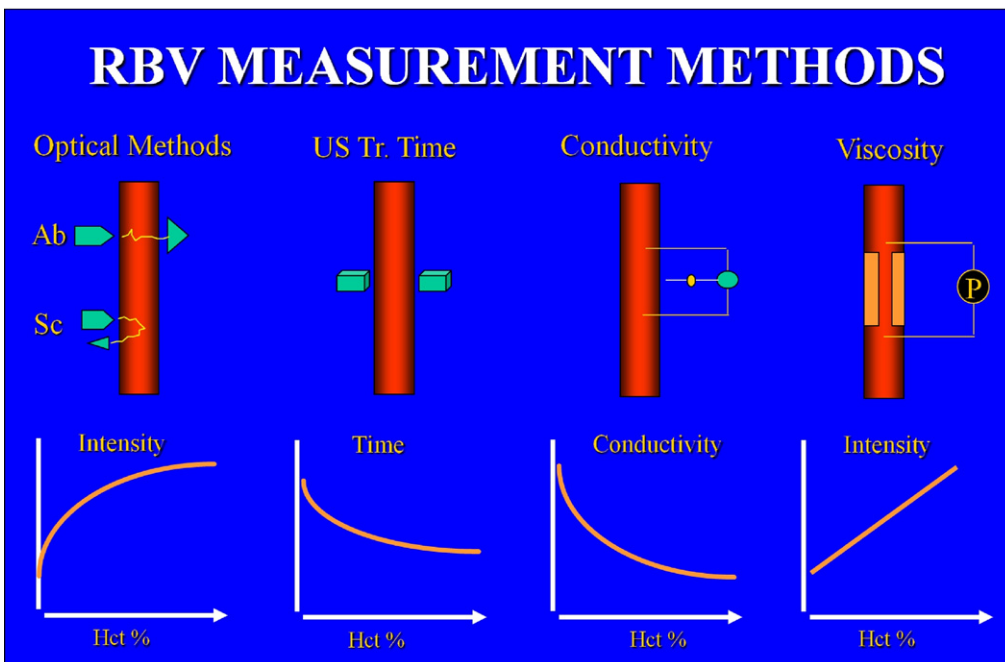
The combination of BNP and BIVA may assist in guiding acute HF therapy. In 186 hospitalized HF patients,<sup>68</sup> serial BNP and BIVA were used to monitor



**Figure 7.** BIVA. The ellipsis describes the hydration and nutrition status domain. Optimal status is at the center of the domain and vector migration toward different directions represents an alteration of the nutritional/hydration status of the patient. Subsequent examinations are useful to establish a trend.

diuretic-induced body fluid changes. The combination of improved BIVA parameters and a discharge BNP of less than 250 pg/mL predicted successful management. A follow-up study then showed that in 166 hospitalized HF patients discharged by a BNP and BIVA, there was improved morbidity compared with 149 patients dis-

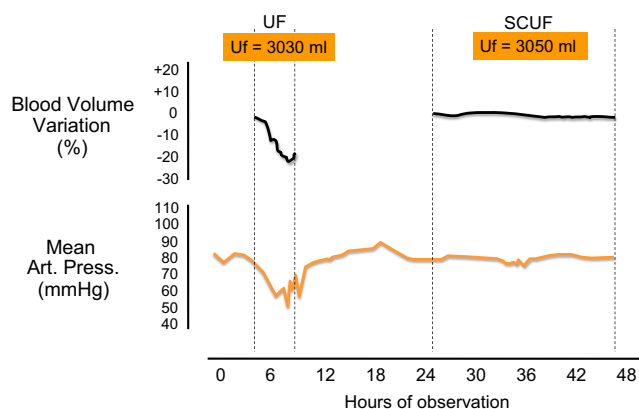
charged based on clinical acumen alone.<sup>69</sup> Patients assessed with BNP and BIVA had lower 6-month re-admissions (23% versus 35%;  $P = .02$ ) and lower overall cost of care. Thus, the combination of clinical acumen and objective measures may improve outcomes over clinical impression alone.



**Figure 8.** Different methods to monitor relative blood volume (RBV) changes during extracorporeal therapies. Changes in hematocrit represent a relative change in plasma water volume.

## Blood Volume

The “5B” approach should consider guidance of management even when the patient is undergoing RRT for fluid overload or for other indications. Because RRT may result in large volume changes, concomitant measure of blood pressure during the use of convective removal techniques, in addition to BIVA and BNP, increases its safety. Measurement of relative blood volume changes during treatment with optical or ultrasound methods (Fig. 8) can complete the assessment of the patient’s status and the dynamic process of fluid removal. Blood volume may be reduced owing to excessive ultrafiltration, leading to a dehydration status. Furthermore, blood volume changes may occur when the ultrafiltration rate is too high and the velocity of fluid removal from the intravascular space cannot be paralleled by an effective refilling from the interstitial space. Reduction in blood volume with ultrafiltration either in repeated acute episodes or continuing at the same rate throughout the therapy may result in hypotension, with the possibility of myocardial stunning, increased potential for arrhythmia, and progression or further deterioration of renal function. Continuous blood volume assessment indicates the need to slow ultrafiltration rates to reduce marked changes in blood volume. Although there are uncertainties, there is little evidence that changes in blood pressure provide the same accuracy of information concerning degree of fluid load as does BIVA + blood volume. In Figure 9, we report a typical example of relative blood volume changes occurring during sessions of ultrafiltration conducted on the same patient with two different modalities. In the first case, ultrafiltration is performed in 3 hours with an overall fluid removal of 3 L and an average ultrafiltration rate of 16 mL/min. In the second case, slow continuous ultrafiltration performed over several hours allows for a similar overall fluid removal with a sig-



**Figure 9.** Hemodynamic changes induced by ultrafiltration in the same patient with different treatment modalities. A short session of ultrafiltration with higher filtration rates induces a significant reduction of circulating blood volume and a consequent crush in blood pressure. This is avoided in the slow continuous ultrafiltration mode during which blood volume is preserved thanks to continuous intravascular refilling.

nificantly smaller ultrafiltration rate (2-3 mL/min). The modality allows for continuous intravascular refilling, thus avoiding changes in blood volume and preventing hemodynamic perturbations.

## SUMMARY

Consideration of the 5Bs presents a pathway for assessing the appropriate degree of hydration and the determination of a neutral fluid balance. At the same time the 5B approach represents an important mnemonic algorithm to guide fluid therapy and to make fluid removal safer and more effective. This combines clinical judgment, biomarkers, technology, and precise nursing to achieve the best outcome for patients in HF associated with fluid overload and varying degrees of renal dysfunction.

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