Body Fluids in End-Stage Renal Disease: Statics and Dynamics

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Keywords

Fluid overload · Hemodialysis · Bioimpedance spectroscopy · Relative blood volume · Absolute blood volume · Oxygen saturation

Abstract

Background: Abnormalities in fluid status in hemodialysis (HD) patients are highly prevalent and are related to adverse outcomes. **Summary:** The inherent discontinuity of the HD procedure in combination with an often compromised cardiovascular response is a major contributor to this phenomenon. In addition, systemic inflammation and endothelial dysfunction are related to extracellular fluid overload (FO). Underlying this relation may be factors such as hypoalbuminemia and an increased capillary permeability, leading to an altered fluid distribution between the blood volume (BV) and the interstitial fluid compartments, compromising fluid removal during dialysis. Indeed, whereas estimates of extracellular volume by bioimpedance spectroscopy are highly predictive of mortality, absolute BV assessed by the saline dilution technique was predictive of intra-dialytic morbidity. Changes in relative BV during HD are positively related to ultrafiltration rate (UFR) and, at least in some studies, nega-

tively to FO. High UFR is also related to changes in central venous oxygen saturation (S_{cvO_2}), a marker for tissue perfusion. On the one hand, high UFR and more pronounced declines in S_{cvO_2} , but on the other hand, flat relative BV curves are also predictive of mortality; the relation between outcome which statics and dynamics of fluid status appears to be complex. **Key Message:** While technological developments enable the clinician to monitor statics and dynamics of fluid status and hemodynamics during HD in an accessible way, the role of technology-based interventions needs further study.

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Introduction

Despite advances in renal replacement techniques over the past decades, abnormalities in fluid balance are highly prevalent in patients with end-stage renal disease and consistently related to adverse outcome [1–4]. Achieving normovolemia is a major goal of dialysis therapy, but this is notoriously difficult. While the discontinuity of hemodialysis (HD), often in combination with insufficient sodium restriction leads to a signifi-

cant fluid gain, the association of ultrafiltration (UF) with dialysis hypotension, which is in itself also related to adverse outcome [5], limits the amount of fluid, which can be removed during a relatively short period of time. Recent studies have substantially increased our understanding regarding the pathophysiology of abnormalities in fluid state and their relationship with outcome, as well as on the effects of HD on fluid dynamics. The aim of this short review is to discuss novel insights in the pathophysiology and monitoring of body fluid regulation in HD patients and the potential of technology-assisted treatment in optimizing fluid regulation.

Fluid Volume Compartments

In the conventional paradigm, total body water (TBW) is subdivided into an extra-cellular volume (ECV) and intra-cellular volume in which the ECV is further subdivided into interstitial fluid volume and blood volume (BV). Although this model is grossly oversimplified [6, 7], it is still useful for clinical purposes. These body compartments can be estimated using tracer dilution methods, although this is impractical in a clinical setting. Recently, a 3-compartment model has been designed based on bioimpedance spectroscopy (BIS) in which an “overhydration” (OH) compartment is defined on the assumptions of a fixed hydration of adipose and lean tissue mass [8]. This model has, even within narrow limits, proven validity in predicting outcome in HD patients [2]. Although abnormalities in ECV are predictive of outcome, changes in the intravascular volume are important for the hemodynamic response to dialysis therapy, which is also an important predictor outcome [5]. Intravascular volume can be expressed by plasma or BV, with tracer dilution techniques as the gold standard [9]. Recently, a method was developed based on the infusion of 240 mL of purified dialysate by which absolute BV is calculated from changes in relative BV [10], which can in turn be measured by changes in hematocrit or proteins by online monitoring [11]. Intravascular volume is a pivotal determinant of effective arterial BV, which is a virtual construct indicating organ perfusion. Nevertheless, effective arterial BV is also influenced by other mechanisms such as cardiac function and (micro)vascular tone [6, 12]. Recently, studies monitoring central venous oxygen saturation (S_{cvO_2}) during dialysis in patients with a dialysis catheter, as a proxy for organ perfusion, have shown the potential of this approach [13].

Non-Osmotic Sodium Storage

According to the classic theorem, TBW compartments are subdivided into an extracellular and intracellular compartment with an isotonic distribution of fluid. Building upon older observations, Titze et al. [7] designed a new paradigm in which the skin attained a novel role in blood pressure regulation by nonosmotic sodium storage. Recently, Olde Engberink et al. [14] observed that after infusion of hypertonic saline in healthy volunteers, only 47% could be retrieved in the urine, suggesting substantial sodium buffering. Another study in patients with heart failure found an increase in glycosaminoglycans in the skin, especially in the more negatively charged (sulfated) subtype [15, 16].

Other authors also suggested that the endothelial surface layer (ESL) may also serve as a buffer for sodium [17]. Using a method in which total BV is compared with an ESL permeable tracer, the ESL, which is estimated to be around 1.5–1.7 l, but was found to be around 0.2 l in patients with type I diabetes mellitus and microalbuminuria [18, 19]. Combining the lines of thought regarding the potential sodium buffering roles of the ESL and the skin, it may be hypothesized that a reduction in buffering function of the endothelium allows sodium to enter the endothelial cell. This may increase vascular stiffness [17, 18]. Further translocation of sodium into the skin can stimulate lymphangiogenesis through the activation of vascular endothelial growth factor and activate the immune system, most notably through the induction of a pro-inflammatory phenotype of macrophages as well as by stimulation of Th-17 cells [7].

The hemodynamic effects of tissue sodium storage in the HD population are likely important but not yet completely clear. It has been shown that using ^{23}Na MRI that HD is able to mobilize skin as well as muscle sodium [20], although the efficacy may be dependent upon local or systemic regulatory mechanisms, as evidenced by the inverse relation between skin sodium and vascular endothelial growth factor levels [16, 21]. At first glance, the nonosmotic storage of sodium would seem to be a beneficial adaptation mechanism to buffer extremes in sodium intake. However, this may be offset by adverse effects such as the induction of proinflammatory effects [7, 17, 18, 22] and insulin resistance [23]. In addition, interstitial sodium stores may possibly induce vascular dysfunction [24]. Moreover, skin sodium stores were significantly related to left ventricular mass, and stronger so as compared to the relation between FO assessed by BIS and left ventricular mass [25]. At present, the concept of nonosmotic so-

dium storage has yielded extremely interesting pathophysiological insights. Future research will likely clarify whether this concept will also lead to therapeutic interventions beyond the traditional paradigm of restricting sodium intake and attainment of normovolemia in the dialysis population.

Abnormalities in Fluid Volume Distribution

While BV and ECV are linearly related [26], the ratio between BV and ECV may still be dependent upon other factors, such as alterations in serum oncotic pressure and an increased capillary permeability [6]. The effect of hypoalbuminemia on body fluid distribution was shown by John et al. [9], who observed a comparable magnitude of the plasma volume compartment despite significantly higher ECV in peritoneal dialysis (PD) with serum albumin levels below the median as compared to patients with albumin levels above this level.

Recent evidence suggests that other factors beyond the decline in colloid osmotic pressure, which is partly compensated by an increase in globulins, are also responsible for the altered fluid distribution in hypoalbuminemic states such as nephrosis and inflammation [27]. Recently, the role of the ESL layer in the pathogenesis of abnormalities in body fluid distribution has been highlighted. Damage of the ESL, as evidenced by the shedding of glyocalix products and/or sidestream darkfield imaging, has been found in several disease states that are associated with increased permeability such as sepsis but was also observed in end-stage renal disease [28–30]. Although fluid loading may lead to ESL shedding by atrial natriuretic peptide [28], there is as yet no direct evidence for a relation between ESL damage and fluid overload (FO) in dialysis patients. However, we recently observed higher levels of the vascular cell adhesion molecule 1 in FO as compared to normovolemic dialysis patients, suggesting a relation between endothelial dysfunction and FO [31]. Also, in chronic kidney disease non-dialysis patients, angiopoietin 2, a factor that stimulates capillary permeability, was significantly related to FO [32].

Non-Cardiovascular Factors on Abnormalities in Fluid Status

Various studies have shown a relation between FO and inflammation [2, 31, 33]. The relation between FO and inflammation is likely complex and has been discussed in

detail in a recent review paper [34]. Although it appears likely that an increased capillary permeability would play a major role in this phenomenon, the single study addressing this subject observed that capillary leakage, assessed by the Iodine-125 albumin method, was more strongly related to markers of platelet activation as compared to inflammatory markers in a cohort of PD patients [35].

In addition, a relation between malnutrition and FO was also observed [36]. In this respect, it should be noted that ECV/TBW ratio, which is also often used in the assessment of fluid status, may also be influenced by a reduction in body cell mass leading to a reduction in intra-cellular volume [37]. We also observed lower levels of lean tissue mass and serum albumin levels in patients with more advanced FO [2]. Conversely, FO was more pronounced in patients with lean tissue index levels <10% and even more so in the concomitant presence of inflammation. Also chronic kidney disease patients with stages 3–5, FO, assessed by BIS, were inversely associated with serum albumin and lean tissue index [38].

The mechanisms of the relation between FO and malnutrition remain to be elucidated and may range from a lack of adjustment of dry weight in cases where a decline in fat or lean tissue mass goes undetected, the combined presence of inflammation and hypoalbuminemia leading to an alteration in fluid distribution or the presence of underlying illness which makes the patient more prone to hemodynamic instability making the achievement of dry weight more difficult [34]. It has also been suggested that malnutrition without renal failure itself leads to an increase in the ECV: weight ratio [39], but this may be also due to a change in the denominator. In the paper of Barac-Nieto et al., who assessed body composition in non-uremic malnourished patients in detail, BV and ECV were comparable in absolute terms between patients with severe and mild nutritional compromise, but their percentual ratios were higher due to the lower body weight [40].

Also, diabetes has an influence on body fluid distribution. Kopp et al. [20] observed that, despite comparable TBW assessed by BIS, ECV was higher in HD patients with type II diabetes mellitus as compared to non-diabetics, whereas intracellular volume was lower. Also, skin and muscle sodium content, assessed by ²³Na MRI, were higher in the diabetics. Of interest, ECV correlated with HbA1C in the diabetics. Summarizing, FO may be part of a spectrum in which comorbidity, malnutrition and inflammation may be present, greatly

contributing to the risk profile [2, 34]. Therefore, it appears prudent to look in fluid-overloaded FO patients carefully for abnormalities in other risk factors, such as the nutritional and inflammatory domains.

The Dry Weight Concept

Dry weight is clinically defined as the body weight at which the patient remains normotensive without antihypertensive medication [41]. Patients in whom dry weight was reached according to this operational definition, using long dialysis hours in combination with meticulous sodium restriction have lower extracellular volume and better survival [41–43]. In general, dry weight is assumed to coincide with normalization of ECV, although substantial differences may be observed between clinical judgment and information obtained by additional technologies [44, 45]. Interestingly, in a cohort study in 639 PD patients, 28% of the population was fluid overload, defined as OH: ECV ratio >7%, in combination with a normal or low blood pressure [1].

When BIS is used to define normovolemia, in contemporary cohorts of both HD and PD patients, a substantial subset of patients remains fluid overloaded even in clinics where this technique is routinely applied [1–3]. The prevalence of FO, defined as a predialytic OH: ECV ratio above 15% or an absolute OH volume of >2.5 l varied between 25 and 46% [3, 4], and 60–63% when a cut-off limit of an absolute OH volume of >1.1 l or an OH: ECV ratio >7% was used [1, 46]. The question as to why it is so difficult to achieve normovolemia in daily clinical practice arises due to an imbalance between fluid and sodium intake, and the possibility to remove fluid adequately despite the discontinuity, which is an integral component of HD. This problem is likely augmented in patients with substantial comorbidity and/or cardiac dysfunction [47, 48]. To make matters even more complex, pre-dialytic fluid depletion is associated with increased mortality as compared to patients with normovolemia, whereas post-dialytic fluid depletion was associated with a better outcome as compared to post-dialytic normovolemia [2]. These results suggest that the optimal limits for fluid status are quite narrow, which also likely necessitates close monitoring of fluid status during the HD procedure. The following sections will address the relevance of dynamics in fluid state in treatment monitoring and optimization.

Dynamics of Fluid State During Dialysis

One important parameter in the tolerance to UF is the ratio between fluid removal and refill of plasma volume from the interstitium, which can be estimated by measuring the change in relative BV or plasma volume during dialysis [49]. High UF volume is associated with increased mortality [50] and a more pronounced drop in RBV [51]. On the other hand, so-called flat RBV curves are associated with increased mortality and are assumed to be a reflection of FO [26, 52, 53], which may be due to increased refill from the interstitium or a too low UF rate (UFR).

By using appropriate methodology like Critline® (Fresenius Medical Care, North America), relative BV changes are very easy to monitor in routine clinical practice. Some caveats with RBV monitoring should be mentioned, as it may underestimate the drop in absolute volume due to the translocation of blood with a relatively lower hematocrit from the microcirculation [11].

Interestingly, the relation between the decline in RBV and fluid status has been debated as Keane et al. [51] did observe a relation between the decline in RBV and UFR but not with FO assessed by BIS. Notably, some of the patients who displayed a “flat curve” were classified as fluid depleted by BIS. Also, vascular refilling rate was found to be independent from pre-dialytic volume status [26] and was not different between dialysis sessions accompanied by morbid events and those that were not [54]. Kron et al. [26] suggested that while the decline in relative BV may be influenced by volume status, refilling rate may be dependent upon UFR. Recently, RBV changes during dialysis were found to be related to outcome. A recent study showed that RBV between 93 and 96% in the first hour and between 86 and 92% in the 3 h of dialysis had the most optimal association with outcome [55].

Another relevant parameter in the intra-dialytic hemodynamic response is the change in $S_{cv}O_2$, which can also be measured using the Critline® device. A study by the Renal Research Institute showed that patients with the largest decline in $S_{cv}O_2$ had the worst survival [13]. At present, the routine estimation of changes in tissue perfusion is only possible in patients with a central venous catheter. Alternative methods such as near-infrared spectroscopy have not yet been evaluated in dialysis patients [56]. Another study by the same group showed that changes in $S_{cv}O_2$ are related to UF volume [57].

Therefore, there appears to be an interesting, and not yet completely solved interaction between different parameters reflecting or influencing intra-dialytic hemody-

namics. On the one hand, FO, which may be associated with flattening RBV curves, is consistently related to mortality. On the other hand, high UFR, which is associated with adverse outcomes, is associated with steeper RBV curves, which are associated with better outcomes but also with a larger decline in $S_{cv}O_2$, which is again associated with worsened outcomes. In addition, high UF volumes are not always associated with the worst outcomes, which were actually observed in a group with both FO and low UF volumes [58]. Most likely, significant comorbidity may have hampered fluid removal in this group of patients and may also be a contributing factor to the paradoxical associations discussed above.

Can Technology Aid the Clinical Decision Process?

In recent years, much published evidence has emerged regarding the role of technology assistance in monitoring fluid status and to a lesser degree, in dialysis treatment prescription. The added value of technology assistance should be regarded in terms of its contribution to the clinical decision process, which can vary from identification of patients at risk to technology-directed treatment leading to improvement in hard outcomes.

Especially BIS, most notably by using the 3 compartment model, has shown to be related to outcome in various studies [3, 59, 60], with an optimal survival found to be within a quite narrow range (pre-dialytic OH between -1.1 and $+1.1$ L) [61]. Also, pre-dialytic fluid depletion was associated with outcome but interestingly only when accompanied by low pre-dialytic systolic blood pressure [46]. Lung comets assessed by ultrasound, which are a marker of regional fluid accumulation, are also predictive of outcome [62]. The relation between outcome, RBV and $S_{cv}O_2$ changes has been discussed in a previous section.

Regarding the prediction of hemodynamic instability during dialysis, an estimation of intravascular fluid holds promise but should be tested in larger populations. In a pilot study, an absolute BV below 65 mL/kg was found to predict intra-dialytic morbid events in 10 out of 12 patients [10]. Absolute BV was more predictive for intra-dialytic morbid events than pre-dialytic OH assessed by BIS [63]. Previously, it was also observed that vena cava diameter, which is also related to intravascular volume, predicted treatment tolerance in an intensive care setting [64].

Data regarding the effects of technology-assisted intervention are scarcer. Although one study showed a reduction in mortality with BIS-guided treatment [65], this did

not reach significance in 2 subsequent meta-analyses. However, a reduction in pre-dialytic blood pressure was observed with the use of BIS, as well as a reduction in [39, 66] FO especially in patients without residual renal function. Enthusiasm for the use of relative BV as a tool for treatment prescription has subsided, since the results of the CLIMB study, which showed that the use of a protocol based on changes in relative BV, was actually associated with an increased mortality. However, it should be noted that the mortality in the control group was unexpectedly low, whereas the protocol used in the study was voluntary and not based on a strictly controlled prescription policy [67]. In the DRIP trial, patients with “flat” relative BV curves showed the greatest decline in interdialytic blood pressure upon reducing dry weight [68].

Regarding the use of absolute BV in the reduction of intra-dialytic morbid events, a small uncontrolled trial combining absolute BV and BIS resulted in a decline of intra-dialytic morbid events from 12.2 to 0.9% [62].

These recent data suggest that a possible strategy would be to use BIS or lung comets to identify patients at risk [61, 69], to use absolute BV (or vena cava ultrasound) to assess the risk of intra-dialytic morbid events, and (when applicable) $S_{cv}O_2$ to monitor the response to dialysis treatment. Monitoring changes in RBV can additionally be used to see whether patients do not display a “flat curve” during UF, which may be an additional argument for FO [70], although given the recent evidence, the interpretation of relative BV curves as marker of fluid state deserves further study.

As an example, in patients who are fluid overloaded according to BIS, but in whom absolute BV is relatively low and the dialysis treatment is accompanied by substantial decrease in $S_{cv}O_2$ and a major decline in relative BV, a shift to more frequent and/or prolonged treatment appears indicated. Assessment of FO, absolute BV and relative BV, as well as $S_{cv}O_2$ necessitates only 2 devices and could be easily evaluated in clinical practice as techniques are simple and operator-independent. It should be acknowledged that this strategy is only based on theory and has not been formally evaluated.

Conclusion

Abnormalities in fluid status, most notably extracellular FO are associated with increased mortality. Despite the fact that there is no discussion regarding the importance of attaining normovolemia, it appears notoriously difficult to achieve in clinical practice. This is due to the

difficulty in removing the fluid gain attributable to the intermittency of the treatment and the inappropriate adherence to a strict salt restricted diet in the short period of time allocated for the dialysis treatment. Easily applicable technology like BIS may aid in identifying patients with extracellular FO at risk for adverse outcomes, whereas measurements of absolute BV may predict the tolerance to dialysis treatment. Monitoring of RBV and

where possible $S_{cv}O_2$ during HD may predict the tolerance of the treatment and identify patients who would tolerate fluid removal without risk of a critical decline in organ perfusion. At present, the proven validity of technology-assisted treatment mainly lies in the identification of patients at risk, but its role in the actual prevention of dialysis-related complications should be addressed in future trials.

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