Assessment of fluid status in dialysis: Clinical importance and diagnostic tools

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INTRODUCTION

The accurate determination of volume status and reliable strategies for the management of fluid accumulation and dry weight adjustment are a leading goal in end-stage renal disease (ESRD) patients.(1,2) Fluid overload is an important adverse factor in patient outcomes. Nevertheless, the importance of fluid depletion is being increasingly recognized. The complex fluid distribution in renal failure needs to be understood to inform assessment of hydration.(3)

Body water is distributed between different compartments: intracellular fluid, which reflects body cell mass (not hydration); extracellular fluid that includes intravascular and extravascular compartments, with the excess leading to oedema. The presence of cardiorespiratory disease, malnutrition and wasting, altered autonomic nervous system function, vascular tone, and vascular permeability affects the fluid exchanges between both compartments.(3)

Overhydration is related to systemic and pulmonary hypertension, left ventricular hypertrophy and congestive heart failure. On the contrary, volume depletion is associated with poor quality of life, intradialytic hypotension, myocardial stunning, myocardial fibrosis, increased risk of arrhythmias and sudden cardiac death.(1)

Volume overload is considered one of the main mechanisms for cardiovascular mortality in dialysis patients. This is the leading cause of mortality (> 50% of deaths with known cause), including coronary heart disease, cerebrovascular disease, peripheral vascular disease, left ventricular hypertrophy (LVH) and heart failure.(6,5)

The routine clinical evaluation of fluid status has a poor diagnostic accuracy. Thus, the need of additional tools for the characterization of the patient volume status is emerging, considering that lung pulmonary congestion is an insidious phenomenon that develops in the previous weeks before the rise of severe symptoms.(6,7)

The aim of this review is to summarize the clinical consequences of volume assessment in haemodialysis (HD) and peritoneal dialysis (PD), the diagnostic tools currently available and the clinical interventions that may lead to euvolemia.

CONSEQUENCES OF FLUID OVERLOAD

Chronic fluid overload and increased interdialytic weight gain (IDWG) in HD patients are considered major factors for high blood pressure (BP) in this population, where the worldwide prevalence is as high as 85%. The IDWG leads to excessive intradialytic weight loss, promoting a cyclical cardiovascular stress. This day-of-week pattern is well known and responsible for the increase in cardiovascular events, about 25%-40% during the first-weekly HD day.(2,6) The intermittent volume gain and removal is not applicable to PD patients. However, most of these individuals are steadily volume overloaded, with the prevalence ranging from 56.3% to 73.1%(9,10)
The excessive intradialytic weight loss demands higher ultrafiltration volume, which leads to more frequent intradialytic hypotensive episodes. This can result in shorter or session interruption, inappropriate adjustment of target dry weight, to increased values or infusion of saline solutions, in turn creating a vicious cycle of overhydration. (6,11) Patient with severe cardiac failure and subsequent pre-dialysis low BP are at higher risk of overhydration. (11) Notably, IDWG prompts the prescription of higher ultrafiltration volumes, leading to diastolic dysfunction and myocardial stunning, possibly due to a rapid decrease of the intravascular fluid compartment. (12)

Volume accumulation causes other important cardiovascular alterations. The arterial stiffness is the most frequent vascular abnormality in ESRD patients and represents the main underlying factor for isolated systolic hypertension and LVH. (13) Therefore, the arterial stiffness contributes to the concentric LVH, whereas the chronic volume overload (increased preload) leads to the eccentric enlargement of the left ventricle. (11) The LVH predisposes to heart failure, arrhythmias, and sudden death. (1,6)

In PD patients, according to a recent study, chronic fluid overload independently predicted LVH dysfunction at 12 months (OR 4.02, 95% CI 1.285–12.573) and echocardiographic parameters only decreased when patients were euvolemic. (14) Continuous volume accumulation leads to left and right atrium enlargement and pulmonary overload, which is present in those on HD and PD. (1) The pulmonary overload is associated with interstitial lung oedema, airway obstruction (i.e., trigger of sleep apnoea), pleural effusions and pulmonary hyperten-

sion. These conditions decreased the quality of life and patients’ performance status. (6) In addition, the increment in BP accompanying interdialytic volume accumulation directly increases cardiac afterload and myocardial oxygen demand, favouring acute ischaemic cardiac events. (15)

In the longest follow-up prospective study so far with 53 European PD patients, there was an increased mortality risk of 50% for each increased litre of extravascular volume (normalized for body surface area). (9)

### CONSEQUENCES OF FLUID DEPLETION

Underhydration is associated with myocardial stunning, which can lead to myocardial fibrosis, systolic dysfunction, and cardiovascular death. (16) Cerebral infarcts, atrophy and leukoaraoisis are common findings in dialysis patients with long-term consequences as cognitive decline, dementia, and stroke. (1) Hypoperfusion is also associated with translocation of endotoxins across the gut wall, which are a robust pro-inflammatory stimulus that may lead to malnutrition and wasting. (1)

Predialysis underhydration was associated with an increased risk of death (HR = 2.03) in a cohort of 8883 European HD patients. Notably, IDG was higher (not lower) in this group compared with euvolemic patients, perhaps due to amplified thirst-driven by hypovolemia. (17)

In PD patients, fluid depletion is associated with rate of decline in residual renal function (RRF). This has great significance given the relationship of RRF to increased survival in these patients. (3,18) Excess fluid removal in PD patients can be a consequence of unnecessary exposure to hypertonic glucose dialysate, which leads to adverse metabolic effects and damages the peritoneal membrane. Also, the excess fluid removal may have an adverse cardiovascular effect, potentially through effects on coronary perfusion and peripheral vascular resistance. (3)

### ASSESSMENT TECHNIQUES

#### Clinical symptoms and physical examination

Frequently, volume status is estimated based on the clinical criteria – patient’s signs and symptoms, peri-dialytic BP measurements and intradialytic haemodynamic instability. (19) Although clinical examination is an inexpensive, readily available, and non-invasive tool, it is imprecise and may be insensitive to significant abnormalities of hydration.

A good example is that pre-HD systolic BP misclassifies the hydration status in 25% of patients (20) and is well established that pre- and post- dialysis BP measurements are poorly reproducible and poorly associated with interdialytic BP assessed with ambulatory BP monitoring. (5) In a study where lung ultrasound (LUS) was used, only 49% and 20% of the HD patients with severe pulmonary congestion had lung crackles or peripheral oedema, respectively. (7) These findings are consistent with the studies developed in the setting of heart failure. (21)

Based in these observations, examination findings should be used in conjunction with other methodology. (3,6)

#### Isotope dilution analysis techniques

The gold-standard methods for fluid status assessment are isotope dilution analysis techniques. Deuterium and tritium dilution are preferred to measure total body water, whereas bromide chloride and sucrose dilution are used for extracellular volume. However, these methods are invasive, expensive, and unfeasible in clinical practice. (9)

To overcome these disadvantages, several methods have been developed, including biochemical biomarkers, chest X-ray, inferior vena cava (IVC) diameter measurement, LUS and bioimpedance techniques. (3,9) Nevertheless, these methods do not assess all body compartments. For instance, bioimpedance can provide estimations of extracellular volume, intracellular volume, and total body weight, whereas IVC diameter measurements, biochemical markers and LUS provide information only about the intravascular compartment. (9)

There are no studies comparing the isotope techniques with the natriuretic peptides and vena cava echography. The comparison with bioimpedance methods is well established and reliable. (9)

#### Chest X-ray

Although chest X-ray can detect signs of pulmonary congestion and cardiac dilatation, the use on a routine basis is not practical and continuous exposition to radiation is deleterious for the patients. (22)
Serological biomarkers

Natriuretic peptides [brain natriuretic peptide (BNP), N-terminal pro-BNP, atrial natriuretic peptide (ANP)] are hormones released by ventricular or atrial myocytes in response to the myocyte stretch and are mainly increased due to extracellular volume overload. Their clearance may be affected by the renal failure, but the severity of structural heart disease defines the levels of the peptide in advanced CKD more than renal clearance itself. Additionally, they are variably removed during HD. In both HD and PD populations, elevated levels of natriuretic peptides are related with increased cardiovascular and overall mortality, rather volume overload.

Hung et al found an inverse relation between fluid overload and serum albumin and a positive relation with IL-6 levels. Sand et al observed higher levels of C-reactive protein (CRP) with incremental levels of fluid overload in bioimpedance spectroscopy (BIS). They defined the interrelation between fluid overload, inflammation (CRP levels > 6 mg/L) and malnutrition and found out worse clinical outcomes to the patients where the three risk factors were present.

Inferior vena cava (IVC) echography

The diameter of the IVC is related to right atrial pressure and plasma volume. The increased pressure in the right atrium is transmitted to the IVC, resulting in reduced collapse with inspiration and IVC dilation. An IVC diameter < 2.1 cm or collapsed > 50% with Valsalva manoeuvres suggests normal right atrial pressure of 3 mmHg. It is simple to perform in most patients and reproducible with experienced clinicians.

Furthermore, this method can be applied in both HD and PD patients. Several studies showed a significant correlation with cardiothoracic ratio, plasma atrial natriuretic peptide and ventricular geometric stratification.

However, there are some important considerations about this technique. There is a wide variation of IVC diameters in healthy individuals. It may be affected by respiration, right-side cardiac disease and is difficult to perform in patients with polycystic kidney disease. There is an inverse correlation between IVC diameters and heart rate, so the precision of intravascular volume assessment is improved by correcting for the heart rate. The timing of measurement should be 2 hours after dialysis to evaluate after the refill of plasma volume from the interstitium after HD, which is not feasible on daily basis.

Lung ultrasound (LUS)

LUS has been increasingly used, mostly in critical patients, to differentiate the presence of pleural effusion, pleural masses, or lung consolidations. Therefore, its benefits are being considered for dialysis patients where the volume assessment may be more accurate using this technique. LUS is accessible, inexpensive, uses non-iodized radiation, and has a quick learning curve.

B-line or “comet tail” sign is the hyperechoic artefact seen in the LUS and that results from excessive lung water in the subpleural interlobular septa.

There are different approaches to assess the extracellular weight manifested by the B lines, usually with the patient in a supine position.

For critical patients, the chest is divided in 8 to 12 areas and a scan is made in each. A positive result is when multiple (diffuse or bilateral) artefacts are present. In nephrology, Jambrik et al defined a more detailed approach – from the second to the fourth (left) or fifth (right side) intercostal spaces are scanned, counting to 28 sites considering the anterior and lateral thoracic wall. A quantification is made in each site, from 0 to 10 (corresponding to white screen), considering the number of lines that were seen.

In a meta-analysis to overview the diagnostic tools for acute heart failure, 3 or more B lines in 2 or more bilateral lung zones (using the method of 8-12 areas scanned) should prompt the diagnosis of pulmonary oedema [sensitivity 94%, specificity 92%]. Torino et al in a randomized multicenter analysis of baseline data from the LUST study, that included 79 HD patients, found that clinical assessment (lung crackles and peripheral oedema) had low agreement with B-line assessment. In this study, the median number of LUS B line (pre-dialysis) was 9 (interquartile range 5-19 lines), which estimates a median accumulation of water about 1.2L (0.5-2.2L). Panuccio et al did not found association between B-lines and clinical assessment in PD patients.

Noble et al found an association with a decrease of 2.7 B-lines for each 500 mL of volume removed during dialysis, acknowledging that B-line resolution has a linear relationship to volume removal.

The LUS cannot evaluate the total amount of body water in patients and B-lines may be present in the very early course of lung congestion.

A cross-sectional study in five Italian PD units studied the association between extravascular lung water and cardiovascular evaluation (clinical, biomarker and echocardiography). There was evident lung congestion in 46% of patients using the lung ultrasound findings (score of 8 lines > 15). When analysing this group, 27% had pedal oedema but 57% had no dyspnoea. Also, only 11% was volume overload using the BIA criteria. The relationship between LUS and natriuretic peptides continues to be debated, whereas the results in the literature are very different according to the populations studied. The same happens with the IVC assessment and BIA.

The LUS has an established prognostic value in heart failure (HF), not only in the readmission prediction but also in mortality. For that reason is considered nowadays as a fundamental test for the assessment of acute HF. Zoccali et al found that patients with severe congestion (> 60 B lines) have increased risk for both all-cause mortality and cardiac events.

Some disadvantages may be pointed to the universal use of LUS. It is observer dependent, requires additional training and is difficult...
to measure in obese patients. It is affected by the presence of diastolic dysfunction and intrathoracic or abdominal pressure changes. LUS does not allow a correct differential between B-lines related with volume overload, interstitial pulmonary fibrosis or acute respiratory distress syndrome. (6,9,24)

The LUS is useful to detect the extravascular lung volume, while BIA provides information about the total body water, extracellular and intracellular water, thus these methods should be considered complementary. (2)

**Blood volume monitoring**

The blood volume monitoring (BVM) is only accessible for HD patients and is a non-invasive method that measures the haematocrit changes during haemodialysis in real time, using the blood velocity that allows the determination of relative blood volume (RBV). A flat BVM curve during dialysis suggests that the plasma refill rate is occurring at an equivalent or higher rate than ultrafiltration (UF), which is frequent in overload patients. Patients with < 5% drop in RBV are considered overhydrated. If the curve shows a ≥ 5% drop in RBV, a plasma refill test should be done (stop ultrafiltration and recheck RBV after 10 minutes). An increase of ≥ 1.5% is consistent with excessive refill from extravascular compartments. (37,38)

Firstly, its use was to avoid intradialytic hypotension. Then, the possibility to assess dry weight with this tool was considered. Hussein et al in a cross-sectional observational study with 169 HD patients found that 31.9% were overloaded despite reaching target dry weight. (39) Maduell et al found that BVM was most sensitive for detecting volume overload > 3 L, but did not have good accuracy for lower volumes. (37) The CLIMB study, a six-center randomized trial, showed that the BVM was associated with higher nonvascular and vascular access-related hospitalizations and mortality compared with conventional monitoring. (38) Therefore, its use to assess volume is not widely accepted.

**Bioimpedance techniques analysis (BIA)**

Bioimpedance is when an alternating electrical current passes through the body and reacts according with the type of tissue and its water content (impedance). There are two related concepts: resistance – which measures the flow of the electrons trough the tissue and is proportional to the amount of fluid; capacitance – that reflects the energy stored and released in each current cycle, and is proportional to the amount of fluid. Each of these methods can be utilized for the whole body (i.e., BCM – whole body BIS device) or segmental (usually calf). (22) The whole-body evaluation is most common, but less accurate in obesity. On the other hand, segmental is only available for HD patients, as it depends on the rapid volume reduction associated with HD session to evaluate the resistance. (19)

BIA depends on different devices and mathematical models, so some prediction errors may occur, and the clinicians should be aware of it. Additionally, the algorithms used derived from healthy white populations, whose body composition is different from dialysis patients. (9) There was a good agreement between BIS and the gold-standard dilution tracers. Additionally, this method is reproducible with a small intra and interobserver variation. (6)

**Haemodialysis**

The potential benefits of BIS measurements in HD patients are improved hypertension control and reduction in intradialytic hypotension. (18)

Nevertheless, in the meta-analysis by Beaubien-Souligny et al, these effects are not significant on decreasing hospitalizations or mortality. (41) Most of the observational studies performed were small, with a short follow-up time. There was only one trial reporting a favourable difference in survival analysis with bioimpedance, with a longer follow-up duration and no deaths until the 20th month of follow-up. (41)

**Peritoneal dialysis**

Most patients in PD are in a moderate to severe hypervolemic state, according to the group of Ronco et al, that used BIA. (42)

Many observational studies postulate the overload (most frequently evaluated by the ratio extracellular weight (ECW)/total body weight (TBW)) as predictor of technique failure due to chronic volume effect on peritoneal membrane. (9) Nevertheless, the ratio ECW/TBW may be affected by body cell mass and nutritional state, and hypoalbuminemia may compromise the use of BIA in PD patients, mostly in high transporters of inflamed patients. (9)

Although the theoretical correlation between better hydration status and preserved RRF (more frequent on PD patients) is reasonable, the observational findings on the literature are inconsistent. (43,44) There is an association between hypervolemia and higher risk of all-cause mortality. The IPOD-PD study, the largest prospective cohort to date, with 1054 incident PD patients in a 3-year follow-up using BIS for volume assessment, found a higher risk of death (HR 1.59, 95% CI 1.08–2.33) in patients with higher relative overhydration. (34) A meta-analysis performed by Shu et al enlightened overhydration (using a higher ratio ECW/TBW) as an increased risk to all-cause mortality (RR 2.19, 95% CI 1.59–3.00) and technique failure (RR 6.20, 95% CI 4.96–7.74). (10) This observation was consistent with other BIA criteria used (i.e., ECW/ intracellular weight (ICW)).

It is controversial if the BIA results may be affected by the presence or absence of the dialysate fluid in the peritoneal cavity. Davenport et al described that ECW/TBW may be overestimate when the dialysate is present in the abdomen. (45) Davison et al contradicted this finding. (46)
It is curious that, when comparing to HD patients, DP groups presented with higher EWC content, but no difference when evaluating levels of natriuretic peptides.\(^9\)

The exact ultrafiltration prescription and the more frequent dry weights adjustments in HD may contribute to more successful results, when comparing to PD groups.\(^{12,38}\)

There was no difference for patients in continuous ambulatory versus automated PD and most studies included were single-centre and retrospective.\(^{10}\) The use of multicenter studies, more representative of PD population, can have a positive impact to standardize the strategies and tools for the BIA.

## MANAGEMENT OF VOLUME OVERLOAD

For the incident dialysis patients, the RRF has an important role in the volume assessment. Its preservation function is associated with improved fluid status and BP control, leading to better cardiovascular and survival results.\(^{47,48}\) For this reason, nephrotoxins (i.e., aminoglycosides) should be avoided in incident dialysis patients.

However, the COMPASS study with 137 Asian PD patients with urine output > 500 mL, BIS guided fluid management did not result in lower RRF preservation, better volume control or blood pressure control compared to conventional clinical assessment after 12 months.\(^{49}\) The benefits of volume control using BIS are clearer in HD patients where improved LVH, blood pressure control and mortality were demonstrated.\(^{50}\)

Some strategies can be implemented in both HD and PD patients. The first example is the use of diuretics (furosemide until 120 mg/day and metolazone 5 mg/day) which help to increase urinary output and therefore to maintain a better fluid state.\(^{48}\) In addition, the minimization of dietary sodium intake (< 100 mmol/day or < 2.3 g/day) is beneficial for blood pressure and volume control. Increased dietary sodium load is associated with higher IDWG and higher ultrafiltration rates.\(^{53}\) There must be behavioural interventions to pursue this goal. Eating less processed foods, increase the confection of meals, improve literacy levels, are some examples that should be applied in the dialysis population to achieve better long-term outcomes.\(^{51}\)

The most important challenge to overcome in HD patients is the disruption of the vicious cycle between overload and the consequences of higher ultrafiltration rates – intra-dialytic hypotension, myocardial stunning and loss of RRF.\(^{6,52}\) Thus, in these patients it is important to avoid intradialytic hypotension and incremental HD seems to be protective.\(^{48}\) However, it is contradictory to consider this in overload patients.

To achieve dry weight, Sinha et al recommends small adjustments (0.2-0.3 kg) per HD session based on the recognition that these small adjustments can be clinically significant and avoid hypotensive episodes.\(^{53}\) On the other side, it must be considered that volume overload without an increase in body weight suggests loss of lean body mass and the need of nutritional support.\(^{51}\)

Longer and more frequent HD schedules have a favourable impact on BP control and may improve clinical outcomes (reverse left ventricular hypertrophy and improve patient survival).\(^{54}\) However, more frequent HD sessions were associated to more frequent vascular access interventions (HR 1.71, 95% CI 1.08-2.73).\(^{54}\)

The dialysate sodium concentration must be reassessed to avoid a positive diffusive balance that favours thirst and excessive IDGW.\(^{52}\) But lower dialysate sodium concentrations have been associated with greater risk of intradialytic hypotension.\(^{53,56}\) So, the dialysate sodium should be individualized based on patients’ pre-dialysis levels.

In PD patients, it has been also hypothesized that incremental PD might be beneficial for the purposes of preserving RRF compared with standard PD.\(^{47}\) In addition, for PD patients, the use of icodextrin in the peritoneal dialysate improved the management of fluid overload, besides its value in the small-solute clearance and serum cholesterol lower levels, comparing to glucose, as suggested in a recent meta-analysis.\(^{56}\)

## CONCLUSION

Volume assessment is crucial in dialysis patients, where euvoelema is necessary for better cardiovascular and survival outcomes. Dry weight assessment is still based on the unreliable clinical findings, but there are many diagnostic tools that assist for a more accurate evaluation. LUS and BIA are the most useful, but they are not widely available in our clinical practice. Their combination could be a strong overload indicator, mostly in patients with impaired cardiac performance, where LUS need to be complemented by BIA. Although volume assessment is pointed as a Nephrology issue for many decades, steps towards this are improving. The clinical tools available nowadays may be used for early diagnosis of volume overload, which is crucial to personalize the dialysis prescriptions and optimize clinical and nutritional measures.

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