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Chapter 5

Assessment of Volume Status in Peritoneal Dialysis Patients

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Abstract

Ideal volume status of patients with end-stage renal disease is one of the main goals of adequate dialysis. Volume overload has been associated with heart failure, left ventricular hypertrophy, and mortality, both in hemodialysis (HD) and peritoneal dialysis (PD) populations. The assessment of normal volume status is traditionally based on clinical parameters such as blood pressure, edema, lung auscultation, and chest X-ray. However, these parameters cannot be trustworthy to direct treatment decisions. Gold standard methods of assessing volume status are mainly isotope dilution analysis techniques. However, these methods are invasive and impractical in clinical routine. A number of handy bedside methods have been developed focusing on objective fluid status assessment, both in HD and PD patients. Bioimpedance techniques can estimate extracellular volume, intracellular volume, and total body water, whereas inferior vena cava diameter measurements, biochemical markers, and lung ultrasound provide information about the intravascular filling state and blood volume. Various studies have used the values of the above-mentioned techniques as tools for determining the overhydration of dialysis patients as well as predictors of mortality. Yet, randomized intervention studies based on these methods with hard end points (like echocardiographic parameters modification) have not been published so far in PD patients.

Keywords: bioimpedance, hemodialysis, lung ultrasound, biomarkers, overhydration, mortality

1. Introduction

Ideal volume status of patients with end-stage renal disease is one of the main objectives of adequate dialysis. Volume overload has been associated with heart failure, left ventricular

hypertrophy, and mortality both in hemodialysis (HD) and peritoneal dialysis (PD) populations [1–5]. One routine clinical way to define volume status is to determine the ideal dry weight of the patients. While dry weight in HD patients has been attempted vigorously to be termed during the last decades [6], such efforts have never been done systematically in PD populations, mainly due to the different nature of the dialysis procedure. Krediet [7] suggested to define optimal volume status as the weight associated with a normal extracellular water/volume (ECV).

Technique	What is estimated	Advantages	Limitations
Dilution tracers	ECV, TBW	Gold standard method	Invasive, not for everyday clinical practice
IVC	Intravascular filling–BV	Correlation with cardiac Function, noninvasive	Experienced cardiologist
Bioimpedance	ECV, ICV, TBW	Easy, noninvasive, fluid volumes in liters	No standardization Influenced by hypoalbuminemia and muscle wasting
Biomarkers	Intravascular filling–BV	Noninvasive	Wide variability Influenced by cardiac dysfunction
Lung ultrasound	Intravascular filling–BV	Noninvasive, easy	No estimation of TBW, ECV Little experience in PD

IVC, inferior vena cava diameter; ECV, extracellular volume; ICV, intracellular volume; TBW, total body water; BV, blood volume.

Table 1. Techniques for assessment of volume status in PD populations.

The assessment of euvolemia—normal volume status—is traditionally based on clinical parameters and examinations such as blood pressure, edema, lung auscultation, and chest X-ray. However, these parameters cannot be reliable to guide treatment decisions. Agarwal et al. [8], in a cross-sectional trial in HD population, showed that pedal edema did not reflect volume status. No study so far has showed a direct relation between clinically assessed fluid overload and outcome in PD patients. Despite the lack of such trials, ISPD guidelines suggest that "hydration status should be assessed clinically on a regular basis during every follow-up visit and more often if clinically indicated" [9].

The clinical aim of defining the ideal volume status is more urgent in PD population, as some trials imply that PD patients are much more volume-overloaded than HD patients [10]. This finding depends on the methods used for assessing volume status; bioimpedance techniques showed that PD patients presented with higher ECV compared with HD patients, even before the hemodialysis session [10, 11], while serum biomarker levels had no differences between them.

Gold standard methods of assessing volume status are mainly isotope dilution analysis techniques. Deuterium and tritium dilution are preferred means to measure total body water (TBW), while bromine chloride and sucrose dilution yield data on ECV [12]. DEXA dual-energy X-ray absorptiometry can provide data about fat mass, lean soft tissue mass, and bone tissue mass [13]. However, these methods are invasive, expensive, and unfeasible in clinical routine.

A number of practical bedside methods have been developed focusing on objective fluid status assessment, both in HD and PD patients. Bioimpedance techniques can estimate ECV, intracellular volume (ICV), and TBW, whereas inferior vena cava diameter measurements, biochemical markers (such as atrial natriuretic peptide, ANP and brain natriuretic peptide, BNP), and lung ultrasound provide information about the intravascular filling state/blood volume (**Table 1**).

2. How to assess fluid status

2.1. Inferior vena cava diameter

Measurement of the diameter of inferior vena cava (IVC) and its decrease on deep inspiration (collapsibility index—CI) by echocardiography allows an accurate assessment of dry weight in hemodialysis patients. The diameter of IVC is usually expressed as an index to the body surface area in mm/m^2 [14]. Similarly, in PD populations, the IVC diameter, especially maximal diameter in quiet expiration (IVC_e), significantly correlates with cardiothoracic ratio and plasma ANP concentration [15]. Toprak et al. [16] proved that IVC index is a useful tool for assessing the volume status in PD patients and an independent predictor of left ventricular geometric stratification.

However, some caveats should be kept in mind: (i) there is a wide variation of IVC diameters in healthy individuals, and single measurements are not helpful; (ii) there is a significant, inverse correlation between IVC diameters and heart rate, and the precision of intravascular volume assessment is improved by correcting for the heart rate; and (iii) the presence of tricuspid insufficiency leads to unreliable results [17]. Based on these remarks, IVC diameters should be performed by an experienced cardiologist. Finally, we should keep in mind that IVC estimates only intravascular volume.

2.2. Biomarkers

BNP is a peptide hormone that is released primarily by the ventricular myocytes in response to myocyte stretch such as increased cardiac filling pressure. It is synthesized as an inactive prohormone (108 amino acid pro-BNP) and is cleaved into the biologically active fragment (32 amino acid c-BNP) and the N-terminal pro-B-type natriuretic peptide (76 amino acid NT-pro-BNP), and both are measurable in plasma or serum. Both provide strong prognostic information in patients with heart failure, coronary artery disease, and acute coronary syndrome. In chronic kidney disease, their concentrations are often increased due to extracellular volume

expansion, concomitant heart disease, and reduced renal clearance [18]. These molecules have been associated with left ventricular hypertrophy [19, 20] and increased cardiovascular and overall mortality in HD and PD populations [21].

In ADEMEX study, only NT-proBNP levels, but not the other peptides, were alone predictive of overall survival and cardiovascular mortality of PD patients, independent of volume overload [22]. Plasma BNP levels are known to decrease significantly after a HD session, implying that volume overload is an important stimulus for BNP secretion. In PD populations, plasma BNP and NT pro-BNP levels are elevated and correlate with volume overload [23]. However, there is uncertainty if elevated levels represent more a cardiac dysfunction than volume overload [24] and doubt its use in determining volume status.

Cardiac troponins T and I (cTnT and cTnI) are subunits of the cardiac actin–myosin complex, which pass through the circulation during myocardial damage, and their detection has been used as a sensitive and specific marker of myocardial cell necrosis. Elevated serum levels of cTnT have been associated with mortality in hemodialysis [25] and CAPD patients [26]. However, as its levels are strongly associated with increased left ventricular mass [26, 27], its prognostic value is controversial. Finally, a study with HD patients from Korea compared three biomarkers (NT-proBNP, hsCRP, and cTnT) regarding the prognosis of mortality. The study concluded that NT-proBNP is a more significant prognostic factor for cardiovascular mortality than cTnT and hsCRP, whereas hsCRP is a more significant predictor than NT-proBNP and cTnT for all-cause mortality [28] So far, the data suggest that the above peptides are elevated in PD patients and correlate well with echocardiographic left ventricular parameters. Their elevated levels independently identify a subset of patients at greater risk for death, but they cannot assess volume status [29].

2.3. Bioelectrical impedance techniques

Bioimpedance techniques pass a low-strength alternating current into the body, and biological tissues react to the flow according to the current frequency and the properties of the tissue (this is called impedance). The two basic properties of impedance are resistance and capacitance; the former measures the flow of the electrons through the tissue, and the latter refers to how much energy is stored and released in each current alternating cycle. Resistance is proportional to the amount of fluid, while capacitance is proportional to the cell mass. Low-frequency currents (<5 kHz) pass through the ECV (they cannot pass the cell membrane), while high-frequency currents pass through both ECV and ICV compartments. There are different methods of capturing these information and illustrate them in a simple way: segmental or whole body bioimpedance spectroscopy (BIS), single or multifrequency, absolute volumes or vectors [30].

In hemodialysis populations, multifrequency bioimpedance spectroscopy (BIS) methods have been used, either segmental (measures the change of the resistance in the arm, trunk, or calf) or whole body. The segmental BIS cannot be used in PD populations, as the method presumes rapid volume reduction (as in a HD session) in order to monitor the resistance. Whole body BIS has been used widely in both populations for years in devices such as Body Composition Monitor (BCM, Fresenius Medical), Hydra (Hitron), Cyprus version 1.0 (BIA-101; RJL/Akern

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Systems), and so on. The devices offer the ability to perform frequent, rapid, noninvasive assessment of the volume status.

The BCM device measures not only 50 frequencies over a range from 3 to 1000 kHz to determine the electrical resistances of TBW and the extracellular water (ECW) status, but it can also evaluate lean body weight and fat mass. This is of great interest, as there is convincing evidence for an association between volume status, inflammation, and nutritional status [31]. The ratio ECW/TBW is most widely accepted to be an index of hydration. Using population data, it also provides an estimate of the amount of overhydration (OH, measured in liters). The vector plot enables visualization of the trend toward the body composition changes, but it is inconvenient as most clinicians prefer the volume to be expressed in liters or kilos [32]. All of the bioimpedance techniques are highly reproducible and validated with dilution methods [33]. However, differences in results may occur mainly due to different devices, mathematical models used for the equations, and lack of standardization.

Numerous studies have proven the ability of BIS to estimate volume status in hemodialysis patients. In a study in HD patients [34], four different techniques for assessment of volume status were compared in order to detect the limits of each method: the measurement of vena cava diameter, vena cava collapsibility index, the blood volume drop during an ultrafiltration bolus, and the ECV determined with whole body BIS. BIS proved to have the best low-detection limit of volume overload. In PD populations, the majority of BIS-associated studies are observational ones. The largest observational longitudinal trial was performed in multiple European centers and included almost 1100 patients (IPOD-PD study) [35]. The study revealed that the majority (56.4%) of patients was overhydrated with a mean absolute value of OH 1.9 ± 2.4 l even at the start of the therapy, despite the fact the clinicians had clinically judged that 40% were normohydrated. Overhydration was commoner in males, diabetics, and fast transporters.

There is an issue if the full abdomen affects BIS measurements. Davenport et al. [36] showed that multifrequency BIS provides different measurements when the abdomen is empty. Electrical resistance increased with fluid instilled, and the BIS software algorithms overestimated muscle mass more than fat mass. This difference is greater in younger patients, in those with a poorer nutrition status (lower body mass index) and in those with a smaller fluid overload. These findings were confirmed by Arroyo et al. [37]. So, the ideal BIS measurements should be performed with empty abdomen. However, as this is clinically impractical, most authors agree that the differences in measurements are probably not clinically significant, provided they are made in a standardized way and are performed serially to document changes rather than absolute values.

In hemodialysis populations, BIS has been widely used as a tool for intervening in the evaluation of ideal dry weight [38, 39]. Similar studies in PD populations have proved the value of BCM measurements in aiding the physicians in clinical decisions [40, 41]. In a randomized controlled study in 160 continuous ambulatory peritoneal patients, fluid status was evaluated by means of repeated BIS analysis versus only clinical assessment, and the intervention group proved to be better controlled [41]. Another large randomized blinded study conducted in the United Kingdom and Shanghai [42] attempted to determine whether

assessment of volume status supported by the longitudinal plot of the BI vector resulted in more stable fluid status than control subjects (where routine clinical judgment was used). Vector plot added little additional value to clinical fluid management.

There is one randomized controlled trial in HD patients, which aimed to prove that volume control guided by objective assessment of fluid overload via BIS led to improved cardiovascular outcome, namely a significant decrease in left ventricular mass index and improved blood pressure control [43]. Such a study has not yet been published in PD populations.

Several studies associated overhydration measured by BIS with mortality [44]. A retrospective study correlated hydration parameters with mortality in a PD population of above 500 patients from the United Kingdom [45]. The study used OH (l), OH/ECW ratio, and ECW/TBW ratio as volume status measurements. The first two parameters were independent predictors of mortality. In a trial from China [46], overhydration (expressed as the ratio of extracellular to intracellular water) was a predictor of mortality. The same conclusion was proved in a Korean population (overhydration was expressed as the ratio of extracellular fluid to total body fluid) [5].

BIS methods have some limitations in PD populations [47]. First, the ratio ECW/TBW is disproportionally increased due to absolute reduction in tissue mass, mainly muscle mass and abnormal tissue hydration [48, 49]. Hypoalbuminemia is another feature of PD patients, more intense than in hemodialysis patients and highly associated with comorbidity. PD patients have large protein losses through the membrane, especially high transporters and inflamed patients [49]. It is proved that in HD population without comorbidity, BIS can identify an increase in TBW and lean body mass, whereas with increasing comorbidity burden, BIS fails to demonstrate increases in tissue hydration identified only by gold standard deuterium methods [50]. As a result, in all dialysis patients, deteriorating fluid status by BIS is strongly correlated with hypoalbuminemia; this association is stronger in PD population. Secondly, clinicians should keep in mind that those absolute values of BIS measurements are based on equations derived from healthy populations (whose body composition and fluid distribution are quite different from dialysis patients). Finally, BIS cannot discriminate intravascular versus extravascular volume.

2.4. Lung ultrasound

It is a novel, reproducible validated technique that has been applied to estimate lung water in ESRD patients. The technique is based on the fact that when lung congestion is present, the ultrasound beam is reflected by thickened interlobular septa, generating hyperechoic artifacts between edematous septa and the overlying pleura (the so-called lung comets, considered as a ultrasound equivalent of B-lines detected in chest X-rays) (**Figure 1**). The number of these lung comets is associated with left ventricular filling pressure. Extravascular lung water is related to the ventricular filling pressure of the left ventricle [51, 52]. The technique can be easily learnt by a noncardiologist and can be performed by the bed.

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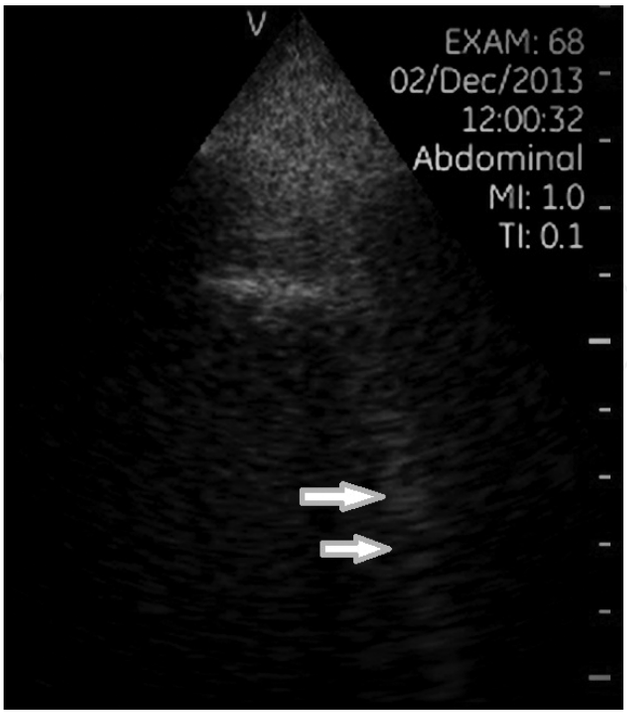

Figure 1. Lung ultrasound. The *arrow* shows a B-line (lung comet).

The power of the method lies in its capacity in detecting clinically asymptomatic pulmonary congestion, which is the most early and important determinator of volume overload [53]. Indeed, in a study which included HD patients [54], lung ultrasound revealed moderate-to-severe lung congestion in 63% of patients before the dialysis, even in asymptomatic ones. The number of the lung comets decreased at the end of HD session. Lung water excess was mainly associated with New York Heart Association (NYHA) functional class, left ventricular ejection fraction, left atrial volume, and pulmonary pressure. Zoccali et al. [55] proved in a multicenter study including hemodialysis patients that lung ultrasound can detect asymptomatic pulmonary congestion, and that the number of lung comets can be a strong, independent predictor of mortality and cardiac events in this population.

Another study from Romania [56] evaluated three different methods—lung ultrasonography (predialysis and postdialysis), bioimpedance spectroscopy (predialysis and postdialysis), and echocardiography (predialysis)—in order to test their prognostic value in mortality. Only predialysis lung comets score and left ventricular mass index were significant factors for survival.

However, similar studies in PD populations are sparse. Only two observational trials have been published. A multicenter study from Italy included 88 PD patients [57] and compared lung echo score, echocardiographic parameters, BIS parameters, and clinical estimation such as edema and NYHA class. Moderate-to-severe lung congestion was evident in 46% of patients, and it was mainly associated with ejection fraction and NYHA class. Edema or BIS measurements did not correlate with the number of lung score. Another study from the United Kingdom [58] assessed fluid status in 27 peritoneal dialysis patients using BIS, lung ultrasound,

and N-terminal pro-brain natriuretic peptide (NT-proBNP). Contrary to the Italian study discussed above [57], the number of patients with lung congestion was lesser (7%). There was a statistically significant correlation between the lung score and NT-proBNP values, but such a correlation was not evident between lung comets and BIS. The authors conclude that as lung echocardiography and biomarkers detect intravascular and pulmonary volume excess while BIS methods estimate overall hydration status, the methods can be complementary.

3. Conclusions

Estimation of ideal volume status of dialysis patients is a critical purpose of everyday clinical practice, since volume overload is highly associated with mortality. The estimation of volume status should be based on objective, practical, reproducible, and by the bed methods such as bioimpedance, inferior vena cava diameter measurements, biochemical markers, and lung ultrasound. Although all these methods can estimate overhydration and do predict mortality, none so far has proved its value as an intervening tool for modifying cardiac parameters, cardiovascular events, and survival in PD patients. As these techniques estimate different fluid compartments of the body, the *information provided by the combination of them* could be complimentary and more effective in the assessment of volume status.

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