Assessment of Dry Weight in Hemodialysis: An Overview

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Abstract. Fluid balance is an integral component of hemodialysis treatments to prevent under- or overhydration, both of which have been demonstrated to have significant effects on intradialytic morbidity and long-term cardiovascular complications. Fluid removal is usually achieved by ultrafiltration to achieve a clinically derived value for “dry weight.” Unfortunately, there is no standard measure of dry weight and as a consequence it is difficult to ascertain adequacy of fluid removal for an individual patient. Additionally, there is a lack of information on the effect of ultrafiltration on fluid shifts in the extracellular and intracellular fluid spaces. It is evident that a better understanding of both interdialytic fluid status and fluid changes during hemodialysis is required to develop a precise measure of fluid balance. This article describes the current status of dry weight estimation and reviews emerging techniques for evaluation of fluid shifts. Additionally, it explores the need for a marker of adequacy for fluid removal.

Fluid removal to achieve fluid balance is an important component of hemodialysis (HD) treatment for end-stage renal disease (ESRD), as both under- or overhydration are associated with deleterious consequences. Despite considerable advances in assessment of dialysis adequacy with respect to solute removal, there is at present no measure of adequacy for fluid removal. The majority of HD treatments incorporate a prescription for fluid removal targeted to a patient’s “dry weight.” In most centers, dry weight is clinically determined and usually reflects the lowest weight a patient can tolerate without intradialytic symptoms and hypotension in the absence of overt fluid overload (1). This trial-and-error method is imprecise and does not account for changes in nutritional status and lean body mass. As a consequence, it is difficult to determine whether an individual patient is over- or underhydrated. Additionally, the dry weight is used to calculate ultrafiltration (UF) volume and rates for each dialysis treatment. It is well recognized that intradialytic complications are influenced by the balance between ultrafiltration rates and plasma refilling. UF rates in excess of plasma refilling capacity predispose to dialysis-induced hypotension. It is evident that better methods of determining volume changes during HD are required for defining the goal for fluid removal and to develop strategies for safer dialysis treatments. This article describes the current status of dry weight estimation and reviews emerging techniques for evaluation of fluid shifts. Additionally, it explores the need for a marker of adequacy for fluid removal.

What is Dry Weight?

The standard HD prescription targets fluid removal to a clinically derived estimate of dry weight. Dry weight is currently defined as the lowest weight a patient can tolerate without the development of symptoms or hypotension (1). Since physiologic dry weight is that weight resulting from normal renal function, vascular permeability, serum protein concentration, and body volume regulation, dry weight in HD should theoretically be lower than physiologic to prophylaxis interdialytic weight gains. In most instances, dry weight is estimated by trial and error, and the degree of imprecision is reflected in the development of intradialytic symptoms or chronic volume overload with poor control of BP (2,3). From a clinical standpoint, the aim of HD is to normalize the milieu interior as much as possible. The healthy human body at steady state is composed of several fluid and solid compartments (Table 1) (4), which are maintained within tight boundaries. An accurate assessment of a patient’s volume status requires knowledge of three factors: (1) the capacity of body compartments (e.g., extracellular fluid [ECF] and intracellular fluid [ICF]); (2) the amount of water in each compartment; and (3) the solute content (e.g., sodium), which may affect fluid shifts between compartments, interdialytic weight gain, and have an effect on the success of fluid removal during HD. Compartment size, amount of water, and content of solutes can be independently estimated by different techniques (as discussed below), however, all three must be considered in the definition of dry weight. Although different terminologies have been used in the literature to express the state of volume deficit or excess, we have used the term hydration status in this article to encompass the three components of volume measurement referred to above.

Problems Associated with an Inaccurate Assessment of Dry Weight

At initiation of dialysis, most patients have typically been catabolic for several months due to chronic illness. At the same
Table 1. Body fluid compartments

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Percent of Total Body Water</th>
<th>Percent of Total Body Weight</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Normal Adult Man</td>
<td>Normal Adult Woman</td>
</tr>
<tr>
<td>Intracellular fluid</td>
<td>55</td>
<td>33</td>
</tr>
<tr>
<td>Extracellular fluid</td>
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<td>27</td>
</tr>
<tr>
<td>Interstitial fluid</td>
<td>20</td>
<td>12</td>
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<tr>
<td>Plasma</td>
<td>7.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Bone</td>
<td>7.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>7.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Transcellular</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Total body water</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>

* Adapted from Edelman and Leibman, 1959 (4).

important to note that in Vertes' study of 40 patients, an early benchmark study of this concept, only five were truly hyperreninemic, all of them responding adversely to volume depletion and favorably to bilateral nephrectomy (7). Also, in Charra's group of patients treated with long, slow hemodialysis, less than 2% remained hypertensive off antihypertensive agents, thus deemphasizing renin-dependent mechanisms of hypertension in the general dialysis population (11). Indeed, Fishbane et al. used plasma atrial natriuretic peptide (ANP), a marker of intravascular hypervolemia, to show that dialysis-resistant hypertensive patients were actually volume overloaded at the end of dialysis (8). Others have confirmed that removing excess salt and water during maintenance hemodialysis normalizes BP in at least 70% of cases (9), while it has also been shown that postdialytic BP correlates with total body water by bioimpedance spectroscopy (10). Although other nonvolume-related mechanisms for dialysis-resistant hypertension have been forwarded, such as sympathetic nervous system hyperactivity (14,15), endothelins (16), and prostaglandins, the preponderance of evidence points toward chronic volume overload as the major cause of hypertension in the ESRD and dialysis population.

Hypertension and Excess Death in Hemodialysis Patients. According to the U.S. Renal Data System (USRDS) (17), cardiovascular disease and stroke are the most prevalent causes of morbidity and mortality in dialysis patients, which in turn have been linked to markers of volume overload. These markers include hypertension, left ventricular dysfunction, and left ventricular hypertrophy. In the general nonuremic population, hypertension is a major cause of cardiovascular and cerebrovascular morbidity and mortality (18,19). As would be expected, hypertension has been linked to excess cardiovascular and cerebrovascular adverse events in dialysis patients as well (20). Indeed, in an analysis of iliac artery biopsies at time of transplant in 50 nondiabetic hemodialysis patients, the presence of atherosclerosis was found to be independent of lipid abnormalities and duration on dialysis, but correlated almost exclusively with the presence of hypertension (21). Others have agreed that BP control is essential for prolonged survival (22). And while Charra et al.'s (11) cohort of patients are younger, narrowly representative of the general dialysis population, and uncontrolled for other unknown beneficial effects of long, slow hemodialysis, their 75% 10-yr survival rate associated with excellent dry weight control of BP remains the most compelling evidence for the beneficial effects of BP control (23). It is thus evident that if dry weight is the major component of hypertension, and hypertension is a major predictor of death in dialysis patients, we should be focusing on dry weight.

Cardiac Dysfunction. Although it is difficult to separate cause and effect when discussing the various cardiac disorders in hemodialysis patients, it seems that an excessive dry weight is a sufficient risk factor allowing the final expression of cardiac dysfunction and indirectly, sudden death. In 1836, Bright first noted autopsy findings of left ventricular hypertrophy in patients dying of ESRD (24). As discussed previously, the majority of patients are hypertensive at presentation to
dialysis, largely due to impaired salt and water excretion, and
given the known association of chronic hypervolemia and
hypertension, and hypertension and left ventricular hypertro-
phy (LVH) (25), it is no surprise that most ESRD patients
present to dialysis with LVH as well (26–29). LVH addition-
ally has been shown to be deleterious to hemodialysis patients
for several reasons: (1) similar to nonuremic patients, it is
predictive of an increased incidence of myocardial infarction
(30), congestive heart failure (31), and sudden death (32); and
(2) LVH can lead to diastolic dysfunction, which has been
linked to an increased incidence of intradialytic morbid events
(33). Indeed, Parfrey et al. showed that 40% of their cohort of
dialysis patients with congestive heart failure had hypertrophic
changes, 43% had either LV dilation or systolic dysfunction,
and only 16% had normal echocardiograms upon presentation
to dialysis (31). LVH was thought to be due to chronically
increased afterload, while dilation and systolic dysfunction
were thought to be due to chronic hypervolemia. Although
these changes did not regress over the 17.5-mo follow-up, there
was no intervention to lower the clinically derived dry weight.
Both forms of left ventricular abnormalities were associated
with a markedly poor median survival from 38 to 56 mo. As
stated above, however, it is probable that both types of ven-
tricular abnormality are volume-related. LV dilation and sys-
tolic dysfunction are probably a form of burnt-out hypertensive
heart disease due to an imbalance between appropriate hyper-
trophy and cell death and fibrosis. Other studies have shown
the link between chronic hypervolemia and the development of
LVH in dialysis patients as well (34).

It is obviously important to recognize that other risk factors
for the development of LVH are increased age, diabetes mel-
litus, anemia, and possibly hyperparathyroidism, and for LV
dilation, anemia, ischemic heart disease, and hypoalbumine-
emia. Likewise, these disorders are present at the initiation of
dialysis, and have not been shown to be reversible in hemodi-
alysis patients. However, regression of LV dilation and LVH
has been shown in studies in normal populations (35), and
perhaps most intriguing are studies showing regression of LVH
in hypertensive ESRD patients started on continuous ambula-
tory peritoneal dialysis (36). It is therefore possible that ag-
gressive control of volume may lead to regression of left
ventricular abnormalities, which are surrogate markers for poor
survival in hemodialysis patients.

**Measuring Dry Weight**

It is obvious from the above discussion that clinical assess-
ment of dry weight is crude and often imprecise. Recently,
several different techniques have been used to derive a more
standard method of assessing dry weight (38–41). However,
no single method has emerged as a gold standard, as there is no
clear-cut definition of what constitutes dry weight. The follow-
ing section reviews these methods as they have been devel-
oped, and offers a critical appraisal of their use.

**Biochemical Markers**

**Atrial Natriuretic Peptide.** ANP is a peptide hormone
synthesized, stored, and released in atrial tissue in response to
changes in atrial transmural pressure. The hormone follows
the usual cleavage synthesis pathway as a prepro-, pro-, and a
biologically active 28 amino acid peptide. It is rapidly de-
graded, primarily by the kidney, but also by other organs, with
a serum half-life of 2 to 4 min. Its end-organ effects and role
in maintenance of salt and water homeostasis, which are well
characterized elsewhere (42), as well as its short half-life and
somewhat minimal clearance by hemodialysis, initiated excite-
ment about its possible role in determining fluid status in
hemodialysis patients. Rascher et al. were the first to suggest
its use as an indicator of volume status in hemodialysis (43).
In this and subsequent studies (44,45), ANP levels were found
to be elevated in hemodialysis patients, before dialysis, relative
to control subjects, and levels were significantly lower after both
hemofiltration (45) and hemodialysis (44). Plasma ANP levels
correlated with BP, and although ANP levels changed signif-
ically during HD, in most studies postdialysis levels remained
significantly higher than controls (43,44). Others (46–48) have
established marked interpatient variability and persistent post-
dialysis elevation. Additionally, ANP levels have been shown

Underestimation of Dry Weight

Underestimation of dry weight is more likely to be recog-
nized due to its immediate consequences of intradialytic mor-
bidity. It usually occurs when there is a failure to adjust the
ultrafiltration prescription to account for increases in either
lean body mass or fat mass over time. A previously stable
patient becomes frequently hypotensive during hemodialysis,
but the change in ultrafiltration prescription is often delayed
either due to physician reluctance to change the dry weight, or
to efforts to investigate other more threatening etiologies of
hypotension. This situation, one of patients’ most frequent
complaints (37), leads to patient dissatisfaction with the dial-
ysis prescription, early withdrawal from dialysis, failure to
arrive at the dialysis unit, and frequent interrupted sessions, all
of which lead to reduced solute removal. The resulting inade-
quate solute removal leads to decreased appetite, poor intake,
and subsequently to poor nutritional status, which have their
own adverse effects on dialysis outcome. On the other hand,
not knowing the true dry weight of a patient, one might attempt
to mitigate frequent hypotensive events due myocardial is-
chemia, pericardial effusion, cardiac arrythmia, or other disor-
ders by increasing the dry weight goal, thus missing the diag-
nosis of a more serious underlying condition.
to be persistently elevated after HD in patients with altered left atrial hemodynamics compared to those with normal left atrial hemodynamics (49), making ANP levels difficult to interpret in this setting. As discussed previously, Fishbane et al.’s (8) cohort of persistently hypertensive patients had high plasma ANP, and were not believed to be at their dry weight, raising the possibility that the persistent postdialysis ANP elevations in the previously mentioned studies might have been due to inadequate dry weight achievement or the presence of altered left atrial hemodynamics. Kojima et al. (46) showed that plasma ANP levels were still routinely elevated after hemodialysis even when patients are determined to be clinically at their dry weight. But in this study, ANP also correlated well with BP. A possible explanation for the persistently elevated levels of ANP in this study may be that these patients were really not at their dry weight as evidenced by the persistent hypertension. Because of these uncertainties, a serum level at which ANP should be predictive of dry weight in a dialysis patient is a matter of considerable controversy. In summary, plasma ANP is sensitive for detecting overhydrated patients, but not specific. Concordantly, it often remains elevated in dry individuals and hence is not sensitive in detecting underhydrated patients. A low ANP value’s specificity for detecting underhydration is unknown.

Cyclic Guanidine Monophosphate (cGMP). cGMP is generated when ANP activates membrane-bound guanylate cyclase, and hence was predicted to be an indicator of volume status in dialysis patients (50). This biochemical marker was perhaps best systematically studied by Lauster et al. (40,51,52). Because cGMP is more stable in serum at room temperature than ANP (53), and the RIA for cGMP is somewhat less arduous, it was believed that cGMP would potentially be a better marker than ANP for the routine assessment of fluid status. Their studies determined: (1) that cGMP levels of 20 pmol/L immediately postdialysis correlated with achievement of clinical dry weight; (2) the majority of those with postdialysis levels greater than 20 pmol/L had evidence of fluid overload or congestive heart failure; (3) that reductions in dry weight in these remaining patients were associated with both a reduction in cGMP levels to approximately 20 pmol/L and clinical resolution of the fluid overloaded state; and (4) those whose levels could not be lowered beyond this point had left ventricular dysfunction. However, these measurements were not validated against other objective parameters, and others have not confirmed these findings. Franz et al. found that 28% of their patients had postdialysis cGMP levels of greater than 20 pmol/L, the majority of which were in sinus rhythm, had no evidence of congestive heart failure, and were not believed to be fluid overloaded (54). As with ANP, the meaning of a low level is unknown, and cGMP levels are influenced by cardiac or valvular dysfunction, thus limiting its clinical utility in this setting.

Vena Cava Diameter

Because echocardiographic examination of the inferior vena cava diameter (VCD) is simple, quick, and noninvasive, efforts to standardize its dimensional characteristics in relationship to central blood volume were first undertaken by Natori et al. in 1979 (55). They showed that supine measurements of caval diameter taken during expiration and its inspiratory decrease in diameter correlated well with central venous pressure. Ando et al. (1985) were the first to quantify VCD changes during hemodialysis (56). In 1989, Cheriex et al. attempted to use this technique to assess dry weight in hemodialysis patients, showing that postdialysis measurement of inferior caval diameter taken subdiaphragmatically correlated with right atrial pressure and circulating blood volume (57). Linear regression to right atrial pressure defined overhydration as a caval diameter greater than 11 mm/m² body surface area or a collapsible index (Expiratory caval diameter − Inspiratory caval diameter/Expiratory diameter × 100%) as less than 40%. Underhydration was defined as a caval diameter of less than 8 mm/m² and a collapsible index of greater than 75%. Nearly two-thirds of their patients who had met clinical criteria for dry weight were actually hypervolemic, according to these criteria. Those who were considered underhydrated by these criteria had greater increases in heart rate and stroke volume, and greater decreases in BP during dialysis when compared to their normally or overhydrated counterparts. Others have not been able to confirm these findings. Mandelbaum et al. found a wide range of caval diameters in their dialysis population, and they were not correlated to age, height, weight, or body surface area of the patients (58), thus rejecting the “nomogram”-based generalization of this measurement to the general dialysis population. Franz et al. divided their patients into three groups of hydration status based on Cheriex et al.’s criteria above and showed that mean cGMP levels were higher in the hypervolemic group compared with the normovolemic and underhydrated patients, but there was no statistically significant linear correlation between caval size and cGMP level (54). In their study, as would be expected, a major limitation of this technique was measuring volume status in patients with heart failure. The presence of tricuspid insufficiency requires its own criteria for assessment of volume status via vena caval diameter (59). On the other hand, Katarzksi et al. used VCD to confirm the volume hypothesis of hypertension in hemodialysis patients (60). They studied two cohorts of hypertensive and normotensive patients and showed that caval diameter was significantly larger postdialysis in their group of hypertensive patients. Leunissen et al. (61) and Kouw et al. (62) have subsequently shown that postdialysis VCD measurements reliably predict hemodynamic changes during dialysis. In summary, while interpatient and interoperator variability and the presence of right-sided failure limit its use, VCD may be better suited than the biochemical markers for prediction of the underhydrated state.

Bioimpedance Analysis and Bioimpedance Spectroscopy

Single or Dual Frequency Bioimpedance Spectroscopy

The basic principles of bioimpedance were initially described by Thomassett in 1963 (63), but the technique first gained prominence in the early 1970s when Nyboer reported that the impedance of the body to an alternating current roughly correlated with changes in blood volume (64). These measure-
ments are based on the basic principle that the electrical impedance of a cylinder is directly proportional to its length and inversely proportional to its cross-sectional area multiplied by its specific resistivity. Application of simple multiplication and rearrangement resulted in the equation for volume $V = L^2/Z$, where $V$ is specific resistivity, $L$ is length, and $Z$ is the measured impedance. Operating on the assumption that the human body is a sum of homogeneous cylinders, and that current would pass only through ion- and water-containing media, in 1969 Hoffer was the first to attempt to measure total body water by this method (65). In his and subsequent analyses (66), Height$^2$/Impedance at a frequency of 50 kHz indeed showed the best-fit regression to deuterium water space with a correlation coefficient of 0.92. Subsequent multiple equations based on variations of this principal, usually with the addition of gender-specific dummy variables or anthropometric parameters have been derived (67–70). Although this technique is simple and remains valid for the measurement of total body water, single frequency analysis is unable to distinguish between intracellular and extracellular compartments. Based on the assumption that a low frequency current would transgress only the extracellular space, Jenin et al. in 1975 first used a low 1-kHz frequency paired with a 100-kHz frequency to estimate ECF volume and ICF volume separately (71). In 1988, Lukaski, using a single frequency method and a regression equation including reactance, improved the correlation to bromide space to 0.83 (70). Standard error of estimate for both single and double frequency methods ranges from 1.5 to 3.5 L.

Bioimpedance Spectroscopy, the Multifrequency Approach. Multiple frequency analyzers were developed to take advantage of the dielectric theory of electrical conduction through mixed, emulsified bodies (72). In this theory, conduction of current through the intracellular space is modeled as flow through innumerable different parallel circuits consisting of a capacitance and a resistance in series, while parallel flow through the extracellular space is limited only by the resistance to flow through ion and water. The result is that at low frequencies, current cannot bridge the cell membrane (capacitor) and will flow only through the extracellular space, while at increasingly higher frequencies the cell membrane capacitors will offer less and less reactance. As reactance approaches zero, impedance is purely resistance, and resistance at this frequency reflects the resistance of total body water (TBW). Current analyzers offer frequency ranges from 1 kHz to 1 MHz, plot impedance loci at these frequencies, and extrapolate reactance to zero along the locus via curve fitting at infinite extremes of frequency. What results are imaginary-real resistances where true resistance for ECF (Re) and resistance for TBW values should theoretically lie (Resistance of ICF [Ri] is computed from the component circuit). These resistance values and the patient’s height, weight, gender, and Hanai mixture equations are used to extrapolate to volume (73). The potential advantages of this approach over linear single and double frequency measurements are: (1) Complex impedance at any single frequency (characteristic frequency) may be different from patient to patient or from time to time. Thus, curve fitting and extrapolation may help smooth out these interpatient and measurement differences. (2) Intuitively, extrapolation of data to zero and infinite frequencies is probably more accurate than arbitrarily choosing a single frequency for analysis, for the same reasons as above.

A few studies have compared the techniques. Ho et al. found that both techniques correlated very well with TBW by deuterium space (74). However, multifrequency modeling of TBW was slightly more precise than the linear equation (6.2 versus 6.7%, respectively). And while multifrequency bioimpedance tended to consistently underestimate TBW, the linear equation both over- and underpredicted TBW with more scatter along the line of identity. Another study revealed that modeled bioimpedance spectroscopy (BIS) and dual frequency resistances showed very little intermeasurement differences ($\pm 0.04$), thus confirming the underlying Cole modeling scheme of BIS (75). Whether one uses single, dual, or multiple frequency modeling, one could make the argument that there is no need to extrapolate these resistances to volume terms, since (1) resistivity constants (or components therein) are derived in a linear manner from nonuremic populations, and (2) their calculation involves the use of Hanai mixture theory, which has not been validated in whole organisms (76).

Bioimpedance and Dry Weight: Clinical Utility. Bioimpedance analysis has proven to be a useful tool in assessment of dry weight in hemodialysis patients. We have shown that BIS measurements during HD track ECF volume change and show excellent correlation to ultrafiltrate removed and change in weight (77). Kouw et al. (78), using multiple frequencies, compared ECF and ICF in 29 hemodialysis patients and 31 control subjects. Compared with control subjects, hemodialysis patients had markedly expanded ECF compartments predialysis, which were reduced to control values after dialysis. Patients classified as underhydrated by comparison to control subjects experienced more hypotension and greater blood volume changes adjusted for ultrafiltration. In a later study (79), they were able to show that gradually increasing dry weight in these underhydrated patients resulted in gradual reductions in the intradialytic change in blood volume and better hemodynamic tolerance of ultrafiltration. Fisch and Spiegel, using resistive index ($L^2/R$) to bone mineral content or lean body mass ratios and multifrequency analysis confirmed that fluid is removed primarily from the extracellular compartment during hemodialysis (80). Katzarski et al. were later able to show that when their patients were divided into two groups based on the presence or absence of hypertension, those with hypertension had larger TBW and ECF expressed as a percentage of body weight (81). Gradual reductions in body weight in these patients were followed by concordant changes in volume by BIS and BP. Thus, even when used singularly, bioimpedance analysis is useful for detecting and managing both the over- and underhydrated state in hemodialysis.

The limitations of this tool, however, are multiple. As discussed previously, extrapolation of Re and Ri into volumetric terms is based on resistivity constants derived by regression against bromide or deuterium space from a nonuremic patient population. Hence, hydric volumes estimated for dialysis patients from these equations must be interpreted with caution.
until more data are available. There has been some concern that changes in electrolyte composition and hematocrit may alter the conducting properties of both the extracellular and intracellular fluid and thereby alter measurement of TBW (82). Sinning et al. (83), using a single frequency bioimpedance analysis measurement, did not find any correlation between changes in electrolytes during the course of HD, whereas changes in hematocrit and protein (reflecting reduction in blood volume [BV]) had a high correlation to measured resistance. Another concern is timing of the measurement. Although initial studies showed that ECF change during hemodialysis tracked well with UF volume, other investigators (84) are not finding this to be the case. Indeed, in these studies (84) ECF change as measured by bioimpedance pre- and posthemodialysis often underestimates UF volume by as much as 30%. There are several possible explanations for this error, but the most likely is the following: During cumulative ultrafiltration, according to Daugirdas’ regional blood flow theory (85), a larger fraction of ultrafiltration is occurring from high flow low resistance flow circuits in the body. That is, as dialysis proceeds, progressively more and more fluid is taken from the trunk. The ability of bioimpedance to detect changes in volume is roughly proportional to the resistance to current flow through that volume bed. Since the trunk contributes only 5% or 20

<table>
<thead>
<tr>
<th>Technique</th>
<th>Benefits</th>
<th>Limitations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical markers</td>
<td>Ease of use</td>
<td>Difficult to use in heart failure, tricuspid/mitral valve disease</td>
<td>Benefits: 40,43,45,46,51,52</td>
</tr>
<tr>
<td></td>
<td>No additional labor cost</td>
<td>Cannot detect the “underhydrated” state</td>
<td>Limitations: 44,47–49</td>
</tr>
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<td></td>
<td>Highly sensitive for the volume overloaded state</td>
<td>“Normal” range?</td>
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</tr>
<tr>
<td></td>
<td>Reflective of intravascular volume status</td>
<td>Meaning of low value?</td>
<td></td>
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<td>Vena cava diameter</td>
<td>Widely available</td>
<td>Difficult to use in heart failure</td>
<td>Benefits: 60–62</td>
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<td>Reflective of intravascular volume status</td>
<td>Overestimates degree of dehydration postdialysis</td>
<td>Limitations: 53,54,57,58,59</td>
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<td>Change in size correlates well with ultrafiltration volume/</td>
<td>Interoperator error</td>
<td></td>
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<td>hemodynamic parameters</td>
<td>Highly variable/difficult to normalize to population</td>
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<td>Bioimpedance</td>
<td>Hydric volumes correlate well with isotope dilution methods</td>
<td>Postdialysis measurements of ECF often underestimate ultrafiltration volume</td>
<td>Benefits: 74,77–79,81</td>
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<td></td>
<td>Ease of use, immediate results</td>
<td>Underestimates volume removed from trunk</td>
<td>Limitations: 76,82–84</td>
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<tr>
<td></td>
<td>Reproducible/repeatable</td>
<td>Accurate measurement of ICF confounded by temperature and ion effect</td>
<td></td>
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<td>Measurement of interstitial space and ICF</td>
<td>Accurate measurement of ECF confounded by effect of recumbency</td>
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<td>Immediate assessment of nutritional status</td>
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<td>Has potential to be readily normalized</td>
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<td>Continuous/hemodynamic and static/dry weight utility</td>
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<td>Sensitive in detecting the underhydrated state</td>
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<tr>
<td>Blood volume monitoring</td>
<td>Ease of use and understanding</td>
<td>Continuous plasma volume dependent on numerous factors other than hydration of the interstitial space</td>
<td>Benefits: 93–95</td>
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<td>Allows for concomitant prevention of hypotension</td>
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<td>Limitations: 89</td>
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<td>May be useful to screen for an inappropriately high or low dry weight</td>
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*ECF, extracellular fluid; ICF, intracellular fluid.
ohm to total body resistance due to its large cross-sectional area, removal of fluid from this segment escapes detection by whole body bioimpedance techniques. Unfortunately, there is no simple solution to this problem, since accurate measurement of resistance to current flow through the trunk would require large, cumbersome electrodes, and the heterogeneous nature of trunk contents might make measured resistances unpredictable. Recently, Levin and Schneditz et al. used “sum of segmental resistances” to confirm this hypothesis (86). And while dry weight, and hence ECF, should be assessed postdialysis, ICF must be measured predialysis. Measurement of high frequency impedance is greatly affected by temperature and ion changes that occur during hemodialysis. The result is the possible overestimation of intracellular fluid volume after hemodialysis. Despite its limitations, bioimpedance is a convenient, safe, and noninvasive tool that, unlike the biochemical markers and VCD (which are markers of intravascular volume), can additionally determine interstitial and intracellular fluid status.

**Blood Volume Monitoring**

Ultrafiltration during dialysis removes fluid from the intravascular compartment and results in a progressive decline in BV (87). However, this decrease is limited by refilling from the interstitial space (88). It is recognized that plasma refilling capacity is influenced by several factors including the tissue hydration state (89). As long as plasma refilling can keep pace with ultrafiltration, hypovolemia can be avoided and intradialytic complications reduced. Several investigators have explored the use of noninvasive methods to monitor BV changes during dialysis (90,91). In general, all of these methods are based on measuring the change in hematocrit or protein concentration during HD. The increase in hematocrit and protein is inversely proportional to the change in BV (91). Thus, it is possible to assess the change in BV in real time during a hemodialysis treatment. Steuer et al. (91,92) have described the use of an optical method to measure hematocrit that is simple, practical, and reliably tracks changes in BV. We have used this device to monitor changes in BV in dialysis patients and confirmed these observations, and demonstrated that in hypotension-prone patients, intradialytic symptoms are usually preceded by a consistent and predictable change in BV (93). Further investigation in this area suggests that it may be possible to identify a threshold for each patient below which intradialytic complications are likely (94). We have further demonstrated that this method can be used to target nonconstant ultrafiltration and reduce complications (95).

As an isolated technique for determination of dry weight, however, BV measurement has its limitations. The difficulty that arises in standardization of this technique is that different patients and disease states dictate different levels of vascular refilling from the interstitial compartment, and thus it is a nonquantifiable method of measurement. For example, there is little agreement on whether rate of change, absolute change, or absolute level of blood volume is or are predictive of hypotension. Different patients respond to different patterns, and their own pattern usually must be established over a period of trial and error. In fact, some patients tolerate as much as 20% change in blood volume, whereas others (e.g., the elderly, diabetic patients, and patients with pulmonary hypertension and congestive heart failure) cannot tolerate even the slightest change. That said, in general, a flat blood volume line throughout dialysis in a patient who tolerated that session well hemodynamically suggests that that patient is not yet at his or her dry weight. On the other hand, multiple early rapid changes in BV accompanied by symptoms are generally predictive of underestimation of dry weight. A hypotensive episode in a patient with a flat blood volume curve might be predictive of a serious underlying problem not related to hydration status, but this remains to be proven.

**Combination and Cross Validation of the Techniques**

Because each of the aforementioned techniques has its limitations (Table 2), several studies have been done in an attempt to cross-validate the methods, or use them in combination in
hopes of better defining fluid shifts during dialysis and determining dry weight.

**Determination of Fluid Shifts.** As changes in BV are proportional to the balance between ultrafiltration rates and plasma refilling, in the absence of ultrafiltration it is possible to determine plasma refilling rates and absolute BV (96). Additionally, if BIS measurements are combined with BV monitoring during dialysis, changes in the ECF and intravascular compartments can be determined, permitting an estimate of plasma refilling (97–99). We have used both of these techniques simultaneously and extended measurements for approximately 1 h after dialysis (Figure 1). Our data show that both BIS (ECF) and hematocrit measurements (BV) have an excellent correlation with the volume of fluid removed (97). Bogaard et al. (98) had similar findings using a single frequency BIS measurement and an optical method of hematocrit determination. These authors used the ratio between change in BV and the volume of ultrafiltrate as a reflection of plasma refilling and found that there were significant differences in the rate of change in BV in dehydrated, normally hydrated, and overhydrated patients. We have calculated absolute plasma volume and plasma refilling rates at the end of dialysis and have shown that at the end of dialysis there is a continued decline in ECF associated with plasma refilling. This suggests that the interstitial fluid compartment contributes fluid for plasma refilling and may replenish the intracellular space (99) (Figure 2). We have subsequently calculated absolute plasma volume for different time points during dialysis and, in conjunction with the ECF measurements done simultaneously, have computed the volume of interstitial fluid. The difference in change in BV and ultrafiltration rate reflects the plasma refilling rate. Our data show that there is a good correlation between interstitial fluid volume and plasma refilling (99). De Vries et al. (79) have further used both techniques to adjust dry weights in hemodialysis patients and thereby reduced the frequency of hypotensive episodes.

**Determination of Dry Weight.** Kouw et al. measured routine hemodynamic parameters noninvasively during dialysis and then stratified patients as over- or underhydrated based on posthemodialysis measurements of caval diameter, conductivity (lower extremity, single frequency [bioimpedance analysis], ECF), cGMP levels, and ANP levels (62). They found that caval diameter and conductivity correlated well with ultrafiltration volume, the dehydrated state, and each other, both pre- and posthemodialysis. There was a weak correlation between postdialysis cGMP levels, change in blood volume, and hemodynamic parameters, indicating that cGMP is less valuable in assessing dry weight than either conductivity or caval diameter. When patients were separated by ANP levels, there was no correlation with change in hemodynamics, caval diameter, or conductivity, indicating that it provides no value in defining dry weight in their study. Notably, caval diameter routinely underestimated dry weight, whereas conductivity overestimated dry weight. Both measurements were taken immediately after dialysis, raising the question as to whether enough time had elapsed to allow refilling of the plasma from the interstitium. Note that this is a slightly different mechanism of overestimation of postdialysis ECF volume than stated in the above discussion of bioimpedance. Another study by the same group that year compared bioimpedance and BV monitoring.

**Figure 2.** Postdialysis volume shifts from extracellular fluid (ECF) compartment as tracked by bioimpedance spectroscopy and simultaneous blood volume monitoring. At the end of dialysis, there is a shift of fluid from the extravascular (interstitial fluid) compartment, which includes a redistribution to the intravascular space and a compartmental shift to the intracellular space. There is a continued decline in ECF up to 30 min postdialysis (as evaluated in these experiments). The influence of dialysate sodium concentration on the compartmental shifts has not been evaluated. VECF, extracellular fluid volume; VICF, intracellular fluid volume; PV, plasma volume.
They stratified patients as underhydrated, normal, or overhydrated based on previously developed conductivity criteria taken postdialysis and then measured blood volume changes and hemodynamic parameters in these three groups (94). They found that in the underhydrated group, there was significantly greater change in overall blood volume corrected for ultrafiltration volume and more hypotensive episodes compared with normal or overhydrated patients. Conversely, Lopot et al. recently stratified patients based on blood volume profiles characterized as overhydrated, normal, and underhydrated, and then compared these profiles with conductivity measurements and VCD (100). Those with blood volume profiles indicative of overhydration had larger postdialysis values of ECF and VCD. Likewise, those characterized as underhydrated on the basis of rapid changes in blood volume had smaller postdialysis ECF and VCD values. This is perhaps the only study utilizing and confirming the blood volume method as a screening tool to detect an inappropriately high dry weight. In the third part of Katzarski et al.’s study showing hypertension as dependent on bioimpedance-determined volume (81), they additionally showed that ECF and VCD decreased in tandem during dialysis and correlated well postdialysis. Thirty minutes postdialysis, VCD increased markedly, likely indicative of plasma refilling from the interstitial space. However, ECF values remained stable. We believe that this might be due to refilling of plasma volume from more easily accessible fluid sites not measured by bioimpedance due to the peripheral arrangement of electrodes in this study.

Beyond Dry Weight? An Index for Adequacy of Fluid Removal

From the above discussion, it is evident that contemporary management of fluid in the dialysis patient is largely dependent on a clinically derived estimate of dry weight. Clinical assessment of dry weight inevitably leads to both overestimation and underestimation of dry weight. Overestimation of dry weight leads to hypertension, stroke, and congestive heart failure, which are the main causes of excess death in dialysis. Underestimation leads to persistent hypertensive episodes, alienating dialysis patients from their caretakers, and affecting delivery of prescribed dialysis. Moreover, the current focus on Kt/V as an index for adequacy of dialysis in terms of solute removal ignores the contribution of volume as an independent factor influencing outcome. Unfortunately, despite this recognition we have not attempted to rectify this problem in any systematic way. It is our belief that a possible approach to this problem is the development of an index for adequacy for fluid management.

Peritoneal dialysis provides the ideal model for achieving dry weight, since slow continuous peritoneal ultrafiltration permits physiologic or perhaps subphysiologic dry body weight control of BP. The goal for fluid removal in HD is to attain a lower than physiologic dry weight immediately postdialysis, allowing a time-averaged physiologic dry weight in the interdialytic period. This would be particularly true for patients without large interdialytic weight gains (<2 L), con-genitive heart failure, left ventricular disorders, diabetic autonomic neuropathy, severe hypoalbuminemia, or other conditions predisposing to hypotension in dialysis. On the other hand, physiologic dry weight might be an appropriate goal for patients with persistent large interdialytic weight gains or the above conditions that predispose to hypotension. Furthermore, the use of nonlinear ultrafiltration may assist dry weight achievement in these patients (95). Because of this complexity, it is easy to recognize that objective tools used for estimating dry weight are necessary. However, the individual techniques each have limitations or are inherently insufficient for singular use in dry weight assessment (Table 2). Therefore, some combination of these tools will need be used to achieve this goal. Furthermore, dry weight assessment might further be stratified into two major categories: (1) the interdialytic measurement of static dry weight and body composition and (2) intradialytic assessment of online data or comparison of pre- and posthemodialysis data. Either might be used on a monthly or other periodic basis as a means of following dry weight and deriving an index of adequacy for fluid removal (101).

We have extensively reviewed the technologic methods for actual measurement of volume status in dialysis patients as they have developed thus far, as well as addressed their limitations. Further development of these techniques is necessary for attaining an easily derived and utilized index for adequacy of fluid removal. The development of this index should be undertaken whereby both interdialytic and intradialytic methods will be described and utilized on a periodic basis. Pending further research and development, the intradialytic measurement of dry weight and body composition will perhaps be best accomplished with bioimpedance spectroscopy, because of its unique ability to provide insight into nutritional status as well. Intradialytic methods will arise out of further interrogation of fluid shifts that occur during dialysis. At some point, these technologies might be incorporated into dialysis machines whereby volumetric control of ultrafiltration will take on a new meaning and result in profiled dialysis. It is obvious that we have a long way to go, however, it is our belief that recognition of the need for this process is an initial step that will hopefully result in further investigation in this field.

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