

Dry Weight and Measurements Methods

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1. Introduction

1.1 Why do we need dry weight for our patients?

The need for a concept of dry weight derives from an awareness of the dangers of being overhydrated or as better expressed, being fluid overloaded. These dangers in the hemodialysis patient are reflected by strain on the heart indicated by left and eventually right ventricular hypertrophy and dilatation, with gradual reduction in the efficiency of the heart. Eventually, heart failure occurs with increased hospitalization and mortality rates. More recently interest in attaining dry weight has been stimulated by awareness that an abnormally low fluid load is also harmful in that it might be associated with unacceptable degrees of low blood pressure and consequently of ischemia of vital organs such as the brain, gut and liver. A working definition of dry weight is required before further discussion. Charra modified earlier thoughts on this as follows: the post dialysis weight at which the patient is and remains normotensive until the next dialysis in spite of interdialytic fluid retention (without ant-hypertensive drugs) (Charra, 2007; Charra *et al.*, 1996). This weight might be compared to the usual range of weights in a person with normal kidney function whose consumption of water in food or as liquids is balanced by loss of fluids through the skin lungs, gut and urine. However, there is always a range of fluid volumes within a liter or two around the true dry weight in patients with clinical dry weight assessment (Jaeger and Mehta, 1999).

Other definitions in dialysis patients have included the weight at which hypotension and symptoms such as muscle cramps, nausea and vomiting occurs (Agarwal and Weir, 2010; Leypoldt *et al.*, 2002). Clinical judgment of dry weight is often based on an educated guess since the one to three liters fluid overload characteristic of many dialysis patients cannot be detected by current routine physical examination (Sinha *et al.*, 2010; Zucchelli and Santoro, 2001). A more sensitive physical sign, which requires training and practice but is not widely taught, is the measurement of internal jugular vein pressure. This clinical sign faithfully represents right atrial pressure which is often increased with fluid overload, The equilibrium blood and interstitial fluid volumes is dependent on the differences between the interstitial and blood oncotic pressures, with accumulation of edema fluid, and increase of compliance (largely due to the normal gel structure being dissipated) As a result large volumes of fluid can accumulate with little increase in hydrostatic pressure. The effect of ultrafiltration (UF) is dependent on the degree of fluid overload in that the blood volume will decrease far more when the patient is close to dry weight (Merouani *et al.* 2011). Further, the blood volume change for the same volume of ultrafiltration is highly dependent on the ultrafiltration rate.

1.2 Blood pressure and hydration

The relationship of blood pressure level, which is a physical sign comparatively easy to measure with accuracy, to over hydration, is frequently discussed in the care of the dialysis patient. From work performed by many authors (Ok and Mees, 2010) (Charra and Chazot, 2003a), reduction in dietary sodium and in sodium loading during dialysis is associated with decrease of blood pressure to close to normotensive levels. While volume increase is associated with predominantly systolic pressure, diastolic pressure is also increased. It is not rare in older patients for the pulse pressure to be increased with low diastolic pressures associated with poorly compliant major blood vessels. This increased rigidity of the aorta and other large blood vessels occurs due to fibrosis with calcification possibly playing a major role. One confounding influence on the blood pressure and fluid overload relationship is a degree of cardiac damage over years so severe that blood pressure might be normal or even below normal (Charra and Chazot, 2003b). Reduction in fluid overload can actually increase blood pressure in such patients. Echocardiography is very useful in distinguishing patients with large failing hearts from those with normal blood pressure following adequate treatment with antihypertensive drugs or salt restriction (Santos and Peixoto, 2010).

1.3 Sodium and fluid overload

Sodium, in the form of salt, plays a major role in the fluid and electrolyte problems of the dialysis patient, to a large extent because the regulation of salt is almost completely absent once the kidneys are not functioning. The dialysis patient is at risk to the same extent as a healthy patient to increased dietary intake of sodium but in addition sodium is often added during the actual dialysis treatment (Matsuoka *et al.*, 1990; Schmieder, 1997). In health the balance of sodium is determined predominantly by renal regulation of tubular re-absorption as influenced directly or indirectly by plasma and extracellular volume. These functions are not present in the dialysis patients, and therefore expansion is obviously accompanied by relative inability to excrete water. Blood pressure increase occurs in most patients as the result of sodium and fluid retention and is considered to be a prime factor in the pathogenesis of the cardiac disease which is the major cause of hospitalization and mortality in dialysis patients, Left ventricular hypertrophy leads to ventricular dilatation and left-sided cardiac failure with pulmonary edema, and pulmonary hypertension. The right ventricle then also hypertrophies and fails with this being the basis for the congestive heart failure seen so often in dialysis patients (Fiaccadori *et al.* 2011). Peripheral edema is obvious, especially in the legs but congestion of visceral organs may be of greater pathognomonic significance. An example is the gut where increased permeability to luminal endotoxin could promote the inflammation characteristic of most dialysis patients. While anti hypertensive drugs are successful in reducing blood pressure, control of salt and water may be more effective. Normal or low blood pressure in the absence of such treatment can be misleading since this can be due to the result of progressive cardiomyopathy and represents a poor prognosis. Recent research suggests that declines in blood pressure occurring in the absence of treatment are associated with poor outcomes (Silver *et al.*, 2008).

1.4 Sodium control

Control of salt intake becomes one of the most relevant aspects of the dialysis treatment; current recommendations are for less than six grams of salt to be ingested daily. Patient education concerning sodium content of individual items has variable effects but is often

swamped by the easy availability of fast foods. However, notable examples exist of the success of this approach particularly in Tassin in France (Charra *et al.*, 2004) where the combination of compliance with a low salt diet, and relatively longer dialysis time has been associated over decades with well controlled blood pressure levels and low mortality (Chazot and Jean, 2008). Asking patients to reduce their fluid intake voluntarily is rarely successful because of the powerful effect of thirst and appeals to limit salt are far more likely to be successful.

Extra sodium may be administered in three ways during dialysis. The first is the use of dialysate sodium concentrations higher than the patient's level (Odudu *et al.* 2011). As much as 3 to 5 g of sodium may be administered during a dialysis (Tetta *et al.* 2011). This attribute of the dialysis treatment has been through a number of cycles. In the early days of dialysis sodium concentrations were low commensurate with long dialysis times and therefore low ultrafiltration rates (Silverstein *et al.*, 1974). As dialysis times were reduced, dialysate sodium concentrations increased but currently are decreasing again with more awareness of the effects of excess sodium. One potentially more precise solution to obtain balance has been the alignment of the dialysate and serum sodium levels which is approximately possible because of the opposite effects of the Gibbs-Donnan equilibrium and the fact that the plasma water concentration is about 7% higher than that of plasma sodium. The second is during priming of the dialysis circuit when the volume of saline administered is variable, depending on the degree of care, but is often 100 to 500 ml per treatment. Adding this volume to the ultrafiltration requirements deals with the problem in part but cannot be relied on to occur due to homodynamic instability. In addition the sodium content of the ultrafiltrate is lower than that of isotonic saline. The third is the use of saline for the management of hypotensive episodes when reductions in ultrafiltration rate are unsuccessful (Santos and Peixoto, 2010). Since the quantities given can be substantial, replacing saline with hypertonic glucose is an acceptable replacement, perhaps with reservations in some diabetic patients.

2. Fluid volume measurements

2.1 Body fluid compartments

Total body water (TBW) can be divided into two compartments: extracellular fluid volume (ECV) and intracellular fluid volume (ICV). Further, the extracellular compartment is divided into interstitial fluid and blood plasma volume (Fig.1).

Accuracy of measurement of extracellular fluid volume (ECV) is an important issue in research and clinical practice. Currently, the standard reference for body fluid measurements are dilution method using deuterated water (D₂O) for total body water and NaBr for ECV measurements (Riek and Gerken, Pierson *et al.*, 1978; Kim *et al.*, 1999). However, with dilution method patients have to wait about 3 hours in order to obtain equilibrium of the diluting substances in the body. In addition, the accuracy of this method has been questioned for example, NaBr might overestimate the ECV (Thomas *et al.*, 1991).

Bioimpedance analysis (BIA) techniques have been used as noninvasive and simple methods to measure body fluid volume. The principle of BIA methodology is based on the physical principle that fluid volume is negative related to electrical resistance, and therefore, ECV and ICV can be calculated as

$$ECV = \rho_{ECV} * L^2 / R_E \quad (1)$$

$$ICV = \rho_{ICV} * L^2 / R_I \quad (2)$$

where R_E and R_I are the extracellular and intracellular resistances calculated with the Cole model using multifrequency spectroscopy (BIS), L is the length of the measuring segment and ρ_{ECV} and ρ_{ICV} are resistivity in extracellular and intracellular fluid considered as constant. TBW can be calculated by sum of ECV and ICV. Current accuracy of estimation of ECV is about 1.0-1.5 L by advanced bioimpedance method (Moissl *et al.*, 2006; Zhu *et al.*, 2006a; Ellis, 2000). Main factors affecting accuracy of BIA or BIS to estimate fluid volume includes 1) error from measurement and 2) error of calculation from inaccurate assumptions. For example, the current standard method is the wrist to ankle (so called "whole body") bioimpedance measurement (De Lorenzo *et al.*, 1997). This method assumes that arm, trunk and leg can be modeled as a cylinder with uniform conductivity when electrical current is injected from hand to foot and voltage is measured between wrist and ankle. Since the different cross sectional areas between trunk and limbs, limbs' resistance (the arm and leg) contribute about 90 % of whole body resistance but the limbs' volume is less than 30 % of total body volume (Zhu *et al.*, 1998a; Zhu *et al.*, 1998b; Bracco *et al.*, 1996). This inhomogeneous distribution between resistance and volume in segments leads to different degrees of error which are associated with variation in body composition and in degrees of body hydration (Thomas *et al.*, 1998). As a result, estimation of fluid volume with whole body bioimpedance methods does not provide accurate information (Cox-Reijven *et al.*, 2001; Earthman *et al.*, 2007).

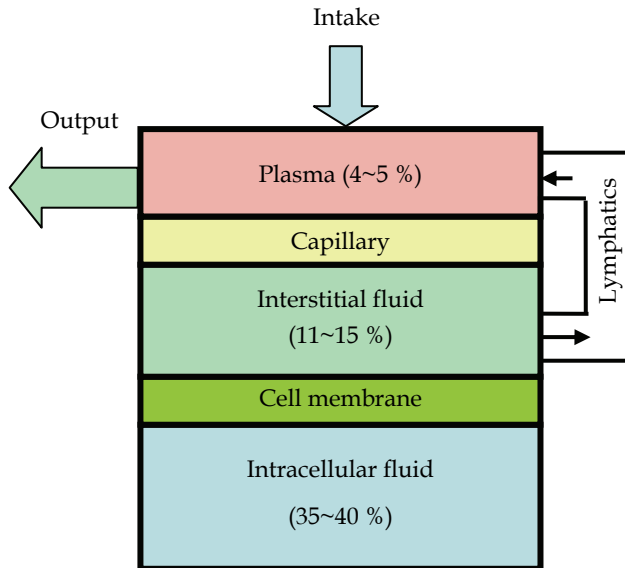


Fig. 1. Body fluid compartments, extracellular fluid volume (ECV) consist of plasma and interstitial fluid volume.

As an example, the problem of inhomogeneous distribution in fluid volume and cross-sectional area of body segments can be observed from an experiment of change in body position (Zhu *et al.*, 1998a).

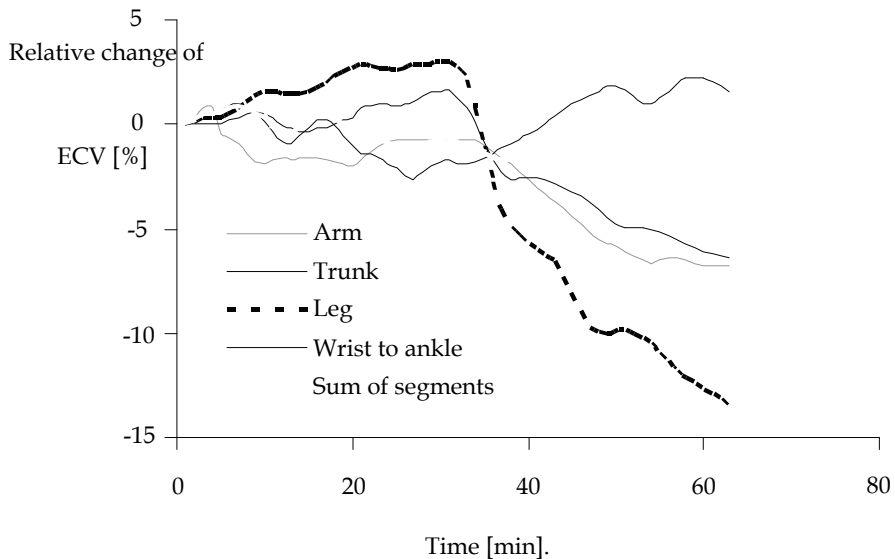


Fig. 2. Change in segmental ECV during change in body position (Modified from Zhu et al., J Appl Physiol 85:497-504, 1998)

Fig.2 shows segmental ECVs changes during 30 minutes standing and then immediately after 30 minutes supine. As shown in Fig.2, the ECV in the leg increased and the trunk decreased about 3 % during the standing position due to the fluid volume accumulating in the leg by gravitational force. After assuming the supine position, ECV shifted back from the leg to the trunk. Although total ECV in the body did not change during the position changes, difference in ECV measured by wrist to ankle increased about 2 % in standing and decreased more than 6 % after being supine. This example clearly demonstrates that change in distribution of fluid volume can make a disproportional change in resistance in the segments because of their different geometric sizes, and therefore, ECV calculated from the sum of the resistances cannot be correct. It has to be noticed that change in fluid redistribution can be made not only by change in body position but also by change in fluid overload (Zhu *et al.*, 2008b).

2.2 Measurement of fluid overload

Fluid overload can be generally defined as the ECV accumulated in the body of greater than a normal degree. Although the measurement of the normal range of ECV (normal hydration, NH) is difficult; degrees of fluid overload estimated by clinical practice have widely been used in clinical practice. Excess fluid volume can be roughly estimated through clinical sign such as hypertension and by a physician's assessment such as increased jugular vein pressure. Accurate assessment of fluid overload or quantitative calculation of excess fluid volume is a challenge due to: 1) lack of a reliable techniques to measure ECV and 2) the normal range of ECV is unknown because of the variability of excess fluid in individuals not only derived from differences in intake of salt but also by variability due to the age or gender in the healthy population (Silva *et al.*, 2008). Body fluid status is a dynamic equilibrium or steady state

condition controlled by physiologic functions. But in dialysis patients this function is lost. From engineering point of view, estimation of fluid status in normal level (dry weight) can be generally divided into two aspects of methods: static and dynamic approaches.

3. Static methods for estimating dry weight

The principle of the static method is based on the degree of fluid overload can be assessed by comparison of a parameter using healthy subjects as reference.

3.1 Bioimpedance vector analysis (RXc graph)

Resistance (R) and reactance (Xc) graph shows relationship of change in impedance vector at 50 kHz in R-Xc plane to estimate degree of hydration or nutrition with the range of tolerance ellipses from healthy subjects (Fig 3) (Piccoli, 2005). This method was suggested by Piccoli et al to identify dry weight in hemodialysis patients according to 50th, 75th and 95th % of vector in healthy population (Piccoli, 1998). The advantage of this method is that the state of tissue hydration and nutrition can be reflected by the length and angle of a vector which consist of resistance and reactance at 50 kHz in R-Xc plan. Since 50 kHz current is applied, the impedance can be affected by electrical properties in both the extracellular and parts of the intracellular fluid compartments.

The major disadvantage with this method is that the state of hydration cannot be separately obtained due to the vector being determined by resistance and reactance. Therefore, this method is useful to generally compare the status of hydration or nutrition in populations but it cannot provide quantitative information about degree of fluid overload.

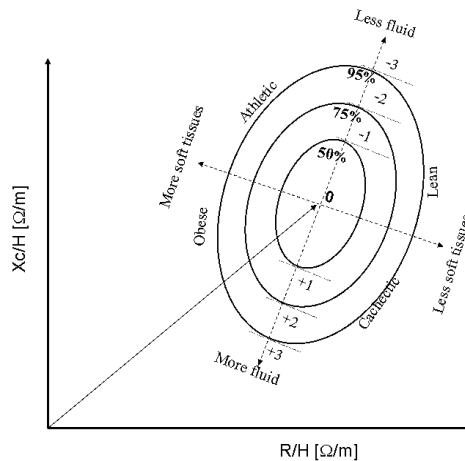


Fig. 3. Principle of phase ankle method (Modified from Piccoli, Contrib Nephrol. Basel, Karger, 2005, vol 149: pp 150-161)

3.2 The ratios of fluid volume

Ratios or percentage of ECV to body mass or one of components, for example ECV/TBW, ECV/ICV or ECV/body mass (BM) should be maintained in an approximately constant level controlled by normal physiologic function. Logically, these parameters should be able to

identify the body hydration state (Lopot *et al.*, 2002; Farnetti *et al.*, 2004; Park *et al.*, 2009; Koziolok *et al.*, 2006; Booth *et al.* 2011.). However, in practice, there are two issues as mentioned above: 1) accuracy of ECV measurement and 2) the normal range in healthy population limits its usefulness in clinical practice. The normal range has been reported as from 0.37 to 0.46 in ECV/TBW and from 0.22 to 0.24 in ECV/BM (Katzarski *et al.*, 1996; Woodrow *et al.*, 2005; Zhu *et al.*, 2011; Chen *et al.*, 2002). The problems of the methods using the ratio of resistance with different frequencies such as ratio of extracellular resistance to intracellular resistance (R_e/R_i) or resistance at 5 kHz to resistance at 200 kHz (R_5/R_{200}) are similar problem to the volume ratios (Spiegel *et al.*, 2000; Zhou *et al.* 2010). A comparison of the ECV/TBW or ECV/BM in HD patients with healthy subjects is showing in Fig 4 (a) and (b). In that study a bioimpedance spectrum analyzer system (Hydra 4200, Xitron Technologies, CA) was used to measure whole body BIS (wBIS) in NS and in (HD) patients to obtain ECV and ICV (Zhu *et al.*, 2011). There was no significant difference in wECV/TBW between BL and DW_{CBIS} in male patients although the patients had lost body fluid. The lack of sensitivity with this method limits the clinical application of wECV/TBW for individual patients (Fig. 4 (a)). The poor sensitivity of wECV/TBW can be explained that 1) since TBW is the sum of ECV and ICV, decrease in ECV produces the similar changes in the numerator and denominator of the ratio of ECV/TBW; 2) the accuracy of ICV measurements by wBIS is still not good enough for clinical use.

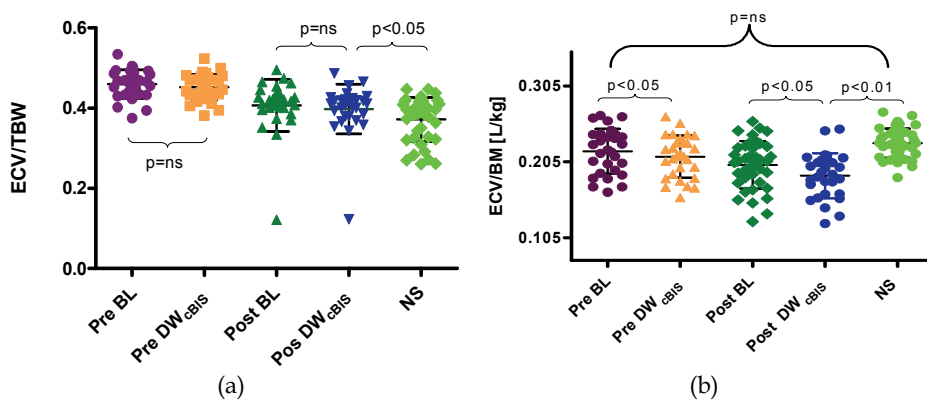


Fig. 4. Comparison of results in patient to NS with ECV/TBW (a) and with ECV/BM (b) (Modified from Zhu *et al.*, *Physiol Meas.* 32:887-902, 2011)

In addition, accuracy of wrist to ankle (wBIS) measurements is affected by body composition and degree of hydration. (Sung *et al.*, 2001) (Bracco *et al.*, 1996) (Zhu *et al.*, 1998b). No difference in wECV/BM between NS and the patients at BL pre-HD might be explained that the ratios of ECV/BM depends on the body composition, such as more or less fat mass in the NS. (Fig.4 (b)).

3.3 Body composition model

Recently a whole body bioimpedance model (WBM) based on functions of body weight, ECV and ICV with wBIS has been developed to calculate degree of excess fluid volume (EFV) with the equation as following (Chamney *et al.*, 2007).

$$EFV = 1.136 \cdot ECV - 0.43 \cdot ICV - 0.114 \cdot BM \quad (3)$$

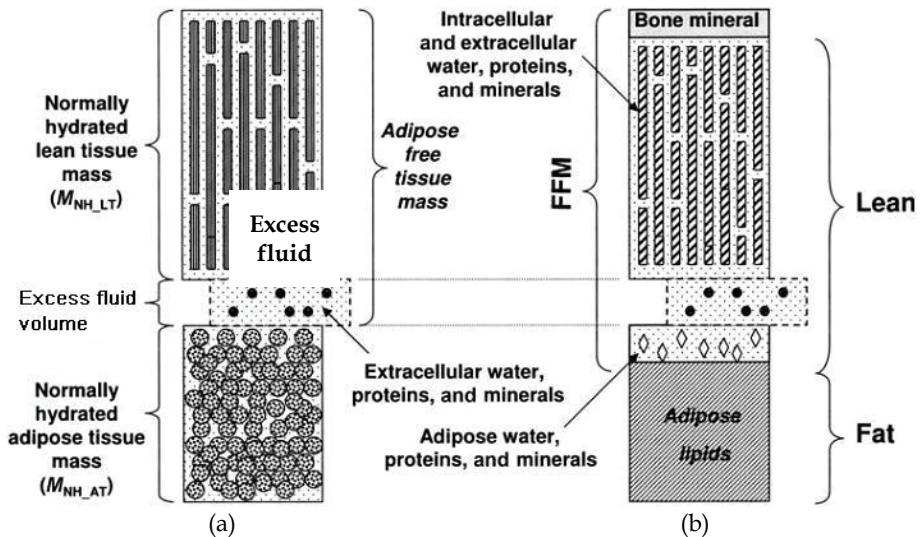


Fig. 5. Principle of whole body model (WBM) (Modified from Chamney et al *Am J Clin Nutr* 2007, 85:80 –9)

The weight at normal hydration (NHW_{WBM}) with whole body model can be calculated by the difference between pre HD BM and excess fluid volume (EFV).

$$NHW_{WBM} = \text{Pre-HD BM} - \text{EFV} \quad (4)$$

The principle of this method is based on the assumption that ECV is proportionally distributed in fat and other body components in healthy subjects (Fig.5). The main advantage with this method is that the model introduces relationships between fluid volume and fat mass which might reduce the error from variability of body composition. However, since this method is using whole body bioimpedance spectroscopy (wbIS) technique for collecting raw data, the problems with wbIS are inherent in the measurement so that accuracy of this method is reduced in subjects with great fluid overload.

3.4 Calf resistivity method

Calf bioimpedance measurement in dialysis patients was reported by Kouw et al to evaluate calf conductance between patients and NS (Kouw *et al.*, 1993). Recently, it was found that the value of calf conductance or resistivity (1/conductance) correlated with BMI (Zhu *et al.*, 2011). To reduce the error, calf resistivity was normalized by BMI (resistivity/BMI) to reflect degree of body hydration. Generally, an assumption is correct that the calf is more hydrated than other segments of the body due to effect of gravity. Moreover, the calf has uniform structure of body composition so that it can reduce the error from bioimpedance measurement. Calf electrodes placement and measurements show in Fig.6.

Calf resistivity (ρ_5) was calculated from resistance (R_5) at 5 kHz and where A and L are the cross sectional areas of the calf and the distance (10 cm) between the sensing electrodes, respectively.

$$\rho_5 = R_5 \times A / L \text{ (}\Omega\text{-cm)} \quad (5)$$

The cross sectional area was calculated by Eq 6, where C_{ave} was the mean of the two measured calf circumferences ($C_{ave} = (C_{Max} + C_{Min})/2$).

$$A = C_{ave}^2 / (4\pi) \tag{6}$$

To reduce the effect of differences in body composition, resistivity ρ_5 was normalized by the body mass index (BMI; calculated as BM [kg] divided by height² [m]²), and reported as calf normalized resistivity ($\rho_{N,5}$) in units of $\Omega m^3/kg$ (Eq 7).

$$\rho_{N,5} = \rho_5 / BMI. \tag{7}$$

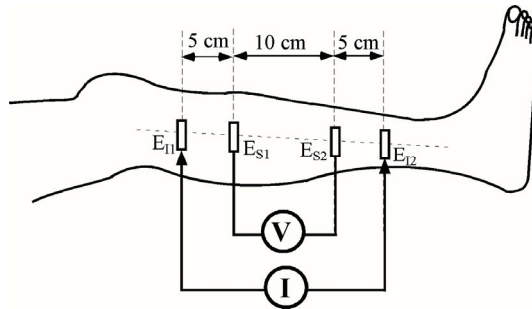


Fig. 6. Four electrodes are placed on the lateral side of calf to inject current (0.8 mA) and measure voltage. One sensing electrode (E_{S1}) is placed on the point of maximal calf circumference (C_{Max}); while the other sensing electrode (E_{S2}) was placed 10 cm below the E_{S1} which was defined at the point as minimal circumference (C_{Min})

Fig.7 shows that the standard deviations in normalized resistivity ($\rho_{N,5}$) was significantly less than the non-normalized values (ρ_5). The average of normalized resistivity in normal subjects (NS) was $20.5 \pm 1.99 \times 10^{-2} (\Omega m^3/kg)$ in males and $21.7 \pm 2.6 \times 10^{-2} (\Omega m^3/kg)$ in females respectively. It can be defined with the values of the mean minus the standard deviation as minimal levels of normal hydration males ($18.5 \times 10^{-2} \Omega m^3/kg$) and in females ($19.1 \times 10^{-2} \Omega m^3/kg$) respectively (Fig.7).

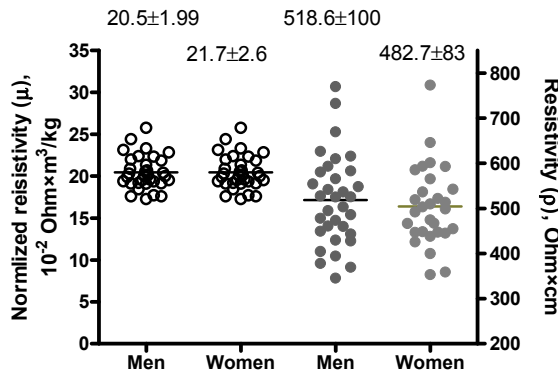


Fig. 7. Comparison of resistivity and normalized resistivity in NS

Normalized resistivity ($\rho_{N,5}$) in NS differed significantly between males and females, but there were no significant differences between the age groups (Fig. 8).

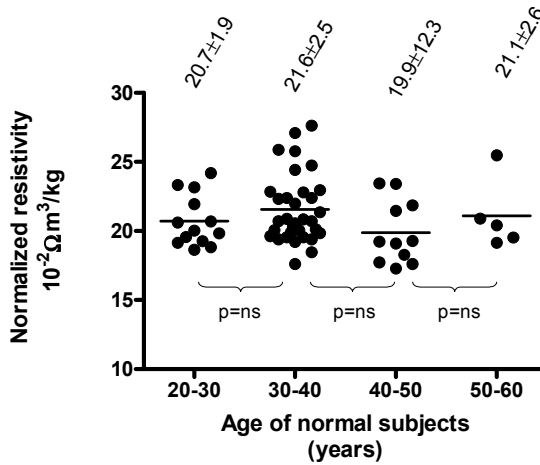


Fig. 8. Comparison of normalized resistivity in NS with different ages. (Modified from Zhu et al., *Physiol Meas.* 32:887-902, 2011)

Fig. 9 demonstrated the change in fluid volume in HD patients from BL with fluid overload to reaching the dry weight. There was no difference in normalized resistivity between NS and the patients who reached dry weight (DW).

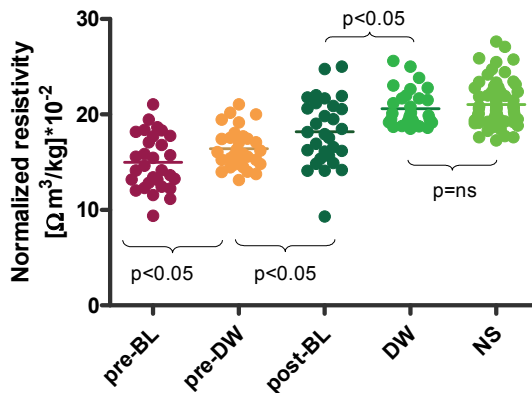


Fig. 9. Comparison of normalized resistivity between HD patients and NS. (Modified from Zhu et al., *Physiol Meas.* 32:887-902, 2011)

The unit of measurement of $\rho_{N,5}$ in $\Omega \cdot [m^3/kg]$, can be interpreted also for its physical meaning. Since m^3/kg is equal to $1/kg/m^3$, which is the reciprocal of density, the parameter $\rho_{N,5}$ can be interpreted as ohm per density measured by bioimpedance, so that it does reflect the relationship of hydration to body density (Zhu et al. 2011).

3.5 Vena cava diameter index

Measurement of inferior vena cava diameter index (IVCD) has been used to indicate hydration by intravascular volume with ultrasound technique (Krause *et al.*, 2001). This is a noninvasive method for fluid volume in blood. However, it cannot indicate the state of interstitial fluid volume because the degree of hydration in intravascular space cannot proportionally reflect fluid overload in interstitial space (Katzarski *et al.*, 1997; Diemel *et al.*, 2000). In addition, variability of healthy subjects is so large that it cannot be applied in patients due to lack of precision of device (Bendjelid *et al.*, 2002; Agarwal *et al.* 2011).

3.6 Biochemical parameters

Serum indicators Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), NT Pro BNP and Cyclic Guanidine Monophosphate (cGMP) have been suggested to indicate degrees of fluid volume expanded in dialysis patients (Ishibe and Peixoto, 2004; van de Pol *et al.*, 2007). The measurements might reflect the fluid status in the blood compartment but cannot be used to determine state of interstitial fluid because the relationship between plasma volume and interstitial fluid volume proportion is unknown for individual patient. As a result, the normal ranges of these parameters were reported with such large variability that they cannot be applied in clinical practice. Cardiac dysfunction and variable removal during dialysis are other problem for its application (Bargnoux *et al.*, 2008).

4. Dynamic methods

4.1 Two compartments model

Change in ECV during HD provides information about body hydration. Relative blood volume (RBV) has been used to monitor reduction of plasma in blood compartment during ultrafiltration (UF) (Leygoldt and Cheung, 1998; Chamney *et al.*, 1999). Since change in RBV reflects the state of vascular refilling, a number of authors have suggested that the curve of RBV either with the slope change or with maximum change in RBV value at the end of treatment might indicate degree of hydration based on change in the state of refilling rate (Sinha *et al.*, 2010; Agarwal *et al.*, 2008). Fig.10 shows the relationship between change in blood volume and interstitial volume (V_{IT}) by UF.

Relationship can be described with a simple two compartments model (Fig.10) by differential equations as following.

$$\frac{dBV}{dt} = k_{IB} \cdot V_{IT} - k_{BI} \cdot BV - UFR \quad (8)$$

$$\frac{dV_{IT}}{dt} = -k_{IB} \cdot V_{IT} + k_{BI} \cdot BV \quad (9)$$

where BV represents plasma volume in blood, k_{IB} and k_{BI} are transfer coefficients between two compartments; UFR is ultrafiltration rate which is the driving force in this dynamic system. From Eq.8 k_{IB} times V_{IT} represents refilling rate (RFR). Although we assume k_{IB} is constant which is determined by pressure gradient between two compartments in the same treatment, k_{IB} can be various in different hydration state. Since k_{BI} times BV is much less than k_{IB} times V_{IT} , the model can be considered as a four parameters system. Then, the equations can be rewritten as following

$$\frac{dBV}{dt} = k'_{IB} \cdot V_{IT} - UFR \tag{10}$$

$$\frac{dV_{IT}}{dt} = -k'_{IB} \cdot V_{IT} \tag{11}$$

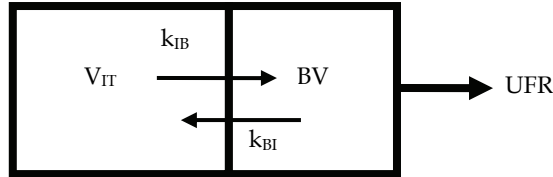


Fig. 10. Two compartment model: blood volume and interstitial fluid volume

4.2 Blood volume monitor

From Eq.10, the changes in RBV depend on the difference between UFR and refilling rate (RFR). RFR is determined by fluid status (V_{IT}) and pressure gradient (k_{IB}) which is associated with individual cardiac function and hemodynamic parameters. In general, absolute or change in RBV have little relationship to body fluid status because RBV indicates the state of difference between UFR and refilling rate (Barth *et al.*, 2003). Even though constant UFR is used in the same patient, RFR is generally not associated with fluid status because the k_{IB} is affected by body hydration, fluid status and cardiac function in individual treatments. A sample shows the relationship between change in RBV and calf normalized resistivity during HD (Fig. 11).

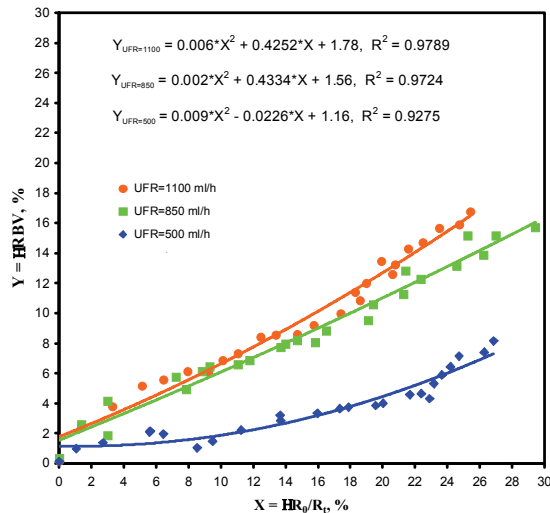


Fig. 11. Relationship between RBV and calf resistance ratio (R_{E0}/R_{ET}) with different UFR in a same patient (From *Sipahioglu et al.*, Blood Purif 2010;29:230-242.)

RBV method provides a simple way to monitor change in plasma volume which indicates change in RFR during HD. Since the RBV shows a relative change, it cannot represent refilling rate from tissue so that it cannot reflect body hydration. Absolute refilling rate can only be calculated if we know the absolute blood volume or refilling volume. RBV can be useful to tell if UFR is correct in individual treatment. A recent study showed that neither in the slope nor maximal change of RBV was observed when patient reduction the post HD weight (Fig.12).

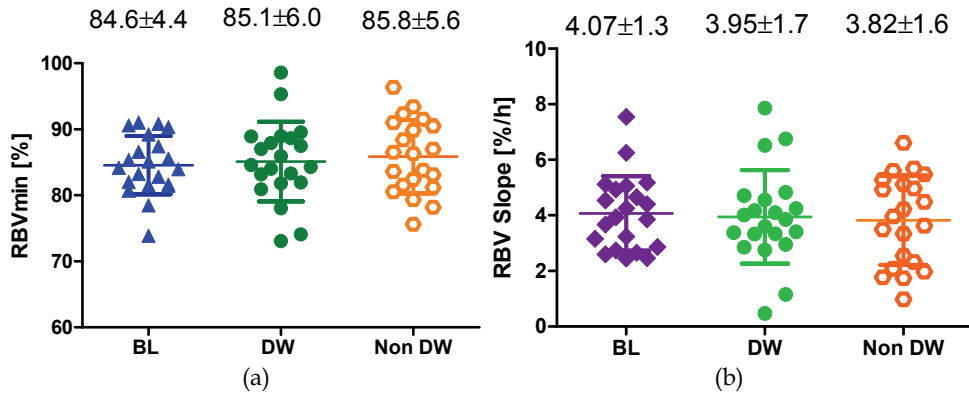


Fig. 12. RBV were compared between BL and dry weight in maximal change of RBV (RBVmin) and in RBV slope. No difference either in slope or in maximal change of RBV were obtained when body fluid reduced.

4.3 Continuous measurement of calf bioimpedance spectroscopy (cBIS)

Calf bioimpedance spectroscopy (cBIS) method provides a way to continuously measure calf ECV during HD. Relative change in ECV can be represented by R_{E0}/R_{Et} where R_{E0} and R_{Et} are extracellular resistance at beginning and at any time until the end of HD. Since the plasma volume only take about ten percent of ECV in the calf, change in R_{E0}/R_{Et} mainly indicate change in interstitial fluid volume. The ratio of R_{E0}/R_{Et} indicates the ratio of extracellular fluid volume in any time (ECVt) to the volume at the beginning (ECV0). The relationship can be described as following (Zhu *et al.*, 2004).

$$\frac{ECV_t}{ECV_0} = \frac{\rho_{ECV} \frac{L^2}{R_{Et}}}{\rho_{ECV} \frac{L^2}{R_{E0}}} = \frac{1}{\frac{R_{Et}}{R_{E0}}} = \frac{R_{E0}}{R_{Et}} \tag{12}$$

where ρ_{ECV} is the resistivity in extracellular fluid volume, L is the length of the measurement area of the calf and R_{E0} and R_{Et} are extracellular resistance at beginning and at any time during dialysis respectively. Since ρ_{ECV} and L are constant in this equation, they are canceled in the ratio of volume so that R_{E0}/R_{Et} is equal to $ECVt/ECV0$. This is the principle why decrease in calf R_{E0}/R_{Et} represents the reduction of extracellular fluid volume. In our previously study, when the curve of R_{E0}/R_{Et} is flattening, it indicates a limitation of excess

fluid in interstitial space so that the state of this hydration can be defined as normal hydration state. Fig.13 show the principle of the continuous monitoring R_{E0}/R_{Et} until reach the flattening in last 20 minutes.

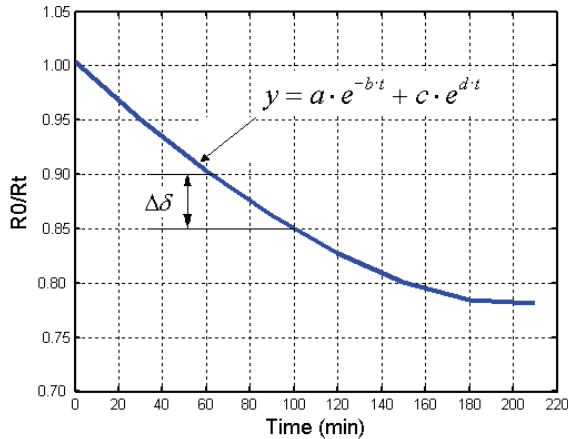


Fig. 13. Shows the principle of curve of R_{E0}/R_{Et} during UF. The curve can be represented as exponential function of two variables and two constants (a and c)

The main advantage with curve of R_{E0}/R_{Et} is the method does not require a normal range from a healthy population but utilizes its slope change as an indicator of tissue hydration. Flattening of the curve during 20 minutes has been defined as excess fluid volume being completely removed in the body when the patients reach dry weight.(Fig.14).

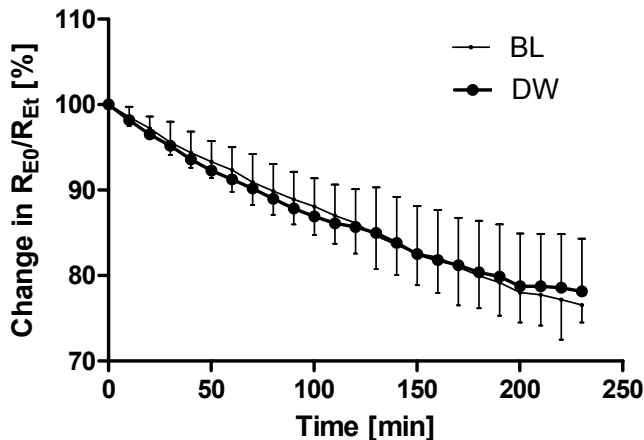


Fig. 14. Comparison of the curve of R_{E0}/R_{Et} in group patients between BL and DW (Modified from Int J Artif Organs 27:104-9, 2004).

Fig 14 shows change in curve of R_{E0}/R_{Et} in a group of patients with different hydration states. However, this method has a problem if the patients with deep vein thrombosis of the calf can stop or reduce the fluid volume from leg back to main circulation and this problem will cause less change in the curve R_{E0}/R_{Et} during HD treatment. In this case, R_{E0}/R_{Et} curve cannot indicate hydration change in the body.

4.4 Combination of static and dynamic method

Principle of the method using R_{E0}/R_{Et} curve and normalized resistivity is shown in Fig.15. The slope of change in resistance represents the removal of excess fluid volume in the calf. The flattening of the resistance curve means that the fluid exchange between intravascular and interstitial compartments has reached an equilibrium state. We hypothesize that DW has been reached if the curve is flattening and the normalized resistivity is in the normal range (Fig. 15). Approaching normalized resistivity value in the calf provides a secondary indication of DW. The system used is a refinement of the Xitron Hydra multifrequency device which measures both extracellular resistance and resistivity (Zhu *et al.*, 2008a). The algorithm used to determine normal hydration state employs two criteria together: a) flattening of the change in resistance (R_{E0}/R_{Et}) curve; and b) normalized resistivity in the range derived from healthy subjects.

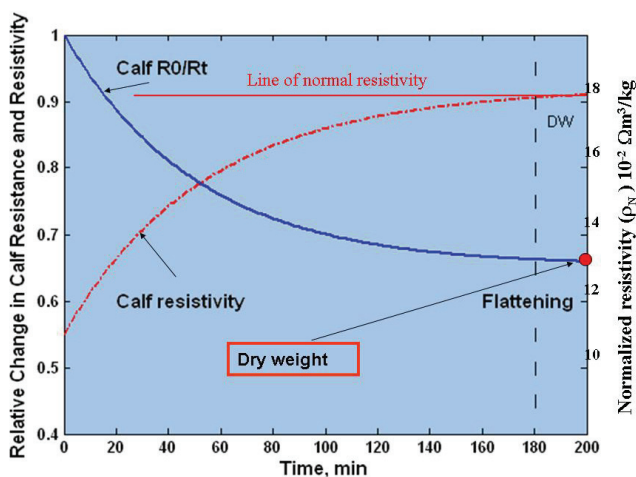


Fig. 15. Determination of dry weight with calf bioimpedance spectroscopy (cBIS)

4.4.1 Definition of flattening of the curve

R_{E0} and R_{Et} represent ECV at different times with change in ECV during whole HD. Since the curve may be affected by a movement of the patient's body during HD, the noise might influence the measurement of R_E . To reduce these interferences, a dynamic filter has been developed to reduce the error.

4.4.2 Continuous curve of the slope of R_{E0}/R_{Et} within specific time

The ratio of $R_{E,i}/R_{E,i+1}$ is collected from any two successive series of data, where subscript i ($i=1, 2, 3, \dots, N$) represent i th value of measurement from a series of N data. The R_E at the start of HD is considered to be the reference of the initial hydration status (R_{E0}).

We have defined that the curve of continuous measurement of the λ is flattening as

$$\delta(\Delta t) < C_1 \quad (13)$$

where $\Delta t = t_m$ represents the time interval between t - t_m minutes which can be present in more general form as follows:

$$\Delta t = t_i - t_{i+m}, \quad (14)$$

where i represents the number of i -th measurement and $i = 0, 1, 2, \dots, N-m$, N is the total number of measurements; m represents the number of measurements and t_m represents the time at m measurements. The flattening of the curve can be defined by Eq.13. At any specific time (t_{i+m}), when the $\delta(\Delta t) < 0.01$ the curve during this 20 minutes is considered as flattening.

4.4.3 Continuous measurement of resistivity

To continuously measure calf resistivity, calf circumference must be measured because at the same time the cross-sectional area is reducing during the treatment. The major issue of continuously calculate resistivity is how to measure the calf circumference during HD. The calf cross sectional area during HD can be calculated based on an assumption that change in circumference during dialysis is due to decrease in the fluid volume of the calf. Therefore, the value of circumference can be calculated by Eq.15

$$\chi_t = \sqrt{\chi_0^2 - \frac{4\pi\rho_0 L}{R_{E,0}} \left(1 - \frac{R_{E,0}}{R_{E,t}}\right)} \quad (15)$$

where χ_0 and $R_{E,0}$ are measured at the start of dialysis. The ρ_0 is a resistivity with constant value which is experimentally calibrated by actual measurements of circumference, L is 10 cm, R_{E0} and R_{Et} are resistance measured by the bioimpedance device at the initial time and by continuous measurement until the end of the treatment. With Eq.15, circumference can be accurately calculated (Zhu *et al.*, 2006b).

4.4.4 Continuous calculation of resistivity change

With Eq.5 to Eq.15, calf resistivity during HD treatment can be calculated in Eq.17.

$$\rho_t = \frac{\chi_t^2 \cdot R_{s,t}}{4\pi L} \Omega \cdot \text{cm} \quad (16)$$

To compare the resistivity and reduce the variation, normalized resistivity is defined as

$$\rho_N = \frac{\rho_t}{BMI} \times 10^{-2} \Omega \cdot \text{m}^3/\text{kg} \quad (17)$$

where BMI is body mass index defined as body weight (Wt) divided by body height (H) squared. Since we know the range of normalized resistivity in NS, the patient's normal hydration level can be obtained by comparing the minimal level of normalized resistivity, which is given by

$$\rho_{N,P} \geq \rho_{N,H} \quad \Omega \cdot \text{m}^3/\text{kg} \quad (18)$$

where $\rho_{N,P}$ represent the patient's value for normalized resistivity and $\rho_{N,H}$ represents a minimal level of normalized resistivity in healthy subjects ($18.3 \cdot 10^{-2} \Omega\text{m}^3/\text{kg}$ for male and $20 \cdot 10^{-2} \Omega\text{m}^3/\text{kg}$ for female respectively) from previous study.

4.4.5 Continuous calculation of body weight

Body weight (W_t) during HD treatment can also be continuously calculated by

$$W_t = W_{Pre} - \sum_i UFR_i \times \Delta t_i - W_V \quad (19)$$

where W_{Pre} is pre HD weight, UFR is ultrafiltration rate, Δt is the treatment time at i -th period of time with constant UFR ($UFR > 0$), W_V is any possible change in weight including use of intravenous or oral fluids. Final, dry weight (DW_t) can be calculated in a general and continuous form as follows.

$$DW_t = W_{Pre} - \int_{t_0}^{t_{DW}} UFR(t) \cdot dt - W_V \quad (20)$$

where $UFR(t)$ is a function of UFR with the time in case UFR is not constant. To obtain a numeric result it is assumed that the initial constant is zero. when the patient reaches dry weight, dry weight can be calculated by pre HD body weight minus ultrafiltration volumes during subsequent treatments (Zhu *et al.*, 2008a).

5. Summary

This chapter presents clinical issues and current new techniques to estimate fluid overload in dialysis patients. During the last decades, many technologies have substantially improved; these advanced tools provide the possibility to understand physiological mechanisms to control and adjust body fluid status in dialysis patients. Body fluid status can be explained with respect to terms such as dry weight, normal hydration and fluid overload.

Fluid overload can be specifically defined as extracellular fluid volume in dialysis patients greater than level of the normal ECV range. However, normal range of ECV must be clearly expressed and it must be a measurable value. Hydration is not the same as fluid overload. In chemistry, hydration is defined as a ratio of water to total mixed components of the system. In the body, hydration can be defined as the ratio of water to the mass of other body components. Since the water or ECV in healthy population is a range, normal hydration should be defined as a range and it is determined by 1) absolute ECV range; 2) total body mass and its components. The main challenge is to find the relationship between ECV and body mass components in a healthy population. The concept of dry weight in dialysis patient is defined as the patient having no excess fluid volume at post dialysis weight. However, body weight consists of different components, such as fat and muscle with variability of fluid content so that if body composition changes, the body hydration does not proportionally follow this change. The main question in the determination of dry weight is how to quantitate the degree of fluid overload.

Methodologies of measuring fluid overload can be generally divided into three techniques: static, dynamic and combination of both methods. With static methods, fluid status is measured in the intravascular compartment such as IVCD, peptides such as ANP, BNP and in both the intravascular and extravascular fluid compartment with methods such as such as

the BIA vector, WBM and calf resistivity. With dynamic method, currently, two methods are reported: RBV monitor measures changes in plasma volume only while continuous measurement of calf R_{E0}/R_{Et} provides information about change in plasma and interstitial fluid volume.

BIA phase angle bioimpedance at 50 kHz technique provides multi information about state of hydration and nutrition but it cannot produce quantitative value of fluid overload for individual. Whole body (Wrist to ankle) bioimpedance spectroscopy techniques have been largely improved to measure fluid volume, however, this method has the inherent problem of body composition influencing measurement of resistance so that its accuracy for measuring fluid overload cannot be further improved. Calf normalized resistivity provides a simple way to measure degree of fluid overload. Other measurements, such as biochemical or IVCD methods, cannot indicate the hydration of extravascular space directly so that they are not reliable in detecting degree of fluid overload. RBV measurement displays change in plasma volume but it cannot provide direct information about fluid overload in interstitial compartment. A general relationship exists between change in blood volume and refilling volume but this complicated by the effect of other factors on refilling such as autonomic tone, vascular tone, splanchnic vasoconstriction and temperature. Calf continuous measurement of R_{E0}/R_{Et} monitors the ECV changes including plasma and interstitial fluid volume. The main advantage of this method is that it does not require a control parameter to estimate fluid overload. However, calf R_{E0}/R_{Et} curve could be affected by lower limb venous thromboses. The combination of calf R_{E0}/R_{Et} curve and normalized resistivity can provide the best information concerning dry weight estimation the individual patient but this method may take a long time because post dialysis weight has to be reduced gradually over a long period of time if the patient is greatly fluid overloaded.

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