Review

The emerging role of biomarkers and bio-impedance in evaluating hydration status in patients with acute heart failure

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Abstract

The quantitative and qualitative estimation of total body fluid content has proven to be crucial for both diagnosis and prognosis assessment in patients with heart failure. The aim of this review is to summarize the current techniques for assessing body hydration status as well as the principal biomarkers associated with acute heart failure (AHF). Although clinical history, physical examination and classical imaging techniques (e.g., standard radiography and echocardiography) still represent the cornerstones, novel and promising tools, such as biomarkers and bio-electrical impedance are achieving an emerging role in clinical practice for the assessment of total body fluid content. In the acute setting, the leading advantages of these innovative methods over device are represented by the much lower invasiveness and the reasonable costs, coupled with an easier and faster application. This article is mainly focused on AHF patients, not only because the overall prevalence of this disease is dramatically increasing worldwide, but also because it is well-known that their fluid overload has a remarkable diagnostic and prognostic significance. It is thereby conceivable that the bio-electrical vector analysis (BIVA) coupled with laboratory biomarkers might achieve much success in AHF patient management in the future, especially for assisting diagnosis, risk stratification, and therapeutic decision-making.

Keywords: acute heart failure; bio-impedance; biomarkers; hydration status; total body water.

Introduction

The total body water (TBW) in the healthy population is estimated to be approximately 60% of the body weight, and is supposed to change during life because it is influenced by age, amount of fat tissues as well as hormonal homeostasis. Although there is a continuous shift of body fluids throughout the cells, they are operatively divided into two compartments, intracellular and extracellular. The intracellular fluid is defined as the water contained within the cell membranes and represents nearly two-thirds of TBW. The remaining one-third is the extracellular compartment that is further divided into interstitial fluid and intravascular fluid (1) (Figure 1). The TBW is constantly adjusted by some important homeostatic mechanisms including the balance between water intake and water loss through renal and gastrointestinal output, breathing and sweating (2). The estimation of TBW content is important in the prognostic assessment of critically ill patients and should be considered a vital parameter coupled with blood pressure, heart and respiratory rates, oxygen saturation and temperature.

The accurate and fast assessment of total fluid balance in critical patients, along with a standard and reliable means for its evaluation, has always been challenging for physicians working in the acute care setting. The current gold standard (i.e., isotope dilution) is not used in everyday clinical practice and is even more difficult to apply when an emergency clinical decision is required (3). Several approaches have been used to estimate the hydration status of patients, including history and physical examination, laboratory testing and imaging techniques (3). The clinical experience has provided unquestionable evidence that fluid overload reflects the worsening of clinical conditions in a variety of severe disorders, such as heart failure (HF), chronic kidney diseases (CKD), and liver cirrhosis (4). Moreover, the invasive catheterization of heart and great vessels only reflects the circulating volume of total fluid content and not the TBW.
In this important scenario, several studies have investigated and have further confirmed the emerging role of biomarkers, such as natriuretic peptides (NPs) (5), assisted by bio-impedance vector analysis (BIVA) in the management of congestion due to increased TBW content in the setting of chronic heart failure (CHF) or acute heart failure (AHF) patients (6, 7).

The aim of this review is thereby to provide some insights on the currently used non-invasive methods for hydration assessment and to describe the appealing results obtained with the various bio-electrical impedance methods coupled with some laboratory parameters in AHF patients, since they represent the most common and evident example of hyperhydration status among critical diseases (7).

**Classical methods**

In this section, we aim to examine the classic, non-invasive techniques and biomarkers for hydration assessment in patients primarily affected by AHF.

**History assessment**

The patient’s history at presentation has been proven useful in the assessment of hydration status in a variety of clinical scenarios. The presence of orthopnea and paroxysmal nocturnal dyspnea (PND) are two hallmark symptoms associated with the diagnosis of fluid overload secondary to AHF. When evaluated more closely in a study of 52 patients with established left ventricular dysfunction, Butman et al. (8) showed that only 50% presented with orthopnea and 35% with PND. In a meta-analysis of over 22 studies on the diagnosis of CHF performed by Wang et al. (9) it was shown that the pooled sensitivities and specificities of common symptoms between the studies yielded only modest values for the diagnosis or exclusion of HF. The presence of PND or orthopnea in the history yielded sensitivities of 41% and 50%, respectively, while providing more useful specificities of 84% and 77%, respectively. These data suggest that when used as criteria for the diagnosis of body fluid congestion secondary to AHF, classic elements of the history may be unable to provide meaningful information to the physician.

**The physical examination**

The physical examination provides important information on the clinical status of the patients. Several studies have assessed the efficacy of the physical exam in diagnosis of volume overload, using decompensated HF as a positive control for the disease. Elevations in jugular venous pressure (JVP) and rales have been proven to be inconsistent diagnostic tests for HF, displaying sensitivities between 37% and 70%, and 24% and 66%, respectively, yet may still provide useful information regarding the severity of disease (8–11). In patients with congestive HF studied in the RESOLVD trial, peripheral edema (Figure 1) was present in 21% of patients with AHF and in only 10% of patients who were free of events (12). This suggests that clinically evident peripheral edema is only present in a minority of patients that have decompensated, and thereby does not sufficiently reflect the hydration status of the patient. Other studies have assessed the presence of a third heart sound (S3) as an informative finding in the diagnosis of acutely decompensated HF. Unfortunately, the presence of an S3 also fails to adequately support a diagnosis of HF.
and fluid overload, with prevalence between 36% and 55% in decompensated patients (9–12). Overall, the reliability of the physical exam in detecting volume overload is questionable (9, 13). Stevenson et al. (14) showed that the evaluation of all volume overload characteristics by means of the presence of a positive physical exam (including evidence of JVD, rales and/or edema) had a rather limited sensitivity (i.e., 58%) in patients with diagnosed HF and volume overload (PCWP >22 mm Hg).

**Standard radiography**

Chest radiography is also frequently used to identify the presence of volume overload in the acutely ill patient (Figure 1). Gao et al. (15) recently showed that chest radiography can be a useful tool for identifying elevated intravascular volumes in peritoneal dialysis patients before treatment, by using the cardiothoracic ratio and the vascular pedicle width. However, chest radiography lacks accuracy in the diagnosis of decompensated HF. In a study analyzing hospitalization rates in 86,376 HF patients from the Acute Decompensated Heart Failure Registry (ADHERE), it was found that the frequency of patient admission with a negative chest radiograph was greater than that of patients with a positive chest radiography, 23.3% vs. 13.0% (16). Although radiography is performed on many patients presenting to the ED with decompensated HF, it is still unclear whether the test would provide correct and appropriate diagnostic information. An important chest radiography parameter is, however, the vascular pedicle width, since its evaluation shows a statistically significant difference (p<0.0004) in AHF patients as compared with healthy controls (6).

**Echocardiography**

The European Society of Cardiology (ESC) (17) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (18) clearly state that echocardiography represents “the single most useful diagnostic test in the evaluation of patients with HF”. Echocardiography is a non-invasive surrogate which can provide hemodynamic data, such as stroke volume and cardiac output. The estimation of pulmonary artery pressure requires the presence of tricuspid valve regurgitation for mean and diastolic pressure determination of vascular fluid content in patients with AHF, but cannot provide reliable information on TBW content.

**Thoracic ultrasound**

Thoracic ultrasound (TUS) is a relatively new imaging technique used for identifying interstitial and/or alveolar edema in volume overloaded patients, especially those with CHF (Figure 1). TUS depends on the identification of sonographic artifact called “B-lines” or lung comets. These findings were first described in 1997 by Lichtenstein and colleagues (21). Liteplo et al. (22) found similar results in a study of 100 patients in the Emergency Thoracic Ultrasound in the Differentiation of the Etiology of Shortness of Breath Study (ETUSES), where it was shown that a positive TUS displayed a likelihood ratio for the diagnosis of CHF of 3.88 (99% CI 1.55–9.73), whereas a negative TUS had a negative likelihood ratio of 0.5 (99% CI 0.30–0.82). These results suggest that TUS alone is effective for diagnosing volume overload secondary to CHF in patients presenting to the ED with shortness of breath.

**Isotopic tracers of water – the gold standard for TBW measurement**

Isotopic tracers of water represent the “gold standard” for TBW measurement (23, 24). These radioisotope assays utilize structural similarity between radioisotopes (D₂O, H₂O, H₂¹⁸O) and water to estimate the TBW after sufficient time for balance. After equilibration, samples are collected and radioisotopes are measured by mass spectrometry. TBW estimation can then be accurately performed based on the atom percentage of the radioisotope compared with water in the sample (25). Although the test is very effective for assessing the fluid volume in a patient with abnormal homeostasis, it...
is unfortunately impractical given the time (often more than 6 h) required for equilibration (26, 27). Therefore, accurate, and even more importantly, practical measures of hydration status are still necessary for the evaluation of patients in a timely manner.

Laboratory biomarkers

The Biomarkers Definitions Working Group of the National Institute of Health (NIH) has reliably defined a biological marker, better known as “biomarker”, as a “...characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (28). According to this definition, biomarkers are now used in a kaleidoscope of clinical conditions in the ED, including diagnosis (29) and prognostic assessment (30) of acute myocardial infarction, diagnosis of acute renal injury (31), acute pancreatitis (32), pre-eclampsia (33), stroke (34), CHF assessment (35) and AHF (Table 1).

Serum blood indices are commonly used for assessment of hydration status abnormalities in AHF patients. Changes in serum sodium concentrations and their associations with diseases including abnormal fluid homeostasis are accurate tools for assessing hydration status. Decreased serum osmolality is a common finding in patients with CHF. In these patients, the heart becomes unable to pump blood forward effectively, thus leading to activation of neurohormonal mechanisms that result in increased serum renin activity and downstream aldosterone secretion (36). The resultant effect is that these patients develop hyponatremia secondary to unequal and pathologic retention of water compared to salt. Hyponatremia can also be used as a metric for disease status. A study of 66 chronic CHF patients with hyponatremia showed that those with neurohormonal hyperactivation required more diuretic (i.e., furosemide) than those without the electrolyte abnormality in order to recompensate (37). Severe hyponatremia is also associated with worse prognosis in HF patients, and this parameter is currently included in the guidelines as an indicator of high mortality outcome for these patients (38).

Changes in hematocrit may also be effective measures of hydration status, especially elevations with decreased blood volume. Although postural variations can affect the hematocrit value, changes in hematocrit are expected in the context of net water gain or loss (39). However, mild to moderate decreases in the water volume are not easily detected by blood indices (40).

Uric acid levels (>9.8 mg/dL (>585 μmol/L) have been associated with a worse outcome in HF patients. Hyperuricemia reflects increased activity of the xanthine oxidase pathway that causes oxidative stress and impair nitric oxide (NO) production, thus worsening cardiovascular condition (41).

The accuracy of brain natriuretic peptide (BNP) in the diagnosis, monitoring, and prognostic stratification of AHF has been unquestionably established in a variety of international trials (42, 43). BNP is the active hormone, composed of 32 amino acids, while N-Terminal pro-brain natriuretic peptide (NT-Pro BNP) is the inactive form, composed of 76 amino acids. They are both produced by the heart in response to volume and pressure overload, and their increase is proportional to systolic and diastolic dysfunction. In patients with acute dyspnea the cut-off value for BNP (1-32) are traditionally established at <100 pg/mL (NT-Pro BNP <400 pg/mL) to rule out HF, and >400 pg/mL (NT-Pro BNP>2000 pg/mL) to confirm HF. Values between 100 and 400 pg/mL (between 400 and 2000 pg/mL for NT-Pro BNP) are considered in the so-called “grey zone”, and require further scrutiny (42). Limitations in using these NPs emerge in certain conditions including renal dysfunction, obesity and atrial fibrillation. Pro-B-type natriuretic peptide 1-108 (proBNP 1-108) is the 108-amino acid prohormone that is cleaved to the 32-amino acids, biologically active brain natriuretic peptide (BNP 1-32), also known as B-type natriuretic peptide, and to the 76-amino acids, biologically inactive N-terminal pro-B-type natriuretic peptide (NTProBNP1-76). Recently, it has been shown that ProBNP (1-108) circulates in the majority of healthy humans in the general population and is a sensitive and specific biomarker for the detection of systolic dysfunction. The proBNP (1-108) to NT-proBNP (1-76) ratio may provide insights into altered proBNP (1-108) processing during HF progression, providing important new insights into the biology of the BNP system (44, 45).

The application of NPs in everyday practice carries, however, undisputed advantages for improving the clinical management of patients with AHF; in that they are useful aids for stratifying the risk in the ED, predicting death and rehospitalization, and guiding therapy (46, 47).

The role of mid-region pro-atrial natriuretic peptide (MR-proANP) has also been investigated. In the diagnosis of AHF a cut-off of 120 pmol/L has been proven to be as accurate as BNP (1-32) (negligible accuracy difference of 0.9%). MR-proANP is considered particularly useful not only in obese and intermediate BNP (1-32) levels patients (48) but also in patients with impaired renal function as compared with BNP (1-32) and NT-ProBNP (1-76) (49).

Recently, in addition to NPs, other interesting and promising biomarkers have proven useful in the management of AHF; and a multimarker panel approach has been suggested to detect different causes of acute dyspnea (50).

Latest results from the biomarkers in acute heart failure (BACH) trial support the role of several innovative biomarkers, such as procalcitonin (PCT). PCT has been investigated for the diagnosis of pneumonia in patients with AHF. Elevated PCT (>0.21 ng/mL) is associated with a worse outcome when antibiotic therapy is not established (p=0.046), while a low PCT value (i.e., <0.05 ng/mL) is associated with a better outcome if not treated with antibiotics (p=0.049) (51).

Another interesting result from the 15-center BACH trial defines the mid-region pro-adrenomedullin (MR-proADM), the precursor of the hypotensive adrenomedullin, an accurate 14-day mortality predictor. This is also confirmed by the area under the curve (AUC) in receiver operating characteristics (ROC) curve of MR-proADM (0.742) which is higher than that of BNP (0.484) and NT-proBNP (0.586) (52). Another promising biomarker is copeptin, the C-terminal part of the vasopressin pro-hormone. It is an independent predictor for
short-term (30 days) mortality, especially in patients with AHF (p<0.0001). The prognostic value of copeptin (>54.2 pmol/L) has been evaluated alone and in association with NT-proBNP and BNP, and their AUC were 0.83, 0.76 and 0.63, respectively (53). Finally, a subanalysis of the BACH trial confirmed that MR-proADM and copeptin in combination have the best 14-day mortality prediction (AUC=0.818), compared with all other markers (52).

A new and still not adequately investigated biomarker is soluble ST2, which is involved in cardiac remodelling and overload (54). An increase in ST2 above 10 ng/mL is considered a predictor of mortality in patients with AHF (p<0.001) (55).

Due to the known, complex and multifaceted interplay between heart and kidneys, AHF is often complicated by acute kidney injury (AKI) in critical patients. This circumstance defines a high mortality condition, called cardiorenal syndrome (56). Classically, an increase of serum creatinine (>150 µmol/L) (16) is used to define renal injury, but it is only marginally associated with the outcome (AUC of 0.57) (57). Neutrophil gelatinase-associated lipocalin (NGAL) is a new biomarker that might help risk stratification in AHF patients. Although not absolutely specific for AKI (it is also produced and released by neutrophils) (58), it is still an early marker of AKI. A discharge value of NGAL >100 ng/mL, combined with BNP values or even measured alone, has been proven to be a powerful predictor of 30-day adverse outcomes (57). Finally, a preliminary study has shown that increased plasma levels of asymmetric dimethylarginine (ADMA) are strong and independent predictor of short- and long-term mortality in AHF patients (NYHA Class III/IV) with reduced EF (59).

### Bio-impedance analysis (BIA)

Bio-electrical impedance is the term used to describe the response of a living organism to an externally applied electric current by surface electrodes. It measures the opposition to the flow of electric current throughout the tissues. Electric current is administered by surface electrodes that need high current (800 mA) and high voltage to decrease the instability related to cutaneous impedance (10,000 ohm²/cm²) (60). This impedance value, termed electrical impedance (Z), consists of two components, resistance (R) and reactance (Xc). In terms of impedance, the human body can be schematically considered as a system composed of several different conductors in parallel, each of which opposes the passage of an alternating current, which passes through two pathways: extracellular tissue and intracellular membranes. Since extracellular (ECW) and intracellular water (ICW) compartments contain ions, they are electrically conductive. Thus, estimations of fluid volume can be based on their impedance to electrical flow as cell membranes may act as capacitors. The resistivity of ECW ionic composition is close to that of saline, but the ICW ionic composition depends on the type of cell and, as a result, resistivity cannot be measured directly. For technical reasons,
impedance meters using surface electrodes are limited to a frequency range of 5–1000 kHz, and the ECW and the TBW resistance must be calculated by extrapolation as proposed by the Cole-Cole model (61).

In bio-impedance analysis (BIA) the angular component of the polar coordinate representation, called the phase angle (PA), is assessed. The principle of measurement is based upon the fact that the condensers in the alternating current circuit lead to a time delay Δt: the current maximum is in advance of the voltage maximum. PA represents the measurement of this time delay between the periodic signals of current and voltage, which vary sinusoidally at the same frequency. It is calculated from resistance and reactance according to the formula: PA=arc-tangent reactance/resistance×180°/π. The PA might be an indicator of cell membrane integrity as well as distribution of ICW and ECW, and it can also be used to assess total cell mass (62). Cox multivariate models have also been used to establish that PA may be considered a significant and independent predictor of mortality in patients with liver cirrhosis (p<0.01) (63).

However, it is important to consider that impedance measurements are rooted in an approximation of the human body as a sum of five interconnected cylinders (limbs and trunk). This approximation is calculated from the length and diameters of the limbs and the trunk through a dimensionless shape factor (Kb) in the resistance–volume relationship for a single cylinder. A value of 4.3 for Kb has been established from statistical anatomical measurements in adults (64). It is also noteworthy that there are several factors impacting BIA including height, weight, position of the body and limbs, intense physical activity before BIA measurements, infection, dermatological conditions, ambient temperature and non-adherence of electrodes (65–68).

In 1871, Thomasset et al. (69) performed the initial study assessing the electrical properties of tissues to measure impedance using two frequencies of 1 kHz and 100 kHz through two subcutaneously inserted needles. Using the Cole-Cole model, he could then estimate the ECW and TBW values. Since then, tetra-polar BIA has been widely investigated in medical epidemiologic studies (75). Of squares (PRESS) statistics, showed the utility of WBIA in assessing the correlation between BIA, weight and deuterium-dilution space. In 1990, BIS was introduced by Xitron as a new method to measure both ECW and ICW volumes using Hanai’s mixture conductivity theory for concentrated disperse systems in evaluating dielectric dispersion due to interfacial polarization (72, 73).

The BIS device, which is able to assess TBW and differentiate between ECW and ICW (TBW–ICW), uses low and high frequencies of 5 kHz–2 MHz and extrapolates resistance values of extracellular and intracellular fluids, respectively, with the Cole-Cole model. From these resistance values, extra- and intra-cellular resistivities are derived with the Hanai model. There is now consolidated evidence that the whole-body technique, as compared with reference methods, can lead to inaccurate assessment of body composition in some circumstances. In 54 patients with end stage renal disease, TBW measurements derived by deuterium dilution and WBIA showed no significant difference (mean difference=–1.221 L, p=0.12) between the two methods in estimating fluid status. Unfortunately, WBIA lacked consistency across all patient populations and significantly overestimated fluid status in obese patients (mean=–6.789 L, p=0.001) (74). In 2003, Sun et al. developed a gender-specific, age- and race-combined equation with the use of a multi-component model including densitometry, isotope dilution and dual-X-ray absorptiometry (DXA). A sample of 1829 patients aged from 12 to 94 years old were studied and their body composition was assessed by SF-WBIA. The final equation, validated by prediction of sum of squares (PRESS) statistics, showed the utility of WBIA in epidemiologic studies (75).

**Single-frequency whole-body BIA (SF-WBIA) and bio-electrical impedance spectroscopy (BIS)**

The whole-body BIA (WBIA) uses four surface electrodes, two placed on the wrist and two on the ankle, at the distal metacarpals and metatarsals, respectively, with the subject supine. A low-level alternating current is administered at either single (50 kHz) or multiple frequencies (e.g., 1, 5, 50, 200, 500 and 2000 kHz), and then whole-body Z, R and Xc are measured. These variables are adjusted for height and then combined with various physical and demographic variables (body weight, age, gender, etc), into regression models to predict volume status.

In 1983, Nyboer et al. (70) used the four-surface electrode WBIA technique, initially presented by Hoffer in 1969, to assess body composition in 144 subjects. A significant correlation was observed between body fat mass (r=0.860), TBW (r=0.947) and lean body weight (r=0.934) with the whole-body impedance and the hydrostatic weighing, which is another method for measuring the body mass density. It is based on Archimedes’ principle and is performed during forced exhalation with residual lung volume (70). By 1986, the WBIA was accurately described and validated by Kushner (71), for assessing TBW by BIA and deuterium-isotope dilution in 58 subjects. He found a significant correlation (r=0.99) between BIA, weight and deuterium-dilution space.

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**Segmental BIA (SBIA)**

Segmental BIA (SBIA) has been developed as a practical alternative to WBIA. It is a four-electrode bio-impedance device with contact (tactile) electrodes that measure impedance in the upper (arm-to-arm) or the lower (leg-to-leg) body of a standing subject (76–79). The main assumptions of this measurement technique are that conductor volume is equally distributed in the upper and lower body, segmental impedance values are proportional to whole-body impedance and whole-body resistance can be derived by the sum of segmental resistances (80, 81). Interestingly, the segmental impedance technique may be used for personal monitoring of body composition because it does not require the presence of an operator. Another type of segmental bio-electrical impedance
uses eight electrodes, four of which are placed in the handles of the machine (in contact with the thumbs and palms) and the other four in the foot scale pads, in contact with the balls of feet and heels. These machines operate at either single or multiple frequencies while the subject stands. A recent study on 112 AHF patients used a segmental multi-frequency bio-electrical analysis to estimate the 6-month prognostic value of pre-discharge edema index, a derived surrogate for hydration status, and established that an edema index >0.390 (i.e., the cut-off value) represents a significant HF-related predictor of re-hospitalization (p=0.04) (82).

**WBIA vs. SBIA**

The clinical application of segmental BIA was assessed for determining fluid accumulation in 30 patients undergoing abdominal surgery. ECW distribution changes (ΔECW) were monitored preoperatively (before the induction of anesthesia) and postoperatively (after recovery from anesthesia). The ΔECW was estimated by the multi-frequency whole-body device and as a sum of five body segments. The most significant resistance decrease was found in the trunk where the fluid composition contributes minimally to the whole body resistance. It was thus concluded that segmental multi-frequency bio-electrical impedance analysis provides ΔECW assessment better then the whole-body technique in patients with non-homogeneous fluid distribution (83). Although BIA cannot be considered as an individual reference tool, newer studies have warranted its broader application in combination with other techniques.

**Bio-electrical impedance vector analysis (BIVA)**

BIVA can be considered an integrated component of BIA measurement, and is a simple and quick method for assessing fluid status and body cell mass (84). It can also be used as a quality control measure for correct analysis of BIA results (85).

BIVA is a non-invasive technique to estimate body composition by bio-electrical impedance measurements, R, Xc and Z (86, 87). All biological structures have a specific resistance, defined as the strength of opposition by a tissue to the electric current flow (7). Fat-free tissues and fluids are good conductors because they offer a low resistance to the electric current flow, while bone and fat tissues are bad conductors because they are electrically resistant. Therefore, the resistance is inversely related with the TBW, thus representing an indirect measure of the amount of body fluid. The measured reactance is dependent upon the presence of inductors and/or electrolytic capacitors. Since all cell membranes act like a small capacitor, reactance can be considered as an indirect measure of cell membrane activity and integrity, and is proportional to body mass (66, 88).

The BIVA technique was developed at the University of Padua (Italy) (7). The machine uses an alternating current flux of 800 μA and an operating frequency of 50 kHz. The results are visualized in two ways, as a vector or as a BIVA-derived hydration percentage. The first method includes a direct impedance plot which measures R and Xc, as a bi-variate vector in a nomogram (85). Reference values adjusted for age, body mass index (BMI), and gender are plotted as so-called tolerance ellipses in the same coordinate system. Three tolerance ellipses are distinguished, corresponding to the 50th, 75th and 95th vector percentile of the healthy reference population (86). The major axis of this ellipse indexes hydration status and the minor axis reflects tissue mass. The second method involves a scale called the Hydrograph (or Hydrogram), which expresses the state of hydration as a percentage. This value is calculated by an independently determined equation that uses the two components of BIVA, R and Xc. A normal value is 73.3% with tolerance between 72.7% and 74.3%, corresponding to the 50th percentile (7) (Figure 1).

Regarding interpretation of values, the length of Z vector is inversely related to fluid volume, whereas the PA offers insight into the relative distribution of fluids. A fundamental outcome of several studies is the delineation of the 75% tolerance ellipse as the indicator of the boundary of normal tissue hydration. Vectors outside the upper pole of the 75% ellipse indicate dehydration, whereas others outside the 75% confidence ellipse of the lower pole are characteristic of fluid overload or overhydration. Thus, short vectors with a smaller PA are associated with edema, whereas longer ones with an increased PA indicate dehydration (86, 89, 90). Moreover, vectors above or below the minor axis (meaning upper-left or lower right half of ellipses) are associated with more or less cell mass in soft tissue, respectively, with extremes along the minor axis. As previously discussed, the normal BIVA-derived hydration values for the hydrograph are comprised between 72.7% and 74.3%, values above or below such relative thresholds indicate a state of hyperhydration (wet) and dehydration (dry) (91). These two classes can be further subdivided into mild, moderate or severe volume abnormalities (92).

The BIVA technique is very handy and can be used at the bedside, with the patient supine with inferior limbs at 45° and superior limbs abducted at 30° to avoid skin contacts with the trunk (66). Four skin electrodes are applied, two on the wrist and two on the ipsilateral ankle. A minimal inter-electrode distance of 5 cm has been recommended to prevent interaction between electrodes. The subject is laid recumbent on a non-conductive surface. Free fluid in thorax and abdomen (lung congestion, pleural effusion, ascites, urine, food) does not affect the impedance values measured by this technique (6).

Despite being relatively new, BIVA is becoming recognized as a superior method for TBW content assessment (93). Clinical studies have been carried out in hospitalized patients with severe renal diseases to assess the utility of BIVA in assessing volume status. Studies involving uremic patients, compared to healthy controls, showed significantly shorter vectors with smaller PAs. As discussed above, shorter vectors (low impedance) are associated with hyperhydration. These vectors then lengthened after dialysis, showing the ability of BIVA to detect significant changes of fluid status after
dialysis. Changes in the volume of fluid removed significantly correlated with changes in vector components ($p<0.001$ in men, $p=0.03$ in women). Vectors of unstable (e.g., adverse outcomes) compared to stable hemodialysis patients were significantly different. It was also found that vectors of unstable patients were longer with smaller PAs, and these differences persisted after hemodialysis (89). Similar findings were found in patients treated with peritoneal dialysis, before and after fluid removal (86).

New application fields are emerging in critical care. In intensive care unit patients, the central venous pressure (CVP) was correlated with impedance measured by BIVA. CVP values are significantly and inversely correlated with individual impedance vector components ($r^2=0.28$ and 0.27 with resistance and reactance, respectively), and with both vector components together ($r^2=0.31$). Specifically, CVP values $>12$ mm Hg were associated with shorter impedance vectors (outside the lower pole of the 75% reference ellipse) in 93% of patients, thus indicating fluid overload. Conversely, CVP values $<3$ mm Hg were associated with long impedance vectors (outside the upper pole of the 75% reference ellipse) in only 10% of patients, indicating tissue dehydration. The progressive increase of CVP values was associated with shorter and down-sloping impedance vectors on the R-Xc graph (94).

The role of BIVA coupled with TUS has shown its effectiveness in discriminating cardiac and non-cardiac acute dyspnea patients presenting in ED ($69\%$ sensitivity, $79\%$ specificity) (95).

**Future directions in managing AHF patients using biomarkers plus BIVA**

The BIVA evaluation is an appealing perspective when applied in patients in the acute setting with congestive HF because of specific fluid overload. A study by Di Somma et al. (6), shows that BIVA data in decompensated AHF patients at admission to the ED are statistically different as compared with controls ($p<0.0007$). AHF patients had a significantly higher value of hydration status ($77\pm4$) as compared with controls ($73\pm2$). Sequential BIVA measurements in AHF patients showed reduction of congestion due to diuretic treatment. A significant correlation with events (death or re-hospitalization) at 3 months was also observed in patients with average hydration values $>80\%$. It was also demonstrated that combined use of BIVA and BNP may improve the management of AHF patients in ED when compared to BNP alone, thus allowing a faster and much more accurate triage. BIVA helped distinguish cardiogenic dyspnea from non-cardiogenic causes and – in combination with BNP – was also useful for management of AHF patients, since both measures were helpful to guide emergency physician’s decisions about diuretic therapy (e.g., preventing overuse).

Valle et al. (91) found that the combination of BNP and BIVA measurements could prevent unnecessary aggressive diuretic therapy, thereby reducing the level of renal complications. BIVA-BNP guided management during hospitalization for HF was associated with lower events after discharge, independent of other prognostic variables (91).

The evaluation of total body fluid has a great utility also in patients with cardiorenal syndrome, and its use in combination with other parameters (e.g., in a multimarker approach) has been proposed as a new model of management of ED patients with cardiorenal syndrome (96).

According to the large number of studies available in the scientific literature, the role of impedance is becoming more and more predominant for the assessment of hydration status. Characteristics, such as quick and simple use, non-invasiveness and low cost would make this device appealing and potentially useful in a kaleidoscope of medical fields. BIVA seems to be more accurate and more reliable when compared with other impedance techniques (Figure 1). Further trials with larger patient populations are obviously needed to express a definitive consensus on the clinical effectiveness of BIVA, as well as for identifying those clinical settings where it can be more advantageous.

The use of BIVA in guiding the treatment of various disease states has not been adequately studied. It would be interesting to standardize BIVA employment in AHF patients, in combination with biomarkers, to guide a proper and correct diuretic therapy. Preliminary data from studies that have monitored the variations of BIVA values in volume overloaded patients has already shown its utility in guiding diuretic treatment, but more clinical evidence is necessary to create BIVA/diuretic guidelines. Another promising application is related to the emerging role of ultrafiltration in unloading CHF patients that do not benefit from diuretic therapy. Regular use of BIVA plus NPs might assist physicians to decide the amount of water to remove, thus avoiding harmful consequences. Due to its quick and easy use, BIVA should also be tested for its efficacy in primary care setting as a means for monitoring congested patients. This application could help primary care physicians in the management of these patients, since exacerbations may be detected sooner, avoiding severe worsening that may require hospitalization.

BIVA alone is probably not the definitive answer to all challenging questions about hydration status, but it seems to be a useful and promising device for everyday use, especially when coupled with biomarker measurement, because it is accurate, non-invasive, cheap and easy to use in combination with other techniques.

**Conflict of interest statement**

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

**References**


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