Use of Bioimpedance Vector Analysis in Critically Ill and Cardiorenal Patients

W. Frank Peacock, IV

Department of Emergency Medicine, The Cleveland Clinic, Cleveland, Ohio, USA

Abstract
Prospective outcome prediction and volume status assessment are difficult tasks in the acute care environment. Rapidly available, non-invasive, bioimpedance vector analysis (BIVA) may offer objective measures to improve clinical decision-making and predict outcomes. Performed by the placement of bipolar electrodes at the wrist and ankle, data is graphically displayed such that short-term morality risk and volume status can be accurately quantified. BIVA is able to provide indices of general cellular health, which has significant prognostic implications, as well as total body volume. Knowledge of these parameters can provide insight as to the short-term prognosis, as well as the presenting volume status.

Accurate volume assessment is necessary for optimal clinical decision-making as mortality is increased when inappropriate therapy is administered to critical patients. Not only is accurate volume assessment necessary, speed is important as delayed therapy is also associated with increased mortality. Unfortunately, volume assessment is challenging. And because the history and physical examination can be inaccurate, there is a significant need for an objective measure. Few testing modalities satisfy the requirement for both accuracy and speed. The chest x-ray is insensitive for volume overload, B-type natriuretic peptide (BNP) is inaccurate in critically ill patients, and the volume assessment gold standard (radioisotopic measurement) is neither rapid nor inexpensive. Bioimpedance vector analysis (BIVA) may fulfill the requirements of an inexpensive, rapid, and accurate tool for evaluating critically ill patients.
Bioimpedance

Determination of hemodynamic status has historically required the insertion of a catheter directly into the heart. Because of the significant morbidity and mortality associated with this invasive procedure, non-invasive techniques are now promoted as an acceptable alternative [1]. One of the more researched non-invasive measurements is impedance cardiography (ICG).

First published in 1826, Ohm's law [2] states that the flow of electrical current (I) is equal to the voltage drop (E) between two ends of a circuit divided by the impedance (Z) to current flow, represented as $E = IZ$. If the current remains constant, then changes in voltage across the circuit are equal to changes in the impedance to current flow. Furthermore, if $Z$ is dependent upon the cross-sectional area ($A$), length ($L$), and resistivity ($\rho$) of the conducting material, then its changes can be related to changes in volume ($V$) of the conductor by $Z = \rho(L^2/V)$. These suppositions are the fundamental principle that supports the fact that impedance changes over time are proportional to the volume of moving fluid and are related to cardiac output.

Using ICG to evaluate hemodynamics is based on the concept that the human thorax is an inhomogeneous electrical conductor [3, 4]. When a high-frequency current is injected across the thorax, impedance can be measured by electrode pairs located at the edge of the chest. Measurements of the average thoracic impedance reflect the static volume of all the combined thoracic compartments. Dynamic voltage changes that result from volumetric and velocity changes occurring within the aorta during cardiac systole are then proportional to cardiac output. By integrating these changes with ECG-derived timing measures, hemodynamic parameters are approximated. The accuracy of the cardiac output measurements obtained with ICG has been compared to invasive measures acquired by thermodilution. A recent meta-analysis of over 200 studies found a correlation of 0.81 for ICG determined stroke volume and cardiac output, when compared to traditional measurements. Besides being non-invasive, the major advantage of ICG technology is that it can also be utilized for continuous monitoring and trend identification.

Limitations to obtaining accurate impedance measures include: (1) erroneous electrode position, e.g. operator error or physiologic complications such as central lines or cutaneous alterations; (2) poor skin-electrode interface, e.g. diaphoresis, excessive hair; (3) uncooperative patient, e.g. dementia, psychiatric disease; (4) contact with an electrical ground (e.g. metal bed frame) or electrical interference, and (5) abnormal body habitus, e.g. severe obesity.

Bioimpedance Vector Analysis

A newer assessment technique is BIVA. BIVA combines bioimpedance with capacitance measures (the time required to charge a circuit). Whole-body
impedance may be considered a combination of resistance, $R$ (the opposition to flow of an alternating current through intra- and extracellular electrolytic solutions), and reactance, $X_c$ (the capacitance produced by tissue interfaces and cell membranes). The arc tangent of $X_c/R$ is termed the phase angle, and represents the phase difference between voltage and current, determined by the reactive component of $R$. In conductors without cells (e.g. saline), no capacitance exists and thus $X_c$ cannot be measured. By including $X_c$, the accuracy of volume assessment is improved over conventional bioimpedance measurements.

Standardized by height ($H$), BIVA results can be displayed graphically, comparing $R/H$ to $X_c/H$, and generates output that simultaneously reflects hydration abnormalities and alterations of soft tissue mass (fig. 1). When obtained as a single measure, BIVA data can be compared to the normal population, represented on the graph by confidence ellipses, with data expected to fall within the reference 75% tolerance ellipse. When presented as a vector, shorter or longer lengths are associated with more or less hydration, respectively. The height of the vector (the arc tangent $X_c/R$), measured in degrees of elevation from the x-axis and termed the phase angle (PA), has been described as a prognostic tool in many clinical situations.

Although the biological meaning of the PA is not completely understood, it reflects not only body cell mass, but is one of the best indicators of cell membrane function. The PA indicates the distribution of water between the intra- and extracellular spaces, and corresponds to a low ratio of extra- to intracellular water [5, 6]. An upward or downward displacement of the PA

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1}
\caption{BIVA results displayed graphically comparing $R/H$ to $X_c/H$. BIVA patterns: major axis $\rightarrow$ tissue hydration, minor axis $\rightarrow$ soft tissue mass.}
\end{figure}
is associated with alterations in soft tissue mass. While there are some controversies about considering it as a nutritional marker, studies in burn victims and sickle cell disease corroborate its ability to evaluate cell membrane function.

Serial BIVA measures are also clinically useful. A shortening or lengthening of the vector over the confidence ellipses is indicative of increasing fluid overload (edema) or the occurrence of dehydration, respectively. Conversely, if the vector of the PA increases or decreases, it is representative of increasing or decreasing, respectively, cell mass.

When interpreting the PA, results must be considered in the context of sex and age. In a study of 1967 healthy aged 18–94-year-old adults, the PA was smaller in women (6.53 vs. 7.488) and decreased with increasing age (from 7.438 in the youngest to 5.888 in the oldest) [5]. In another study of 653 20- to 90-year-old volunteers [6], age was reported as the strongest predictor of PA in a stepwise multiple regression analysis (fig. 2).

Most importantly, PA is predictive of mortality, although the absolute cutpoints are variable when comparing studies due to a lack of standardization. In a study of HIV patients, a PA <5.38 was the most important survival predictor, with performance exceeding the CD4 count [7]. Another HIV study found an increase of the PA of only 1° represented a 29% increase in survival [8]. PA measures have also been found to be prognostic in cancer. In lung cancer, values <4.58 were associated with a 25% higher mortality (OR = 1.25) [9], and in other studies of advanced colorectal [10] and pancreatic cancer [11], a PA >5.58 was a strong predictor of survival.
PA measurement may also be prognostic of mortality in other conditions, including sepsis. In 30 patients meeting two or more SIRS criteria [12], an initial PA >4° was correlated with survival. This compared to all patients who died where the PA was <4° (p = 0.038). Finally, PA measurements may predict postsurgical outcomes. In 225 adult patients undergoing gastrointestinal surgery [13], nutritional status was assessed by several methods. They found that only the PA predicted postoperative complications (relative risk = 4.3 for a low PA).

BIVA is also useful for prediction of hydration status as the vector length is proportional to whole-body fluid volume [14, 15], has a correlation coefficient of 0.996, and a measurement error that ranges from 2 to 4%. BIVA has been validated in kidney [16], liver, and heart disease for the prediction of volume status [17–19]. In one study, using BIVA as a proxy for the adequacy of ultrafiltration in >3,000 hemodialysis patients, vector length indices corresponding to greater soft tissue hydration (less adequate ultrafiltration) were associated with a significant mortality increase [20]. In another study of 217 patients consisting of 86 healthy controls, 55 mild-to-terminal chronic renal failure in conservative treatment (15% with apparent edema), 36 idiopathic nephrotic proteinuria (58% with apparent edema), and 40 obese subjects, BIVA accurately identified edematous versus normovolemic populations [21] (fig. 3). Finally, in a population of 2,092 patients (1,116 hemodialysis, 726 healthy controls, 200 CAPD, and 50 nephrotic patients), total body water was estimated by anthropometry and BIVA measures [22]. They reported that while anthropometry measures were misleading, indicating the same hydration for edematous and non-edematous

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**Fig. 3.** BIVA accurately defines volume status. CS = Controls, CRF = chronic renal failure, NS = nephrotic syndrome, OS = obese subjects, H = height, Xc = reactance, R = resistance.
states, BIVA was very sensitive to fluid overload, indicating a 10% excess of fluid in volume overloaded patients. They also noted that BIVA vectors from patients with edema were displaced downward on the RXc graph, out of the 75% ellipse (88% sensitivity, 87% specificity) and similar to vectors from nephritic patients.

BIVA has also been evaluated in heart failure (HF). In a study of 22 HF patients, using deuterium dilution as a gold standard for total body water evaluation, BIVA demonstrated excellent correlation with total body water measures ($r = 0.93, p = 0.01$) [23]. In another analysis of 243 HF patients, BIVA measurements were an objective measure of New York Heart Association Class [24]. The authors concluded that BIVA allows an easier and more objective evaluation of body composition and might be particularly useful to stratify the severity of HF.

The use of BIVA to evaluate HF has also been examined in the context of existing myocardial stress measures. In a prospective study combining BIVA and BNP measurement in 292 dyspneic patients [25], 58.9% who had acute decompensated heart failure (ADHF) and the remainder were non-ADHF; ADHF patients showed significantly ($p < 0.001$) higher BNP values ($591.8 \pm 501$ vs. $69.5 \pm 42$ pg/ml). Regression analysis revealed that whole-body BIVA was a strong predictor of ADHF alone or in combination with BNP. In fact, the combination of BNP and BIVA measures resulted in the most accurate volume status determination (fig. 4). As both BNP and BIVA are available as ‘point of care’ testing, providing results within minutes of contact with the medical system, this strategy may have a role in the early evaluation of patients presenting with dyspnea of unknown etiology.

BIVA has also been used to assist in guiding acute HF therapy. In 186 hospitalized HF patients undergoing BNP-guided therapy [26], the definition of stability and eligibility for discharge included no orthopnea, stable hemodynamics, diuresis >1 liter daily, and improvement in body hydration status as defined by BIVA. They found that a discharge BNP <250 pg/ml predicted successful management and that BIVA was able to monitor diuretic therapy, assess changes in body fluids, and increase the usefulness of BNP as a guide to therapy. When these objective discharge criteria were validated in a separate study of 166 hospitalized HF patients and compared 149 patients discharged based on clinical acumen [27], the objective group had 12% fewer 6-month readmissions (23 vs. 35%, $p = 0.02$) and a lower overall cost of care (EUR 2,978 vs. 2,781, $p < 0.01$). This suggests that the combination of clinical acumen and objective measures improve outcomes over clinical impression alone.

BIVA can be utilized to evaluate volume status in patients undergoing hemodialysis. Piccoli [28] reported on 1,367 patients stratified as 726 healthy controls and 641 receiving weekly hemodialysis. Of the hemodialysis cohort, 251 were considered unstable due to symptomatic hypotension, or a systolic blood
pressure <90 mm Hg during >30% of dialysis sessions. BIVA was performed before and after dialysis. They found significantly shorter impedance vectors in either hemodialysis population compared to controls. Further, in both men and women, unstable hemodialysis patients had longer vectors (303 vs. 294 Ω/m

| Diagnostic strategy | Area under the ROC curve (standard error) | 95% CI  
|---------------------|------------------------------------------|--------
| BIA + BNP           | 0.989 (0.005)                            | 0.965–0.996 |
| BNP alone           | 0.970 (0.008)                            | 0.952–0.990 |
| Segmental Rz BIA Rz, Ω | 0.963 (0.012)                               | 0.965–0.982 |
| Whole-body BIA Rz, Ω | 0.934 (0.016)                               | 0.902–0.961 |
| Left ventricular ejection fraction | 0.814 (0.027)                              | 0.764–0.857 |
| Framingham score    | 0.681 (0.031)                            | 0.625–0.734 |

**Fig. 4.** Receiver operator characteristic curve (ROC) for HF diagnosis using various parameters [25].
and 373 vs. 355 Ω/m, respectively) and smaller PAs (4.5 vs. 5.1 and 4.2 vs. 4.7, respectively) compared to the stable hemodialysis cohort. After dialysis, the vector displacement caused by fluid removal was shorter and less steep in the unstable patients, as compared to the stable cohort, despite having similar volumes removed.

Outcomes associated with BIVA measures in hemodialysis have also been studied. Pillon et al. [20] reported on 3,009 patients with BIVA measured before each three times weekly dialysis session. They found vector length was longer in women than men (mean 340 vs. 270 Ω/m), African-Americans, and non-diabetics, and the relative risk of death associated with each 100 Ω/m vector length increase was 0.75 (95% CI 0.57–0.88). Defining 300–350 Ω/m as the normal vector length, the relative risks of death were 1.54 (95% CI 1.08–2.21) and 2.83 (95% CI 1.55–5.14) for vector lengths of 200–250 and <200 Ω/m, respectively. They concluded that shorter predialysis bioimpedance vectors, indicating greater soft tissue hydration, were associated with diminished survival in hemodialysis patients and validated clinical observations linking longevity to maintenance of dry body weight. They suggested BIVA may be used to evaluate the adequacy of ultrafiltration in hemodialysis.

BIVA is not without limitations that should be considered in the interpretation of its results. Because total body resistance is calculated with BIVA, accurate body position is required (limb abduction with arms separated from trunk by about 30° and legs separated by about 45°). Another limitation of BIVA is its failure to distinguish compartmentalized edema such as pericardial, pleural, or abdominal effusion [29]. Lastly, BIVA is standardized for Western Europeans and normal values for African heritage patients are not yet established [30].

Alternatively, BIVA does offer advantages over simple bioimpedance measurements as it requires measurement on only one side of the body. Thus, where bioimpedance may be limited in patients with unilateral abnormalities, BIVA can simply be measured on the contralateral side. Finally, BIVA does not demonstrate the same sensitivity to errors in accurate electrode placement location as occurs with bioimpedance.

**Conclusion**

BIVA is a simple, rapid, reproducible, non-invasive, and objective tool to better understand prognosis and hemodynamic status such that optimized evaluation and treatment may occur.
References


