

Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations

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Purpose of review

The bioelectrical impedance analysis is not a direct method for estimating body composition. Its accuracy depends on regression equations, and recent papers have suggested that this approach should not be used in several clinical situations. Another option is to obtain information about the electrical properties of tissues by using raw bioelectrical impedance measurements, resistance and reactance. They can be expressed as a ratio (phase angle) or as a plot (bioelectrical impedance vector analysis). This review describes their use in clinical practice.

Recent findings

The phase angle changes with sex and age. It is described as a prognostic tool in many clinical situations. 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. Bioelectrical impedance vector analysis allows a semi-quantitative estimation of body composition from information from tissue hydration and soft-tissue mass in a plot. It can be used in healthy individuals or patients, for a population or individual evaluation of fluid imbalance or an assessment of soft-tissue mass. It has also been used as a prognostic tool in dialysis and cancer patients.

Summary

The phase angle can be considered a global marker of health, and future studies are needed to prove its utility in intervention studies. Bioelectrical impedance vector analysis has increased its utility in clinical practice, even when the equations may be inaccurate for body composition analysis.

Keywords

bioelectrical impedance analysis, bioelectrical impedance vector analysis, phase angle, prognostic factors

Abbreviations

BCM	body cell mass
BIA	bioelectrical impedance analysis
BIVA	bioelectrical impedance vector analysis
BMI	body mass index
ECW	extracellular water
PA	phase angle
SGA	subjective global assessment
SPA	standardized phase angle

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Introduction

Bioelectrical impedance analysis (BIA) became popular in the past decade because of its practical advantages of being a non-invasive, safe, inexpensive and portable method for assessing body composition. Since 1990, more than 1600 papers have been published using this methodology [1^{••}].

BIA is not a direct method for body composition assessment. Several prediction equations have been derived using linear regression, in order to estimate body composition from BIA measurements of tissue impedance and reactance. Body composition reference methods, such as dual-energy X-ray absorptiometry, have been used to provide the dependent variable for regression models [2]. Thorough accounts of the BIA methodology have been presented in recent reviews [3^{••},4^{••}].

Some basic assumptions have been made in the process of the development of these prediction equations, and must be respected in order to guarantee their accuracy: the shape of the body (considered as five connected cylinders), the relationship between trunk and leg lengths, the level of hydration (as lean body mass hydration is considered 73%) and the fat fraction. Because these characteristics may vary according to age, ethnic group, body shape, or clinical conditions, it is impossible to have one 'universal equation' that works for everyone; all the equations are situation and population specific [4^{••}]. It is thus necessary to choose from several validated equations for different age, ethnic group and clinical situations the one that is most similar to the population being studied.

Even choosing an adequate population-specific equation, it must be considered that the prediction error of BIA is caused by five errors: the lack in standardized

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methodology for measurements; the regression error (standard error from the equation); the limitation of the reference method used in validation; the different body geometry (not a cylinder); and the biological variability of patients [5[•]]. The range of actual error of 0.0–1.8 kg considered ideal in regression equations could be considered unacceptable for individual interpretations in the clinical setting. BIA precision also limits the longitudinal follow-up of weight gain or loss, because the changes in body compartments cannot be detected if they are less than 1.5–2.0 kg [6]. BIA can be considered an option for body composition analysis only in healthy individuals or patients with no fluid imbalance or body shape abnormalities, with a body mass index (BMI) between 16 and 34 kg/m² and using an appropriate equation (age, sex and ethnic group specific) [1^{••}].

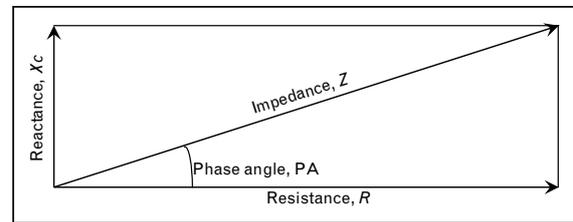
In clinical practice, it is very common to find situations in which the ‘BIA rules’ are broken; our patients are usually out of the BMI range (16–34 kg/m²), have fluid and electrolyte imbalances, and body shape abnormalities, such as oedema in the extremities or ascites. In this population, even when multifrequency or segmental techniques are used, the limits of agreement with reference methods are inadequate for clinical application, requiring further validation [1^{••},3^{••}].

Information about tissue hydration and integrity through the electrical properties of tissues can be obtained from raw BIA measurements, resistance and reactance using two indicators. One is the phase angle (PA) and the other is a plot of the impedance vector against a known distribution (bioelectrical impedance vector analysis; BIVA). The great advantage of this approach is that it is independent of regression equations or weight, and it can be carried out even in situations in which BIA assumptions are not valid to estimate body composition and body fluid compartments. The objective of this review is to discuss the value of PA and BIVA in clinical practice.

Phase angle: what is it?

The overall opposition that a body presents to an alternative electric current (bioelectric impedance) has two components. The first is resistance (R), the restriction to the flow of an electrical current through the body, primarily related to the amount of water present in the tissues. The second is capacitive reactance (X_c), resistive effect produced by the tissue interfaces and cell membranes. Part of the electric current is stored by the cell membranes, which act as capacitors, creating a phase shift, quantified geometrically as PA. The bioelectric impedance (Z) is the result of the two vectors representing R and X_c , as shown in Fig. 1, where it can be seen that the PA is the angle between Z and R . Therefore, the PA depends both on the capacitive behaviour of the tissues

Figure 1. Graphical representation of impedance and phase angle



Their values can be calculated as $Z = \sqrt{X_c^2 + R^2}$ and phase angle (PA) = $\text{arc-tangent}(X_c/R) \times 180^\circ/\pi$.

(associated with tissue cellularity and cell size, i.e. body cell mass; BCM), and their pure resistive behaviour (primarily related to tissue hydration) and membrane permeability [7,8]. The higher the reactance, the larger the PA will be for a given resistance.

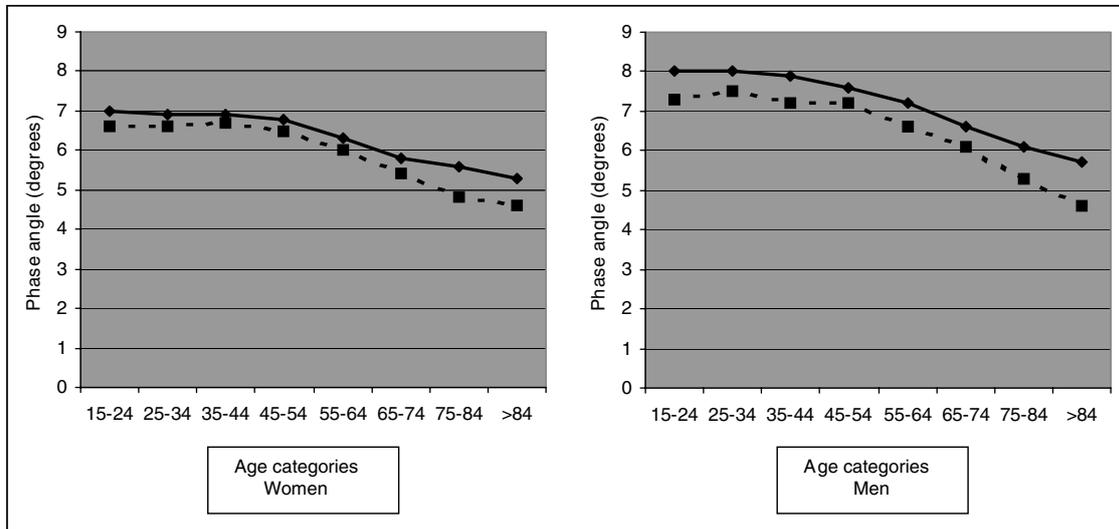
Although the biological meaning of PA is not completely understood, it reflects not only BCM, but is also one of the best indicators of cell membrane function, related to the ratio between extracellular water (ECW) and intracellular water [9,10[•]]. PA and resistance were also considered to be significant predictors of the basal metabolic rate in severely obese patients, after adjusting for weight [11].

Effects of age and sex on phase angle in healthy individuals

Once PA is representative of BCM and the function of cell membrane, some changes are expected to occur in its values as a result of sex and ageing. In a study of 1967 American healthy individuals, aged 18–94 years, PA was smaller in women (6.53 versus 7.48[°]) and decreased with age (from 7.43[°] in the younger to 5.88[°] in the older group) [12]. The same results were found in Swiss populations [13] (Fig. 2). The absence of difference found by Selberg and Selberg [7] could be explained by a small sample and consequently a lack of power. Dittmar [10[•]] reported age as the strongest predictor of PA in a stepwise multiple regression analysis, in a sample of 653 German volunteers, aged 20–90 years. Interestingly, physical activity was positively correlated with PA, even after adjustment for age effects, suggesting that physical inactivity could be one of the reasons for a smaller PA in older individuals.

Another PA presentation is in biagram vector, which is derived from the graphical plotting of capacitive reactance and PA. Savino *et al.* [14[•]] studied 174 infants under one year, plotting the biagram vector for groups from each 4 months of life. There was an increasing trend from the younger to the older group, explained by the variation of

Figure 2. Reference values for phase angle in American (solid lines) [12] and Swiss [13] population (dotted lines) by sex and age categories



body composition that occurs during the first year of life, detected by this method.

In conclusion, PA differs between the sexes and decreases with ageing, like other biological parameters. Its positive association with physical activity suggests that it might assess function and not only the evaluation of body composition.

Phase angle in clinical practice

In the past decade, several papers have investigated the role of PA as a prognostic, nutritional, membrane cell function or health marker in various disease conditions.

One of the first articles showed that PA decreased in septic patients who died, whereas survivors showed an increase in its values [15]. In HIV-infected patients, a PA value of less than 5.3° was considered to be the most important single predictor of survival (representing the lowest quartile), with a better performance than the CD4 cell count and other clinical parameters [16]. The reduction in PA does not seem to be a consequence of body cell mass loss only, because it remained low even after highly active antiretroviral treatment, leading to an improvement in the wasting syndrome in HIV patients [17]. That study showed that an increase of 1° in PA could represent a 29% increase in the survival rate.

Toso *et al.* [18] showed that PA values lower than 4.5° were significantly associated with a 25% higher mortality (odds ratio 1.25) in lung cancer patients. In patients with advanced colorectal and pancreatic cancer, Gupta *et al.*

[19,20] showed PA to be a strong predictor of survival, using PA values of 5.57° and 5° as a cut-off, respectively.

Different cut-off values were used in all the studies that showed PA to be a prognostic factor. The cut-off values were defined in each study as the median or lower quartile of PA in the study sample or compared with values from a control sample. This occurs because there is a lack of reference values for the PA healthy population. Because PA changes with age and sex, samples with a different sex and age distribution should not be compared. One way to make such values comparable is to standardize them, as is commonly done with the nutritional status, and transform them into a Z-score. The standardized phase angle (SPA) can be obtained from the expression $SPA = (PA - \text{mean})/s.d.$, where the mean is the age and sex-specific mean and s.d. is the age and sex-specific standard deviation of the healthy population. In a study of prognostic factors in surgical patients, Barbosa-Silva and Barros (unpublished data) used this approach, creating SPA from the American reference values and -0.8 as the SPA cut-off. Patients with an SPA of 0.8 or less increased four times the risk of postoperative complications in a multivariate analysis, whereas subjective global assessment (SGA) was not considered to be a prognostic factor after adjusting for SPA.

Kidney patients on dialysis or those with liver cirrhosis are adversely affected by malnutrition, but renal or hepatic disease processes might confound the commonly used nutritional parameters. Therefore, fluid retention may invalidate the use of BIA equations for estimating body composition. The moment of BIA evaluation is also

important, and it should be performed in a dry-weight state [21[•]]. Several papers have described PA as a useful prognostic tool in these populations. Maggiore *et al.* [22] were among the first authors to report that PA was superior to the usual nutritional parameters as a predictor of survival in haemodialysis patients, confirmed by Chertow *et al.* [23] and by Mushnick *et al.* [24[•]]. Fein *et al.* [25] reported similar findings with patients on peritoneal dialysis, whereas Selberg and Selberg [7] showed the same results in a liver cirrhosis sample. Pupim *et al.* [26[•]] tried to differentiate the influence of the inflammation status from the nutritional impact in survival in haemodialysis patients in a longitudinal study. They showed that levels of serum albumin, prealbumin, creatinine and PA predict all-cause mortality, even after controlling for inflammatory parameters, and low PA increased 20 times the risk of cardiovascular death in this sample. Such studies brought the idea that PA captures different dimensions of nutritional status, and this implies a stronger prognostic power.

One of the questions about PA is whether small values could be interpreted as malnutrition, defined as decreased BCM. As PA seems to be a good estimator of this body compartment, it could be used as a nutritional marker. The literature, however, is controversial about the relationship between PA and nutritional markers. Only a modest correlation ($r \leq 0.29$) was found between BIA parameters and biochemical nutritional markers, such as albumin, prealbumin, transferrin and cholesterol [22]. On the other hand, a stronger correlation ($r = 0.54$, $P < 0.001$) was found between PA, prealbumin and albumin [24[•]] and between PA and albumin ($r = 0.54$, $P < 0.01$) [25].

When PA and SGA were compared in preoperative patients, there was a strong positive association, with PA showing a linear trend among SGA categories. The smallest PA values were found in patients classified as severely malnourished through SGA (C grade), with a mean PA value of 4.7° in men and 4.22° in women [27[•]]. Edefonti *et al.* [28] suggested that a combination of anthropometric methods with BIA measurements, as a new nutritional score, could be more sensitive to assess the nutritional status in children on chronic peritoneal dialysis, because each method can reveal a different aspect of malnutrition.

Nagano *et al.* [29] presented a very interesting study comparing malnourished and healthy children. PA was significantly lower in malnourished children, and showed a good correlation with other anthropometric measures. All malnourished patients increased PA after the nutritional therapy, except one, who was receiving chemotherapy. When anorexic adolescent patients were submitted to a refeeding treatment, PA became similar to controls after 15 weeks of nutritional therapy, even though BMI

was still under the normal values [30]. Such studies suggested that PA could be a sensitive tool to evaluate the effectiveness of nutritional interventions.

It is also possible to use the PA values to compare the nutritional status in populations with different anthropometric characteristics. Most of the children from a study in northern Nigeria are stunted and underweight when compared against World Health Organization standards [31]. Nonetheless, their PA was not different from similarly aged healthy American children. The authors concluded that, despite anthropometric differences, African children have their function preserved, and somehow the differences might be explained by genetic patterns.

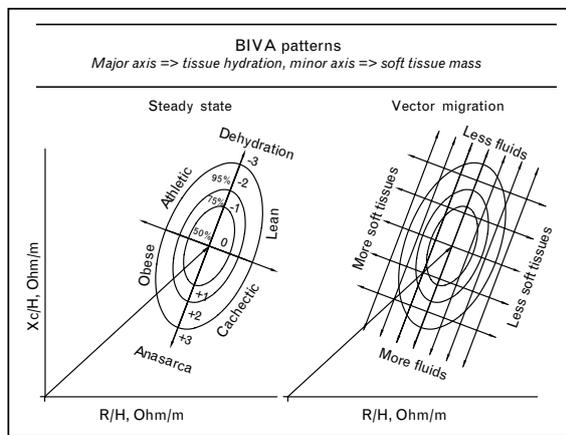
Shah *et al.* [32] studied the role of PA as a measure of disease severity in HIV-infected patients with tuberculosis co-infection. PA was significantly smaller when tuberculosis and HIV were present, and the smallest PA values were found in advanced HIV-infected patients, when the CD4 lymphocytes count was below 200 cells/ μ l. In another group of HIV-infected patients with tuberculosis co-infection, Van Lettow *et al.* [33[•]] showed that fat mass, BMI and PA were independent predictors of lung disease severity. De Luis *et al.* [34[•]] investigated which are the nutritional and biochemical parameters that could influence PA in HIV patients, and they found positive associations of PA with protein and somatomedin C levels. In a multivariate analysis, only somatomedin C, an anabolic hormone, had a significant positive association with the PA values.

In a study in burn victims, Zdosek *et al.* [35] proposed that PA was able to detect the effects of burn and sepsis in cellular membranes, because it significantly decreased in the post-burn period, with the lowest values being found in patients who died. VanderJagt and colleagues [36[•],37] also suggested that when the cell membrane functions are altered, as in sickle-cell disease, PA is smaller and correlates with the lipid composition of cell membranes.

In a longitudinal study, Johansen *et al.* [38^{••}] showed that PA and physical activity decreased significantly in haemodialysis patients, even with no changes in body composition or laboratory parameters, also suggesting a functional assessment by PA. Regional PA decreased in neuromuscular disease progression and increased after corticosteroid therapy in studies in neuromuscular diseases, suggesting that regional PA could have a potential usefulness as a new method to assess neuromuscular integrity and function [39[•]].

The idea of PA as a general indicator of health [8] is confirmed by the high correlation found between PA and other clinical co-morbidity indices [40[•]]. Studies in end-stage renal disease patients and renal transplant

Figure 3. Bioelectrical impedance vector analysis and RXc graph



A shortening or lengthening of the vector is associated with alterations in tissue hydration. An upward or downward displacement of the vector is associated with alterations in soft-tissue mass [2]. BIVA, Bioelectrical impedance vector analysis. The author has courteously given this figure.

recipients showed that they had increased ECW and lower PA when compared with the healthy population [41°,42°], independently of alterations in body compartments. In patients in early stages after kidney transplant, BIA results were able to differentiate bad transplants from borderline or good transplants, because the former group presented a smaller PA and an increased ECW [43°]. Overweight and obese haemodialysed patients also had smaller PA when compared with BMI-matched controls [44].

Such studies showed PA variability in several clinical conditions. In spite of a lack of standardized cut-off values, PA seems to play an important role as a morbidity and mortality marker, and lower PA stands for a general indicator of sickness. Future studies may also show its usefulness in monitoring nutritional interventions.

Bioelectrical impedance vector analysis

Piccoli and colleagues [2,45], in an analogy with electrocardiogram, proposed a new way to interpret the BIA information: the BIVA. Using this method, impedance (Z) is plotted as a bivariate vector from its components R (X axis) and Xc (Y axis), after being standardized by height (H) (Fig. 3). PA is still the arctangent of Xc/R (angle between Z vector and R axis) and the 95% confidence interval of the mean vector is plotted for a population group to allow statistical analysis. The plot uses R and Xc obtained at 50 kHz (standard single-frequency BIA), and multifrequency BIA does not provide any additional information for this method [5°].

A single individual measurement can be compared with confidence ellipses drawn from a healthy population, and

a normal individual impedance vector is expected to fall within the reference 75% tolerance ellipse [46,47]. Repeated measurements in the same individual can be evaluated by the vector displacements (vector migration in Fig. 3). A shortening or lengthening of the vector over the confidence ellipses means a fluid overload (oedema) or dehydration, respectively. If the vector increases or decreases its PA, it can be interpreted as more or less cell mass. By the combined analysis of PA with the length of the vector, it is possible to differentiate obese (short vector, high PA) from athletic individuals (long vector, high PA) in the left side of the RXc graph, and lean (long vector, low PA) from cachectic individuals (short vectors, low PA) in the right side of the graph. The great advantage of this method is that it allows information to be obtained simultaneously about changes in tissue hydration or soft-tissue mass, independent of any regression equation, or body weight. Further useful information derived from the BIVA measurement is that it could be a preliminary test for the use of regression equations; individual vectors outside the 75% tolerance interval of a reference ellipse may have unsatisfactory results from BIA equations [2].

Effects of age and sex in bioelectrical impedance vector analysis in a healthy population

Population subgroups with significantly different mean vectors have separate 95% confidence ellipses. In a large study with data from the NHANES III population, Piccoli *et al.* [46] showed that sex, race, BMI and age groups are determinant factors in vector distribution patterns in the American population. Mean vectors are longer in women and in BMI between 19 and 25 kg/m², suggesting less fluid (total body water) in these individuals. Race and age determines differences in the Xc/H component, expressed by a decreasing PA from non-Hispanic blacks to non-Hispanic whites and from younger to older individuals, suggesting less soft tissues (BCM). The same pattern of vector displacement was seen in Italian elderly [48°] and obese subjects [49].

BIVA also detected significant differences in mean vectors from groups of breast-fed and formula-fed infants, suggesting that they could present qualitative changes in body composition [50°]. Reference vector graphs for Italian children aged from 2 to 15 years showed that there is a progressive vector shortening as age increases, and with sex-specific vector differences by sex only over 14 years of age, suggesting that body composition differences caused by puberty could be detected by BIVA [51].

Several studies have recently demonstrated the utility of BIVA as a prognostic tool in haemodialysis patients [52°,53,54°], detecting fluid imbalances or helping to define the optimal hydration state in continuous ambulatory peritoneal dialysis patients [55°]. In lung cancer

patients, BIVA was able to identify modifications in body composition at different disease stages, presented as decreased capacitive reactance (smaller PA) [18,56**].

In conclusion, BIVA can give a semi-quantitative evaluation of body composition from BIA measurements, once it combines information from fluids and soft tissues. Part of its prognostic power is derived from PA, but the additional information about tissue hydration could increase its usefulness in clinical practice, mainly in situations of fluid imbalance, as in dialysis and cirrhosis patients.

Conclusion

BIA could represent an option of a portable method for body composition assessment in groups of healthy individuals, without fluid and electrolyte imbalances, body shape abnormalities and BMI between 16 and 34 kg/m². Even when an adequate population-specific equation is used, individual interpretation should be avoided because of unacceptable actual errors from the equations.

PA and BIVA, two indicators derived from resistance and reactance, can be used even in situations in which BIA assumptions are not valid, as cited above. In reviewing the recent data, although the biological meaning of PA is not clearly understood, it seems to be an indicator of cell membrane function. There is some evidence in the literature of the utility of PA as a morbidity and mortality marker in several clinical situations. Longitudinal studies are needed to show whether PA could monitor nutritional and therapeutic interventions. BIVA is a method of assessing body composition in a semiquantitative way and it allows information to be obtained simultaneously about changes in tissue hydration or the nutritional state, independent of any regression equation. This method allows individual or group comparisons, and it has shown its utility principally in situations in which fluid imbalances are present and BIA equations are not valid. It has also been useful as a prognostic tool in other clinical situations. These two approaches, PA and BIVA, make the BIA method useful in clinical situations in which BIA regression equations are not accurate to estimate body composition or fluid compartmentalization.

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- This paper shows that the variability of BIA measures depends on age, sex and body mass and it highlights the importance of physical activity in PA decrease over ageing.
- A study of PA variation in the first year of life.
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