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Low standardized phase angle predicts prolonged hospitalization in critically ill patients

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SUMMARY

Objective: Evaluate the performance of phase angle (PA) in identifying malnutrition and in predicting clinical outcomes in critical adult patients.
Methods: A longitudinal observational study with secondary data from Nossa Senhora da Conceição Hospital (Porto Alegre) and Risoleta Tolentino Neves Hospital (Belo Horizonte) involving critically ill patients assessed for nutritional status by subjective global assessment (SGA) and by anthropometry in the first 48 h after admission to the intensive care unit (ICU). The PA was evaluated from the realization of the bioelectrical impedance. Patients were followed up until hospital discharge to verify the other outcomes of interest: death, hospitalization time and in ICU, and duration of mechanical ventilation.
Results: A total of 169 patients (60.3 ± 16.7 years, 56.7% men, 46.7% surgical) were followed for 23.0 (14.0–40.8) days. The accuracy of standardized PA (SPA) reduced in identifying malnourished patients was 60.6% (ROC curve AUC = 0.606, 95% CI 0.519–0.694). Reduced SPA increased in about three times the chance of having malnutrition (OR = 2.79, 95% CI 1.39–5.61) and 2 times the chance of prolonged hospital stay (OR = 2.27; 95% CI 1.18–4.34) in an adjusted analysis for the origin hospital and for the severity score.
Conclusion: Reduced SPA showed satisfactory predictive validity for malnutrition and prolonged hospital stay in critically ill patients, reinforcing the applicability of BIA in the routine of nutritional care in ICU, since it is a simple, fast and low cost method.

1. Introduction

Bioelectrical impedance (BIA) is a simple, fast, easy and low cost method for nutritional assessment that indirectly estimates body composition through the passage of an electrical current of low amplitude (800 mA) and fixed (50 kHz) or multiple (1–500 kHz) frequency, through all the body, based on the total body resistance to its passage, measuring impedance, resistance (R), reactance (Xc) and phase angle (PA), in addition to total body water (TBW), intracellular water (ICW) and extracellular water (ECW) [1–3]. Due to the water retention commonly observed in the critically ill patient after volume replacement, the applicability of BIA to assess body composition is limited in these patients, since estimates of fat and muscle mass are influenced by their hydration status. However, recent studies have demonstrated the validity of some BIA parameters for the identification of nutritional status and clinical

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outcomes in these patients, among them the PA measurement is noted [4–10].

PA is obtained from the measurements of R and Xc (PA = tangent arc Xc/R), and it is a direct measure of cell stability, being interpreted as an indicator of cell membrane integrity and predictor of body cell mass (BCM) [2]. PA has been identified as a prognostic marker and predictor of survival in some clinical situations, such as pancreas, colorectal, breast and lung cancer, as well as in patients with acquired immunodeficiency syndrome, with cirrhosis, renal failure, bacteremia/sepsis and in surgical patients [9,11–15].

The performance of PA in identifying malnourished patients in the intensive care unit (ICU) and/or predicting worse clinical outcomes in critically ill patients has been explored by some studies in recent years. A study involving 66 critical patients identified higher PA values in patients classified as well nourished according to serum albumin values and showed an association between PA and mortality, with lower values of PA among non-survivors [4]. Correlation between PA and anthropometric indicators such as arm circumference (AC), triceps skinfold (TS) and calf circumference (CC) was demonstrated in a study involving 110 critical patients, in whom the PA was also inversely correlated with the hospitalization time [8]. In a recent cohort study low PA was identified as a predictor of low muscularity and lower survival in critically ill patients [7]. On the other hand, in another study, PA was a good prognostic indicator only in critical patients with sepsis, in which it presented a significant correlation with the APACHE II severity score [9].

Most of the studies [5,8] that evaluated the PA performance in identifying malnourished critically ill patients adopted methods for the diagnosis of malnutrition whose applicability in the ICU is questionable, such as anthropometry and plasma proteins [16]. Furthermore, in many of the studies [5,8,9] the predictive validity of PA is analyzed from the association with clinical outcomes in models not adjusted for confounders. Also, in many studies [5,8] it is unclear whether PA differed between men and women and/or between adults and the elderly, conditions in which standardized PA (SPA) calculation is recommended, which adjusts of AF for gender and age [17]. In view of these limitations, the present study aimed to evaluate the performance of PA in identifying critically ill malnourished patients with subjective global assessment (SGA) as a reference method - because it had satisfactory predictive validity in several studies performed with this population [18–20]. In addition, the association between PA and hospitalization time, length of ICU stay, duration of mechanical ventilation, and mortality was analyzed with adjustment for potential confounders.

2. Methods

2.1. Design

A prospective cohort study with secondary data from two projects developed at Nossa Senhora da Conceição Hospital (HNSC) in Porto Alegre (Rio Grande do Sul, Brazil) and Risoleta Tolentino Neves Hospital (HRTN) in Belo Horizonte (Minas Gerais, Brazil).

2.2. Sample

Critically ill patients hospitalized in the ICU of the two hospitals mentioned above, of both genders, aged ≥18 years. Patients with pacemakers, anasarca, pregnant women and patients with a BMI less than 16 kg/m^2 or greater than 35 kg/m^2, were excluded because they were contraindications for BIA. Also, those with limbs amputations or any other situation that prevented the placement of the electrodes were excluded, as well as them in palliative care or diagnosed with brain death.

The sample size calculation considered the difference in the PA among survivors (4.1 ± 1.3) and non-survivors (3.2 ± 1.5) found in the study conducted by Lee et al. [5]. Based on this difference, at a power of 90%, significance level of 5% and additional of 20% for adjustments in multivariate analysis, the estimated sample size was 125 patients. The sample size was calculated using the online OpenEpi calculator, available at http://www.openepi.com/SampleSize/SSMean.html

2.3. Logistics of the study

The project was approved by the Research Ethics Committee of the Hospital Conceição Group (number: 360.639) and the Federal University of Minas Gerais (number: 63688016.8.0000.5149) and data collections were done after signing the consent form by patients or their relatives and/or caregivers. The research protocol was conducted in accordance with the ethical assumptions of Brazilian Resolution 466/12 for researches involving humans.

The data collections were performed at the HNSC between June 2016 and March 2017, while in the HRTN they occurred between May and October 2017. General patient data (age, gender) and information related to hospitalization were obtained from the medical records. ICU admission reasons, length of stay in ICU and in hospital, use and duration of mechanical ventilation (MV), and the APACHE II (Acute Physiology and Chronic Health Assessment) severity score calculated on admission to the ICU were obtained.

The nutritional evaluation was performed within 48 h of ICU admission and the measurements of arm circumference (AC) and calf circumference (CC). The CB was measured at the midpoint between the acromion and the olecranon and the CC in the largest circumference, with inelastic tape measure. Weight and height was estimated as proposed by Chumlea et al. [21–23]. SGA was applied with the patient or his relative (when the patient was not able to respond to the detailed nutritional history) and the patient was classified according to nutritional status in well-nourished (SGA A), moderately malnourished or suspected of malnutrition (SGA B) or severely malnourished (SGA C) [24].

The BIA was performed with the fixed frequency device, Biodynamics® (model 310E) with the patient lying supine, with legs, hands and arms away from the body. Four adhesive and disposable electrodes were placed on the dorsal surface of the hand and right foot on dry and disinfected skin at predetermined anatomical sites. The resistance (R), reactance (Xc) and phase angle (PA) were measured [1,2]. PA calculated by the BIA was transformed into the standardized phase angle (SPA) from the SPA equation = [(measured PA − mean population reference PA)/standard deviation of the reference population]. The mean PA and the standard deviation according to the adopted gender and age were those proposed by Barbosa-Silva et al. for the population of the south of Brazil. Patients were classified as having reduced SPA values when found value was $<-1.65°$ and as having normal PA when found value was $\geq -1.65°$ (corresponding to Percentile 5) [17].

Outcomes of interest in the present study were: presence of malnutrition, hospital mortality, length of ICU and hospital stay (LHS), and duration of mechanical ventilation (MV).

2.4. Data analysis

Descriptive statistics were calculated for categorical variables (absolute and relative frequency) and quantitative variables (mean and standard deviation or median and interquartile range). The normality of the quantitative variables was evaluated by the Kolgomorov Smirnov test.

The correlation between PA and anthropometric indicators and outcomes of interest (LHS, length of ICU stay and duration of MV) was assessed by the Spearman correlation coefficient. Characteristics related to nutritional status and outcomes of interest were compared among patients with reduced SPA and normal SPA by Student's t-tests for independent samples (parametric quantitative variables), Mann–Whitney test (non-parametric quantitative variables), or Chi–Square test (categorical variables).

The performance of the SPA in predicting malnutrition was evaluated from the construction of the ROC curve, the area under the curve being calculated and its respective 95% confidence interval, sensitivity and specificity values, positive and negative predictive value, using SGA as method of reference.

The predictive validity of the SPA was assessed by logistic regression, adjusted for origin hospital and APACHE II severity score of disease, with length of stay in the ICU prolonged (cut-off point established from the median of six days) and LHS (cut-off point established from the median of 23.5 days) as dependent variables.

The analyzes were performed in the statistical package SPSS version 20.0, being considered significant values of $P < 0.05$.

3. Results

A total of 169 patients were evaluated, of whom 76 were admitted to the HNSC ICU and 93 were submitted to the HRTN ICU. The general characteristics and nutritional status of the total sample and the patients grouped according to the hospital of origin are presented in Table 1. HRTN patients presented higher severity score, longer ICU stay and longer duration of MV compared to HNSC patients, who presented longer LHS and greater frequency of malnutrition. The PA, SPA, AC and CC values did not differ among the patients of the two hospitals.

PA differed between males and females ($4.82 \pm 1.40°$ vs. $5.75 \pm 1.83°$, $p < 0.001$) and among adults and the elderly ($5.69 \pm 1.78°$ versus $5.12 \pm 1.72°$, $p = 0.045$); so SPA was considered for subsequent analyzes. Almost half of the patients presented reduced SPA (n = 79; 46.7%).

Table 2
Nutritional characteristics and clinical outcomes of critically ill patients according to the standardized phase angle classification.

Characteristic	Reduced SPA (n = 79)	Normal SPA (n = 90)	P
AC (cm)[a]	27.54 (4.62)	29.79 (3.69)	0.001[1]
CC (cm)[a]	32.32 (3.88)	33.51 (4.17)	0.065[1]
Subjective global assessment[c]			0.007[2]
SGA A	41.1%	62.5%	
SGA B	39.7%	29.5%	
SGA C	19.2%	8.0%	
LHS (days)[b]	31.0 (15.0–44.0)	20.0 (12.0–34.5)	0.032[3]
ICU stay (days)[b]	7.0 (4.0–13.0)	5.0 (3.0–10.0)	0.040[3]
MV duration (days)[b]	3.0 (1.0–8.25)	1.0 (1.0–5.0)	0.062[3]
APACHE II[b]	19.5 (12.0–28.0)	17.0 (10.8–26.3)	0.244[3]
Death[c]	45.3%	54.7%	0.471[2]

[1]Student's t-test. [2]Chi-Square Test. [3]Man-Whitney Test. Data presented in: [a]mean (standard deviation); [b]median (interquartile range); [c]relative frequency.
Abbreviations: SPA = standardized phase angle; AC = arm circumference; CC = calf circumference; SGA = subjective global assessment; LHS = length of hospital stay; ICU = intensive care unit; MV = mechanical ventilation; APACHE II = Acute Physiology and Chronic Health Assessment II.

The SPA showed a weak correlation with AC ($r = 0.300$, $p < 0.001$) and it was not correlated with CC ($r = 0.145$, $p = 0.066$). Table 2 shows the anthropometric parameters and the classification of the nutritional status of the patients according to the SPA classification. It was observed that patients with reduced SPA have significantly lower AC values compared to patients with normal SPA and that a higher proportion of patients with reduced SPA presents severe malnutrition.

The performance of reduced SPA in identifying patients malnourished by SGA was tested using the ROC curve, with AUC under the ROC curve equal to 0.606 (95% CI = 0.519–0.694, $p = 0.020$), with sensitivity equal to 56.6% and specificity equal to 64.7%. The positive and negative predictive values were 58.9% and 62.5%, respectively.

In a multiple logistic regression analysis, the dependent variable being the presence of malnutrition according to SGA, adjusted for origin hospital and APACHE II severity score, reduced SPA increased by about three times the chance of patients present malnutrition, as shown in Table 3.

Table 1
Characteristics of the sample according to the origin hospital.

	Total sample (n = 169)	HNSC (n = 76)	HRTN (n = 93)	P
Clinical features				
Age (years)[a]	60.27 (16.74)	60.98 (14.09)	59.43 (19.04)	0.561[1]
Male Gender[b]	56.8%	63.3%	51.1%	0.111[2]
ICU admission reason[b]				<0.001[2]
Surgical	46.7%	100%	3.3%	
Clinical	46.2%	0%	83.3%	
Trauma	7.1%	0%	13.3%	
LHS (days)[c]	23.0 (14.0–40.8)	30.0 (18.0–44.0)	19.0 (11.0–35.0)	0.003[3]
ICU stay (days)[c]	6.0 (3.0–11.0)	3.0 (2.0–6.0)	8.0 (5.0–15.0)	<0.001[3]
MV[b]	79.9%	97.5%	64.4%	<0.001[2]
MV duration (days)[c]	2.0 (1.0–6.5)	1.0 (1.0–1.0)	6.0 (3.0–11.5)	<0.001[3]
APACHE II[c]	19.3 (11.0–27.0)	11.0 (7.0–15.0)	26.0 (20.0–32.5)	<0.001[3]
Death[b]	23.8%	17.7%	29.2%	0.103[2]
Characteristics of nutritional status				
PA (degrees)[a]	5.34 (1.72)	5.43 (1.29)	5.27 (2.02)	0.548[1]
SPA (degrees)[c]	−1.51 (−2.78; −0.20)	−1.05 (−2.55; −0.20)	−1.74 (−3.05; −0.20)	0.274[3]
AC (cm)[a]	28.74 (4.29)	29.18 (3.44)	28.33 (4.93)	0.204[1]
CC (cm)[a]	32.95 (4.07)	33.23 (3.62)	32.71 (4.44)	0.417[1]
Subjective global assessment				0.002[2]
SGA A	52.8%	41.8%	63.4%	
SGA B	34.2%	36.7%	47.3%	
SGA C	13.0%	21.5%	4.9%	

[1]Student's t-test. [2]Chi-Square Test. [3]Man-Whitney Test. Data presented in: [a]mean (standard deviation); [b]relative frequency; [c]median (interquartile range).
Abbreviations: HNSC = Nossa Senhora da Conceição Hospital; HRTN = Risoleta Tolentino Neves Hospital; ICU = intensive care unit; LHS = Length of hospital stay; MV = mechanical ventilation; APACHE II = Acute Physiology and Chronic Health Assessment II; PA = phase angle; SPA = standardized phase angle; AC = arm circumference; CC = calf circumference; SGA = subjective global assessment.

The prognostic value of the SPA was evaluated from the correlation with the length of stay in the ICU ($r = -0.159$, $p = 0.039$), LHS ($r = -0.159$, $p = 0.040$) and MV duration ($r = -0.169$; $p = 0.048$), with a weak inverse correlation between PA and the three morbidity indicators. Patients with reduced SPA had LHS and length of stay in ICU significantly higher than patients with normal SPA, with no significant difference between groups in MV duration and in the APACHE II severity score. The incidence of death was not different in patients with reduced SPA compared to those with normal SPA (Table 2).

In multivariate analysis, with adjustment for severity score and origin hospital, reduced SPA increased the chance of prolonged hospitalization by 2.26 times (Table 3). After adjustment for potential confounders, reduced SPA was not associated with length of stay in ICU.

4. Discussion

The present study aimed to evaluate the performance of PA in predicting malnutrition and clinical outcomes in critically ill patients of two Brazilian public hospitals. Reduced SPA increased the chance of patients be diagnosed as malnourished and prolonged hospitalization, not associated with ICU length of stay, mortality, severity of disease or duration of MV.

In this study, patients with reduced SPA values were more likely to be malnourished compared to patients with normal SPA values, although the accuracy of reduced SPA in identifying malnourished patients was unsatisfactory (<75%). Adam Kuchnia et al. [7], in a multicenter study involving 71 critical patients, demonstrated that PA may be a useful parameter in assessing the nutritional impairment of these patients because reduced PA values are associated with lower values of muscle area evaluated by computed tomography. It is known that the critically ill patient has an important loss of muscle mass (−6 to −1.6%/day) and that changes in muscle structures are associated with longer ICU stay [25]. Lower PA values in malnourished patients were also demonstrated in an observational study involving 66 Korean critically ill patients [4]. It should be emphasized that in this study the nutritional status was evaluated through serum albumin concentrations, which is not an appropriate method for nutritional diagnosis in critically ill since its values will be influenced by the presence of inflammation [26]. In another observational study involving 110 critically ill patients, those with reduced PA values presented significantly lower AC, CC, triceps skinfold and arm muscle area compared to patients with normal values of PA, according to gender [8]. No other studies have been identified that have used SGA as a reference method to verify the concurrent validity of PA in the nutritional assessment of critically ill patients. In addition, it is believed that this is the first study involving critically ill patients that has evaluated SPA as an indicator of nutritional status. It should be remembered that the PA varies between men and women and according to age, being the use of SPA appropriate when differences in PA values are observed between the genders and among adults and the elderly [17], as occurred in the present study.

The predictive validity of PA in critically ill patients was assessed in the present study and reduced SPA increased the chance of patients having prolonged hospital stay (>23.5 days), not associated with ICU length of stay, mortality, disease severity, or duration of MV. A prospective cohort study performed at a surgical ICU in Korea with 241 patients showed a significant association between PA and mortality. In addition, in this study the performance of PA in predicting mortality was stronger than the severity scores (APACHE II, SOFA and SAPS III). However, the association between PA and mortality was not adjusted for any severity score and the authors did not describe the PA values according to gender and age group [5]. In another study involving 31 critical patients PA $\leq 3.8°$ presented sensitivity of 88.9% and specificity of 77.3% in predicting mortality [6]. A prospective study involving 931 critically ill patients showed a reduction in the risk of death equal to 14% for each increase of 1° in PA [10]. On the other hand, a study conducted by Reis et al., with 110 cardiac critical patients, did not show an association between PA and mortality, and PA cut-off points adopted for women were <4.6 and men <5.0 [8]. None of the studies cited evaluated SPA, and age and gender were considered confounders in the analysis of only a few of them [5,10].

The severity of the disease was assessed by the APACHE II score in the present study. No difference was observed in the values of this score when compared patients with reduced SPA to those with normal SPA. On the other hand, a study involving critical surgical patients demonstrated that PA was able to predict the severity of the disease evaluated by different scores, among them APACHE II (accuracy of 65.4%) [5]. In another study involving 95 critically ill patients the authors demonstrated a weak inverse significant correlation between APACHE II and PA ($r = -0.241$) and it was recognized as a prognostic marker only in those critically ill patients with sepsis. However, it is noted that the 95% CI of the AUC under the ROC curve calculated in this study varied between 36.4% and 72.7% [9], which makes the clinical applicability of this finding questionable. Although PA is an indicator of membrane integrity and predictor of body cell mass, its association with disease severity has not been confirmed in the present study and the available literature on this is scarce and of limited quality. Therefore, this aspect requires further research.

In the present study, reduced SPA increased the chance of prolonged hospitalization by about 2.3 times, considering the severity of the disease. The association between PA and LHS in critically ill patients has not been explored so far. We identified a study in the literature that demonstrated a significant inverse correlation between PA and LHS when evaluating 110 critically ill patients [8]. However, in this study only univariate analysis was performed. After adjustment for disease severity, in the present study, SPA was not a significant predictor of prolonged ICU stay. Our findings were similar to those evidenced by a recent observational study involving 299 critical patients, in which hospitalization time was higher in patients with reduced PA while the length of ICU stay did not differ between groups. In multivariate analysis PA was an independent predictor of prolonged hospitalization [27].

Table 3
Association between reduced SPA, malnutrition and clinical outcomes in critically ill patients: multivariate analysis.

Dependent variable	Reduced SPA Independent variable			
	Crude OR (CI 95%)	P	Adjusted OR (CI 95%)[1]	P
Malnutrition (SGA B + C)	2.333 (1.234–4.412)	0.009	2.793 (1.390–5.614)	0.004
Prolonged hospital stay (>23.5 days)	2.020 (1.090–3.746)	0.026	2.265 (1.182–4.343)	0.014
Longer ICU hospitalization (>6 days)	1.479 (0.804–2.721)	0.208	1.312 (0.653–2.638)	0.445

Multiple logistic regression. [1] adjusted for APACHE II and hospital of origin.
Abbreviations: SPA = standardized phase angle; OR = odds ratio; CI 95% = confidence interval; SGA = subjective global assessment; ICU = intensive care unit.

Combining data from two different hospitals increases the external validity of the findings of the present study. It is a heterogeneous sample of critically ill patients with a high disease severity score. In clinical and surgical ICUs, performing BIA within the first 24–48 h after patient admission may be useful for nutritional assessment and clinical prognosis, since prolonged hospitalization is associated with an increased risk of nosocomial infections. In the present study, the SPA was employed, since the PA values obtained in the BIA differed between men and women and among the participants over 60 years of age or older. It is suggested that this correction be used in clinical practice.

On the other hand, some limitations should be considered in the interpretation of the results: hospitals differed regarding LHS, length of stay in the ICU, MV duration, APACHE II and frequency of malnutrition, and the origin of the patients was a potential confounder. This possible bias was controlled in the multivariate analysis of the data, considering the hospital of origin as a variable for adjustment. The BIA was not performed with fasted patients and was not applied at different times; the use of diuretics was not discontinued. However, these behaviors are consistent with the reality of the ICU, where drugs cannot be suspended and patients receive infusions of the enteral diet for 20–24 h, and it is not possible to evaluate BIA with patients in fasting. In addition, a single BIA measurement was performed on patient admission to the ICU. Future studies that perform serial measures of the BIA to evaluate possible changes in PA are necessary to evaluate the applicability of this parameter in the nutritional monitoring of critically ill patients, which is a major challenge in the clinical practice of the ICU dietitian.

5. Conclusion

Reduced SPA increased the chance of malnutrition and prolonged hospital stay in critically ill patients, reinforcing the applicability of BIA in the routine of nutritional care in the ICU.

Statement of authorship

Silva FM designed the study. Gattermann T and Fink JS collected data at HNSC, while Rocha CDN, Saldanha MF and Moreira THS collected data at HRTN. Silva FM analyzed the data. Silva FM, Fink JS and Jansen AK wrote the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflict of interest statement

The authors have no conflict of interest to declare.

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