Nutrición Hospitalaria

Original

Phase angle as a nutritional evaluation tool in all stages of chronic liver disease

W. A. F. Peres[1], D. F. Lento[2], K. Baluz[3] and A. Ramalho[4]

[1]Department of Nutrition and Dietetics. Josué de Castro Institute of Nutrition. Federal University of Rio de Janeiro. Rio de Janeiro. Brazil. [2]Josué de Castro Institute of Nutrition. Federal University of Rio de Janeiro. Rio de Janeiro. Brazil. [3]Department of Clinical Nutrition. National Cancer Institute. Rio de Janeiro. Brazil. [4]Department of Social Nutrition. Josué de Castro Institute of Nutrition. Federal University of Rio de Janeiro. Rio de Janeiro. Brazil.

Abstract

Introduction: Malnutrition is commonly and frequently under-diagnosed in clinical settings in patients with chronic liver disease(CLD) due to the limitations of nutritional evaluation methods in this population. We hypothesized that the bioelectrical impedance analysis derived phase angle (BIA-derived PhA) might be considered as a nutritional indicator in CLD since it represents either cell death or malnutrition characterized by changes in cellular membrane integrity.

Objective: The aim of this study was to evaluate the BIA-derived PhA as a nutritional evaluation tool in all stages of CLD, including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). Liver-related death and survival were evaluated.

Methods: A total of 66 patients were enrolled in a cross-sectional study. For the nutritional diagnosis, mid-arm circumference (MAC), triceps skinfold thickness (TST), mid-arm muscle circumference (MAMC) and Subject Global Assessment (SGA) were evaluated. Biochemical and clinical evaluations were performed.

Results: Our results showed that PhA was higher in well-nourished patients, according to SGA and in the patients without hepatic encephalopathy. PhA correlated significantly with MAMC, MAC and albumin and was inversely correlated with age. No correlation was found between PhA values and the Child-Pugh score and ascites. PhA was strongly associated with survival and PhA ≤ 5.18° with relative risk increase of 2.5 for death.

Conclusions: We conclude that the BIA-derived PhA is a relevant nutritional evaluation tool in chronic hepatitis, liver cirrhosis and HCC and the role of PhA in the prediction of survival in CLD should be examined further in a controlled study.

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Key words: *Phase angle. Subject global assessment. Chronic liver diseases. Nutritional status. Anthropometry.*

ÁNGULO DE FASE COMO UNA HERRAMIENTA PARA EVALUAR EL ESTADO NUTRICIONAL EN TODAS LAS ETAPAS DE LA ENFERMEDAD HEPÁTICA CRÓNICA

Resumen

Introducción: La malnutrición es común y frecuentemente subdiagnosticada en el ámbito clínico en pacientes con enfermedad hepática crónica (EPC), ya que las limitaciones de los métodos de evaluación nutricional en esta población. La hipótesis de que el análisis de impedancia bioeléctrica derivada del ángulo de fase (AF) puede ser considerado como un indicador nutricional en la EPC, ya que representa tanto la muerte celular o la desnutrición se caracteriza por los cambios en la integridad de la membrana celular.

Objetivos: El objetivo de este estudio fue evaluar la AF como un instrumento de evaluación nutricional en todas las etapas de la EPC, incluyendo hepatitis crónica, cirrosis hepática y carcinoma hepatocelular (CHC).

Métodos: Se evaluó la muerte relacionada con el hígado y la supervivencia. Un total de 66 pacientes fueron incluidos en un estudio de corte transversal. Para el diagnóstico nutricional, circunferencia del brazo (CB), el pliegue del tríceps (PT), circunferencia del brazo muscular (CBM) y la valoración global subjetiva (VGS) fueron evaluados. Evaluaciones bioquímicas y clínicas se llevaron a cabo.

Resultados: Nuestros resultados mostraron que la AF fue mayor en los pacientes bien nutridos, de acuerdo con VGS y en los pacientes sin encefalopatía hepática. El AF se correlacionó significativamente con la CBM, CB y la albúmina y se correlaciona inversamente con la edad. No se encontró correlación entre los valores de la AF y la puntuación de Child-Pugh y la ascitis. La AF está fuertemente asociada con la supervivencia y la AF ≤ 5,18 ° con el aumento de riesgo relativo de 2,5 para la muerte.

Conclusiones: Llegamos a la conclusión de que la AF es una herramienta relevante la evaluación nutricional en la hepatitis crónica, cirrosis hepática y carcinoma hepatocelular y el papel de la AF en la predicción de la supervivencia de la EPC debe seguir siendo examinado en estudios controlados.

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Palabras clave: *Ángulo de fase. Valoración global subjetiva. Enfermedades crónicas del hígado. Estado nutricional. Antropometría.*

Abbreviations

CLD: Chronic liver disease.
BIA: Bioelectrical impedance analysis.
PhA: Phase angle.
HCC: Hepatocellular carcinoma.
MAC: Mid-arm circumference.
TST: Triceps skinfold thickness.
MAMC: Mid-arm muscle circumference.
SGA: Subject Global Assessment.
PTA: Prothrombin time activity.
BCM: Body cell mass.
R: Resistance.
Xc: Reactance.
PCR: Polymerase chain reaction.
CT: Computed tomography.
RM: Scan and/or magnetic resonance imaging.
HIV: Human immunodeficiency virus.
CI: Confidence interval.

Introduction

Patients with chronic liver disease (CLD) carry a risk of specific life threatening complications and co-morbidities. The nutritional status has been proposed as a prognostic factor in cirrhotic patients and was originally suggested as a prognostic factor for cirrhosis by Child and Turcotte.[1-3] Malnutrition is highly prevalent among patients with CLD, occurring early in the natural history of the disease and accompanying functional hepatic deterioration, thereby contributing to overall mortality and complications rate.[4-6] Although the course of CLD varies according to several factors, the need for a nutritional evaluation tool is highlighted in order to manage the patient's response to therapy, thus reducing the complications of the treatment.[7,8]

Traditionally, assessment of nutritional status has included measures of anthropometry and Subject Global Assessment (SGA). Anthropometric measurements are one of the most useful indices of nutritional evaluation in patients with CLD[6] and MAMC is considered the most sensitive marker of body cell mass (BCM).[9] Hasse et al.[10] have shown there is some benefit in using SGA to evaluate adult liver-transplant candidates, however, it remains controversial whether or not SGA underestimates the nutritional status in patients with liver cirrhosis.[11] Therefore, the lack of a valid and reliable tool to measure nutritional status in these patients is still a challenge as CLD affects most of the traditional tools of nutritional evaluation.

The bioelectrical impedance analysis (BIA) is a promising nutritional assessment tool that incorporates both functional and morphological evaluation. BIA is a simple, non-invasive, and reproducible technique that measures body composition.[12] BIA uses body resistance (R) and reactance (Xc) to a flow of alternating electrical current to determine impedance. Resistance is inversely proportional to the amount of body water and electrolyte. Reactance is related to the capacitance properties of the cell membrane since the applied current will charge cell membranes, and variations can occur depending on its integrity, function and composition.[13] Phase angle (PhA) is obtained from the direct measurements of R and Xc and is calculated as the arct-angent of the ratio of Xc to R.[14] PhA can be interpreted as an indicator of fluid distribution or electric resistance and cellular membranes capacitance of the human body. Theoretically, PhA might be considered as a nutritional indicator, since malnutrition is characterized by alterations in fluid balance and changes in cellular membrane integrity.[15] Lower PhA appears to be consistent with low Xc or with cell death or a breakdown in the selective permeability of the cell membrane and thus it may be a predictive factor for survival.[16]

Findings from other studies indicate that PhA is a good prognostic indicator. It has been suggested that PhA represents the body cell mass and indicates nutritional status, with significant prognostic power, in HIV-infected patients,[17] and further in patients with liver cirrhosis,[18] in peritoneal dialysis patients,[19] in cancer patients,[20-23] in amyotrophic lateral sclerosis,[24] in advanced cancer,[25] in hepatitis C infection following antiviral therapy,[26] in preoperative patients[27] and hospitalized patients.[28]

The role of PhA for nutritional evaluation in all stages of CLD still remains to be investigated inasmuch as it has been previously studied only in liver cirrhosis.[18] Our hypothesis is that PhA might be considered as an indicator of nutritional status in CLD. To clarify this issue, the objective of the present study was to evaluate the association between BIA derived PhA and traditional methods of nutritional evaluation considering all stages of CLD, including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC).

Methods and materials

Subjects

In the cross-sectional phase of the present study, data were collected from January 2009 to December 2010 at the University Hospital of the Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. Patients with age ≥ 18 years with chronic hepatitis, liver cirrhosis and HCC were eligible for enrolment in the study.

The diagnosis of hepatitis was based on polymerase chain reaction (PCR). The diagnosis of liver cirrhosis was based on clinical manifestations and laboratorial test, as well as on ultrasonographic imaging and histological evaluation whenever necessary. The diagnosis of HCC was based on computed tomography (CT), scan and/or magnetic resonance imaging (RM) finding and serum alpha-fetoprotein. The degree of ascites and hepatic encephalopathy were based on ultrasound data or on clinical evaluation, respectively.

The number of liver-related deaths was recorded during the observation period. The Kaplan-Meier method was used to calculate survival.

Exclusion criteria comprised patients with cardiac pacemaker, amputated limbs, aneurysm clip, metal implants, chronic renal failure, hemodialysis, active alcohol abuse or history of respiratory or cardiovascular disease, co-infection with human immunodeficiency virus (HIV) and unwillingness to participate in the study.

The study protocol was approved by the Research Ethics Committee of the University Hospital of the Federal University of Rio de Janeiro, protocol 068/01, and it conforms to the provisions of the Declaration of Helsinki. An informed written consent was requested from all subjects before they enrolled in the study.

Clinical variables were recorded during the study by the same investigator. The laboratory data collected included albumin, bilirubin and prothrombin time which were measured by previously established standard laboratory methods. Laboratory data and degree of ascites and hepatic encephalopathy were used to calculate the Child-Pugh score. The patients were then stratified as A, B, or C in accordance with the Child-Pugh classification criteria.[2]

The patients selected for the study underwent baseline nutritional evaluations which included anthropometry, BIA and SGA, conducted at the same time by the same trained nutritionist.

Phase angle

BIA measurements were taken on the right side of the body using a tetrapolar BIA-101 impedance analyzer (RJL Systems Inc., Clinton Township, MI, USA), at 800 mA and a single frequency of 50 KHz. The measurements were taken in the morning after each participant had fasted for at least 8 hours and with an empty bladder. All impedance measurements were conducted while the participants were lying supine on bed, with legs apart and arms not touching the torso. The four electrodes were placed separately. Two on the dorsal surface of the right wrist, medially between the distal prominences of the radius and the ulna and on the dorsal surface of the right ankle, between the medial and lateral malleoli; two on the dorsal surface of the right hand and foot at the third metacarpophalangeal and metatarsophalangeal joints, respectively. R and Xc were directly measured in ohms (W). The PhA was calculated using the following equation:

$$PhA = \text{arc-tangent reactance/resistance} \times 180°/p$$

Anthropometry

Anthropometric parameters like mid-arm circumference (MAC) and triceps skinfold thickness (TST) were measured with a tape and a Lange skinfold caliper, respectively. TST was measured to the nearest 0.1 mm with calipers at the triceps. Measurements were taken midway between the tip of acromion and olecranion process on the non-dominant arm, being the patient in a relaxed position. To minimize practical variability, the average of three consecutive measurements for TST was recorded. The mid-arm muscle circumference (MAMC) was calculated by the formula MAMC (cm) = MAC − [P x TSF (cm)][29]. For the nutritional diagnosis, the anthropometric parameter was compared with Frisancho's reference standard.[29]

Subjective global assessment

SGA was performed using a standard questionnaire as proposed by Hasse et al. adapted to liver disease[10]. On the basis of the patient history, physical appearance and existing clinical conditions focused on nutritional aspects, the patients were classified as not, moderately or severely malnourished. For the purpose of this article, malnutrition was defined as either moderately or severely malnourished.

Statistical analysis

The Statistical Package for Social Science software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Data were expressed as median and range. For the Kaplan-Meier survival analysis, PhA measurements were categorized into two equal and mutually exclusive groups with a median PhA score of 5.18° as the cut-off. The influence of possible risk factors on patient survival was analyzed by Cox multivariate regression. Kruskal-Wallis one-way analysis of variance, Mann–Whitney U test and Spearman's correlation test (r) were used in the statistical analysis. Significance level was defined as $P < 0.05$.

Results

A total of 66 patients with CLD who met the inclusion and exclusion criteria were enrolled. The median age was 59 years (range 41-79). There were 34 male patients (57.6%). The etiology of the CLD was as follows: 60.8% chronic hepatitis C infection, 24.0% chronic hepatitis B infection and 15.2% alcohol-related. According to liver disease severity, there were 14 patients in the chronic hepatitis group, 8 in the cirrhosis Child-Pugh A group, 11 in the Child-Pugh B group, 14 in the child-Pugh C group and 19 in the HCC group. In the HCC group, 15 patients were Child-Pugh A and 4 were Child-Pugh B.

All patients in the cross-sectional sample were followed for at least 17 months.

Table I

Descriptive statistics for bioelectrical parameters by chronic liver disease stage

CLD stages	PhA (degrees)*	Resistance (Ω)*	Reactance (Ω)*
Chronic hepatitis (n = 14)	5.6 (4.0-6.9)	512 (401-612)	49 (32-58)
Cirrhosis child A (n = 8)	5.4 (1.9-6.4)	524 (338-646)	56 (11-63)
Cirrhosis child B (n = 11)	4.6 (4.1-6.7)	502 (396-712)	54 (28-69)
Cirrhosis child C (n = 14)	4.4 (3.2-7.4)	495.5 (386-589)	41 (22-63)
H < CC (n = 19)	4.8 (2.9-6.7)	494 (360-710)	39 (26-69)
P-value**	0.36	0.55	0.15

*Values are expressed as median (minimum-maximum).
**Differences between groups were tested with Kruskal-Wallis at 5% probability.
Note: BIA: Bioelectrical impedance; CLD: Chronic liver disease; PhA: Phase angle; HCC: Hepatocellular carcinoma.

The parameters of BIA distribution in chronic hepatitis, liver cirrhosis and HCC are shown in table I. There were no statistically significant differences with respect to PhA, R and Xc median values between chronic hepatitis, liver cirrhosis and HCC ($P = 0.36$, $P = 0.55$ and $P = 0.15$, respectively).

The median (range) of PhA regarding all the patients was 5.18° (range 1.86-8.40).

The median PhA was 5.31° (range 3.45-7.42) in well-nourished patients being significantly higher than malnourished patients (4.35°, range 1.86-6.73) ($P = 0.005$), according to SGA results.

Correlation coefficients between PhA and age, liver function test and anthropometry parameters in CLD patients are shown in Table 2. PhA correlated significantly with MAMC ($r = 0.29$, $P = 0.015$), MAC ($r = 0.29$, $P = 0.023$) and albumin ($r = 0.27$, $P = 0.036$). The PhA was correlated inversely and significantly with age ($r = -0.48$, $P < 0.001$). The median age was 63.5 years (range 43-79) and 55.0 years (range 41-68) for the below median and above median PhA groups respectively ($P = 0.015$). There was no significant difference in PhA values between the sexes ($P = 0.59$).

A comparison of phase angle between the groups with presence or absence of hepatic encephalopathy and ascites has shown that the median of PhA was 4.17° (range 3.19-7.42) in patients with hepatic encephalopathy being significantly lower than in patients without hepatic encephalopathy (5.04°, range 1.86-6.89) ($P = 0.003$).

The median PhA was 4.62° (range 1.86-7.42) in patients with ascites and 5.03° (range 2.94-6.89) in patients without ascites with lower values of PhA in patients with ascites, but the results have not shown statistical significance, only a strong tendency ($P = 0.05$). With respect to hepatocellular function evaluated according to the Child-Pugh score, no statistically significant correlation was found between PhA, R and Xc values and Child-Pugh score ($P = 0.17$, $P = 0.29$ and $P = 0.16$, respectively).

During the study period, there were 37 patients who died and 25 were censored (reached the end of their follow-up period without experiencing death). PhA was strongly associated with survival ($P = 0.013$). The
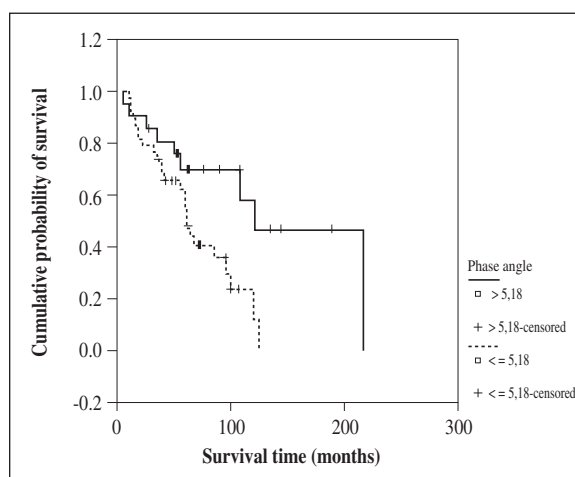

Fig. 1.—*Survival time stratified by median phase angle (PhA) categories of ≤ 5.18° (dashed line) or > 5.18° (solid line). Vertical lines indicate censored patients, i.e., those who reached the end of their follow-up without experiencing death.*

survival curves were stratified by median (fig. 1). Patients with PhA lower or equal than 5.18° (n = 38) had a median survival time of 62 months (95% confidence interval [CI]: 55.5-68.5) while those with PhA > 5.18° (n = 21) had a median survival time of 122 months (95% CI: 67-177). The difference was statistically significant ($P = 0.01$).

In a multivariate Cox regression analysis, after adjusting for age, PhA ≤ 5.18° was found to be associated with a hazard ratio increase of 2.5 for death (95% CI: 1.85-6.01) ($P = 0.032$).

The median phase angle of patients who died within the observation period was significantly lower than the median phase angle of patients who survived (median 4.55° compared to 5.28°, $P = 0.01$).

Discussion

This study adds a growing body of evidence on the clinical applications of BIA derived phase angle beyond its use in body composition equations.

Table II
Correlation coefficients between phase angle and age, liver functions test and anthropometry parameters in CLD patients

Variables	PhA (r)	p-value
Age	-0.48	< 0.001
Albumin	0.27	0.036
Bilirubin	0.033	0.80
MAC	0.290	0.023
MAMC	0.29	0.015
TST	0.21	0.10

r = Spearman correlation coefficient.
Note: CLD: Chronic liver disease; PhA: Phase angle; MAC: Mid-arm circumference; MAMC: Mid-arm muscle circumference; TST: Triceps skinfold thickness.

The inverse relationship between age and PhA observed in the current study supports results of a previous study on healthy subjects.[30] It has been speculated that the decrease in PhA values correlating with increasing age could be an indicator of a reduction in skeletal muscle mass and general health in the elderly.[31,32] At the same time, there was no statistically significant difference with respect to PhA and sex, a finding that is similar to the results obtained by Baumgartner et al.[13] and Selberg and Selberg[18], but not to those obtained from other studies on healthy adults.[30,33]

In the present study, the median of R, Xc and PhA was lower than the values described by Selberg and Selberg[18] in healthy control subjects. In addition, our results of PhA values found in chronic hepatitis, cirrhosis Child A, B, C and HCC were lower than the population reference values described by Barbosa et al.[34] that ranged between 7.90° and 5.64°.

PhA and Xc are directly reflecting the intra/extra cellular masses proportion (ECM/BCM) and malnutrition is characterized by both increased ECM and decreased BCM, so changes of the ECM to BCM ratio are probably associated with changes in PhA.[35]

PhA is also related with the BIA estimated extracellular water (ECW), and intracellular water (ICW) ratio and wasting diseases are reported to be associated with intracellular dehydration.[15] In fact, results of other studies support the idea that markedly loss of body protein, which occurs in critically ill patients, is triggered and maintained by cell shrinkage secondary to cellular dehydration.[15,36,37,38] Previous studies have demonstrated that the decrease of intracellular water (ICW) and the increase of the extracellular water (ECW) are indicators of the catabolic reaction of the sepsis.[36,38] Finn et al.[36] demonstrated that such patients lose approximately 15% to 20% of protein and potassium in about 21 days of illness and the cellular volume also decreases around 15% to 20%.

It has been suggested that PhA values reflect quantities of intact cell membranes and BCM. In this study, according to the diagnosis of a traditional method of nutritional assessment, significantly higher PhA was found in well-nourished patients and correlated with MAMC and MAC, in agreement with findings from a previous concept that states that PhA represents a simple muscle index.[18]

Besides, our results that PhA was related to albumin, an important parameter of liver function, is in agreement with findings from other studies on liver cirrhosis.[18]

This study found lower PhA in hepatic encephalopathy, suggesting a relation between a decrease in BCM, malnutrition and hepatic encephalopathy. The loss of BCM has been described in the advanced stages of liver cirrhosis[5], and the protein-restricted diets usually prescribed for cirrhotic patients in order to treat or prevent hepatic encephalopathy may deplete the muscle mass compartment without resulting in an improvement of hepatic encephalopathy.[39]

Moreover, patients with malnutrition suffered more frequently from hepatic encephalopathy,[40,41] supporting an experimental study that suggested that low energy intake and malnutrition may facilitate the development of hepatic encephalopathy.[42]

Patients with ascites showed a tendency towards lowered values of PhA (p = 0.05). It is likely that the lack of statistical significance is due to the small number of patients with ascites (n = 25). These findings support observations from clinical practice where there is greater degree of malnutrition in patients with ascites. Sorrentino et al.[43] observed in their study that liver-cirrhosis patients with ascites are malnourished despite numerically adequate calorie-intake.

PhA was not associated with chronic hepatitis, liver cirrhosis and HCC. In patients with liver cirrhosis and HCC, PhA did not correlate with the Child-Pugh score, although there is a tendency towards reduced PhA values with the concurrent worsening of the liver cirrhosis. The findings of our study do support the previous study[18] that demonstrated that PhA is not simply associated with the stage of liver cirrhosis, as assessed using the Child-Pugh score.

Considering all stages of CLD, our results show, after controlling for age, that patients with PhA equal or less than 5.18° had shorter survival. A similar study conducted in 57 cirrhotic patients demonstrated that patients with PhA equal or less than 5.4° had shorter survival than patients with higher PhA.[18] In the present study, it is possible to point the role of PhA as a potential predictor of survival in CLD after controlling for age. Nonetheless, it is still necessary to conduct studies with larger sample sizes that assess the prognostic role of PhA, considering all stages of CLD.

Moreover, the median PhA of the patients who died was significantly lower than that of the patients who survived, with median less than 18.5°, thereby reinforcing the findings of low survival rates in patients with lower PhA that are associated with cell death or decrease in cellular integrity.

Findings from other studies have previously demonstrated that low BIA derived PhA values may indicate

worse prognosis in many clinical situations.[17-25,27,28] Gupta et al.[20-22] found that PhA values above 5.0°, 5.6° and 5.3° were associated with improved survival in patients with advanced pancreatic cancer, breast cancer and stage IIIB and IV non-small cell lung cancer, respectively. In addition, PhA lower than 6.0° has been shown to be an adverse predictor of survival in peritoneal dialysis patients.[19] In the present study our median PhA value was similar to the results obtained in pancreatic cancer[20] and in patients suffering from cirrhosis.[18]

In conclusion, our results are consistent with the hypothesis of the present study and concur for the relevance of BIA derived PhA as an indicator of nutritional status in patients with CLD. BIA-derived PhA may become a useful surrogate tool for the nutritional evaluation and could help clinical practitioners aiming to attest malnutrition diagnosis in CLD. Nevertheless, it is necessary to define further the threshold values for PhA as a nutritional evaluation tool in CLD and evaluate the role of PhA in the prediction of survival in chronic hepatitis, liver cirrhosis and HCC patients in a controlled study.

Acknowledgments

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