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Mini Review

Clinical Significance of Phase Angle and Extracellular Water-to-Total Body Water Ratio Measured by Bioelectrical Impedance Analysis

Taiki Hori[1,2], Shingen Nakamura[3*], Ken-ichi Aihara[3,4]

[1]Department of Hematology, Endocrinology and Metabolism, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan; [2]Department of Internal Medicine, Tokushima Prefectural Kaifu Hospital, Tokushima, Japan; [3]Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan; [4]Department of Internal Medicine, Anan Medical Center, Tokushima, Japan

ABSTRACT

Bioelectrical Impedance Analysis (BIA) is a simple and noninvasive method used to estimate body composition, Phase Angle (PhA), and Extracellular Water-to-Total Body Water Ratio (ECW/TBW). PhA serves as an indicator of cell mass, cellular integrity, and healthiness of the cell membranes. ECW/TBW is an indicator of cellular volume valance. Both metrics can be used to comprehensively assess the structural integrity of the body, including nutritional status and inflammation. Evidence suggests a close correlation of these parameters with prognosis and disease progression in non-cancer patients such as diabetes mellitus and in cancer patients, including those with hematological malignancies. BIA may be a valuable tool for assessing the current body status as well as for future predictions across different disease domains.

Keywords: Bioelectrical impedance analysis; Phase angle; Extracellular water-to-total body water ratio

INTRODUCTION

Evaluating body composition is crucial for assessing nutritional status and has undergone extensive research. Dual-Energy X-Ray Absorptiometry (DXA) measures body composition and fat, muscle, and bone densities. Total Body Water (TBW) and Extracellular Water (ECW) are assessed using Deuterium Oxide (D2O) and Sodium Bromide (NaBr) dilutions, respectively. These methods are recognized as the most accurate. However, implementing them is difficult due to their time-consuming, labor-intensive nature, and the need for specialized knowledge and techniques.

Bioelectrical Impedance Analysis (BIA) has recently emerged as a method for estimating body composition. Direct Segmental Multifrequency Bioimpedance Analysis (DSM-BIA) was conducted using an 8-point tactile electrode system, with 30 impedance measurements obtained using multiple frequencies at each segment. DSM-BIA has been used to measure the Phase Angle (PhA), which is an angular shift (phase difference) between electrical voltage and current sinusoidal waveforms, indicating cell mass, cellular integrity, and healthiness of cell membranes [1,2]. The segmental impedance and reactance at multiple frequencies determine the TBW, ECW, and Extracellular Water-To-Total Body Water Ratio (ECW/TBW). BIA is used and studied in various clinical settings because it is a simple and noninvasive method.

LITERATURE REVIEW

Factors that affect PhA and ECW/TBW

PhA can comprehensively assess the structural integrity of the body, including nutritional status and inflammation. However, the precise mechanisms that affect PhA values are unknown. PhA was positively correlated with Body Mass Index (BMI) and male sex and negatively correlated with age and percentage fat mass [3]. Kyle, et al., reported that PhA was significantly associated with the Nutritional Risk Screening (NRS-2002) score, Subjective Global Assessment (SGA), and serum albumin level in patients at hospital admission [4]. PhA has also been

Correspondence to: Shingen Nakamura, Department of Community Medicine and Medical Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan, E-mail: shingen@tokushima-u.ac.jp

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reported to be negatively associated with High-Sensitivity C-Reactive Protein (hs-CRP) levels in both sexes after adjusting for age, physical activity, BMI, waist circumference, and adherence to the Mediterranean diet. PhA ≤ 5.5° in males (Area Under the Curve (AUC) 0.811, 95% Confidence Interval (CI): 0.779-0.842) and PhA ≤ 5.4° in females (AUC 0.850, 95% CI 0.825-0.874) could predict hs-CRP levels above the median value (2.33 ng/mL in males and 1.90 ng/mL in females) [5]. These studies revealed that PhA is a cellular health biomarker that indicates malnutrition and inflammatory status. Furthermore, we previously reported that the duration of diabetes mellitus and insulin use were negatively associated with PhA after adjusting for age and sex [6]. In contrast, no correlation was observed between the PhA and antidiabetic drugs other than insulin [6].

ECW/TBW is thought to be an indicator of cellular volume valance positively correlated with age and volume index, and negatively correlated with serum albumin levels in patients undergoing hemodialysis, regardless of sex [7]. Evidence suggests that hs-CRP positively correlates with ECW/TBW in patients on peritoneal dialysis, and was found to be an independent risk factor for hypervolemia in a multivariate analysis [8]. Our previous study has revealed a negative correlation between ECW/TBW and PhA, and the duration of diabetes mellitus was positively associated with ECW/TBW after adjusting for age, sex, and the use of antidiabetic drugs in Japanese diabetic patients [6]. Interestingly, PhA positively correlated with Hemoglobin (Hgb) and Hematocrit (Hct) levels in both men and women. In contrast, ECW/TBW was negatively correlated with Hgb and Hct levels regardless of sex. These associations remained even after adjusting of clinical confounding factors. Therefore, aberrant PhA and ECW/TBW values suggest a risk of anemia in diabetic patients [6].

DISCUSSION

Clinical utility of PhA and ECW/TBW in non cancer patients

Since PhA can comprehensively assess the structural integrity of the body, including nutritional status and inflammation, it was reported to be an independent factor associated with sarcopenia in the elderly (Odds ratio: 0.59, 95% CI: 0.40-0.87, p=0.008). The optimal PhA cutoff value to detect sarcopenia was ≤ 4.55° [9]. A low PhA (Men: 3.070°-5.646°, Female: 2.655°-5.419°) was found to be associated with significantly higher odds of frailty after adjusting for age, race, ethnicity, and comorbidity [10]. Over a 12-year follow-up period in patients aged 60 years or older, the adjusted mortality hazard ratio associated with low PhA was 2.2 (95% CI: 1.7-2.9) in men and 2.4 (95% CI: 1.8-3.1) in women [10]. Consequently, PhA is a useful for screening tool to predict future mortality in relation to sarcopenia and frailty.

ECW/TBW has been studied as an indicator of body fluid volume in patients with Chronic Kidney Disease (CKD) and those with chronic liver diseases. Along with its use for evaluating body fluid volume, ECW/TBW is reportedly associated with chronic kidney disease progression in type 2 diabetes [11]. ECW/TBW 0.39-0.40 and >0.40 were associated with a 45% and 78% higher risk of CKD progression, respectively. Patients with an increase in ECW/TBW had a 40% higher risk of CKD progression than those with no change or reduction in ECW/TBW. Additionally, ECW/TBW showed a significant positive correlation with erythropoietin hypo responsiveness in patients undergoing long-term continuous ambulatory peritoneal dialysis [12]. ECW/TBW may be useful not only for assessing current body fluid volume but also for the future prediction of disease progression and erythropoietin responsiveness in patients other than those with CKD.

PhA and ECW/TBW as a prognostic indicator in cancer patients

PhA has been associated with known prognostic indicators, including palliative performance status, palliative prognostic score, and palliative prognostic index in hospitalized patients with advanced cancer. In this study, the median survival with PhA 2°-2.9°, 3°-3.9°, 4°-4.9°, 5°-5.9°, and ≥ 6° was 35, 54, 112, 134, and 220 days, respectively [13]. A systematic review and meta-analysis involving 14 studies covering 2625 cancer patients demonstrated a positive correlation between PhA and cancer survival, and that PhA plays a significant prognostic role in the survival of cancer patients [14].

The ECW/TBW ratio is increasingly recognized as a prognostic indicator in patients with cancer. Zheng et al., have reported that ECW/TBW ≥ 0.40 was a risk factor for malnutrition in patients with advanced cancer. Kaplan-Meier curves for all participants were stratified with significant differences at a cutoff of 0.40 [15].

A few studies have reported the usefulness of BIA in patients with hematological malignancies. A reduced baseline PhA (<5° in men and <4.6° in women) was associated with poor progression-free survival (7.1 months *vs.* 11.6 months, p=0.001) and Overall Survival (OS) (8.2 months *vs.* 12.1 months, p=0.011). Moreover, a multivariate analysis revealed that reduced PhA independently predicted disease progression (HR 3.13; 95% CI: 1.21-8.11, p=0.019) after adjusting for age, BMI, NRS-2002 score, lactate dehydrogenase, and creatinine in newly diagnosed patients with acute myeloid leukemia [16]. Furthermore, in patients with acute lymphoblastic leukemia, statistical significance was observed in leukemia-free survival compared with the Kaplan-Meier curves at a cutoff value of 4° (p=0.0235) [17]. A high ECW/TBW (>0.397) was associated with shorter 3-year OS (46.8% *vs.* 70.5%, p=0.03) in elderly patients with hematological malignancies [18]. In patients with leukemia, BIA parameters may be associated with prognosis reflecting the tolerability of chemotherapy and general conditions including sarcopenia. In patients receiving hemodialysis, regardless of gender, ECW/TBW is believed to be a measure of cellular volume valance that is negatively connected with serum albumin levels and favorably correlated with age and volume index. Research indicates that in peritoneal dialysis patients, hs-CRP positively correlates with ECW/TBW and was identified as an independent risk factor for hypervolemia in a multivariate analysis. After controlling for age, sex, and the use of antidiabetic medications in Japanese diabetic patients, our earlier study found a positive link between ECW/TBW and

PhA and a negative correlation between ECW/TBW and the length of diabetes mellitus. It's interesting to note that PhA positively associated with both men's and women's levels of Hematocrit (Hct) and Hemoglobin (Hgb).

CONCLUSION

BIA is a simple and noninvasive method used to estimate body composition in various clinical settings. PhA and ECW/TBW measured by BIA are cellular health biomarkers that disclose nutritional and inflammatory status. Both metrics may be useful for assessing the current body status and predicting future disease prognosis. Further research on PhA and ECW/TBW is required to clarify their clinical significance in the assessment of hematological disorders, including leukemia.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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