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Phase angle in applications of bioimpedance in health and disease

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Bioelectrical impedance (BI) is wide-ranging term that includes the passive electrical conduction of an applied electrical current to evaluate physiological attributes in health and disease. The history of development and application of BI methods is extensive and comprises many scientific disciplines [1, 2]. Since the 1980's, body composition assessment using many bioimpedance applications has burgeoned from an innovative method to an emerging clinical tool [3]. Several factors limited the widespread acceptance of BI in research and practice. Variable hydration of the fat-free mass (FFM) in certain conditions (e.g., obesity, malnutrition, fluid overload, etc.) directly affects tissue resistivity and reliance on multiple regression approaches and theoretical models with dubious assumptions restricts the progression of BI applications to predict body composition variables parameters for individuals [4–7].

Avoiding the doubtful assumption of constant hydration and dependence on indeterminate models, Piccoli [8, 9] demonstrated the value of basic BI measurements to classify hydration and nutritional status, and to monitor changes in response to treatments in individual patients. This return to this basic measurement approach concomitantly renewed awareness of phase angle (PhA), as first shown by Barnett and Bagno [10], to have unique prognostic value in patient evaluation and care.

The special issue on PhA provides a comprehensive description of the basic physical concepts and measurements of PhA and practical applications in monitoring muscle hypertrophy and identification of severity of skeletal muscle injury, sarcopenia and frailty, weight loss. Experimental data provide validation of reactance (Xc), a predominant contributor to PhA, as an indicator of cell and tissue damage and fluid disturbances. Compilation of clinical data show the value of PhA in treatment of patients with disease-related fluid imbalance, risk of malnutrition and prognosis. Inflammation with potential oxidative damage is a potential common mechanism affecting PhA in health and pathology. A global vision for advancement of BI and PhA concludes this issue.

For the biomedical and clinical researcher, the terms BIA and PhA can be vague. Lukaski and Talluri [11] concisely describe a simple conceptual framework for bioelectrical impedance analysis (BIA) that associates bioelectrical measurements and empirical models with hydration and body cell mass. They provide evidence from diverse experimental models and clinical findings to develop valid interpretations of the BI measurements of resistance (R), Xc and PhA for fluid distribution and cell membrane integrity. A key point is awareness that cells, tissue and fluids exist as a network of complex parallel circuits that highlight the importance of the cell membrane. This empirical evidence provides a basis for understanding the impact of pathology-related perturbations on the BIA measurements. Ward and Brantlov [12] expand the technical discussion of physical principles underlying PhA and emphasize the role of cell membranes to hinder passage of an administered alternating current, which is measured as a time delay between current and voltage and reported as Xc. They also discuss the potential of using bioelectrical impedance spectroscopy as a candidate for hydration assessment.

Skeletal muscle is the largest conductive tissue in the body. Hence, PhA is highly correlated with FFM. Sardinha and Rosa [13] evaluate the effects of resistance training (RT)

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on BI measurements within the context of cellular mechanisms of muscle hypertrophy. Muscle hypertrophy results in an increase in muscle cell and tissue volume attributable to protein accretion with marked gains in intracellular water and glycogen, which is a function of the type and duration of strength training. Hypertrophy is accompanied by changes in the resistive path of the electric current (R) and capacitive properties of the human body (Xc) that directly impact PhA.

Traumatic muscle injury is endemic in sport. Nescolarde et al. [14] describe the innovative method of localized BIA (L-BIA) and its application to identify the severity of injury and track healing until the injury has healed adequately to return to play. They carefully elucidate the technical criteria for valid L-BIA measurements including placement of electrodes on injured and contralateral non-injured region of interest to reliably determine pathology-induced perturbations in L-BIA measurements. One key experimental finding is that Xc is the sensitive indicator of graded muscle membrane damage, as verified with radiological data, thus affecting PhA value. Additionally, in vitro studies determined that Xc is an indicator of cells in fluid based on fluid injection into meat.

Observational studies report strong associations between PhA and various measures of FFM, risk of malnutrition and prognosis. In the elderly, PhA values decrease substantially compared to younger adults. Norman et al. [15] examine the role PhA as a screening tool for increased risk of geriatric syndromes including malnutrition, sarcopenia, frailty (impaired muscle function), and clinical outcomes. They highlight the recent noteworthy proteomic finding that PhA is directly related to specific proteins linked with cell growth and metabolism in elderly adults.

An important question is the potential of physical training to ameliorate geriatric syndromes of muscle loss and muscle function. Campa et al. [16] report the results of a meta-analysis of the effects of RT on PhA in elderly adults. Consistent with the findings of Norman et al. [15] and depending on the type and amount of RT, PhA values increase largely due to an increase in Xc and a decrease in R due to muscle hypertrophy, indicating an increase in muscle cell volume, and strength gain. Whereas these observations are encouraging, the clinical outcomes of the increased PhA remain to be demonstrated.

Overweight and obesity classified using body mass index (BMI) are risk factors for chronic and cardiometabolic disease. Controversy exists regarding any association between BMI and PhA due to weak co-dependencies with FFM and expansion of the extracellular fluid. Cancello et al. [17] postulate the use of PhA in the screening of individuals with elevated BMI values may be useful to identify increased risk of morbidity. Additionally, they recommend serial determinations of PhA patients participating in lifestyle interventions for fat loss with emphasis to monitor for the anticipated increase in PhA that is related to maintenance or gain in muscle or body cell mass (BCM) with normalization of fluid distribution.

Acute and serial BI measurements afford a practical opportunity to identify and track disease-related fluid imbalance, malnutrition and prognosis. Scicchitano and Massari [18] evaluate the role of PhA in the assessment of diagnosis of congestion (central and peripheral fluid accumulation), managing therapeutic interventions and prognosis of patients with heart failure. They conclude that PhA is a holistic indicator of broad risk stratification and contributes to the multiparametric assessment, including molecular biomarkers, of patients with heart failure.

Cancer can increase the risk of malnutrition, depletion of body muscle and fat, reduction in physical function and risk of death. Amano et al. [19] report a consensus that PhA is inversely related to the size of some tumors, assessments of malnutrition, fluid imbalance, sarcopenia, and impaired quality of life measures in patients with advanced cancers. Thus, higher PhA values may indicate a better prognosis in patients with cancer. The authors stress the need for determination of threshold PhA values associated with better prognosis. Another need is to clarify the effects of edema in localized cancers on PhA and prognosis. A fundamental concern is the need for standardization of BIA technology and methods to address these concerns in patients with cancer and other diseases.

Patients with chronic respiratory diseases have impaired nutritional status, reduced muscle mass and limited physical function that are associated with poor gas exchange and exacerbated by inflammation. De Benedetto et al. [20] report low PhA values in patients with certain obstructive respiratory diseases that were more predictive of risk of malnutrition compared to BMI. They further identify PhA as a surrogate for depletion of muscle mass and BCM and prediction of reduced ventilatory function and gas exchange. Targeted supplementation to boost muscle function significantly increased PhA values that were related to improvements in walking performance and activities of daily living.

Diseases of the liver and digestive system reduce food intake and impair nutrient utilization resulting in loss of body weight and subsequent reductions in muscle and BCM. Additionally, fluid imbalances accompany these diseases. Although weight change and BMI are global indicators of these disease-related changes in body composition, they are insensitive indicators of graded alterations. Casirati et al. [21] report decreased PhA values in patients with inflammatory digestive diseases were reliably related to increased risk of malnutrition and depletion of FFM and sarcopenia. Further, low PhA was related to disease stage and severity,

and prognosis as well as a useful gauge of fluid shifts and responses to interventions.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection presents with acute respiratory, nervous and musculoskeletal symptoms that can result in complications such as sepsis, acute respiratory distress syndrome, thromboembolic events, coagulopathies, renal or cardiac failure, and even systemic organ failure. Cornejo-Parejo et al. [22] ascertain the prognostic value of PhA in patients with SARS-CoV-2 using a systematic review with meta-analysis of the growing literature. They determined that low PhA was a significant predictor of poor clinical outcomes, including an increased risk of severe risk of complications and mortality, in these patients.

Although it is well demonstrated that static factors, including age, sex, BMI, body composition (e.g., FFM) are associated with PhA, accumulating information indicates that dynamic factors, such as inflammation and oxidative damage, can directly impact PhA values in conditions that affect cell membrane integrity and function. Da Silva et al. [23] review the emerging experimental evidence of mechanistic roles for associations of inflammation and oxidative damage in diversity of PhA values in health and disease.

A crucial aspect for the future is the development of scientific research lines on PhA. Bellido et al. [24] review different key issues to be considered in future PhA research, such as detailed consideration of measurement technique, assessment of clinical conditions and patient phenotype, as well as establishing outcomes focusing on prognostic value in terms of overall mortality, cause-specific mortality, medical and surgical complications, length of hospital stay and use of healthcare resources. They also address the controversial role of BIA in characterizing altered fluid status and malnutrition in patients with chronic kidney disease, and emphasize the need to evaluate PhA together with impedance vector analysis to discover the coincident presence of malnutrition with fluid overload or dehydration. Future research should aim to assess how different treatments that modify PhA produce a prognostic change in morbidity and mortality. Due to the inherent limitations of the BIA technique, external validation with other techniques such as nutritional ultrasound or hand grip strength (morphofunctional assessment) show a good degree of agreement with body composition values from a morphological and functional approach. Recently an Expert Consensus on Morphofunctional Assessment in Disease-Related Malnutrition has been published [25]. This study develops evidence-based recommendations on the prognostic value of a series of morphofunctional tools and tests to assess malnutrition or the risk of malnutrition including PhA. In addition, the expert consensus was sought on the usefulness and feasibility of these tools and tests in routine clinical practice.

In conclusion, this special issue serves as an updated resource of experimental findings on the physical basis, validation and applications of PhA in health and biomedical research. It also provides guidance for future investigations to elucidate the value of PhA in studies of fluid disruption and prognosis emphasizing clinical outcomes.

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