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Phase angle and impedance ratio: Two specular ways to analyze body composition

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Abstract

A high metabolic rate, occurring in cancer or other inflammatory diseases, impairs body composition. To date, scientific literature recognizes to Bioelectrical Impedance Analysis (BIA)-derived Phase Angle (PhA) a strong prognostic value in several oncological diseases. IR is a ratio between two impedances (at 5 and 200 kHz), obtained by multi-frequency BIA; it is simple and easy to measure, and it may discriminate different hydration status in several diseases. The aim of this work is to present the correlation between PhA and Impedance Ratio (IR) in different clinical settings (227 subjects).Our data show a strong inverse correlation between PhA and IR in all patients: the lower is PhA, the higher is IR. Further studies are needed to correlate IR to clinical outcomes.

Introduction

Given its simplicity and reliability, Bioelectrical Impedance Analysis (BIA) has become in the last decade a widespread technique, both in clinical and non-clinical settings, to verify body composition and detect the percentage of Fat Mass (FM) and Free-Fat Mass (FFM) [1].

BIA method is based on the principle that the passage of an alternate electric current in a body may find a resistance (impedance) related to the subject's body composition [2]. The impedance (Z) to the passage of a current through the body consists of two components: resistance (R) and reactance (Xc). R arises from Extracellular Water (ECW) and Intracellular Water (ICW). Conversely, Xc arises from cell membranes. Xc is the cell membrane's quality of taking an electric load and liberate it in a second moment, after a brief delay. It could be compared to a vessel-capacitance-like property [3].

BIA methods are essentially two: the Single-Frequency (SF) and the Multi-Frequency (MF). The most used in clinical practice is the first one. At single-frequency (50 kHz), the main re-

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sistance is offered by ECW, with a very low contribution of ICW. Conversely, in MF-BIA, current could pass at several frequencies (5, 50, 100, 200 to 500 kHz): at low frequencies (lower than 50 kHz), it estimates R of the ECW, while at higher ones it also evaluates R of ICW, given its capacity to pass through cell membranes. Therefore, an MF-BIA gives back information about FFM, TBW, ICW and ECW.

SF-BIA is commonly used to estimate Total Body Water (TBW) and Fat-Free Mass (FFM); conversely, MF-BIA allows the advantage of differentiation between ICW and ECW [1].

In the clinical setting, BIA-derived Phase Angle (PhA) has gained noteworthy popularity. PhA is calculated from R and Xc using the formula:

$$PhA = \arctan (Xc/R) \times (180/\pi)$$

It results from a numerical value (in degrees), and may slightly differ according to sex, age, body mass index (BMI) and presence of disease [4,5].

To date, PhA is largely used as a prognostic indicator of poor clinical outcome in several illnesses including neoplastic diseases [6-9].

The Impedance Ratio (IR), derived by an MF-BIA measurement, is defined in the ESPEN "Blue" Book, a "newer way to evaluate cell membrane function" and it should be a "reliable guide to prognosis" of patients in intensive care units [3]. IR is the ratio between the impedance measured at 200 kHz and 5 kHz:

$$IR = (Z \text{ at } 200kHz)/(Z \text{ at } 5kHz)$$

As mentioned above, at 200 kHz, the current penetrates the cell membrane, and therefore total body water (ECW+ICW) can be measured. At 5 kHz, only ECW is measured. In healthy body tissues, the variance between the two impedance values is high, so the ratio is lower than 1. During systemic illness, cell membranes may be disrupted, allowing protein leakages and fluids and electrolytes shift in extracellular space. Therefore, Z at 200 kHz is similar to that at 5 kHz, and the IR is much closer to 1.00. Such value may indicate poorer cellular health and/or extreme fluid overload. Possible cut-offs for abnormal IR have been proposed by LD Plank in female and male subjects (respectively >0.820 and > 0.780) [10].

Methods and statistical analysis

We evaluated hospitalized patients in several clinical conditions, during the daily clinical practice in our center, "Fondazione Policlinico Universitario A. Gemelli", Rome. Our local ethic committee approved this cross-sectional hospital study. A set of apparently healthy subjects was also enrolled. Each patient was evaluated using the MF-BIA Bodystat 5000 (Bodystat®), a phase-sensitive bioimpedancedevice. The instrument directly measures Xc, R and PhA through specifics in the electronic circuitry (these are direct measures; they are not calculated). We used low inherent impedance electrodes, specifically made for Bodystat® (electrode conformity agreement is available, on request from the Company).

PhA at 50 kHz,IR, anthropometric and lab values were collected. We compared PhA and IR values, using the Pearson correlation coefficient and linear regression was performed.

Data are shown as mean (±standard deviation) and numbers (percentage). Normality distribution of data was assessed using Kolmogorov-Smirnov test. PhA and IR mean values between groups were analyzed using ANOVA.

All statistical analyses were conducted using STATA® statistical software version 15.

Results

From December 2016 to October 2017 data from 227 subjects were collected. Of these, 161 were admitted to the Gastroenterology Department, 26 in Pediatric Oncology Unit, 23 were neurologic outpatients affected by myotonic dystrophy type 1 (Steinert disease); 17 healthy subjects have also been examined [11,12].

Main subjects' characteristics are shown in the Tables 1-4.

In gastroenterological patients mean PhA and IR were respectively 4.47 ±1.19 and 0.853 ±0.040; in childhood cancer patients 4.20±1.02 and 0.854±0.039; in patients affected by Steinert disease 3.72±1.38 and 0.863±0.045; in healthy subjects 5.53±0.70 and 0.801±0.023 (ANOVA: $p<0.0001$). Correlations between PhA and IR are shown in Figures 1-5.

A strong inverse correlation was found between the two variables, with an r ranging from 0.861 (gastroenterology patients) to 0.979 (healthy subjects).

Discussion

The inflammatory response, as in cases of cancer, or in acute or chronic diseases, causes tissue breakdown and body composition changes [13]. This clinical picture may be associated with worse clinical outcomes [1].

Both PhA and IRare simple variables obtained by raw bioelectrical data without the use of complex equations.

Norman et al. [14], in a sample of 399 cancer patients found a significant correlation between a low PhA and low nutritional and functional status, impaired quality of life and increased mortality. Moreover, in this setting, using Receiver Operating Characteristic (ROC) curve analysis, PhA seemed to be a 6-months survival stronger indicator than Subjective Global Assessment (SGA) and disease severity (defined through Union Contre le Cancer [UICC)] score). Several PhA cut-offs have been proposed as survival prognostic scores in oncologic cohorts [7-9].

A possible limitation of large use of PhA as a prognostic marker in several contexts of clinical practice could be the need to be adjusted for sex and age [4] and the poor discrimination between cachexia with dehydration and normal weight with fluid overload [15]. The gold standard methods to investigate body fluid volumes are isotopic dilution techniques. They include deuterium oxide for the measurement of TBW, bromide dilution for the measurement of ECF and total-body potassium for the determination of ICF [16]. In chronic hemodialysis patients, multi-frequency BIA significantly correlated with direct estimation methods [16], even if some reports showed that multi-frequency impedance method could slightly underestimate TBW and overestimate ECW volumes compared to reference methods, both in adult kidney transplant recipients [17] and in children and adolescents treated with dialysis [18]. Lukaski et al. [15] defined IR as a practical approach to identify malnutrition and prognosis by depicting individual fluid distribution; they also recommend an assessment of hydration status, because inflammation, present in disease-related malnutrition and aging, affects fluid distribution.

However, a few studies investigated the role of IR as indicator of nutritional status and fluid overload. Indeed, the use of multi-frequency BIA devices is not widespread. To date, the prognostic role of IR appeared clear in patients admitted in Intensive Care Unit (ICU) [19] and in patients affected by head and neck cancer [20] and hemodialysis patients [21].

The relationship between PhA and IR, in our knowledge, was already investigated in a hospital study (109 patients) in which a strong inverse correlation (r= -0.97, p<0.0001) was found between the two variables. IR was found to have a greater sensitivity compared to PhA, in detecting malnutrition among gastroenterological hospitalized patients [10].

To confirm these data in several clinical conditions, we compared PhA and IR across three series of patients (commonly examined during our daily clinical practice in our center), and a set of healthy subjects.

In our report, neurological patients (affected by Steinert disease) show the worst values of both PhA (3.72±1.38) and IR (0.863±0.045); not surprisingly, healthy subjects have a higher PhA (5.53±0.70) and a lower IR (0.801±0.023) compared to those of the other cohorts.

IR and PhA are clearly correlated. However, although the commonly generated PhA depends on Reactance (Xc) and Resistance (R) at 50 kHz (single-frequency BIA), IR is the ratio between two impedances at 200 kHz and 5 kHz. Impedance (Z) and resistance (R) have different values depending on the frequencies at which they are measured. Indeed, at 50 kHz, current does not cross the cell membranes, and the Z is practically determined only by R (Z=R); instead, at higher frequencies (100-200 kHz), current goes through the cell membranes, reactance increases and resistance decreases. Z is given by both of R and Xc.

In norm-hydrated patients, Z is lower at 200 kHz than at 5 kHz and IR is lower than 1. Instead, in settings of "sick" cell membranes, Z is high, even at 200 KHz, so the ratio of the two impedances approaches unity.

Our study confirms the specular relation between PhA and IR: this confers to IR reliability for analyzing nutritional status. Moreover, IR may be useful to evaluate hydration status in patients with fluid overload such as in settings of decompensated heart or renal failure or decompensated cirrhosis.

We think IR may have in the next future a large diffusion in clinical settings, given its non-invasiveness, quickness and easiness to use.

This study did not use clinical endpoints to validate IR; it is focused only on the relationship between PhA and IR. We confirmed, in different clinical contexts, the inverse correlation between PhA and IR. Further studies are needed to correlate IR to clinical outcomes and validate its clinical use in altered fluid distribution settings.

Conclusion

As previously reported, we confirm the strong inverse correlation between PhA and IR in different clinical conditions. IR may have a larger diffusion than now in several clinical settings, given its non-invasiveness, quickness and easiness to use. Further studies are needed to find the clinical role of IR in different settings.

Tables

Table 1: Main characteristics of patients admitted to Gastroenterology Department.

	GastroenterologyDepartment (161 patients)
Age (ys)	63.1 ± 17.7
Female	62 (39%)
BMI (kg/m^2)	24.89 ± 4.95
Albumin (g/l)	30.9 ± 6.9
Creatinine (mg/dl)	0.9 ± 0.5
NRS-2002[11] ≥ 3	80 (50%)
PhA	4.47 ± 1.19
IR	0.853 ± 0.040

Abbreviations: BMI: Body Mass Index; NRS-2002: Nutritional Risk Screening 2002; PhA: Phase Angle; IR: Impedance Ratio

Table 2: Main characteristics of patients admitted to Pediatric Oncology Unit.

	PediatricOncology Unit (26 patients)
Age (ys)	12.4 ± 4.3
Female	11 (58%)
BMI (kg/m^2)	20.39 ± 4.74
Albumin (g/l)	39.2 ± 4.3
Creatinine (mg/dl)	0.8 ± 0.1
STRONGkids[12] ≥ 3	13 (50%)
PhA	4.20 ± 1.02
IR	0.854 ± 0.039

Table 3: Main characteristics of patients affected by Steinert disease.

	Steinertdisease (23 patients)
Age (ys)	48.3 ± 16.3
Female	12 (52%)
BMI (kg/m^2)	24.02 ± 4.34
NRS-2002[11] ≥ 3	4 (18%)
PhA	3.72 ± 1.38
IR	0.863 ± 0.045

Abbreviations: BMI: Body Mass Index; PhA: Phase Angle; IR: Impedance Ratio

Table 4: Main characteristics of patients affected by Steinert disease.

	Healthy controls (17 subjects)
Age (ys)	57.7 ± 0.5
Female	9 (53%)
BMI (kg/m^2)	25.98 ± 4.65
NRS-2002[11] ≥ 3	1 (5%)
PhA	5.53 ± 0.70
IR	0.801 ± 0.023

Abbreviations: BMI: Body Mass Index; NRS-2002: Nutritional Risk Screening 2002; PhA: Phase Angle; IR: Impedance Ratio

Figures

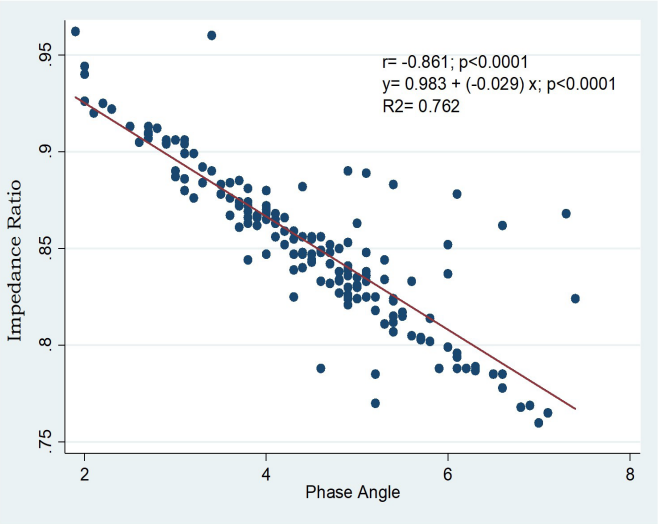

Figure 1: Correlation between PhA and IR in Gastroenterology admitted patients.

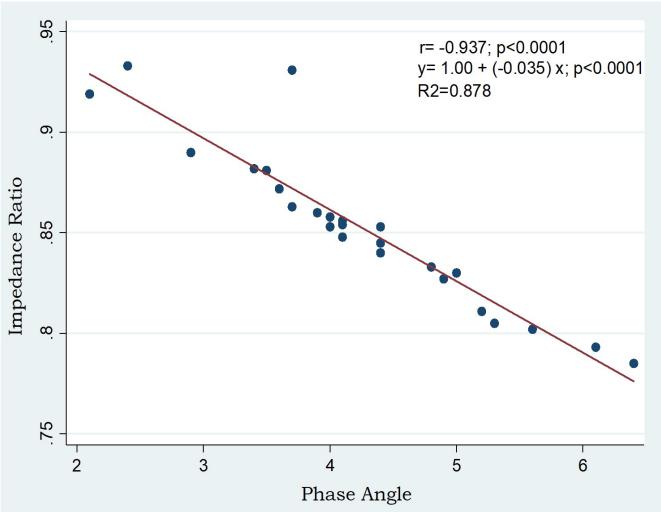

Figure 2: Correlation between PhA and IR in Pediatric Oncology Unit.

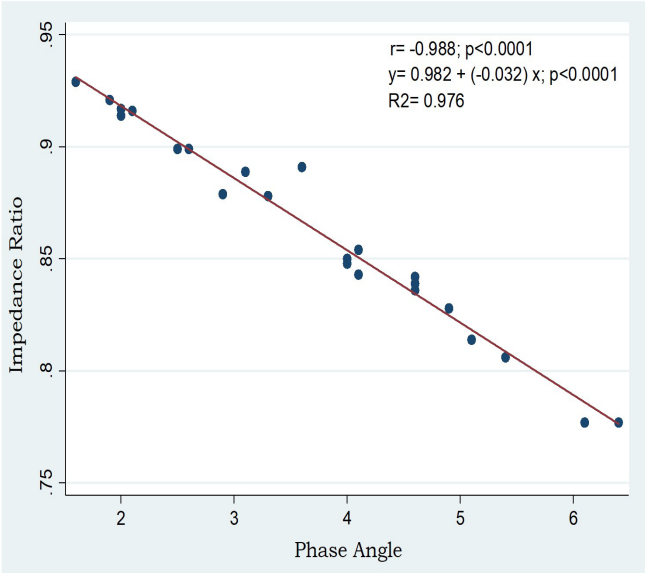

Figure 3: Correlation between PhA and IR in patients affected by Steinert disease.

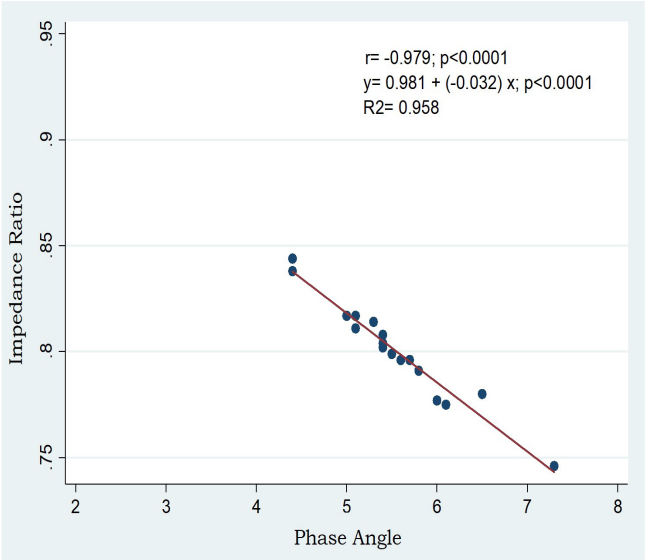

Figure 4: Correlation between PhA and IR in healthy control subjects.

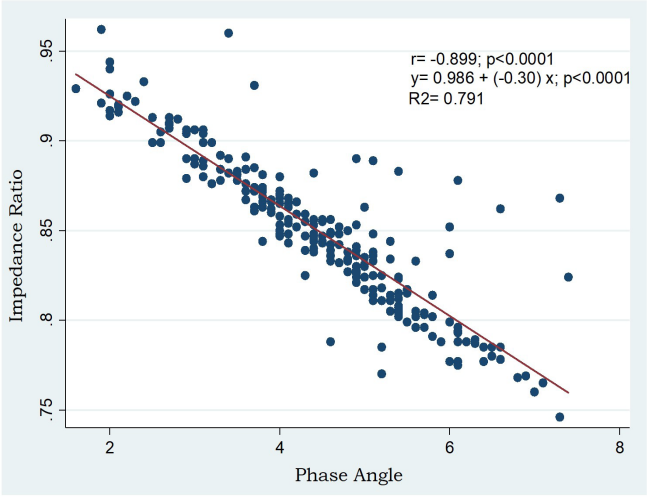

Figure 5: Correlation between PhA and IR in overall population (227 subjects).

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