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Original article

Bioelectrical impedance phase angle relates to function, disease severity and prognosis in stable chronic obstructive pulmonary disease

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SUMMARY

Background & aims: Bioelectrical impedance analysis (BIA) provides a simple method to assess changes in body composition. Raw BIA variables such as phase angle provide direct information on cellular mass and integrity, without the assumptions inherent in estimating body compartments, e.g. fat-free mass (FFM). Phase angle is a strong functional and prognostic marker in many disease states, but data in COPD are lacking. Our aims were to describe the measurement of phase angle in patients with stable COPD and determine the construct and discriminate validity of phase angle by assessing its relationship with established markers of function, disease severity and prognosis.

Methods: 502 outpatients with stable COPD were studied. Phase angle and FFM by BIA, quadriceps strength (QMVC), 4-m gait speed (4MGS), 5 sit-to-stand time (5STS), incremental shuttle walk (ISW), and composite prognostic indices (ADO, iBODE) were measured. Patients were stratified into normal and low phase angle and FFM index.

Results: Phase angle correlated positively with FFM and functional outcomes ($r = 0.35–0.66$, $p < 0.001$) and negatively with prognostic indices ($r = -0.35$ to -0.48, $p < 0.001$). In regression models, phase angle was independently associated with ISW, ADO and iBODE whereas FFM was removed. One hundred and seventy patients (33.9% [95% CI, 29.9–38.1]) had a low phase angle. Phenotypic characteristics included lower QMVC, ISW, and 4MGS, higher 5STS, ADO and iBODE scores, and more exacerbations and hospital days in past year. The proportion of patients to have died was significantly higher in patients with low phase angle compared to those with normal phase angle (8.2% versus 3.6%, $p = 0.02$).

Conclusion: Phase angle relates to markers of function, disease severity and prognosis in patients with COPD. As a directly measured variable, phase angle offers more useful information than fat-free mass indices.

1. Introduction

Skeletal muscle dysfunction and changes in body composition are important extra-pulmonary manifestations of chronic obstructive pulmonary disease (COPD) that occur in all stages of disease [1] and are associated with poor outcome [2,3]. Bioelectrical impedance analysis (BIA) provides a portable, non-invasive and simple method to assess body composition through the measurement of resistance; the opposition of tissue to a current, and reactance; the delay in the flow of current caused by tissue capacitance [4]. Phase angle is an established raw BIA variable, calculated as the ratio of resistance over reactance, and expressed

Abbreviations: ADO, age dyspnea obstruction; BIA, bioelectrical impedance analysis; BMI, body mass index; iBODE, body mass index, obstruction, dyspnea, exercise capacity index; COPD, chronic obstructive pulmonary disease; CAT, COPD assessment test; FFM, fat-free mass (FFM); FFMI, fat-free mass index; GOLD, global initiative for chronic obstructive lung disease; MRC, Medical Research Council; QMVC, quadriceps maximum voluntary contraction; 4MGS, 4-m gait speed; 5STS, 5 sit-to-stand; ISW, incremental shuttle walk.

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as a degree [4]. It provides information on hydration status, cellular mass and quality, and is not limited by the inherent assumptions when using BIA to estimate body compartments [4,5].

In the healthy population, phase angle typically ranges between 5 and 7° and varies accordingly to age (reduced with), gender (reduced in females) and BMI (increases with) [5,6]. A larger phase angle suggests greater cell quantity and/or cellular health, while a smaller phase angle suggests cellular loss or reduced cellular integrity [5]. Across numerous disease states including cancer, heart failure, liver cirrhosis and HIV/AIDS phase angle is reduced and is associated with levels of inflammation, malnutrition and physical inactivity [6,7]. It is also a consistently strong functional and prognostic indicator [7–10]. However, very limited data exist in patients with COPD as BIA in this population is most often used to estimate fat free mass (FFM) using disease-specific algorithms [11,12].

The aims of this study were to first describe the measurement of phase angle in patients with stable COPD and second to determine the construct and discriminate validity of phase angle in this group by assessing its relationship with established markers of function, disease severity and prognosis. A final aim was to compare phase angle to FFM according to the ability to discriminate patients according to physical functioning and disease severity.

2. Materials and methods

2.1. Participants

Patients diagnosed with COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) [13] guidelines were recruited from respiratory outpatient clinics at Harefield Hospital (Harefield, UK) between December 2012 and January 2014. Exclusion criteria included an, exacerbation within the preceding 4 weeks, unstable cardiac disease, or a contraindication to BIA including an implanted pacemaker, defibrillator or joint prosthesis. All participants gave written informed consent and the study was approved by the London Camberwell St Giles and the West London Research Ethics Committees (11/LO/1780 and 11/H0707/2 and respectively).

2.2. Bioelectrical impedance

Whole-body BIA was performed after a fast of ≥1.5 h with empty bladder using a Bodystat Quadscan 4000 analyzer (Bodystat Ltd., Isle of Man, UK) with no moderate or vigorous exercise in the preceding twelve hours. A single tetrapolar measurement of resistance (R) and reactance (Xc) was taken by applying an alternating current of 800 μA (μA) at 50 Hz. Patients were positioned supine on a non-conductive surface with their arms and legs abducted at 30° throughout and rested for 15 min before measurement. Surface electrodes (Bodystat Ltd.) were placed on the dorsum of the hand, wrist, ankle and foot of the dominant side of the body. Reliability of within-day measurements has been reported as <2% for R and <3.5% for Xc [14].

Phase angle was calculated using the equation: phase angle (°) = arctan (Xc/R) × (180°/π) using Phase Angle Software (Bodystat Ltd.). Individual phase angles were categorized as being low or normal; falling below or above the fifth percentile of age-, sex- and BMI-stratified reference values derived from a large healthy cohort (n = 214,732) [14]. Individual standardized phase angles were also calculated using reference values and calculated as: standardized phase angle = (observed phase angle − mean phase angle)/SD of phase angle, where mean and SD are taken from healthy reference values [14].

Fat-free mass (FFM) and fat-free mass index (FFMI kg/m^2 = FFM/height^2) were calculated using a disease- and sex-specific regression equations; males = 8.383 + 0.465height^2/R + 0.213weight; females = 7.610 + 0.474height^2/R + 0.184weight [11,12,15]. Individual FFMI values were categorized as being low or normal; falling below or above the fifth percentile of age-, sex- and BMI-stratified reference values from the UK Biobank (n = 186,975) [16].

2.3. Additional measurements

Body Mass Index (BMI) was calculated as the ratio of weight, measured to the nearest 0.1 kg, and height-squared (kg/m^2). Forced Expiratory Volume in one second (FEV_1) and forced vital capacity (FVC) were assessed by spirometry, breathlessness using the Medical Research Council (MRC) dyspnea scale [17] and comorbidities recorded using the age-adjusted Charlson Index [18]. Functional measures included quadriceps maximum voluntary contraction (QMVC) [19], 4-m gait speed (4MGS) [20], 5-repetition sit-to-stand (5STS) [21] and incremental shuttle walk (ISW) [22]. Health-related quality of life was assessed using the St Georges Respiratory Questionnaire (SGRQ) [23] and the COPD Assessment Test (CAT) [24,25]. Composite prognostic indices, the BODE index (iBODE) [26] and Age Dyspnea Obstruction (ADO) index [27], were used as surrogates of global disease severity. The number of exacerbations (defined as any increase in breathlessness, cough or sputum production that led to a change in usual medication) and hospital inpatient days (length of stay >24 h) in the previous year were obtained by patient self-report and corroborated by primary care and hospital records. Participants were followed up prospectively and deaths were identified from next of kin, hospital and general practice records.

2.4. Statistical analysis

Data were presented as proportions with 95% confidence intervals or median [inter-quartile range, IQR] where data were not normally distributed. Spearman's correlation coefficient was used to quantify the relationship between phase angle, FFM and FFMI with other variables. Comparisons between patients with a low and a normal phase angle or FFMI were performed using a Mann–Whitney U test.

Multivariable regression was used to investigate determinants of square-root transformed ISW distance, 4MGS, 5STS and ADO scores. Phase angle, FFMI, age, sex, BMI, FEV_1 % predicted, MRC Dyspnea, QMVC and Charlson index were considered as independent variables. Age, FEV_1 % predicted and MRC Dyspnea were not considered for the ADO score model as they are components of this composite index. After checking for co-linearity between independent variables ($r < 0.5$), a stepwise approach was used to retain or remove them from the model; entry criterion $p < 0.05$, removal criterion $p \geq 0.10$.

To explore prognostic utility, the cohort was followed up to September 2014 and the proportion of deaths in groups according to low and normal phase angle and FFMI were compared using Pearson's chi-squared test. To control for Type I errors in view of multiple testing a p value <0.01 was considered statistically significant. Statistical analysis and graphical presentations were performed using SPSS version 19 (IBM, New York, USA) and GraphPad Prism 5 (GraphPad software, San Diago, USA) respectively.

3. Results

Five-hundred and two patients with stable COPD were included in the study; phenotypic data on some of these patients has been previously reported [21,22]. Participants (295 male/207 female)