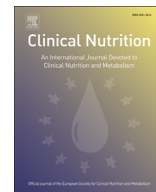




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Original article

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.

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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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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

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 μ A (μ A) 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 ($^{\circ}$) = $\arctan(Xc/R) \times (180^{\circ}/\pi)$ 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 $\text{kg}/\text{m}^2 = \text{FFM}/\text{height}^2$) were calculated using a disease- and sex-specific regression equations; males = $8.383 + 0.465\text{height}^2/\text{R} + 0.213\text{weight}$; females = $7.610 + 0.474\text{height}^2/\text{R} + 0.184\text{weight}$ [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 Diego, 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)

had a median [IQR] age of 71 [64–77] years, BMI of 24.7 [23.5–32.4] kg/m², FEV₁% predicted of 45 [32–62] and MRC dyspnea score of 3 [3–4]. Nine percent, 33%, 38% and 20% of patients had GOLD spirometric stage I, II, III and IV disease respectively [13]. Forty-eight (10%) and 34 (7%) patients were prescribed ambulatory and long term domiciliary oxygen respectively. The median [IQR] Charlson index was 1 [1–2] with 2 [1–4] exacerbations reported in the preceding year.

3.1. Cross-sectional measurement of phase angle

The median [IQR] phase angle was 4.7° [4.0–5.4°] and ranged from 1.8° to 7.6°. As known determinants, phase angle was expectedly higher in males compared to females (4.9 (1.0) vs. 4.3 (0.9); $p < 0.001$) and correlated positively with BMI ($r = 0.37$, $p < 0.001$) and negatively with age ($r = -0.47$, $p < 0.001$). The use of standardized phase angles showed that 55.4% [95% CI 51.0–59.7%] and 28.9% [25.1–33.0%] of patients had phase angles more than 1 SD below and between –1 and 0 SD of population norms respectively and only 15.7% [12.8–19.2%] had values over population means (Fig. 1).

3.2. Characteristics associated with phase angle

Phase angle correlated positively with FEV₁% predicted, QMVC, ISW and 4MGS, and negatively correlated with MRC and ADO score, iBODE, 5STS and the SGRQ activity domain. Phase angle was moderately and positively correlated with FFM ($r = 0.47$, $p < 0.001$). For all variables the correlation with phase angle was stronger than that with FFM (Table 1).

ISW was independently associated with phase angle (β 52.87 [95% CI 35.28–70.18] $p < 0.001$) when adjusted for age, sex, MRC score, BMI and QMVC. Neither FFMI ($p = 0.59$), age ($p = 0.62$), FEV₁% predicted ($p = 0.17$) nor Charlson index ($p = 0.51$) were significantly related to ISW and were removed from the model.

4MGS was independently associated with phase angle (β 0.06 [95% CI 0.03–0.09] $p < 0.001$) when adjusted for sex, BMI, MRC score and QMVC. Neither FFMI ($p = 0.24$), age ($p = 0.56$), FEV₁% predicted ($p = 0.90$) or Charlson index ($p = 0.28$) were significantly related to 4MGS and were removed from the model.

5STS was independently associated with phase angle (β –1.14 [95% CI –2.18 to –0.10] $p < 0.001$) when adjusted for sex, BMI, MRC score and QMVC. Neither FFMI ($p = 0.41$), age ($p = 0.08$), FEV₁%

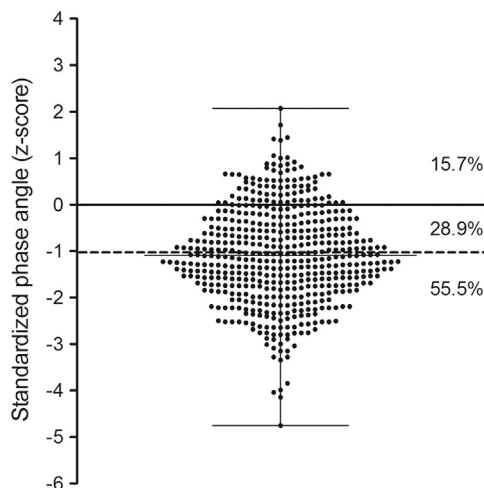


Fig. 1. Distribution of standardized phase angles in COPD; z-scores indicate the patient's deviation from age-, sex- and BMI-stratified population norms.

Table 1

Relationships between phase angle, fat free mass or fat free mass index and physical function or disease severity in patients with COPD.

	Phase angle		FFM		FFMI	
	ρ	p-value	ρ	p-value	ρ	p-value
Age	–0.47	<0.001	–0.17	0.11	0.04	0.38
BMI, kgm ^{–2}	0.37	<0.001	0.47	<0.001	0.64	<0.001
FEV ₁ % predicted	0.21	<0.001	0.13	0.003	0.17	<0.001
MRC dyspnea score	–0.19	<0.001	–0.01	0.75	0.08	0.048
ADO score	–0.48	<0.001	–0.09	0.04	–0.02	0.68
iBODE	–0.35	<0.001	–0.11	0.02	–0.04	0.34
QMVC, kg	0.66	<0.001	0.65	<0.001	0.50	<0.001
ISW distance, m	0.43	<0.001	0.11	0.02	–0.02	0.71
4MGS, ms ^{–1}	0.35	<0.001	0.13	0.01	0.05	0.31
5STS time, s	–0.30	<0.001	0.06	0.31	0.05	0.38
SGRQ						
Symptoms	0.04	0.41	–0.01	0.83	–0.03	0.58
Activity	–0.14	0.01	–0.13	0.01	–0.11	0.03
Impact	0.01	0.90	–0.03	0.51	–0.05	0.35
Total	–0.05	0.29	–0.07	0.18	–0.07	0.15
CAT score	–0.07	0.18	–0.07	0.18	–0.09	0.09

BMI, body mass index; FEV₁, forced expiratory volume in one second; MRC, Medical Research Council; QMVC, quadriceps maximum voluntary strength; ISW, incremental shuttle walk; 4MGS, 4 m gait speed; 5STS, 5 sit-to-stand; SGRQ, St George's Respiratory Questionnaire; CAT, COPD assessment test.

predicted ($p = 0.17$) or Charlson index ($p = 0.83$) were significantly related to 5STS and were removed from the model.

ADO score was independently associated with phase angle (β –0.96 [95% CI –1.13 to –0.78] $p < 0.001$) adjusted for BMI and sex. Neither FFMI ($p = 0.62$), QMVC ($p = 0.08$) or Charlson index ($p = 0.55$) were significantly related to ADO score and were removed from the model. Phase angle was the only variable to be retained in the regression model for iBODE (β –0.73 [95% CI –0.98 to –0.50] $p < 0.001$).

3.3. The low phase angle phenotype

One hundred and seventy patients (33.9% [95% CI, 29.9 to 38.1]) had a phase angle below the fifth percentile of age, sex- and BMI-stratified reference values. Patients with a low phase angle had significantly reduced quadriceps strength, ISW, 4MGS and increased 5STS time compared to patients with a normal phase angle (all $p < 0.001$) (Table 2, Fig. 2). The activity domain of the SGRQ was significantly reduced in patients with a low phase angle, though symptom and impact domains, and total SGRQ score were similar. Patients with a low phase angle had higher CAT, ADO and iBODE scores, and reported more exacerbations and hospital inpatient days in the previous year (Table 2).

A similar proportion of the sample, 34.1% [95% CI 30.1–38.3], had a low FFMI. Compared to phase angle, the cut-offs for FFMI were less discriminate with regards to physical functioning and disease severity (Table 2). Patients with a low FFMI had significantly reduced QMVC but an increased ISW distance compared to those with a normal FFMI (Table 2).

3.4. Prognostic utility of phase angle

There was no loss to follow up and median (range) follow up duration was 469 (132–680) days and did not differ between groups according to a low or normal phase angle ($p = 0.70$) or FFMI status ($p = 0.22$). In total, 25 deaths (5.0%) occurred during the follow-up period. The proportion of patients to have died was significantly higher in patients with a low phase angle compared to those with a normal phase angle (8.2% versus 3.6%, $p = 0.02$). In contrast, the number of deaths observed were

Table 2
Physical functioning and disease severity according to phase angle or fat-free mass index in patients with COPD.

	Phase angle			FFMI		
	Low	Normal	p-value	Low	Normal	p-value
Number (%)	170 (33.9)	332 (66.1)		171 (34.1)	331 (65.9)	
FEV ₁ % predicted	40 [28–58]	48 [36–64]	<0.001	43 [27–64]	48 [35–65]	0.30
MRC score	4 [3–4]	3 [2–4]	<0.001	3 [2–4]	3 [3–4]	0.22
ADO	6 [5–7]	5 [4–6]	<0.001	5 [3–6]	5 [4–6]	0.02
iBODE	6 [5–8]	5 [3–6]	<0.001	5 [2–6]	5 [3–7]	0.22
QMVC, kg	19.6 [11.7–25.2]	23.9 [19.5–39.6]	<0.001	23.1 [18.0–29.1]	26.6 [18.9–34.0]	0.002
ISW distance, m	130 [70–210]	250 [140–335]	<0.001	250 [170–350]	210 [140–283]	0.003
4MGS, ms ⁻¹	0.78 [0.60–0.94]	0.95 [0.80–1.08]	<0.001	0.98 [0.80–1.12]	0.93 [0.80–1.05]	0.30
5STS time, s	14.4 [12.6–19.4]	13.0 [10.9–15.5]	<0.001	12.6 [10.8–15.0]	13.3 [11.5–16.4]	0.06
SGRQ						
Symptoms	67.4 [51.5–90.4]	64.6 [37.9–79.3]	0.32	67.3 [50.9–86.4]	69.3 [51.5–82.1]	1.00
Activity	80.7 [59.5–92.5]	67.7 [53.6–85.6]	0.001	72.8 [59.35–85.8]	72.4 [54.4–85.9]	0.64
Impact	39.0 [21.0–56.9]	32.7 [22.6–46.8]	0.39	32.6 [21.1–50.4]	37.1 [22.8–50.3]	0.63
Total	58.1 [37.9–71.6]	50.4 [37.4–61.2]	0.08	50.9 [38.8–62.4]	53.2 [39.9–64.5]	0.85
CAT score	23 [17–27]	20 [15–24]s	0.005	20 [14–26]	21 [16–26]	0.59
Exacerbations	3 [1–5]	2 [1–4]	0.003	2 [1–4]	2 [1–4]	0.31
Hospital Days	1 [0–5]	0 [0–2]	<0.001	0 [0–1]	0 [0–2]	0.15

Data are median [interquartile range] unless stated otherwise. BMI, body mass index; MUST, malnutrition universal screening tool; FEV₁, forced expiratory volume in one second; MRC, Medical Research Council; QMVC, quadriceps maximum voluntary strength; ISW, incremental shuttle walk; 4MGS, 4 m gait speed; 5STS, 5-repetition sit-to-stand; SGRQ, St George's Respiratory Questionnaire; CAT, COPD assessment test.

similar between patients with a low or normal FFMI (6.4% versus 4.2%, $p = 0.18$).

4. Discussion

In a stable cohort of 502 outpatients with COPD, we have demonstrated that phase angle is independently associated with measures of physical function and disease severity. Stratification of patients by 5th percentile sex-, age- and BMI-specific population norms identified patients with significant impairment in exercise capacity and greater levels of disease severity, including prognostic indices, exacerbations and hospital admissions. In both regards, phase angle was supported as a valid functional and prognostic biomarker, and offered information beyond FFMI, which did not identify patients with the greatest level of impairment or disease severity.

4.1. Critique of the method

This is the first study of phase angle to be reported in COPD, with the exception of an abstract with no quantitative data [28]. Strengths include the large cohort of patients with comprehensive clinical phenotypic data, and the use of generalizable cut-off values which are based on population norms stratified by the major determinants of phase angle [6,14]. This is an advantage over studies examining phase angle in other populations [8] and previous studies investigating FFM in COPD [29], which derive cut-offs from within the study population and are not generalizable. Using standardized phase angles to quantify individual patient deviation from population norms we demonstrated over half of the stable population (55.4% [95% CI 51.0–59.7%]) to have values >1 SD below age-, sex- and BMI-specific reference values. Another novel observation was the relative discriminative value of phase angle compared with FFM indices, the most commonly derived variables from bioelectric impedance analysis in studies of patients with COPD.

We acknowledge limitations to the study. We did not include a non-BIA measure of muscle mass. To our knowledge phase angle has not been validated against muscle mass nor been used for this purpose. The cross-sectional data provides information about plausible associations with functional markers, but longitudinal

data are required to examine if phase angle can predict risk of functional decline. The close alignment with quadriceps muscle voluntary contraction, exercise capacity and composite prognostic indices (all previously demonstrated to have an association with survival [27]), suggests that phase angle may also predict mortality as it does in several other diseases [7–10]. Our initial analysis of survival supports this notion; however the follow-up time was short for the population and there were only a small number of observed events. A formal evaluation of prognostic utility is required before recommending phase angle as a clinically useful variable. Additional BIA measures, including multi-frequency outputs may also have prognostic value and require further study. Finally, the limited fasting period prior to the measurement, and use of multiple examiners may have introduced variability bias, though a standardized protocol was followed and there is consistently strong reliability data from our group [20,21].

4.2. Significance of the findings

BIA offers a practical means to assess estimate body composition in the clinical setting [11,12]. Potentially more accurate methods exist to assess muscle mass, e.g. computed tomography or magnetic resonance imaging [30], dual energy X-ray absorptiometry [11], but are expensive, and often poorly accessible in some health settings.

In COPD, fat free mass has been validated as a measure of whole-body muscle mass showing high correlations with gold-standard reference methods [12,31] and with fiber cross sectional area [32]. It demonstrates modest utility as a prognosis marker [12,33,34]. Most recently, FFMI was shown to predict all-cause mortality at 3 years in the ECLIPSE cohort (hazard ratio 0.85 [95% CI 0.75–0.96]) [36]. The relationships between FFM and markers of physical function or disease severity are less well understood. FFMI has been used to discriminate patients according to exercise capacity in small studies [15,35]. However, in the largest cohort ($n = 1795$), FFMI was not associated with exercise capacity and values were identical ($17(3) \text{ kg/m}^2$) in patients walking more or less than 350 m [36]. In other stable populations similar MRC dyspnea and health status scores have been observed in patients with low and normal FFMI [34,37]. There is ongoing debate about what constitutes a low or normal FFMI [29], though this issue has recently been helped by age-, sex- and BMI-stratified reference

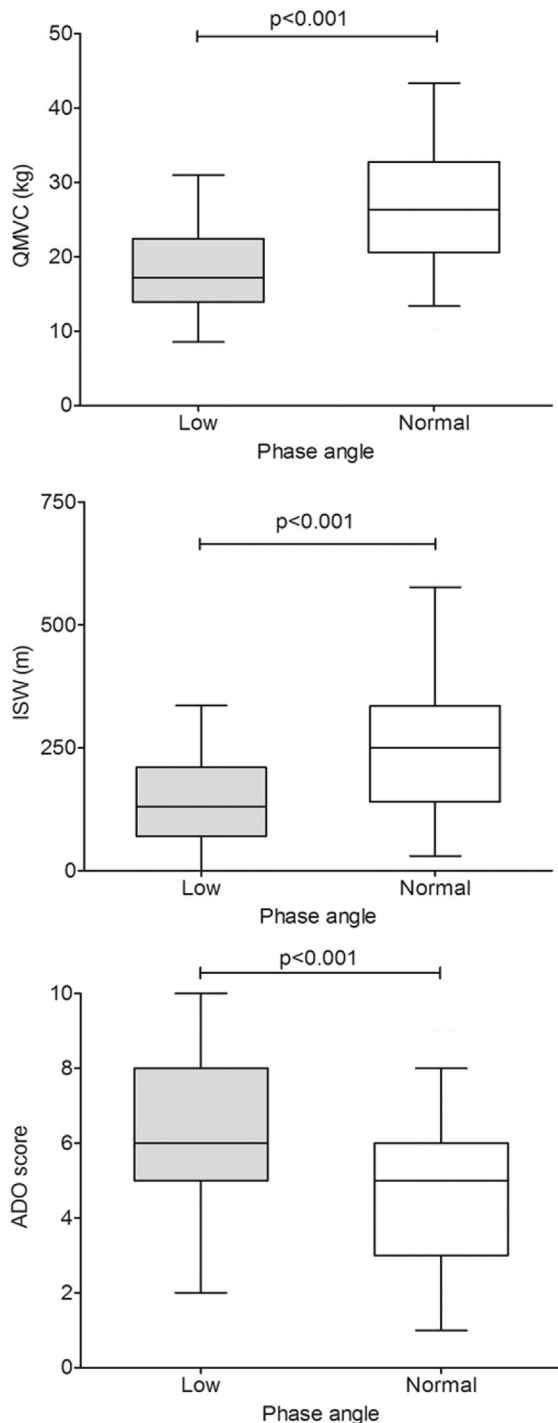


Fig. 2. Quadriceps strength, functional exercise capacity and disease severity in patients with COPD according to a low or normal phase angle.

values used in this study [16]. In our stable population, phase angle was more closely related to functional outcomes and markers of disease severity than FFM and FFMI. Phase angle was significantly correlated with a range of function outcomes, e.g. QMVC, ISW and 4MGS, and markers of disease severity, e.g. MRC and ADO score. For all variables tested, correlation with phase angle was stronger than that with FFM or FFMI. Phase angle was also retained in multivariate regression models for ISW (with BMI, FEV₁% predicted and age) and for ADO score (with BMI and sex), whereas FFM and the Charlson index were removed.

By stratifying patients according to age-, sex- and BMI-stratified population norms, we have also described the low phase angle phenotype, which exhibited reduced quadriceps strength, ISW, 4MGS and increased 5STS time, as well as higher CAT, ADO and iBODE scores compared to those with a normal phase angle. Comparatively, FFMI was less discriminate and could not discriminate patients according to physical functioning and disease severity, in cases offering conflicting information for example reduced strength and increased exercise capacity. Neither measure was closely related to health related quality of life and only the activity domain of the SGRQ aligning with phase angle. This may reflect the previously observed U-shaped relationship between measures of body composition and quality of life [34].

Our findings add to evidence regarding clinical applications of BIA beyond use in body composition equations [5]. As a direct measure, phase angle can be used in scenarios where the assumptions for FFM equations are violated, such as obese patients [12] and in acute settings where hydration is disturbed by fluid shift [5,38]. Where FFM can be reliably estimated, we propose that phase angle provides additional and complementary information. The population based cut off used in this study allow stratification of patients who might benefit most from nutritional, anabolic or exercise interventions, though such approaches required testing and values from different BIA devices differ slightly. Given the respective relationships between phase angle and prognostic indices, we hypothesize that phase angle will be a strong prognostic marker, but longitudinal studies are required to confirm this.

In conclusion, phase angle derived from bioelectrical impedance analysis is a valid marker of function and disease severity in stable COPD and demonstrates promising prognostic utility. As a directly measured variable, phase angle offers more useful information than fat-free mass indices.

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Statement of authorship

WD-CM & MM designed the research. SK, SEJ, JLC, CN, MM conducted the research. MM, WG, WD-CM analyzed data and performed statistical analysis, which was reviewed by MIP, IH & WD-CM. MM, SEJ & GW produced a first draft of the manuscript. WD-CM had primary responsibility for final content. All authors read and approved the final manuscript.

Conflicts of interests

There are no conflicts of interest to declare.

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