Original Article

Clinical usefulness of phase angle as an indicator of muscle wasting and malnutrition in inpatients with cardiovascular diseases

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Background and Objectives: Extracellular water is increased in patients with edema, such as those with chronic heart failure, and it is difficult to assess skeletal muscle mass with the skeletal muscle mass index when extracellular water is high. We investigated the relationship between phase angle and physical function, nutritional indices, and sarcopenia in patients with cardiovascular diseases, including chronic heart failure. **Methods and Study Design:** In 590 patients with cardiovascular diseases (372 men), handgrip strength, gait speed, and anterior mid-thigh muscle thickness by ultrasound were measured, and the skeletal muscle mass index, phase angle, and the extracellular water: total body water ratio were measured with a bioelectrical impedance analyzer, and presence of sarcopenia was evaluated. **Results:** Phase angle, but not the skeletal muscle mass index, was correlated with serum albumin ($r = 0.377$, $p < 0.001$) and hemoglobin values in women. Multivariate regression analysis showed that at the extracellular water: total body water ratio below 0.4, both phase angle and skeletal muscle mass index were independent determinants of handgrip strength and log mid-thigh muscle thickness in men, after adjustment for age and presence of chronic heart failure. In contrast, for the ratio of 0.4 or greater, after adjustment for age and presence of chronic heart failure, phase angle was a stronger independent determinant of handgrip strength and log mid-thigh muscle thickness than the skeletal muscle mass index in men. **Conclusions:** Phase angle is a good marker of muscle wasting and malnutrition in patients with cardiovascular disease, including chronic heart failure.

Key Words: phase angle, extracellular water, sarcopenia, malnutrition, cardiovascular disease

INTRODUCTION

Malnutrition and muscle wasting are frequently observed among hospitalized patients and those with cardiovascular disease (CVD),[1,2] and muscle wasting has been reported to be associated with higher mortality and morbidity.[3,4] Therefore, assessment of the skeletal muscle mass index (SMI) is important for diagnosis to prevent sarcopenia in the elderly, including patients with CVD.[5-8] Chronic heart failure (CHF) has an incidence of 1-2% in the overall population.[9] It has a serious impact on quality of life due to its symptoms, is a common cause of hospitalization, and is associated with greater overall mortality. Patients with CHF and low appendicular skeletal muscle mass have an increased risk of reduced muscle function,[10] and sarcopenia in patients with CHF may ultimately lead to tissue wasting or cardiac cachexia, which is associated

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with a very poor prognosis.[11-13] Thus, the diagnosis of sarcopenia is necessary in patients with CHF, but it has been reported that patients with CVD, especially those with CHF, are typically overhydrated, and use of the SMI to diagnose sarcopenia can often cause errors. Extracellular water (ECW) content can be assessed with the extracellular water: total body water (TBW) ratio (ECW/TBW) using bioelectrical impedance analysis (BIA), and an ECW/TBW of 0.4 or greater indicates ECW overload. In a recent study of elderly subjects, the SMI was significantly associated with handgrip strength in those with an ECW/TBW below 0.4, but not in those with an ECW/TBW of 0.4 or greater,[14] suggesting that the SMI is inaccurate in patients with high ECW content.

On the other hand, phase angle (PhA), calculated using BIA, is an angle that expresses the resistance of cell membranes and is closely related to the nutritional status of cells and cell membranes, which is reflected in somatic cell volume.[15-17] In normal cells with structurally perfect cell membranes, such as healthy individuals and athletes, PhA is measured to be high, while in damaged cells with structurally damaged cell membranes or reduced cell density, such as aging or cancer, PhA is measured to be low. PhA is known to be a predictor of life span in some conditions, such as kidney disease,[18] CVD[17] and cancer.[19] PhA also indicates the average nutritional and inflammatory status over a period of time, which has led to PhA being a predictor of life span.[18] We recently reported that PhA and the SMI correlated with grip strength and knee extension strength in hospitalized patients with CVD,[20] and PhA appears to be a useful marker for sarcopenia, malnutrition, and cachexia. However, it is not clear whether physical function and nutritional indices are determined by PhA or the SMI in patients with ECW overload.

In the present study, we aimed to elucidate whether PhA can determine muscle function and nutritional indices in patients with CVD including CHF, compared to the SMI.

METHODS

Participants

Eligible participants were patients who underwent cardiac rehabilitation on admission due to CVD. We excluded the following types of patients: (1) patients with cerebrovascular disease and those undergoing arthroscopic joint surgery; (2) patients with chronic diseases, such as severe orthopedic disorders, malignancies, or cognitive dysfunction; and (3) patients with pacemaker implantation and a contraindication for BIA methods. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the institutional human research committee. The study protocol was approved by the Regional Ethics Committee of Dokkyo Medical University Hospital (approval number: 27077).

All participants underwent complete laboratory chemistry and hematologic evaluation. Fasting venous blood samples were collected in tubes containing ethylenediaminetetraacetic acid sodium (1 mg/mL) and in polystyrene tubes without an anticoagulant. Plasma was immediately separated by centrifugation at 3000 rpm at 4 °C for 10 min, and serum was collected by centrifugation at 1000 rpm at room temperature for 10 min. Blood hemoglobin (Hb), albumin (Alb), total peripheral lymphocyte count, and total cholesterol (TChol) concentrations were analyzed with routine chemical methods in the Dokkyo Medical University Hospital clinical laboratory.

Controlling Nutritional Status (CONUT) score

The CONUT score, which is calculated based on the serum Alb concentration (range: 0-6), the total peripheral lymphocyte count (range: 0-3), and TChol concentration (range: 0-3), was developed as a screening tool for early detection of poor nutritional status. The sum of the three components comprised the final CONUT score, with a possible range of 0-12. A score of zero indicated a normal nutritional status.[21]

Measurement of gait speed, grip strength, and voluntary isometric contraction

Maximum voluntary isometric contraction (MVIC) of the handgrip was determined with a factory-calibrated hand dynamometer (TKK 5401, TAKEI Scientific Instrument Co., Ltd., Tokyo, Japan). Each subject underwent two trials, and the highest value of the two trials was used for analysis. The gait speed was measured as the time needed to walk 4 m at an ordinary pace. The MVIC of the knee extensors was determined with a digital handheld dynamometer (μTas MT-1, ANIMA Co., Ltd., Tokyo, Japan) as described previously.[22,23] Each subject performed two trials with an interval of at least 2 min between trials, and the highest score was used for analysis.

Measurements with the bioelectrical impedance analyzer

A multi-frequency bioelectrical impedance analyzer, InBody S10 Biospace device (Biospace Co., Ltd., Seoul, Korea/Model JMW140) was used according to the manufacturer's guidelines as described in detail previously.[22,23] Thirty impedance measurements were obtained using 6 different frequencies (1, 5, 50, 250, 500, and 1000 kHz) at the following 5 segments of the body: right and left arms, trunk, and right and left legs. The measurements were carried out while the subjects rested quietly in the supine position, with their elbows extended and relaxed along their trunk. BIA-derived body components, such as skeletal muscle volume, ECW/TBW, and PhA values were recorded. The impedance actually measured by BIA is a generic term for the component that blocks the current, and its resistance value is broadly divided into resistance and reactance. The charge storage capacity of a capacitor is its capacitance, and reactance expresses the difficulty of current flow, and the larger the reactance, the smaller the current flow. Meanwhile, resistance corresponds to the resistance of body water with intra- and extracellular fluid as conductors. The relationship between reactance and capacitance in a capacitor can be expressed as $Xc = 1 / (2\pi fC)$ (where Xc: reactance, f: frequency, C: capacitance), where the larger the capacitance, the smaller the reactance and the larger the current [24]. Impedance is the sum of reactance and resistance squared, expressed as $Z^2 = R^2 + Xc^2$ (where Z: impedance, R: resistance, Xc: reactance), and PhA is the arctangent value of reactance divided by resistance, expressed as PhA = arctangent

(Xc/R) × (180/π) (where Xc: reactance, R: resistance).[25,26] PhA has values ranging from a maximum of 90° to a minimum of 0°, with PhA increasing proportionally as reactance increases and PhA decreasing as reactance decreases. PhA was calculated with resistance and reactance measured at 50 kHz. The value of ECW/TBW was calculated based on the ratio of ECW to TBW.

Appendicular skeletal muscle mass was measured as the sum of lean soft tissue of the two upper limbs and the two lower limbs. The value of SMI was calculated based on the ratio of the appendicular skeletal muscle mass (kg) to height squared (m^2). In the present study, sarcopenia was defined according to the Asian Working Group for Sarcopenia [5] criteria (handgrip strength, < 26 kg for men and < 18 kg for women; gait speed, ≤ 0.8 m/s; SMI, < 7.0 kg/m^2 for men and < 5.7 kg/m^2 for women). ECW/TBW ≥ 0.4 has been considered to indicate overhydration,[14,27,28] and the participants were divided into two groups: ECW/TBW < 0.40 and ECW/TBW ≥ 0.40.

Measurement of muscle thickness by ultrasound

Quadriceps muscle thickness was measured by ultrasound evaluation at the midpoint of the thigh length with a real-time linear electronic scanner with a 10.0-MHz scanning head and ultrasound probe (L4-12t-RS Probe, GE Healthcare, Tokyo, Japan) and LOGIQ e ultrasound (GE Healthcare, Tokyo, Japan) as previously described.[22,23] The scanning head was coated with a water-soluble transmission gel to provide acoustic contact without depressing the dermal surface. The subcutaneous adipose tissue-muscle interface and the muscle-bone interface were identified from the ultrasound image. The perpendicular distance from the adipose tissue-muscle interface to the muscle-bone interface was considered to represent the quadriceps muscle thickness. The anterior mid-thigh muscle thickness (MTH) was measured in the supine position; the measurement was performed twice at each side of the thigh, and the average value was adopted.

Statistical analysis

Data are presented as the mean ± SD. Data normality was evaluated using the Kolmogorov-Smirnov test. The comparison of means between two groups was carried out with the Mann-Whitney U-test, Student t-test or Chi-square test. The comparison of means among three and more groups was performed with a one-way analysis of variance test or the Kruskal-Wallis test. Associations among parameters were evaluated with Pearson or Spearman correlation coefficients. Multivariate linear regression analysis with physical data or clinical laboratory data as the dependent variable was performed to identify the independent factors (PhA or SMI) that influenced it. Age and presence of CHF were covariates. When the residuals of the dependent or independent data were not normally distributed, they were logarithmically transformed to achieve a normal distribution. Receiver operating characteristic (ROC) curves were plotted to identify an optimal PhA cutoff for detecting sarcopenia. With or without sarcopenia as the dependent factor, the sensitivity, specificity, and false positive rate (1-specificity) of the PhA were calculated to obtain the ROC curve. At this time, the Youden index (sensitivity + specificity - 1) was calculated from the obtained sensitivity and specificity, and the point at the maximal value was taken as the optimum cutoff value. All analyses were performed with SPSS version 28 (IBM Corp., New York, NY, USA) for Windows. A *p*-value less than 0.05 was regarded as significant.

RESULTS

A total of 590 patients were included in this study. Their baseline characteristics are summarized in Table 1. Three hundred and seventy-two patients were men (63%) and 218 patients were women (37%). The mean age and body mass index (BMI) of the men were 68.8 ± 12.3 years and 23.1 ± 3.9 kg/m^2, respectively. The mean age and BMI of the women were 73.8 ± 12.6 years and 22.1 ± 4.5 kg/m^2, respectively. One hundred and four patients underwent coronary artery bypass grafting, 165 had valve replacement or repair, and 62 had aortic surgery, including endovascular aneurysm repair and artificial blood vessel replacement. Nine had arteriosclerosis obliterans, and 76 had transcatheter aortic valve implantations. One hundred and fifty-six patients had CHF, and 148 patients had ischemic heart disease, including angina pectoris and myocardial infarction.

Figure 1 shows the regression equation for ECW/TBW < 0.4 and ECW/TBW ≥ 0.4 and the correlation coefficients and *p* values of the SMI and PhA with the ECW/TBW. The SMI and PhA were significantly corre-

Table 1. Patient physical characteristics

	Men (n = 372)	Women (n = 218)
Specific diseases, n (%)		
Surgical disease		
CABG	83 (22.3%)	21 (9.6%)
Valve surgery	103 (27.7%)	62 (28.4%)
Aortic surgery	49 (13.2%)	13 (6.0%)
ASO	7 (1.9%)	2 (0.9%)
TAVI	27 (7.3%)	49 (22.5%)
Others	18 (4.8%)	10 (4.6%)
Internal disease		
CHF	95 (25.5%)	61 (28.0%)
IHD	113 (30.4%)	35 (16.1%)
Others	182 (48.9%)	122 (56.0%)

CABG: coronary artery bypass graft; ASO: arteriosclerosis obliterans; TAVI: transcatheter aortic valve implantations; CHF: congestive heart failure; IHD: ischemic heart disease lated with the ECW/TBW in men and women. With regard to the relationship between the SMI and ECW/TBW at ECW/TBW ≥ 0.4, the correlation disappeared in men and women (Figure 1A), which was different from that between PhA and the ECW/TBW (Figure 1B).

Figure 2 shows the correlation coefficients and *p*-values of the SMI and PhA and clinical data in men and women. The SMI was correlated with handgrip strength (r = 0.526, $p < 0.001$, Figure 2Aa), Alb (r = 0.133, $p < 0.019$, Figure 2Ab), and Hb (r = 0.232, $p < 0.001$) in men, and it was correlated with handgrip strength (r = 0.494, $p < 0.001$, Figure 2Ad), and inversely correlated with the CONUT score (r = -0.301, $p = 0.002$, Figure 2Af) in women. PhA was correlated with handgrip strength (r = 0.635, $p < 0.001$, Figure 2Ba), Alb (r = 0.363, $p < 0.001$, Figure 2Bb), and Hb (r = 0.418, $p < 0.001$), and inversely correlated with the CONUT score (r = -0.483, $p < 0.001$, Figure 2Bc) in men, and it was correlated with handgrip strength (r = 0.577, $p < 0.001$, Figure 2Bd), Alb (r = 0.377, $p < 0.001$, Figure 2Be), and Hb (r = 0.399, $p < 0.001$), and inversely correlated with the CONUT score (r = -0.492, $p < 0.001$, Figure 2Bf) in women.

Multivariate linear regression analysis with handgrip strength, MTH, and the CONUT score as the dependent variables, and PhA and the SMI as the independent variables was performed for ECW/TBW < 0.4 and ECW/TBW ≥ 0.4, as shown in Table 2. This analysis showed that for ECW/TBW < 0.4, PhA and SMI were independent variables to predict handgrip strength (PhA: β = 0.242, $p = 0.006$; SMI: β = 0.291, $p = 0.001$, Table 2Aa) and log MTH (PhA: β = 0.258, $p = 0.002$; SMI: β = 0.421, $p < 0.001$, Table 2Ab) in men after adjusting for age and presence of CHF. For ECW/TBW < 0.4, PhA was also an independent variable to predict log MTH (β = 0.487, $p = 0.001$, Table 2Ab) in women after adjusting for age and presence of CHF. For ECW/TBW < 0.4, PhA was an independent variable to predict the CONUT score (β = -0.361, $p = 0.004$, Table 2Ac) in men after adjusting for age and presence of CHF.

For ECW/TBW ≥ 0.4, multivariate regression analysis showed that PhA and SMI were independent determinants of handgrip strength (PhA: β = 0.386, $p < 0.001$; SMI: β = 0.275, $p = 0.006$, Table 2Ba) and log MTH (PhA: β = 0.472, $p < 0.001$; SMI: β = 0.380, p < 0.001, Table 2Bb) in men, and log MTH (PhA: β = 0.337, $p = 0.001$; SMI: β = 0.356, p = 0.001, Table 2Bb) in women, after adjusting for age and presence of CHF. PhA was a stronger independent determinant of handgrip strength and log MTH than the SMI in men. For ECW/TBW ≥ 0.4, PhA was also an independent variable to predict handgrip strength (β = 0.363, $p < 0.001$, Table 2Ba) in women after adjusting for age and presence of CHF. For ECW/TBW ≥ 0.4, PhA was an independent variable to predict the CONUT score (β = -0.569, $p < 0.001$, Table 2Bc) in men after adjusting for age and presence of CHF.

Table 3 shows the comparison of various parameters between four groups based on high/low SMI and high/low PhA in men and women with ECW/TBW ≥ 0.4. In men, compared to other groups, the mean handgrip strength (vs. high SMI and low PhA: 22.1 ± 6.2 vs. 27.3 ± 7.4 kg, $p < 0.01$, Table 3A) and MTH (vs. high SMI and low PhA: 1.92 ± 0.49 vs. 2.52 ± 0.50 cm, $p < 0.001$) were significantly lower in those with low SMI and low PhA. Also in women, compared to other groups, the mean handgrip strength (vs. low SMI and high PhA: 13.9 ± 4.0 vs. 18.7 ± 2.4 kg, $p < 0.001$, Table 3B) and MTH (vs.

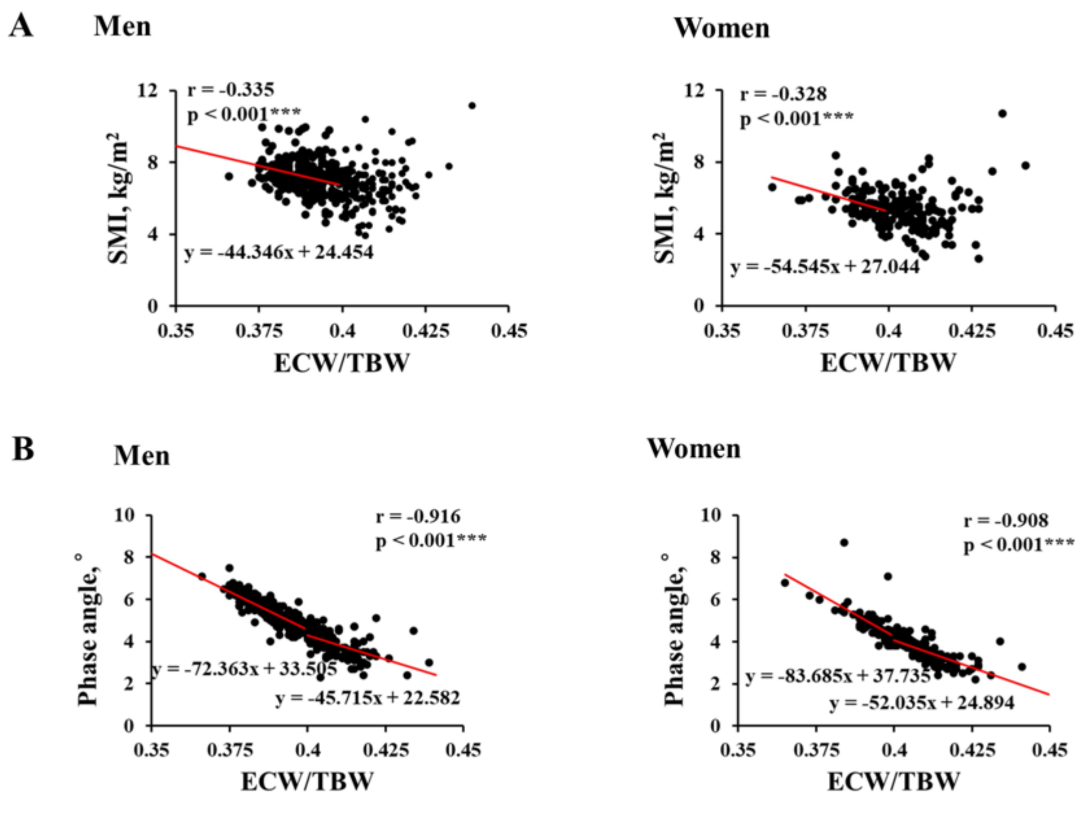


Figure 1. Regression equation for ECW/TBW (< 0.4 and ≥ 0.4) and the correlation coefficients and p values of (A) SMI and (B) phase angle in men and women. ECW/TBW, extracellular water: total body water ratio; SMI, skeletal muscle mass index

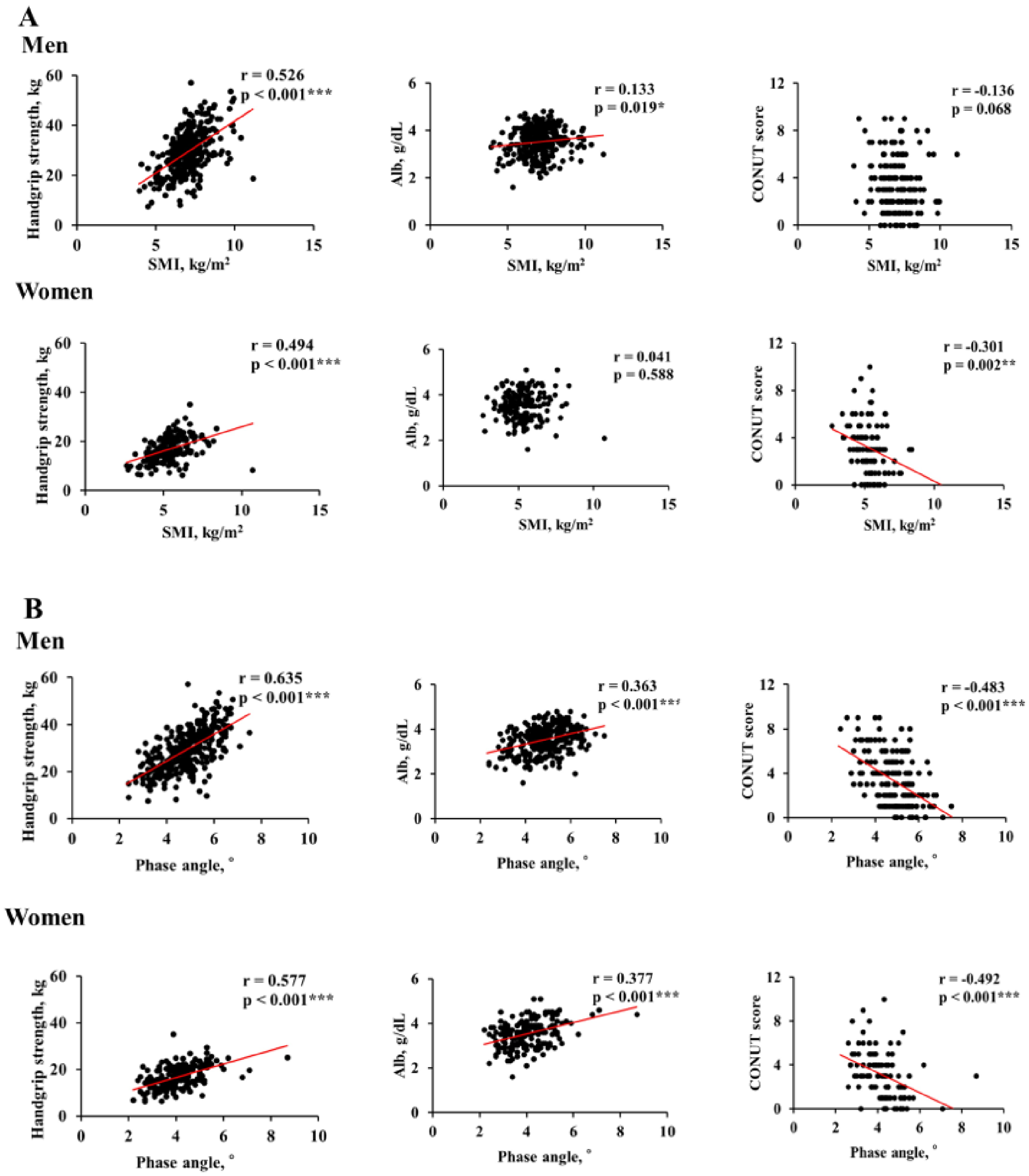


Figure 2. Correlations between handgrip strength, Alb, CONUT score and (A) SMI or (B) phase angle in men and women. SMI: skeletal muscle mass index; Alb: albumin

high SMI and high PhA: 1.81 ± 0.56 vs. 2.54 ± 0.45 cm, $p < 0.001$) were significantly lower, and the mean CONUT score (vs. high SMI and high PhA: 4.4 ± 2.0 vs. 2.5 ± 1.4, $p < 0.05$) was significantly higher in those with low SMI and low PhA.

The mean PhA was significantly lower in patients with sarcopenia in men (4.18 ± 0.77 vs. 5.20 ± 0.82°, $p < 0.001$, Table 4A) and women (3.61 ± 0.62 vs. 4.53 ± 1.02°, $p < 0.001$, Table 4B). In men, handgrip strength (22.2 ± 5.2 vs. 32.9 ± 7.5 kg, $p < 0.001$), MTH (2.18 ± 0.88 vs. 2.85 ± 0.69 cm, $p < 0.001$), Alb (3.3 ± 0.6 vs. 3.6 ± 0.6 g/dL, $p < 0.001$), and Hb (11.3 ± 1.7 vs. 12.3 ± 2.1 g/dL, $p < 0.001$) were significantly lower, and CONUT score (4.1 ± 2.3 vs. 2.9 ± 2.1, $p = 0.002$) was significantly higher in those with sarcopenia. Also in women, handgrip strength (13.9 ± 3.4 vs. 19.7 ± 5.0 kg, $p < 0.001$), MTH (1.91 ± 0.49 vs. 2.46 ± 0.66 cm, $p < 0.001$), Alb (3.4 ± 0.5 vs. 3.7 ± 0.6 g/dL, $p = 0.008$), and Hb (10.6 ± 1.4 vs. 11.7 ± 1.9 g/dL, $p < 0.001$) were significantly lower, and the CONUT score (3.6 ± 2.3 vs. 2.4 ± 1.7, $p = 0.009$) was significantly higher in those with sarcopenia.

Figure 3 shows ROC curves for PhA detecting sarcopenia. In all men, the ROC curve for the presence of sarcopenia using PhA showed a cutoff value of 4.65°, an area under the curve (AUC) of 0.811, a sensitivity of 75.3%, and a specificity of 70.5% (Figure 3A). Also in all women, the ROC curve for the presence of sarcopenia using PhA showed a cutoff value of 3.95°, an AUC of

Table 2. Multivariate linear regression analysis of grip strength, mid-thigh muscle thickness, and CONUT score, and phase angle and SMI (men/women) in patients with ECW/TBW < 0.4 and those with ECW/TBW ≥ 0.4†

	β-Value (*p*) Men/Women		
	Model 1	Model 2	Model 3
ECW/TBW < 0.4			
Handgrip			
phase angle	0.284(0.001)/ 0.322(0.025)	0.244(0.005)/ 0.235(0.122)	0.242(0.006)/ 0.235(0.121)
SMI	0.317(0.000)/ 0.125(0.375)	0.290(0.001)/ 0.108(0.441)	0.291(0.001)/ 0.119(0.395)
MTH (log)			
phase angle	0.309(0.000)/ 0.473(0.001)	0.264(0.001)/ 0.467(0.002)	0.258(0.002)/ 0.487(0.001)
SMI	0.437(0.000)/ 0.258(0.055)	0.416(0.000)/ 0.253(0.069)	0.421(0.000)/ 0.271(0.053)
CONUT			
phase angle	-0.395(0.001)/ -0.244(0.161)	-0.381(0.002)/ -0.268(0.149)	-0.361(0.004)/ -0.240(0.207)
SMI	0.183(0.125)/ 0.042(0.805)	0.202(0.108)/ 0.032(0.854)	0.193(0.120)/ 0.026(0.885)
ECW/TBW ≥ 0.4			
Handgrip			
phase angle	0.369(0.000)/ 0.371(0.000)	0.385(0.000)/ 0.373(0.000)	0.386(0.000)/ 0.363(0.000)
SMI	0.334(0.000)/ 0.230(0.015)	0.276(0.006)/ 0.179(0.077)	0.275(0.006)/ 0.177(0.078)
MTH (log)			
phase angle	0.477(0.000)/ 0.337(0.001)	0.501(0.000)/ 0.339(0.001)	0.472(0.000)/ 0.337(0.001)
SMI	0.409(0.000)/ 0.396(0.000)	0.364(0.000)/ 0.354(0.001)	0.380(0.000)/ 0.356(0.001)
CONUT			
phase angle	-0.590(0.000)/ -0.097(0.593)	-0.583(0.000)/ -0.103(0.566)	-0.569(0.000)/ -0.066(0.709)
SMI	0.097(0.445)/ -0.214(0.242)	0.036(0.818)/ -0.082(0.677)	0.030(0.847)/ -0.070(0.718)

ECW/TBW: the extracellular water: total body water ratio; MTH: mid-thigh muscle thickness; SMI: skeletal muscle mass index
†Model 1, unadjusted; Model 2, adjusted for age; Model 3, adjusted for age and presence or absence of chronic heart failure.

Table 3. Comparison of various parameters between four groups based on high/low SMI and high/low phase angle in men and women with ECW/TBW ≥ 0.4

	High SMI, high phase angle, n=9	High SMI, low phase angle, n=33	Low SMI, high phase angle, n=5	Low SMI, low phase angle, n=80	*p*-value
Men					
Handgrip strength, kg	31.7 ± 4.2	27.3 ± 7.4	23.7 ± 7.4	22.1 ± 6.2**, ††	<0.001
MTH, cm	2.93 ± 0.60	2.52 ± 0.50	2.93 ± 0.47	1.92 ± 0.49**, †††, ‡	<0.001
Albumin, g/dL	3.6 ± 0.5	3.2 ± 0.7	3.5 ± 0.5	3.2 ± 0.6	0.400
Hemoglobin, g/dL	10.8 ± 1.9	10.9 ± 2.1	12.8 ± 1.1	10.9 ± 1.5	0.072
CONUT score	2.6 ± 0.5	4.5 ± 2.5	3.0 ± 1.4	4.8 ± 2.3	0.167
Women					
Handgrip strength, kg	18.5 ± 4.4	16.8 ± 6.4	18.7 ± 2.4	13.9 ± 4.0*, ‡‡	<0.001
MTH, cm	2.54 ± 0.45	2.11 ± 0.61	2.04 ± 0.25	1.81 ± 0.56**, †	0.001
Albumin, g/dL	3.5 ± 0.8	3.2 ± 0.5	3.6 ± 0.6	3.3 ± 0.5	0.226
Hemoglobin, g/dL	12.0 ± 2.4	10.2 ± 1.8	10.9 ± 1.7	10.4 ± 1.3	0.163
CONUT score	2.5 ± 1.4	3.7 ± 1.6	3.3 ± 2.8	4.4 ± 2.0*	0.040

SMI: skeletal muscle mass index; ECW/TBW: the extracellular water:total body water ratio; MTH: mid-thigh muscle thickness
Data show mean ± SD values
**p* < 0.05, ***p* < 0.001 vs. high SMI and high phase angle
†*p* < 0.05, ††*p* < 0.01, †††*p* < 0.001 vs. high SMI and low phase angle
‡*p* < 0.01, ‡‡*p* < 0.001 vs. low SMI and high phase angle.

0.790, a sensitivity of 72.0%, and a specificity of 73.8% (Figure 3B).

Table 5 shows the prevalence ratio of sarcopenia determined by the cutoff value of PhA (men 4.65°, women 3.95°) and SMI (men 7.0 kg/m^2, women 5.7 kg/m^2). In men, the prevalence ratio of sarcopenia as determined by PhA and SMI was higher for ECW/TBW ≥ 0.4 than for ECW/TBW < 0.4, respectively (PhA: 59.2% vs. 6.5%, *p* < 0.001; SMI: 50.5% vs. 17.2%, *p* < 0.001). Also in women, the prevalence ratio of sarcopenia as determined by PhA and SMI was higher for ECW/TBW ≥ 0.4 than for ECW/TBW < 0.4, respectively (PhA: 66.7% vs. 6.6%, *p* < 0.001; SMI: 64.9% vs. 32.3%, *p* < 0.001).

DISCUSSION

The major findings of the present study were as follows: (1) In a total of 590 hospitalized patients with CVD, both the SMI and PhA were correlated with handgrip strength in both sexes. The SMI and PhA were correlated with Alb and Hb in men. In women, PhA, but not the SMI, was correlated with Alb and Hb. (2) PhA showed an inverse correlation with the ECW/TBW, and the SMI also showed an inverse correlation when the ECW/TBW was less than 0.4, but the correlation was abolished at the range above 0.4, suggesting that the ECW/TBW affects the SMI value, probably due to edema. (3) Multivariate regression analysis showed that at an ECW/TBW below 0.4, both PhA and SMI were independent determinants of

Table 4. Comparison of various parameters between the presence and absence of sarcopenia in men and women

	Sarcopenia (+)	Sarcopenia (-)	*p*-value
Men	n=79	n=189	
Age, year	76.3 ± 8.9	65.8 ± 12.0	<0.001***
BMI, kg/m^2	20.8 ± 2.9	24.2 ± 3.6	<0.001***
Handgrip strength, kg	22.2 ± 5.2	32.9 ± 7.5	<0.001***
Knee extension strength, kg	20.0 ± 6.1	31.4 ± 9.9	<0.001***
Gait speed, m/s	0.83 ± 0.23	1.09 ± 0.23	<0.001***
Albumin, g/dL	3.3 ± 0.6	3.6 ± 0.6	<0.001***
Hemoglobin, g/dL	11.3 ± 1.7	12.3 ± 2.1	<0.001***
CONUT score	4.1 ± 2.3	2.9 ± 2.1	0.002**
MTH, cm	2.18 ± 0.88	2.85 ± 0.69	<0.001***
Phase angle, °	4.18 ± 0.77	5.20 ± 0.82	<0.001***
SMI, kg/m^2	6.00 ± 0.69	7.48 ± 0.90	<0.001***
Women	n=83	n=76	
Age, year	79.3 ± 7.8	67.4 ± 14.3	<0.001***
BMI, kg/m^2	20.4 ± 3.5	24.2 ± 4.8	<0.001***
Handgrip strength, kg	13.9 ± 3.4	19.7 ± 5.0	<0.001***
Knee extension strength, kg	12.8 ± 4.0	19.6 ± 6.9	<0.001***
Gait speed, m/s	0.73 ± 0.25	0.99 ± 0.26	<0.001***
Albumin, g/dL	3.4 ± 0.5	3.7 ± 0.6	0.008**
Hemoglobin, g/dL	10.6 ± 1.4	11.7 ± 1.9	<0.001***
CONUT score	3.6 ± 2.3	2.4 ± 1.7	0.009**
MTH, cm	1.91 ± 0.49	2.46 ± 0.66	<0.001***
Phase angle, °	3.61 ± 0.62	4.53 ± 1.02	<0.001***
SMI, kg/m^2	4.69 ± 0.66	6.08 ± 0.97	<0.001***

BMI: body mass index; MTH: mid-thigh muscle thickness; SMI: skeletal muscle mass index
Data show mean ± SD values
** $p < 0.01$, *** $p < 0.001$

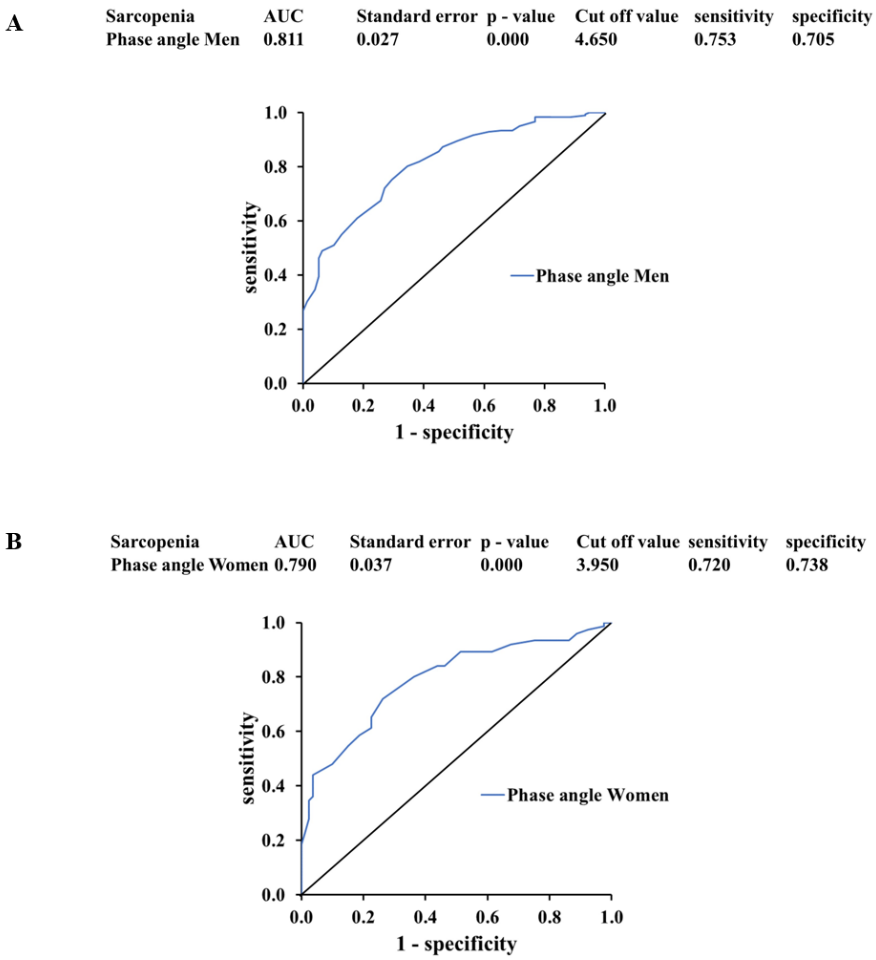


Figure 3. ROC curves to identify the optimal cutoff of phase angle for detecting sarcopenia in men (A) and women (B). To generate ROC curves shown, phase angle cutoffs were used to predict sarcopenia, with true positives (sensitivity) plotted on the vertical axis and false positives (1 - specificity) plotted on the horizontal axis

Table 5. Prevalence ratio of sarcopenia determined by the cutoff value of SMI and phase angle in men (SMI 7.0 kg/m^2, phase angle 4.65°) and women (SMI 5.7 kg/m^2, phase angle 3.95°)

	All patients	ECW/TBW <0.4	ECW/TBW ≥0.4	*p*-value
Men	n=372	n=224	n=148	
Sarcopenia (SMI)	79/268 (29.5%)	29/169 (17.2%)	50/99 (50.5%)	<0.001***
Sarcopenia (Phase angle)	69/267 (25.8%)	11/169 (6.5%)	58/98 (59.2%)	<0.001***
Women	n=218	n=83	n=135	
Sarcopenia (SMI)	83/159 (52.2%)	20/62 (32.3%)	63/97 (64.9%)	<0.001***
Sarcopenia (Phase angle)	70/160 (43.8%)	4/61 (6.6%)	66/99 (66.7%)	<0.001***

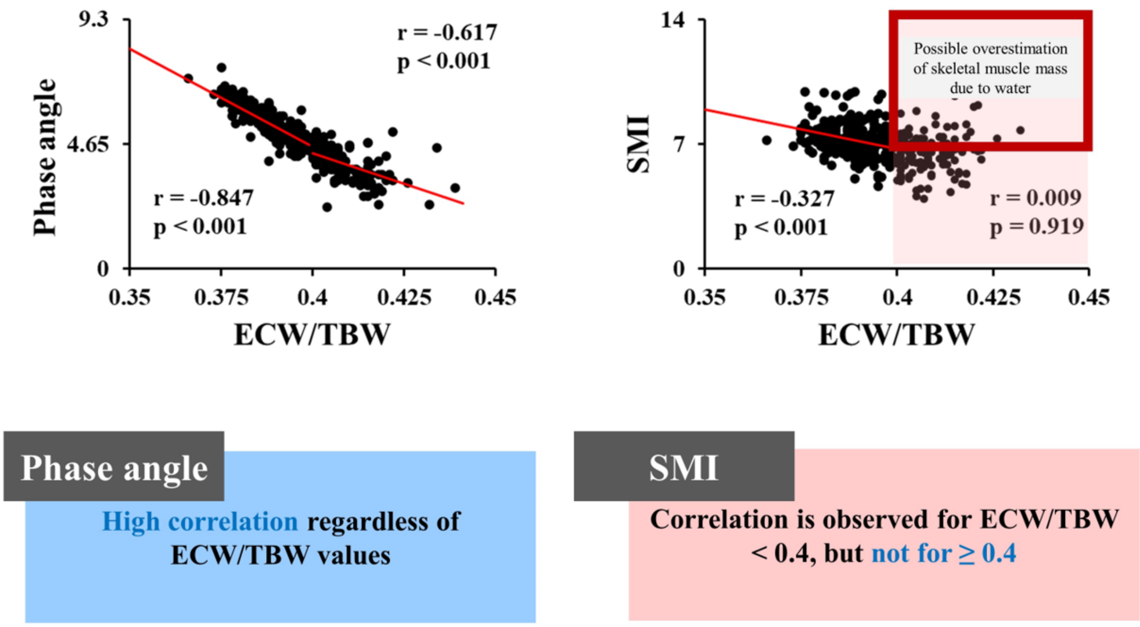
SMI: skeletal muscle mass index; ECW/TBW: the extracellular water: total body water ratio
*** $p < 0.001$.

handgrip strength and log MTH in men, after adjustment for age and presence of CHF. Also, PhA, but not the SMI, was an independent determinant of the CONUT score in men and log MTH in women, after adjusting for age and presence of CHF. In contrast, for an ECW/TBW of 0.4 or greater, PhA, not the SMI, was an independent determinant of the CONUT score in men and handgrip strength in women, after adjustment for age and presence of CHF. Also, at an ECW/TBW of 0.4 or greater, PhA was a stronger independent determinant of handgrip strength and log MTH than the SMI in men. (4) Sarcopenia was found in 29.5% of men and 52.2% of women, and PhA was significantly lower in the group with sarcopenia in both sexes. The PhA cutoff for detecting sarcopenia obtained from ROC curves was 4.65° for men and 3.95° for women. The present study provides evidence showing that PhA may be useful as a marker for muscle wasting and malnutrition in patients with CVD including CHF.

The biomembrane, which constitutes the cell membrane, has a lipid bilayer structure consisting mainly of phospholipids, with an internal hydrophobic region and hydrophilic regions on both sides.[29] The hydrophobic region corresponds to an insulator, which is difficult for charge to move, and the hydrophilic region corresponds to a conductor, which is easy for charge to move. Therefore, the cell membrane functions as a capacitor when a voltage is applied to both sides of the biomembrane, and current flows through it. This cell membrane is not a space like a normal capacitor, but has other components such as membrane proteins in addition to phospholipids. Electrical capacitance is proportional to the area of the lipid bilayer and inversely proportional to the amount of membrane proteins, which are reflected by reactance.[29] As the density of lipids and membrane proteins in the cell membrane increases, the reactance increases and PhA increases because the capacitance decreases, and as the density of lipids and membrane proteins in the cell membrane decreases, the reactance decreases and PhA decreases because the capacitance increases. PhA is attracting attention as a prognostic predictor of various diseases and as a nutritional indicator, since it reflects the health and overall nutritional status of cells.[15-17] In addition, PhA has the advantage of not being directly affected by excess body fluid as well as height and weight, since it is an actual measurement value calculated by passing a weak electric current through the human body and directly measuring the resistance value of cell membranes.[16,17,30] Thus, the significance of measuring PhA is that it can be used for nutritional evaluation as an indicator of somatic cell volume and the level of structural integrity and physiological function of cells.

Malnutrition leads to sarcopenia, and we previously investigated the usefulness of PhA as a marker of sarcopenia and malnutrition in hospitalized patients with CVD.[20] In that study, the SMI and PhA were correlated with handgrip strength in both sexes. PhA was more strongly correlated with Hb, Alb, and the CONUT score than the SMI in men. Also, that study showed that PhA, but not the SMI correlated with Hb and Alb, and the CONUT score in women. The findings of the present study were compatible to those of our previous study. PhA has been reported to correlate with physical function, frailty, and sarcopenia[15,17,20,31] as well as various parameters of nutritional status.[20,31-34] In the present study of 590 hospitalized patients with CVD, PhA was correlated with handgrip strength, Hb, and Alb and inversely correlated with the CONUT score in both sexes. In addition, the present study showed that at an ECW/TBW below 0.4, PhA was an independent determinant of handgrip strength, log MTH and the CONUT score in men and log MTH in women, and that at an ECW/TBW of 0.4 or greater, it was an independent determinant of handgrip strength, log MTH and the CONUT score in men, and handgrip strength and log MTH in women. Thus, for an ECW/TBW above 0.4, PhA, but not the SMI, might predict muscle wasting and malnutrition.

Sarcopenia is highly prevalent among older patients with CVD,[5-8] and is associated with all-cause mortality and CVD morbidity.[6,35] However, patients with CVD, especially those with CHF, are typically overhydrated and often have other commonplace conditions that can cause errors in the SMI used to diagnose sarcopenia.[36,37] On the other hand, among BIA indices, PhA is less affected by excess water content and has been reported to be a good index of clinical outcome.[16,17,30] Mullie et al.[17] found that in patients undergoing cardiac surgery, after adjusting for Society of Thoracic Surgeons predicted mortality, lower preoperative PhA was associated with a higher mortality rate at 1 month (hazard ratio 3.57 / PhA 1° decrease, 95% CI 1.35-9.47) and at 12 months (hazard ratio 3.03 / PhA 1° decrease, 95% CI 1.30-7.09), associated with a higher overall morbidity rate (hazard ratio 2.51 / PhA 1° decrease, 95% CI 1.32-4.75) and longer hospital stay (β 4.8 days / PhA 1° decrease, 95% CI 1.3-8.2 days). Thus, the



Graphical abstract

malnutrition and sarcopenia due to low PhA in patients with CVD shown in the present study may lead to poor clinical outcomes.

In the ROC curve analysis of the present study, the PhA cutoff for detecting sarcopenia was 4.65° in men and 3.95° in women. Our previous study showed that in patients with CVD, the PhA cutoff for presence of sarcopenia was 4.55° in men and 4.25° in women.[20] Tan et al.[31] also showed that in patients on maintenance hemodialysis, the PhA cutoff for detecting protein-energy wasting, which was in 34.1% of all patients on dialysis, was 4.6. The results of the present study were similar to the results of those studies for men, but lower for women. The reason for the lower PhA cutoff in women in the present study might be that the prevalence of sarcopenia was higher in women. Therefore, these results may suggest that PhA is useful as a biomarker for presence of sarcopenia in patients with CVD.

In the present study, PhA showed an inverse correlation with the ECW/TBW, and the SMI also showed an inverse correlation with the ECW/TBW at the range below 0.4. However, the correlation of the SMI with the ECW/TBW was abolished at the range above 0.4, suggesting that the SMI is overestimated in the presence of edema. A previous study used the BIA method in patients with cirrhosis and evaluated its impact on sarcopenia and prognosis.[38] In that study, the SMI was measured by site and compared to that of patients with diabetes, and included arm index (skeletal muscle mass of arms / height^2), leg index (skeletal muscle mass of legs / height^2), and limb index (skeletal muscle mass of extremities / height^2). That study showed that the arm index was clearly lower in patients with cirrhosis than in patients with diabetes for both sexes, and the prognosis for the subgroup with the lower arm index was clearly worse. Also, it suggested that in patients with cirrhosis, the arm index should be measured rather than the leg index to assess skeletal muscle mass. Therefore, the SMI value including the leg index might not be accurate in the presence of edema.

There are two mechanisms by which the ECW/TBW can be elevated. The first is that the ECW/TBW is high due to increased ECW content. In cases of diseases with edema such as CHF, renal failure, liver failure, diabetes mellitus, and lymphedema, and cases of sudden increases in body fluid due to postoperative infusions, the ECW/TBW is higher.[39,40] That is because the rate of increase in ECW is higher while both ECW and intracellular water (ICW) are abnormally increased. The second is that the ECW/TBW is high with a decrease in ICW content. Ohashi et al.[41] measured body composition in 1992 healthy Japanese subjects and examined the association between the ratio of ECW to ICW content (ECW/ICW) and age. That study showed that the ECW/ICW increased with age because the decrease in ICW content was steeper than that in ECW content, especially after age 70. Also, it suggested that imbalance between ICW and ECW content was due to a decrease in cell mass associated with aging and muscle wasting, and that ICW decreases with aging and nutritional deterioration, as the muscle-constituting body cells decrease in volume. The present study showed that at an ECW/TBW of 0.4 or greater, PhA was affected little by the adjustment of age and presence of CHF as factors determining handgrip strength, log MTH, and the CONUT score. In contrast, the present study showed that the SMI was affected more by those adjustments than PhA. Thus, at an ECW/TBW of 0.4 or greater, the SMI might be overestimated, while PhA could potentially be used.

The present study has several limitations. First, the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment of diabetes mellitus with CHF is recently reported to be advisable,[42,43] and a recent previous study showed that low PhA was an independent predictor of CHF for diabetic hemodialysis patients.[44] However, the present study did not examine the presence or absence of diabetes or SGLT2 inhibitors in patients including CHF.

Secondary, the present study did not provide sociodemographic, dietary pattern, or therapeutic information, which might have effects on the results of PhA and sarcopenia. Thus, further studies using sociodemographic, dietary pattern, and therapeutic information including SGLT2 inhibitors are required to clarify whether PhA can be a useful marker of sarcopenia in patients including CHF.

Conclusions

The present study provided evidence showing that phase angle may be a useful marker of muscle wasting and malnutrition in patients with cardiovascular disease including chronic heart failure. Thus, bioelectrical impedance analysis-derived phase angle may become a useful surrogate for muscle function and nutritional evaluation, and could help clinical practitioners aiming to diagnose muscle wasting and malnutrition in patients with cardiovascular disease.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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