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学位論文

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Mid-arm muscle circumference as an indicator of exercise tolerance in chronic heart failure

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Aim: Skeletal muscle mass is associated with exercise tolerance in patients with chronic heart failure (CHF). Anthropometric indicators are used to evaluate skeletal muscle mass, as these can be easily assessed in clinical practice. However, the association between anthropometric indicators and exercise tolerance is unclear. This study aimed to investigate the association between anthropometric indicators and exercise tolerance in CHF patients.

Methods: We evaluated 69 patients with CHF. Mid-arm circumference, mid-arm muscle circumference (MAMC), calf circumference and body mass index were measured as the anthropometric indicators. Exercise tolerance was evaluated according to the peak oxygen uptake (VO_2). Correlation analyses were carried out to determine the association between peak VO_2 and anthropometric indicators. Furthermore, univariate and multiple regression analyses were carried out using peak VO_2 as the dependent variable, and age, male, left ventricular ejection fraction, angiotensin II receptor blocker or angiotensin converting enzyme inhibitor, diuretics, B-type natriuretic peptide, estimated glomerular filtration rate, hemoglobin and anthropometric indicators as the independent variables.

Results: There were significant positive correlations between the peak VO_2 and mid-arm circumference ($r_s = 0.378$, $P = 0.001$), MAMC ($r = 0.634$, $P < 0.001$) and calf circumference ($r = 0.292$, $P = 0.015$). In multiple regression analysis, MAMC ($\beta = 0.721$, $P < 0.001$) and estimated glomerular filtration rate ($\beta = 0.279$, $P = 0.007$) were independent factors associated with peak VO_2.

Conclusions: MAMC is independently associated with peak VO_2 in CHF patients. Thus, MAMC could be an indicator of exercise tolerance, which is closely related to the severity and prognosis of CHF. **Geriatr Gerontol Int 2021; 21: 411–415.**

Keywords: anthropometric indicators, chronic heart failure, exercise tolerance, mid-arm muscle circumference, muscle mass.

Introduction

Patients with chronic heart failure (CHF) have reduced exercise tolerance, and this has been shown to be closely related to the severity and prognosis of CHF.[1,2] Muscle mass is in turn related to exercise tolerance in patients with CHF.[3–5] Skeletal muscle abnormalities, including abnormal energy metabolism, transition of muscle fibers from type I to type II, mitochondrial dysfunction, reduction in muscular strength and muscle atrophy, have been shown to play a central role in reduced exercise tolerance.[6] The relationship between muscle bulk at the cross-sectional midthigh area and peak oxygen uptake (VO_2) is stronger in patients with CHF than in healthy individuals.[7] In addition, skeletal muscle mass in patients with CHF is related to the peak VO_2, and is independent of age, body mass index (BMI), left ventricular ejection fraction (LVEF), E/e′ and anemia.[3,5] Thus, muscle mass has a significant effect on exercise tolerance.

Muscle mass can be measured through several methods, including magnetic resonance imaging, computed tomography, dual energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis.[8] However, it is generally not easy to measure skeletal muscle mass using these methods, because they require specialized equipment in addition to being costly and time-consuming.[8,9]

Anthropometry is commonly used as a method of measuring body composition, and has been shown to be associated with nutritional status, muscle mass and mortality in older individuals.[10,11]

Even in CHF patients, mid-arm circumference (MAC) and calf circumference (CC) correlated well with muscle mass.[12] Several previous studies have used mid-arm muscle circumference (MAMC) as an indicator of nutritional status and muscle mass in patients with CHF.[13,14] Anthropometric indicators are advantageous for assessment, as they are easily evaluable in routine clinical practice with no associated costs.

Table 1 Patient characteristics

Age (years)	74 (67–80)
Male, *n* (%)	58 (84.1)
Height (cm)	162.4 ± 7.1
Weight (kg)	63.5 (57.1–71.4)
BMI (kg/m^2)	24.2 (22.0–26.6)
NYHA functional class, *n* (%)	
I/II/III	14 (20.3)/45 (65.2)/10 (14.5)
Etiology of HF, *n* (%)	
IHD	46 (66.7)
Cardiomyopathy	8 (11.6)
Valvular disease	8 (11.6)
Other	7 (10.1)
Atrial fibrillation, *n* (%)	19 (27.5)
LVEF (%)	50.0 ± 13.4
E/e′	12.6 (9.3–15.8)
Medications, *n* (%)	
β-Blocker	60 (87.0)
ARB or ACEI	51 (73.9)
Calcium antagonist	26 (37.7)
Diuretics	33 (47.8)
Statin	50 (72.5)
Antiarrhythmic	1 (1.4)
Oral cardiotonic	4 (5.8)
Laboratory data	
BNP (pg/dL)	121.7 (98.0–165.4)
Creatinine (mg/dL)	1.0 (0.8–1.3)
eGFR (mL/min/1.73 m^2)	51.8 ± 16.7
Hemoglobin (g/dL)	13.6 ± 1.9
Anthropometric indicators	
Mid-arm circumference (cm)	27.2 (26.3–28.9)
Mid-arm muscle circumference (cm)	24.0 ± 2.5
Calf circumference (cm)	35.1 ± 3.3
Peak VO_2 (mL/min/kg)	15.3 ± 3.8

Data are presented as the mean ± standard deviation, median (with lower and upper quartiles) or numbers (with percentages). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VO_2, oxygen uptake.

However, to our knowledge, the association between anthropometric indicators and exercise tolerance in patients with CHF has not been investigated. Understanding the relationship between anthropometric indicators and exercise tolerance in patients with CHF might be useful to improve the prediction of exercise tolerance. Thus, the present study aimed to investigate the relationship between anthropometric indicators and exercise tolerance in patients with CHF.

Methods

Study design and population

The participants were outpatients with clinically stable CHF who underwent cardiopulmonary exercise testing (CPX) for cardiac rehabilitation at the KKR Takamatsu Hospital between March 2017 and February 2018. The inclusion criterion for this study was clinically stable CHF, defined as New York Heart Association functional class I, II or III with no worsening of symptoms or exacerbations of heart failure within the past 3 months. Patients with hemodialysis, chronic respiratory disease and congestive findings were excluded.

The present cross-sectional study was carried out according to the principles outlined in the Declaration of Helsinki, and was approved by the ethical committee of KKR Takamatsu Hospital (approval no. E116). Written informed consent was obtained from all patients.

Anthropometric indicators

MAC, MAMC, CC and BMI were measured as anthropometric indicators according to standard methods.[15] MAC and CC were measured to the nearest 0.1 cm with a rigid measuring tape. MAC was measured at the mid-point between the acromion and olecranon process of the non-dominant arm, with both arms hanging at the sides. The CC was measured at the largest point of the left calf in a sitting position. Triceps skinfold thickness was measured to the nearest 1 mm with an Adipometer caliper at the same site as the AC, slightly pulling the skinfold of the non-dominant arm away from the muscle tissue. For each measurement, three consecutive values were obtained, and the average was considered as the final result. MAMC was calculated using the following equation: MAMC (cm) = MAC (cm) − 0.314 × triceps skinfold thickness (mm).[15] The BMI was calculated as bodyweight (kg) divided by the square of height (m^2). Given that anthropometric measures are vulnerable to error, all measurements in this study were carried out by a single experienced measurer to eliminate interrater errors.[16]

Peak VO_2

Exercise tolerance was evaluated according to peak VO_2 measured through CPX. CPX was carried out using a cycle ergometer (Well Bike BE-260; Fukuda Denshi, Tokyo, Japan) with breath-by-breath respiratory gas measurements using a computerized metabolic cart (AE-310S; Minato Medical Science, Osaka, Japan). After a 3-min rest on the ergometer, exercise began with a 3-min warm-up at 10 W and 50 repetitions/min followed by 10 W ramp loading every minute. During CPX, the 12-lead electrocardiogram was continuously monitored with an exercise stress test device (MLX-1000; Fukuda Denshi, Tokyo, Japan), and blood pressure was measured every minute. The test was terminated when the patient showed the following: (i) maximal volitional fatigue; (ii) VO_2 leveling off; (iii) excessively high blood pressure (i.e. systolic blood pressure >250 mmHg); or (iv) electrocardiogram abnormalities. The highest value of VO_2 during exercise was calculated as peak VO_2 and corrected by bodyweight (mL/kg/min). CPX was carried out by a different examiner than the anthropometric measurer. Other information, such as echocardiography parameters, laboratory data and medication status, were collected from the most recent medical records of each patient.

Outcomes

The primary outcome was to determine the association between anthropometric indicators and peak VO_2 in patients with CHF. The secondary outcome was to identify independent factors associated with peak VO_2.

Statistical analysis

The typical values and degree of dispersion are reported as the mean ± standard deviation for parametric variables, and as the

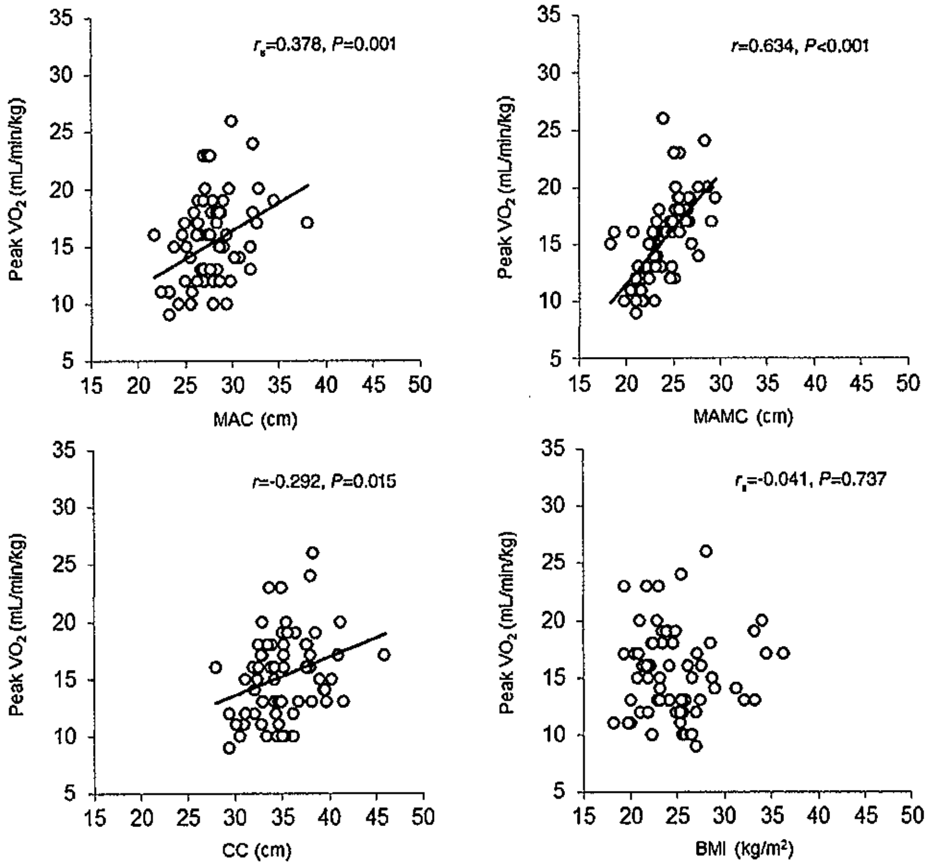

Figure 1 Correlation between peak oxygen uptake (VO_2) and mid-arm circumference (MAC), mid-arm muscle circumference (MAMC), calf circumference (CC) and body mass index (BMI). Peak VO_2 was significantly associated with MAC, MAMC, and CC.

median (interquartile range) for non-parametric variables. The Shapiro–Wilk test was used to test the normality of each variable. The Pearson's correlation coefficient was used in regression analysis to determine the correlations between the peak VO_2 and MAMC and CC. The Spearman's rank correlation coefficient was used to evaluate the relationships between peak VO_2 and MAC and BMI. Univariate regression analyses were carried out to investigate the association between peak VO_2 and age, male sex, BMI, LVEF, angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor, diuretics, B-type natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), hemoglobin, MAC, MAMC and CC. Furthermore, multiple regression analysis was carried out using peak VO_2 as the dependent variable, and variables with a *P*-value <0.10 in the univariate regression analyses as independent variables. The multicollinearity between the independent variables was carefully checked. When we set the effect size $f^2 = 0.25$ in reference to the study by Ho *et al.*[17] and set the following value of $\alpha = 0.05$, $1\text{-}\beta = 0.8$ and eight predictors, the appropriate sample size for multiple regression analysis was 69 patients.

All statistical analyses were carried out using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[18] A *P*-value of <0.05 was considered statistically significant.

Table 2 Univariate regression analyses of the association of peak oxygen uptake and each variable

Variable	R^2	*P*-value
Age	0.203	<0.001
Male	0.051	0.062
BMI	<0.001	0.864
LVEF	0.002	0.693
ARB or ACEI	0.025	0.195
Diuretics	0.030	0.154
BNP	0.066	0.034
eGFR	0.223	<0.001
Hemoglobin	0.124	0.003
MAC	0.134	0.002
MAMC	0.402	<0.001
CC	0.085	0.015

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CC, calf circumference; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; VO_2, oxygen uptake.

Results

In total, 69 patients were evaluated in the present study. The patient characteristics are shown in Table 1. The median age and BMI were 74 years and 24.2 kg/m^2, respectively, and 84.1% of the patients were male. A total of 59 patients were classified as New York Heart Association functional class I or II. The etiology of CHF was ischemic disease in 46 patients. The average LVEF of the patients was 50.0 ± 13.4%, the median BNP was 121.7 pg/dL and 60 patients were taking β-blockers. The median MAC was 27.2 cm, and the

Table 3 Multiple regression analysis for the predictors of peak oxygen uptake in patients with chronic heart failure

Independent variables	Dependent variable: Peak VO_2				
	B	Standard error	β	t-statistic	P-value
Age	−0.077	0.046	−0.215	−1.682	0.098
Male	−0.766	1.181	−0.074	−0.649	0.519
BNP	−0.003	0.003	−0.085	−0.897	0.373
eGFR	0.063	0.023	0.279	2.787	0.007
Hemoglobin	0.072	0.211	0.037	0.343	0.733
MAC	−0.444	0.243	−0.330	−1.828	0.073
MAMC	1.107	0.255	0.721	4.341	<0.001
CC	−0.109	0.160	−0.095	−0.681	0.498
	R^2 = 0.555, adjusted R^2 = 0.495, ANOVA $P < 0.001$				

β, standardized partial regression coefficient; ANOVA, analysis of variance; B, partial regression coefficient; BNP, B-type natriuretic peptide; CC, calf circumference; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; VO_2, oxygen uptake.

average MAMC and CC were 24.0 ± 2.5 cm and 35.1 ± 3.3 cm, respectively. The average peak VO_2 was 15.3 ± 3.8 mL/kg/min.

Figure 1 shows correlation coefficients between the peak VO_2 and the anthropometric indicators. There were significant positive correlations between the peak VO_2 and MAC (r_s = 0.378, P = 0.001), MAMC (r = 0.634, $P < 0.001$) and CC (r = 0.292, P = 0.015), but there was no significant association with BMI.

In univariate analyses, age, BNP, eGFR, hemoglobin, MAC, MAMC and CC significantly associated with peak VO_2 (Table 2). In the multiple regression analysis, MAMC ($P < 0.001$) and eGFR (P = 0.007) were statistically significant predictors of peak VO_2 independent of age, male sex, BNP, hemoglobin, MAC and CC. The standardized partial regression coefficients were 0.721 for MAMC and 0.279 for eGFR. The adjusted R^2 value was 0.495 (Table 3). The variance inflation factors for each independent variable were all <5.0.

Discussion

The present observational study showed that the anthropometric indicators, MAC, MAMC and CC, were significantly associated with exercise tolerance in patients with CHF. In particular, the MAMC was most strongly associated with peak VO_2, independent of other important clinical indicators of CHF, such as age, BNP, eGFR and hemoglobin. To the best of our knowledge, this is the first observational study to show such an association.

Several studies have reported that anthropometric indicators are a measure of muscle mass,[12,13] and muscle mass is associated with exercise tolerance[3–5] in patients with CHF. However, the direct association between anthropometric indicators and exercise tolerance in CHF has not been investigated to date. In contrast, several studies have shown that anthropometric indicators are an important determinant of exercise tolerance in patients with chronic obstructive pulmonary disease.[17,19] Several functional and structural changes in limb muscles that have been reported in patients with chronic obstructive pulmonary disease, including muscle atrophy, weakness, transition of muscle fiber type and mitochondrial dysfunction,[20] have also been observed in patients with CHF.[6] As with chronic obstructive pulmonary disease patients, the anthropometric indicators reflect the state of skeletal muscles, and is considered to be related to exercise tolerance in CHF patients.

MAC and MAMC measured at the upper limb were more strongly associated with peak VO_2 than CC measured at the lower limb. When assessing muscle mass in older patients with edema, the accuracy of CC has been shown to be limited and needs to be adjusted.[21] Kamiya et al. showed that, in patients with cardiovascular disease, MAC is a better predictor of mortality than CC.[22] Furthermore, they reported that MAC might be a better measure of muscle mass than CC given that some conditions, especially leg edema, might potentially alter CC. These results suggest that, in patients with cardiovascular disease, including those with CHF, anthropometric indicators at the upper limbs rather than those at the lower limbs are more associated with muscle mass.

Of the anthropometric indicators measured in the present study, MAMC was the strongest and was independently associated with peak VO_2 in CHF. To our knowledge, there is no report directly comparing the association between MAMC and muscle mass in patients with CHF. However, in older adults, MAMC is a more accurate predictor of sarcopenia than CC.[23] In addition, a study involving maintenance hemodialysis patients has shown a strong correlation between muscle mass measured by DEXA and MAMC.[24] Compared with MAC, CC and BMI, MAMC is a measurement that excludes the factor of fat; thus, it better reflects muscle mass. Therefore, it is assumed that MAMC is associated with exercise tolerance, even in patients with CHF. However, the actual muscle mass was not measured in the present study; thus, further studies regarding this topic are necessary. In healthy individuals, women have lesser muscle mass[8,25] and lower peak VO_2[26] than men. Sex differences in peak VO_2 have also been observed in patients with CHF.[27] Therefore, although there are sex differences in body composition and exercise tolerance, there was no significant association between peak VO_2 and sex in this study. Because the study population included a smaller number of women, further investigation is required to determine the effects of sex on the relationship between anthropometric indicators and exercise tolerance. A previous study showed that muscle strength is related to peak VO_2, but muscle strength is highly dependent on muscle mass in CHF patients.[7] As the main aim of the present study was to determine the relationship between anthropometric indicators and exercise tolerance, muscle strength was not included as a variable.

The results of the present study showed that eGFR was also independently associated with peak VO_2. A previous study showed that eGFR is a predictor of peak VO_2 in male CHF patients with chronic kidney disease.[28] Furthermore, in CHF patients with reduced LVEF, eGFR was associated with peak VO_2 independently of significant covariates, and those with both reduced eGFR and peak VO_2 had the poorest prognosis.[29] Consistent with these findings, the current study also showed that eGFR was an important factor associated with exercise tolerance in patients with CHF. However, our results suggested that MAMC is more strongly associated with exercise tolerance than eGFR.

The combination of MAMC and eGFR might also be useful for estimating exercise tolerance in older patients who are unable to carry out CPX due to cognitive or physical dysfunction.

The present study had several limitations. First, the sample size was small, and the participants were from only one hospital, thus limiting the generalizability of the results. Second, the number of female patients in this study was limited. The applicability of the study results to female patients with CHF requires further investigation. Third, we did not carry out a direct measurement of muscle mass; for example, using magnetic resonance imaging, computed tomography or DEXA. Therefore, it was impossible to compare the anthropometric indicators to these guideline-recommended modalities in exercise tolerance. Although previous studies have shown that MAMC is well correlated with muscle mass measured by computed tomography[30] and DEXA,[24] further investigation is required to confirm the interrelationship between MAMC and muscle mass and exercise tolerance. Finally, the present study included only outpatients with clinically stable CHF. The applicability of the results to patients with more severe or acute heart failure requires further investigation.

In conclusion, MAMC is independently associated with peak VO_2 in patients with CHF. Thus, MAMC could be an indicator of exercise tolerance, which is closely related to the severity and prognosis of CHF.

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Disclosure statement

The authors declare no conflict of interest.

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