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The relationship between skeletal muscle and ventilatory response to exercise in myocardial infarction

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ABSTRACT

Background: Skeletal muscle is important to determine physical activity and exercise capacity in cardiovascular disease. This study aims to investigate the relationship between skeletal muscle volume measured by bioelectrical impedance analysis and ventilation indices assessed by cardiopulmonary exercise test in patients with myocardial infarction.

Methods: A total of 60 patients (57 men; 59 ± 9 years) who underwent percutaneous coronary intervention for ST-elevation myocardial infarction were enrolled into this study. All patients performed cardiac rehabilitation and then achieved physical activity of daily life. No patient was complicated by diabetes mellitus. In symptom-limited cardiopulmonary exercise test, minute ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) were continuously obtained. A volume of skeletal muscle measured by bioelectrical impedance analysis was normalized for height (skeletal muscle index).

Results: The skeletal muscle index showed a significant inverse correlation with peak $\dot{V}E/\dot{V}O_2$ ($p = 0.02$, $r = -0.39$) and peak $\dot{V}E/\dot{V}CO_2$ ($p = 0.02$, $r = -0.30$). In addition, the skeletal muscle index inversely correlated with $\dot{V}E/\dot{V}CO2$ slope ($p = 0.02$, $r = -0.30$). On the other hand, the skeletal muscle index did not significantly correlate with peak $\dot{V}O_2$ ($p = 0.56$, $r = 0.08$) and peak $\dot{V}CO_2$ ($p = 0.99$, $r = 0.001$). Besides, the skeletal muscle index did not significantly correlate with $\Delta\dot{V}O_2/\Delta$work rate slope ($p = 0.60$, $r = 0.07$).

Conclusions: The increase in skeletal muscle index was associated with the amelioration of ventilatory efficacy to exercise at the peak level. Furthermore, the increase in skeletal muscle index may account for favorable prognosis. These findings could strengthen the role of skeletal muscle in exercise capacity of patients with myocardial infarction.

1. Introduction

Impaired capacity of physical function is associated with morbidity and mortality in cardiovascular disease [1,2]. Exercise capacity was an independent predictor of mortality in thrombolysed patients for acute myocardial infarction [3]. In heart failure, the limited exercise capacity was determined by peripheral hemodynamics rather than central hemodynamics [4,5]. In this regard, skeletal muscle played an important role in determining anaerobic metabolism during exercise in patients with chronic heart failure [6,7]. Previous studies showed that decreased blood flow to the skeletal muscle [8] and altered metabolism in skeletal muscle [9,10] were closely associated with exercise intolerance.

Bioelectrical impedance analysis (BIA) allows the determination of body compositions [11]. The use of BIA has been widespread in clinical practice [12]. With the technical progress of BIA, it is feasible to measure skeletal muscle volume with the convenient method [13,14]. However, whether skeletal muscle volume measured by this simple method is associated with exercise capacity is unknown. Cardiopulmonary exercise testing (CPET) is a remarkably versatile tool that can assess exercise capacity, which quantitatively measures the consumption of oxygen and the production of carbon dioxide [15]. Besides, CPET precisely provides detailed information on ventilatory response to exercise and prognosis in patients with cardiovascular disease [16,17].

Therefore, this study aims to investigate the relationship between skeletal muscle volume measured by BIA and ventilation indices assessed by CPET in patients with myocardial infarction.

2. Methods

2.1. Study population

This study enrolled patients who underwent percutaneous coronary intervention for ST-elevation myocardial infarction in the Hospital of

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Shiga University of Medical Science. Patients with diabetes mellitus were excluded from this study. All patients enrolled in this study performed cardiac rehabilitation before performing progressively increasing, symptom-limited CPET. Patients' physical activities were in New York Heart Association (NYHA) functional class II or III, when CPET was performed. Each patient's drug therapy was optimized before the entry into this study. Patients did not have pulmonary rale and were clinically stable before the study. Patients with severe concomitant extracardiac disease limiting exercise performance were excluded from this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee and informed consent was obtained from all patients enrolled in this study.

2.1.1. Body composition measurement

Body composition was assessed using 8-electrode segmental bioelectrical impedance analysis (X-SCAN PLUS, Tanita Co., Tokyo, Japan) in a standing posture before exercise. The total volume of skeletal muscle and the skeletal muscle volume in each upper and lower limb was also measured under a fasting condition. Body weight and height were simultaneously measured, providing skeletal muscle index (the weight in kilograms divided by the square of the height in meters).

2.2. CPET procedures and data collection

All patients underwent a familiarization bicycle exercise test before performing CPET. Patients were instructed to exercise maximally to symptomatic end points using an isokinetic ergometer (AEROBIKE 75XLII, Minato Medical Science Co. Ltd., Osaka, Japan) under medications. A mask was placed covering the nose and the mouth, the patient breathed through a non-rebreathing valve. Air was delivered to the O_2 and CO_2 analyzer (AEROMONITOR 300S, Minato Medical Science Co. Ltd., Osaka, Japan). Breath-by-breath gas exchange measurement was performed, permitting continuous measurements of ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) on-line. The instrument was calibrated using reference gases before every test. During the test, a standard 12-lead ECG (CASE, GE Healthcare, Wauwatosa, WI, Wisconsin, and United States) was interfaced and heart rhythm was monitored continuously throughout the exercise test. Blood pressure was measured using a standard cuff sphygmomanometer every 1 min. After stationary warm-up exercise with an equivalent of 15 W for 3 min, a ramp protocol with incremental steps equivalent of 20 W/min was used at a rate of approximately 50 rotation/min. All subjects performed an active cool-down, at the initial workload of the exercise protocol, for at least 3 min after the cessation of ramping exercise. A modified Borg scale was used to facilitate communication with the patient with regard to symptoms. From the ventilatory data, minute ventilation ($\dot{V}E$), respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$), and ventilatory equivalents for O_2 and CO_2 ($\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$) were calculated. Peak oxygen consumption (peak $\dot{V}O_2$) was expressed as the highest attained $\dot{V}O_2$ during the final 30 s of ramping exercise. Anaerobic threshold was measured with the $\dot{V}$-slope analysis from the plot of $\dot{V}CO_2$ versus $\dot{V}O_2$ on equal scales. The anaerobic threshold value was also confirmed by ventilatory equivalents (increase of $\dot{V}E/\dot{V}O_2$ with a constant $\dot{V}E/\dot{V}CO_2$) and end-tidal pressure (increase of end-tidal $\dot{V}O_2$ with constant end-tidal $\dot{V}CO_2$). The $\dot{V}O2$/work rate relationship was evaluated throughout the entire exercise, during the ramping period, after elimination of the increase in work rate during the first 120 s to account for the time constant for the $\dot{V}O2$ response to the work rate increase. The $\dot{V}E$ versus $\dot{V}CO_2$ slope was calculated by linear regression, excluding the nonlinear part of the data after the onset of ventilatory compensation for metabolic acidosis. Exercise tests were supervised by an expert team consisting of physiotherapists and physicians who were unaware of results of body composition and echocardiography.

2.3. Echocardiographic assessment

Echocardiography was performed using a 2.5-MHz transducer and connected to computerized hemodynamic instruments. Examinations were performed with the head of the examining table elevated about 30° in a partial decubitus position. Biplane left ventricular end-diastolic and end-systolic volumes were measured using modified Simpson's rule from paired apical 4-chamber and apical 2-chamber echocardiographic images. Left ventricular ejection fraction (LVEF) was obtained from the orthogonal apical views as a parameter of left ventricular systolic function. The parasternal acoustic window was used to record at least 3 consecutive beats of 2-dimensional and M-mode recordings of the left ventricular internal diameter and wall thicknesses just below the tips of the anterior mitral valve leaflets in both the long- and short-axis views. Pulsed-wave Doppler sample volume was placed at the center of the mitral annulus from an apical view to record the early phase of diastolic transmitral blood flow (E). Left ventricular myocardial velocities were evaluated by tissue Doppler imaging. Pulsed tissue Doppler imaging was performed in an apical view to acquire the peak early diastolic mitral annular velocity (e′). To avoid the influence of regional function on the velocity, tissue Doppler signals were recorded at 2 sites: the septal and the lateral sides of the mitral annulus. The ratio of E to e′ (E/e′) was calculated at the both sites, and then the average E/e′ of these was used for representing left ventricular diastolic function. The measurements were composed by the average of ≥3 consecutive cardiac cycles. Heart rate was simultaneously recorded.

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical data are presented as numbers (percentages). A linear regression analysis was applied to determine correlation between skeletal muscle index and ventilation indices measured. A p value <0.05 was considered significant.

3. Results

The study consisted of 60 consecutive patients (57 men; mean age, 59 ± 9 years). The underlying disease was hypertension in 20 patients and dyslipidemia including familial hypercholesterolemia in 18 patients. All patients had a history of smoking. Table 1 lists medication use. Table 2 shows measurements of body composition, echocardiography, and CPET. Skeletal muscle volume averaged 23.4 ± 4.4 kg, and skeletal muscle index averaged 8.3 ± 1.5 kg/m^2. Echocardiographic analysis showed that left ventricular ejection fraction averaged 53.7 ± 9.3%, and E/e′ averaged 10.1 ± 3.5. All patients performed CPET safely and without any complications. Exercise duration excluding warm-up period was 294.4 ± 69.9 s. The anaerobic threshold was measurable and the maximal work was attained in all patients tested. The limiting symptom was leg fatigue in all patients enrolled. The maximum load of ramping exercise averaged 110.3 ± 23.1 W.

Table 1
Medication use.

Drugs	No. of patients
Angiotensin-converting enzyme inhibitor	37 (62)
Angiotensin receptor blocker	18 (30)
Calcium antagonist	3 (5)
β blocker	39 (65)
Loop diuretic	10 (17)
Aldosterone receptor antagonist	26 (43)
Nitrate	10 (17)
Statin	46 (77)
Antiplatelet agent	53 (88)

Numbers are presented as N (%).

Table 2
Measures of body composition, echocardiography, and cardiopulmonary exercise testing.

Body composition	
Height (cm)	167.4 ± 6.3
Weight (kg)	65.4 ± 9.4
BMI (kg/m^2)	23.3 ± 2.7
Skeletal muscle (kg)	23.4 ± 4.4
Skeletal muscle index (kg/m^2)	8.3 ± 1.5
Echocardiography	
LV end-diastolic diameter (mm)	51.8 ± 5.8
LV end-systolic diameter (mm)	36.5 ± 6.7
LV ejection fraction (%)	53.7 ± 9.3
E/e′	10.1 ± 3.5
Cardiopulmonary exercise testing	
Peak heart rate (beats/min)	124.4 ± 21.6
Peak work rate (W)	110.3 ± 23.1
Peak $\dot{V}E$ (mL/kg/min)	716.6 ± 157.9
Peak $\dot{V}O_2$ (mL/kg/min)	17.6 ± 3.9
Peak $\dot{V}CO_2$ (mL/kg/min)	21.7 ± 5.0
Peak RER	1.2 ± 0.2
Peak Mets	5.0 ± 1.2
Peak $\dot{V}E/\dot{V}O_2$ (/kg)	0.7 ± 0.2
Peak $\dot{V}E/\dot{V}CO_2$ (/kg)	0.5 ± 0.2
$\dot{V}E/\dot{V}CO_2$ slope	27.8 ± 5.2
$\Delta\dot{V}O_2/\Delta$work rate slope	7.4 ± 1.2

Values are mean ± SD. BMI = body mass index; V/S ratio = visceral to subcutaneous fat ratio; LV = left ventricle; E = early mitral inflow velocity; e′ = early diastolic mitral annulus motion velocity; $\dot{V}O_2$ = minute oxygen uptake; $\dot{V}E$ = minute ventilation; $\dot{V}CO_2$ = minute carbon dioxide production; respiratory exchange ratio = RER; metabolic equivalents = Mets.

3.1. Skeletal muscle and CPET parameters

Fig. 1 shows a relation between skeletal muscle index and CPET parameters regarding ventilatory efficacy to exercise. There were significantly inverse correlations between skeletal muscle index and peak $\dot{V}E/\dot{V}O2$ ($r = -0.39$, $p = 0.002$; Fig. 1A) and between skeletal muscle index and peak $\dot{V}E/\dot{V}CO2$ ($r = -0.30$, $p = 0.02$; Fig. 1B). Skeletal muscle index showed a significant inverse correlation with $\dot{V}E/\dot{V}CO_2$ slope ($r = 0.30$, $p = 0.02$; Fig. 2). However, no significant correlations were found between skeletal muscle index and peak $\dot{V}E$ ($r = 0.23$, $p = 0.08$), between skeletal muscle index and peak $\dot{V}O_2$ ($r = 0.08$, $p = 0.56$), between skeletal muscle index and peak $\dot{V}CO_2$ ($r = 0.001$, $p = 0.99$), and between skeletal muscle index and $\Delta\dot{V}O_2/\Delta$work rate slope ($r = 0.07$, $p = 0.60$).

4. Discussion

Exercise is of value in primary, secondary, and tertiary prevention in cardiovascular diseases. CPET is a remarkably versatile tool that provides valuable diagnostic and prognostic information regarding patients with cardiovascular diseases [16,18]. In CPET, peak $\dot{V}O_2$ (the highest rate of oxygen uptake) and $\dot{V}E/\dot{V}CO_2$ slope (the rate of increase in ventilation per unit increase in carbon dioxide production) are widely accepted as useful prognostic markers [19,20]. Skeletal muscle plays an important role in determining exercise capacity. In this study, we compared skeletal muscle index with various ventilation indices obtained from CPET in patients with myocardial infarction. The major findings of this study are as follows: 1) skeletal muscle index was associated with the amelioration of ventilatory efficacy at the peak level and 2) the inverse correlation between skeletal muscle index and $\dot{V}E/\dot{V}CO_2$ slope suggests that skeletal muscle index may be attributed to better prognosis.

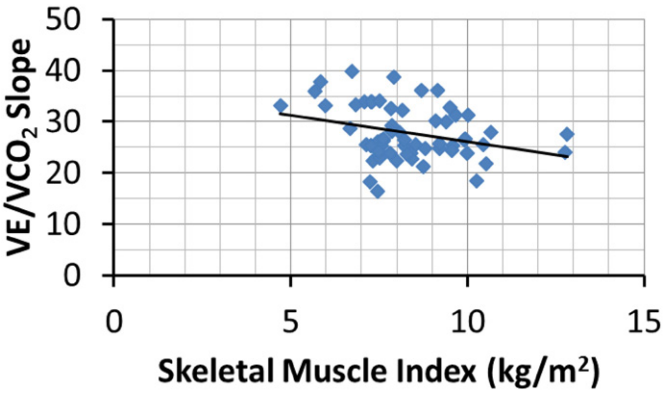

Fig. 2. Relation between skeletal muscle index and $\dot{V}E/\dot{V}CO_2$ slope.

It is undoubtedly necessary to perform cardiac rehabilitation in patients with cardiovascular disease. It is therefore essential to evaluate exercise capacity for those patients. Skeletal muscle is one of the important determinants of exercise capacity [5]. Previous studies have shown fundamental mechanisms underlying exercise capacity in association with skeletal muscle. Harrington et al. reported that muscular atrophy in the lower limbs was a major determinant of exercise capacity [21]. Sullivan et al. reported that a decrease in type I fibers and an increase in type IIb fibers of skeletal muscle were observed in heart failure [22] and reduced aerobic enzyme activity in skeletal muscle was associated with exercise intolerance in heart failure [6]. In addition, an intrinsic muscle abnormality is considered to be responsible for exercise capacity. Impaired skeletal muscle function resulted in ergoreflex activation, leading to increased ventilation [23], and depleted peripheral muscle mass was associated with ergoreflex overactivity and exercise limitation in heart failure [24]. Recently, Dhakal et al. demonstrated that utilization of oxygen in skeletal muscle determined exercise capacity in heart failure with preserved ejection fraction [25]. Consistent with the previous reports, the present study showed that an increase in skeletal muscle index ameliorated ventilatory efficacy at peak exercise level in patients with myocardial infarction. This is because skeletal muscle index may reflect alteration of histology, metabolism, ergoreflex, and oxygen consumption in this disorder. The novelty of the present study is that simply measured skeletal muscle by BIA is attributed to exercise capacity in terms of ventilatory efficacy.

CPET provides valuable parameters: 1) peak $\dot{V}O_2$ reflecting maximal cardiac output during exercise, 2) $\dot{V}E/\dot{V}CO_2$ slope reflecting cardioventilatory function during exercise, 3) $\Delta\dot{V}O_2/\Delta$work rate reflecting

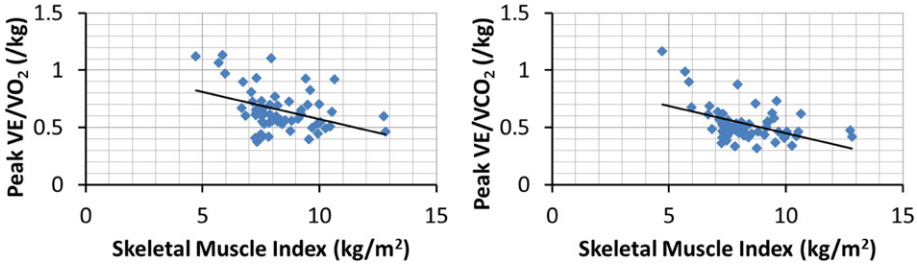

Fig. 1. Relation between skeletal muscle index and peak $\dot{V}E/\dot{V}O_2$ (A) and between skeletal muscle index and peak $\dot{V}E/\dot{V}CO_2$ (B).

the rate of the increase in cardiac output during incremental exercise, and 4) anaerobic threshold reflecting exercise intensity at which lactic acidosis occurs. $\dot{V}E$ increases as a function of hyperbolic state. Above the level of anaerobic threshold, lactic acidosis stimulates ventilation further, thus leading to an increase in tidal volume to eliminate the excessive production of CO_2. Such ventilatory drive progressively increases $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$, both of which indicate ventilatory equivalent to O_2 uptake and CO_2 excretion, respectively. The ventilatory equivalent markers are reflected by several factors such as lactic acidosis, hyperventilation, and chemosensitivity. In addition, increased $\dot{V}E/\dot{V}CO_2$ during exercise was related to an increase in ventilation–perfusion mismatch due to increased dead space ventilation in heat failure [26]. This study demonstrated inverse relation between skeletal muscle index and peak $\dot{V}E/\dot{V}O_2$ and between skeletal muscle index and peak $\dot{V}E/\dot{V}CO_2$, indicating that skeletal muscle was associated with the amelioration of ventilatory efficacy at the peak exercise level.

The steep slope of $\dot{V}E/\dot{V}CO_2$ slope is associated with multiple factors such as reduced cardiac output during exercise, increased pulmonary artery and capillary wedge pressures, increased dead space/tidal volume ratio, and augmented chemoreceptor sensitivity. Thus, the increased $\dot{V}E/\dot{V}CO_2$ slope is due to both ventilation–perfusion mismatch arising from hemodynamic dysfunction and the altered control of ventilation. Our study also demonstrated inverse relation between skeletal muscle index and $\dot{V}E/\dot{V}CO_2$ slope, implying that skeletal muscle may gain support of improvement of prognosis in myocardial infarction. Although both peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope are related to cardiovascular prognosis, $\dot{V}E/\dot{V}CO_2$ slope is a better predictor of clinical outcomes than peak $\dot{V}O_2$ [19,20,27]. This is because peak $\dot{V}O_2$ may not accurately reach to a plateau level and is also affected by the motivation of patients. Our study showed that skeletal muscle index was associated with $\dot{V}E/\dot{V}CO_2$ slope but not with peak $\dot{V}O_2$, indicating that skeletal muscle index may be associated with ventilatory efficacy to exercise but not with exercise capacity.

There are several limitations in this study. First, we measured skeletal muscle quantitatively, but did not perform qualitative analysis of skeletal muscle such as muscle power. Because the primary aim of this study is to determine whether or not skeletal muscle measured by BAI is clinically useful, we focused on the quantitative analysis of skeletal muscle. Second, $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ were standardized by body weight in this study, because other ventilation indices were standardized in CPET.

Skeletal muscle is one of the pathophysiological links with exercise capacity in cardiovascular disease. Despite this crucial association, the detailed mechanisms are yet to be determined. Our study demonstrated that skeletal muscle index inversely correlated with ventilatory efficacy at peak exercise level. In addition, skeletal muscle index negatively correlated with the best prognostic marker (i.e., $\dot{V}E/\dot{V}CO2$ slope) obtained from CPET. These findings can explain that skeletal muscle is intimately associated with ventilatory response to exercise. However, further studies are needed to elucidate the fundamental pathophysiological mechanisms on which the role of skeletal muscle in ventilatory efficacy is based. In addition, it is necessary to study whether the increase in skeletal muscle improves the prognosis in the population of the present study.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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