Evaluation of oxygen uptake adjusted by skeletal muscle mass in cardiovascular disease patients with type 2 diabetes

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Abstract. [Purpose] We aimed to evaluate oxygen uptake adjusted by total skeletal muscle mass in patients with cardiovascular disease with or without type 2 diabetes mellitus. [Participants and Methods] The participants included 54 males ≥50 years of age without heart failure who underwent cardiopulmonary exercise testing during cardiac rehabilitation. We divided the participants into two groups: patients with type 2 diabetes mellitus (DM group) and patients without type 2 diabetes mellitus (NDM group). [Results] We found no significant differences in age, weight, fat mass, or skeletal muscle mass between the groups. There were also no differences in cardiac function, body composition, and heart rate response. The DM group showed significantly lower peak oxygen uptake values adjusted by skeletal muscle mass, despite the absence of significant differences in skeletal muscle mass. A significant positive correlation was found between peak oxygen uptake and age, weight, and skeletal muscle mass. Stepwise regression analysis revealed that age, skeletal muscle mass, and medical history of diabetes were independent predictors of absolute peak oxygen uptake. [Conclusion] Peak oxygen uptake adjusted by skeletal muscle mass in patients with cardiovascular disease and type 2 diabetes mellitus is lower than that in those without type 2 diabetes mellitus.

Key words: Cardiopulmonary exercise testing, Peak oxygen uptake, Skeletal muscle mass

INTRODUCTION

Cardiopulmonary exercise testing (CPX) is a useful way to evaluate prognosis, risk of metabolic diseases, condition of diseases, determination of exercise intensity, and efficacy of exercise therapy1–5). The most popular marker is peak oxygen uptake (VO2). Low peak VO2 is an independent risk factor for cardiovascular and metabolic diseases6–8). Recently, it has been reported that total skeletal muscle mass (SMM) is associated with prognosis in patient with cardiovascular disease (CVD)9), and its evaluation is also important.

Although VO2 adjusted by body weight (VO2/w) is used to evaluate the exercise capacity, body weight includes fat mass and SMM. VO2 is not proportional to body weight9,10) because it is often greatly affected by the amount of fat. In previous studies, it was reported that VO2 per lean body mass was more effective for evaluating exercise capacity in healthy subjects, obese patients, metabolic syndrome patients, and patients during cardiac rehabilitation, because peak VO2/w only standardizes differences in body size9,11–13). In addition, the decrease in VO2 due to aging and gender is also associated with an
increase in percent body fat mass and decrease in percent skeletal muscle mass. Many studies have evaluated VO2 in cardiac rehabilitation patients[14-10]. Previous reports have suggested that peak VO2 is frequently impaired in CVD patients with type 2 diabetes (T2DM)[17, 18]. These reports measured VO2/w in patients with CVD. Nevertheless, there are no studies that VO2 adjusted by SMM (VO2/SMM) in CVD patients with T2DM. Therefore, the aim of this study was to evaluate VO2/SMM in CVD patients with or without T2DM.

PARTICIPANTS AND METHODS

This study was approved by the Kansai Medical University Ethics Committee (approval no. 2017135). The main aims, details, and risks were explained to the participants, all of whom provided written informed consent prior to participating. The participants were 54 male cardiac rehabilitation outpatients, aged ≥50 years, who underwent CPX between April 2013 and February 2017. To eliminate disparities due to cardiac and pulmonary function, we excluded patients with heart failure or with chronic obstructive pulmonary disease and other lung diseases. Patients who were undergoing hemodialysis, those with pacemakers, and those who discontinued CPX for reasons other than symptomatic limits were also excluded. All procedures performed in studies involving human participants were under both the ethical standards of the Kansai Medical University Ethics Committee and 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The basic characteristics and medical histories, including the diagnosis of T2DM, were obtained from the medical records. The participants were divided into two groups: patients with HbA1c ≥6.5% (based on the results of biochemical tests) and/or who received oral diabetes drugs were classified as the T2DM group (DM group); the rest were allocated to the group without T2DM (the NDM group).

Body composition was measured using an InBody720 body composition analyzer (InBody, Seoul, Korea). The validity of this bioelectrical impedance analysis has been documented in previous studies[19, 20].

Echocardiographic studies and blood examinations were performed before the cardiac rehabilitation program. Those results were obtained from the medical records. Casual blood was analyzed to determine glucose and glycosylated hemoglobin (HbA1c) levels, lipid profiles, hemoglobin, hematocrit, creatinine, estimated glomerular filtration rate, and amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Left ventricular ejection fraction (LVEF), left atrial dimension, early diastolic transmitral flow velocity (E), the mitral annular velocity at the early diastolic phase on tissue Doppler (e′), E/e′, and the ratio of transmitral early and late peak filling rate (E/A) were evaluated using echocardiographic studies. Patients with an LVEF <60% and an NT-proBNP >200 pg/mL were classified as the T2DM group (DM group); the rest were allocated to the group without T2DM (the NDM group).

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For the cardiopulmonary exercise testing, a symptom-limited exercise stress test, using the ramp method, was conducted using an expiration gas analyzer (AE300S, Minato Medical Science Co., Ltd., Osaka, Japan) and an ergometer cycle (AEROBIKE 75XL; Combi, Tokyo, Japan) with a 12-lead electrocardiogram. After a 5-min rest on the ergometer, the exercise began with a 4-min warm-up at 10–20 watts and 50 rpm, followed by the 10–20-watt ramp method. Heart rate (HR), VO2, and carbon dioxide excretion volume (VCO2) were measured at the point of rest, warm-up, anaerobic threshold (AT), and maximum oxygen uptake (peak VO2) using the breath-by-breath method. The AT was determined using the V-slope method. Peak VO2 and work rate (WR) were defined as the peak values during incremental exercise. These results were used to calculate 1) respiratory exchange ratio (R=VCO2/VO2), an energy indicator; 2) VE (minute ventilation)/VCO2 slope, a ventilation efficiency indicator; 3) O2 pulse=VO2/HR, a pulse output indicator; 4) change in VO2/change in WR (ΔVO2/ΔWR), a cardiac function indicator; and 5) change in heart rate/change in work rate (ΔHR/ΔWR), an autonomic nerve indicator. AT and peak VO2 were calculated by adjusting for both SMM and weight.

All statistical analyses were conducted using SPSS software version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). The measured values are expressed as mean ± standard deviation. Normal distribution was confirmed using the Shapiro-Wilk test. The unpaired t-test and the χ2 test were used for inter-group comparisons. Pearson’s correlation coefficients and stepwise multiple regression analyses were used to measure peak VO2 and peak VO2/SMM. All tests were two-sided, and a value of p<0.05 was considered significant.

RESULTS

The characteristics of the participants are shown in Table 1. There were no significant differences in terms of age, weight, and %fat between the two groups. The DM group had significantly higher body mass index (24.5 ± 3.0 vs. 22.7 ± 2.5 kg/m², p=0.034). The DM group showed significantly higher HbA1c and blood sugar levels. There were no significant differences in terms of hepatic function, lipid metabolism, or renal function. There were also no significant differences in echocardiography findings, including the cardiac function indicators LVEF and NT-proBNP. A significant difference was found only for administration of oral anti-diabetic drugs (84.6% [DM group] vs. 0.0% [NDM group], p<0.001). There were no differences in terms of other orally administered drugs, including anti-hypotensive and lipid-lowering agents or insulin therapy.

Body composition profiles are shown in Table 2. No significant differences were seen between the DM and NDM groups in terms of SMM, and those of the arms, trunk, and legs. No significant difference was found for fat mass.

The CPX results are shown in Table 3. Peak VO2/w was significantly lower in the DM group (DM: 19.1 ± 3.4 vs. NDM: 22.6 ± 4.7 mL/kg/min, p=0.017). No significant differences were seen in the AT R or the peak R (AT: 0.89 ± 0.04 vs. 0.90 ±
Table 1. Clinical characteristics of the study groups

|                      | DM (n=13)       | NDM (n=41)      | p-value |
|----------------------|-----------------|-----------------|---------|
| Age (years)          | 68.6 ± 7.0      | 67.6 ± 7.1      | 0.665   |
| Weight (kg)          | 66.4 ± 9.5      | 63.8 ± 9.7      | 0.407   |
| BMI (kg/m²)          | 24.5 ± 3.0      | 22.7 ± 2.5      | 0.034*  |
| % Fat (%)            | 25.0 ± 5.0      | 22.2 ± 5.6      | 0.113   |
| LVEF (%)             | 68.5 ± 6.7      | 68.7 ± 5.8      | 0.928   |
| LAD (mm)             | 39.4 ± 7.2      | 36.9 ± 4.9      | 0.157   |
| e' (n = 13/36) (m/sec)| 0.06 ± 0.01    | 0.08 ± 0.08     | 0.310   |
| E/e' (n = 13/36)     | 11.5 ± 1.9      | 10.1 ± 3.8      | 0.107   |
| NT-proBNP (pg/dL)    | 0.81 ± 0.25     | 0.85 ± 0.21     | 0.554   |
| HbA1c (%)            | 46.2 ± 1.8      | 43.1 ± 1.1      | 0.838   |
| Glu (mg/dL)          | 6.6 ± 0.8       | 5.7 ± 0.4       | <0.001* |
| Glu (mg/dL)          | 153.8 ± 41.5    | 106.5 ± 22.1    | 0.001*  |
| TG (n=13/40) (mg/dL) | 154.0 ± 53.6    | 148.6 ± 79.3    | 0.820   |
| HDL-cho (n=12/41) (mg/dL) | 46.5 ± 15.3 | 49.6 ± 12.3 | 0.470   |
| LDL-cho (n=13/40) (mg/dL) | 83.4 ± 17.9 | 90.5 ± 23.5 | 0.325   |
| Cre (mg/dL)          | 0.98 ± 0.45     | 0.91 ± 0.16     | 0.571   |
| eGFR (mg/dL)         | 67.9 ± 22.4     | 66.7 ± 12.0     | 0.848   |

History of cardiovascular disease (%)

- Coronary artery disease: 84.6 vs. 85.4
- Myocardial infarction: 46.2 vs. 53.7
- Angina: 38.5 vs. 31.7
- Vascular disorders: 15.4 vs. 9.8
- Thoracic aortic aneurysm: 7.7 vs. 7.3
- Abdominal aortic aneurysm: 7.7 vs. 2.4
- Valve disease: 7.7 vs. 12.2
- Aortic valve stenosis: 0 vs. 9.8
- Mitral valve stenosis: 7.7 vs. 2.4
- Percutaneous coronary intervention: 76.9 vs. 70.7
- Coronary artery bypass grafting: 7.7 vs. 14.6
- Valve replacement: 7.7 vs. 12.2
- Aortic replacement, endovascular aortic repair: 15.4 vs. 9.8

Results are expressed as mean ± SD.
DM: diabetes group; NDM: non-diabetes group; BMI: body mass index; Cre: creatinine; eGFR: estimated GFR; GLU: glucose; HbA1c: hemoglobin Alc; Hb: hemoglobin; HDL-cho: high density lipoprotein cholesterol; HTC: hematocrit; LAD: left anterior descending; LDL-cho: low density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal proatrial natriuretic peptide; TG: triglyceride.

Table 2. Results of the body composition analysis

|                      | DM (n=13)       | NDM (n=41)      | p-value |
|----------------------|-----------------|-----------------|---------|
| Total skeletal muscle mass (kg) | 27.1 ± 3.0    | 27.1 ± 3.5      | 0.965   |
| Arm muscle mass (kg)  | 2.7 ± 0.4       | 2.8 ± 0.5       | 0.735   |
| Trunk muscle mass (kg) | 22.1 ± 2.4     | 22.0 ± 2.7      | 0.931   |
| Leg muscle mass (kg)  | 7.6 ± 0.9       | 7.8 ± 1.1       | 0.597   |
| Total fat mass (kg)   | 16.9 ± 5.4      | 15.1 ± 5.8      | 0.169   |
| Arm fat mass (kg)     | 1.1 ± 0.4       | 0.9 ± 0.5       | 0.207   |
| Trunk fat mass (kg)   | 8.7 ± 3.2       | 7.2 ± 3.2       | 0.156   |
| Leg fat mass (kg)     | 2.5 ± 0.7       | 2.2 ± 0.7       | 0.174   |

Results are expressed as mean ± SD.
DM: diabetes group; NDM: non-diabetes group;
The DM group showed significantly lower peak VO$_2$/SMM (DM: 47.5 ± 9.1 vs. NDM: 53.4 ± 8.8 mL/kg/min, p=0.041). However, no significant difference was seen for the AT VO$_2$/SMM. No significant differences were observed for the O$_2$ pulse at the AT or the peak (AT: 8.8 ± 1.9 vs. 9.4 ± 1.7, p=0.297 and peak: 10.9 ± 1.9 vs. 11.7 ± 2.2, p=0.257), ΔVO$_2$/ΔWR (AT: 10.9 ± 5.6 vs. peak: 10.4 ± 2.9, p=0.800), or VE/VCO$_2$ slope (AT: 26.0 ± 4.7 vs. peak: 26.3 ± 4.7, p=0.750). No significant difference was found for ΔHR/ΔWR, the marker of autonomic nerve function (AT: 0.59 ± 0.51 vs. peak: 0.54 ± 0.18, p=0.743).

Table 4 shows the peak VO$_2$-related factors. A significant negative correlation was found between peak VO$_2$ and age (r=−0.500, p<0.001), while significant positive correlations were observed between peak VO$_2$ and weight (r=0.462, p<0.001) and between peak VO$_2$ and SMM (r=0.638, p<0.001). The stepwise multiple regression analysis identified age, SMM, and a medical history of diabetes as independent predictors of peak VO$_2$ regression (β=−0.282/p=0.011, β=0.526/p<0.001, and β=0.204/p=0.042, respectively).

### DISCUSSION

We observed lower peak VO$_2$/w and VO$_2$/SMM in CVD patients with T2DM than in those without T2DM. There was no significant difference in body weight between groups; however, the BMI in the DM group was significantly higher than that of the NDM group. Previous studies reported that patients with diabetes have higher body weight and BMI than those without...
diabetes\textsuperscript{22–24)} similar to what we found in this study. However, SMM was not significantly different between groups, and the DM group tended to have a larger amount of body fat. The absolute peak VO\textsubscript{2} depends on body weight; however, this value in the DM group tended to be lower than that of the NDM group. In previous studies, weight-corrected VO\textsubscript{2} was affected by body fat mass, SMM, and intramyocellular lipid content\textsuperscript{10–13)} In other words, lower peak VO\textsubscript{2}/w in the DM group might result from greater body fat mass in the patients with T2DM. Peak VO\textsubscript{2}/SMM excluding the effect of fat mass was also lower in DM group than in the NDM group despite their being no significant difference in the SMM. These findings suggest that the low exercise capacity of diabetic patients may be a problem not only in body fat but also in skeletal muscle quality, and VO\textsubscript{2}/SMM might be useful marker for evaluation to exercise capacity. This is the first report to evaluate peak VO\textsubscript{2}/SMM in CVD patients with or without T2DM. Nevertheless, we only found a difference in peak VO\textsubscript{2}/SMM, not in AT VO\textsubscript{2}/SMM. The reason was unclear; however, VO\textsubscript{2}/SMM may reflect the quality of skeletal muscle and may represent the condition of skeletal muscle at higher intensity loads than low intensity such as AT level.

SMM was an independent factor of absolute peak VO\textsubscript{2}. We selected patients without cardiac systolic dysfunction and respiratory dysfunction to eliminate any unexpected influence of cardiac and respiratory function. The CPX results revealed no significant differences in cardiac function indicators such as ΔVO\textsubscript{2}/ΔWR and peak O\textsubscript{2} pulse, and autonomic nervous indicators such as ΔHR/ΔWR. These results suggest that the difference of peak VO\textsubscript{2}/SMM might be an effect of skeletal muscle metabolism. Impairment of skeletal muscle metabolism in patients with diabetes\textsuperscript{25–29)} reduces exercise tolerance due to impairment of carbohydrate metabolism, lipid metabolism\textsuperscript{30)}, insulin resistance, and insulin sensitivity\textsuperscript{31–33)}. Recent genetic research in patients with diabetes revealed a positive correlation between general aerobic capacity and the expression of a coregulated subset of oxidative phosphorylation (OXPHOS) genes (OXPHOS-CR) regulated by PGC-1α, which is positively correlated with general VO\textsubscript{2}\textsuperscript{34)}. Our finding of a lower peak VO\textsubscript{2} in patients with diabetes mellitus may be related to muscle metabolism, as described in previous studies\textsuperscript{25–34)}. Endothelial dysfunction in diabetic patients is also one of the causes of impaired exercise tolerance\textsuperscript{35)}, however, it could not be evaluated in this study.

There were some limitations in our study. First, the number of participants in the DM group was small. The characteristics of the DM group might become clearer in studies involving a higher number of participants. Multivariate analysis in 13 patients in the DM groups lacked statistical power. Second, this was a cross-sectional study; therefore, we were unable to establish a cause–effect relationship between oxygen uptake and SMM. While the influence exerted by skeletal muscle during exercise has been frequently reported\textsuperscript{31, 32, 36–38)}, future studies are needed to determine how peak VO\textsubscript{2}/SMM changes from before to after exercise intervention. Finally, bioimpedance was used to measure biological components instead of the DEXA method, which is the gold standard for body composition measuring. Nevertheless, we excluded patients with heart failure or prominent edema. We also recorded impedance values in participants.

In conclusion, peak VO\textsubscript{2}/SMM of CVD patients with T2DM was lower than that of patients without T2DM, despite the absence of significant difference in the SMM. The difference of peak VO\textsubscript{2}/SMM may be due to the effect of skeletal muscle metabolism.

Presentation at a conference
The part of our research was presented in the Annual Meeting of the Japanese Association of Cardiac Rehabilitation 2020.

Funding
The authors declare no funding for this study.

Conflicts of interest
The authors have no conflicts of interest relevant to this article.

ACKNOWLEDGEMENT

We thank the staff members of the Health Science Center of Kansai Medical University.

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