



Original Article

## A predictor of aerobic threshold for patients with heart failure with reduced ejection fraction

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**Abstract.** [Purpose] The initial cardiopulmonary response to exercise is hypothesized to be a useful predictor of aerobic threshold in patients with heart failure. This study aimed to evaluate the correlation between aerobic threshold and cardiopulmonary responses to exercise onset by comparing patients with heart failure using preserved ( $\geq 50\%$ ) and reduced ( $< 50\%$ ) left ventricular ejection fractions. [Participants and Methods] Twenty-eight males (age, 36–82 years; 12 with preserved and 16 with reduced left ventricular ejection fractions) underwent a progressive submaximal cardiopulmonary exercise test using a cycle ergometer. The aerobic threshold, time constant, and area under the oxygen uptake curve for the first 4 min ( $\dot{V}O_2AUC$ ) were determined. [Results] A significant association was observed between aerobic threshold and  $\dot{V}O_2AUC$  in the reduced group but not in the preserved group. No significant correlations were found between time constant and  $\dot{V}O_2AUC$  or between aerobic threshold and time constant in either group. [Conclusion] The results suggest that  $\dot{V}O_2AUC$  measured from exercise onset to an initial 4-min period could provide an easily and safely obtained predictor to assess aerobic capacity in people with reduced left ventricular ejection fractions.

**Key words:** Reduced ejection fraction, Left ventricular ejection fraction, Aerobic threshold

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### INTRODUCTION

Heart failure is highly prevalent and is increasing globally. Left ventricular diastolic dysfunction plays a considerable role in heart failure. Patients with heart failure can be divided into those with preserved left ventricular ejection fraction (LVEF) and reduced LVEF (HFpEF and HFrEF, respectively)<sup>1, 2</sup>. Cardiac dysfunction can lead to decreased aerobic capacity<sup>3</sup>; conversely, higher aerobic capacity is associated with reduced mortality in heart failure<sup>4, 5</sup>. Oxygen uptake ( $\dot{V}O_2$ , defined as the product of cardiac output and arterial-mixed venous oxygen difference), increases during exercise. Maximal oxygen uptake ( $\dot{V}O_2 \max$ ), a measure of aerobic capacity, is an important consideration in people with heart failure. However, because of lack of muscle strength, fatigue, symptoms, or psychological factors, it can be difficult for patients with heart failure to attain the maximal exercise level needed to determine  $\dot{V}O_2 \max$ <sup>6</sup>. Therefore, a safe and simple method is needed to determine the aerobic capacity of patients with heart failure.

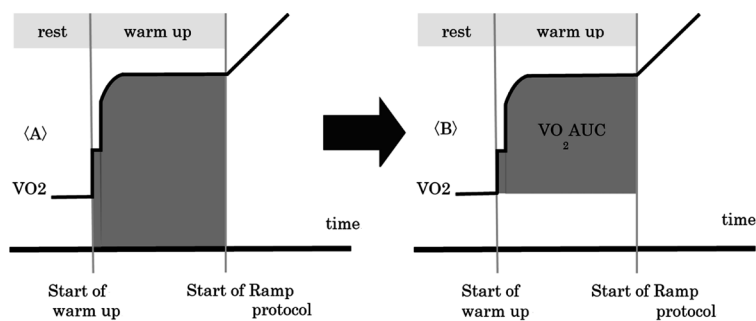
We had earlier attempted to expect anaerobic threshold (AT) as an initial response to exercise. However, little is known about how this response changes with different aerobic capacities<sup>3, 7</sup>. The present study aimed to investigate the relationship between AT and the cardiopulmonary response to exercise onset in patients with heart failure, comparing this between HFpEF and HFrEF.

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**Fig. 1.** Method to calculate  $\dot{V}O_2$  area of under curve ( $\dot{V}O_2AUC$ ).  $\dot{V}O_2AUC <B>$  was obtained by subtracting the integrated  $\dot{V}O_2$  value during warm-up period from the total value  $<A>$ .

## PARTICIPANTS AND METHODS

The study included 28 males with heart failure (age, 36–82 years). All participants had been admitted for cardiac rehabilitation because of heart failure.

The participants were divided into two groups based on their LVEF: the HFpEF group with LVEF  $\geq 50\%$  ( $n=12$ ; mean age, 68.7 years; range, 58–82 years) and the HFrEF group with LVEF  $< 50\%$  ( $n=16$ ; mean age, 60.4 years; range 36–81 years). Prior to the exercise test, the participants' health history, risk factors for coronary disease, age, height, weight, and physical characteristics were recorded. Informed consent was obtained from all patients before their participation in the study. Inclusion criteria included diagnosis of heart failure, participation in cardiac rehabilitation programs, and aerobic capacity determined using cardiopulmonary exercise test (CPET). Exclusion criteria included detection of lethal arrhythmia on CPET, inability to decide AT, and oscillatory ventilation.

The participants underwent a submaximal CPET using a cycle ergometer, with expiratory gas analysis to determine their  $\dot{V}O_{2max}$ . There were rest and warm-up phases of 4 min each before initiation of Ramp protocol. The initial workload was set at 10 W and was subsequently increased by 10 W/min using Ramp protocol. The pedaling frequency was monitored to ensure it remained at  $\geq 50$  revolutions per min. The endpoint of CPET was determined by the appearance of a symptom associated with coronary disease or when the participant or the observer declared that the participant had reached his limit. Throughout the test, the participant was continuously monitored using electrocardiography.

Pulmonary ventilation and gas exchange parameters were determined breath-by-breath throughout the CPET using an Aeromonitor AE-300 (Minato Medical Science Co., Ltd., Osaka, Japan). The system was calibrated before each test using gas mixtures of known compositions.

The participant's AT, time constant (TC), and area under the oxygen uptake curve ( $\dot{V}O_2AUC$ ) were evaluated. AT was determined using several methods based on conventional criteria: the point during the CPET at which there was the first departure from linearity in the plot of carbon dioxide output ( $\dot{V}CO_2$ ) against  $\dot{V}O_2$  (the V-slope method), the point when  $\dot{V}O_2$  increased after being stable or decreased while  $\dot{V}CO_2$  remained constant or was decreasing, and the point when the gas exchange ratio began to increase more steeply after being stable or slowly rising<sup>3</sup>). TC was determined from the initial increase in  $\dot{V}O_2$  following exercise onset in the warm-up phase.  $\dot{V}O_2AUC$  was calculated as the area under the  $\dot{V}O_2$  curve from the onset of exercise through the initial 4 min of the warm-up phase. This calculation excluded the influence of the resting state (Fig. 1).

Data are reported as means (SD). Independent t-tests were used to compare age, body mass index (BMI), LVEF, TC,  $\dot{V}O_2AUC$ , and AT between the HFpEF and HFrEF groups. The correlations between TC,  $\dot{V}O_2AUC$ , and AT were assessed using Pearson product-moment correlation coefficients.  $p < 0.05$  was considered statistically significant. All analyses were performed using IBM SPSS Statistical software (version 24).

This study was approved by the ethics committee of Tokyo Metropolitan University (approval number: 13099) and the ethics committee of Ukima Central Hospital (approval number: H25-1) and was conducted in accordance with the principles of the Declaration of Helsinki.

## RESULTS

Table 1 showed the mean (SD) value for characteristics of the participants in the HFpEF ( $n=12$ ) and HFrEF ( $n=16$ ) groups in this study (Table 1). LVEF in the HFpEF and HFrEF groups were 65.7 (10.6%) and 36.1 (8.9%), respectively. There were no significant differences between any of the other measured parameters.

The prevalence of risk factors for coronary diseases and the participants' indications for admission were determined

**Table 1.** The characteristics of participants

	HFpEF N=12	HFrEF N=16
Age (years)	68.7 (7.7)	60.4 (12.3)
Height (cm)	164.7 (5.1)	166.3 (6.0)
Weight (kg)	67.6 (7.8)	64.8 (16.2)
BMI (kg/m <sup>2</sup> )	24.9 (2.7)	23.2 (4.7)
LVEF* (%)	65.7 (10.6)	36.1 (8.9)
TC (sec)	88.3 (52.2)	59.6 (23.0)
$\dot{V}O_2AUC$ (ml/kg)	8.4 (1.7)	9.7 (1.4)
AT (ml/kg/min)	8.9 (1.5)	9.3 (1.4)

Mean (SD) values for the HFpEF and HFrEF groups. HFpEF: heart failure with preserved left ventricular ejection fraction; HFrEF: heart failure with reduced left ventricular ejection fraction; BMI: body mass index; LVEF: left ventricular ejection fraction; TC: time constant;  $\dot{V}O_2AUC$ : area of under oxygen uptake curve; AT: aerobic threshold. Independent t-test had been adopted to compare participants with HFpEF and HFrEF. No significant differential had been recognized between HFpEF and HFrEF eliminated LVEF. \*p<0.05.

**Table 2.** Prevalence of risk factors for coronary diseases and New York Heart Association grade (NYHA) on admission of HFpEF and HFrEF

	HFpEF	HFrEF
Risk factors for coronary diseases		
Hypertension	10	11
Hyperlipidemia	4	7
Hyperuricemia	4	6
Diabetes	7	7
Smoking	8	13
NYHA		
I	0	1
II	5	6
III	3	3
IV	4	6

**Table 3.** Pearson's product-moment correlation coefficient

	HFpEF	HFrEF
AT and $\dot{V}O_2AUC$	0.39 (p=0.21)	0.67 (p<0.05)
TC and $\dot{V}O_2AUC$	0.14 (p=0.67)	-0.22 (p=0.42)
AT and TC	-0.04 (p=0.91)	-0.05 (p=0.86)

according to the New York Heart Association (NYHA) classification in the HFpEF and HFrEF groups was shown (Table 2).

Pearson's product-moment correlation coefficients for the HFpEF and HFrEF groups were shown (Table 3). Significant correlation showed between  $\dot{V}O_2AUC$  and AT in the HFrEF group.

## DISCUSSION

A major finding of the current study was that  $\dot{V}O_2AUC$  and AT showed a strong, significant correlation in participants with HFrEF but not in those with HFpEF. Our study results suggest that  $\dot{V}O_2AUC$  with cardiac dysfunction such as HFrEF is associated with AT. Left ventricular diastolic dysfunction is a major factor of HFpEF<sup>1)</sup>. In this study, we divided the participants into the HFpEF and HFrEF groups according to their LVEF. We expected these two groups would have different hemodynamic reactions owing to their left ventricular differences. Asanoi et al.<sup>8)</sup> reported that left ventricular end-diastolic volume increased below AT, whereas left ventricular end-systolic volume decreased above AT, suggesting that left ventricular systolic function increases above the AT level. Thus, left ventricular diastolic dysfunction affected oxygen conveyance below AT in participants with HFpEF, whereas left ventricular systolic dysfunction affected oxygen conveyance above AT in participants with HFrEF.

We compared the differences in cardiac dysfunction between the two groups to test our hypothesis that AT could be predicted from parameters associated with the onset of exercise in participants with the absence of left ventricular systolic dysfunction such as HFrEF.

The AT has been shown to be related to oxygen conveyance<sup>9)</sup> as a component of exercise capacity. The oxygen uptake response, particularly of the TC of oxygen uptake, at the onset of exercise has been of remarkable value<sup>10)</sup> because of its correlation with aerobic capacity or cardiac output. AT is considered the level of exercise-related  $\dot{V}O_2$  above which aerobic energy production is supplemented by anaerobic mechanisms; it is reflected by an increase in the lactate/pyruvate ratio in muscles or arterial blood<sup>11)</sup>. Thus, consideration of both oxygen conveyance and uptake is needed to predict AT from factors related to exercise onset.

In the present study, the participants in both groups showed an increased TC and decreased AT. An increased TC suggests that the impaired cardiac function is due to poor left ventricular diastolic dysfunction in participants with HFpEF and poor left ventricular systolic dysfunction in participants with HFrEF. The decreased AT suggests moderate or severe cardiac dysfunction as described by the Weber-Janicki grade<sup>9)</sup>; in the HFpEF group, the mean value was 8.4 ml/kg/min, whereas in the HFrEF group, it was 9.3 ml/kg/min.

Beside ventilation and muscle function, cardiac function plays a considerable role in human fitness<sup>11)</sup>. In addition, cardiac function such as LVEF and stroke volume begun to decline at AT<sup>12)</sup>. We believe that the reduced reserve of oxygen conveyance

above AT in participants with HFrEF. Oxygen conveyance and oxygen utilization is associated with aerobic capacity such as AT. Reduced LVEF affected oxygen conveyance above AT, and led to appear the oxygen utilization. Thus, there were no correlations between  $\dot{V}O_2AUC$  and AT, TC and AT, or  $\dot{V}O_2AUC$  and TC in the HFpEF group.  $\dot{V}O_2AUC$  is an indicator of oxygen usage and is associated with AT in people with left ventricular systolic dysfunction, such as in participants belonging to the HFrEF group. Other factors associated with AT include ventilation, lactic acid metabolism, muscle function, and mitochondrial function.

In this study,  $\dot{V}O_2AUC$  and TC were both determined soon after the onset of exercise; therefore, we expected to find a correlation between them. However, there was no significant correlation between the two parameters in either group. This suggests that  $\dot{V}O_2AUC$ , unlike TC, was influenced by oxygen use rather than oxygen conveyance.  $\dot{V}O_2AUC$  and TC were independent of oxygen use.

In addition, we found no significant correlation between AT and TC in either groups. The TC of oxygen uptake is important, particularly given its significant association with cardiac output at the onset of exercise<sup>13</sup>). Cardiac output pursued increasing; however, it has been reported that stroke volume and LVEF decline after AT<sup>10</sup>). These previously described results suggest that there are several complex mechanisms underlying complementation in human physical fitness. Cardiac dysfunction can be improved by cardiac rehabilitation because oxygen conveyance is associated with cardiac output, expansion of blood vessels<sup>14</sup>), and blood pressure; however, this does not improve LVEF. Furthermore, we expected that participants with HFpEF would show increased myocardial oxygen consumption because of retraction during exercise below the AT.

This study had several limitations. We could not find data on factors related to oxygen utilization such as muscle mass, fiber type, and mitochondrial function; thus, we could not determine correlations between  $\dot{V}O_2AUC$  and factors related to oxygen utilization. Moreover, we included only males, even though morbidity and mortality related to heart failure are higher in females. However, it discussed some knowledges with gender on human physical fitness, and we should include women in our future studies. We did not consider any mediating effects of insulin resistance or blood insulin concentration treatments, such as thiazolidinedione or sulfonylureas. Independent echocardiography data for cardiac diastolic dysfunction was not considered; however, oxygen pulse would be particularly suitable for determining stroke volume during exercise.

In conclusion, the findings of this study suggested that  $\dot{V}O_2AUC$  measured from exercise onset through the initial 4-min period of the warm-up phase is an easily and safely measured predictor of physical fitness, which could be useful for assessing the aerobic capacity in people with HFrEF.

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There are none.

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