Usefulness of anaerobic threshold to peak oxygen uptake ratio to determine the severity and pathophysiological condition of chronic heart failure

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Abstract

Background: Anaerobic threshold (AT) and peak oxygen uptake ($\dot{V}O_2$) are well known as indicators of severity and prognosis of heart failure. Since these parameters are regulated by many factors, multiple organ dysfunction may occur in chronic heart failure, and these two parameters would vary among patients. However, it is not clear whether AT and peak $\dot{V}O_2$ deteriorate similarly. Therefore, we planned to compare the degree of deterioration of these two parameters using a ratio of AT and peak $\dot{V}O_2$ (%AT/peak), and evaluated its significance in heart failure subjects.

Methods: One hundred ninety-four stable heart failure patients who had optimal medical treatment for at least 3 months were enrolled. Cardiopulmonary exercise testing, echocardiography, and blood sampling were examined within one week. Since %AT/peak varied from 50.3% to 108.5%, we divided patients into tertiles of %AT/peak [Group A, 50.1-70.0 (n=112), Group B, 70.1-90.0 (n=64), Group C, 90.1-110.0 (n=18)], and compared factors relating with skeletal muscle and heart failure among these 3 groups.

Results: In Group A, ratio of measured AT against predicted value (%AT) and measured peak $\dot{V}O_2$ against predicted value (%peak $\dot{V}O_2$) were similar (80.3±19.0% and 80.4±17.1%, respectively). Peak $\dot{V}O_2$ became lower as %AT/peak increased (Group B; 65.6±14.8%, p<0.01 vs. Group A, Group C; 38.3±9.7%, p<0.01 vs. Group B). On the other hand, %AT in Group B (77.1±18.5%) was similar to Group A, and diminished in Group C (58.0±8.2%, p<0.05 vs. Group B). Peak work rate and lean body mass were smaller in Group B than those in Group A. Although, left ventricular ejection fraction and E/E' deteriorated in Group B compared with Group A, plasma B-type natriuretic peptide and estimated glomerular filtration rate stayed constant in Group B and deteriorated in Group C.

Conclusions: %AT/peak showed negative correlation with peak $\dot{V}O_2$. In chronic heart failure, muscle weakness occurs at an early stage, and this can be evaluated using %AT/peak.

Introduction

Both anaerobic threshold (AT) and peak oxygen uptake ($\dot{V}O_2$) are established parameters of exercise tolerance. AT [1,2] and peak $\dot{V}O_2$ [3,4] are well documented indicators of severity and prognosis of heart failure. This is because these parameters are regulated by many factors that affect mortality such as cardiac function [5,6], skeletal muscle function [7,8], endothelial cell function [9,10], autonomic nerve function [11] and others, each of which are essential factors to determine patients' prognosis.

Usually, AT appears to be 50% to 60% of peak exercise during an incremental exercise protocol [12-14]. Exercise intensity at AT is the moderate intensity at which stroke volume nearly reaches plateau [15], where sympathetic nerve function becomes active [16], and participation of type 2 fiber in skeletal muscle starts to increase. At the intensity of AT, maximal muscle strength is not required. On the other hand, at the peak exercise, it is necessary to use these functions, including muscle strength, enough to achieve the maximum performance. Therefore, it is supposed that regulatory mechanism of AT and peak $\dot{V}O_2$ would be different, and that the ratio of AT against peak $\dot{V}O_2$ (%AT/peak) would not be constant among patients.

In aged subjects, %AT/peak is reported to be greater [12]. However, as for chronic heart failure, there is no report to evaluate how AT and the peak $\dot{V}O_2$ decreases, and how %AT/peak changes as heart failure exaggerates. Therefore, we planned to clarify the relationship between AT and peak $\dot{V}O_2$ in stable chronic heart failure and related factors that regulate %AT/peak.

Methods

Subjects

Chronic heart failure patients who were admitted to our hospital from 2004 to 2014 were enrolled. Patients who did not receive optimal medical treatment, treated less than 5 months, in decompensated stage, and had severe other diseases were excluded as shown in Table 1. Finally, 194 patients were enrolled.

All patients performed cardiopulmonary exercise test (CPX) and echocardiography and blood sampling within a week without any problems. Patients were divided into three groups according to %AT/peak. Since %AT/peak varied from 50.3% to 108.5% in this study, we divided patients into tertiles of %AT/peak as follows: Group A, 50.1-70.0%

(n=112), Group B, 70.1-90.0% (n=64), Group C, 90.1-110.0% (n=18).
This study was approved by the Ethics Committee of Gunma Prefectural Cardiovascular Center and was conducted in accordance with the Declaration of Helsinki.

Cardiopulmonary exercise testing

AT and peak $\dot{V}O_2$ were evaluated using a symptom-limited cardiopulmonary exercise testing on an upright, calibrated cycle ergometer (StrengthErgo 8, Mitsubishi Electric Engineering, Tokyo, Japan) with electrocardiograph (ML-9000, Fukuda Denshi Ltd. Tokyo, Japan). CPX was performed 2 to 4 hours after a light meal. This test began with three minutes of rest and three minutes of warm-up at 0 watts followed by continuous increasing of work rate by 1 watt every 6 seconds until exhaustion, as recommended by Buchfuhrer et al. [17], and previously reported by us [18]. It was determined whether exercise load was taken enough or not by the gas exchange ratio (R) and/or rating of perceived exertion. When R is more than 1.1 and/or perceived exertion was more than Borg 17, we judged enough exercise load was taken as previously reported [19]. Work rate increase levels were chosen on the basis of fitness of the subjects to keep the exercise period between 8 and 15 minutes [17]. $\dot{V}O_2$, carbon-dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were measured on a breath-by-breath basis using a gas analyzer (MINATO 300S, Minato Science Co. Ltd., Osaka, Japan). Peak $\dot{V}O_2$ was determined as the highest $\dot{V}O_2$ achieved during exercise. The AT was measured by the V-slope method [20]. In group C, because the size of the change of $\dot{V}O_2$ is small, moreover because the latter part of V-slope is short, it is difficult to determine the AT. However, in such cases zooming the X-axis helps us to recognize the breaking point at the end of V-slope. Breaking point of $\dot{V}E/\dot{V}O_2$ in trend graph is also helpful to determine the AT.

Echocardiography

Cardiac function at rest was evaluated using echocardiography within a week of cardiopulmonary exercise testing by a standard procedure for recording images and making measurements [21,22]. Ultrasound equipment used was either Vivid 5 or 7 (General Electric Medical Systems, Milwaukee, WI, USA). Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method. Diastolic function was evaluated using pulsed Doppler recordings of mitral inflow velocities of E and A

waves, deceleration time (DcT), and tissue-Doppler derived early diastolic mitral annular motion at septum (E'), and the ratio of E and E' (E/E'). In patients with pulmonary regurgitation, end-diastolic velocity of pulmonary regurgitant flow was measured by continuous-wave Doppler echocardiography, and the Doppler-determined pressure gradient at end-diastole was added to right atrial pressure estimated by inferior vena cava morphology [23].

Data Analysis

All data are expressed as mean±standard deviation. Differences between the three groups were assessed by one way analysis of variance with Bonferroni analysis as post-hoc analysis. Chi square analysis was also used where applicable. These analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). A value of $p<0.05$ was considered significant.

Results

As shown in Table 1, there were no differences in age, body weight, basal disease, and use of pharmaceutical agents among the three groups. The ratio of females gradually increased as %AT/peak increased (Group A, 14.3%, Group B, 31.2%, Group C, 38.9%, $p<0.01$).

A representative case of each group is shown in Figure 1. The value of peak $\dot{V}O_2$ and AT is shown to get closer in order of A, B, C. The relationship between %AT/peak and peak $\dot{V}O_2$ is shown in Figure 2A. There was a negative relationship (r=-0.590) between them. When %AT/peak was above 90%, peak $\dot{V}O_2$ of all patients was below 15 mL/min/kg. The relationship between AT and %AT/peak is shown in Figure 2B. There was not a strong relationship between them. Parameters of exercise tolerance of the 3 groups are shown in Table 2. Average peak R was above 1.15, from which it can be decided that exercise test was performed strenuously enough. Peak $\dot{V}O_2$ and peak work rate significantly decreased in Group B compared with Group A ($p<0.01$, 0.05, respectively). It decreased more in Group C than Group B ($p<0.01$ both). On the other hand, AT stayed constant in Group B, and decreased in Group C compared with Group

B (p<0.01).

Parameters relating to skeletal muscle strength and cardiac function in heart failure in the 3 groups are also shown in Table 2. Peak work rate and lean body mass (LBM) in Group B were smaller than those in Group A (p<0.01, both). Figure 3 is a graph showing the relationship between %AT/peak and peak work rate. There was a negative relationship between them (r = -0.591).

On the other hand, among the parameters of cardiac function, only LVEF and E/E' showed abnormal data in Group B (p<0.01, both, Table 2). Plasma B-type natriuretic peptide (BNP) level increased and estimated glomerular filtration rate (eGFR) decreased in Group C compared with Group B (p<0.05, both). Other parameters showed no difference among the 3 groups.

Discussion

In this study, it was revealed that the ratio of AT against peak $\dot{V}O_2$ (%AT/peak) had a negative correlation with peak $\dot{V}O_2$, not with AT. That is, deterioration of peak VO_2 was the dominant mechanism to increase the %AT/peak. This is the first study to clarify the relationship between exercise tolerance and %AT/peak in stable chronic heart failure. Since regulatory mechanisms of AT and peak $\dot{V}O_2$ are multiple, it is useful to evaluate the %AT/peak to understand the patients' pathophysiological condition.

From our data that peak $\dot{V}O_2$ and parameters relating with skeletal muscle strength decreased in Group B although AT did not, it was revealed that deterioration of skeletal muscle strength occurs at the early stage of heart failure. Conventionally, decrease in skeletal muscle strength and its atrophy has been thought to be the final phenomenon of heart failure known as cardiac cachexia. However, in this study, skeletal muscle weakness was revealed to occur at the early stage, and its influence was shown to be obvious at the peak exercise. It is suggested that when %AT/peak becomes greater, skeletal muscle training to elevate the muscle strength is necessary. From our data that peak $\dot{V}O_2$ and parameters relating with skeletal muscle strength decreased in Group B although AT did not, it was revealed that deterioration of skeletal muscle strength occurs at the early stage of heart failure.

Since AT is determined as the $\dot{V}O_2$ at which the critical capillary PO_2 has been reached for a given work task [24], AT becomes lower when oxidation capacity of skeletal muscle

diminishes as was reported previously [25]. Oxidation capacity is regulated by activity of oxidizing enzyme in a skeletal muscle cell and O_2 transport to the working muscle. Therefore, skeletal muscle function, cardiac pump function, and vascular endothelial cell function are all essential modulators for AT, and skeletal muscle strength does not affect AT to a great deal.

On the other hand, at the peak exercise, not only oxidative function but also skeletal muscle strength is necessary to achieve exercise completely. The importance of skeletal muscle mass on peak $\dot{V}O_2$ has already been reported [26-28], and addition of arm exercise to maximal leg exercise was reported to produce increases in peak $\dot{V}O_2$ [29]. As well, a previous study also reported that elevation of muscle strength by electrical stimulation increased peak exercise capacity greater than AT [30]. That is, skeletal muscle strength is strongly correlated with peak exercise. This might be the reason why peak work rate was related with increase of %AT/peak in this study.

%AT/peak showed negative correlation to peak work rate as shown in Figure 1. However, at around 80% of %AT/peak, there seems to be a breaking point in regression line. When the range of %AT/peak is limited to less than 80%, the degree of leaning of the regression line becomes -1.65, while analyzed at above 80%, it becomes -1.15. That is, it can be seen that %AT/peak and peak work rate do not appear to have straight line relations. From these data, it can be thought that the effect of muscle strength appears at the early stage.

As for the cardiac function, although LVEF and E/E' showed a similar change to peak work rate, BNP and eGFR changed in the later period and other parameters showed no change. Since these data were obtained from chronic heart failure patients, cardiac function might have already deteriorated. Therefore, influence of cardiac function on %AT/peak would be weak. Lack of relationship between cardiac function and exercise tolerance has already been reported [31], and our data are compatible with them.

Usually, the lowest value of AT is 40% of predicted peak $\dot{V}O_2$. And %AT/peak tends to rise with increasing age [12-14,32]. This might be because muscle mass and/or strength of elderly subjects is usually lower than younger subjects. Our study also revealed that diminished muscle strength decreased peak exercise performance, resulting in the elevation of %AT/peak. On this point, our data are compatible with the previous reports.

%AT/peak of several patients was 100%. This is sometimes seen in patients with respiratory disease, however none of the patients in this study had severe pulmonary disease. Clinical characteristics of these subjects included extremely weak muscle power. They could not continue pedaling at 60 rpm near peak exercise, resulting in the flat or diminishment of oxygen uptake compared to AT.

We treated lean body mass as one of the indicators of skeletal muscle strength. Since lean body mass is mainly composed of a bone and muscle, and muscle hypertrophy is related with muscle strength [33], it would be suitable that lean body mass is a parameter of muscle strength. A previous study reported that leg lean body mass is positively related with peak $\dot{V}O_2$ [34]. This study also supports our concept.

We used plasma hemoglobin levels and eGFR as parameters of chronic heart failure-related systemic condition. This is because renal function is known to deteriorate in heart failure [35], and at the same time, anemia enhances as heart failure worsens [36]. In this study, eGFR of Group A was similar to that of Group B. On the other hand, it worsened significantly in Group C. That is, effect of heart failure on %AT/peak becomes clearer at the stage where peak $\dot{V}O_2$ decreased enough.

In Group C, although BNP and eGFR were aggravated, LVEF, E/E' and lean body mass did not decrease any more. Usually, when heart failure worsens, these parameters also become abnormal. The reason why these parameters stayed constant in Group C is not clear, but because they were already worsened enough at the earlier stage, there might be no room to be aggravated further.

Study limitations

The number of subjects was not enough. If the number of subjects were greater, the pathophysiological condition of Groups A, B, and C would be clearer. As well, we did not evaluate body composition or oxidative enzyme activity. This is because there is no precise maneuver to evaluate the body composition, and examining the muscle strength and muscle biopsy routinely is not practical in the clinical setting. Therefore, we used surrogate parameters.

Conclusion

In conclusion, it was revealed that %AT/peak increases as heart failure worsened, and increase of %AT/peak was accounted for mainly by deterioration of peak $\dot{V}O_2$, which was first due to loss of skeletal muscle strength. By evaluating %AT/peak, the target of treatment might be clarified.

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Conflicts of interest

The authors declare there are no conflicts of interest.

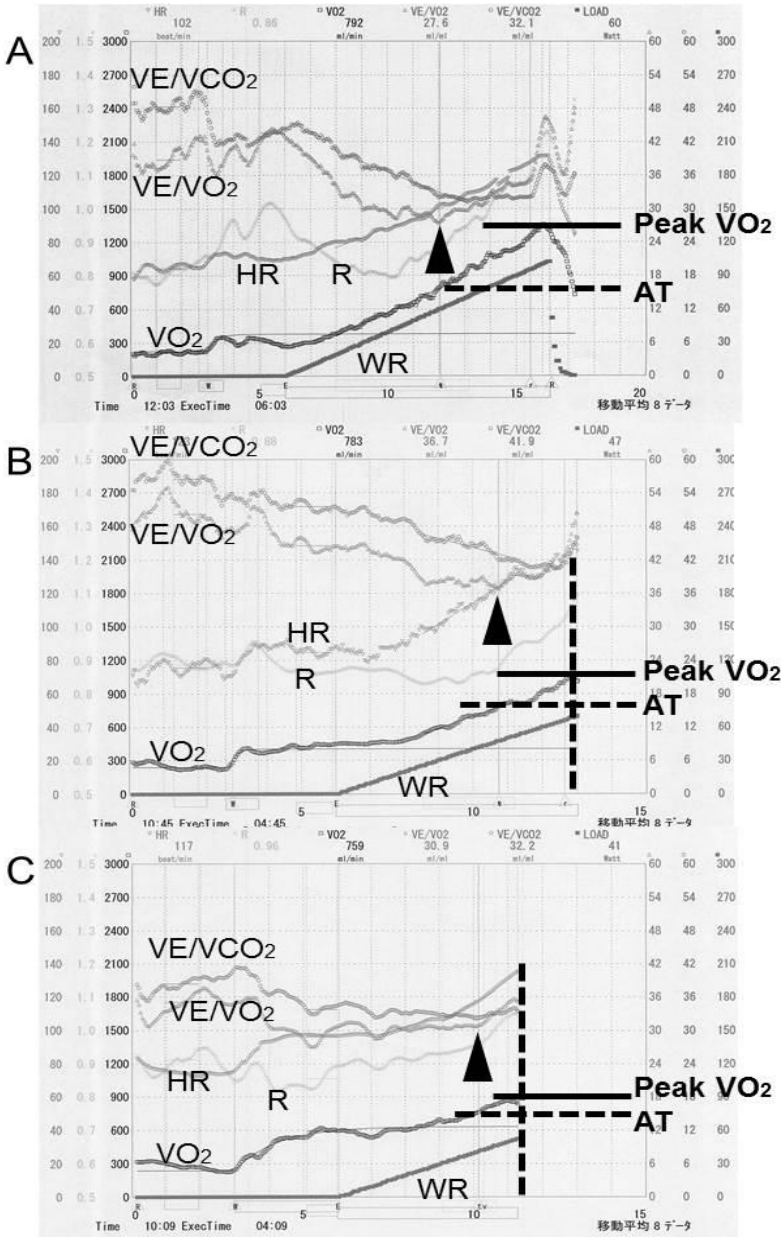

Figure 1 Representative cases of each group

Solid line is peak VO2, dashed line is AT. Triangle indicates AT.

R, respiratory exchange ratio; WR, work rate; VE, minute ventilation; VCO2, carbon dioxide output; VO2, oxygen uptake; HR, heart rate; AT, anaerobic threshold.

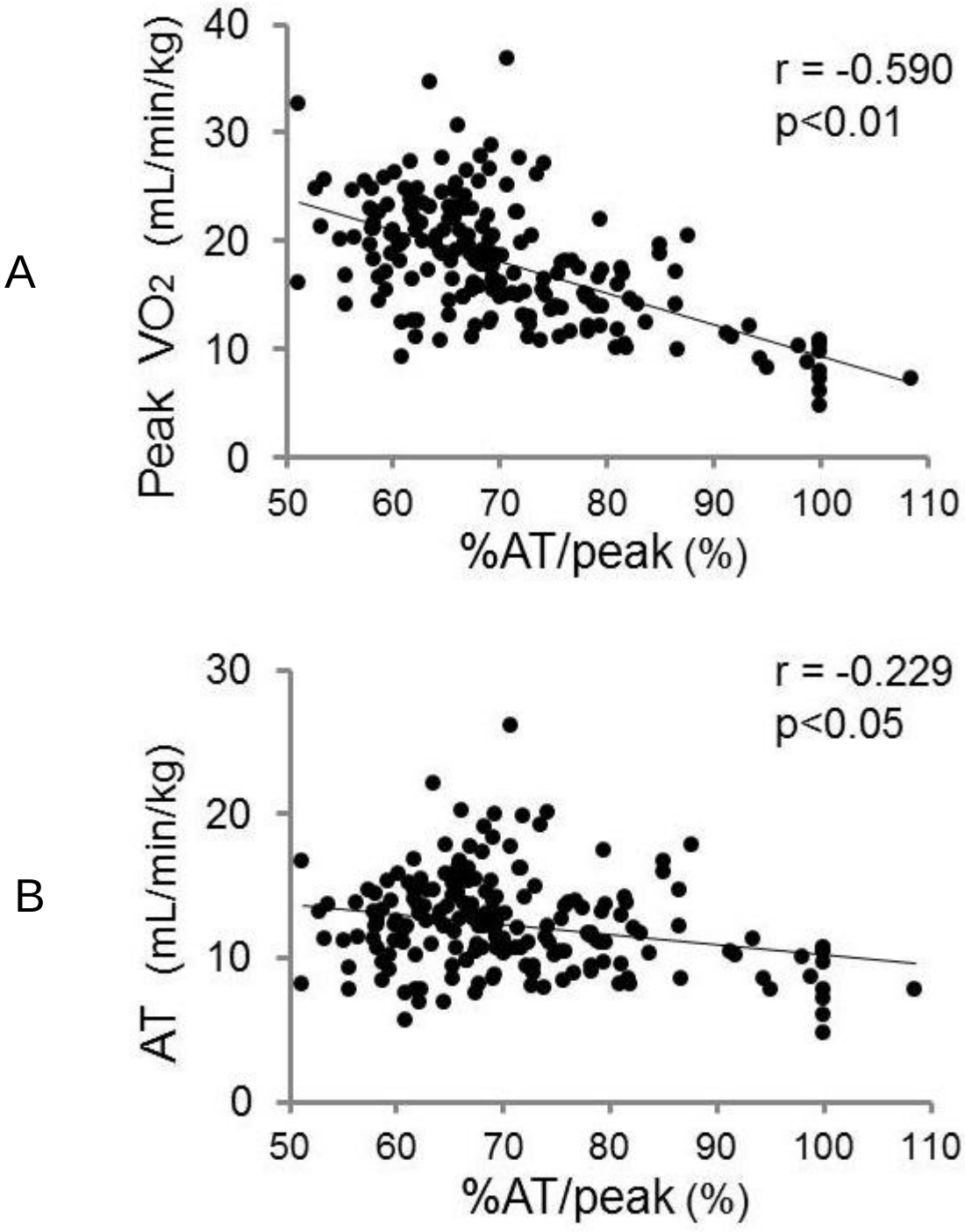

Figure 2 Relationship between % AT/peak and exercise tolerance

%AT/peak showed significant negative correlation with peak $\dot{V}O_2$, but not with AT.

AT, anaerobic threshold; $\dot{V}O_2$, oxygen uptake.

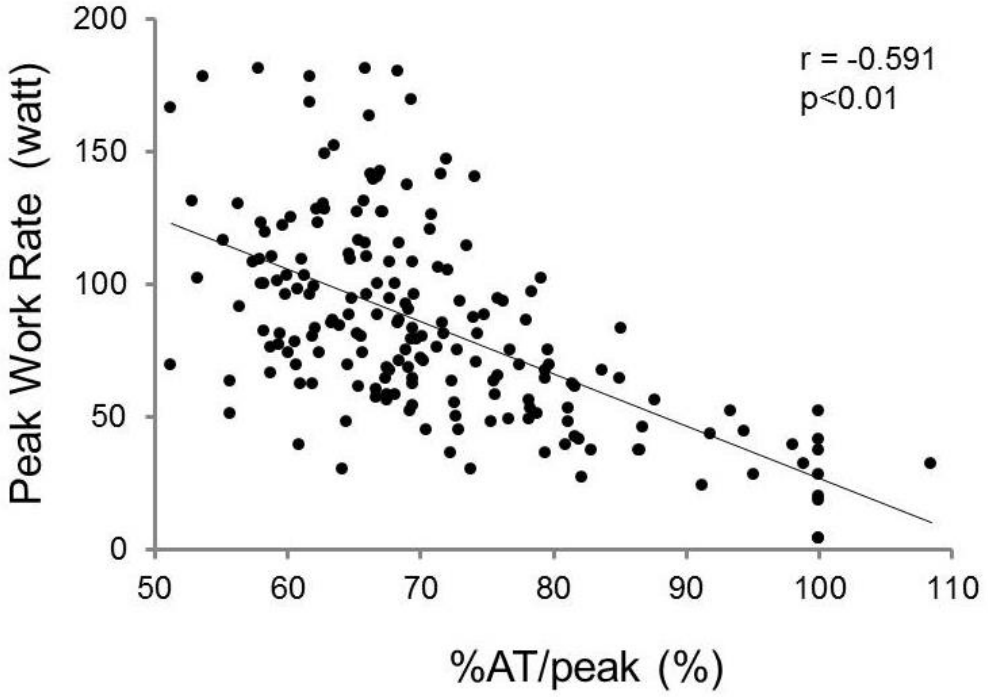

Figure 3 Relationship between %AT/peak and peak work rate.
AT, anaerobic threshold.

Table 1 Patients' profiles

	Group A	Group B	Group C
Age (years)	59.1±13.8	62.7±14.0	68.2±10.5
BH (cm)	166.0±8.0	160.4±12.4	159.6±8.4
BW (kg)	67.4±15.0	61.4±18.7	56.9±10.1
BMI	24.3±4.2	23.6±4.4	22.3±3.5
Cardiomyopathy (%)	22.3	25.0	27.8
Coronary heart disease (%)	31.3	32.8	38.9
HHD (%)	24.1	21.9	22.2
BB (%)	92.9	89.0	88.9
ACEi/ARB (%)	86.6	82.8	83.3

BH, body height; BW, body weight; BMI, body mass index; HHD, hypertensive heart disease; BB, beta blocker; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2 Exercise tolerance, muscle strength, and cardiac function

	Group A	Group B	Group C
Peak VO_2 (mL/min/kg)	20.1±4.8	16.1±3.3**	9.1±2.1$^{\$\$}$
AT (mL/min/kg)	12.7±3.0	12.3±2.8	8.9±1.9$^{\$\$}$
Peak WR (watt)	99.4±34.2	70.6±19.4**	31.1±14.6$^{\$\$}$
VE vs. VCO_2 slope	32.0±8.0	32.5±6.9	45.6±11.6$^{\$\$}$
Peak R	1.18±0.08	1.16±0.09	1.19±0.09
Borg scale (LF)	17.0±1.0	16.9±1.8	17.0±1.5
Borg Scale (SOB)	13.6±1.6	13.7±0.9	14.2±1.8
WR at AT (watt)	55.9±22.6	45.0±17.9**	28.9±8.4$^{\$}$
LBM (%)	50.6±8.3	46.1±12.4**	43.9±10.6
Gender (F/M)	16/96	20/44	7/11
LVEF (%)	39.7±12.0	31.6±14.0**	25.4±12.7
E/A	1.1±0.9	0.9±0.7	1.1±0.9
DcT (msec)	237.8±68.9	225.3±59.8	213.0±84.4
E/E’	8.4±3.5	11.9±6.8**	15.2±6.4
SV (mL)	68.1±22.6	64.7±25.8	54.8±18.3
PAWP (mmHg)	14.5±6.7	14.3±7.1	18.7±8.7
BNP (pg/mL)	165.0±204.1	227.0±203.6	599.9±491.2$^{\$}$
Hb (mg/dL)	14.1±1.7	13.7±2.9	12.5±2.1
eGFR (mL/min/1.73m^2)	61.7±19.9	59.6±12.0	40.6±19.2$^{\$}$

*: $p<0.05$ vs. Group A, **: $p<0.01$ vs. Group A

$^{\$}$: $p<0.05$ vs. Group B, $^{\$\$}$: $p<0.01$ vs. Group B

AT, anaerobic threshold; WR, work rate; R, respiratory exchange ratio; LF, leg fatigue; SOB, shortness of breath; LBM, lean body mass; F, female; M, male; LVEF, left ventricular ejection fraction; DcT, deceleration time; SV, stroke volume; PAWP, pulmonary artery wedge pressure; BNP, brain natriuretic peptide; Hb, hemoglobin; eGFR, estimated glomerular filtration rate.

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