Original article

Influence of stroke volume and exercise tolerance on peak oxygen pulse in patients with and without beta-adrenergic receptor blockers in patients with heart disease

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ARTICLE INFO

ABSTRACT

Background: In a given individual, a consistent relationship exists between oxygen uptake (VO_2) and heart rate (HR) during exercise. The quotient of VO_2 and HR (VO_2/HR) is called the oxygen pulse (O_2 pulse), and its value is dependent on stroke volume (SV). However, it is difficult to believe that the O_2 pulse would indicate the SV when HR has been modified as with the use of beta-adrenergic receptor blockers (BB). Until now, the effect of BB on peak O_2 pulse has not been precisely studied. We tried to clarify the effect of BB on the relationship between O_2 pulse and SV.
Methods: Of 699 consecutive heart disease subjects who performed cardiopulmonary exercise tests (CPX) from 2012 to 2014, we enrolled 430 subjects who had sinus rhythm and could perform CPX until exhaustion. One hundred and fifty-seven subjects were taking BB. SV was evaluated during CPX using impedance cardiography, and we compared the peak O_2 pulse with peak SV between patients without BB (Group A) and with BB (Group B).
Results: The HRs at rest and peak exercise in Group A were greater than those in Group B (74.4 ± 13.0/min vs. 71.8 ± 11.3/min, $p < 0.01$, 134.9 ± 21.7/min vs. 124.9 ± 23.6/min, $p < 0.01$, respectively). The regression line of the peak O_2 pulse against the peak SV was steeper in Group B than in Group A. When we divided the patients into two groups according to the average values of the peak SV and peak VO_2, O_2 pulse/SV ratio in Group B above the average was greater than that in Group A, whereas it was similar in the two groups that were below average.
Conclusion: We found that the increase in the O_2 pulse was disproportionately greater than the SV that was measured by impedance cardiography when a BB was used in patients with preserved SV and exercise tolerance.

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Introduction

The quotient of oxygen uptake (VO_2) and heart rate HR is called the O_2 pulse (VO_2/HR). It is the volume of oxygen taken up by the pulmonary blood during the period of a heartbeat and depends on the volume of oxygen extracted by the peripheral tissues. This measurement is a product of stroke volume (SV) and the arterial-mixed venous blood O_2 difference [$C(a-v)O_2$].

In normal subjects and in patients with heart failure, the maximum $C(a-v)O_2$ reaches an almost constant value of 13–14 mL/dL [1,2]. Therefore, the O_2 pulse at peak exercise can be expressed as follows: peak VO_2/HR = peak $SV \times k$, where k is a constant as mentioned above, and the peak O_2 pulse can be regarded as an indicator of cardiac pump function. In clinical settings, the O_2 pulse can be used to determine cardiac output during exercise [3] and to detect the onset of myocardial ischemia [4].

Beta-adrenergic receptor blockers are recommended for various types of heart diseases, such as ischemic heart disease, heart failure, and hypertension [5–7]. By suppressing sympathetic nerve activity, they diminish heart rate at rest as well as during exercise [8]. That is, the O_2 pulse may be higher than expected, and estimating cardiac function during exercise using this value with beta-adrenergic receptor blocker usage may be misleading.

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However, the influence of beta-adrenergic receptor blockers on the peak O_2 pulse has not been precisely studied. The influence of beta-adrenergic receptor blockers on peak O_2 pulse can be estimated using an equation of O_2 pulse divided by the measured SV (O_2 pulse/SV ratio). If this parameter is greater than expected in patients taking beta-adrenergic receptor blockers, this finding would be attributed to a decreased heart rate. Thus, we planned to quantify the effect of beta-adrenergic receptor blockers on the O_2 pulse using the O_2 pulse/SV ratio.

Method

Subjects

We performed 699 cardiopulmonary exercise (CPX) tests from the latter half of 2012 to early 2014. Of these consecutive 696 CPX tests, 430 patients who had sinus rhythm and could perform CPX until exhaustion were enrolled. Patients with residual myocardial ischemia were excluded. One hundred and fifty-seven subjects were taking beta-adrenergic receptor blockers. Patients taking an insufficient dose (carvedilol < 5 mg/day or bisoprolol < 2.5 mg/day) of beta-adrenergic receptor blockers, and patients with lung emphysema or moderate-to-severe anemia (Hb <10 mg/dL) were excluded. Patients, in whom the effect of the beta-adrenergic receptor blocker was not sufficient, that is, the heart rate at rest did not decrease ≥5 beats/min, were also excluded. Patients who did not take beta-adrenergic receptor blockers were assigned to Group A, and patients who took beta-adrenergic receptor blockers were assigned to Group B. Patients' profiles are shown in Tables 1 and 2. To test whether the influence of the beta-adrenergic receptor blocker varied based on exercise tolerance and peak SV at peak exercise, each group was divided into two groups according to the average values of the %peak VO_2, peak SV, or left ventricular ejection fraction (LVEF).

Cardiopulmonary exercise test

The anaerobic threshold (AT) and peak VO_2 were evaluated using symptom-limited CPX testing on an upright, calibrated cycle ergometer (StrengthErgo 8, Mitsubishi Electric Engineering, Tokyo,

Table 1
Characteristics of study population.

Parameters	Group A	Group B	p
N	281	149	
Male/female	223/58	125/24	0.25
Age (years)	61.5 ± 16.4	63.4 ± 12.9	0.99
BMI	23.0 ± 3.0	23.5 ± 3.8	0.37
Underlying heart disease (n, (%))			
Previous myocardial infarction	71 (25.3)	48 (32.2)	0.13
Previous PCI	115 (40.9)	36 (24.2)	<0.01
Previous open heart surgery	61 (21.7)	17 (11.4)	0.01
DCM/HHD	8 (2.8)	38 (25.5)	<0.01
Great vessel disease	7 (2.5)	3 (2.0)	0.75
Others	19 (6.8)	7 (4.7)	0.39
Comorbidities			
Diabetes mellitus			
HbA1c (%)	6.19 ± 0.80	6.21 ± 0.67	0.73
Hypertension (n, (%))	184 (65.5)	98 (65.8)	0.95
Dyslipidemia (n, (%))	143 (50.9)	94 (63.1)	0.02
Hb (mg/dL)	13.5 ± 1.5	14.0 ± 1.5	0.02
Echocardiographic findings			
EF (%)	62.3 ± 12.7	46.5 ± 19.4	<0.01
E/A	1.17 ± 0.52	1.17 ± 0.73	0.57
DcT (ms)	216.5 ± 64.7	206.3 ± 56.0	0.24
E/E′	8.18 ± 2.76	10.60 ± 5.54	<0.01

BMI, body mass index; PCI, percutaneous coronary intervention; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; Hb, hemoglobin; EF, ejection fraction; DcT, deceleration time.

Table 2
Hemodynamic and metabolic responses in the two groups.

	Group A	Group B	p
N	281	149	
Rest HR (/min)	74.4 ± 13.0	71.8 ± 11.3	<0.01
Peak HR (/min)	134.9 ± 21.7	124.9 ± 23.6	<0.01
$\Delta HR/\Delta WR$	0.63 ± 0.21	0.62 ± 0.28	0.54
Peak $\dot{V}O_2$ (mL/min/kg)	19.8 ± 5.6	17.8 ± 5.1	<0.01
Peak $\dot{V}O_2$ (%)	80.1 ± 19.6	72.8 ± 21.1	<0.01
AT (mL/min/kg)	13.0 ± 3.3	11.9 ± 3.1	<0.01
AT (%)	81.7 ± 20.3	75.6 ± 19.8	<0.01
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	34.2 ± 28.6	34.6 ± 9.7	<0.01
Peak O_2 pulse (mL/beat)	9.34 ± 2.34	9.15 ± 2.75	0.45
R at peak exercise	1.20 ± 0.08	1.20 ± 0.09	0.38
SV at peak (mL/beat)	89.2 ± 17.4	85.8 ± 22.3	0.08
O_2 pulse–SV ratio (Peak O_2 pulse/peak SV × 100)	10.7 ± 2.8	10.9 ± 2.8	0.44

HR, heart rate; WR, work rate; AT, anaerobic threshold; $\dot{V}O_2$, oxygen uptake; AT, anaerobic threshold; $\dot{V}E$, minute ventilation; $\dot{V}CO_2$, carbon dioxide production; O_2 pulse, oxygen pulse; R, gas exchange ratio; SV, stroke volume.

Japan) with an electrocardiograph (ML-9000, Fukuda Denshi Ltd., Tokyo, Japan). CPX was performed 2–4 h after a light meal. This test began with 3 min of rest and 3 min of warm-up at 0 W followed by continuous increase of the work rate by 1 W every 6 s until exhaustion, as recommended by Buchfuhrer et al. [9] and as reported by us [10]. To certify that patients performed CPX with enough vigor, they were forced to keep pedaling until the respiratory quotient (R) reached >1.10. The work rate increase levels were chosen on the basis of the fitness of the subjects to keep the exercise period between 8 and 15 min [9]. VO_2, carbon-dioxide production (VCO_2), and minute ventilation (VE) were measured on a breath-by-breath basis using a gas analyzer (MINATO 300S, Minato Science Co. Ltd., Osaka, Japan). The peak VO_2 was determined as the highest VO_2 achieved during exercise. AT was measured by the V-slope method [11].

Impedance cardiography

The SV was evaluated during CPX using impedance cardiography (Physio Flow Lab-1, Manatec Biomedical, Paris, France). The PhysioFlow device is a range of non-invasive hemodynamic monitors. It has been reported to provide continuous, accurate, reproducible, and sensitive measurements for cardiac output and other parameters [12,13]. It has shown non-inferiority to the predicate device thermodilution Swan-Ganz catheter [14,15] and superiority to a standard impedance cardiography [16]. Before starting the exercise protocol, the patients were attached to the impedance cardiograph electrodes of impedance cardiograph as previously described [17,18]. In brief, a constant sinusoidal alternating current (1.8 mA, 75 kHz) was applied between the couples of electrodes placed on the supraclavicular fossa at the left base of the neck and along the xiphoid. The associated voltage was detected by two inner electrode pairs positioned 5 cm apart from the corresponding couples of electrodes that were parallel to the current path. This voltage was transmitted to an amplifier and an impedance signal (z) was produced. The SV was calculated using the following formula by Sramek–Bernstein: SV = volume of electrically participating intrathoracic tissue × ventricular ejection time × index of contractility, which was the ratio of the peak rate of change in the thoracic bio-impedance (dZ/dt_{max}) and the thoracic fluid index or total thoracic impedance.

Echocardiography

Cardiac function at rest was evaluated using echocardiography within a week of the CPX by a standard procedure for recording

images and making measurements [19,20]. The ultrasound equipment that was used was either Vivid 5 or 7 (General Electric Medical Systems, Milwaukee, WI, USA). The LVEF was calculated using the modified Simpson method. The diastolic function was evaluated using pulsed Doppler recordings of the mitral inflow velocities E and A waves, deceleration time (DcT), and the tissue Doppler-derived early diastolic mitral annular motion at the septum (E′), and the ratio of E and E′ (E/E′).

Data analysis

All data were expressed as mean ± standard deviation. The difference between two groups was assessed using Student's t-test. Chi square analyses were also used where applicable. The differences between the three groups were assessed by one-way analysis of variance with a Bonferroni analysis as a post hoc analysis. These analyses were performed using SPSS version 18. (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant. The relationship between the peak O_2 pulse and the peak SV was calculated by a linear regression analysis. To quantify the discrepancy between the peak O_2 pulse and the SV at peak exercise, the ratio of the peak O_2 pulse against the peak SV (the 'O_2 pulse–SV ratio') was calculated as follows: peak O_2 pulse/peak SV × 100. For example, if the peak O_2 pulse was 100 mL/beat and peak SV was 10 mL, the O_2 pulse–SV ratio was 10.0.

This study was approved by the Ethics Committee of Gunma Prefectural Cardiovascular Center and was conducted in accordance with the Declaration of Helsinki.

Results

There were no significant differences in age and HbA1c among the participants; these types of differences have been known to have an effect on heart rate response. LVEF and E/E′ were significantly lower in Group B (Table 1).

As shown in Table 2, heart rates at both rest and peak were lower in Group B although there was no difference in the heart rate response to the exercise between two groups. As for the exercise tolerance, the peak VO_2, AT, and $\dot{V}E$ vs. $\dot{V}CO_2$ relationship were lower in Group B than in Group A. There was no difference in the peak O_2 pulse between two groups. The O_2 pulse–SV ratio was similar in two groups. The peak R was >1.15 in both groups, which indicated that the maximum exercise test was achieved.

The relationships between the peak SV and peak O_2 pulse in Groups A and B are shown in Fig. 1. The regression line of the peak O_2 pulse against the peak SV in Group B was steeper than that in Group A. The regression line of the lower part of Group B was almost the same as or smaller than that of Group A. However, the two lines gradually diverged from each other, and the line of Group B became greater than that of Group A as the peak SV increased.

When we divided each group into two categories according to the average value of the peak SV (88.0 mL), impaired category and preserved category, and compared the O_2 pulse–SV ratio between Groups A and B within each category, the O_2 pulse–SV ratios for Groups A and B were similar in the impaired category. On the other hand, or the preserved category, the O_2 pulse–SV ratio was greater in Group B than in Group A as shown in Fig. 2. The cardiac function of these subjects is shown in Table 3. In the preserved SV group, although there was a significant difference in EF between Groups A and B, both sets of data were within normal limits. When we divided each group according to the average value of peak VO_2 (19.0 mL/min/kg), similar results were obtained as is shown in Fig. 3.

We also evaluated the effect of beta-adrenergic receptor blockers on the O_2 pulse–SV ratio in patients with preserved LVEF [≧50%, n = 250 (Group A), 65 (Group B)]. As shown in the right
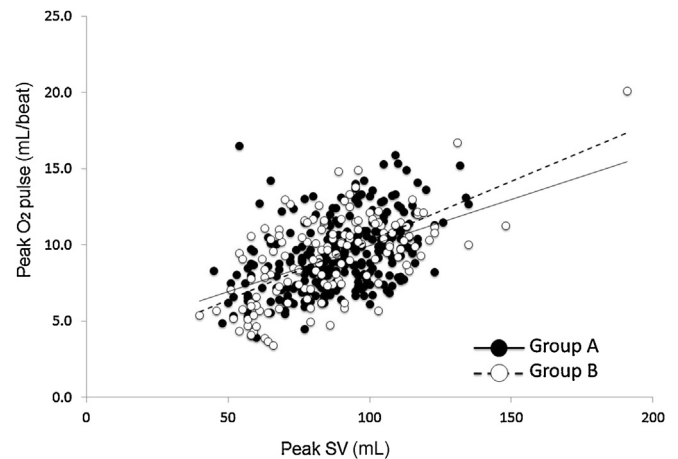

Fig. 1. Relationship between peak stroke volume and peak O_2 pulse. It is shown that the regression line of Group B is steeper than that of Group A, and as the peak stroke volume becomes greater, the difference between two lines becomes larger. SV, stroke volume.
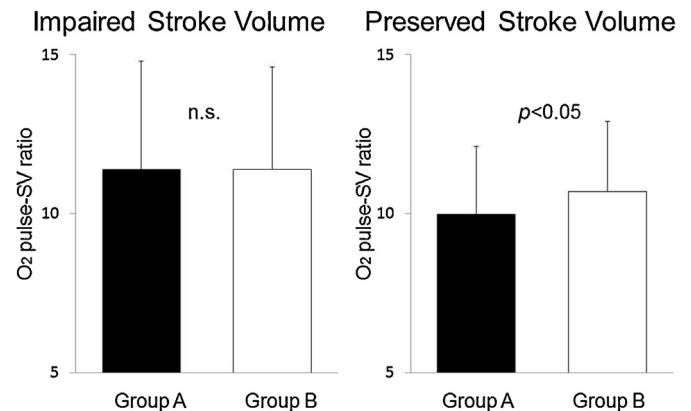

Fig. 2. Difference of 'O_2 pulse–SV ratio' between two groups. In the category of preserved stroke volume, O_2 pulse–SV ratio of Group B is greater than that of Group A. SV, stroke volume.

panel of Fig. 4, although it tended to be higher in Group B compared with Group A, there was no significant difference between the two groups ($p = 0.058$).

The differences among Group A, the carvedilol group, and bisoprolol group are shown in Table 4. The average doses of carvedilol and bisoprolol were 9.2 ± 6.3 mg and 2.9 ± 2.8 mg, respectively. There was no difference in the peak O_2 pulse–SV ratio among the three groups.

Because there is a possibility that the effect of beta-adrenergic receptor blocker on the O_2 pulse–SV ratio is greater in patients

Table 3
Cardiac function of Groups A and B in impaired or preserved stroke volume.

	Impaired SV		Preserved SV	
	Group A	Group B	Group A	Group B
N	126	65	155	84
EF (%)	63.0 ± 12.8	43.9 ± 19.7	$62.7 \pm 9.2^{**}$	$51.1 \pm 17.4^{**}$
E/A	0.9 ± 0.4	1.3 ± 0.9	$1.2 \pm 0.6^{*}$	1.0 ± 0.5
DcT (ms)	231.0 ± 55.5	193.0 ± 53.6	208.8 ± 57.4	224.5 ± 52.7
E/E′	8.5 ± 2.4	10.4 ± 5.6	$7.7 \pm 2.6^{**}$	$10.9 \pm 5.4^{**}$

EF, ejection fraction; E, early diastolic velocity; A, peak late diastolic velocity; DcT, deceleration time; E′, early diastolic velocity at the mitral annulus.
* $p < 0.05$ vs. matched impaired SV group.
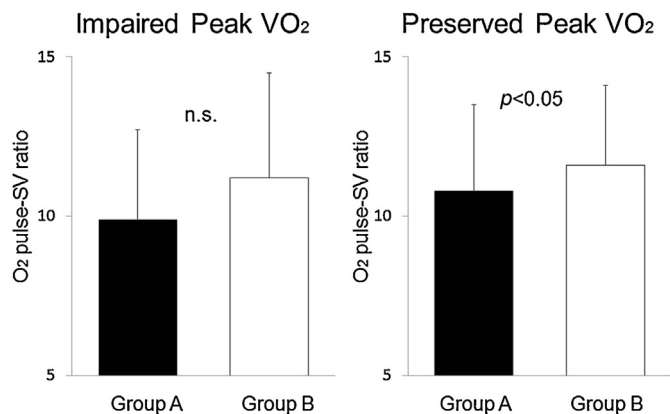** $p < 0.01$ vs. matched impaired SV group.

Fig. 3. Difference in 'O$_2$ pulse–SV ratio' between the two groups. In the category of preserved peak VO$_2$, O$_2$ pulse–SV ratio of Group B is greater than that of Group A. SV, stroke volume; VO$_2$, oxygen uptake.
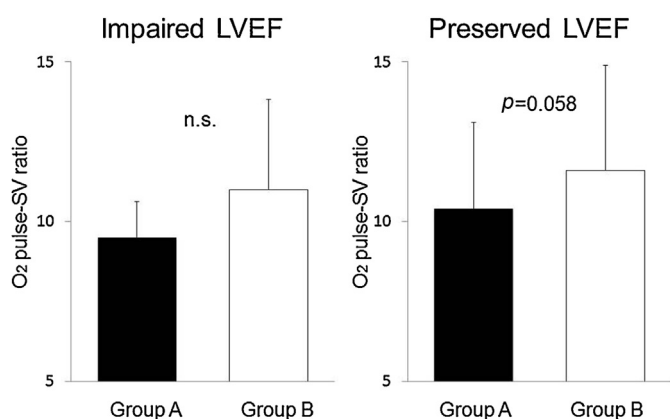

Fig. 4. Difference in 'O$_2$ pulse–SV ratio' between the two groups. LVEF, left ventricular ejection fraction; SV, stroke volume.

with chronic heart failure, we compared it between patients with and without beta-adrenergic receptor blocker in patients with chronic heart failure [low SV (<88.0 mL), low exercise tolerance (peak VO$_2 < 19.0$ mL/min/kg) and low EF ($<50\%$)]. However, the O$_2$ pulse–SV ratio in Groups A and B was 10.6 ± 3.4 and 10.8 ± 3.4, respectively, and there was no significant difference between them.

Discussion

This study provided novel information demonstrating that the effect of beta-adrenergic receptor blocker was not constant during exercise. When a subject is taking beta-adrenergic receptor

Table 4
Hemodynamic difference among the three groups.

	Group A	Group B	
		Carvedilol	Bisoprolol
n	281	89	56
Rest HR	74.4 ± 13.0	74.2 ± 10.0	$69.6 \pm 11.8^{+}$
Peak HR	134.9 ± 21.7	130.3 ± 24.7	$115.7 \pm 20.0^{++,**}$
Peak SV	89.2 ± 17.4	$83.6 \pm 21.0^{**}$	86.0 ± 24.1
Peak O$_2$ pulse	9.3 ± 2.3	8.7 ± 2.6	9.8 ± 3.2
Peak O$_2$ pulse–SV ratio	10.7 ± 2.8	10.6 ± 2.5	11.7 ± 3.4

n, number; HR, heart rate; SV, stroke volume; O$_2$ pulse, oxygen pulse.
** $p < 0.01$ vs. carvedilol.
+ $p < 0.05$ vs. Group A.
++ $p < 0.01$ vs. Group A

blockers, his/her exercise tolerance is preserved and/or he/she can increase SV during exercise, the peak O$_2$ pulse does not indicate the peak SV. However, it indicated a relatively higher value. This phenomenon became more apparent as the exercise tolerance was greater. To the best of our knowledge, this study was the first to investigate the effect of beta-adrenergic receptor blockers using the O$_2$ pulse–SV ratio. There were two patients in whom the SV and O$_2$ pulse values were 191 mL and 54 mL, and 20.1 mL/beat and 16.5 mL/beat respectively, as shown in Fig. 1, and these two numerical values were prominent. It appeared as if these persons steepened or shallowed the regression lines of Groups B and A. However, even if these persons were omitted as inappropriate samples, the inclinations of the regression lines did not change. Therefore, these prominent patients did not affect the conclusion. Usually, as the peak value for C(a-v)O$_2$ is approximately 14 [1,2], peak SV can be calculated by the following equation: peak SV = peak O$_2$ pulse/14 $\times$ 100. Because O$_2$ pulse is a quotient of VO$_2$ and heart rate (VO$_2$/heart rate), the O$_2$ pulse is influenced by heart rate. When the heart rate slows because of beta-adrenergic receptor blocker administration, the O$_2$ pulse would be higher than expected. On the other hand, the SV should be constant or diminished when beta-adrenergic receptor blockers are administered [21]. Therefore, the peak O$_2$ pulse/peak SV would become greater. However, in this study, the O$_2$ pulse–SV ratio was similar in patients with lower exercise tolerance although beta-adrenergic receptor blockers were used. One reason for this would be that, in these patients, heart rate decreased and the peak VO$_2$ diminished because of multi-factorial factors such as the onset of myocardial ischemia, increase of mitral regurgitation, or aggravation of diastolic dysfunction. That is, in the equation for VO$_2$/heart rate, both denominator and numerator decreased simultaneously. Hence, VO$_2$/heart rate did not increase. Because O$_2$ pulse–SV ratio is a C(a-v)O$_2$, increase of regression line in Fig. 1 would be affected by increase of C(a-v)O$_2$ although the variation of the peak value of C(a-v)O$_2$ is not so great. However, in Group B, steepness of the regression line was greater than Group A. This difference in steepness cannot be explained by the difference of C(a-v)O$_2$. Rather, it is thought that this is because the change of the sympathetic nerve activity is different between Groups A and B when exercise intensity increased.

The oxygen pulse has been shown not to predict SV in heart failure patients [22]. Actually, when the oxygen pulse was observed at a submaximal exercise intensity, it would not represent the SV if the exercise intensity was not presented as %peak exercise because the C(a-v)O$_2$ varied at various intensities. However, although there was a slight variety in the peak C(a-v)O$_2$ according to the subjects' background [23], it almost converged at approximately the constant value (11–16 mL/dL) [1–3]. In this study, we used the peak value. Therefore, there should be no problem treating the oxygen pulse as a representative of SV.

On the other hand, in patients with preserved exercise tolerance, the discrepancy in the peak O$_2$ pulse and peak SV was apparent. In these patients, the impairment of the VO$_2$ was less than that of the heart rate. This may be the reason why the discrepancy was greater. Usually, the linear increase in the SV and ejection fraction was blunted at the 50–60% of peak exercise during a ramp protocol [24,25]. From that period, increase of heart rate enhances in order to maintain the linear increase of cardiac output. The increase of the cardiac pump function is essential to increase the peak VO$_2$ [26]. Therefore, a lack of normal heart rate response during exercise may lead to a depressed peak VO$_2$. In our study, the peak heart rate was lower in Group B, the enhanced increase in the heart rate was blunted. However, the O$_2$ pulse–SV ratio was increased in this study. The reason that the increase in the peak VO$_2$ was relatively maintained remained unclear. But it was probable that an increase in the C(a-v)O$_2$ would occur because

patients with preserved exercise tolerance usually did not reach the nadir of critical capillary PO_2 during the peak exercise.

In the right panel of Fig. 2, we showed differences of the O_2 pulse–SV ratio between Groups A and B in patients with preserved SV. In Table 3, we presented the cardiac function of these subjects. There were significant differences in the EF and E/E′ between the two groups with preserved SV. However, when we checked if these data whether they are within normal limits or not, EF in Group B was within normal limits and E/E′ was on the border line. Therefore, it may be acceptable that this panel was a representative of the comparison of beta-blockers in almost normal cardiac function.

We added the examination concerning the difference of O_2 pulse–SV ratio between Groups A and B in patients with preserved LVEF (Fig. 4). As a result, there was no significant difference between them. This may be because of the physiological characteristics of the LVEF. Although the LVEF has been widely used as a tentative marker for severity of heart failure, it has been widely known that there was a lack of connection between the LVEF and peak oxygen uptake [27,28], and that LVEF does not necessarily represent heart failure severity. As well, although the cardiac uptake of metaiodobenzylguanidine (MIBG) has been reported to be positively associated with LVEF, the MIBG uptake was uneven and had no relationship with LVEF in patients with preserved EF [29]. From these data, we assumed that the effects of beta-adrenergic receptor blockers were variable. These would be the reason that there was no apparent difference in the O_2 pulse–SV ratio.

In this study, the plasma hemoglobin level was lower in Group A than in Group B, although patients with moderate to severe anemia were excluded. Although anemia can increase the heart rate, and lower hemoglobin may enhance the heart rate response the value of plasma hemoglobin in Group A was 13.5 mg/dL. This was not the range of anemia. Therefore, the effect of the lower hemoglobin level in Group A may be minimal.

As for the different hemodynamic effects of carvedilol and bisoprolol, it was revealed that there was no hemodynamic difference between the two drugs. However, because the drug dose was different between the two groups, it was not clear whether this phenomenon was a class effect or drug effect.

Study limitations

In this present study, SV was measured using impedance cardiography. This range has been reported to be accurate [12–16]. However, in some cases, signals may not be detected and not measured. Because such cases cannot be used, it decreased the number of study participants. Further investigations with more participants will be required.

Nowadays, a number of beta-adrenergic receptor blockers can be used for heart disease. In this study, four types of beta-adrenergic receptor blockers were used. The effect of beta-adrenergic receptor blockers on heart rate response differs by beta-adrenergic receptor selectivity and/or co-existent alpha-adrenergic receptor blocking action. In this study, because the number of patients with beta-adrenergic receptor blockers was not sufficient, we could not clarify the difference in the beta-adrenergic receptor blockers. More precise evaluation will be needed.

Conclusion

It was shown that the increase of the O_2 pulse was disproportionately greater than the measured SV when beta-adrenergic receptor blockers were used in patients with preserved SV and exercise tolerance. Careful consideration will be necessary when the peak O_2 pulse is used to evaluate the cardiac function during exercise.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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