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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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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.

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×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, 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 ($\dot{V}E$) 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].

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
ΔHR/ΔWR	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.

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

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