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Original article

Importance of compensatory heart rate increase during myocardial ischemia to preserve appropriate oxygen kinetics

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ABSTRACT

Background: Myocardial ischemia induces cardiac dysfunction, resulting in insufficient oxygen supply to peripheral tissues and mismatched energy production during exercise. To relieve the insufficient oxygen supply, heart rate (HR) response is augmented; however, beta-adrenergic receptor blockers (BB) restrict HR response. Although BB are essential drugs for angina pectoris, the effect of BB on exercise tolerance in patients with angina has not been studied. The aim of this study was to clarify the importance of HR augmentation to preserve exercise tolerance in patients with angina pectoris.
Methods: Forty-two subjects who underwent cardiopulmonary exercise testing (CPX) to detect myocardial ischemia were enrolled. CPX was performed until exhaustion or onset of significant myocardial ischemia using a ramp protocol. Subjects were assigned to three groups (Group A: with ST depression during CPX with significant coronary stenosis and taking BB; Group B: with ST depression and not taking BB; Group C: without ST depression and not taking BB). HR response to exercise was evaluated during the following two periods: below and above ischemic threshold (IT). In Group C, it was evaluated during the first 2 min and the last 2 min of a ramp exercise.
Results: No significant differences were observed among the three groups with regard to patients' basic characteristics. Below IT, there were no differences in oxygen pulse/watt (O_2 pulse increasing rate), HR/watt ($\Delta HR/\Delta WR$), and $\Delta\dot{V}O_2/\Delta WR$. Above IT, O_2 pulse increasing rate was greater in Group A than in Group B. $\Delta HR/\Delta WR$ was smaller in Group A than in Group B. $\Delta\dot{V}O_2/\Delta WR$ became smaller in Group A than in Group B. There was no difference in anaerobic threshold, and peak $\dot{V}O_2$ was smaller in Group A than in Group B.
Conclusions: Restriction of HR response by a BB is shown to be one of the important factors in diminished exercise tolerance.

Introduction

Regional myocardial ischemia is widely known to cause abnormality of cardiomyocyte activity, and it is associated with diminished stroke volume [1–4]. Because the human body requires appropriate nutrition and oxygen to produce ATP, sufficient blood flow is necessary. Cardiac output is the product of stroke volume and heart rate (HR); therefore, to maintain appropriate blood flow to organs, HR response is augmented during myocardial ischemia. Beta-adrenergic receptor blockers (BB) are recommended for treatment of stable angina pectoris [5–7]. By suppressing sympathetic nerve activity, they diminish HR at rest and during exercise [8]. They also restrain the compensatory activation of the sympathetic nervous system during myocardial ischemia. By this mechanism, cardiac muscle cells under ischemic condition are relieved from ischemic cell injury. This is one of the principal mechanisms by which BB relieve chest pain in patients. However, in skeletal muscle cells, there is restraint of cardiac pump function; therefore, blood flow induces diminishment of oxygen supply, resulting in impaired exercise tolerance.

Cardiopulmonary exercise testing (CPX) can evaluate cardiac pump function during exercise, HR response, and exercise tolerance. One of the indicators of cardiac pump function is peak $\dot{V}O_2/HR$. Peak $\dot{V}O_2/HR$ (oxygen pulse) is satisfactorily correlated with stroke volume at peak exercise. This is explained by Fick's principal; that is, $\dot{V}O_2$ is a product of cardiac output and $c(A\text{-}V)O_2$

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difference. This is usually adopted at peak exercise, because c(A-V)O_2 difference reaches almost the same value of 14–17 vol.%. However, increase in the rate of c(A-V)O_2 difference during a ramp exercise is reported to be constant [9,10]. Therefore, an increase in oxygen pulse rate depends on an increase in oxygen uptake rate. That is, we could estimate cardiac pump function by evaluating the increased rate of oxygen pulse during exercise.

HR increase during myocardial ischemia is encountered in clinical settings. However, how HR augmentation during myocardial ischemia affects oxygen uptake with or without BB is not fully understood. Hereby, we investigated the effect of HR increase on exercise tolerance in these patients.

Methods

Study population

Forty-two consecutive patients with chest pain were enrolled. Patients underwent a cineangiography (CAG) and CPX to clarify the reason for their chest pain. The patients were assigned to one of the following three groups: Group A: those with at least one significant stenotic lesion by CAG and who are taking BB (n = 15); Group B: those with significant coronary arterial stenosis and not taking BB (n = 13); and Group C: those without any stenotic lesions and not taking BB (n = 14). Patients in Group C did not have any ischemic heart disease. Patients' characteristics are shown in Table 1. Drug information of BB is also described in Table 1. Eighty-seven percent was carvedilol and the rest was bisoprolol. Both drugs do not have intrinsic sympathetic activity. The number of coronary arteries with stenosis and distribution of coronary stenosis lesion are shown in Table 1. There was no difference in lesion number and distribution.

Coronary cineangiography

CAG was performed by the standard technique using 5-Fr. catheters. When the narrowest coronary artery diameter was >75% compared to the reference diameter, the lesion was diagnosed as significant stenosis.

Cardiopulmonary exercise testing

CPX was performed using an upright, calibrated cycle ergometer (StrengthErgo 8, Mitsubishi Electric Engineering, Tokyo, Japan) with an electrocardiograph (ML-9000, Fukuda Denshi Ltd., Tokyo, Japan). Gas samples were collected by breath-by-breath method and oxygen uptake ($\dot{V}O_2$). Carbon-dioxide production ($\dot{V}CO_2$) and minute ventilation (VE) were measured by gas analyzer (AE-300E, Minato Ikagaku Ltd., Osaka, 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 in work rate by 1 W every 6 s until exhaustion, as recommended by Buchfuhrer et al. [11] and reported formerly by us [12,13]. To certify that patients performed CPX until exhaustion, they were forced to keep pedalling until the respiratory quotient (R) reached at least 1.10. The work rate increase was chosen according to patient fitness, and the exercise period was kept between 8 and 15 min [11]. In the end, all patients performed 10 W/min increasing rate.

Ischemic threshold (IT) was defined by one of the following signs: (i) the development of horizontal or downsloping ST-segment depression of ≥0.10 mV, at 60 ms, after the J point, in three consecutive beats; (ii) the development of upsloping ST-segment depression of ≥0.20 mV, at 60 ms, after the J point, in three consecutive beats; or (iii) the development of ST-segment elevation of ≥0.10 mV, at 60 ms, after the J point, in three consecutive beats [14]. Exclusion criteria of this study were the following: (i) left ventricular ejection fraction <40%; (ii) moderate to severe pulmonary disease; (iii) ST-segment alteration at rest, as a result of myocardial ischemia, left ventricular hypertrophy, digitalis, or antiarrhythmic drugs; (iv) pacemaker; (v) uncontrolled diabetes mellitus with severe diabetic neuropathy; (vi) uncontrolled hypertension; (vii) atrial fibrillation; (viii) left-bundle-branch block; (ix) severe anemia (hemoglobin <10 g/dL). Because

Table 1
Patients' background.

	Group A (n = 15)	Group B (n = 13)	Group C (n = 14)	
Age (years)	63.3 (6.7)	64.2 (10.8)	64.7 (18.1)	n.s.
Gender (M/F)	12/3	12/1	9/5	n.s.
Body height (cm)	164.0 (11.4)	162.8 (5.6)	159.7 (6.4)	n.s.
Body weight (kg)	59.5 (11.1)	63.2 (12.7)	58.8 (7.9)	n.s.
BMI	22.0 (2.3)	23.7 (3.5)	22.9 (1.6)	n.s.
Hypertension (%)	80.0	69.2	50.0	n.s.
Diabetes mellitus (%)	80.0	53.8	50.0	n.s.
Hb (mg/dL)	12.7 ± 0.9	12.3 ± 1.2	12.6 ± 1.3	n.s.
ACE/ARB (%)	53.3	33.3	50.0	
β-Blocker (C/B)	13/2	–	–	
Lesion number	1.73 (0.80)	1.54 (0.52)		n.s.
1VD (%)	46.7	46.2	–	
LAD/LCx/RCA	2/3/2	1/0/5		n.s.
2VD (%)	33.3	53.8	–	
LAD/LCx/RCA	4/4/2	3/7/4		n.s.
3VD (%)	20.0	0	–	
LVEF (%)	59.1 (14.8)	57.2 (11.3)	59.9 (5.3)	n.s.
HR at rest (n/min)	68.9 ± 8.9	75.4 ± 6.8	74.8 ± 10.4	<0.05
HR at IT (/min)	105.0 ± 11.0	116.8 ± 17.0	–	<0.05
Peak HR (n/min)	119.0 ± 14.6	140.2 ± 16.2	134.0 ± 20.2	<0.01
SBP at rest	138.7 ± 21.1	124.9 ± 21.3	126.9 ± 16.2	n.s.
SBP at peak	177.7 ± 29.5	198.1 ± 26.8	181.1 ± 25.8	n.s.
$\dot{V}E/\dot{V}CO_2$ at RCP	34.3 ± 3.2	32.5 ± 5.8	32.4 ± 4.6	n.s.
$\dot{V}E$ vs. $\dot{V}CO_2$ slope	31.3 ± 4.6	30.6 ± 5.7	29.2 ± 3.5	n.s.
Peak R	1.13 ± 0.03	1.14 ± 0.02	1.14 ± 0.02	n.s.

BMI, body mass index; Hb, hemoglobin; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; LVEF, left ventricular ejection fraction; HR, heart rate; IT, ischemic threshold; SBP, systolic blood pressure; RCP, respiratory compensation point; R, gas exchange ratio.

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