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Original article

Clinical significance of the overshoot phenomena of respiratory gas indices during recovery from maximal exercise testing

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ABSTRACT

Background: Overshoot phenomena of the gas exchange ratio (R:VCO_2/VO_2), ventilatory equivalent for O_2 (VE/VO_2), and end-tidal O_2 pressure ($PETO_2$) are commonly observed during recovery from maximal cardiopulmonary exercise testing (CPX). We investigated the clinical significance of the overshoots of these indices by comparing their magnitudes between healthy subjects and cardiac patients with left ventricular dysfunction.

Methods: In total, 121 subjects (73 healthy subjects and 48 cardiac patients with left ventricular ejection fraction $< 40\%$) who underwent CPX and achieved peak $R \geq 1.10$ were enrolled. We evaluated and calculated the presence and magnitude of the overshoot phenomena of R, VE/VO_2, and $PETO_2$.

Results: The overshoot phenomena of R, VE/VO_2, and $PETO_2$ were observed in all the subjects. The magnitudes of the R ($21.4 \pm 12.4\%$ vs. $29.3 \pm 10.0\%$, $p < 0.001$), VE/VO_2 ($45.5 \pm 23.5\%$ vs. $77.5 \pm 28.5\%$, $p < 0.001$), and $PETO_2$ ($5.3 \pm 3.4\%$ vs. $10.1 \pm 4.2\%$, $p < 0.001$) overshoots were significantly lower in cardiac patients than in healthy subjects. In cardiac patients, the magnitude of the $PETO_2$ overshoot showed significant positive correlations with the peak O_2 uptake (VO_2) ($r = 0.52$, $p < 0.001$), anaerobic threshold ($r = 0.43$, $p = 0.003$), and ratio of the increase in VO_2 to the increase in the work rate ($r = 0.41$, $p = 0.005$), and a negative correlation with the slope of the increase in ventilation versus the increase in CO_2 output ($r = -0.50$, $p < 0.001$). The magnitudes of the R and VE/VO_2 overshoots showed the same patterns of significant correlation with the CPX indices.

Conclusions: We concluded that the overshoots of R, VE/VO_2, and $PETO_2$ during recovery from maximal exercise reflect the natural cardiopulmonary adaptation after exercise and are more prominent in subjects with better cardiopulmonary function.

Introduction

Cardiopulmonary exercise testing (CPX) is one of the most useful clinical tools for evaluating the severity of disease and the limitations of physical activities in cardiac patients [1]. The O_2 uptake (VO_2), which is defined by the Fick equation, is the product of cardiac output and arterial-mixed venous O_2 difference. The peak VO_2 noninvasively reflects maximal cardiac output during exercise and is accordingly considered the gold standard for predicting prognosis in cardiac patients and selecting patients for cardiac transplantation [2,3]. The slope of the increase in ventilation (VE) versus the increase in CO_2 output (VCO_2) during exercise ($VE–VCO_2$ slope), another important index obtained from

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CPX, relates to cardiopulmonary dysfunction and poor prognosis in cardiac patients [4]. While a number of studies have focused on cardiopulmonary response during exercise, cardiopulmonary response during recovery from maximal exercise is incompletely understood.

The overshoot phenomenon of VO_2, a transient increase in VO_2 during recovery from maximal exercise, has been reported in relatively severe cardiac patients [5–7]. This phenomenon has been attributed to the transient increase in cardiac output caused by mismatch between cardiac contractility and afterload reduction [7,8]. On the other hand, overshoots of the gas exchange ratio (R:VCO_2/VO_2), ventilatory equivalent for O_2 (VE/VO_2), and end-tidal O_2 pressure ($PETO_2$) are commonly observed during recovery from maximal exercise [9]. The R value at peak exercise is used as an objective index to evaluate exercise effort [1]. In general, VE/VO_2 reflects ventilation perfusion (V/Q) mismatch and $PETO_2$ reflects arterial O_2 pressure [10,11].

In the present study, we investigated how frequently the overshoot phenomena of R, VE/VO_2, and $PETO_2$ are observed during recovery from maximal exercise. We also aimed to clarify the clinical significance of the overshoots of these indices by comparing their magnitudes between cardiac patients with left ventricular dysfunction and age-matched healthy subjects and evaluating whether their magnitudes relate to cardiopulmonary function during exercise.

Methods

Study subjects

The subjects for this study were 599 consecutive subjects who underwent CPX for the screening of cardiac disease or evaluation of exercise capacity and/or severity of cardiac disease at the Cardiovascular Institute between January 2013 and March 2014. As a peak R of equal to or greater than 1.10 is considered good effort under current guidelines [1], subjects with peak R values of less than 1.10 were excluded from this study. Also, cardiac patients with left ventricular ejection fraction (LVEF) equal to or greater than 40% were excluded. By these, 48 cardiac patients with left ventricular dysfunction (62.5 ± 12.1 years) were selected (Table 1). The etiology of heart disease in cardiac patients was coronary artery disease in 20 patients, idiopathic dilated cardiomyopathy in 17 patients, valvular heart disease in 6 patients, and other cardiac disease in 5 patients. Among the 20 cardiac patients with coronary artery disease, 19 patients had previous myocardial infraction. Among the initial 599 subjects, we selected 73 healthy subjects whose age equal to or greater than 30 years, in order to match the age with that of cardiac patients. Subjects were defined as healthy when cardiac disease was ruled out by electrocardiogram, echocardiography, CPX, or other standard examinations. The protocol was approved by the human subjects committee of the Cardiovascular Institute. Its purposes and risks were explained to the patients, and informed consent was obtained from each.

Exercise testing and respiratory gas analysis

An incremental symptom limited exercise test was performed using an upright, electromagnetically braked cycle ergometer (Strength Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan). The exercise test began with a 4 min rest on the ergometer followed by a 4 min warm-up at 0 or 20 W at 60 rpm. The work rate of warm-up exercise (0 W or 20 W) was determined according to subject's daily activity. The load was then increased incrementally by 1 W every 6 s (10 W/min). After the termination of exercise, cool-down pedaling was performed at 0 W for 1 min in 72 subjects (29 cardiac patients and 43 healthy subjects) and for 2 min in 38 subjects (9 cardiac patients and 29 healthy subjects) to prevent sudden drops in blood pressure or other adverse events related to the parasympathetic reflex.

VO_2, VCO_2, and VE were measured throughout the test using an Aeromonitor AE-300s (Minato Medical Science, Osaka, Japan). The Aeromonitor AE-300s consists of a microcomputer, a hot wire flowmeter, and a gas analyzer containing a sampling tube, filter, suction pump, infrared CO_2 analyzer, and an O_2 analyzer composed of a paramagnetic oxygen cell. The VO_2 and VCO_2 were calculated breath-by-breath based on the mathematical analysis described by Beaver et al. [12]. The time alignment between the concentration and flow was performed based on the time delays of the O_2 and CO_2 analyzers (the flow delay from the sampling site to the analyzer plus the response time of the analyzer) [13]. Before the parameters from the respiratory gas analysis were calculated, breath-by-breath data were interpolated to give second-by-second values. These second-by-second values were then calculated as successive 3-second averages, and the averages were translated into a 5-point moving average.

Table 1
Clinical characteristics of the study subjects.

Characteristic	Healthy subjects (n = 73)	Cardiac patients (n = 48)	p-Value
Male/female	48/25	44/4	<0.001
Age (years)	60.3 ± 12.7	62.5 ± 12.1	NS
Height (cm)	165.6 ± 7.3	168.3 ± 8.9	NS
Weight (kg)	64.1 ± 12.0	67.1 ± 14.1	NS
Body mass index (kg/m^2)	23.2 ± 3.5	23.6 ± 3.7	NS
Etiology			
Coronary artery disease		20 (41.7%)	
Idiopathic dilated cardiomyopathy		17 (35.4%)	
Valvular disease		6 (12.5%)	
Other cardiac disease		5 (10.4%)	
Medication			
β-blockers		39 (81.3%)	
Diuretics		38 (79.2%)	
ACEI/ARB		33 (68.8%)	
Ca-channel blockers		7 (14.6%)	
Nitrates		7 (14.6%)	
Digitalis		5 (10.4%)	

Data are presented as the mean ± SD or no. (%) of patients unless otherwise indicated.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NS, not significant.

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