Original Article

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Clinical significance of respiratory compensation during exercise testing in cardiac patients

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Summary **Ventilation (VE) increases linearly with the increase of carbon dioxide output (VCO2) during cardiopulmonary exercise testing. VE-VCO2 slope rises in parallel with exercise intensity, reaches a turning point (called the RC point), then steepens because of respiratory compensation for lactic acidosis. While this RC point can be identified universally, it is undetectable in some patients. In this study we evaluated whether the respiratory compensation during exercise testing has clinical significance in cardiac patients. In total, 152 cardiac patients with a respiratory exchange ratio at peak exercise (peak R) of between 1.10 and 1.20 were enrolled. Cardiopulmonary parameters were compared between patients who manifested the RC point (n = 118) and those who did not (n = 34). The peak R did not significantly differ between these two groups. Compared to the patients without the RC point, those with the RC point had a higher oxygen uptake at peak exercise (peak VO2) (20.2 ± 5.3 *vs* 13.6 ± 3.4 mL/min/kg, $p < 0.001$), higher anaerobic threshold (AT) (12.4 ± 3.2 *vs* 9.2 ± 2.3 mL/min/kg, $p < 0.001$), and lower VE-VCO2 slope (31.7 ± 5.8 *vs* 37.8 ± 9.6, $p = 0.001$). Brain natriuretic peptide (BNP) tended to be lower in the patients with the RC point (175.4 ± 364.7 *vs* 327.9 ± 381.1 pg/mL, $p = 0.067$). Peak VO2, the marker of cardiopulmonary function, was found to be the independent predictor of the presence of the RC point. The present findings suggest that the phenomenon of respiratory compensation during heavy exercise indicates better cardiopulmonary function in cardiac patients within a prescribed range of effort.**

Keywords: Exercise testing, respiratory compensation point, cardiac patients

1. Introduction

Cardiopulmonary exercise testing (CPX) offers clinicians the ability to obtain an abundance of information useful for the management of complex cardiovascular and pulmonary diseases (*1*). Five parameters noninvasively obtained from this testing reflect the severity of heart disease and the activities of daily living in cardiac patients: the peak O_2 uptake (VO2), anaerobic threshold (AT), rate of increase in ventilation (VE) per unit increase in CO2 output (VCO2) during exercise (VE-VCO2 slope), and ratio of the increase in VO2 to the increase in the work rate (ΔVO2/ΔWR) (*1-4*). Among these parameters, the peak VO2 reflects maximal cardiac output during exercise and is accordingly considered the main indicator of cardiopulmonary function and a gold standard in selecting patients for cardiac transplantation (*1-3*). However, it has a limitation and may not be accurately obtained if patients would not perform maximal effort until reaching peak exercise. The respiratory exchange

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ratio (R), defined as the ratio between VCO2 and VO2 in respiratory gas analysis, is used to evaluate a subject's effort objectively. Under current guidelines, the R of equal to or greater than 1.10 at peak exercise is generally considered an indication of excellent subject effort during CPX (*1*). The VE-VCO2 slope is the rate of increase in VE per unit increase in VCO2, and is therefore used to describe the ventilatory response to exercise.

The respiratory compensation (RC) point is an important concept in exercise physiology as it forms the boundary between the heavy and severe exercise intensity domains, a point which marks the onset of hyperventilation during incremental exercise (*5,6*). V-slope method is now generally used to identify the RC point (*7,8*). It is determined when the ratio of VE to VCO2 starts to increase after a period of decrease or stasis, and/or when the end-tidal CO2 pressure (PETCO2) started to decrease after reaching a maximum level (*5*).

In some patients, however, no identifiable RC point is reached in the course of exercise testing, although with excellent effort. To gain further insight, we investigated whether the presence or absence of RC point during exercise testing is clinically meaningful to cardiac patients.

2. Materials and Methods

2.1. *Study subjects*

The subjects for this study were 416 consecutive cardiac patients who underwent CPX at the Cardiovascular Institute between January 2013 and December 2013 for the screening of cardiac disease or evaluation of exercise capacity and/or severity of heart failure. Since a peak R of equal to or greater than 1.10 is thought to reflect good exercise effort under current guidelines (*1,5*), we selected 152 cardiac patients with the peak R of between 1.10 to 1.20 to ensure the sufficient and similar effort by excluding patients with an R above or below that range (Table 1). The protocol and procedures for the exercise testing were approved by the Human Subjects Committee of the Cardiovascular Institute. Every patient gave his or her informed consent to participate in the study after receiving an explanation of the purposes and risks.

2.2. *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 during the warm-up exercise (0 W or 20 W) was determined according to subject's habitual daily activity. The load was then increased incrementally by 1 W every 6 s (10 W/min) or every 3s (20 W/min). VO2, VCO2, and VE were measured from 4 min before the start of exercise until the end of exercise using an Aeromonitor AE-300s (Minato Medical Science, Osaka, Japan). The Aeromonitor AE-300s consists of a microcomputer, a hot-wire flow meter, and a gas analyzer composed of a sampling tube, filter, suction pump, paramagnetic oxygen cell for O2 analysis, and infrared CO2 analyzer. The VO2 and VCO2 were calculated by the Aeromonitor AE-300s breath-by-breath based on a mathematical analysis described by Beaver *et al*. (*7*). The concentration and flow were aligned synchronously by compensating for the time delays of the O2 and CO2 analyzers (flow delay from the sampling site to the analyzer plus the response time of the analyzer) with respect to the flow signal (*8*).

Before the parameters from the respiratory gas analysis were calculated, breath-by-breath data were interpolated to give second-by-second values. The second-by-second values thus obtained were then converted into successive 3-second averages and translated into a 5-point moving average. The peak VO2 was calculated as the average of the values obtained during the last 15 seconds of incremental exercise. The percentage of predicted peak VO2 (%peak VO2) was calculated by dividing the measured peakVO2 by the predicted peak VO2 determined in a normal Japanese population (*9*). The AT was determined by V-slope analysis (*7*). ΔVO2/ΔWR was calculated by least-squares linear regression from the data recorded from 30 seconds after the start of incremental exercise to 30 seconds before the end of exercise (*4*). The RC point was defined as the point at which the ratio of VE to VCO2 started to increase after a period of decrease or stasis (*5*). The VE-VCO2 slope during incremental exercise was calculated from the start of incremental exercise to the RC point by least-squares linear regression, as previously described (*4,5*). When no RC point could be identified, the VE-VCO2 slope was calculated from the data recorded between the start of incremental exercise to the end of the exercise (*10*). The left ventricular ejection fraction (LVEF) was measured by echocardiography in 139 patients (108 of whom exhibited an RC point and 31 of whom did not), and brain natriuretic peptide (BNP) was measured in 105 patients (78 of whom exhibited an RC point and 27 of whom did not).

2.3. *Statistical analysis*

Data are presented as the mean ± standard deviation (SD). Student's *t* tests were used to assess differences of continuous variables between groups. χ^2 tests were used to assess differences between categorical variables. Variables were tested for their power to predict the appearance of an RC point in univariable binary logistic regression analyses. Variables with a value of $p < 0.05$

were then considered for inclusion in the multivariable models to determine independent predictors. All analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, Illinois). A 2-sided value of $p < 0.05$ was considered statistically significant for all comparisons.

3. Results

The clinical characteristics of the study subjects are shown in Table 1. Compared to the patients who exhibited the RC point (RC group), those not exhibiting the RC point (non-RC group) were older and had lower body weight. There was no significant difference in etiology between the two groups, and the only difference in the medications received was the prescription of diuretics. The cardiopulmonary indices of the study subjects are shown in Table 2. Compared to the non-RC patients, the RC patients had a higher peak VO2 (20.2 ± 5.3 *vs* 13.6 ± 3.4 mL/min/kg, $p < 0.001$), higher %peak VO2 (81.9 ± 19.8 *vs* 58.1 ± 14.8 %, $p < 0.001$), higher AT (12.4 ± 3.2 *vs* 9.2 ± 2.3 mL/min/kg, $p < 0.001$), and lower VE-VCO2 slope (31.7 ± 5.8 *vs* 37.8 ± 9.6, $p = 0.001$). The heart rate and blood pressure at peak exercise were also higher in the RC patients, while the BNP in the RC patients tended to be lower (175.4 ± 364.7 *vs* 327.9 ± 381.1 pg/mL, $p = 0.067$).

The variables were tested for their power to predict

Table 1. Clinical Characteristics of RC non-RC Patients

Characteristics	RC Patients ($n = 118$)	Non-RC Patients ($n = 34$)	p value
Age (years)	63.3 ± 12.6	69.8 ± 11.7	0.008
Male/female	99/28	25/9	NS
Height (cm)	166.9 ± 9.3	162.1 ± 7.6	0.007
Body weight (kg)	66.9 ± 13.9	58.7 ± 10.8	0.002
Body Mass Index	23.5 ± 3.5	22.2 ± 3.08	0.017
Etiology			
Valvular disease	42 (36)	16 (47)	NS
Coronary artery disease	41 (35)	12 (35)	NS
Arrhythmia	13 (11)	1 (3)	NS
Dilated cardiomyopathy	10 (8)	2 (6)	NS
Hypertrophic cardiomyopathy	4 (3)	1 (3)	NS
Other cardiovascular disease	8 (7)	2 (6)	NS
Medication			
Nitrates	14 (12)	8 (24)	NS
Calcium-channel blockers	36 (31)	12 (35)	NS
Diuretics	34 (29)	20 (59)	0.002
Digitalis	5 (4)	1 (3)	NS
β-Blockers	58 (49)	22 (65)	NS
ACEI/ ARB	23 (20)	10 (29)	NS

Data are presented as mean ± SD. NS, not significant. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Cardiopulmonary Parameters

Characteristics	RC Patients ($n = 118$)	Non-RC Patients ($n = 34$)	p value
BNP (pg/mL)	175.4 ± 364.7	327.9 ± 381.1	0.067
LVEF (%)	58.0 ± 15.9	55.6 ± 19.9	NS
At rest			
Heart rate (beats/min)	74.5 ± 13.0	74.9 ± 12.5	NS
Systolic blood pressure (mmHg)	119.3 ± 16.8	117.4 ± 22	NS
Diastolic blood pressure (mmHg)	72.1 ± 12.2	68.1 ± 10.4	NS
R	0.90 ± 0.08	0.91 ± 0.06	NS
At peak exercise			
Heart rate (beats/min)	145 ± 29 .3	116 ± 20.3	< 0.001
Systolic blood pressure (mmHg)	186 ± 33.6	161 ± 38.9	< 0.001
Diastolic blood pressure (mmHg)	84 ± 16.2	76 ± 13.5	0.011
R	1.15 ± 0.03	1.14 ± 0.03	NS
Peak VO2 (mL/min/kg)	20.2 ± 5.3	13.6 ± 3.4	< 0.001
Peak VO2 (%)	81.9 ± 19.8	58.1 ± 14.8	< 0.001
AT VO2 (mL/min/kg)	12.4 ± 3.2	9.2 ± 2.3	< 0.001
AT VO2 (%)	74.5 ± 18.5	55.5 ± 14.5	< 0.001
VE-VCO2 slope	31.7 ± 5.8	37.8 ± 9.6	0.001
ΔVO2/ΔWR (mL/min/W)	9.51 ± 1.58	7.22 ± 1.56	< 0.001

Data are presented as mean ± SD. NS, not significant. BNP, brain-type natriuretic peptide; LVEF, left ventricular ejection fraction; R, gas exchange ratio; VO2, O2 uptake; AT, anaerobic threshold; VCO2, CO2 output; VE/VO2, ventilatory equivalent for O2; ΔVO2/ΔWR, ratio of the increase in VO2 to the increase in the work rate.

Table 3. Independent correlates of the RC point by logistic regression analysis

Variables	Univariable logistic regression				Multivariable logistic regression			
	OR	95% CI, Lower	95% CI, Upper	*p* value	OR	95% CI, Lower	95% CI, Upper	*p* value
Age	0.949	0.912	0.988	0.010	1.01	0.959	1.064	0.708
Height	1.060	1.015	1.107	0.009	0.959	0.883	1.041	0.319
Body weight	1.053	1.018	1.089	0.003	1.07	1.005	1.139	0.035
Peak VO2 (%)	1.072	1.043	1.101	< 0.001	1.328	1.124	1.570	0.001
VE-VCO2 slope	0.886	0.832	0.943	< 0.001	0.99	0.910	1.077	0.817
HR at peak exercise	1.047	1.026	1.068	< 0.001	1.023	0.998	1.048	0.069
SBP at peak exercise	1.022	1.009	1.035	0.001	0.995	0.980	1.011	0.559

CI, confidence interval; OR, odds ratio. HR, heart rate; SBP, systolic blood pressure.

the appearance of the RC point. The univariable binary logistic regression analysis identified the variables of age, height, body weight, %peak VO2, VE-VCO2 slope, and heart rate and systolic blood pressure at peak exercise as significant prognostic indexes of the RC point (Table 3). In contrast, the multivariate logistic regression analysis identified the %peak VO2 as a sole independent predictor of the RC point among the cardiopulmonary indices entered into the analysis.

4. Discussion

4.1. *CPX and cardiopulmonary function*

Parameters obtained from CPX reflect the severity of heart disease and the activities of daily living in cardiac patients (*1*). In 1991, Mancini *et al*. proposed that cardiac transplantation could be safely deferred in ambulatory patients with severe left ventricular dysfunction when the peak VO2 was greater than 14 mL/min/kg (*3*). Since then, peak VO2 has been considered a key index to list for cardiac transplantation. Other investigators have reported adequate evidence in support of peak VO2 measurement for predicting prognosis (*1,4*). Since peak VO2 is affected by age, sex, muscle mass and conditioning status, %peak VO2 is suggested the superiority and widely used (*1,10*). The VE-VCO2 slope, is the most widely used index of ventilatory efficiency (*1,4*). It ranges from approximately 24 to 34 in normal subjects and a steeper VE-VCO2 slope is considered an indication of worse cardiopulmonary function and higher mortality (*1,11*). In the present study we found that the non-RC patients had a lower peak VO2 (%) and higher VE-VCO2 slope than the RC patients, a finding indicative of worse cardiopulmonary function and lower respiratory efficiency during exercise in the former.

4.2. *VE-VCO2 slope and respiratory compensation*

Generally, as the work rate increases in a progressive exercise test, VO2, VCO2, and VE increase linearly with the work rate until exercise lactic acidosis develops, that is, until the AT point is reached (*5*). Above the AT point, VCO2 increases more rapidly than VO2 because CO2 generated by the bicarbonate buffering of lactic acid is added to the VCO2 produced by the aerobic metabolism (*5*). When the work rate is increased further, the carotid bodies respond to the decreasing pH and ventilatory stimulation is intensified (*12*). This respiratory compensation results in a greater VE amount per VCO2, which manifests as a steepening of the VE/VCO2 slope and a decrease in PETCO2. The point above which respiratory compensation occurs is referred to as the RC point (Figure 1) (*5,8*).

Studies of the mechanisms responsible for elevated VE-VCO2 slope in chronic heart failure suggest that is it multifactorial (*13*). This steeper VE/VCO2 slope is associated with increased ventilation-perfusion mismatching (adequate ventilation and poor perfusion) (*1*), reduced cardiac output during exercise (*14*), increased pulmonary artery and capillary wedge pressures, increased dead space/tidal volume ratio (*14,15*) and, more recently, an augmented chemoreceptor sensitivity (*16*).

4.3. *The carotid body chemoreflexes and ventilatory response*

The chemoreflexes are the main mechanisms of control and regulation of the ventilatory responses to the changes in arterial oxygen and CO2 concentrations (*17*). The peripheral chemoreceptors located in the carotid body and aortic body, respond primarily to hypoxia via afferents to the respiratory center in the medulla oblongata and the nucleus of the solitary tract (*17-19*). In humans, carotid body chemosensitivity plays a dominant role in constraining variations of arterial pH in response to the acute metabolic acidosis induced by heavy exercise (*19*). Previous studies on chronic heart failure patients have demonstrated that the exaggerated response from peripheral chemoreceptors leads to a rapid ventilator augmentation, albeit with lower ventilatory efficiency, during exercise (*18-20*).

In our study, the non-RC patients showed a steeper VE/VCO2 slope after the onset of exercise, a finding indicative of earlier and higher ventilatory response activity. Agree with Nariko Takano (*21*), we suppose that this hyperventilate in non-RC patients may

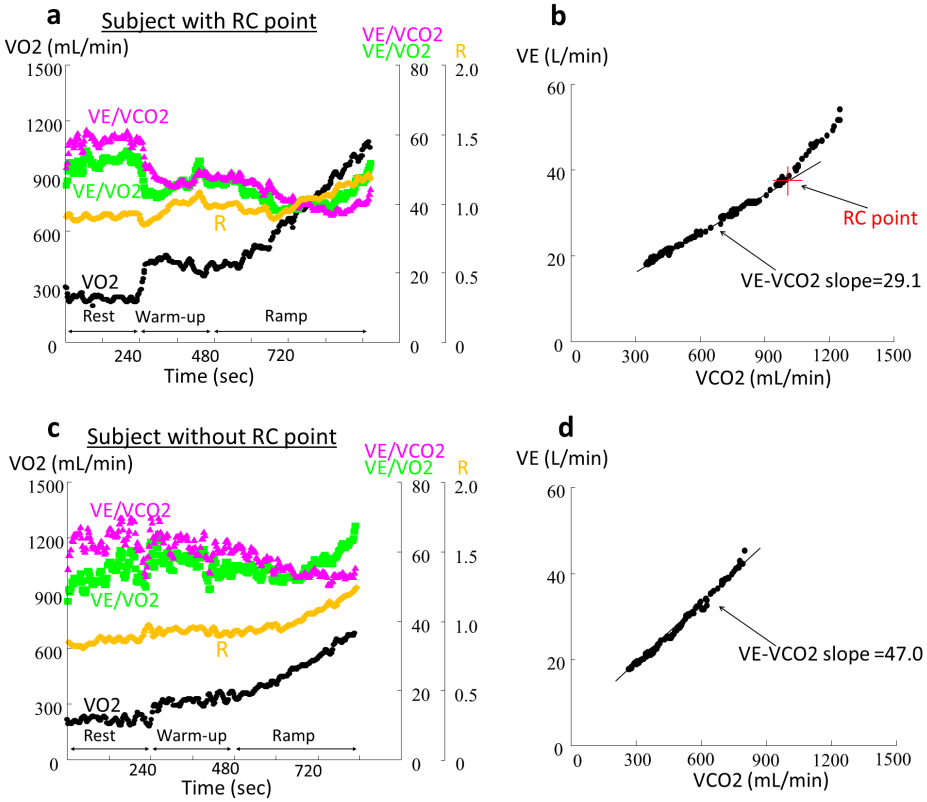

Figure 1. Panel (a) shows the parameter changes with time during incremental exercise from one RC patient; Panel (b) shows the VE/VCO2 slope in the same patient. Panel (c) shows the parameter changes from one non-RC patient; panel (d) shows the VE-VCO2 slope in the same patient.

attributed to the hypersensitivity of carotid body. The previous research by Nariko Takano suggest that the individuality of RC point depends partly on the rate of lactic acid increase and chemosensitivity of the carotid bodies during incremental exercise (*21*). The latter, in turn, may be related to sympathetic overactivity or altered central command (*22,23*). Animal model studies of chronic heart failure indicated that the carotid body chemoreceptors became hyperactive, resulting in an activation of the pre-sympathetic neurons in the brainstem and increases in efferent sympathetic outflow to the kidneys and heart (*24,25*).

Patients with worse cardiopulmonary function might tend to hyperventilate earlier before AT due to the hypersensitivity of carotid body and the lower ventilatory efficiency. Thus, in non-RC patients, their ventilatory response may not be further strengthened by carotid body during hypercapnia after AT, which might prevent them from presenting an identifiable RC point, *i.e.*, hyperventilation above the RC point.

There are several limitations to our study. According to the definition of the RC point, the appearance of the point first depends on the patient' physical effort during cardiopulmonary exercise testing. If the exercise is terminated at submaximal level, the RC point may not be reached. Thus, we selected patients with R at peak exercise in a relatively narrow range (between 1.10 to 1.20). The frequency of the appearance of respiratory compensation must depend on the level of R achieved at peak exercise. In addition, the patients' long-term outcomes were not available for follow-up. Although our results implied the guiding significance that the absent of RC point indicates a worse cardiopulmonary function, we cannot confirm the significance of RC point in predicting mortality in cardiac patients. A further study will be worth of expecting.

In summary, the present findings suggest that the phenomenon of respiratory compensation during heavy exercise indicates better cardiopulmonary function in cardiac patients.

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