Determination of the $\text{VE/\!VCO}_2$ Slope from a Constant Work-Rate Exercise Test in Cardiac Patients

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Abstract: Incremental exercise testing to a symptom-limited maximum has been used to measure the ratio of the increase in ventilation (VE) to the increase in CO$_2$ output (VCO$_2$) during exercise (VE/VCO$_2$ slope), a valuable index reflecting the severity of the ventilation-perfusion mismatch in heart failure. Here we studied whether this same value for the slope of VE/VCO$_2$ could be determined from a short constant work-rate exercise test of moderate intensity. Twenty-three patients with a previous myocardial infarction underwent moderate-intensity (69 ± 15 W) constant work-rate exercise for 6 min and an incremental work-rate exercise test to the max. The VE/VCO$_2$ slope was calculated from the incremental exercise test from the start of increasing the work-rate to the ventilatory compensation point. The VE/VCO$_2$ slope was similarly calculated from the start of constant work-rate exercise until the 4th minute, when VE and VCO$_2$ changed minimally. The VE/VCO$_2$ slope determined from incremental exercise was 33.8 ± 5.9, ranging from 20.9 to 42.8. The slope obtained from constant work-rate exercise was 32.9 ± 5.7. The VE/VCO$_2$ slopes obtained from the two exercise tests did not differ significantly. The slope obtained from constant work-rate exercise was significantly positively correlated with the slope obtained from the incremental exercise ($r = 0.84$, $p < 0.0001$). The VE/VCO$_2$ slope can be determined from constant work-rate exercise at a moderate intensity. This indicates that the relationship between ventilation and CO$_2$ output is consistent and independent of the mode of exercise testing.

Key words: myocardial infarction, respiratory gas analysis, exercise testing.

Cardiopulmonary exercise testing has been recognized as a useful clinical tool for evaluating the severity of disease and the limitations of activities of daily living in cardiac patients [1]. Among the parameters obtained from cardiopulmonary exercise testing, the peak $\text{O}_2$ uptake ($\text{VO}_2$) is traditionally considered the gold standard for identifying patients with a poor prognosis and selecting candidates for cardiac transplantation [2]. The ratio of the increase in ventilation (VE) to the increase in CO$_2$ output (VCO$_2$) during exercise (VE/VCO$_2$ slope) is also an established index, reflecting the severity of the ventilation-perfusion mismatch in heart failure patients [3, 4].

Traditionally, incremental exercise testing to a symptom-limited maximum has been used to obtain the VE/VCO$_2$ slope. It is known that VE increases in a tight relationship with the increase in VCO$_2$ during an incremental exercise until the near maximum level, i.e., the ventilatory compensation point [5]. Although the slope becomes steeper above the ventilatory compensation point, the slope below this point is known to be quite linear. Therefore maximum exercise testing is not necessary to determine the VE/VCO$_2$ slope.

It is known that VCO$_2$ plotted as a function of VO$_2$ during incremental exercise exhibits a breakpoint, i.e., the anaerobic threshold resulting from the development of metabolic acidosis, at approximately 60% of the peak VO$_2$ [1]. Below the breakpoint, VCO$_2$ increases approximately linearly with VO$_2$. Above it, the slope of the increase in VCO$_2$ with respect to VO$_2$ becomes steeper because of the additional formation of CO$_2$ resulting from the buffering of lactic acid by bicarbonate [1]. In 1996, it was found that the relation between VCO$_2$ and VO$_2$ during constant work-rate exercise is similar to the relation during incremental exercise, exhibiting a similar breakpoint for both exercise tests [6]. However, the relation between VE and VCO$_2$ during constant work-rate exercise has yet to be examined. If the relation between VE and VCO$_2$ during exercise is consistent irrespective of the mode of exercise testing, the VE/VCO$_2$ slope may be determined from a short period of constant work-rate exercise rather than from a more taxing incremental exercise test.
In the present study, we examined whether the value of the slope for increasing VE relative to V\textsubscript{CO\textsubscript{2}} could be determined from a short constant work-rate exercise test of moderate intensity in cardiac patients, and whether it would be the same as that for a progressively increasing work-rate test.

**METHODS**

**Study patients.** Twenty-three consecutive patients with a history of anterior myocardial infarction (New York Heart Association functional class I–II) were recruited for the study. Twenty patients were men and 3 were women, ranging in age from 43 to 77 years (59 ± 9 years). The mean left ventricular ejection fraction was 34 ± 5%. No patient had a myocardial infarction in the month preceding the study. At the time of the study, all subjects were clinically stable and in sinus rhythm. We excluded patients who needed sublingual nitrates during maximal exercise and those with documented lung disease. Medications including calcium antagonists, nitrates, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, digitalis, and diuretics were withheld for at least 24 h prior to the study to avoid their influence on the cardiopulmonary variables during exercise. 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.

**Protocol of exercise testing.** An upright, electromagnetically braked cycle ergometer (WLP-400, Lode, Holland) was used for the exercise tests. On the day prior to starting the study, all subjects performed a symptom-limited incremental exercise test to determine the anaerobic threshold and peak work rate. On the study day, a 6 min constant work-rate test of moderate intensity (69 ± 15 W) and an incremental exercise test to the symptom-limited maximum were performed by each subject in this sequence. The interval between the tests was approximately 30 min. For the constant work-rate exercise, we selected the work rate at 40% of the difference between the work rate at the anaerobic threshold and the peak work rate. The incremental exercise test consisted of cycling at 60 rpm on the ergometer for 3 min at 20 W and then progressively increasing the work rate by 1 W every 6 s (10 W/min). Breath-by-breath VO\textsubscript{2}, V\textsubscript{CO\textsubscript{2}}, and VE were measured throughout the test until the end of exercise using a Respirometer RM 300 (Minato Medical Science, Osaka, Japan), as previously described [7]. The system was carefully calibrated before each study. The dead space of the system was 220 ml for men and 210 ml for women. The preliminary incremental exercise test was performed within 2 weeks of the day of the study.

**Data analysis.** Prior to any calculation of the parameters from the respiratory gas analysis, a five-point moving average of the breath-by-breath data was performed. The peak VO\textsubscript{2} was defined as the average values obtained during the last 10 s of incremental exercise. The anaerobic threshold was determined by the V-slope analysis [1, 8, 9]. For the incremental exercise tests, the VE/V\textsubscript{CO\textsubscript{2}} slope was calculated from the start of incremental exercise to the ventilatory compensation point by the least-squares linear regression [4]. The ventilatory compensation point was determined using the following criteria [5]: (1) the ratio of VE to V\textsubscript{CO\textsubscript{2}} starts to increase after a period of decrease or constancy, and (2) the PETCO\textsubscript{2} starts to decrease after a period of constancy. When the ventilatory compensation point could not be identified, the VE/V\textsubscript{CO\textsubscript{2}} slope was calculated from the data recorded between the start of increasing exercise and the end of the exercise [4]. For the constant work-rate exercise, the VE/V\textsubscript{CO\textsubscript{2}} slope was determined from the start of the constant work-rate exercise to its 4 min mark. The data from 4 to 6 min were ignored because both VE and V\textsubscript{CO\textsubscript{2}} nearly reach the steady-state values at approximately 4 min, thereby creating an accumulation of similar values on the plots of VE vs. V\textsubscript{CO\textsubscript{2}}, as shown in a representative subject in Fig. 1.

**Statistics.** Data are presented as the mean ± SD. Comparisons of the VE/V\textsubscript{CO\textsubscript{2}} slopes between the 2 tests were performed using Student’s paired t-test. Correlations of the VE/V\textsubscript{CO\textsubscript{2}} slopes between the 2 tests were assessed both by linear regression analysis and the method of Bland and Altman. For all comparisons, p < 0.05 was considered statistically significant.

**RESULTS**

The peak work rate, peak VO\textsubscript{2}, and anaerobic threshold obtained from the incremental maximal exercise tests were 101 ± 21 W, 20.0 ± 3.8 ml/min/kg, and 13.6 ± 2.1 ml/min/kg, respectively. As shown in Fig. 2 in a representative subject, in which the VE vs. V\textsubscript{CO\textsubscript{2}} relationships are plotted for the constant work-rate exercise and the increasing work-rate exercise, VE increased in a tight relationship with the increase in V\textsubscript{CO\textsubscript{2}} irrespective of the exercise protocol. In all subjects, the VE/V\textsubscript{CO\textsubscript{2}} slopes of the 2 exercise tests could be determined. Figure 3 shows the relationship between the VE/V\textsubscript{CO\textsubscript{2}} slope determined from the incremental exercise and the slope determined from the constant work-rate exercise. There was a significant positive correlation between these 2 slopes (r = 0.84, p < 0.0001). The slope determined from the constant work-rate exercise was 32.9 ± 5.7 on average and did not significantly differ from that determined from the incremental exercise test (33.8 ± 5.9, p = 0.18).

**DISCUSSION**

Cardiopulmonary exercise testing is a useful tool for stratifying patients with heart failure and identifying...
Determination of the VE/VCO₂ Slope

**Fig. 1.** CO₂ output (VCO₂) (panel A) and ventilation (VE) (panel B) during a constant work-rate test and an incremental exercise test in a representative subject (64-year-old male subject). After a 3-min rest on the ergometer, a constant work-rate exercise was performed for 6 min. Incremental exercise was started with a 3-min warm-up at 20 W and continued with a progressive increase in the work rate (10 W/min).

**Fig. 2.** The relation between VE and VCO₂ during a constant work-rate test and an incremental exercise test in a representative subject (64-year-old male subject). The plots were constructed from the data shown in Fig. 1. For the constant work-rate test, the data collected from the start of exercise to the 6th min of exercise are plotted. For the incremental exercise, the data collected from the start of incremental exercise to maximal exercise are plotted. The VE/VCO₂ slope of constant work-rate exercise was calculated from the start of exercise until the 4th min of exercise. For the incremental exercise, the slope was calculated from the start of incremental exercise to the maximal exercise point in this subject.

**Fig. 3.** Relationship of the VE/VCO₂ slope determined from the constant work-rate exercise to the slope determined from the incremental exercise (panel A) and the Bland and Altman method, with horizontal lines corresponding to the mean and the 2 SD above and below the mean, showing differences between the VE/VCO₂ slopes measured in the two tests (the slope of the constant work-rate exercise – the slope of the incremental exercise) (panel B).
those with poor prognoses. In 1991, Mancini et al. [2] proposed that cardiac transplantation can be safely deferred in ambulatory patients with severe left ventricular dysfunction when the peak VO$_2$ is more than 14 ml/min/kg. Since then, the peak VO$_2$ has been considered a key index to refer to in determining cardiac transplantation. In 1997, Chua et al. [3] found that cardiac patients with a higher VE/VCO$_2$ slope had a poorer prognosis. Another investigation suggests that the prognostic power of the VE/VCO$_2$ slope is more powerful than that of peak VO$_2$ in cardiac patients with a preserved left ventricular ejection fraction [4].

It has been reported that the VE/VCO$_2$ slope ranges from approximately 24 to 34 in healthy subjects and becomes steeper in cardiac patients according to the severity of heart failure [3, 10, 11]. Theoretically, a steep VE/VCO$_2$ slope is assumed to relate to an increased ratio of pulmonary dead space to tidal volume (VD/VT) or to a decrease in the regulatory set point for PaCO$_2$. The increase in VD/VT in these patients is probably due to ventilation/perfusion mismatching, i.e., reduced or absent perfusion in the well-ventilated lung [12, 13]. Since cardiac patients are reported to have reduced FEV1 and vital capacity according to the severity of heart disease [13], a higher VE/VCO$_2$ slope in these patients might be attributed partly to their impaired lung function.

We determined the work rate of constant work-rate exercise by calculating the difference between the work rate at peak exercise and the anaerobic threshold and then increasing the work rate at the anaerobic threshold by 40% of that difference. Such constant work-rate exercise tests for a 6 min period have been used when we evaluate cardiopulmonary kinetics during the onset of exercise [14, 15]. To select work intensity high enough to exceed the anaerobic threshold, the additional amount of work rate above the anaerobic threshold has usually been set at 40% or 50% of the difference between the work rate at the anaerobic threshold and the peak work rate [14, 15], as used in the present study. The work rate of constant work-rate exercise of the present study (69 ± 15 W) was corresponded to 68% of the peak work rate obtained from the incremental exercise test. All subjects of the present study could perform this constant work-rate exercise test for 6 min without difficulty. Thus to obtain the VE/VCO$_2$ slope, we recommend 4 min constant work-rate exercise at 60 to 70 W in patients with mild heart failure. In patients with more advanced heart failure, the constant exercise at a lower work rate would be appropriate.

In the present study, the VE/VCO$_2$ slope obtained from the constant work-rate exercise was a little lower than the slope obtained from the incremental exercise test, although statistically not significant. If the work rate of constant work-rate exercise is too low, the difference of the VE/VCO$_2$ slopes between a constant work-rate exercise test and an incremental exercise test might become greater because of a relatively higher noise-to-signal ratio of respiratory gas data in the lower intensity constant work-rate exercise. The VE/VCO$_2$ slope in the incremental exercise test was calculated based on the respiratory parameters obtained as a function of exercise intensity. On the other hand, the slope in the constant work-rate exercise test was calculated from those obtained as a function of time. Because of the methodological difference in determining the slopes, we cannot completely exclude the possibility that the physiological mechanism on respiratory responses during exercise might be different between two tests.

In the field of clinical cardiology, the largest population recruited in the exercise testing would be patients with coronary artery disease. Among these, we selected only patients with previous anterior myocardial infarction to obtain relatively homogeneous subjects with left ventricular dysfunction. The slight difference between the two slopes might occur depending on the exercise capacity or on the severity of cardiac disease of the subjects.

We calculated the VE/VCO$_2$ slope of the constant work-rate exercise using the data points from the start of exercise to its 4 min mark because of the accumulation of similar values on the plots of VE vs. VCO$_2$ after this period. VCO$_2$ actually reached the steady-state value by the 4 min mark in 14 out of 23 patients. VE also reached steady state by the 4 min mark in 9 patients. Even though the VE/VCO$_2$ slope during constant work-rate exercise was determined using the data points from the start of exercise to its 3 min mark, rather than the 4 min mark, we could obtain similar VE/VCO$_2$ slopes. However, the correlation between the 2 slopes was slightly weaker: $r = 0.79$ for the relation between the slope obtained from the first 3 min of constant work-rate exercise and the slope obtained from the incremental exercise. Also, the slope obtained from the first 3 min of constant work-rate exercise was slightly but significantly lower than the slope obtained from the incremental exercise. Thus we feel that 3 min may not be enough to calculate the VE/VCO$_2$ slope from the constant work-rate exercise.

The VE/VCO$_2$ slope, a clinically useful parameter obtained from cardiopulmonary exercise testing, can be determined from constant work-rate exercise even when performed at a moderate intensity. This reflects the consistent relationship between ventilation and CO$_2$ output, independent of the mode of exercise testing.

REFERENCES

1. Wasserman K. New concepts in assessing cardiovascular function. Circulation. 1988;78:1060-71.
2. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83:778-86.
3. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJ. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol. 1997;29:1585-90.

4. Koike A, Itoh H, Kato M, Sawada H, Aizawa T, Fu LT, Watanabe H. Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. Chest. 2002;121:1581-8.

5. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 33-4.

6. Koike A, Yajima T, Kano H, Koyama Y, Marumo F, Hiroe M. Relation between oxygen uptake and carbon dioxide output during constant work-rate exercise in patients with mild congestive heart failure. Am J Cardiol. 1996;77:602-5.

7. Koike A, Hiroe M, Adachi H, Yajima T, Yamauchi Y, Nagami A, Ito H, Miyahara Y, Korenaga M, Marumo F. Oxygen uptake kinetics are determined by cardiac function at onset of exercise rather than peak exercise in patients with prior myocardial infarction. Circulation. 1994;90:3224-32.

8. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986;60:2020-7.

9. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Chest. 1988;94:931-8.

10. Metra M, Dei Cas L, Panina G, Visioli O. Exercise hyperventilation chronic congestive heart failure, and its relation to functional capacity and hemodynamics. Am J Cardiol. 1992;70:622-8.

11. Koike A, Hiroe M, Taniguchi K, Marumo F. Respiratory control during exercise in patients with cardiovascular disease. Am Rev Respir Dis. 1993;147:425-9.

12. Buller NP, Poole-Wilson PA. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. Br Heart J. 1990;63:281-3.

13. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, Agostoni PG. Lung function and exercise gas exchange in chronic heart failure. Circulation. 1997;96:2221-7.

14. Koike A, Wasserman K, McKenzie DK, Zanconato S, Weiler-Ravell D. Evidence that diffusion limitation determines oxygen uptake kinetics during exercise in humans. J Clin Invest. 1990;86:1698-706.

15. Koike A, Wasserman K, Taniguchi K, Hiroe M, Marumo F. Critical capillary oxygen partial pressure and lactate threshold in patients with cardiovascular disease. J Am Coll Cardiol. 1994;23:1644-50.