

ROBUSTNESS OF THE OXYGEN UPTAKE EFFICIENCY SLOPE TO EXERCISE INTENSITY IN PATIENTS WITH CORONARY ARTERY DISEASE

REIZO BABA^{1,2}, KAZUO TSUYUKI², HIROYOSHI YANO²,
KENJI NINOMIYA² and KUNIO EBINE³

¹*Department of Perinatal and Neonatal Medical Center,
Aichi Medical University School of Medicine, Nagakute, Japan*
²*Department of Cardiology and Department of Cardiovascular Surgery,
Odawara Cardiovascular Hospital, Odawara, Japan*
³*Department of Cardiovascular Surgery, Toho University School of Medicine,
Meguro-ku Tokyo, Japan*

ABSTRACT

Oxygen uptake efficiency slope (OUES) and ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ slope) are widely used as submaximal measurements of cardiopulmonary exercise testing as the evaluator or prognosticator of cardiac diseases. However, very few studies have compared the effects of submaximal exercise on these measurements. A total of 58 patients with coronary artery disease underwent maximal cardiopulmonary exercise testing on a treadmill. We compared the values obtained from the first 75% ($\dot{V}E/\dot{V}CO_2$ slope₇₅ and OUES₇₅) and 90% ($\dot{V}E/\dot{V}CO_2$ slope₉₀ and OUES₉₀) of the exercise period with the entire duration ($\dot{V}E/\dot{V}CO_2$ slope₁₀₀ and OUES₁₀₀). Although OUES₁₀₀, OUES₉₀ and OUES₇₅ were virtually identical, submaximal calculations of $\dot{V}E/\dot{V}CO_2$ slope underestimated the measurements. The Bland-Altman method revealed that submaximal measurements of OUES agreed very well with maximal OUES (limits of agreement -5.0% to +6.0% for OUES₉₀, and -11.5% to +12.9% for OUES₇₅). However, the submaximal calculations of $\dot{V}E/\dot{V}CO_2$ slope showed rather poor agreement with the maximal calculations (limit of agreement -11.8% to +3.1% for $\dot{V}E/\dot{V}CO_2$ slope₉₀, and -20.8% to +5.3% for $\dot{V}E/\dot{V}CO_2$ slope₇₅). These results revealed that both the OUES and the $\dot{V}E/\dot{V}CO_2$ slopes are not overly influenced by exercise.

Key Words: Oxygen uptake efficiency slope, Submaximal exercise, Bland-Altman method, Ventilatory efficiency

INTRODUCTION

Maximal oxygen uptake ($\dot{V}O_{2max}$) is considered to be the most reliable index of the cardiorespiratory functional reserve of a patient with chronic heart failure since it is an indirect estimate of maximal cardiac output and is accepted as a determinant of survival in patients with chronic heart failure.¹⁾ This index is defined as the point at which oxygen uptake ($\dot{V}O_2$) reaches a plateau despite further increases in the work rate. However, a true plateau in $\dot{V}O_2$ is rarely observed in standard incremental exercise testing.²⁾ Peak $\dot{V}O_2$, measured at the end of a test, is widely used as a substitute and is presently considered the diagnostic/prognostic gold standard

Corresponding Author: Reizo Baba

Department of Perinatal and Neonatal Medical Center, Aichi Medical University,
21 Karimata-Yazako, Nagakute-town, Aichi 480-1195, Japan

Phone: +81-561-62-3311, Fax: +81-561-61-1864, E-mail: babar@aichi-med-u.ac.jp

in patients with heart failure.^{3,4)} However, the end point of an exercise test is greatly influenced by motivation on the part of the patients and the testing personnel.⁵⁾

To address this problem, submaximal exercise parameters claiming to be independent of subject motivation have been investigated. The most frequently used method involves the relationship between minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope), which has been shown to be an excellent prognosticator.⁵⁻⁹⁾ As the $\dot{V}E/\dot{V}CO_2$ relationship is generally considered to be linear, it is theoretically independent of exercise intensity attained in incremental exercise testing. Recently, the oxygen uptake efficiency slope has also been used as a measure of the cardiorespiratory functional reserve.¹⁰⁻¹⁹⁾ The oxygen uptake efficiency slope (OUES) is also shown to be a prognostic tool for patients with heart failure.^{14,16)} Since the OUES is derived from the slope of the relationship between $\dot{V}O_2$ and minute ventilation ($\dot{V}E$) during incremental exercise, theoretically, this index as well is not influenced by exercise intensity. Recently, Davies *et al.* reported that the OUES is a good prognostic indicator which remains so also if only a portion (as low as 50%) of the exercise is evaluated.¹⁶⁾

However, there have been few studies that compared the effects of submaximal exercise on these measurements. Therefore, the present study was intended to elucidate the effects of submaximal exercise on the measurements of cardiopulmonary exercise testing, especially focusing on the OUES and $\dot{V}E/\dot{V}CO_2$ slopes.

SUBJECTS AND METHODS

Study subjects

A total of 83 angiographically diagnosed patients with stable coronary arterial disease were referred to our exercise laboratory during the period between January 1, 2005 and December 31, 2005. Patients with myocardial infarction within 4 weeks or who had pulmonary rales at the time of exercise testing were excluded from the study. Those who had not reached maximum exercise during cardiopulmonary exercise testing (a respiratory exchange ratio (RER) of <1.0), regardless of the reasons for termination, were also excluded. Eventually, 58 patients were enrolled in the present study (Table 1), among whom 14 showed stable New York Heart Association (NYHA)

Table 1 Characteristics of subjects

Patient characteristics (N=58)	
Sex (M/F)	52/6
Age (years)	60±9
BMI (kg/m ²)	23.7±2.6
Diagnosis (n)	
Angina pectoris	17
Myocardial infarction	41
Treatment (n)	
Stent	26
POBA	13
CABG	2
Medical only	17

Abbreviations: BMI = body mass index (kg/m²); POBA = plain old balloon angioplasty; CABG = coronary artery bypass grafting

functional class I to III chronic heart failure. All were on medications that included digoxin, diuretics, β -blockers, angiotensin receptor blockers, or angiotensin converting enzyme inhibitors, which were not discontinued prior to exercise testing. The procedure and its potential risks were explained, and written informed consent was obtained from each subject before the study. The investigation was approved by the Local Ethics Committee and therefore conformed with the principles outlined in the Declaration of Helsinki.

Exercise testing

Exercise tests were performed using a Marquette Case 12 computerized treadmill system (Marquette Electronics, Milwaukee, WI) according to a symptom-limited original or modified Bruce protocol. The 12-lead electrocardiograms and heart rates were monitored throughout the test. Cuff blood pressure was measured every min with a manual manometer. Subjects were encouraged to continue the exercise until they experienced exhaustion. A supervising physician stood ready to stop the exercise testing based on the following criteria: (1) development of significant symptoms, such as chest pain or dizziness; (2) marked systolic hypotension or hypertension; (3) development of dangerous or potentially dangerous arrhythmias; or (4) ST-segment deviation (horizontal or downsloping depression > 80 ms from the J point) or elevation in non-Q wave leads of >0.1 mV.

Analysis of expired gas

Carbon dioxide production ($\dot{V}CO_2$, [ml/min, STPD]), oxygen uptake ($\dot{V}O_2$ [ml/min, STPD]), minute ventilation ($\dot{V}E$ [l/min, BTPS]), tidal volume (l, BTPS), respiratory rate (breaths per minute), and the mixed expiratory carbon dioxide concentration (%) were continuously measured on a breath-by-breath basis with the CPX Metabolic Measurement Cart (Medical Graphics Corporation, Minneapolis, MN) equipped with an oxygen and carbon dioxide analyzer. The flow, oxygen and carbon dioxide sensors were calibrated before each test. Data were averaged every 15 sec. The maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$) was calculated for each subject who had reached his or her maximum, by averaging the values obtained during the final 60 sec of exercise. We tentatively considered that an exercise test had reached its maximum when a respiratory exchange ratio (RER) of >1.0 had been attained, regardless of the reasons for termination.

The $\dot{V}E/\dot{V}CO_2$ slope was obtained by linear regression analyses of the relation between $\dot{V}E$ and $\dot{V}CO_2$ during the exercise test. The following equation was used to determine the relation between $\dot{V}O_2$ (ml/min/kg) and $\dot{V}E$ (l/min/kg) during an incremental exercise test:

$$\dot{V}O_2 = a \times \log \dot{V}E + b$$

where the constant a was defined as the OUES.¹⁰⁾ Theoretically, both the OUES and the $\dot{V}E/\dot{V}CO_2$ slope are not affected by exercise intensity. To be certain, we calculated these measurements for each patient who had reached maximal exercise using the values obtained during the first 75% ($\dot{V}E/\dot{V}CO_2$ slope₇₅ and OUES₇₅) and 90% ($\dot{V}E/\dot{V}CO_2$ slope₉₀ and OUES₉₀) of the exercise period, as well as for its entire duration ($\dot{V}E/\dot{V}CO_2$ slope₁₀₀ and OUES₁₀₀).

Statistical analysis

Data were analyzed using a commercially available statistical software program (SPSS 11.0, SPSS Inc., Chicago, Illinois (USA)). Results were expressed as the mean value \pm SD. Differences in the mean values were analyzed by the analysis of variance (ANOVA). The correlations between $\dot{V}O_{2max}$ and the OUES, and between $\dot{V}O_{2max}$ and the $\dot{V}E/\dot{V}CO_2$ slope were assessed by linear regression analysis. Agreements between the measurements obtained from the different levels of exercise intensity were assessed by the Bland-Altman methods.²⁰⁾ Correlations between $\dot{V}O_{2max}$

and the OUES, and $\dot{V}O_{2\max}$ and the $\dot{V}E/\dot{V}CO_2$ slope were analyzed by regression analysis. A level of $p < 0.05$ was considered statistically significant.

RESULTS

The effects of shortened exercise on the measurements of exercise testing are listed on Table 2. Although $\dot{V}O_2$, heart rate, respiratory exchange ratio, and the $\dot{V}E/\dot{V}CO_2$ slope were significantly affected by shortened exercise, whereas the values of OUES both corrected and uncorrected by body mass were not (Table 2). The Bland-Altman method revealed that although agreements of

Table 2 Effects of shortened exercise duration on measurements of cardiopulmonary exercise testing

Exercise duration	100%	90%	75%	<i>p</i> value
$\dot{V}O_2$ (ml/ min)	1695 ± 491	1508 ± 446	1337 ± 385	<0.0001
$\dot{V}O_2$ (ml/kg/min)	27.4 ± 8.0	24.4 ± 7.2	21.6 ± 6.2	<0.0001
Heart rate (beats/min)	159 ± 19	140 ± 15	124 ± 26	<0.0001
RER	1.15 ± 0.11	1.07 ± 0.09	1.01 ± 0.08	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope	31.2 ± 4.3	29.8 ± 4.1	28.8 ± 4.1	0.01
OUES	2147 ± 499	2158 ± 508	2162 ± 491	0.98
OUES/kg	34.8 ± 7.2	35.0 ± 7.2	35.1 ± 7.1	0.98

Data are expressed as mean ± SD. Abbreviations: $\dot{V}O_2$ = oxygen uptake; RER = respiratory exchange ratio; $\dot{V}E/\dot{V}CO_2$ slope = regression slope between minute ventilation and carbon dioxide production; OUES = oxygen uptake efficiency slope

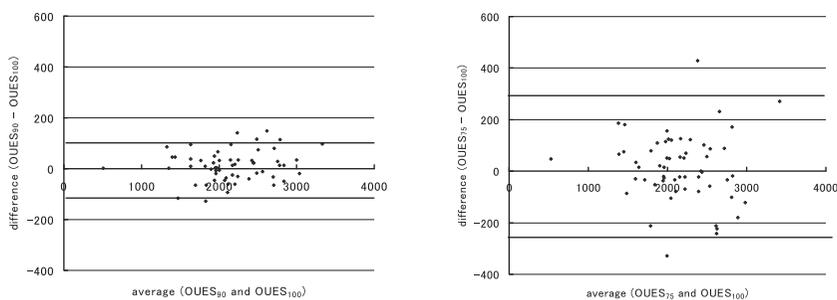


Fig. 1

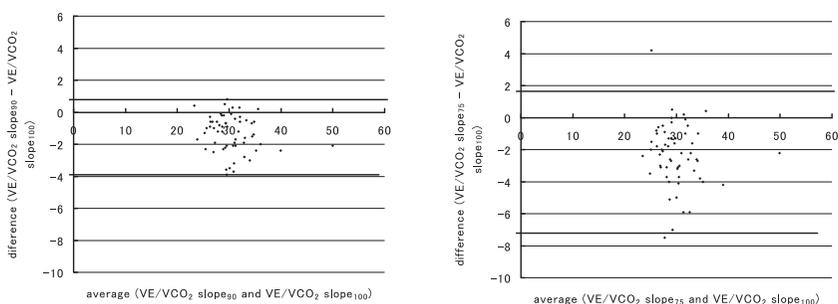


Fig. 2

ROBUSTNESS OF OUES TO EXERCISE

Table 3 Results of regression analyses between $\dot{V}O_2\text{max}$ and OUES, and $\dot{V}O_2\text{max}$ and $\dot{V}E/\dot{V}CO_2$ slope calculated by data of maximal and foreshortened exercise durations

	OUES			OUES/kg			$\dot{V}E/\dot{V}CO_2$ slope		
	100%	90%	75%	100%	90%	75%	100%	90%	75%
Exercise duration	100%	90%	75%	100%	90%	75%	100%	90%	75%
<i>p</i> value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001
Correlation coefficient	0.85	0.85	0.82	0.8	0.79	0.75	0.39	0.49	0.52
SEE	261	265	287	4.2	4.2	4.6	6.3	6.0	5.9

Regression analyses were conducted between $\dot{V}O_2\text{max}$ (uncorrected by body mass) and OUES (uncorrected by body mass), $\dot{V}O_2\text{max}/\text{kg}$ and OUES/kg, and $\dot{V}O_2\text{max}/\text{kg}$ and the $\dot{V}E/\dot{V}CO_2$ slope. Abbreviations: SEE = standard error of estimation, OUES = oxygen uptake efficiency slope; $\dot{V}E/\dot{V}CO_2$ slope = the regression slope between minute ventilation and carbon dioxide production; $\dot{V}O_2\text{max}$ = maximal oxygen uptake

the values of OUES calculated from the exercise data of different exercise durations were excellent, those of the $\dot{V}E/\dot{V}CO_2$ slope were poor (Fig. 1 and Fig. 2). Correlations between $\dot{V}O_2\text{max}$ and the OUES, and $\dot{V}O_2\text{max}$ and the $\dot{V}E/\dot{V}CO_2$ slope were listed in Table 3.

DISCUSSION

The present study focused on the effects of foreshortened exercise duration on the measurements of the OUES in comparison with the $\dot{V}E/\dot{V}CO_2$ slope. Results showed the robustness of the OUES to exercise intensity. On the other hand, submaximal exercise led to a slight underestimation in measurements of the $\dot{V}E/\dot{V}CO_2$ slope. These data added to our body of knowledge regarding the usefulness of the OUES as the most reliable submaximal method for evaluating exercise tolerance in patients with coronary heart disease.

Analysis of variance of repeated measurements revealed that the OUES₉₀ and OUES₇₅ did not differ significantly from OUES₁₀₀ (Table 2). OUES₉₀ and OUES₇₅ overestimated the OUES (uncorrected by body mass) only by 0.51% and 0.69%, respectively (Table 3). Also, the upper and lower limits of agreement between OUES₁₀₀ were kept within very narrow ranges in these submaximal measurements of OUES (Fig. 1). These data are compatible with previous studies that the OUES is not largely affected by exercise intensity.^{10,13,16,18} Moreover, the OUES was free from interobserver variability with excellent test-retest agreement,²² and was shown to be independent of treadmill exercise protocols.¹¹ In addition, OUES showed strong correlations with $\dot{V}O_2\text{max}$, even when calculated by submaximal exercise data (Table 3).

On the other hand, we observed a significant influence of foreshortened exercise durations on the calculated values for the $\dot{V}E/\dot{V}CO_2$ slope. Our data showed that both $\dot{V}E/\dot{V}CO_2$ slope₉₀ and $\dot{V}E/\dot{V}CO_2$ slope₇₅ underestimated the measurements by 4.3% and 7.8%, respectively. These results can probably be attributed to the acidosis-induced hyperventilation at the end stages of exercise testing. Interestingly, correlation coefficients between $\dot{V}O_2\text{max}$ and the $\dot{V}E/\dot{V}CO_2$ slope were greater when the exercise data of shorter exercise durations were used (Table 4). This finding seems somewhat puzzling when we consider that $\dot{V}O_2\text{max}$ is the gold standard. Our present data also appear to be compatible with the report by Arena et al. that showed an excellent intraclass correlation coefficient (0.94) among $\dot{V}E/\dot{V}CO_2$ slopes calculated from different levels of exercise intensity.²³ However, the ICC has a fatal limitation, i.e., it cannot detect systematic errors as found in the present study confirming that submaximal calculations of the $\dot{V}E/\dot{V}CO_2$ slope showed systematic underestimations. In such cases, the Bland-Altman method would be a better one for the analysis of agreement.²⁰ At least, we believe that care must be taken in the

interpretation of the measurements of the $\dot{V}E/\dot{V}CO_2$ slope to determine whether it is obtained from maximal or submaximal exercise data.

In conclusion, the present study has revealed that the OUES is equally or slightly superior to the $\dot{V}E/\dot{V}CO_2$ slope in that it is robust in exercising intensity. These results may add to the growing body of data indicating that the oxygen uptake efficiency slope is a useful submaximal tool for evaluating exercise tolerance.

REFERENCES

- 1) Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. exercise standards: a statement for health-care professionals from the American Heart Association. *Circulation*, 1995; 91: 580–615.
- 2) Myers J, Walsh D, Buchanan N, Froelicher VF. Can maximal cardiopulmonary capacity be recognized by a plateau in oxygen uptake? *Chest*, 1989; 96: 1312–1316.
- 3) 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: 778–786.
- 4) Pardaens K, Van Cleemput J, Vanhaecke J, Fagard RH. Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. *Circulation*, 2000; 101: 1152–1157.
- 5) 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: 1585–1590.
- 6) Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, Sperfeld A, Glaser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation*, 2000; 101: 2803–2809.
- 7) Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, Coats AJ. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$. *Eur Heart J*, 2000; 21: 154–161.
- 8) Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, Florea V, Banasiak W, Poole-Wilson PA, Coats AJ, Anker SD. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation*, 2001; 103: 967–972.
- 9) Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M. Development of a ventilatory classification system in patients with heart failure. *Circulation*, 2007; 115: 2410–2417.
- 10) Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, Nishibata K. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol*, 1996; 28: 1567–1572.
- 11) Baba R, Nagashima M, Nagano Y, Ikoma M, Nishibata K. Role of the oxygen uptake efficiency slope in evaluating exercise tolerance. *Arch Dis Child*, 1999; 81: 73–75.
- 12) Baba R, Tsuyuki K, Kimura Y, Ninomiya K, Aihara M, Ebine K, Tauchi N, Nishibata K, Nagashima M. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol*, 1999; 80: 397–401.
- 13) Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol*, 2000; 36: 194–201.
- 14) Thomas McRae AT, Young JB, Aikotob ML, Pothier Snader CE, Blackstone EH, Lauer MS. The oxygen uptake efficiency slope as a predictor of mortality in chronic heart failure. *J Am Coll Cardiol*, 2002; 39: 183A.
- 15) Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope: a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J*, 2005; 149: 175–180.
- 16) Davies LC, Wensel R, Georgiadou P, Ciccoira M, Coats AJ, Piepoli MF, Francis DP. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J*, 2006; 27: 684–690.
- 17) Van Laethem C, Van de Veire N, De Sutter J, Bartunek J, De Backer G, Goethals M, Vanderheyden M. Prospective evaluation of the oxygen uptake efficiency slope as a submaximal predictor of peak oxygen uptake in aged patients with ischemic heart disease. *Am Heart J*, 2006; 152: 297.e9–15.
- 18) Van de Veire NR, Van Laethem C, Philippe J, De Winter O, De Backer G, Vanderheyden M, De Sutter J.

ROBUSTNESS OF OUES TO EXERCISE

- VE/VCO₂ slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVO₂. *Eur J Cardiovasc Prev Rehabil*, 2006; 13: 916–923.
- 19) Van Laethem C, Van De Veire N, De Backer G, Bihija S, Seghers T, Cambier D, Vanderheyden M, De Sutter J. Response of the oxygen uptake efficiency slope to exercise training in patients with chronic heart failure. *Eur J Heart Fail*, 2007; 9: 625–629.
 - 20) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1986; 1: 307–310.
 - 21) Tsuyuki K, Kimura Y, Chiashi K, Matsushita C, Ninomiya K, Choh K, Hase H, Dohi S. Oxygen uptake efficiency slope as a monitoring tool for physical training in chronic hemodialysis patients. *Ther Apher Dial*, 2003; 7: 461–467.
 - 22) Baba R, Kubo N, Morotome Y, Iwagaki S. Reproducibility of the oxygen uptake efficiency slope in normal healthy subjects. *J Sports Med Phys Fitness*, 1999; 39: 202–206.
 - 23) Arena R, Humphrey R, Peberdy MA. Prognostic ability of VE/VCO₂ slope calculations using different exercise test time intervals in subjects with heart failure. *Eur J Cardiovasc Prev Rehabil*, 2003; 10: 463–468.

