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

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ABSTRACT

Oxygen uptake efficiency slope (OUES) and ventilatory efficiency (VE/VO2 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% (VE/VO2 slope75 and OUES75) and 90% (VE/VO2 slope90 and OUES90) of the exercise period with the entire duration (VE/VO2 slope100 and OUES100). Although OUES100, OUES90 and OUES75 were virtually identical, submaximal calculations of VE/VO2 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 VE/VO2 slope showed rather poor agreement with the maximal calculations (limit of agreement –11.8% to +3.1% for VE/VO2 slope90, and –20.8% to +5.3% for VE/VO2 slope75). These results revealed that both the OUES and the VE/VO2 slopes are not overly influenced by exercise.

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

INTRODUCTION

Maximal oxygen uptake (VO2max) 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.1,2 This index is defined as the point at which oxygen uptake (VO2) reaches a plateau despite further increases in the work rate. However, a true plateau in VO2 is rarely observed in standard incremental exercise testing.2,3 Peak VO2, measured at the end of a test, is widely used as a substitute and is presently considered the diagnostic/prognostic gold standard.

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in patients with heart failure.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10-19} The oxygen uptake efficiency slope (OUES) is also shown to be a prognostic tool for patients with heart failure.\textsuperscript{14,16} Since the OUES is derived from the slope of the relationship between VO\textsubscript{2} and minute ventilation (VE) 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.\textsuperscript{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)
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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 (VCO₂, [ml/min, STPD]), oxygen uptake (VO₂ [ml/min, STPD]), minute ventilation (VE [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 VO₂ (VO₂max) 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 VE/VCO₂ slope was obtained by linear regression analyses of the relation between VE and VCO₂ during the exercise test. The following equation was used to determine the relation between VO₂ (ml/min/kg) and VE (l/min/kg) during an incremental exercise test:

\[ \text{VO}_2 = a \times \log \text{VE} + b \]

where the constant \( a \) was defined as the OUES.\(^{10} \) Theoretically, both the OUES and the VE/VCO₂ 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% (VE/VCO₂ slope\(_{75}\) and OUES\(_{75}\)) and 90% (VE/VCO₂ slope\(_{90}\) and OUES\(_{90}\)) of the exercise period, as well as for its entire duration (VE/VCO₂ slope\(_{100}\) and OUES\(_{100}\)).

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 ± SD. Differences in the mean values were analyzed by the analysis of variance (ANOVA). The correlations between VO₂max and the OUES, and between VO₂max and the VE/VCO₂ 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 VO₂max...
and the OUES, and VO\textsubscript{max} and the VE/V\textsubscript{CO}\textsubscript{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 in Table 2. Although VO\textsubscript{2}, heart rate, respiratory exchange ratio, and the VE/V\textsubscript{CO}\textsubscript{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>
<thead>
<tr>
<th>Exercise duration</th>
<th>100%</th>
<th>90%</th>
<th>75%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2} (ml/min)</td>
<td>1695 ± 491</td>
<td>1508 ± 446</td>
<td>1337 ± 385</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VO\textsubscript{2} (ml/kg/min)</td>
<td>27.4 ± 8.0</td>
<td>24.4 ± 7.2</td>
<td>21.6 ± 6.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>159 ± 19</td>
<td>140 ± 15</td>
<td>124 ± 26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RER</td>
<td>1.15 ± 0.11</td>
<td>1.07 ± 0.09</td>
<td>1.01 ± 0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VE/V\textsubscript{CO}\textsubscript{2} slope</td>
<td>31.2 ± 4.3</td>
<td>29.8 ± 4.1</td>
<td>28.8 ± 4.1</td>
<td>0.01</td>
</tr>
<tr>
<td>OUES</td>
<td>2147 ± 499</td>
<td>2158 ± 508</td>
<td>2162 ± 491</td>
<td>0.98</td>
</tr>
<tr>
<td>OUES/kg</td>
<td>34.8 ± 7.2</td>
<td>35.0 ± 7.2</td>
<td>35.1 ± 7.1</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. Abbreviations: VO\textsubscript{2} = oxygen uptake; RER = respiratory exchange ratio; VE/V\textsubscript{CO}\textsubscript{2} slope = regression slope between minute ventilation and carbon dioxide production; OUES = oxygen uptake efficiency slope

![Fig. 1](image1)
![Fig. 2](image2)
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Table 3  Results of regression analyses between VO₂max and OUES, and VO₂max and VE/VCO₂ slope calculated by data of maximal and foreshortened exercise durations

<table>
<thead>
<tr>
<th>Exercise duration</th>
<th>OUES</th>
<th>OUES/kg</th>
<th>VE/VCO₂ slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.85</td>
<td>0.85</td>
<td>0.82</td>
</tr>
<tr>
<td>SEE</td>
<td>261</td>
<td>265</td>
<td>287</td>
</tr>
</tbody>
</table>

Regression analyses were conducted between VO₂max (uncorrected by body mass) and OUES (uncorrected by body mass), VO₂max/kg and OUES/kg, and VO₂max/kg and the VE/VCO₂ slope. Abbreviations: SEE = standard error of estimation, OUES = oxygen uptake efficiency slope; VE/VCO₂ slope = the regression slope between minute ventilation and carbon dioxide production; VO₂ max = maximal oxygen uptake

the values of OUES calculated from the exercise data of different exercise durations were excellent, those of the VE/VCO₂ slope were poor (Fig. 1 and Fig. 2). Correlations between VO₂max and the OUES, and VO₂max and the VE/VCO₂ 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 VE/VCO₂ 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 VE/VCO₂ 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. Moreover, the OUES was free from interobserver variability with excellent test-retest agreement and was shown to be independent of treadmill exercise protocols. In addition, OUES showed strong correlations with VO₂max, 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 VE/VCO₂ slope. Our data showed that both VE/VCO₂ slope₉₀ and VE/VCO₂ 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 VO₂max and the VE/VCO₂ slope were greater when the exercise data of shorter exercise durations were used (Table 4). This finding seems somewhat puzzling when we consider that VO₂max 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 VE/VCO₂ slopes calculated from different levels of exercise intensity. 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 VE/VCO₂ slope showed systematic underestimations. In such cases, the Bland-Altman method would be a better one for the analysis of agreement. 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


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