SHORT ORIGINAL ARTICLE

Prognostic value of a new cardiopulmonary exercise testing parameter in chronic heart failure: oxygen uptake efficiency at peak exercise — comparison with oxygen uptake efficiency slope

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KEYWORDS
Heart failure; Exercise testing; Prognosis

Abstract

Introduction: A growing body of evidence shows the prognostic value of oxygen uptake efficiency slope (OUES), a cardiopulmonary exercise test (CPET) parameter derived from the logarithmic relationship between $O_2$ consumption ($VO_2$) and minute ventilation (VE) in patients with chronic heart failure (CHF).

Objective: To evaluate the prognostic value of a new CPET parameter — peak oxygen uptake efficiency (POUE) — and to compare it with OUES in patients with CHF.

Methods: We prospectively studied 206 consecutive patients with stable CHF due to dilated cardiomyopathy — 153 male, aged 53.3±13.0 years, 35.4% of ischemic etiology, left ventricular ejection fraction 27.7±8.0%, 81.1% in sinus rhythm, 97.1% receiving ACE-Is or ARBs, 78.2% beta-blockers and 60.2% spironolactone — who performed a first maximal symptom-limited treadmill CPET, using the modified Bruce protocol. In 33% of patients an cardioverter-defibrillator (ICD) or cardiac resynchronization therapy device (CRT-D) was implanted during follow-up.

Peak VO2, percentage of predicted peak VO2, VE/VCO2 slope, OUES and POUE were analyzed. OUES was calculated using the formula: $VO_2$ (l/min) = OUES (log10VE) + b. POUE was calculated as $pVO_2$ (l/min) / log10peakVE (l/min). Correlation coefficients between the studied parameters were obtained. The prognosis of each variable adjusted for age was evaluated through Cox proportional hazard models and R2 percent (R2%) and V index (V6) were used as measures of the predictive accuracy of events of each of these variables. Receiver operating characteristic (ROC) curves from logistic regression models were used to determine the cut-offs for OUES and POUE.

Results: $VO_2$: 20.5±5.9; percentage of predicted peak VO2: 68.6±18.2; VE/VCO2 slope: 30.6±8.3; OUES: 1.85±0.61; POUE: 0.88±0.27. During a mean follow-up of 33.1±14.8 months, 45 (21.8%) patients died, 10 (4.9%) underwent urgent heart transplantation and in three patients (1.5%) a left ventricular assist device was implanted. All variables proved to be independent predictors.
of this combined event; however, VE/VCO₂ slope was most strongly associated with events (HR 11.14). In this population, POUE was associated with a higher risk of events than OUES (HR 9.61 vs. 7.01), and was also a better predictor of events (R²: 28.91 vs. 22.37).

Conclusion: POUE was more strongly associated with death, urgent heart transplantation and implantation of a left ventricular assist device and proved to be a better predictor of events than OUES. These results suggest that this new parameter can increase the prognostic value of CPET in patients with CHF.

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Introduction

Several cardiopulmonary exercise testing (CPET)-derived parameters have an established role in prognostic stratification of patients with chronic heart failure (CHF). In recent years the number of these variables has continued to grow.

In 1996, Baba et al.¹ reported a new CPET-derived parameter, oxygen uptake efficiency slope (OUES), a marker of ventilatory efficiency that represents the relationship between minute ventilation and oxygen uptake during exercise. In that study, OUES showed a highly significant correlation with peak oxygen uptake (VO₂) in a group of patients, predominantly children, with CHF.
Although this first study and others\textsuperscript{2} emphasized the value of OUES as a submaximal, effort-independent and objective parameter to estimate cardiorespiratory functional reserve, more recently it has been claimed to have enhanced prognostic value in CHF patients\textsuperscript{3,4}. Myers et al.\textsuperscript{3}, when defining a CPET score for predicting outcomes in this context, considered OUES to be a stronger predictor of risk than peak VO\textsubscript{2}.

The aim of the present study was to evaluate the prognostic value, in CHF patients, of another new CPET parameter of ventilatory efficiency proposed by our group — peak oxygen uptake efficiency (POUE). We set out to compare this easily obtained parameter with OUES, as well as with the prognostic value of other CPET-derived variables.

**Methods**

This study was a single-center analysis that included patients with CHF due to left ventricular systolic dysfunction (LVSD) referred to our laboratory for a first CPET evaluation. Only patients with left ventricular ejection fraction <40% and free of exercise-limiting comorbidities such as cerebrovascular disease, musculoskeletal impairment, or peripheral vascular disease were included. Also, only patients with no significant respiratory disease, excluded by clinical history, physical examination and chest X-ray, were considered for the study. Patients gave informed consent for participation.

We prospectively studied 206 patients with CHF due to LVSD, 35.4% of ischemic etiology. There were 153 men (74.3%), mean age was 53.3±13.0 years (range 21 to 80), body mass index 26.4±4.2 kg/m\textsuperscript{2} (17.1 to 38.1), 81.1% in sinus rhythm, echocardiographic left ventricular end-diastolic dimension 39.6±5.7 mm/m\textsuperscript{2} (32 to 69) and ejection fraction 27.7±8.0% (10 to 39). According to the referring physician, 78.2% of the patients were in New York Heart Association class II. Ninety-seven percent were medicated with an angiotensin-converting enzyme inhibitor or/and an angiotensin receptor blocker, 89.0% with a diuretic, 78.2% with a beta-blocker and 60.2% with spironolactone. Thirty-three percent presented or were treated during follow-up with a beta-blocker and 60.2% with spironolactone. Thirty-three

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study population</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>53.3±13.0</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>153 (74.3%)</td>
</tr>
<tr>
<td>Body mass index (kg/m\textsuperscript{2})</td>
<td>26.4±4.2</td>
</tr>
<tr>
<td>Ischemic etiology of LVSD, n (%)</td>
<td>74 (35.4%)</td>
</tr>
<tr>
<td>NYHA functional class II, n (%)</td>
<td>161 (78.2%)</td>
</tr>
<tr>
<td>Sinus rhythm, n (%)</td>
<td>167 (81.1%)</td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm/m\textsuperscript{2})</td>
<td>39.6±5.7</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>27.7±8.0</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.7±1.6</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>2297±2349</td>
</tr>
<tr>
<td>Prescribed ACE-I and/or ARB, n (%)</td>
<td>200 (97.1%)</td>
</tr>
<tr>
<td>Prescribed diuretic, n (%)</td>
<td>183 (89.0%)</td>
</tr>
<tr>
<td>Prescribed beta-blocker, n (%)</td>
<td>161 (78.2%)</td>
</tr>
<tr>
<td>Prescribed spironolactone, n (%)</td>
<td>124 (60.2%)</td>
</tr>
<tr>
<td>Treated with ICD or CRT-ICD, n (%)</td>
<td>68 (33.0%)</td>
</tr>
</tbody>
</table>

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator; LV: left ventricular; LVSD: left ventricular systolic dysfunction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.
Statistical analysis

Results are expressed as means ± one standard deviation. Correlations between variables were assessed by linear regression analysis. Correlation coefficients were compared using the Fisher r-to-z transformation. A p value of <0.05 was considered statistically significant.

The prognostic value of each variable was assessed through Cox proportional hazard models adjusted for age. R² percent (R²%) and V index (V6) were used as measures of the predictive accuracy of each of these variables. ROC (receiver operating characteristic) curves from logistic regression models were used to find cut-offs for OUES and POUE and to evaluate their specificity and sensitivity.

All tests were performed using the statistical program R Development Core Team. R: (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

The CPET results are presented in Table 2.

A significant and strong correlation was found between OUEP and OUES — r = 0.914, r² = 0.836, p < 0.001 (Figure 1). The correlations between OUES and OUEP with peak VO₂ expressed in l/min were, respectively, r = 0.876, r² = 0.768 (p < 0.001) and r = 0.983, r² = 0.966 (p < 0.001) (comparison between correlations: p < 0.001). For the same variables the correlations with peak VO₂ in ml/kg/min were, respectively, r = 0.744, r² = 0.554 (p < 0.001) and 0.834, r² = 0.696 (p < 0.001) (comparison between correlations: p = 0.0147).

Peak VO₂ also presented significant correlations with VE/VCO₂ slope, the highest being when it was expressed in ml/kg/min — r = 0.624, r² = 0.389 (p < 0.001), but this correlation was weaker than any obtained between peak VO₂ and OUES or OUEP (p < 0.025).

During follow-up, 45 patients (21.8%) died, 10 (4.9%) underwent urgent heart transplantation and in three patients (1.5%) a left ventricular assist device was implanted as a bridge for transplantation. All studied parameters were shown to be independent predictors of the combined event (Table 3, Figure 2).

Of all the studied parameters, VE/VCO₂ slope was the most closely associated with events, followed by percentage of predicted peak VO₂ and POUE (hazard ratio 11.14, 11.06 and 9.61 respectively). These three variables were also the best predictors of events (Table 3). In this population, POUE was more strongly associated with increased risk of death, urgent transplantation or left ventricular assist device implantation when compared directly with OUES (HR 9.61 vs. 7.01), and also proved to be a better predictor of events (R²% 28.91 vs. R²% 22.37 and V6 0.31 vs. V6 0.23). Figure 2 shows Kaplan-Meier curves for the studied parameters.

The ROC curve plotted for OUES showed an area under the curve (AUC) = 0.819. The AUC for POUE was similar (0.815) (Figure 3). For OUES a cut-off value of 1.60 had sensitivity of 76% and specificity of 76% for the occurrence of events.
For POUE a cut-off value of 0.73 showed sensitivity of 72% and specificity of 86% for events.

In a subset of 50 patients we evaluated OUEAT — mean=0.79±0.22 (0.32 to 1.47). OUEAT correlated both with OUES (r=0.901, r²=0.811, p<0.001) and with OUEP (r=0.959, r²=0.919, p<0.001), the latter correlation being stronger (p<0.001). OUEAT also showed a significant correlation with peak VO₂ (r=0.930, r²=0.966, p<0.001), and this correlation was also stronger than that between OUES and peak VO₂ (p=0.0025), although weaker than for OUEP (p<0.001).

**Discussion**

OUES is a non-linear measure of the ventilatory response to exercise derived from the single-segment logarithmic relation between oxygen uptake and minute ventilation.
It should be emphasized that the established role of OUES as a submaximal and objective parameter to estimate cardiorespiratory functional reserve was not called into question by our study, as only its value for the entire exercise duration was analyzed.

Ventilatory efficiency has been more widely evaluated by the relation between VE and VCO₂. Both the value obtained from the slope of the regression line relating VE to VCO₂ during exercise — the VE/VCO₂ slope — and their simple ratio at peak exercise showed prognostic value in patients with CHF due to LVSD. Arena et al. found that, although not identical, VE/VCO₂ slope and ratio at peak exercise provide similar prognostic information. Nevertheless, ventilatory efficiency has been typically expressed as the VE/VCO₂ slope, and several studies have reported it as being the strongest prognostic marker in patients with CHF when assessed at peak exercise. In our study we did not evaluate the VE/VCO₂ ratio at peak exercise. The VE/VCO₂ slope provided greater prognostic information than peak VO₂ and OUES, confirming the results of other authors.

We studied a young population with CHF. This may explain why most of the patients were referred for heart transplantation evaluation. It may also explain the stronger prognostic value of the percentage of predicted peak VO₂, achieved over the absolute value of peak VO₂. A study by Bard et al. evaluated a typical population referred for heart transplantation in the United States of America, with mean age 50.6±10.2 years, 72% men, 55% with LVSD of nonischemic etiology, left ventricular ejection fraction 21.5±7.7%, peak VO₂ 17.3±5.0 ml/kg/min, and percentage of predicted peak VO₂ achieved 58.7±18.2%. Comparison with our study population prompts the comment that in Portugal the most important factor leading to referral for heart transplantation is left ventricular ejection fraction, even more than the patient’s functional capacity.

Conclusions

According to our results, for prognostic assessment in patients with CHF due to LVSD, OUEP is superior to OUES and even to peak VO₂, and inferior to VE/VCO₂ slope. However, these are the results of a single-center study, and should be confirmed or refuted by others.

Conflicts of interest

The authors have no conflicts of interest to declare.

References
