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Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope

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KEYWORDS
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Aims Predicting survival from peak exercise oxygen uptake (peak VO_2) in chronic heart failure (CHF) is hindered by its reduction if exercise duration is submaximal. The oxygen uptake efficiency slope (OUES) is a non-linear description of the ventilatory response to exercise, which has the potential to describe abnormalities even early in exercise. We evaluated the physiology of OUES and assessed its potential for prognostic information in patients with CHF.
Methods and results Two hundred and forty-three patients with CHF (mean age 59 $\pm$ 12 years) underwent cardiopulmonary exercise testing between May 1992 and July 1996. Mean peak VO_2 was 16.2 $\pm$ 6.7 mL/kg/min, VE/VCO_2 slope 38 $\pm$ 12.5, ventilatory anaerobic threshold 10.9 $\pm$ 3.5 mL/kg/min, and OUES 1.6 $\pm$ 0.7 L/min. The value for each variable fell across the New York Heart Association classes ($P < 0.0001$ by analysis of variance for each). When only the first 50% of each exercise test was used to calculate the variables, the value obtained for OUES changed the least (peak VO_2 25% difference and OUES 1% difference). After a median of 9 years of follow-up, 139 patients (57%) had died. Each of the exercise variables was a significant univariate predictor of prognosis but in a multivariable model, only OUES was identified as the sole significant independent prognostic variable.
Conclusion OUES provides an effective, independent measure of pathological exercise physiology. Its numerical value is relatively insensitive to the duration of exercise data from which it is calculated. Its prognostic value seems to be stronger than the best available existing measures of exercise physiology.

Introduction

Chronic heart failure (CHF) is an increasingly common disorder, causing high mortality and morbidity, despite modern developments in medical therapy.[1] Assessing prognosis is particularly important because of the high cost and limited availability of definitive surgical intervention. Cardiopulmonary exercise testing with metabolic monitoring is the gold standard for the prognostic assessment of such patients.[2]

Landmark studies[3–7] have established peak oxygen uptake (VO_2) as the key measure of exercise physiology, and low peak VO_2 is widely recognized as a predictor of poor prognosis.[2] Recent work has observed that not only peak VO_2 but also the slope of the ventilatory response to exercise (VE/VCO_2 slope) can predict prognosis. Moreover, studies comparing the prognostic power of VE/VCO_2 slope with peak VO_2 have revealed a greater prognostic value of VE/VCO_2 slope.[8–12] Efforts to find better non-invasive predictors of prognosis in CHF have continued and at the same time, there has been interest in developing techniques to handle the problem of limited patient motivation which results in submaximal exercise.

Recently, a non-linear measure of the ventilatory response to exercise [the oxygen uptake efficiency slope (OUES)] has been described, initially in young patients (mean age 12 years) with cardiac disease.[13] It describes the relationship between VO_2 and VE during incremental exercise, via a logarithmic transformation of ventilation. OUES is defined as the regression slope 'a' in $VO_2 = a \log VE + b$. Validation of this measure has been carried out in normal elderly subjects and a small number of patients with CHF.[14] The characteristics of this measure in patients with CHF have not been previously evaluated and its prognostic usefulness over standard variables, such as peak VO_2 and VE/VCO_2 slope, is not known.

Measurement of peak VO_2 relies entirely on data from the last segment of exercise and is therefore potentially

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sensitive to many factors including motivation. The VE/VCO_2 slope has the advantage of being derived from the whole of exercise on a plot that is almost linear and so it may be less sensitive to exact exercise duration. OUES not only has the advantage of using the whole of the exercise data, but also its log transformation reduces curvature, which gives a further potential opportunity for a measure resistant to disruption by early termination of exercise.

In this study, we have assessed OUES in a large number of patients with CHF and examined its prognostic value when compared with standard cardiopulmonary exercise-derived variables.

Methods

Subjects

All raw exercise physiological data for two hundred and forty-three patients with CHF who underwent cardiopulmonary exercise testing at the Royal Brompton Hospital between March 1992 and July 1996 were reviewed. The diagnosis of CHF was based on a history of dyspnoea and exercise intolerance with signs of pulmonary or peripheral oedema and echocardiographic or radionucleide ventriculographic evidence of left ventricular systolic dysfunction. Patients with neuromuscular disease or recent clinical instability were not included. Survival was determined from the registry maintained by the Office of National Statistics and hospital records.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed on a motorized treadmill. A modified Bruce protocol[15] was used with an additional 'Stage 0' (3 min, speed 1 m.p.h., 5% gradient). Minute ventilation (VE), oxygen uptake (VO_2), and carbon dioxide production (VCO_2) were monitored continuously using a respiratory mass spectrometer and calibrated pneumotachograph (Amis 2000, Innovision, Odense, Denmark). Patients were encouraged to exercise to the limit of their symptoms by the supervising physician. There was continuous ECG monitoring and blood pressure was measured at each stage of exercise. Exercise data were stored on disk and analysed off-line by custom-designed software.

Peak VO_2 was defined as the highest 30 s average during the last 60 s of exercise. Respiratory exchange ratio (RER) equal to VCO_2/VO_2 was calculated at the same time point as peak VO_2. A value >1.0 was taken to represent adequate effort. The VE/VCO_2 slope, which relates the rate of increase in VE per unit increase in CO_2 production, was obtained by linear regression using the whole exercise period.[16] It has been previously shown[17] that the VE/VCO_2 slope calculated from the whole exercise period has greater prognostic value than if the portion prior to isocapnic buffering is used. VE/VO_2 slope was calculated in a similar way. Ventilatory anaerobic threshold (VAT) was calculated by the V-slope method.[18] OUES was defined as the gradient of the linear relationship of $\log_{10}$ VE to VO_2.[13] Predicted values for OUES were calculated from the equations published by Hollenberg and Tager.[14] In men, OUES (L/min) $= [1320 - (26.7 \times \text{age}) + (1394 \times \text{body surface area})]/1000$. In women, OUES (L/min) $= [1175 - (15.8 \times \text{age}) + (841 \times \text{body surface area})]/1000$.

In order to assess the potential effect of foreshortened exercise duration, we used an automated process to calculate peak VO_2 and OUES, not only with the full exercise duration but also with only the first 50% of exercise data.

Statistical analysis

Statistical calculations were performed using Statview 4.5 (Abacus Concepts, Berkeley, CA, USA). Numerical values are presented as mean $\pm$ standard deviation. Comparisons between group mean values were carried out by an overall analysis of variance. Comparison between obtained and predicted results was carried out using the paired *t*-test. Correlations between variables were assessed by the Pearson product-moment method. Several hypothesis tests are carried out in this study. As we had chosen to reject the null hypothesis in each case if $P < 0.05$, there is a likelihood of some spurious associations (type I errors) in the study as a whole. This should be taken into account when interpreting the *P*-values stated. The prognostic value of exercise parameters considered as continuous variables was determined using the Cox proportional hazards regression model. OUES and peak VO_2 required log transformation to provide variables that demonstrated proportional hazards.[19] Receiver operating characteristic (ROC) curves were calculated via MedCalc v5, using data censored to 83 months (the shortest duration of follow-up in the study), and used to select the cut-offs to dichotomize the data for Kaplan–Meier analysis. $P < 0.05$ was considered significant.

Results

Patient characteristics

The mean age of the 243 patients was 59 ± 12 years and 212 were male. Fifteen per cent of the patients were in New York Heart Association (NYHA) class I, 35% in class II, 38% in class III, and 12% in class IV. The aetiology of CHF was ischaemic heart disease in 58%. Radionucleide ventriculography ($n = 176$) showed an average left ventricular ejection fraction of $29 \pm 15\%$. At the time of exercise testing, 67% of patients were taking ACE-inhibitors, 55% diuretics, 33% digoxin, and 31% β-blockers.

Exercise data

All patients successfully performed exercise testing without any untoward events. VAT could only be calculated in 191 patients (79%). A total of 194 patients (80%) achieved a peak RER >1.0. The results of the exercise data are shown in *Table 1*. Patients in different NYHA classes had significantly different mean values of all the exercise-derived variables (*Figure 1*).

Comparison of actual OUES values with predicted values

Predicted values for OUES were calculated for each patient according to the equations of Hollenberg and Tager.[14] The values obtained from the patients were significantly lower than those predicted, as shown in *Table 2*.

Effect of foreshortened exercise on cardiopulmonary variables

Each exercise variable was found to be altered if only a foreshortened segment of exercise data was examined.

Table 1 Cardiopulmonary exercise test data

Variable	Mean value	SD
Exercise duration (min)	7.5	3.3
RER at peak exercise	1.1	0.2
Peal VO_2 (mL/kg/min)	16.2	6.7
VE/VCO_2 slope	38.0	12.5
VE/VO_2 slope	42.8	17.3
VAT (mL/kg/min)	10.9	3.5
OUES (L/min)	1.6	0.7

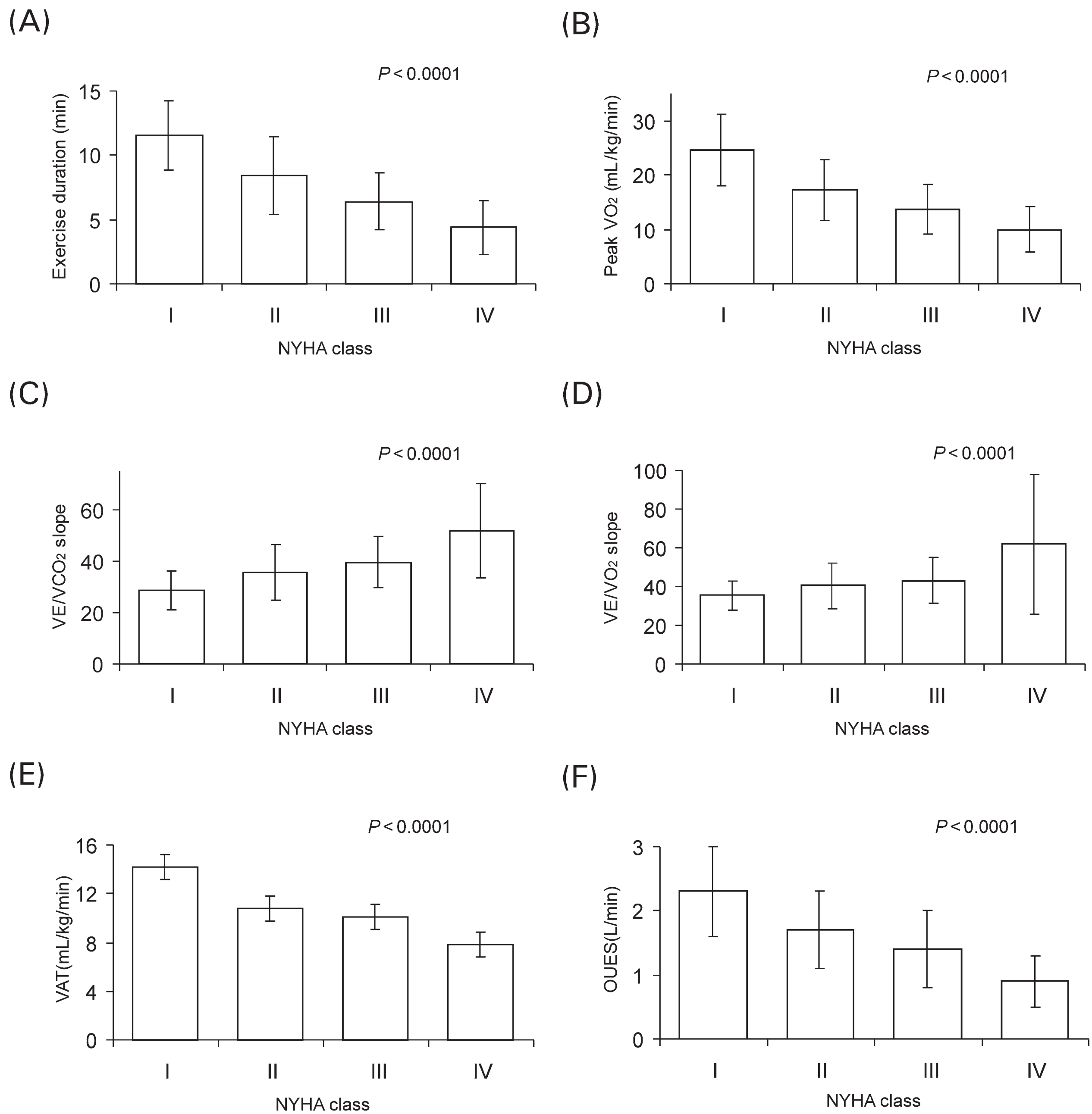

Figure 1 A graph showing mean values of (*A*) exercise duration, (*B*) peak VO_2, (*C*) VE/VCO_2 slope, (*D*) VE/VO_2 slope, (*E*) VAT, and (*F*) OUES split by NYHA class. Error bars represent 1 SD.

This effect was much smaller for OUES than for the other variables, although it was statistically significant for all variables. For example, when only half of the exercise duration was used, OUES was only 1% different from its value obtained with the full data. However, this difference was 25% for peak VO_2.

Interactions between exercise variables

OUES was strongly correlated with peak VO_2, and less so with VE/VCO_2 slope, VAT, VE/VO_2 slope, and VE (*Table 3*).

Prognostic value of OUES

At the end of the follow-up period in January 2005, 139 patients had died with a median time to death of 31 months [interquartile range (IQR) 11–58 months]. The median follow-up of survivors was 109 months (IQR 103–127 months). Causes of death were not classified.

On univariate analysis, the cardiopulmonary exercise test variables were significant predictors of mortality (*Table 4*). Of the variables derived from the oxygen uptake vs. ventilation relationship (log OUES, log peak VO_2, VE/VO_2 slope, VAT), log OUES was the most powerful prognosticator. A multivariable model was constructed using this together

Table 2 Comparison between actual and predicted values for OUES

	Actual OUES (L/min)	SD	Predicted OUES (L/min)	SD	*P*
Males	1.6	0.7	2.5	0.5	<0.0001
Females	1.3	0.5	1.7	0.3	<0.0001

Table 3 Correlation between OUES and other cardiopulmonary exercise test variables

Variable	*r*	*P*
Peak VO_2	0.81	<0.0001
VE/VCO_2 slope	−0.62	<0.0001
VE	0.38	<0.0001
VE/VO_2 slope	−0.54	<0.0001
VAT	0.62	<0.0001

Table 4 Univariate Cox proportional hazards analysis of predictors of mortality

Variable	X^2	*P*-value
log OUES	44.7	<0.0001
log peak VO_2	42.2	<0.0001
VE/VCO_2 slope	40.6	<0.0001
VE/VO_2 slope	28.7	<0.0001
Exercise duration	23.9	<0.0001
VAT	19.9	<0.0001
Peak VE	5.3	0.02

with important potential confounders (age, VE/VCO_2 slope, exercise duration). In this, only log OUES was found to be a significant predictor of mortality.

A variety of cut-off values was applied to OUES, peak VO_2, VE/VCO_2 slope, and AT and the specificity and sensitivity (for predicting mortality) were assessed for each variable in the form of ROC curves. The follow-up data were censored at 83 months, which was the shortest period of follow-up in those patients who survived. The areas under the curves are shown in *Table 5*.

Optimal cut-off values were obtained for each of the exercise variables. The sensitivity, specificity, and positive and negative predictive values are shown in *Table 6*.

The Kaplan–Meier survival plots were constructed to illustrate the prognostic significance of peak VO_2, VE/VCO_2 slope, VAT, and OUES (*Figure 2*). The optimal cut-off values obtained from the ROC analysis were used to dichotomize the patient group.

Discussion

In this study, we have found that the value of OUES is significantly reduced in patients with CHF and fall with worsening symptoms. It is a powerful prognostic marker in CHF. In addition, its value is relatively resistant to disruption by foreshortened exercise, with the value obtained from the first half of exercise data being only 1% different from that obtained with the full data.

Table 5 Area under curve of ROC curve data

Variable	Area under curve	95% CI
OUES	0.82	0.76–0.87
Peak VO_2	0.80	0.74–0.86
VE/VCO_2 slope	0.76	0.69–0.82
VAT	0.74	0.66–0.81

CI, confidence intervals.

Table 6 Optimal cut-off values of exercise variables

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
OUES (L/min)	1.47	71	82	84	68
Peak VO_2 (mL/kg/min)	14.7	73	77	81	68
VE/VCO_2 slope	36.5	70	73	78	65
VAT (mL/kg/min)	10.2	72	73	80	64

PPV, positive predictive value; NPV, negative predictive value.

Cardiopulmonary exercise testing and CHF

CHF is associated with high morbidity and mortality.[1] Cardiopulmonary exercise data are known to provide an objective and reproducible measurement of exercise limitation and are a keystone of prognostic assessment of these patients, particularly for the selection of those who may benefit from cardiac transplantation.[2,3] Low values of peak VO_2 can be caused by a variety of factors[20] including limitation in cardiac output, poor peripheral blood flow[16,21] and impaired skeletal muscle metabolism with early development of acidosis,[22] and reduced patient motivation. Despite recent studies that suggest that the VE/VCO_2 slope may provide superior prognostic information,[8–12] peak VO_2 remains the most widely used marker for grading patients with CHF.

To combat the significant drawback of peak VO_2 on its dependence on maximal patient effort, several indices have been proposed. VAT[23] has been used to assess the degree of exercise impairment in patients with CHF, although there is no accepted automated method to provide a unique result reliably in all patients without individual operator intervention.[24–26] More than 10 years ago, there was an attempt to extrapolate maximal oxygen consumption (EMOC)[27] by using a quadratic function. However, it has not proved useful enough to be widely adopted.

Oxygen uptake efficiency slope

More recently, Baba *et al.*[13] developed an objective, independent measure of cardiorespiratory functional reserve by introducing a single-segment logarithmic curve-fitting model to describe the ventilatory response to exercise. The slope of this relationship has been termed OUES. In the original study performed in young patients with heart disease, the correlation between maximum VO_2 and OUES

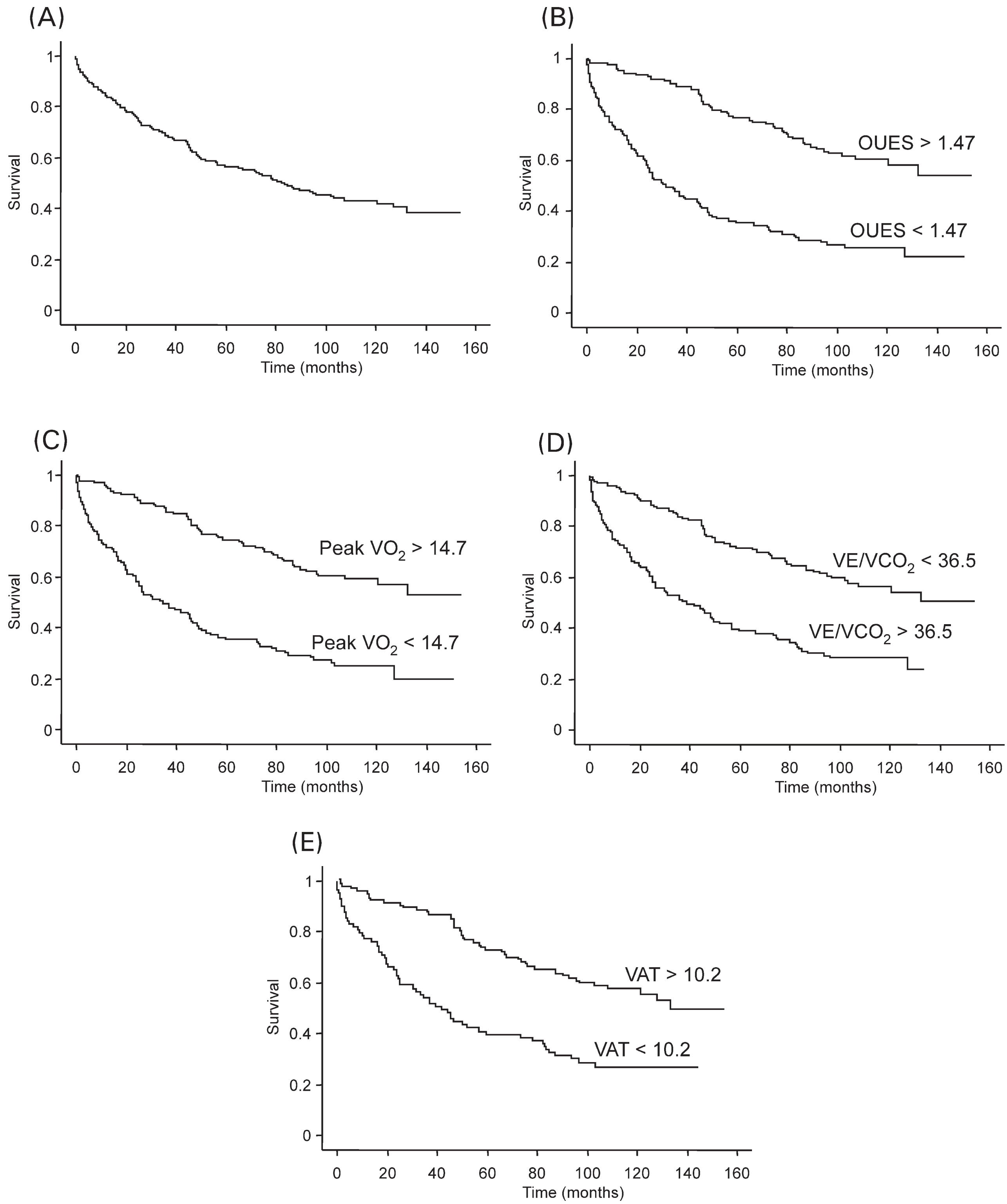

Figure 2 The Kaplan–Meier survival curves for (*A*) total population, (*B*) OUES, (*C*) peak VO_2, (*D*) VE/VCO_2 slope, and (*E*) VAT. Optimal values of OUES, peak VO_2, VE/VCO_2 slope, and VAT obtained from the ROC analysis were used to dichotomize the patients for the purpose of display. $P < 0.0001$ for all variables.

was stronger than that between maximum VO_2 and anaerobic threshold, VE/VCO_2 slope, or EMOC. The OUES values were also relatively stable when the later parts of exercise data were deleted. A subsequent assessment in elderly normal patients[14] confirmed that OUES calculated from the first 75% of the exercise data differed by only 1.9% from the values obtained from the complete exercise test. In a small sample ($n = 12$) of patients with CHF, OUES was depressed when compared with healthy controls. More recently, Van Laethem *et al.*[28] have shown that the value of OUES remains stable over the entire exercise duration and is lower in a population of heart failure patients. They

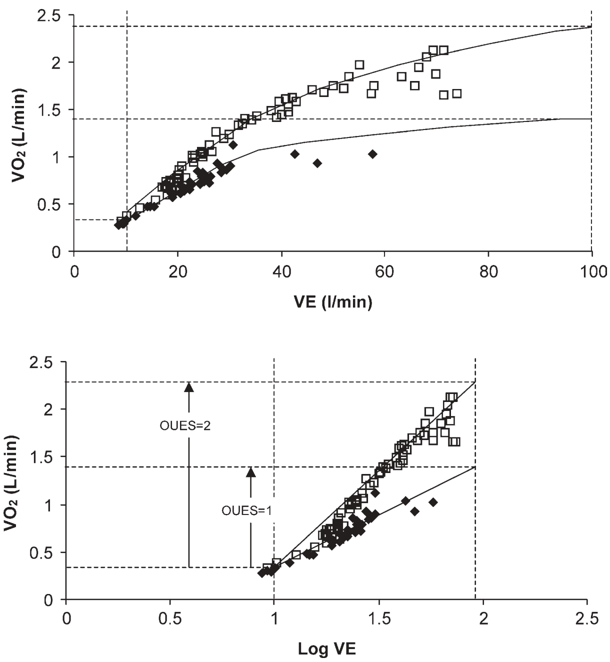

Figure 3 Physiological meaning of OUES. Open squares represent data from a patient whose oxygen uptake efficiency is good; closed diamonds represent data from a patient whose oxygen uptake efficiency is poor. From the definition of OUES, namely, the value of '*a*' in the regression relationship $VO_2 = a \log 10\ VE + b$, it can be seen that '*a*' is the slope of VO_2 upon log 10 VE. Therefore, put simply, OUES is the absolute increase in VO_2 associated with a 10-fold rise in ventilation.

suggested that it might be useful in the assessment of patients unable to perform a maximal exercise test. No prognostic data were provided in this study.

Physiological meaning of OUES

The strong prognostic value of OUES may relate to its physiological meaning. OUES represents, in essence, the absolute rate of increase in VO_2 per 10-fold increase in ventilation (*Figure 3*). Patients with CHF show a greater increase in ventilation per unit increase in VO_2 (or VCO_2)[29] because of various metabolic, reflex, and gas exchange abnormalities.[30–34] Therefore, they have a smaller increase in VO_2 for a given increase in ventilation, i.e. a lower OUES.

Distinction between OUES and conventional slopes

OUES differs in principle from measures such as VE/VCO_2 slope in that it considers changes in ventilation in terms of scale factor, i.e. in multiples of the baseline value. Thus, any abnormalities that raise ventilation by a constant proportion, both at rest and during exercise, will not directly affect OUES. Only abnormalities that increase ventilation during exercise by a greater proportion than at rest will be able to depress the OUES. We speculate that OUES may quantify the specific pattern of ventilatory response to exercise having automatically 'controlled' for abnormalities present at rest. As heart failure is a disease of holistic exercise physiology, it may be plausible that the isolation of the exercise-induced abnormalities of the ventilation–VO_2 relationship from those present at rest may improve prognostic value.

Study limitations

This is a retrospective study looking purely at exercise variables and does not include data obtained from echocardiography, which also provides prognostic information. In addition, data such as peak heart rate and blood pressure are not available. Although we speculate on the mechanism of OUES, we have not confirmed it in this study and only provide a simple explanation of the meaning of the numerical value and suggest why it may be advantageous. We have only compared OUES with peak VO_2 and cannot make assumptions about its relationship with VO_2 max. A relatively small number of patients failed to reach an appropriate RER, which does not allow us to provide survival data for this group.

Conclusion

OUES can be seen to be a measure of the ability to increase VO_2 per 10-fold rise in ventilation. It is easy to measure in patients with CHF undergoing incremental treadmill exercise, as it requires no further measurements. Its value is remarkably resistant to foreshortening of exercise duration (1% change vs. 25% change with peak VO_2). It has strong prognostic value, which is better than that of standard cardiopulmonary exercise test-derived variables. We speculate that this may be because its calculation specifically separates the exercise-induced changes in ventilation from any baseline hyperventilation.

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