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Oxygen Uptake Efficiency Slope Predicts Major Cardiac Events in Patients With End-Stage Heart Failure

Y.-S. Lin, H.-Y. Huang*, W.-H. Lin, J. Wei, J.-C. Chen, L.-Y. Kuo, C.-L. Hsu, B.-Y. Chen, and F.-H. Cheng

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ABSTRACT

Introduction. Oxygen uptake efficiency slope (OUES) has been shown as a predictor of stable heart failure (HF) survival. However, there is a lack of evidence for end-stage HF.

Objectives. We aimed to investigate the prognostic value of OUES in end-stage HF patients.

Methods. The study design was a retrospective cohort. End-staged HF patients who had cardiopulmonary exercise testing (CPET) for evaluation between 2004 and 2009 were included. The primary outcomes were cardiac death and heart transplantation. The independent survival predictors were determined using Cox regression hazard model adjusted for demographics, New York Heart Association (NYHA) classification, medication, and left ventricular ejection fraction (LVEF). The Kaplan-Meier survival curves and log-rank test were used. Probability values less than .05 were considered significant.

Results. Mean age of the 128 patients was 50 ± 12 years and 93 were male. Mean LVEF was 23% ± 9%. Forty-three subjects suffered cardiac events (5 cardiac deaths and 38 urgent heart transplantations) during the 2-year follow-up period. Cox regression indicated that OUES and diuretics were significant predictors of 2-year survival, although peak oxygen uptake and ventilatory equivalent of carbon dioxide were not. Patients with high OUES ($\geq$1.6) had a higher survival rate ($P < .001$; odds ratio [OR], 13.10; 95% confidence interval [CI], 3.30–58.63). The Kaplan-Meier curves show survival was significantly higher in those with OUES $\geq$1.6.

Conclusions. OUES might be an aid in prognosis of patients with end-stage HF and useful in the assessment of patients unable to perform maximal exercise testing.

PEAK oxygen uptake (peak VO_2) has been widely used to predict long-term prognosis for the heart failure (HF) population since 1991. Peak VO_2 is defined as the highest VO_2 achieved at maximal effort during incremental cardiopulmonary exercise testing (CPET) [1,2]. However, peak VO_2 relies entirely on data from the peak segment of exercise and is, therefore, potentially sensitive to many factors, including motivation and insufficient effort. In addition, previous study has proved that significant advances have been made in the treatment of HF; the trend of using beta blockers had a significant impact on survival without improving peak VO_2 [3].

In recent years, investigators have found that oxygen uptake efficiency slope (OUES) may be a better method for estimating prognosis. OUES, which incorporates cardiovascular, musculoskeletal, and respiratory function into a single index, represents the ventilation efficiency variables in CPET. It has been shown to be less confounded and more predictive than peak VO_2 in HF patients [2,3].

Most studies have included stable HF patients. However, the end-stage HF patients in our study had debilitated status, which made it difficult to perform exercise testing to optimal effort.

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We aimed to investigate the prognostic value of OUES in end-stage HF patients.

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Study Design and Population

The study was a retrospective cohort. Patients with end-stage HF, who had CPET for evaluation between 2004 and 2009, were included in the study.

End Points

The primary outcome was major cardiac events, defined as cardiac-related death and heart transplantation. All subjects were followed up for 2 years via medical record review.

CPET Procedures and Data Collection

Symptom-limited CPET was conducted according to the American Heart Association guidelines [4], and was performed using a treadmill (h/p/Cosmos Sports & Medical, Mercury, Germany) or an upright cycle ergometer (Lode B.V. Medical Technology, Type 917900, Groningen, Netherlands) depending on patient balance and safety. A modified Bruce protocol was followed for treadmill testing. For cycle ergometry, the initial power was 10 W, followed by increases of 10 W every 2 minutes. Breath by breath recording of respiratory gas exchange occurred throughout the entire CPET. Two outliers were removed from 7 breathing intervals data by Vmax system analysis (SensorMedics Vmax Encore, Yorba Linda, Calif, United States). Each test was followed by standard calibration for gas and sensor. Oxygen uptake and minute ventilation (VE) values were acquired from the initiation to peak for regression analysis for OUES.

Statistical Analysis

The independent 2-year survival predictors were determined using Cox regression hazard model adjusted for demographic factors, New York Heart Association (NYHA) functional classification, medication, and left ventricular ejection fraction (LVEF). The Kaplan-Meier survival curves and log-rank test were used. The primary predictor, OUES, was dichotomized by previous research [5]. Probability values less than .05 were considered significant. All analyses were performed in SPSS (version 19.0, SPSS, Inc., Chicago, Ill, United States).

RESULTS

Patient Characteristics

Mean age of the 128 patients was 50 ± 12 years and 93 (72.7%) were male. Basic demographics and clinical features are presented in Table 1. Mean LVEF was 23% ± 9%. NYHA functional class I, II, and III accounted for 19%, 43%, and 37% of patients, respectively. Forty-three percent of patients took β blockers. Forty-three subjects suffered cardiac events (5 cardiac deaths and 38 heart transplantations) during the 2-year follow-up period. The overall 2-year survival rate was 34.4%.

Table 1. Basic Characteristics

	n = 128	%
Demographic		
Male	93	72.7
Age (y, mean ± SD)	50.3	12.4
Diagnosis		
Congestive heart failure	97	75.8
Dilated cardiomyopathy	81	63.3
Ischemic cardiomyopathy	30	23.4
Valve heart disease	47	36.7
LVEF (%, mean ± SD)	23.4	9.6
NYHA		
I	24	19.2
II	55	44.0
III	46	36.8
Medications		
Angiotensin-converting enzyme inhibitors	39	30.5
Angiotensin II receptor blockers	17	13.3
Beta blockers	55	43.3
Diuretics	112	87.5

Abbreviations: LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association functional classification.

Prognostic Value of OUES

Cox regression procedure was used to assess the relationship between survival time and covariates, such as gender, age, NYHA classification, and LVEF. Cox regression analyses indicated that OUES was a significant predictor of 2-year survival. Patients with high OUES (≥1.6) had a higher 2-year survival rate than patients with low OUES (<1.6; $P = .01$; odds ratio [OR], 4.27; 95% confidence interval [CI], 1.33–13.70; Table 2). The Kaplan-Meier survival curves in Figure 1 show an important difference in 2-year survival was associated with OUES. Survival was higher in those with OUES ≥1.6 compared with others (82.4% and 55.1%, respectively; log-rank test, $P = .005$).

DISCUSSION

In this article, we present the predictive results of OUES in HF patients. Survival was significantly higher among patients with OUES ≥1.6 compared with those with lower OUES. Even after adjusting for gender, age, NYHA

Table 2. Multivariate Cox Regression Analysis

Variable	Hazard Ratio	95% CI	*P*
Multivariate			
Female	0.86	0.42–1.77	.68
Age	0.99	0.97–1.02	.72
NYHA I			
NYHA II	0.71	0.26–1.94	.51
NAHA III	0.82	0.40–1.65	.57
LVEF	0.99	0.96–1.03	.73
OUES <1.6	4.27	1.33–13.70	.01*
VO_2 <10.0	1.74	0.82–3.68	.15

Abbreviations: NYHA, New York Heart Association functional classification; LVEF, Left ventricular ejection fraction; OUES, Oxygen uptake efficiency slope; VO_2, oxygen uptake.

*$P < .05$ in multivariate Cox regression analysis.

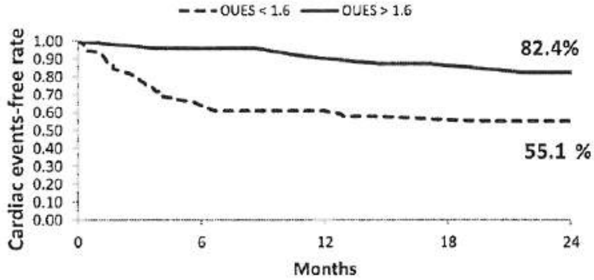

Fig 1. The Kaplan-Meier survival curves show an important difference in 2-year survival was associated with OUES. Survival was higher in those with OUES $\geq$1.6 compared with others (82.4% and 55.1%, respectively; log-rank test, $P = .005$).

classification, and LVEF, HF patients with OUES <1.6 had higher risk of cardiac events than patients with higher OUES. We can conclude that OUES predicted major cardiac events significantly.

Unlike with OUES, foreshortened exercise duration has a profound impact on peak VO_2 and VE/VCO_2 slope [6]. Because peak VO_2 relies entirely on peak exercise, it is potentially sensitive to exercise performance. Previous studies observed that OUES remained stable over the entire exercise duration [5,7,8]. Thus, it was not surprising that the results of our study conflicted with those of Arena et al, who claimed that VE/VCO_2 slope may be the single best indicator of risk for adverse events, not OUES [9]. This apparent conflict may be due to differences in the study populations. The participants in our study showed a lower functional capacity and higher NYHA functional class related to early termination of exercise.

OUES is calculated using a simple mathematical formula and has been proven as a consistent parameter less affected by observer variability [10]. OUES could easily be transformed from CPET tabular data in the clinical setting; hence, OUES appears to be a reasonable measurement of cardiopulmonary endurance. Although there are advantages, we need to exercise caution in its practical use. Akkerman et al reported that OUES is reliable and easily determinable when the breath by breath method of respiratory gas analysis is used [11]. Furthermore, OUES improves significantly after 6 months of exercise training or after orthotropic heart transplantation in HF patients [12,13]. Our study demonstrates the easy availability of OUES, and points to new possibilities for future research. The use of OUES in the whole HF population and training benefits will be the next steps to make HF treatments more precise.

One limitation is that cardiac events might be related with multiple factors in end-stage HF patients. As such, we conducted a multivariable model constructed with important potential confounders (age, gender, NYHA, and LVEF). Another issue is the study yielded limited information about HF patients with higher functional capacity. Therefore, the findings and implications of the study should be generalized only to the extent that future groups of HF patients are similar to the participants of this study.

In conclusion, OUES was strongly associated with cardiac death and urgent heart transplantation; furthermore, it has been shown to be more independent of patient-achieved effort level. Thus, OUES might be an aid in prognosis of patients with end-stage HF and useful in the assessment of patients unable to perform maximal exercise testing.

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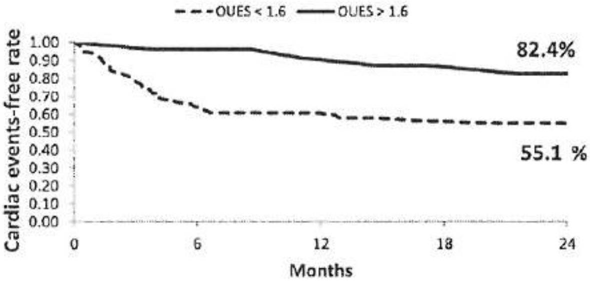

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