ORIGINAL RESEARCH

Oxygen Uptake Efficiency Slope Predicts Poor Outcome in Patients With Idiopathic Pulmonary Arterial Hypertension

Yi Tang, MD; Qin Luo, PhD; Zhihong Liu, PhD; Xiuping Ma, MD; Zhihui Zhao, PhD; Zhiwei Huang, MD; Liu Gao, MD; Qi Jin, MD; Changming Xiong, PhD; Xinhai Ni, PhD

***Background*—**Few published studies have evaluated the power of the oxygen uptake efficiency slope (OUES) to predict outcomes in patients with idiopathic pulmonary arterial hypertension (IPAH), who typically die of right-sided heart failure. Our study sought to evaluate the power of OUES to predict clinical worsening and mortality in patients with IPAH.

***Methods and Results*—**Patients with newly diagnosed IPAH who underwent symptom-limited cardiopulmonary exercise testing from November 11, 2010, to June 25, 2015, in our hospital were prospectively enrolled and followed for up to 66 months. Clinical worsening and mortality were recorded. A total of 210 patients with IPAH (159 women; mean age, 32±10 years) were studied with a median follow-up of 41 months. Thirty-one patients died, 1 patient underwent lung transplantation, and 85 patients presented with clinical worsening. The univariate analysis revealed that OUES, OUESI (OUESI=OUES/body surface area), peak oxygen uptake ($\dot{V}O_2$), peak $\dot{V}O_2$/kg, ventilation ($\dot{V}E$)/carbon dioxide output ($\dot{V}CO_2$) slope, peak systolic blood pressure, heart rate recovery, pulmonary vascular resistance, cardiac index, N-terminal prohormone brain natriuretic peptide, and World Health Organization functional class were all predictive of clinical worsening and mortality (all $P<0.05$). Multivariate analysis demonstrated that OUESI and cardiac index were independently predictive of clinical worsening, and OUESI and N-terminal prohormone brain natriuretic peptide were independently predictive of mortality. Patients with OUESI ≤ 0.52 m^{-2} had a worse 5-year survival rate than patients with OUESI >0.52 m^{-2} (41.9% versus 89.8%, $P<0.0001$).

***Conclusions*—**The OUES, a submaximal parameter obtained from cardiopulmonary exercise testing, provides prognostic information for predicting clinical worsening and mortality in patients with IPAH. **(*J Am Heart Assoc*. 2017;6:e005037. DOI: 10.1161/JAHA.116.005037.)**

Key Words: cardiopulmonary exercise testing • idiopathic pulmonary arterial hypertension • oxygen uptake efficiency slope

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by increased remodeling of pulmonary vasculature that leads to right-sided heart failure and death. It is important to identify patients with a higher risk of poor outcome early in order to treat them with optimal drugs, such as initial combination therapy for patients with a higher risk of mortality.[1] Several key parameters obtained from cardiopulmonary exercise testing (CPET), including peak oxygen uptake (peak $\dot{V}O_2$), end tidal partial pressure of carbon dioxide at anaerobic threshold, ventilation ($\dot{V}E$)/carbon dioxide output ($\dot{V}CO_2$) slope or ratio at anaerobic threshold, and heart rate recovery have been widely used to assess disease severity, therapeutic responses, and prognosis estimation in patients with PAH.[2,3]

In recent years, the oxygen uptake efficiency slope (OUES), representing the rate of increase in oxygen uptake ($\dot{V}O_2$) in response to a 10-fold increase in ventilation ($\dot{V}E$) during incremental exercise ($\dot{V}O_2 = a \log\dot{V}E+b$; a=OUES), has been introduced by Baba et al.[4,5] The advantages of OUES are that it can be calculated from submaximal exercise data and it is stable even when 50%, 75%, or 100% of the exercise data are used for the calculation. In addition, it is independent of interobserver and intraobserver variability.[6]

Tan et al[7] demonstrated that OUES was significantly lower in patients with idiopathic PAH (IPAH) compared with that in healthy controls. Woods et al[8] showed that OUES was able to differentiate between patients with mild and severe pulmonary hypertension.[8] Only one study, with a relatively small number of patients, has shown that OUES was a better predictor than $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ and could

From the Center for Pulmonary Vascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

Correspondence to: Zhihong Liu, PhD, Center for Pulmonary Vascular Diseases, Fuwai Hospital, 167 BeiLiShi Road, Xicheng District, Beijing 100037, China. E-mail: zhihongliufuwai@163.com

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Clinical Perspective

What is New?

- In this study, we demonstrated that oxygen uptake efficiency slope, a submaximal parameter, is more strongly associated with clinical worsening and all-cause mortality than minute ventilation/carbon dioxide output slope, and peak oxygen consumption in patients with idiopathic pulmonary arterial hypertension.

What are the Clinical Implications?

- Oxygen uptake efficiency slope appears to be one of the strongest prognostic markers among exercise variables obtained from cardiopulmonary exercise testing in patients with idiopathic pulmonary arterial hypertension.

predict poor outcome in 98 patients with PAH. Among them, 48 patients had IPAH and 50 patients had PAH with associated conditions.[9] It is still controversial whether OUES is better than the $\dot{V}E/\dot{V}CO_2$ slope for predicting adverse events in patients with left-sided heart failure.[10,11] Recently, time to clinical worsening (CW) has become a better primary end point for randomized controlled trials in patients with PAH[12,13]; however, no study has evaluated the value of OUES in predicting CW in patients with IPAH. Therefore, the aim of this study was to assess the prognostic value of OUES for CW and mortality in patients with IPAH.

Methods

Study Participants

Consecutive adult patients with newly diagnosed IPAH admitted to Fuwai Hospital were prospectively enrolled from November 11, 2010, to June 25, 2015. IPAH was defined according to the 2009 European Society of Cardiology/European Respiratory Society guideline for the diagnosis and treatment of pulmonary hypertension.[14] Patients who were unable to perform an exercise test or had contraindications to exercise testing were excluded. Basic demographics, medications, hemodynamic measurements from right-sided heart catheterization, and World Health Organization functional class (WHO-FC) were obtained from the medical records. This study complies with the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from all participants.

Cardiopulmonary Exercise Testing

Symptom-limited CPET was performed using the COSMED Quark CPET system on all recruited patients with IPAH at baseline, before they received specific drug therapy. All patients rested for 3 minutes followed by 3 minutes of unloaded pedaling and exercise using a progressively increasing work rate of 5 to 20 $W \cdot min^{-1}$ (the rate of increasing work rate depended on the estimated exercise capacity of each patient) to a maximum tolerance on an electromagnetically braked cycle ergometer. Cardiac rhythm, measured by a standard 12-lead ECG, and oxyhemoglobin saturation were continuously recorded. Heart rate was recorded at 1-minute intervals. Blood pressure was measured every 3 minutes and at the peak of the exercise. The test was performed by experienced medical staff, and the equipment was calibrated before each test.

Calculation of CPET Measures

Gas exchange variables were measured by a metabolic cart (COSMED) on a breath-by-breath basis and averaged over 10-second intervals. Peak $\dot{V}O_2$ was defined as the highest 30-second average of oxygen consumption in the last minute of exercise. Other peak values were also calculated at the same time point. Anaerobic threshold was determined by the V-slope method and corroborated using other plots. Peak $\dot{V}O_2$/heart rate was calculated as peak $\dot{V}O_2$ divided by peak heart rate. Since previous studies show that $\dot{V}E/\dot{V}CO_2$ slope calculated using the whole exercise period, as opposed to from the start of exercise to the ventilatory compensation point in patients with left-sided heart failure and PAH, has better prognostic value,[11,15,16] $\dot{V}E/\dot{V}CO_2$ slope was determined by linear regression using the whole exercise period. OUES was determined by the slope of the regression line between $\log_{10}$ minute ventilation $\dot{V}E$ (x axis, $L \cdot min^{-1}$) and $\dot{V}O_2$ (y axis, $L \cdot min^{-1}$) during the whole exercise period ($\dot{V}O_2 = a \log\dot{V}E+b$; a=OUES). A higher OUES (steeper slope) represents more efficient oxygen being delivered in the body; while a lower OUES (more flat slope) represents a higher amount of ventilation required in response to a given oxygen uptake (Figure 1A and 1B).[4] Predicted values for OUES were calculated from the equations introduced by Hollenberg and Tager:[17] In men, OUES=[1320−(26.7×age)+(1394×body surface area)]/1000 and, in women, OUES=[1175−(15.8×age)+(841×body surface area)]/1000. Percent predicted peak $\dot{V}O_2$ was calculated based on normative values proposed by Hansen and Wasserman et al.[18,19] Heart rate recovery was calculated as maximum heart rate-postexercise heart rate after 2 minutes during the recovery period.

Other Measures

Right-sided heart catheterization with standard hemodynamic measurements was performed at baseline within 3 days of each patient's CPET study, as we previously reported.[20] NT-

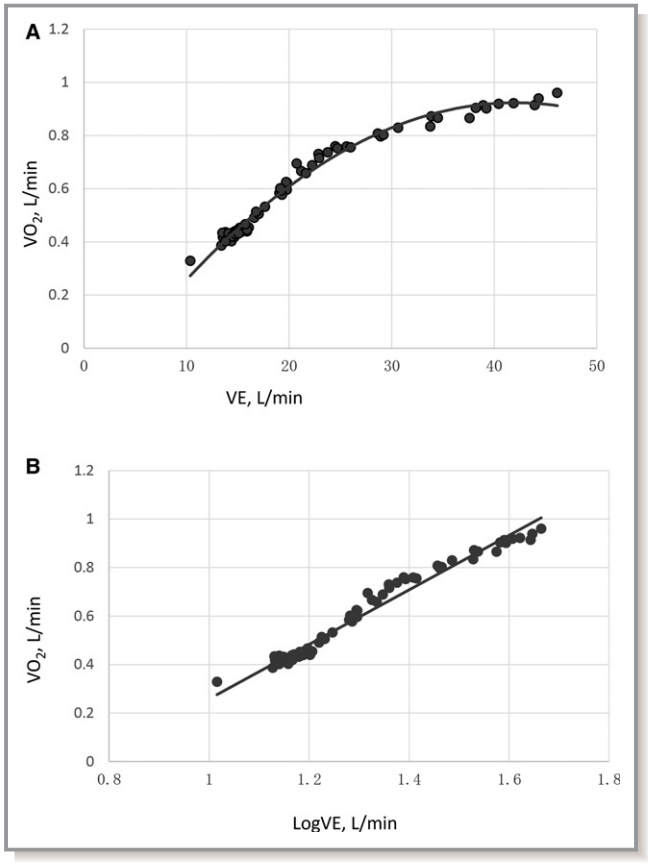

Figure 1. The relationship between $\dot{V}O_2$ and $\dot{V}E$ during incremental exercise in a 58-year-old woman with idiopathic pulmonary arterial hypertension. Linear (A) and semi-log (*x* axis) plots of the data (B) are presented.

proBNP (N-terminal prohormone brain natriuretic peptide) was determined at baseline using an enzyme immunoassay kit (Biomedica Medizinprodukte GmbH&CoKG).

Follow-Up

Patients were followed-up every 3 months for 1 year, then every 6 months after they were discharged. WHO-FC, medications and side effects, the date and cause of lung transplantation, and death were documented at each follow-up. The end point of mortality was defined as all-cause mortality or lung transplantation. The end point of CW was defined as the time from CPET to the first event, which included the following: all-cause mortality, lung transplantation, hospitalization for worsening of PAH, the need for epoprostenol therapy, and interventional procedures (performance of balloon atrial septostomy).[12,21] If patients experienced CW before death or lung transplantation, they were included in the analyses of both mortality and CW. The follow-up time was calculated from the date of CPET to the end point date or May 1, 2016.

Statistical Analysis

Continuous variables were expressed as mean±SD and categorical variables as a number or percentage as appropriate. Comparisons between groups were performed using independent-samples Student *t* tests or 1-way ANOVA for normally distributed variables and Mann–Whitney *U* test for non-normally distributed variables. Chi-square test was used for categorical variables. Multiple linear regression analysis (stepwise) was performed to assess the association between OUES and independent variables, which included age, sex, height, weight, body surface area (BSA), and body mass index. Correlations between 2 variables were explored using either the Pearson or Spearman correlation coefficient as appropriate.

A Cox proportional hazards regression analysis was used to detect predictors associated with CW and survival. The variables predictive of CW and survival by univariate analysis ($P<0.05$) were then entered into a multivariable Cox regression analysis with a forward procedure (likelihood ratio) to determine independent predictors of CW and survival. Since there were not enough events, in order to avoid overfitting, for CW, we put only WHO-FC, NT-proBNP, pulmonary vascular resistance (PVR) cardiac index, peak $\dot{V}O_2$/kg, OUESI, $\dot{V}E/\dot{V}CO_2$ slope, heart rate recovery, and peak systolic blood pressure into the multivariable forward stepwise Cox analysis, and for mortality, we put only NT-proBNP, PVR, peak $\dot{V}O_2$/kg, OUESI, and $\dot{V}E/\dot{V}CO_2$ slope into the multivariable forward stepwise Cox analysis, considering both *P* values of the variable in univariate Cox analysis and their clinical significance.

Receiver operator characteristic curve analysis was used to identify the cutoff point for parameters associated with CW and survival, using data censored to 10 months (the shortest duration of follow-up in our study). Kaplan–Meier survival charts were created to determine differences in the rate of cardiac events between patients with values above or below the cutoff point. Curves were compared using the log-rank test. A 2-sided $P<0.05$ was considered statistically significant. Receiver operator characteristic curve analysis was performed using MedCalc for Windows, version 13.0 (MedCalc Software), and other statistical analyses were performed using SPSS version 19.0 (SPSS, Inc).

Results

Baseline Characteristics

A total of 213 patients were identified with IPAH and underwent CPET. Three patients were lost to follow-up and not included in the analysis. The mean age was 32±10 years, and 75.7% of patients were women. A total of 112 patients presented with WHO-FC I and II, and 98 patients presented with WHO-FC III and IV. The mean

Table 1. Demographic and Clinical Data of CW vs Non-CW and Survivors vs Nonsurvivors in Patients With IPAH

Variables	CW (n=85)	Non-CW (n=125)	Nonsurvivors (n=32)	Survivors (n=178)
Age, y	32.8±11.2	31.9±9.9	33.9±14.4	32.0±9.6
Women, % (No.)	74.1 (63)	76.8 (96)	65.6 (21)	77.5 (138)
BSA, m^2	1.64±0.15	1.64±0.17	1.64±0.14	1.64±0.17
BMI, $kg \cdot m^{-2}$	22.4±3.3	22.6±3.6	22.0±3.3	22.6±3.5
WHO-FC, No.				
I or II	35	77*	10	102*
III or IV	50	48	22	76
NT-proBNP, pg/mL	1669.5±1052.7	1052.4±800.1†	1172.1±821.4	2026.0±1301.7†
Mono/combination therapy, n	81/4	121/3	30/2	173/5
Hemodynamics				
RAP, mm Hg	6.4±5.0	4.5±3.9*	7.7±5.4	4.8±4.1*
mPAP, mm Hg	62.1±15.7	55.7±16.3†	65.4±16.2	57.0±16.1*
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.4±0.6	3.0±1.0†	2.4±0.7	2.9±0.9‡
PVR, Wood units	15.0±6.7	10.9±5.4†	15.8±8.2	12.0±5.7*
CPET				
Peak $\dot{V}O_2$, $mL \cdot min^{-1}$	669.2±186.8	828.6±250.6†	647.0±166.7	785.1±245.0*
Peak $\dot{V}O_2$/kg, $mL \cdot kg^{-1} \cdot min^{-1}$	11.2±2.6	13.9±3.6†	11.0±2.5	13.1±3.6†
Peak $\dot{V}O_2$, % predicted	33.2±10.1	40.8±11.6†	31.8±9.4	38.8±11.7†
AT, $mL \cdot kg^{-1} \cdot min^{-1}$	9.2±2.3	10.2±2.5*	9.1±2.4	9.9±2.5
OUES	0.79±0.22	1.04±0.33†	0.78±0.19	0.97±0.32†
OUESI, m^{-2}	0.48±0.12	0.63±0.18†	0.46±0.10	0.59±0.18†
OUES, % predicted	36.3±10.7	47.2±14.7†	34.7±9.5	44.3±14.5†
$\dot{V}E/\dot{V}CO_2$ slope	55.8±20.0	43.4±13.8†	58.1±19.1	46.7±16.8†
$PETCO_2$@AT, mm Hg	26.3±5.4	30.5±4.9†	25.9±5.1	29.3±5.4†
Peak $\dot{V}O_2$/heart rate, $mL \cdot min^{-1} \cdot beat^{-1}$	5.0±1.4	5.8±1.7†	5.0±1.6	5.6±1.6‡
Peak work rate, W	62.0±22.3	77.8±25.0†	63.4±26.6	72.9±24.7
Peak RER	1.11±0.24	1.11±0.12	1.16±0.37	1.10±0.11
Peak heart rate, min^{-1}	136.5±20.3	146.1±20.2*	134.1±26.4	143.7±19.3
HRR, min^{-1}	17.9±11.2	23.9±14.7†	15.2±12.6	22.6±13.7*
Peak SBP, mm Hg	116.8±26.0	135.5±36.1†	110.5±18.3	131.1±34.8†
Peak DBP, mm Hg	82.8±19.6	86.4±21.8	77.7±12.7	86.2±21.9‡

Data are presented as percentage (number) or mean±SD. AT indicates anaerobic threshold; BMI, body mass index; BSA, body surface area; CPET, cardiopulmonary exercise testing; CW, clinical worsening; DBP, diastolic blood pressure; HRR, heart rate recovery; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; OUES, oxygen uptake efficiency slope; OUESI, oxygen uptake efficiency slope index (OUES/BSA); $PETCO_2$@AT, end tidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; SBP, systolic blood pressure; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption; WHO-FC, World Health Organization functional class.

*$P<0.01$.

†$P<0.001$.

‡$P<0.05$.

pulmonary vascular resistance was 12.5±6.3 Wood units and the mean cardiac index was 2.8±0.9 $L \cdot min^{-1} \cdot m^{-2}$. Anaerobic threshold could not be identified in 17 patients. Twenty-one patients were treated with calcium channel blockers, 182 patients were treated with monotherapy (7 patients with prostacyclins, 33 patients with endothelin receptor antagonists, and 142 patients with phosphodiesterase type 5 inhibitors), and 7 patients were treated with combination therapy. The median duration of follow-up was 41±15 months. During the follow-up period, 31 patients

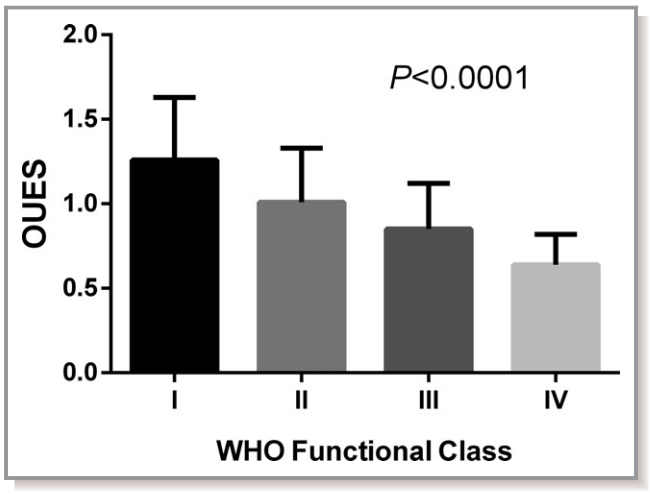

Figure 2. Mean values of oxygen uptake efficiency slope (OUES) divided into World Health Organization (WHO) functional classes.

died, 1 patient underwent lung transplantation, and 85 patients presented with CW.

Differences in Variables Between Groups

Patients with subsequent CW had a similar sex distribution, age, BSA, and body mass index compared with patients without subsequent CW (non-CW). However, patients with subsequent CW had a poorer WHO-FC, higher NT-proBNP, and much more severe hemodynamic parameters. In addition, patients who presented with CW had significantly lower peak $\dot{V}O_2$, OUES, end tidal partial pressure of carbon dioxide at anaerobic threshold, heart rate recovery, and peak systolic blood pressure, along with higher $\dot{V}E/\dot{V}CO_2$ slope. There was no difference in the peak respiratory exchange ratio between patients with and without subsequent CW. These results also apply to the comparison between survivors and nonsurvivors (Table 1).

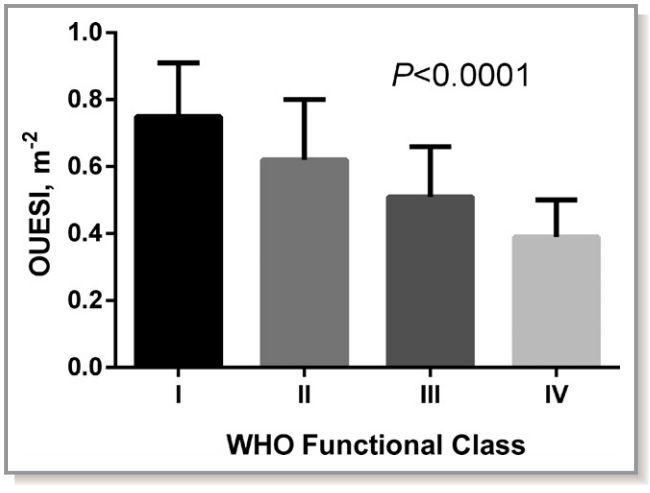

Figure 3. Mean values of oxygen uptake efficiency slope index (OUESI) divided into World Health Organization (WHO) functional classes.

Oxygen Uptake Efficiency Slope

Multivariate linear regression analysis showed that OUES only increased linearly with BSA (R=0.40, P<0.0001), therefore we defined the OUES index (OUESI) as OUES divided by BSA. The mean value of OUES was 0.94±0.31 and the mean value of OUESI was 0.57±0.171 m^{-2}. The mean values of OUES and OUESI were significantly different among the different WHO-FCs (all P<0.0001; Figures 2 and 3). Predicted values for OUES were calculated according to the equations of Hollenberg and Tager. The mean predicted value of OUES was 2.23±0.49 and mean percent predicted OUES was 42.8±14.2%. The mean OUES in men was higher than that in women (1.04±0.39 versus 0.90±0.28, P<0.02). OUES was significantly correlated with peak $\dot{V}O_2$/kg (r=0.71, P<0.0001), $\dot{V}E/\dot{V}CO_2$ slope (r=−0.67, P<0.0001), cardiac index (r=0.36, P<0.0001), and PVR (r=−0.55, P<0.0001).

Predictors for Long-Term Outcomes

On univariate analysis, WHO-FC, NT-proBNP, and variables obtained from right-sided heart catheterization and CPET, except for age and sex, were all significant predictors of CW and mortality (Table 2). Multivariable forward stepwise Cox analysis was performed including WHO-FC, NT-proBNP, PVR, cardiac index, peak $\dot{V}O_2$/kg, OUESI, $\dot{V}E/\dot{V}CO_2$ slope, heart rate recovery, and peak systolic blood pressure. Results showed that OUESI (χ^2: 26.54; hazard ratio [HR], 0.99 [95% CI, 0.99–0.99], P<0.0001) and cardiac index (χ^2: 7.23; HR, 0.62 [95% CI, 0.44–0.88], P<0.007) were independently predictive of CW. The forward stepwise and backward stepwise analysis yielded the same results. With respect to mortality, because of the occurrence of only 32 events, we put only NT-proBNP, PVR, peak $\dot{V}O_2$/kg, OUESI, and $\dot{V}E/\dot{V}CO_2$ slope into the multivariable forward stepwise Cox analysis. The results showed that NT-proBNP (χ^2: 9.88; HR, 1.001 [95% CI, 1.000–1.001], P<0.002) and OUESI (χ^2: 8.66; HR, 0.99 [95% CI, 0.99–0.99], P<0.003) were independently predictive of mortality. The forward stepwise and backward stepwise analyses yielded the same results.

The specificity and sensitivity for predicting CW and mortality and the area under the receiver operator characteristic curve (AUC) for each variable are shown in Table 3. The AUC for OUESI was higher than the $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$/kg for predicting both CW and mortality. The AUC for the percent-predicted OUES was lower than OUES for predicting both CW and mortality. In addition, the AUC for the percent-

Table 2. Univariate Cox Analysis of Proportional Risks for Clinical Worsening and All-Cause Mortality in Patients With IPAH

	Clinical Worsening			Mortality		
Variables	χ^2	HR (95% CI)	*P* Value	χ^2	HR (95% CI)	*P* value
Age	0.003	1.00 (0.98–1.02)	0.957	0.59	1.01 (0.98–1.04)	0.44
Sex	0.35	1.08 (0.84–1.37)	0.552	2.18	0.58 (0.28–1.20)	0.14
WHO-FC	12.09	1.84 (1.31–2.59)	<0.0001	10.32	2.51 (1.43–4.41)	<0.002
NT-proBNP	21.66	1.001 (1.000–1.001)	<0.0001	22.22	1.001 (1.000–1.001)	<0.0001
RAP	9.08	1.08 (1.03–1.13)	<0.003	9.13	1.11 (1.04–1.18)	<0.003
mPAP	8.65	1.02 (1.01–1.03)	<0.0001	6.48	1.02 (1.00–1.04)	<0.01
Cardiac index	21.38	0.46 (0.33–0.64)	<0.0001	5.46	0.55 (0.33–0.91)	<0.02
PVR	25.08	1.07 (1.04–1.10)	<0.0001	9.50	1.06 (1.02–1.11)	<0.002
Peak $\dot{V}O_2$	28.40	0.99 (0.99–0.99)	<0.0001	11.13	0.99 (0.99–0.99)	<0.001
Peak $\dot{V}O_2$/kg	34.65	0.80 (0.74–0.86)	<0.0001	12.28	0.80 (0.71–0.91)	<0.0001
Peak $\dot{V}O_2$, % predicted	26.73	0.94 (0.92–0.96)	<0.0001	11.24	0.94 (0.90–0.97)	<0.001
AT	10.24	0.87 (0.80–0.95)	<0.0001	4.03	0.87 (0.76–0.99)	<0.045
OUES	37.09	0.99 (0.99–0.99)	<0.0001	13.92	0.99 (0.99–0.99)	<0.0001
OUESI	41.91	0.99 (0.99–0.99)	<0.0001	15.84	0.99 (0.99–0.99)	<0.0001
OUES, % predicted	36.40	0.95 (0.93–0.97)	<0.0001	14.45	0.95 (0.92–0.97)	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope	26.03	1.02 (1.01–1.03)	<0.0001	10.26	1.02 (1.00–1.04)	<0.001
$PETCO_2$@AT	29.11	0.90 (0.87–0.94)	<0.0001	9.79	0.91 (0.86–0.97)	<0.002
Peak $\dot{V}O_2$/heart rate	16.04	0.71 (0.60–0.84)	<0.0001	4.55	0.75 (0.58–0.98)	<0.033
Peak work rate	24.52	0.97 (0.96–0.98)	<0.0001	5.05	0.98 (0.97–0.99)	<0.025
Peak heart rate	10.23	0.99 (0.98–0.99)	<0.001	5.69	0.98 (0.97–0.99)	<0.017
HRR	16.86	0.95 (0.93–0.98)	<0.0001	10.66	0.94 (0.91–0.98)	<0.001
Peak SBP	11.06	0.99 (0.98–0.99)	<0.001	7.28	0.98 (0.97–0.99)	<0.007

AT indicates anaerobic threshold; HR, hazard ratio; HRR, heart rate recovery; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; OUES, oxygen uptake efficiency slope; OUESI, oxygen uptake efficiency slope index (OUES/body surface area); $PETCO_2$@AT, end tidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SBP, systolic blood pressure; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption; WHO-FC, World Health Organization functional class.

predicted peak $\dot{V}O_2$ was also slightly lower than peak $\dot{V}O_2$/kg for predicting CW. The optimal cutoff values of cardiac index and OUESI for predicting CW are 2.90 $L{\cdot}min^{-1}{\cdot}m^{-2}$ and 0.62 m^{-2}, respectively. The optimal cutoff values of NT-proBNP and OUESI for predicting mortality are 1105.5 pg/mL and 0.52 m^{-2}, respectively. When these parameters were expressed dichotomously, peak $\dot{V}O_2$/kg, $\dot{V}E/\dot{V}CO_2$ slope, and OUES all predicted CW and mortality well. OUESI was superior to peak $\dot{V}O_2$/kg and $\dot{V}E/\dot{V}CO_2$ slope as indicated by the log-rank score (CW: 38.46>36.41>23.16, respectively; mortality: 29.78>12.85>21.55, respectively). Patients with OUESI $\leq$0.52 m^{-2} had a worse 5-year survival rate than patients with OUESI >0.52 m^{-2} (41.9% versus 89.8%, $P < 0.0001$). The unadjusted HR was 8.07 (95% CI 3.31–19.66), and after adjustment for age, sex, and body mass index, the HR was 7.94 (95% CI, 3.22–19.60). Patients with OUESI $\leq$0.62 m^{-2} had a worse 5-year CW-free rate than patients with OUESI >0.62 m^{-2} (17.6% versus 83.5%, $P< 0.0001$). The unadjusted HR was 7.29 (95% CI, 3.51–15.15), and after adjustment for age, sex, and body mass index, the HR was 7.23 (95% CI, 3.48–15.04). The Kaplan–Meier curves of OUESI are shown in Figures 4 and 5.

Discussion

In this study, we evaluated the prognostic value of exercise parameters obtained from CPET and hemodynamic parameters from right-sided heart catheterization and NT-proBNP. We found that the value of OUES fell with worsening symptoms and correlated well with peak $\dot{V}O_2$ in patients with IPAH. In addition, the results of our present study found that OUESI, which was superior to peak $\dot{V}O_2$/kg and $\dot{V}E/\dot{V}CO_2$ slope, was an independent prognostic marker of mortality and CW among exercise parameters in patients with IPAH.

Table 3. ROC Curve Analysis for Variables in Predicting Clinical Worsening and All-Cause Mortality

	Clinical Worsening			Mortality		
Variables	AUC	Sensitivity/ Specificity, %	*P* Value	AUC	Sensitivity/ Specificity, %	*P* Value
WHO-FC	0.64 (0.56–0.69)	59/62	<0.0004	0.66 (0.59–0.72)	69/57	<0.001
NT-proBNP	0.69 (0.64–0.76)	66/66	<0.0001	0.71 (0.65–0.77)	78/58	<0.0001
RAP	0.61 (0.54–0.68)	49/81	<0.0045	0.65 (0.59–0.72)	59/71	<0.0077
mPAP	0.64 (0.56–0.70)	69/54	<0.0008	0.66 (0.60–0.74)	54/79	<0.0012
Cardiac index	0.70 (0.64–0.76)	85/46	<0.0001	0.64 (0.56–0.69)	44/77	<0.0185
PVR	0.70 (0.64–0.76)	84/50	<0.0001	0.66 (0.58–0.71)	84/40	<0.0072
Peak $\dot{V}O_2$	0.69 (0.62–0.75)	76/55	<0.0001	0.67 (0.60–0.74)	86/42	<0.0003
Peak $\dot{V}O_2$/kg	0.71 (0.64–0.77)	95/42	<0.0001	0.68 (0.61–0.74)	94/45	<0.0001
Peak $\dot{V}O_2$, % predicted	0.69 (0.62–0.75)	44/84	<0.0001	0.68 (0.61–0.74)	50/81	<0.0005
AT	0.61 (0.54–0.67)	89/44	<0.0064	0.58 (0.51–0.65)	54/62	0.1267
OUES	0.74 (0.67–0.80)	64/76	<0.0001	0.71 (0.65–0.77)	75/66	<0.0001
OUESI	0.76 (0.69–0.81)	89/50	<0.0001	0.73 (0.67–0.79)	81/66	<0.0001
OUES, % predicted	0.72 (0.66–0.78)	61/74	<0.0001	0.70 (0.64–0.77)	54/80	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope	0.72 (0.66–0.79)	75/60	<0.0001	0.70 (0.64–0.77)	47/86	<0.0001
$PETCO_2$@AT	0.72 (0.66–0.78)	75/62	<0.0001	0.69 (0.62–0.75)	64/72	<0.0004
Peak $\dot{V}O_2$/heart rate	0.65 (0.58–0.71)	68/55	<0.0001	0.64 (0.57–0.70)	78/54	<0.0091
Peak work rate	0.68 (0.61–0.74)	55/74	<0.0001	0.60 (0.54–0.66)	40/79	0.0956
Peak heart rate	0.64 (0.56–0.69)	46/74	<0.0009	0.58 (0.51–0.65)	40/85	0.1879
HRR	0.64 (0.57–0.70)	42/81	<0.0005	0.66 (0.59–0.74)	54/76	<0.0024
Peak SBP	0.67 (0.60–0.74)	67/64	<0.0001	0.69 (0.62–0.75)	88/51	<0.0001

AT indicates anaerobic threshold; AUC, area under the receiver operating characteristic curve; HRR, heart rate recovery; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone brain natriuretic peptide; OUES, oxygen uptake efficiency slope; OUESI, oxygen uptake efficiency slope index (OUES/body surface area); $PETCO_2$@AT, end tidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; RAP, right atrial pressure; ROC, receiver operator characteristic; SBP, systolic blood pressure; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption; WHO-FC, World Health Organization functional class.

OUES, a submaximal exercise parameter, represents the absolute rate of increase in oxygen consumption per 10-fold increase in ventilation. It indicates how effectively the oxygen was extracted and utilized. Three main factors can affect OUES: (1) arterial pCO_2 (CO_2 set point), (2) metabolic carbon dioxide production, (3) physiologic pulmonary dead space ventilation.[4,17] Sullivan and Cobb[22] demonstrated that the arterial carbon dioxide set point did not differ during exercise between patients with heart failure and normal individuals. Therefore, the distribution of blood to the skeletal muscles (systemic perfusion) determining the production of carbon dioxide and the perfusion to the lungs determining pulmonary dead space ventilation can both affect OUES.

OUES is obviously resistant to foreshortening of exercise duration, which makes it useful in the assessment of patients who are unable to perform maximal exercise.[6] While peak $\dot{V}O_2$ is a maximal exercise parameter, patients with low peak $\dot{V}O_2$ can be underestimated because of lack of motivation and premature termination of exercise by the examiner. Previous studies showed that OUES was strongly correlated with peak $\dot{V}O_2$ and provided greater prognostic information over peak $\dot{V}O_2$ in patients with left-sided heart failure.[10,23,24] These results were consistent with the results of our study conducted in patients with IPAH.

With respect to the $\dot{V}E/\dot{V}CO_2$ slope, Arena et al[11] demonstrated that the $\dot{V}E/\dot{V}CO_2$ slope was superior to OUES in predicting major cardiac-related events in patients with left-sided heart failure. However, Davies et al[10] found that log OUES, rather than peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope, was the most powerful prognostic marker from his study of 243 patients with left-sided heart failure and a median of 9 years of follow-up. The proportion of β-blocker use and the length of the tracking period may account for the difference. However, a study conducted in patients with PAH still found that OUES was the strongest independent prognostic marker, better than the $\dot{V}E/\dot{V}CO_2$ slope.[9] The $\dot{V}E/\dot{V}CO_2$ slope relates to physiologic pulmonary dead space and indicates the status of pulmonary perfusion. OUES reflects not only the status of pulmonary perfusion but also systemic perfusion, which may be the reason why OUES provides prognostic information that

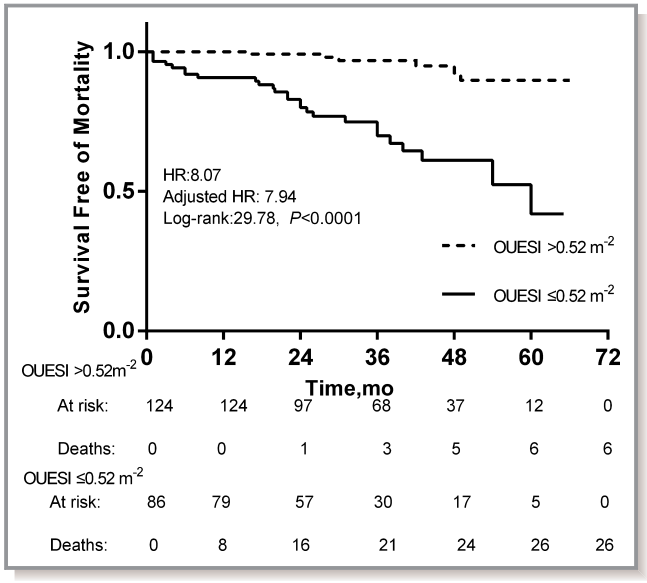

Figure 4. Kaplan–Meier analysis of oxygen uptake efficiency slope index (OUESI) for 5-year mortality. Adjusted HR indicates hazard ratio (HR) adjusted for age, sex, and body mass index.

is superior to that provided by the $\dot{V}E/\dot{V}CO_2$ slope.[9] However, patients with PAH and its associated conditions were also included in their study population, in addition to 48 patients with IPAH. In fact, Deboeck et al[13] demonstrated that exercise variables obtained from a CPET were less accurate predictors of outcome in associated PAH because of inhomogeneity of the study population. Therefore, our result may be more representative when it is applied to patients with IPAH.

When OUES was corrected for BSA, it had greater power than OUES in predicting CW and mortality; however, when the predicted values for OUES were calculated according to the equations of Hollenberg and Tager, the predictive power of percent-predicted OUES was not greater than OUES. This may have been attributable to the differences in study populations between the different studies.[6,25] The mean value of OUES in patients with IPAH in our study and other studies were obviously lower than that in patients with left-sided heart failure (0.72–1.08 versus 1.60–1.96).[7,9–11] These results were consistent with the results from our previous studies,[26,27] which showed that patients with right-sided heart failure had worse exercise capacity compared with patients with left-sided heart failure.

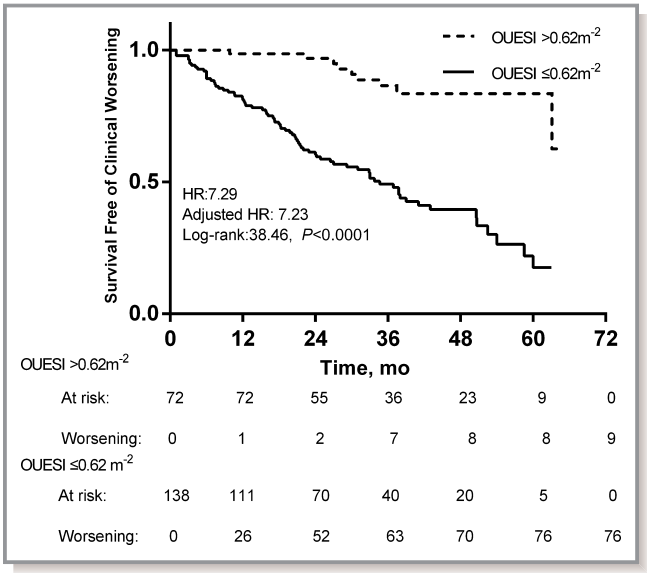

Figure 5. Kaplan–Meier analysis of oxygen uptake efficiency slope index (OUESI) for 5-year clinical worsening. Adjusted HR indicates hazard ratio (HR) adjusted for age, sex, and body mass index.

Study Limitations

Exercise variables that predict survival in patients with IPAH cannot predict survival in patients with associated PAH[13]; therefore, our results only apply to patients with IPAH. Future studies need to explore whether OUES can also predict outcomes in patients with associated PAH. In addition, the sample size of our study was relatively small, and this may have led to the insignificant differences in AUC between the OUESI, $\dot{V}E/\dot{V}CO_2$ slope, and peak $\dot{V}O_2$/kg. A multicenter, large-scale study will be needed to validate these findings.

Conclusions

CPET provides excellent prognostic information in patients with IPAH. OUES, as an objective submaximal measure of cardiorespiratory fitness, appears to be one of the strongest prognostic markers among exercise variables for predicting CW and mortality.

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Disclosures

None.

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