Oxygen Uptake Efficiency Plateau Best Predicts Early Death in Heart Failure

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Background: The responses of oxygen uptake efficiency (ie, oxygen uptake/ventilation = $\dot{V}O_2/\dot{V}E$) and its highest plateau (OUEP) during incremental cardiopulmonary exercise testing (CPET) in patients with chronic left heart failure (HF) have not been previously reported. We planned to test the hypothesis that OUEP during CPET is the best single predictor of early death in HF.

Methods: We evaluated OUEP, slope of $\dot{V}O_2$ to $\log(\dot{V}E)$ (oxygen uptake efficiency slope), oscillatory breathing, and all usual resting and CPET measurements in 508 patients with low-ejection-fraction (<35%) HF. Each had further evaluations at other sites, including cardiac catheterization. Outcomes were 6-month all-cause mortality and morbidity (death or >24 h cardiac hospitalization). Statistical analyses included area under curve of receiver operating characteristics, ORs, univariate and multivariate Cox regression, and Kaplan-Meier plots.

Results: OUEP, which requires only moderate exercise, was often reduced in patients with HF. A low % predicted OUEP was the single best predictor of mortality ($P < .0001$), with an OR of 13.0 ($P < .001$). When combined with oscillatory breathing, the OR increased to 56.3, superior to all other resting or exercise parameters or combinations of parameters. Other statistical analyses and morbidity analysis confirmed those findings.

Conclusions: OUEP is often reduced in patients with HF. Low % predicted OUEP (<65% predicted) is the single best predictor of early death, better than any other CPET or other cardiovascular measurement. Paired with oscillatory breathing, it is even more powerful.

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Abbreviations: AT = anaerobic threshold; AUC = area under the curve; BVP/CRT = biventricular pacing/cardiopersion therapy; CPET = incremental cardiopulmonary exercise testing; HF = chronic left heart failure; O_2 = oxygen; OB = oscillatory breathing; OUE = oxygen uptake efficiency; OUE@AT = oxygen uptake efficiency at the anaerobic threshold; OUEP = oxygen uptake efficiency plateau; OUES = oxygen uptake efficiency slope; ReThinQ = Resynchronization Therapy in Patients With Heart Failure and Narrow QRS Complexes; RHYTHM = Resynchronization for Hemodynamic Treatment for Heart Failure Management; ROC = receiver operator characteristic curve; STPD = standard conditions of 0°C, 760 mm Hg, dry; $\dot{V}CO_2$ = minute CO_2 output; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = minute O_2 uptake

Despite recent improvements in therapy, chronic left heart failure (HF) frequently requires hospitalization or is lethal.¹⁻³ We postulated that management of such patients could be improved by adding more sensitive predictors, further refining well-known predictors, or by combining predictors. Currently, in such patients, gas exchange measurements during incremental cardiopulmonary exercise testing (CPET) such as peak oxygen uptake (peak $\dot{V}O_2$) at standard conditions of 0°C, 760 mm Hg, dry (STPD); anaerobic threshold (AT); peak oxygen pulse; lowest ratio of minute ventilation ($\dot{V}E$) at body temperature, ambient atmo-

spheric pressure, saturated with water vapor to minute CO_2 output ($\dot{V}CO_2$) STPD; $\dot{V}E$ -vs- $\dot{V}CO_2$ slope; oscillatory breathing (OB) pattern³⁻¹⁰; and the slope of $\dot{V}O_2$ to $\log \dot{V}E$ (oxygen uptake efficiency slope [OUES])¹¹⁻²¹ have been found to be useful in predicting mortality and morbidity and guiding therapy.³⁻¹⁰ However, the full exercise response pattern of oxygen uptake efficiency (OUE) ($\dot{V}O_2/\dot{V}E$, mL/L) and specifically the measurement of its highest average plateau (OUEP) (mL/L) have not been evaluated.

As the CPET core laboratory for two St. Jude Medical multicenter studies^{3,22,23} involving 508 patients

with HF, we previously reported the CPET parameters listed here, plus resting and exercise heart rates, systemic BP, 6-min walk distance, left ventricular ejection fraction, quality of life, and New York Heart Association classification for their value in predicting 6-month mortality and cardiac hospitalizations. Our recent report presenting OUEP and OUES reference values²⁴ for normal subjects allowed us to now evaluate OUEP and OUES as additional prognosticating parameters in patients with HF.

MATERIALS AND METHODS

Setting and Participants

With approval from the Institutional Review Board Committee for Pre-Clinical/Clinical Trials of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (12105-01), we acted as the CPET core laboratory for St. Jude Medical biventricular pacing and cardiac resynchronization therapy (BVP/CRT) trials: Resynchronization for Hemodynamic Treatment for Heart Failure Management (RHYTHM) and Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS Complexes (ReThinQ) (ClinicalTrials.gov number, NCT00132977) as previously reported.^{3,22,23} After obtaining informed consent, satisfactory baseline CPET studies were obtained in 508 patients with low (<35%) ejection fraction HF. Each received a biventricular implantable cardioverter defibrillator and was randomized into pacemaker OFF or pacemaker ON subgroups.

Quality Control, Protocol, Gas Exchange Measurement, and Follow-up

Sixty-nine laboratories, using six different commercial systems, sent raw breath-by-breath CPET data to our laboratory for monitoring/review/calculation/analyses. Repeat studies were requested and obtained for any studies considered questionable.³ Author-investigators were blinded to patient assignments, catheterization findings, and imaging results at the time of data analysis. The mortality outcome was all-cause death; morbidity outcome included death or a cardiac hospitalization for ≥ 24 h within the 6-month follow-up period.

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Table 1—Demographics and Selected Resting and Exercise Measurements in Patients With HF

Measurements (No.)	All Patients, N = 508
Demographics	
Sex, No. (%)	
Male	355 (70)
Female	153 (30)
Age, y	64 $\pm$ 12 (20-89)
Height, cm	172 $\pm$ 10 (137-198)
Weight, kg	87 $\pm$ 22 (35-172)
Non-CPET measurements	
Resting HR, beats/min	77 $\pm$ 14 (42-131)
Resting SBP, mm Hg	118 $\pm$ 19 (80-201)
Resting DBP, mm Hg	71 $\pm$ 11 (42-105)
LVEF, %	26 $\pm$ 7 (10-48)
QRS interval (ms)	138 $\pm$ 33 (60-220)
QRS interval > 120 ms, No. (%)	284 (56)
BVP/CRT: ON/OFF, No. (%)	362/146 (71/29)
NYHA, No. = II/III/IV	52/440/16
Quality of life (score) ^a	51 $\pm$ 25 (1-103)
6-min walking distance, m	291 $\pm$ 101 (20-561)
CPET measurements	
Peak HR, beats/min	108 $\pm$ 21 (54-173)
Peak SBP, mm Hg	141 $\pm$ 26 (70-210)
Peak DBP, mm Hg	77 $\pm$ 14 (40-120)
Peak $\dot{V}E$, L/min	43 $\pm$ 15 (14-97)
Peak workload, W	60 $\pm$ 37 (0-314)
Peak RER, ratio of $\dot{V}CO_2/\dot{V}O_2$	1.07 $\pm$ 0.13 (0.76-1.59)
Peak $\dot{V}O_2$	
% predicted	53 $\pm$ 16 (16-115)
mL/min/kg	12.1 $\pm$ 4.0 (3.9-32.3)
L/min	1.00 $\pm$ 0.40 (0.26-2.87)
AT (n = 491)	
% predicted	57 $\pm$ 16 (18-130)
mL/min/kg	8.8 $\pm$ 2.5 (2.8-17.3)
L/min	0.72 $\pm$ 0.26 (0.22-1.71)
Peak O_2 pulse	
% predicted	77 $\pm$ 23 (24-148)
mL/beat	9.4 $\pm$ 3.6 (2.8-26.1)
Lowest $\dot{V}E/\dot{V}CO_2$, 90 s	
% predicted	137 $\pm$ 34 (87-403)
Ratio	39.2 $\pm$ 10.2 (23.6-73.1)
$\dot{V}E$ -vs- $\dot{V}CO_2$	
Slope (% predicted)	120 $\pm$ 59 (58-574)
Slope	35.3 $\pm$ 17.1 (12.7-130.8)
OB, No. (+/-)	250/258

Data are mean $\pm$ SD unless otherwise specified. AT = oxygen uptake rate at anaerobic threshold; BVP/CRT-ON or -OFF = biventricular pacemaker/cardiac resynchronization setting is "on" or "off"; CPET = cardiopulmonary exercise testing; DBP = diastolic BP; HF = chronic left heart failure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification; O_2 pulse = oxygen uptake per min/heart rate; OB = oscillatory breathing; RER = respiratory gas exchange ratio (ie, CO_2 output per min [standard conditions of 0°C, 760 mm Hg, dry]/oxygen uptake per min [standard conditions of 0°C, 760 mm Hg, dry]); SBP = systolic BP; $\dot{V}CO_2$ = CO_2 output per min (standard conditions of 0°C, 760 mm Hg, dry); $\dot{V}E$ = minute ventilation (body temperature, ambient atmospheric pressure, saturated with water vapor); $\dot{V}E/\dot{V}CO_2$ = ratio of minute ventilation (body temperature, ambient atmospheric pressure, saturated with water vapor) to CO_2 output per min (standard conditions of 0°C, 760 mm Hg, dry); $\dot{V}E$ -vs- $\dot{V}CO_2$ slope = minute ventilation (body temperature, ambient atmospheric pressure, saturated with water vapor) as a function of CO_2 output per min (standard conditions of 0°C, 760 mm Hg, dry); $\dot{V}O_2$ = oxygen uptake per min (standard conditions of 0°C, 760 mm Hg, dry).

^aQuality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire, with scores ranging from 0 to 105 and with higher scores indicating a poorer quality of life.²³

Table 2—OR, AUC, With 95% CI, and Best Cutoff Values for Mortality in HF

Measurement and Best Cutoff Value	OR (95% CI)	AUC (95% CI)	P Value
Non-CPET measurements			
Resting HR > 85 beats/min	2.10 (1.16-3.03)	0.585 (0.448-0.722)	0.21
Resting SBP < 110 mm Hg	2.15 (1.20-3.09)	0.591 (0.453-0.729)	0.19
Resting DBP < 70 mm Hg	0.73 (–0.27-1.72)	0.463 (0.330-0.596)	0.59
LVEF < 25%	1.77 (0.80-2.74)	0.574 (0.443-0.705)	0.71
QRS interval > 120 ms	1.74 (0.76-2.76)	0.565 (0.438-0.692)	0.34
BVP/CRT OFF	2.18 (0.93-3.43)	0.434 (0.312-0.556)	0.33
NYHA class IV	2.99 (0.43-5.55)	0.538 (0.402-0.675)	0.57
Quality-of-life score > 50	1.61 (0.36-2.86)	0.532 (0.401-0.662)	0.64
6-min walking distance < 250 m	3.77 (2.80-4.74)	0.644 (0.513-0.776)	0.03
CPET measurements			
Peak HR < 105 beats/min	1.19 (0.27-2.11)	0.522 (0.390-0.654)	.75
Peak SBP < 140 mm Hg	3.16 (2.11-4.20)	0.635 (0.511-0.760)	.051
Peak DBP < 90 mm Hg	4.17 (2.15-6.20)	0.571 (0.450-0.691)	.31
Peak $\dot{V}E$ < 50 L/min	3.58 (2.11-5.06)	0.596 (0.481-0.710)	.15
Peak workload < 50 W/min	2.80 (1.80-3.79)	0.608 (0.480-0.736)	.11
Peak RER ratio < 1.10	1.87 (0.84-2.91)	0.569 (0.444-0.694)	.31
Peak $\dot{V}O_2$			
< 50% predicted	5.95 (4.83-7.07)	0.701 (0.590-0.813)	.003
< 11 mL/min/kg	4.64 (3.60-5.68)	0.652 (0.532-0.771)	.025
< 0.80 L/min	4.46 (3.47-5.45)	0.679 (0.555-0.802)	.008
AT (n = 491)			
< 60% predicted	5.06 (3.57-6.55)	0.661 (0.549-0.772)	.024
< 9 mL/min/kg	5.86 (4.37-7.35)	0.643 (0.529-0.757)	.047
< 0.60 L/min	5.12 (3.86-6.38)	0.645 (0.512-0.779)	.042
Peak O_2 pulse			
< 75% predicted	5.81 (4.56-7.06)	0.683 (0.576-0.790)	.007
< 7.5 mL/beat	4.63 (3.51-5.75)	0.682 (0.575-0.789)	.007
Lowest $\dot{V}E/\dot{V}CO_2$, 90 s			
$\geq 155\%$ predicted	9.35 (8.36-10.34)	0.748 (0.624-0.872)	< .001
Ratio ≥ 40	5.81 (4.77-6.85)	0.706 (0.589-0.823)	.002
$\dot{V}E$ -vs- $\dot{V}CO_2$			
Slope $\geq 140\%$ predicted	7.58 (6.62-8.54)	0.723 (0.594-0.852)	.001
Slope ≥ 40	5.70 (4.74-6.66)	0.700 (0.572-0.829)	.003
OB+	5.54 (4.29-6.79)	0.674 (0.566-0.781)	.009

AUC = area under the receiver operating characteristics curve. See Table 1 legend for expansion of other abbreviations.

The exercise protocol required multiple measurements during 3 min of rest, 3 min of unloaded cycling or comparable warm-up on the treadmill, followed by progressively increasing work by 5 to 15 W/min (usually 10 W/min) in a ramp pattern or 1-min step intervals to maximum tolerance. Fifty-eight percent of studies were performed on the cycle ergometer and 42% on the treadmill. For measurements other than OUE, the methodology and prognostic values of all other data listed in the introduction and CPET have been previously reported.^{3,22,25-30}

OUE Measurement

Three relationships between $\dot{V}O_2$ and $\dot{V}E$ data were graphically evaluated, identified, and calculated for each subject as follows: (1) OUEP was the 90 s average of the highest consecutive values for $\dot{V}O_2$ (mL/min, STPD)/ $\dot{V}E$ (L/min, at body temperature, ambient atmospheric pressure, saturated with water vapor) (Fig 1); (2) OUE at the AT (OUE@AT) was the 60 s average of consecutive values at and immediately before the AT (Fig 1); and (3) OUES was the slope of linear regression of $\dot{V}O_2$ (L/min)-vs- $\log \dot{V}E$ (L/min) for all exercise values. Percent of predicted values for OUEP and OUES were based on age, sex, and body size.²⁴ The lowest $\dot{V}E/\dot{V}CO_2$ were determined over a 90-s period.^{3,26}

Oscillatory Breathing

The breathing pattern was scored as oscillatory breathing positive (OB⁺) or negative (OB[–]). The determination of an OB⁺ pattern required all of the following: (1) the amplitude of oscillatory ventilation must exceed 30% of concurrent mean ventilation^{3,7,8,31,32}; (2) three or more consecutive cyclic fluctuations of ventilation or $\geq 60\%$ of entire CPET period^{3,7-10,31,32}; (3) an oscillatory frequency of 40 to 140 (56 ± 5.2) s³; and (4) visible oscillations of similar frequency in three or more of the following variables: oxygen pulse, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E/\dot{V}CO_2$, respiratory exchange ratio, or end-tidal pressures for oxygen (O_2) and CO_2 .³

Statistical Analyses

Data, expressed as mean $\pm$ SD unless specially noted, were first analyzed by unpaired *t* and χ^2 tests. A two-tailed *P* value < 0.05 was considered significant. Using all-cause mortality and morbidity as outcomes, receiver operator characteristic curves (ROCs) analyses were performed. Optimal cutoff values were determined by the shortest distance on each ROC for all CPET and non-CPET variables, including steps of whole numbers for OUEP, two decimals for OUES, and 1% for % predicted.^{3,33} Sensitivity, specificity and area under the curve of ROC (AUC) were calculated. Using

FIGURE 1. OUE patterns during cardiopulmonary exercise testing (CPET) in a normal subject and three patients with HF. The response patterns of OUE (ie, $\dot{V}O_2/\dot{V}E$) from rest to peak exercise during CPET in the normal subject (gray solid circle)²⁴ and patients with HF (black, dark gray, and gray inverted triangle) and are reasonably parallel. The OUE varies minimally during rest, increases during warmup, and then increases further to its highest level or plateau (90-s average oxygen uptake efficiency plateau, mL/L [OUEP]) just before the AT. Thereafter, the OUE invariably decreases as exercise intensity increases. As the severity of HF increases, the OUEP decreases. An oscillatory breathing (OB) pattern was found in many patients with severe and very severe HF. AT = anaerobic threshold; HF = chronic left heart failure; O_2 = oxygen; OUE = oxygen uptake efficiency; $\dot{V}O_2/\dot{V}E$ = minute oxygen uptake/minute ventilation.

optimal cutoff values of all CPET and non-CPET variables without predetermined priorities, univariate and multivariate regression analyses disclosed prognostic predictors for the optimal model.^{3,34,35} To evaluate OB, step-by-step repeated multivariate analyses were used to obtain the next model by excluding the prior most significant variables. OR were calculated for single and combined predictors and tested by Wald logistic regression model. Kaplan-Meier survival curves and log-rank tests were used to compare single and combined predictors. For the dual-predictors model, Kaplan-Meier survival curves compared all four options. For relationships of peak $\dot{V}O_2$ with OUEP and OUES, linear regression analyses of patients with HF vs normal subjects were compared. SPSS Statistics 17.0, Origin 7, and Sigma Plot 8.0 statistical software were used; graphs were generated using Origin 7.

RESULTS

Demographics, Usual Cardiovascular, and OB Data

Satisfactory resting cardiovascular measurements and CPET were obtained for 355 male and 153 female stable patients with HF (Table 1).³ Thirty-six of the 508 baseline studies were not of optimal quality and needed to be repeated. The patients' mean age, height, and body weight were 64 years, 172 cm, and 87 kg, respectively. New York Heart Association functional classifications were II (n = 52), III (n = 440), and IV (n = 16). There were 362 ON and 146 OFF for the

BVP/CRT settings; 271 patients in RHYTHM (QRS interval ≥ 150 milliseconds) and 237 patients in RethinQ (QRS interval ≤ 130 milliseconds, including 67 nonrandomized patients in the registry group). All 508 patients received angiotensin-converting enzyme inhibitors (82%) or angiotensin receptor blockers (18%); 86% received β -adrenergic blockers. All

FIGURE 2. OUEP, OUE@AT, and OUES in patients with HF and healthy subjects. Each symbol is an individual patient with HF (open black inverted triangle), normal subject (solid gray circle), or very fit (open gray circle) subject. The regression lines are for normal subjects only (gray) or all patients with HF (black). The equations are for patients with HF only because those for normal subject data were previously presented.²⁴ A, OUEP vs OUE@AT indicates their similarity for normal subjects or patients with HF. B, OUEP vs OUES. The wider distribution of data and differing regression lines indicate differences between the two groups. OUE@AT = 60-s average oxygen uptake efficiency at the anaerobic threshold (mL/L); OUES = oxygen uptake efficiency slope, slope of $\dot{V}O_2$ vs $-\log \dot{V}E$ [L/min/log (L/min)]. See Figure 1 legend for expansion of other abbreviations.

Table 3—OUE Values Linked to Mortality, Morbidity, and Severity of HF

	No.	OUEP, 90 s		OUES	
		mL/L	% Predicted	L/min/log (L/min)	% Predicted
Patients with HF (range)	508	30.4 ± 7.3 (6.7-60.7)	82.3 ± 18.8 (13.7-143.9)	1.290 ± 0.534 (−0.050-3.906)	72.6 ± 30.3 (5.2-198.1)
Mortality					
–	489	30.6 ± 7.2	82.9 ± 18.6	1.303 ± 0.533	73.3 ± 30.4
+	19	25.0 ± 7.0	66.5 ± 17.1	0.956 ± 0.467	56.2 ± 19.8
<i>P</i> values		.0012	.0007	.0028	.0021
Morbidity					
–	401	31.1 ± 7.3	84.3 ± 18.7	1.348 ± 0.538	74.5 ± 29.6
+	107	27.7 ± 6.3	74.8 ± 18.1	1.072 ± 0.460	65.7 ± 31.8
<i>P</i> values		<.0001	<.0001	<.0001	.0122
OB					
–	258	32.1 ± 6.7	87.2 ± 16.9	1.480 ± 0.546	79.2 ± 29.5
+	250	28.7 ± 7.1	77.6 ± 19.4	1.105 ± 0.451	66.2 ± 29.6
<i>P</i> values		<.0001	<.0001	<.0001	<.0001
Functional severity by peak $\dot{V}O_2$ as % predicted					
~Normal (≥ 80% predicted)	29	31.5 ± 5.3	102.7 ± 16.2	1.666 ± 0.525	109.5 ± 24.9
Mild (65%-79% predicted)	77	29.1 ± 4.2 ^a	92.3 ± 14.0 ^b	1.497 ± 0.537	89.9 ± 29.8 ^b
Moderate (50%-64% predicted)	165	27.9 ± 5.4 ^{b,e}	86.2 ± 17.3 ^{d,f}	1.361 ± 0.447 ^{b,f}	77.0 ± 25.7 ^{d,g}
Severe (35%-49% predicted)	176	26.1 ± 4.9 ^{d,h,j}	77.8 ± 15.3 ^{d,h,j}	1.217 ± 0.531 ^{c,h,j}	64.3 ± 26.6 ^{d,h,j}
Very severe (<35% predicted)	61	21.1 ± 5.6 ^{d,h,k,l}	62.4 ± 16.3 ^{d,h,k,l}	0.869 ± 0.450 ^{d,h,k,l}	48.0 ± 23.2 ^{d,h,k,l}

Values are mean ± SD (range). The *P* values between the positive and negative for mortality and morbidity are by unpaired *t* test. – = negative; + = positive; ANOVA = analysis of variance; OUE = oxygen uptake efficiency (ie, $\dot{V}O_2/\dot{V}E$, mL/L); OUEP = 90-s average oxygen uptake efficiency plateau (mL/L); OUES = slope of $\dot{V}O_2$ to log $\dot{V}E$ [L/min/log(L/min)]. See Table 1 legend for expansion of other abbreviations. Comparisons of functional severity by ANOVA are

vs “~Normal” group:

^a*P* < .05.

^b*P* < .01.

^c*P* < .001.

^d*P* < .0001.

vs “Mild” group:

^e*P* < .05.

^f*P* < .01.

^g*P* < .001.

^h*P* < .0001.

vs “Moderate” group:

ⁱ*P* < .01.

^j*P* < .001.

^k*P* < .0001.

vs “Severe” group:

^l*P* < .0001.

patients were accounted for during 6-month follow-up: 19 patients (3.7%) died, and 107 patients (21%) died or had one or more cardiac hospitalizations lasting greater than 24 h.³

The mean resting heart rates and systolic and diastolic BPs were 77 beats/min and 118/71 mm Hg, respectively. Mean left ventricle ejection fractions were 26%; 6-min walking distances were 291 m. Mean peak $\dot{V}O_2$, peak oxygen pulse, and the lowest $\dot{V}E/\dot{V}CO_2$ were, respectively, 1.00 L/min (53% pre-

dicted), 9.4 mL/beat (77% predicted), and 39.2 (137% predicted). The mean AT, detected in 491 patients, was 0.72 L/min (57% predicted). Two hundred fifty-eight patients were identified as OB⁺ and 250 as OB[−].³ The ORs, 95% CIs, and AUC analyses for mortality for resting measures (including cardiac catheterization and echocardiography) and many CPET measures excluding OUEP and OUES are shown in Table 2. Other than CPET measurements, only higher resting heart rate, lower

Table 4—Best Cutoff Values, Sensitivity, Specificity, AUC, and 95% CI of OUE for Mortality in HF

Measurements	OUEP, 90 s		OUES	
	mL/L	% Predicted	L/min/log (L/min)	% Predicted
Best cutoff value	< 25 mL/L	< 65% predicted	< 1.05	< 65% predicted
Single measurement				
Sensitivity	0.68	0.68	0.68	0.68
Specificity	0.79	0.84	0.65	0.68
AUC	0.729	0.748	0.680	0.731
(95% CI)	(0.609-0.849)	(0.628-0.868)	(0.565-0.795)	(0.616-0.846)
P values	< .001	< .001	.004	< .001
Combined with positive OB				
AUC	0.783	0.800	0.724	0.765
(95% CI)	(0.684-0.881)	(0.702-0.899)	(0.615-0.833)	(0.616-0.846)
P values	< .001	< .001	< .001	< .001

See Table 1-3 legends for expansion of abbreviations.

resting systolic BP, and shorter 6-min walking tests had OR confidence limits over 1.00. For AUC, only 6-min walking distance was statistically significant. In contrast, OR and AUC analyses of CPET measures yielded highly statistically significant findings for absolute or % predicted peak $\dot{V}O_2$, peak O_2 pulse, AT and $\dot{V}E:\dot{V}CO_2$ relationships, and some statistical significance for peak BP, ventilation, and workload. Essential morbidity data are given in Figure 3 and its legend.

OUE Responses

Figure 1 shows the response patterns of OUE (ie, ratio of $\dot{V}O_2/\dot{V}E$ in mL/L) from rest to peak exercise in a normal subject and three patients with different severity HF. In all patients, OUE increased when exercise started, soon reached a plateau (OUEP) just before the AT, and then decreased until exercise ended. Because gas exchange data were often oscillatory at rest and with early exercise, OUEP values for each individual were their 90-s average highest values, while OUE@AT values were averaged for 60 s at and before AT. Figure 2A indicates the near identity of the OUEP and OUE@AT in all 491 patients with HF who had a detectable AT ($r = 0.99$, $P < .0001$). Figure 2B shows the more scattered relationship between the OUEP and OUES.

Table 3 compares OUEP and OUES values of patients with HF to normal subjects and each other. Values of both absolute and % predicted OUEP and OUES were markedly decreased in patients with HF ($P < .001$) and useful in predicting mortality, morbidity, OB, and severity (all $P < .01$ to .0001).

Both OUEP and OUES as either absolute or % predicted were powerful predictors ($P < .001$) for early death, but OUEP measurements were superior (Tables 3, 4). With the best cutoff of 25 mL/L and 65% predicted, OUEP had the highest AUC of 0.729

and 0.748, respectively, which significantly ($P < .001$) increased to 0.783 and 0.800 when combined with OB. For OUES, AUC were 0.680 (absolute) and 0.731 (% predicted), with greater ($P < .05$) increases to 0.724 and 0.765, respectively, with OB. AUC % predicted values were always higher than absolute values ($P < .05$).

The mortality OR analyses for OUEP were consistently higher than for OUES ($P < .01$) (Fig 3A), while OR of % predicted values were invariably higher than those of absolute values ($P < .01$). The OR of absolute and % predicted OUEP reached 9.8 and 13.0, respectively. Combined with OB, the % predicted OR reached 56.3. All ORs of absolute and % predicted OUEP with and without OB were significantly ($P < .05$) superior to any other CPET parameter (Table 2 and Fig 3 of this article and the previously published Fig 2A³) ($P < .01$), while other cardiovascular measurements were not significant for early death.³ The morbidity OR analyses for OUEP and OUES were statistically significant, but less than for mortality (Fig 3B). Adding OB⁺ increased morbidity ORs minimally.

Using Kaplan-Meier and stepwise multivariable regression analysis (reducing all other CPET and non-CPET measures except only OB to nonsignificance), a low OUEP (< 65% predicted) was again the best single predictor of early mortality (Fig 4). The optimal predictor model was the combination of low % predicted (< 65% predicted) OUEP with OB⁺. Six-month survival rates were 98.4% in patients with HF with OUEP $\geq$ 65% predicted, and 82.6% in those OUEP < 65% predicted. Survival rates for the four combinations of OUEP and OB ranged from 99.6% to 80.4% ($P < .001$).

Figure 5 identifies the early deaths and shows the relationships of individual OUEP and OUES values (x-axis) vs peak $\dot{V}O_2$ values (y-axis), expressed in three ways, to compare patients with HF vs normal subjects. Using OUEP, the slopes and intercepts of the

FIGURE 3. ORs of OUEP and OUES, alone and combined with OB+, for mortality and morbidity of patients with HF. **A, Mortality.** The left column shows the optimal absolute and % predicted cutoff values for each variable. The center column (gray bars) shows OR mean and 95% CI for single lower OUE measurements. The right column (black bars) shows OR for combined lower OUE and OB+ measurements. The stepwise selected optimal predictor model uses only two-predictor variables of decreased OUEP (<65% predicted) with OB+ by stepwise multivariate regression analysis ($P < .001$) since all other CPET and non-CPET variables are then nonsignificant ($P > .05$). OR values were invariably higher using % predicted values and were always higher using OUEP than OUES. The best single predictor of early mortality is OUEP <65% predicted (OR = 13.0) and the best combination is OUEP <65% predicted with OB+ (OR = 56.3). All OR values of absolute and % predicted OUEP with and without OB were superior to all other key CPET parameters,³ respectively ($P < .05$). As shown in Figure 2A of our previous published data,³ the highest single OR values of lowest $\dot{V}_E/\dot{V}_{CO_2}$, $\dot{V}_E$ -vs- $\dot{V}_{CO_2}$ slope, peak $\dot{V}_{O_2}$, peak O_2 pulse, and AT, respectively, were 9.4, 7.6, 6.0, 5.8, and 5.1 for % predicted values, and 5.8, 5.7, 4.5, 4.6 and 5.1 for absolute values. Combined with OB+, they were 38.9, 19.7, 19.5, 16.2, and 18.1 for % predicted values, and were 22.6, 15.1, 12.7, 15.4, and 14.1 for absolute values, respectively. **B, Morbidity.** Data are displayed as in panel A. Although the OR values are

patients with HF differed markedly from those of the normal subjects. Using OUES, the slopes and intercepts of the patients with HF and normal subjects were almost identical.

DISCUSSION

The life-sustaining function of the cardiovascular system is to transport O_2 and CO_2 between the lungs and the systemic organs. It is not surprising then that CPET measures such as peak $\dot{V}_{O_2}$, AT, peak oxygen pulse, lowest $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E$ -vs- $\dot{V}_{CO_2}$ slope, and OUES are good measures of cardiovascular performance and predictive of survival in patients with HF.³⁻¹⁰ Another measurement, perhaps even more useful, is the OUEP. Surprisingly, to the best of our knowledge, the measurements of OUEP (or lowest $\dot{V}_E/\dot{V}_{O_2}$ or highest $\dot{V}_{O_2}/\dot{V}_E$), either for a fraction of a minute or longer durations, have not been carefully analyzed or reported for prognosis or severity of disease in the past.

Logically, by Fick's principle,^{26,36-38} the ratio of oxygen uptake to ventilation (ie, $OUE = \dot{V}_{O_2}/\dot{V}_E$), should evaluate cardiovascular performance, as it is dependent on three factors: cardiac output, arterial-mixed venous oxygen content difference, and lung ventilation.^{26,36-38} The OUEP tended to be higher in healthier individuals.²⁴ For reasons that may not be intuitively obvious, in both normal subjects²⁴ and patients with HF, the OUE was not highest at rest or at maximal exercise, but during moderate exercise (Fig 1). The highest OUE (OUEP) does not occur at rest because cardiac output is lowest; ventilation is less efficient (anatomic dead space volume is a higher proportion of tidal volumes); and arterial-mixed venous oxygen content difference is lowest because the oxygen saturation of mixed venous blood is higher both in normal subjects and patients at rest than during exercise (so that not as much O_2 can be extracted from inhaled air at rest). In both normal subjects²⁴ and patients with HF, the OUEP does not occur at heavy, very heavy, or maximal exercise, even though mixed venous oxyhemoglobin saturation is low and the ratio of anatomic dead space to alveolar ventilation is optimal. This is because, with more intense exercise, increasing production of lactate, metabolic CO_2 , excess CO_2 , and increasing H^+ stimulate ventilation. Because ventilation does not normally limit exercise, this stimulation results in increasing CO_2 output but less increasing O_2 loading equally, lowering the alveolar and arterial CO_2 partial pressure.

lower, they parallel the mortality findings. None of the OR morbidity values for other CPET measures exceeded those of OUEP. OB+ = positive oscillatory breathing; pred = predicted. See Figure 1 and 2 legends for expansion of other abbreviations.

FIGURE 4. Kaplan-Meier survival curves of patients with HF using status of OUE, singly, and combined with OB. The numbers of patients at risk for each curve are given at 60-day intervals. A, Comparison of the OUEP $\geq 65\%$ predicted (gray) vs OUEP $< 65\%$ predicted (black) ($P < .001$). B, Comparison from top to bottom: OUEP $\geq 65\%$ predicted and OB-, OUEP $\geq 65\%$ predicted and OB+, OUEP $< 65\%$ predicted and OB-, and OUEP $< 65\%$ predicted and OB+. The bottom curve values were significantly lower than the values of the upper two curves ($P < .001$), but not for values of the third curve ($P > .05$). OB- = negative oscillatory breathing. See Figure 1 and 3 legends for expansion of other abbreviations.

This, in turn, further reduces ventilatory efficiency as more ventilation is required to remove CO_2 to balance the declining bicarbonate levels and reduce acidemia. As exercise intensity increases, ventilatory drive to reduce acidemia decreases $\dot{V}\text{CO}_2/\dot{V}\text{E}$ and $\dot{V}\text{O}_2/\dot{V}\text{E}$ (equivalent to increasing $\dot{V}\text{E}/\dot{V}\text{CO}_2$ and $\dot{V}\text{E}/\dot{V}\text{O}_2$). The time of decreasing $\dot{V}\text{O}_2/\dot{V}\text{E}$ at AT (Fig 1) is earlier than that of decreasing $\dot{V}\text{CO}_2/\dot{V}\text{E}$ at the ventilatory compensation point.²⁶ Thus, the OUEP occurs during less than maximal exercise (below AT level) in both normal subjects²⁴ and patients with HF. It assesses the optimal

capacity to match the increasing lung perfusion of mixed venous partially deoxygenated blood with the increasing ventilation and to load O_2 into the systemic circulation. In normal subjects and patients with HF without significant ventilatory limitation or primary lung disease, the OUEP appears to reflect overall cardiovascular function of loading and transporting O_2 well. Initially, the OUEP was found to be dependent on age, sex, body size, and fitness in over 474 healthy subjects; reference equations from 417 normal subjects were presented.²⁴ Now, it is evident that the OUEP also indicates disease severity in over 500 patients with HF (Fig 1, Table 3). In these patients, the % predicted OUEP, based on age, sex, and height, turns out to be the strongest single predictor of early survival (Figs 3A, 4). While the $\dot{V}\text{E}-\dot{V}\text{CO}_2$ relationship better reflects ventilatory efficiency,^{25,26} the OUEP appears to better reflect the efficiency of oxygen uptake, which depends on systemic and lung perfusion, just before ventilation is stimulated by exercise-induced acidemia.

In this group of patients with HF, it appears that values of OUEP have an advantage over OUES, peak $\dot{V}\text{O}_2$, AT, $\dot{V}\text{E}/\dot{V}\text{CO}_2$, and $\dot{V}\text{E}-\text{vs}-\dot{V}\text{CO}_2$ values or any other invasive or noninvasive measurement in assessing early mortality and morbidity.³ This superiority is evident by AUC, OR, stepwise multivariable regression selection, and Kaplan-Meier analyses (Figs 2-4, Tables 2-4, and our prior report³). Multivariate analysis selected OUEP ahead of other CPET parameters, despite the overlapping of their physiologic information and relatively high correlations. Manually adding the other key CPET measures did not add significant prognostic importance to OUEP, which was superior to OUES. Alone, a decreased % predicted OUEP was superior to any other measurement (Fig 3A and our previous published Figure 2A³). For both OUEP and OUES, the % predicted values were superior to absolute values (Fig 3A), probably because % predicted lessens differences between sex, body size, and age. The fact that OUEP is measured during submaximal rather than maximal exercise is also advantageous in evaluating patients with HF.^{24,39,40}

The fact that the intercepts of OUES vs peak $\dot{V}\text{O}_2$ are so close to zero in both patients with HF and normal subjects (Fig 5) strongly suggests that OUES and peak $\dot{V}\text{O}_2$ measure similar phenomenon, and thus may be somewhat redundant. In contrast, the dissimilarity of the slopes and intercepts of OUEP vs peak $\dot{V}\text{O}_2$, suggests, that though they are related, they likely represent somewhat different phenomena.

OB is also a significant independent predictor,^{3,7-10,31,32} and in combination with OUE measurements, is even more powerful ($P < .001$). Adding OB increased the OR for both OUEP and OUES twofold to fourfold (Fig 3A). The OR of OUEP using 65% predicted as a

FIGURE 5. Relationships of OUEP and OUES vs peak $\dot{V}O_2$ in HF. Each symbol represents an individual normal (solid gray circle) or very fit (open gray circle) healthy subject²⁴ or survivor (open black inverted triangle) or deceased (solid black inverted triangle) patient with HF. The gray regression lines are for normal subjects²⁴; the equations and black regression lines are for all patients with HF. A-C, OUEP vs peak $\dot{V}O_2$. Linear regression line slopes and intercepts of patients with HF and normal subjects invariably differ. For HF, the OUEP varies over a wider range than peak $\dot{V}O_2$; for normal subjects, peak $\dot{V}O_2$ varies over a wider range than OUEP ($P < .001$). D-F, OUES vs peak $\dot{V}O_2$. Regression lines and intercepts of normal subjects and HF are similar ($P > .05$). See Figure 1-3 legends for expansion of abbreviations.

cutoff with and without OB were 13 and 56, respectively, higher than those of OUES with or without OB. Although the number of deaths ($n = 19$) over the 6-month follow-up period were modest, the parallel changes in morbidity ($n = 107$) confirm the value of OUE measurements.

A limitation of this study is the small number of deaths in this population; however, the parallel findings in morbidity somewhat balance this limitation. The findings here, confined to patients with left ven-

tricular dysfunction and wide QRS complexes, may or may not be found in larger series or in patients with other cardiac disorders.

In conclusion, this study finds that OUEP combined with OB strongly prognosticates an increased risk of early death and hospitalization in patients with HF. OUEP $< 65\%$ predicted is the best single predictor for early mortality with an OR of 13.0. Adding OB increases the OR to 56.3. CPET measurements of OUEP and OB, which are noninvasive, inexpensive,

and do not require maximal exercise, should be useful in clinical trials and in evaluating and managing individual cardiac patients. Thus, it would be useful for other clinical investigators managing patients with cardiovascular disease, including those being evaluated for cardiac transplantation, to retrospectively or prospectively analyze their gas exchange data to ascertain whether the measurement of OUEP is useful in grading severity, prognosis, and/or guiding therapy for their patients.

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