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QUARTERLY FOCUS ISSUE: HEART FAILURE

Oscillatory Breathing and Exercise Gas Exchange Abnormalities Prognosticate Early Mortality and Morbidity in Heart Failure

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Objectives The goal of this study was to identify better predictors of early death in patients with chronic left ventricular heart failure (CHF). Potential predictors, derived from cardiopulmonary exercise testing, were compared with other commonly used cardiovascular measurements.

Background The prediction of early death in patients with CHF remains challenging.

Methods Five hundred eight patients with CHF due to systolic dysfunction underwent resting cardiovascular measurements, 6-min walking tests, and cardiopulmonary exercise testing. The peak oxygen uptake ($\dot{V}O_2$), peak oxygen pulse, anaerobic threshold, ratio of ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$), slope of $\dot{V}E$ versus $\dot{V}CO_2$, and presence or absence of a distinctive oscillatory breathing pattern (OB) were ascertained. Outcomes were 6-month mortality and morbidity, the latter a sum of cardiac hospitalizations and deaths.

Results The single best predictor of mortality was an elevated lowest $\dot{V}E/\dot{V}CO_2$ (≥155% predicted). Adding OB on the basis of stepwise regression (optimal 2-predictor model), the odds ratio for mortality increased from 9.4 to 38.9 ($p < 0.001$). The slope of $\dot{V}E$ versus $\dot{V}CO_2$ slope, peak $\dot{V}O_2$, peak oxygen pulse, and anaerobic threshold combined with OB were also strong predictors. OB also increased the odds ratio 2- to 3-fold for each of these ($p < 0.01$). Kaplan-Meier survival curves and area under the receiver-operating characteristic curve confirmed that lowest $\dot{V}E/\dot{V}CO_2$ and OB were superior. For morbidity, elevated lowest $\dot{V}E/\dot{V}CO_2$ or lower peak $\dot{V}O_2$ with OB were the best predictors. No nonexercise measurements discriminated mortality and morbidity.

Conclusions Cardiopulmonary exercise testing parameters are powerful prognosticators of early mortality and morbidity in patients with CHF, especially the optimal 2-predictor model of a combination of elevated lowest $\dot{V}E/\dot{V}CO_2$ and OB. (J Am Coll Cardiol 2010;55:1814–23) © 2010 by the American College of Cardiology Foundation

The incidence of chronic left ventricular heart failure (CHF) remains high despite improvements in its management (1,2). Annual mortality rates as high as 20% to 30% have been reported during the past decade (3–6). The selection of accurate predictors of early death in patients with CHF remains challenging. Three reasonable approaches are to: 1) further refine well-known predictors; 2) evaluate new and more sensitive prognostic indicators; and 3) combine predictors.

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Many reports have noted that gas exchange parameters elicited from cardiopulmonary exercise testing (CPX) help quantify severity and predict survival in patients with CHF (7–14). These parameters are peak oxygen uptake ($\dot{V}O_2$, l/min at 0°C, 760 mm Hg, dry), peak oxygen pulse (i.e., $\dot{V}O_2$/heart rate), $\dot{V}O_2$ at anaerobic threshold (AT), and measures of ventilatory efficiency, that is, the relationship of minute ventilation ($\dot{V}E$, l/min at body temperature, ambient atmospheric pressure, saturated with water vapor) to carbon dioxide output ($\dot{V}CO_2$, l/min at 0°C, 760 mm Hg, dry) expressed as a ratio ($\dot{V}E/\dot{V}CO_2$) or as the slope of $\dot{V}E$ versus $\dot{V}CO_2$. Ventilatory efficiency measures, reflecting ventilation-perfusion mismatch, have been shown to predict death better than peak $\dot{V}O_2$ in

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patients with CHF (14–22). Recent studies have shown that oscillatory breathing pattern (OB) during CPX in patients with CHF also predicts premature death (23–27). Whether survival is worse in those patients who stop exercise because of dyspnea is disputed (28–32).

As the CPX core laboratory for 2 St. Jude Medical (St. Paul, Minnesota) multicenter studies, we analyzed the baseline CPX and 6-month survival and cardiac hospitalizations of 508 patients with CHF. We also compared these CPX parameters plus OB with 6-min walk distance, resting and exercise heart rate, systemic arterial systolic and diastolic blood pressure, left ventricular ejection fraction, quality of life, and New York Heart Association functional classification.

Methods

Patients. The studies were sponsored and financed by St. Jude Medical using CPX protocols designed by us. Our role as the CPX core laboratory had Harbor-UCLA Institutional Review Board approval. In this study, we evaluated the baseline studies of 508 patients with systolic dysfunction left ventricular failure who participated in 2 St. Jude Medical biventricular pacing (BVP) and cardiac resynchronization pacing trials: RHYTHM (Resynchronization for Hemodynamic Treatment for Heart Failure Management) (33) and RethinQ (Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS Complexes) (34). Each patient, selected by a cardiologist or electrophysiologist at each site, received a biventricular implantable cardioverter-defibrillator. Informed consent was obtained at each site. Each patient's drug therapy was optimized before his or her entry into the study. The core laboratory investigators were blinded to patient assignments and imaging results at the time of data analysis but were aware of each patient's age, sex, height, weight, and New York Heart Association functional class.

Quality control, protocol, and systems. Prior to patient testing, each site had to demonstrate that it could follow the exercise protocol satisfactorily for 2 consecutive tests on a normal subject with good reproducibility in peak $\dot{V}O_2$, AT, peak oxygen pulse, and lowest $\dot{V}E/\dot{V}CO_2$ ratio. Our core lab reviewed the tabular and graphical data (see the next paragraph) from each study for evident breaches in protocol and calibration. Sites that failed to qualify were disqualified from study participation. Six different exercise systems were used at 69 sites. The mean ± SD values between qualified replicate tests for the 69 sites were 5.1 ± 4.1%, 5.2 ± 5.1%, 5.0 ± 5.6%, and 4.0 ± 3.0% for the 4 parameters, respectively. As previously described (33), we, St. Jude Medical, and personnel at each site took care to minimize failures by oversight, training, and proven reproducibility before CPX was performed on patients. If we questioned results, the relevant site lab had to prove its validity by requalification and repeat patient testing. The baseline CPX studies were done within 2 weeks of device implantation. The exercise protocol required measurements during 3 min of rest, 3 min of unloaded cycling, or comparable warm-up on the treadmill, followed by a progressively increasing work rate of 5 to 15 W/min (usually 10 W/min) in a ramp pattern or 1-min step intervals to maximal tolerance. Fifty-eight percent of studies were performed on the cycle ergometer. Work rate increases were individually selected so that subjects would reach their maximal tolerated work rate in 6 to 15 min of exercise, whether on the cycle or treadmill (33–35). After recovery, the patient was asked to report the reason(s) for stopping. Peak $\dot{V}O_2$, peak oxygen pulse, and AT values from treadmill exercise were reduced by 11%, to be comparable with cycle values (35). Ventilatory efficiency and heart rate values were not adjusted.

Abbreviations and Acronyms

- **AT** = anaerobic threshold
- **AUC** = area under the receiver-operating characteristic curve
- **BVP** = biventricular pacing
- **CHF** = chronic heart failure
- **CPX** = cardiopulmonary exercise testing
- **CRT** = cardiac resynchronization therapy
- **OB** = oscillatory breathing pattern
- **OR** = odds ratio
- **%pred** = percent of predicted value
- **$\dot{V}CO_2$** = carbon dioxide output per minute (0°C, 760 mm Hg, dry)
- **$\dot{V}E$** = minute ventilation (body temperature, ambient atmospheric pressure, saturated with water vapor)
- **$\dot{V}O_2$** = oxygen uptake per minute (0°C, 760 mm Hg, dry)

Data analysis, display, and gas exchange measurements. To minimize the interobserver and system variability, all systems were used only to collect the raw breath-by-breath CPX data, which were transmitted to the core laboratory for analyses. The following method of data analysis was used (33). Breath-by-breath CPX data were interpolated second by second and sequentially averaged in 10-s bins. To best analyze the physiological responses, data were placed into uniform tabular formats, and optimally scaled 15 exercise variables were displayed in 9-panel graphs (Fig. 1) (33,35,36).

Peak $\dot{V}O_2$ was determined as the highest average value during a sequential 30-s period (Fig. 1C). Peak heart rate and peak oxygen pulse were determined as concurrent 30-s averages (Fig. 1B). The AT was measured by the V-slope method (37) using 10-s averages (Fig. 1E). The lowest $\dot{V}E/\dot{V}CO_2$ was the lowest average 90-s value during exercise (38,39) (Fig. 1F). The slope of $\dot{V}E$ versus $\dot{V}CO_2$ and intercept (Fig. 1D) were determined by linear regression below the ventilatory compensation point (Fig. 1D) (16,38,39).

Percents of predicted values (%pred) for peak $\dot{V}O_2$, peak oxygen pulse, and AT values depend on age, size, sex, and form of ergometry (33,35,36,39). The %pred of the lowest $\dot{V}E/\dot{V}CO_2$ and slope of $\dot{V}E$ versus $\dot{V}CO_2$ values depend on age, sex, and size (38).

OB. OB was defined as 3 or more consecutive cyclic fluctuations of ventilation during CPX. To be defined as positive, the amplitude of oscillatory ventilation must exceed 30% of concurrent mean ventilation with a complete oscillatory cycle within 40 to 140 s. Oscillations of similar

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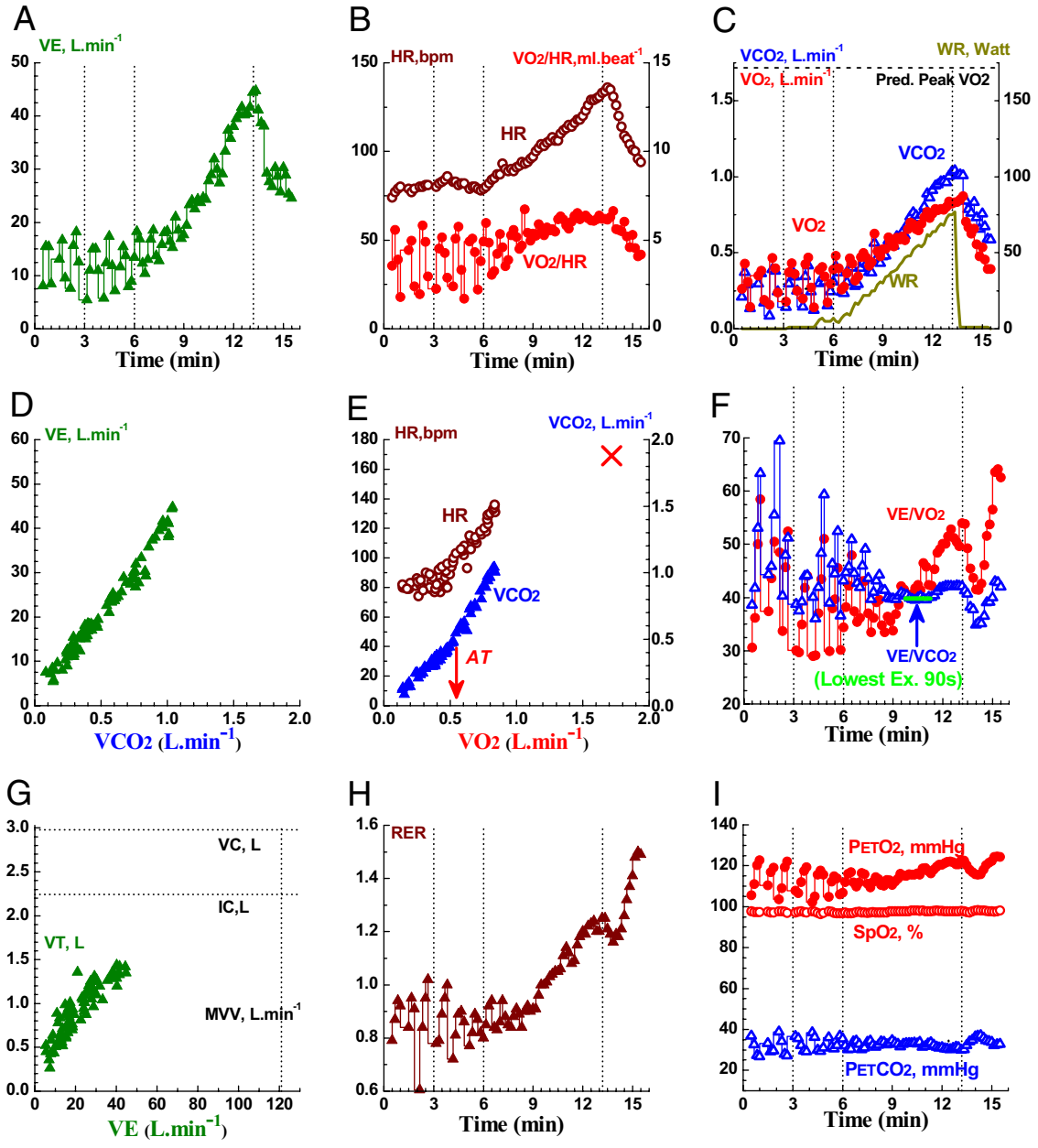

Figure 1 9-Panel Display of CPX Data in an OB Patient With CHF

There are clear oscillatory patterns of minute ventilation ($\dot{V}_E$) **(A)**, oxygen pulse **(B)**, oxygen uptake per minute ($\dot{V}_{O_2}$) and carbon dioxide output per minute ($\dot{V}_{CO_2}$) **(C)**, $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ **(F)**, respiratory exchange ratio (RER) **(H)**, and end-tidal P_{O_2} ($P_{ET}O_2$) and end-tidal P_{CO_2} ($P_{ET}CO_2$) **(I)** from rest to the anaerobic threshold (AT) level. The 10-s averaged values are plotted against time for rest (0 to 3 min), constant very low level exercise (3 to 6 min), increasing–work rate (WR) exercise (6 min to **right vertical dashed line**), and recovery (right of **right vertical dashed line**) for $\dot{V}_E$ **(A)**; heart rate (HR) and oxygen pulse **(B)**; $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and WR, including predicted peak $\dot{V}_{O_2}$ **(horizontal dashed line) (C)**; $\dot{V}_E$ versus $\dot{V}_{CO_2}$ **(D)**; HR and $\dot{V}_{CO_2}$ plotted against $\dot{V}_{O_2}$ (+ = predicted peak HR and predicted peak $\dot{V}_{O_2}$) and AT by V-slope method (**arrow** to x-axis) **(E)** (37); ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}_{O_2}$) and carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$), with a **short green horizontal line** indicating the 90-s average of the lowest $\dot{V}_E/\dot{V}_{CO_2}$ ratio during exercise (38) **(F)**; tidal volume (VT) versus $\dot{V}_E$ with inspiratory capacity (IC) and vital capacity (VC) as **horizontal lines** intersecting on the y-axis and maximal voluntary ventilation (MVV) intersecting on the x-axis **(G)**; RER **(H)**; and $P_{ET}O_2$ and $P_{ET}CO_2$ and oximetric oxyhemoglobin saturation (SpO_2) **(I)**. CHF = chronic left ventricular heart failure; CPX = cardiopulmonary exercise testing; OB = oscillatory breathing pattern.

frequency must also be visible in 3 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 (i.e., $\dot{V}_{CO_2}/\dot{V}_{O_2}$), or end-tidal pressures for oxygen and carbon dioxide (Fig. 1).

Other data. At each site, resting and exercise heart rate, systemic arterial systolic and diastolic blood pressure, 6-min walk distance, New York Heart Association functional classification, electrocardiographic, left ventricular ejection

fraction, echocardiographic (interpreted by the echocardiography core laboratories), and quality-of-life data were measured. The latter used the Minnesota Living With Heart Failure Questionnaire, with scores ranging from 0 to 105, with higher scores indicating poorer quality of life (34). These baseline measurements and 6-month outcomes were evaluated only after completing our CPX analyses. The mortality outcome was all-cause death; the morbidity outcome included death or a cardiac hospitalization for 24 h or more.

Statistical analysis. Data, expressed as mean ± SD unless specially noted, were first analyzed using unpaired *t* and chi-square tests. New York Heart Association functional classes were analyzed using the Mann-Whitney *U* test (40). A 2-tailed p value <0.05 was considered significant. Using all-cause mortality or morbidity at 6 months as outcome, receiver-operating characteristic curve analyses were performed. To detect an optimal cutoff value, we computed and searched for the shortest distance on its receiver-operating characteristic curve, that is, distance = $\sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2}$ (41) by changing levels as follows: 2 decimals for absolute values, whole numbers for weight-normalized values, and 5% for %pred. On the basis of the optimal cutoff value, sensitivity, specificity, and area under the receiver-operating characteristic curve (AUC) were reported. Using the optimal cutoff value, univariate and multivariate regression analyses were performed to obtain the optimal predictor model and to evaluate prognostic values (42,43). To evaluate the effect of adding OB on the key CPX measures, we used step-by-step repeated multivariate analyses to obtain the next model by excluding the most significant variables of prior analysis. Odds ratios (ORs) were calculated and tested using a Wald logistic regression model and are presented for important single and combined predictors. The OR of the combined 2-predictor model compared these of 2 measurements both abnormal with these of 2 measurements both normal. Kaplan-Meier survival curves were constructed, and log-rank tests were performed to compare the most important single and combined predictors. Statistical software used were SPSS version 15.0 (SPSS, Inc., Chicago, Illinois), Origin version 7 (OriginLab Corporation, Northampton, Massachusetts), and SigmaPlot version 8.0 (Aspire Software International, Ashburn, Virginia). Graphs were generated using Origin or SigmaPlot.

Results

Resting and preliminary data. Patient demographics and resting measurements are shown in Table 1. During 6-month follow-up, 19 patients died and 489 patients survived, with a total mortality rate of 3.7%. One hundred seven patients had 1 or more cardiac hospitalizations lasting >24 h or death, with a total morbidity rate of 21%. Two hundred fifty-eight patients with CHF (51%) were identified as OB positive. Approximately three-quarters of patients were men; the mean age, height, and weight were 64 years, 172 cm, and 87 kg, respectively. Survivors were heavier ($p < 0.001$), but sex, age, and height were not significantly different ($p > 0.05$). Resting heart rate and systemic arterial systolic and diastolic blood pressure did not differ ($p > 0.05$). Most patients were in New York Heart Association functional class III (n = 440 [87%]), with 52 (10%) in class II and 16 (3%) in class IV. Survivors' New York Heart Association functional classifications were less severe than those of nonsurvivors ($p = 0.031$). Survivors' left ventricular ejection fractions were significantly higher than those of nonsurvivors (26 ± 7% vs. 22 ± 6%, $p = 0.023$). Neither QRS interval duration nor quality-of-life scores differed significantly ($p = 0.85$ and $p = 0.67$, respectively).

Table 1 Demographics, Clinical Characteristics, and Resting Measurements and Their Comparisons of Between Positive and Negative Mortality, Morbidity, and OB Subgroups in Patients With CHF

Variable	All Patients (n = 508)	−Mortality (n = 489)	+Mortality (n = 19)	−Morbidity (n = 401)	+Morbidity (n = 107)	−OB (n = 258)	+OB (n = 250)
Men	355 (70%)	340 (70%)	15 (79%)*	278 (69%)	77 (72%)	183 (70%)	172 (67%)
Age (yrs)	64 ± 12	64 ± 12	66 ± 14	64 ± 12	64 ± 14	63 ± 12	64 ± 13
Height (cm)	172 ± 10	172 ± 10	171 ± 7	172 ± 10	171 ± 7	173 ± 10	171 ± 10*
Weight (kg)	87 ± 22	88 ± 22	76 ± 11‡	88 ± 22	83 ± 21	89 ± 22	85 ± 21*
Resting HR (beats/min)	77 ± 14	76 ± 13	86 ± 22	76 ± 13	80 ± 17*	76 ± 14	78 ± 14
Resting SBP (mm Hg)	118 ± 19	118 ± 19	115 ± 21	118 ± 19	116 ± 21	119 ± 19	117 ± 19
Resting DBP (mm Hg)	71 ± 11	71 ± 11	71 ± 9	71 ± 11	71 ± 11	72 ± 11	70 ± 11
NYHA functional class II/III/IV	52/440/16	52/423/14	0/17/2*	47/345/9	5/95/7*	21/228/9	31/212/7
LVEF (%)	26 ± 7	26 ± 7	22 ± 6*	26 ± 7	25 ± 7	27 ± 7	25 ± 7‡
QRS interval (ms)	138 ± 33	138 ± 33	142 ± 25	138 ± 33	138 ± 32	137 ± 33	140 ± 32
QRS interval >120 ms	284 (56%)	271 (55%)	13 (68%)†	265 (69%)	71 (72%)	132 (51%)	152 (61%)*
Quality of life (score)	51 ± 25	51 ± 26	53 ± 23	50 ± 26	55 ± 22*	48 ± 24	54 ± 27*
6-min walk distance (m)	291 ± 101	293 ± 100	239 ± 106	300 ± 99	264 ± 104†	312 ± 94	270 ± 103‡
BVP/CRT on	363 (71%)	348 (71%)	15 (79%)	283 (70%)	80 (74%)	182 (72%)	181 (71%)

Data are expressed as n (%) or mean ± SD. *$p < 0.05$, †$p < 0.01$, and ‡$p < 0.001$, positive groups versus negative groups using chi-square test, unpaired *t* test, or *U* test.

BVP = biventricular pacing; CHF = chronic left ventricular heart failure; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OB = oscillatory breathing pattern; SBP = systolic blood pressure.

Table 2 CHF Population Deaths and Hospitalizations in 6 Months

Study	BVP/CRT	Death	Cardiac Hospitalization (Including Death)
RethinQ (n = 237)*	On (n = 152)*	5 (3.3%)	31 (20.4%)
	Off (n = 85)	2 (2.3%)	17 (20.0%)
RHYTHM (n = 271)†	On (n = 210)	9 (4.3%)	48 (23.0%)
	Off (n = 61)	3 (4.9%)	11 (17.7%)

*Includes patients in registry group for BVP or CRT on (34). †Includes all patients with baseline cardiopulmonary exercise testing but excludes data of crossover patients (33).

RethinQ = Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS Complexes; RHYTHM = Resynchronization for Hemodynamic Treatment for Heart Failure Management; other abbreviations as in Table 1.

The 6-minute walk distance was borderline lower in nonsurvivors (239 ± 106 m vs. 293 ± 100 m, p = 0.056). Neither the presence nor the absence of cardiac resynchronization therapy (CRT) settings influenced 6-month survival. The trends in morbidity were similar to those in mortality (Table 1). However, the presence of OB increased the likelihood and statistical significance of poorer left ventricular ejection fraction, quality of life, and 6-min walk distance.

There were 210 on and 61 off for the BVP and CRT settings of RHYTHM patients (QRS interval ≥150 ms). There were 152 on (including 67 nonrandomized patients in the registry group) and 85 off for the BVP and CRT settings of RethinQ patients (QRS interval ≤130 ms). There were no differences in mortality and morbidity between differing study groups (Table 2). All patients were reported to be on stable medical regimens for CHF treatment. All received angiotensin-converting enzyme inhibitors (82%) or angiotensin receptor blockers (18%); 86% received beta-adrenergic blockers.

CPX measurements. All patients performed baseline CPX safely and without complications: 58% used the cycle and 42% used the treadmill. Seventeen patients (3%) completed their exercise before the end of 3-min warm-up; the remaining 491 (97%) exercised longer. Exercise duration, including warm-up, was 8.4 ± 3.3 min. The AT was indeterminate in 17 patients (15 survivors and 2 nonsurvivors and 3 OB negative and 14 OB positive). One hundred ninety-five patients (38%) stated they were predominantly limited by dyspnea, 289 (56%) by fatigue, and 24 (5%) by other factors. The limiting symptom was not significantly related to early death at 6 months (OR: 0.99; 95% confidence interval: 0.01 to 1.97).

Table 3 compares mortality, morbidity, and OB for each CPX parameter. Exercise capacity decreased in all patients,

Table 3 CPX Measurements and Their Comparisons of Between Negative and Positive Mortality, Morbidity, and OB Subgroups in Patients With CHF

Measurement	All Patients (n = 508)	−Mortality (n = 489)	+Mortality (n = 19)	−Morbidity (n = 401)	+Morbidity (n = 107)	−OB (n = 258)	+OB (n = 250)
Dyspnea-limited exercise	194 (37%)	187 (38%)	7 (36%)	160 (33%)	34 (32%)	104 (40%)	90 (36%)
Peak HR (beats/min)	108 ± 21	108 ± 20	109 ± 27	108 ± 21	107 ± 22	110 ± 21	106 ± 20*
Peak SBP (mm Hg)	141 ± 26	142 ± 26	132 ± 24	142 ± 26	137 ± 25	145 ± 25	137 ± 25‡
Peak DBP (mm Hg)	77 ± 14	77 ± 14	74 ± 10	77 ± 14	76 ± 13	78 ± 13	76 ± 14*
Peak $\dot{V}_E$ (l/min)	43 ± 15	43 ± 15	37 ± 10*	44 ± 15	40 ± 14*	45 ± 15	40 ± 14‡
Peak work load (W)	60 ± 37	61 ± 37	39 ± 29†	63 ± 38	51 ± 31†	68 ± 39	53 ± 33‡
Peak RER (ratio)	1.07 ± 0.13	1.07 ± 0.13	1.01 ± 0.16	1.07 ± 0.13	1.08 ± 0.14	1.07 ± 0.13	1.08 ± 0.14
Peak $\dot{V}_{O_2}$							
%pred	53 ± 16	53 ± 16	40 ± 14§	54 ± 16	46 ± 15§	56 ± 16	49 ± 16§
ml/min/kg	12.1 ± 4.0	12.2 ± 4.0	9.6 ± 3.5‡	12.4 ± 4.1	10.7 ± 3.4§	13.1 ± 4.1	11.0 ± 3.7§
l/min	1.00 ± 0.40	1.01 ± 0.40	0.72 ± 0.31‡	1.04 ± 0.40	0.86 ± 0.36§	1.10 ± 0.40	0.90 ± 0.37§
AT (n = 491)							
%pred	57 ± 16	57 ± 16	47 ± 13†	59 ± 16	51 ± 13§	60 ± 15	54 ± 16‡
ml/min/kg	8.8 ± 2.5	9.1 ± 2.6	8.0 ± 2.2*	9.0 ± 2.6	8.0 ± 2.2§	9.4 ± 2.6	8.2 ± 2.3§
l/min	0.72 ± 0.26	0.73 ± 0.26	0.57 ± 0.20†	0.75 ± 0.26	0.63 ± 0.23§	0.78 ± 0.27	0.67 ± 0.23§
Peak oxygen pulse							
%pred	77 ± 23	78 ± 23	58 ± 20†	79 ± 23	68 ± 22§	81 ± 22	73 ± 23§
ml/beat	9.4 ± 3.6	9.5 ± 3.6	6.6 ± 2.3†	9.7 ± 3.6	8.2 ± 3.4§	10.2 ± 3.7	8.6 ± 3.3§
Lowest $\dot{V}_E/\dot{V}_{CO_2}$ ratio							
%pred	137 ± 34	135 ± 33	173 ± 40§	133 ± 34	149 ± 34§	129 ± 25	145 ± 40§
Ratio	39.2 ± 10.2	38.8 ± 10.1	50.1 ± 12.6‡	38.3 ± 10.2	42.7 ± 10.5§	36.7 ± 7.9	41.6 ± 11.9§
Slope of $\dot{V}_E$ versus $\dot{V}_{CO_2}$							
%pred	120 ± 59	119 ± 59	161 ± 46§	116 ± 59	136 ± 55‡	114 ± 38	126 ± 74†
Slope	35.3 ± 17.1	34.9 ± 17.0	46.9 ± 14.6†	34.1 ± 17.1	40.0 ± 16.0†	33.6 ± 8.8	37.4 ± 22.1†
Intercept	3.0 ± 3.3	3.1 ± 3.3	2.3 ± 3.4	3.2 ± 3.3	2.6 ± 3.5	3.6 ± 3.0	2.6 ± 3.5‡

Data are expressed as mean ± SD. *p < 0.05, †p < 0.01, ‡p < 0.001, and §p < 0.0001, positive groups versus negative groups using chi-square test or unpaired *t* test.

AT = anaerobic threshold; oxygen pulse = $\dot{V}_{O_2}$/HR; %pred = percent of predicted value; RER = respiratory exchange ratio (i.e., $\dot{V}_{CO_2}/\dot{V}_{O_2}$); slope of $\dot{V}_E$ versus $\dot{V}_{CO_2}$ = $\dot{V}_E$ as a function of $\dot{V}_{CO_2}$; $\dot{V}_{CO_2}$ = carbon dioxide output per min (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 $\dot{V}_E$ to $\dot{V}_{CO_2}$; $\dot{V}_{O_2}$ = oxygen uptake per minute (0°C, 760 mm Hg, dry); other abbreviations as in Table 1.

especially in nonsurvivors and those hospitalized or with OB. Absolute and %pred values for peak $\dot{V}O_2$, AT, peak oxygen pulse, lowest $\dot{V}E/\dot{V}CO_2$ ratio, and slope of $\dot{V}E$ versus $\dot{V}CO_2$ were all significantly worse in nonsurvivors ($p < 0.05$). Peak $\dot{V}E$ and peak work load were also lower in nonsurvivors ($p < 0.05$). Peak exercise heart rate, systemic arterial systolic and diastolic blood pressure, and respiratory exchange ratio were not discriminatory ($p > 0.05$). The CPX patterns for morbidity and OB were similar to those for mortality, often with increasing statistical significance (Table 3).

Sensitivity and specificity analyses, cutoff values, and AUC analyses for single or combinations of parameters are shown in Table 4. The order of most to least significance was lowest $\dot{V}E/\dot{V}CO_2$ ratio, slope of $\dot{V}E$ versus $\dot{V}CO_2$, peak $\dot{V}O_2$, peak oxygen pulse, OB, AT, and 6-min walk distance ($p < 0.001$ to $p < 0.05$). With the best cutoff of 155%pred, the lowest $\dot{V}E/\dot{V}CO_2$ ratio had the highest AUC of 0.748, which increased to 0.797 when combined with OB. The left ventricular ejection fraction, QRS interval duration, quality of life, and New York Heart Association functional classification were not significant predictors of nonsurvival.

OR mortality analyses, combining OB and gas exchange parameters (Fig. 2A), were invariably consistent with the AUC analyses in Table 4. The combination of the lowest $\dot{V}E/\dot{V}CO_2$ ratio with OB, the optimal 2-predictor model, yielded an OR of 38.9 (Fig. 2A). Using best cutoff values, the ORs of %pred values were higher than those of the absolute values for the lowest $\dot{V}E/\dot{V}CO_2$ ratio, slope of $\dot{V}E$ versus $\dot{V}CO_2$, peak $\dot{V}O_2$, peak oxygen pulse, and AT (Fig. 2A). The elevated lowest $\dot{V}E/\dot{V}CO_2$ ratio was also the best single predictor by both OR (Fig. 2A) and Kaplan-Meier plot analyses (Fig. 3A). Using stepwise multivariate regression analysis, the lowest $\dot{V}E/\dot{V}CO_2$ ratio was invariably picked first, reducing all other CPX measurements except OB to nonsignificance. There were significant increases in OR for lowest $\dot{V}E/\dot{V}CO_2$ ratio, slope of $\dot{V}E$ versus $\dot{V}CO_2$, peak $\dot{V}O_2$, peak oxygen pulse, and AT, by combining OB. However, there were no significant increases in OR by combining peak $\dot{V}O_2$, peak oxygen pulse, or AT with lowest $\dot{V}E/\dot{V}CO_2$ ratio. Morbidity OR analyses were significant for absolute and normalized values (Fig. 2B). The morbidity OR values were lower than those of mortality; adding OB always increased the OR values.

Figure 3 shows the Kaplan-Meier curves for lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred) and OB for mortality (Fig. 3A) and morbidity (Fig. 3B). The 6-month survival rate was 87.6% in patients with elevated lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred), 93.8% in those with positive OB, and 84.6% in those with both elevated lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred) and positive OB. For patients with more normal lowest $\dot{V}E/\dot{V}CO_2$ ratio or negative OB or both, the

Table 4 Sensitivity, Specificity, AUC With 95% CI, and Best Cutoff Values for Mortality in Patients With CHF

Measurement and Best Cutoff Value	Single Measurement				Combined With OB	
	Sensitivity	Specificity	AUC (95% CI)	p Value	AUC (95% CI)	p Value
Peak $\dot{V}O_2$						
<50%pred	0.79	0.59	0.701 (0.590–0.813)	0.003	0.760 (0.661–0.860)	<0.001
<11 ml/min/kg	0.74	0.60	0.652 (0.532–0.771)	0.025	0.747 (0.646–0.848)	<0.001
<0.80 l/min	0.68	0.65	0.679 (0.555–0.802)	0.008	0.744 (0.632–0.856)	<0.001
AT (n = 491)						
<60%pred	0.88	0.39	0.661 (0.549–0.772)	0.024	0.723 (0.616–0.829)	0.001
<9 ml/min/kg	0.88	0.42	0.643 (0.529–0.757)	0.047	0.712 (0.605–0.819)	0.002
<0.60 l/min	0.82	0.51	0.645 (0.512–0.779)	0.042	0.686 (0.579–0.794)	0.006
Peak oxygen pulse						
<75%pred	0.84	0.50	0.683 (0.576–0.790)	0.007	0.751 (0.650–0.851)	<0.001
<7.5 ml/beat	0.68	0.66	0.682 (0.575–0.789)	0.007	0.747 (0.660–0.834)	<0.001
Lowest $\dot{V}E/\dot{V}CO_2$ ratio						
≥155%pred	0.68	0.78	0.748 (0.624–0.872)	<0.001	0.797 (0.701–0.893)	<0.001
Ratio ≥40	0.74	0.65	0.706 (0.589–0.823)	0.002	0.763 (0.665–0.862)	<0.001
Slope of $\dot{V}E$ versus $\dot{V}CO_2$						
≥140%pred	0.63	0.79	0.723 (0.594–0.852)	0.001	0.774 (0.663–0.885)	<0.001
Slope ≥40	0.63	0.74	0.700 (0.572–0.829)	0.003	0.757 (0.646–0.868)	<0.001
OB+	0.84	0.49	0.674 (0.566–0.781)	0.009		
Dyspnea-limited exercise+	0.37	0.59	0.493 (0.361–0.625)	0.92		
LVEF <25%	0.61	0.51	0.574 (0.443–0.705)	0.71		
QRS interval >120 ms	0.68	0.43	0.565 (0.438–0.692)	0.34		
BVP/CRT off	0.16	0.68	0.434 (0.312–0.556)	0.33		
Quality-of-life score >50	0.61	0.42	0.532 (0.401–0.662)	0.64		
6-min walk distance <250 m	0.61	0.68	0.644 (0.513–0.776)	0.033	0.728 (0.629–0.827)	0.001
NYHA functional class ≥IV	0.11	0.94	0.538 (0.402–0.675)	0.57		

AUC = area under the receiver-operating characteristic curve; CI = confidence interval; other abbreviations as in Tables 1 and 3.

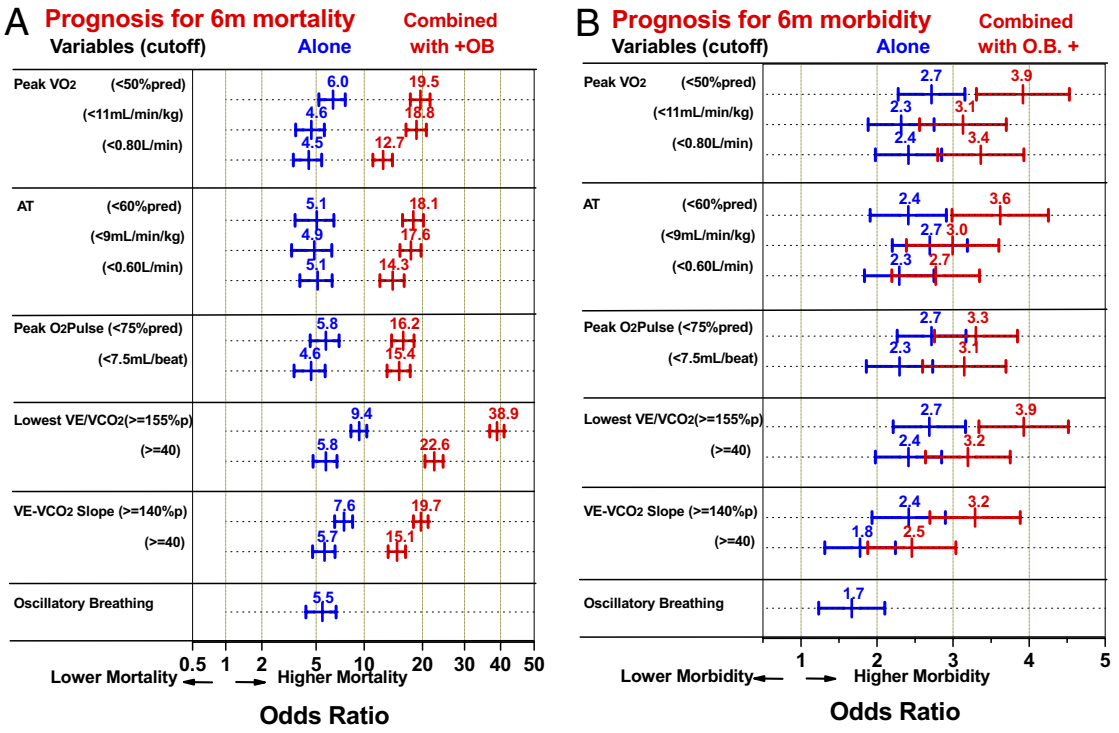

Figure 2 OR of CPX Variables, Alone and Combined With Positive OB Pattern, for 6-Month Mortality and Morbidity in CHF

(A) Mortality. The **left column** shows the optimal cutoff values for each variable with their mean odds ratios (ORs) and 95% confidence intervals. The **blue bars** are ORs for single measures alone; the **red bars** are ORs for the CPX measures combined with +OB. All key CPX measures and +OB alone have significant ORs. The optimal predictor model is a 2-predictor model of the lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155% of predicted value [%pred]) with +OB by stepwise multivariate regression analysis ($p < 0.001$; all others become nonsignificant, $p > 0.05$). All other 2-predictor models (1 of key CPX measures with OB) on the **right side** are obtained by the step-by-step repeated stepwise multivariate regression analysis, excluding the most significant CPX measures at the last analysis, to evaluate the effect of adding OB on key CPX measures for prognosis. All obtained models are always the 2-predictor model combining 1 of the key CPX measures with OB. There is no predictor model using any 2 of the CPX key measures. When key CPX measures were combined with +OB, the ORs were significantly increased ($p < 0.05$ to $p < 0.001$). For each CPX measurement and the combination with OB, the prognostic significance from high to low is %pred > per kilogram > absolute. The best single predictor is lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred) (OR: 9.4), and the best combination is lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred) with +OB (OR: 38.9). **(B)** Morbidity. Although the ORs are lower, the trends confirm the mortality data. Abbreviations as in Figure 1.

survival rates were significantly higher (98.5%, 98.8%, and 99.5%, respectively) (Fig. 3A). Morbidity Kaplan-Meier analyses (Fig. 3B) were similar to those of mortality (Fig. 3A). The 6-month hospitalization-free rates were 64.6% for elevated lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred), 74.7% for positive OB, and 56.6% for patients with both elevated lowest $\dot{V}E/\dot{V}CO_2$ ratio (≥155%pred) and positive OB, compared with 82.5% for lowest $\dot{V}E/\dot{V}CO_2$ ratio <155%pred, 83.1% for negative OB, and 83.3% for patients with both $\dot{V}E/\dot{V}CO_2$ ratio <155%pred and negative OB.

Discussion

OB in CHF. OB has been linked to strokes and advanced CHF (23–27). The prevalence of OB in our patients with CHF approximates 50%, quite similar to that of other reports (24–27). Prior standards for the recognition of OB focused on the magnitude of the oscillations ($\dot{V}E$ by ≥25% [25] or ≥30% [26,27]) and required 2 or more consecutive oscillations (24–26) or occurred over 60% of the exercise time (27). To be OB positive, we required that: 1) $\dot{V}E$ have 2 or more consecutive oscillations with amplitudes ≥30% of the mean; 2) 3 or more other gas exchange variables also oscillate at the same frequency; and 3) each oscillatory cycle duration be between 40 and 140 s. In this and other reports (24–27), a close linkage between OB and clinical and physiological severity has been found.

Abnormal exercise gas exchange and OB can predict mortality and increasing morbidity. In our study, OB was found to be an independent and good prognostic indicator not only of early death but also of increasing morbidity in patients with CHF. Alone, it is not superior to peak $\dot{V}O_2$ or slope of $\dot{V}E$ versus $\dot{V}CO_2$, as some have found (25–27). However, it is clear from this study that OB is a significant independent predictor and, in combination with other abnormal CPX gas exchange measurements, makes them even more important in predicting both mortality and morbidity. It increases the prognostic importance of all other abnormal CPX gas exchange parameters. For clinical application of CPX, it would seem appropriate to add OB as one of the

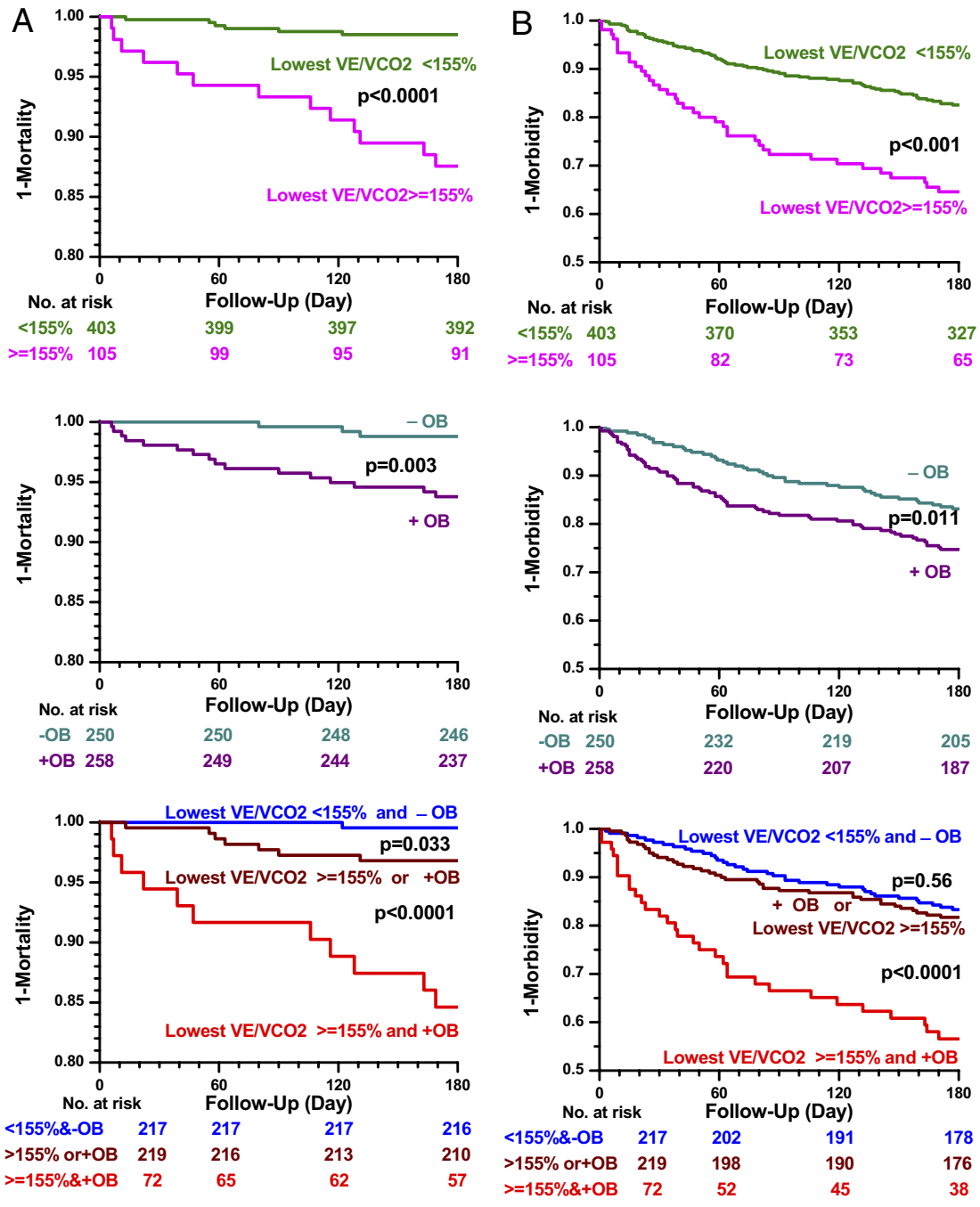

Figure 3 **Kaplan-Meier Survival Curves of Lowest $\dot{V}E/\dot{V}CO_2$ and OB, Singly and Combined, for 6-Month Mortality and Morbidity in CHF**

(A) 1 − mortality and **(B)** 1 − morbidity (i.e., hospitalization-free rate). The numbers of patients at risk for each curve are given at 60-day intervals. **Top panels** compare the lowest $\dot{V}E/\dot{V}CO_2$ ratio <155%pred versus ≥155%pred ($p < 0.001$). **Middle panels** compare positive (+OB) versus negative OB (−OB) ($p < 0.05$). **Bottom panels** compare the lowest $\dot{V}E/\dot{V}CO_2$ ratio <155%pred and −OB **(blue)**; $\dot{V}E/\dot{V}CO_2$ ≥155%pred or +OB **(brown)**; and lowest $\dot{V}E/\dot{V}CO_2$ ≥155%pred and +OB **(red)**. The p values of **red** versus both of **blue** and **brown** are <0.0001. Abbreviations as in Figures 1 and 2.

important factors for grading the severity of CHF. Therapy that decreases OB should be welcomed.

Many prior studies have demonstrated the importance of exercise gas exchange parameters in evaluating patients with CHF (7–27). Our findings of decreased aerobic functional capacity (lower peak $\dot{V}O_2$, lower AT, and/or lower peak oxygen pulse) and decreased ventilatory efficiency (elevated lowest $\dot{V}E/\dot{V}CO_2$ ratio and steeper slope of $\dot{V}E$ versus $\dot{V}CO_2$) were consistent with those of others (7–32). Our multivariate analysis demonstrated that the magnitude of ventilatory inef-

ficiency, presumably reflecting the degree of ventilation-perfusion mismatch secondary to low cardiac output, was a better predictor of early death than peak $\dot{V}O_2$. More important, in our study, the combination of a positive OB and lowest $\dot{V}E/\dot{V}CO_2$ ratio ≥155%pred or slope of $\dot{V}E$ versus $\dot{V}CO_2$ ≥140%pred or AT <60%pred or peak $\dot{V}O_2$ <50%pred or peak oxygen pulse <75%pred had 13 or more times higher risk for death within 6 months than if these findings were not present. Adding OB increased the OR for single measurements 2- to 4-fold. For all key CPX measurements, the %pred cutoff values were superior to absolute values, probably because it lessens differences between sex, body size, and age. Adding peak $\dot{V}O_2$, peak oxygen pulse, or AT did not add significant prognostic importance to the lowest $\dot{V}E/\dot{V}CO_2$ ratio, probably because of the overlapping of their physiological information and high correlations with each other.

Comparing prognosis using other measurements. Although some investigators have reported that dyspnea rather than fatigue as the symptom terminating exercise indicates a worse prognosis in CHF (28–30), other reports and this study do not confirm this (31,32). We found by *t* test that higher body weight, lower New York Heart Association functional classification, and higher left ventricular ejection fraction significantly improved survival (Table 1). But by AUC analysis using best the cutoff (Table 4), they were not significant predictors ($p > 0.05$). However, lower 6-min walk distance with OB during CPX worsened 6-month survival. No other single or combined measurements reached significance comparable with the combination of OB and CPX gas exchange parameters.

Study limitations. LOW DEATH RATE. A limitation of this analysis is the modest number of deaths (n = 19) over the 6-month follow-up period. However, the prognostic analysis of morbidity (n = 107) confirms the key findings for the mortality analysis. Each key CPX parameter and OB are independent indicators of mortality and morbidity. Combining CPX parameters with OB increases their prognostic importance. The risk for type I error may exist because of the large number of variables tested.

SAMPLING BIAS. A potential selection bias may have occurred, because the patients with CHF analyzed in this study were enrolled in CRT clinical trials and thus not representative of the whole spectrum of patients with CHF. These patients could have been protected by their devices, although we did not find a difference in survival between the CRT-off group and CRT-on group. In addition, this analysis included patients with normal QRS interval durations (<120 ms) from the RethinQ study, who do not meet current indications for CRT (34). The low overall 6-month death rate of 3.7% in the patients with CHF with a mean age of 65 years may be due to better physician management, treatment improvements, and cardioverter-defibrillator and/or pacemaker use. In general, BVP or CRT may improve synchronization in CHF (33,34,44), and that improvement might have been a potential contributor to the low death rate of this study.

QUALITY CONTROL AND STANDARD DATA ANALYSIS OF CPX FOR THE MULTICENTER STUDY. CPX gas exchange measurements are dependent on the quality of the equipment, the skills of technicians, and the calculation methods of software. After being qualified for the studies, if we questioned results on a patient's test, the relevant site lab had to prove its validity by requalification and repeat patient testing. This occurred 14 times at 12 laboratories and required 36 additional full CPX tests before we requalified the laboratories and accepted patients' test results. Therefore, the bias resulting from system errors were minimized. Although there were 6 different systems and many different versions of software at the 69 sites, we used them only for raw data collection rather than data analysis and reporting. Only one standard method of data analysis and reporting was used, so that the bias of interobserver and system software variability was minimized.

Although we used both treadmills and stationary cycles, each patient was always exercised on the same ergometer. Prior studies (35) have indicated that treadmill increases peak $\dot{V}O_2$, peak oxygen pulse, and AT by an average of 11% over cycle values but does not influence peak heart rate, peak $\dot{V}E$, lowest $\dot{V}E/\dot{V}CO_2$ ratio, or slope of $\dot{V}E$ versus $\dot{V}CO_2$ (38).

Conclusions

In this study, we found that the combination of OB and gas exchange data collected during CPX are powerful indicators of 6-month survival or death and morbidity of patients with CHF. For mortality, the lowest $\dot{V}E/\dot{V}CO_2$ ratio, with cutoff of 155%pred, was the best single predictor, with an OR of 9.4 and an AUC of 0.748. Adding OB increased the OR to 38.9 and the AUC to 0.797. For future clinical trials and daily practice, the lowest $\dot{V}E/\dot{V}CO_2$ ratio and/or other parameters (e.g., peak $\dot{V}O_2$, AT, peak oxygen pulse), when combined with OB, provide objective grading of heart failure severity. This might be preferable to the subjective grading of heart failure severity, as is commonly used in the recruitment of patients with CHF into clinical trials. It would have the advantage of obtaining more uniform patient responses. Finally, it needs to be recognized that good quality control is essential for clinical trials, particularly involving multiple centers.

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Key Words: heart failure ■ cardiopulmonary exercise testing ■ oscillatory breathing ■ early death ■ gas exchange.