

Ventilatory and Heart Rate Responses to Exercise Better Predictors of Heart Failure Mortality Than Peak Oxygen Consumption

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Background—An abnormally low chronotropic response and an abnormally high ventilatory response (\dot{V}_E/\dot{V}_{CO_2}) to exercise are common in patients with severe heart failure, but their relative prognostic impacts have not been well explored.

Methods and Results—Consecutive patients with heart failure referred for metabolic stress testing who were not taking β -blockers or intravenous inotropes ($n=470$) were followed for 1.5 years. The chronotropic index was calculated while peak \dot{V}_{O_2} and \dot{V}_E/\dot{V}_{CO_2} were directly measured. Chronotropic index and peak \dot{V}_{O_2} were considered abnormal if in the lowest 25th percentiles of the patient cohort, whereas \dot{V}_E/\dot{V}_{CO_2} was considered abnormal if in the highest 25th percentile. For comparative purposes, a group of 17 healthy controls underwent metabolic testing as well. Compared with controls, heart failure patients had markedly abnormal ventilatory and chronotropic responses to exercise. In the heart failure cohort, there were 71 deaths. In univariate analyses, predictors of death included high \dot{V}_E/\dot{V}_{CO_2} , low chronotropic index, low \dot{V}_{O_2} , low resting systolic blood pressure, and older age. Nonparametric Kaplan-Meier plots demonstrated that by dividing the population according to peak \dot{V}_E/\dot{V}_{CO_2} and peak \dot{V}_{O_2} , it is possible to identify low, intermediate, and very high risk groups. In multivariate analyses, the only independent predictors of death were high \dot{V}_E/\dot{V}_{CO_2} (adjusted relative risk [RR] 3.20, 95% CI 1.95 to 5.26, $P<0.0001$) and low chronotropic index (adjusted RR 1.94, 95% CI 1.18 to 3.19, $P=0.0009$).

Conclusions—The ventilatory and chronotropic responses to exercise are powerful and independent predictors of heart failure mortality. (*Circulation*. 1999;100:2411-2417.)

Key Words: heart failure ■ mortality ■ exercise ■ heart rate ■ ventilation

Currently 3.5 million people carry the diagnosis of heart failure in the United States, and the number is expected to increase to 6 million by the year 2030.¹ As cardiac transplantation has become a viable treatment option for patients with end-stage disease, it has become more incumbent on physicians to acquire precise prognostic information in order to provide accurate risk stratification.² Although several potential predictive variables have been studied, functional capacity, as defined by direct measurement of maximal oxygen consumption, has emerged as the most consistent and powerful predictor of mortality.³⁻⁵ Recently, reduced heart rate variability, as well as abnormal ventilatory and heart rate responses to exercise, have been found to be common in patients with severe heart failure.⁶⁻⁸ Whether they provide additional prognostic information, either alone or in combination, over peak oxygen consumption has not been well studied. Therefore, the purpose of this study was to carefully examine the predictive properties of the chrono-

tropic and ventilatory responses to exercise among patients referred for exercise testing who manifest chronic heart failure.

Methods

Study Population

The heart failure study cohort consisted of consecutive adults aged 18 to 70 who suffered from chronic heart failure and were referred for metabolic stress testing as part of a heart transplant evaluation. Patients were excluded if taking beta-adrenergic blockers or intravenous inotropes. For comparative purposes, a control cohort of 17 healthy adults underwent metabolic stress testing as well.

Clinic Data

Before each metabolic stress test, a structured interview and chart review yielded data on demographics, left ventricular ejection fraction, medications, cause of heart failure, standard cardiac risk factors, and other comorbidities. The definition of hypertension was based on JNC V criteria,⁹ whereas chart review and use of hypoglycemic medications established the diagnosis of diabetes.

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TABLE 1. Comparison of Selected Characteristics Between Healthy Controls and Heart Failure Patients

Characteristic	Controls (n=17)	Heart Failure (n=470)
Age, y	41±13	52±11
Female	7 (41%)	134 (29%)
Smoking	2 (12%)	116 (25%)
Height, m	1.8±0.1	1.7±0.1
Weight, kg	80±18	83±18
Resting heart rate, bpm	67±11	85±18
Resting systolic blood pressure, mm Hg	123±17	111±18
Resting diastolic blood pressure, mm Hg	79±14	76±11
Peak oxygen consumption, mL · kg ⁻¹ · min ⁻¹	32±8	18±6
Oxygen consumption at AT, mL · kg ⁻¹ · min ⁻¹	19±7	13±7
Peak respiratory exchange ratio	1.17±0.12	1.14±0.09
Peak heart rate, bpm	172±19	144±25
Peak systolic blood pressure, mm Hg	169±29	140±32
Chronotropic index	0.94±0.16	0.71±0.28
Peak minute ventilation, L/min	91±29	64±20
Peak respiratory rate, breaths/min	39±17	38±9
Peak tidal volume, L	2.4±0.8	1.7±0.5
\dot{V}_E/\dot{V}_{CO_2}	31.0±3.3	39.6±9.9

AT indicates anaerobic threshold.

Exercise Testing

Symptom-limited metabolic stress testing was performed according to the Naughton protocol and recorded on a MedGraphics cardiopulmonary system. Measurements of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), heart rate, minute ventilation (\dot{V}_E), tidal volume (\dot{V}_T), end-tidal carbon dioxide tension (P_{ETCO_2}), and tidal oxygen tension (P_{ETO_2}), and respiratory rate were made after steady state at rest and every 30 seconds during exercise. Also, during each stage of exercise, data on symptoms, rhythm, blood pressure (by indirect sphygmomanometry), and ST segment changes were prospectively collected. The ventilatory response to exercise was defined as the value of \dot{V}_E/\dot{V}_{CO_2} at peak exercise. Anaerobic threshold was determined by V-slope method if possible,¹⁰ otherwise, by inspection of ventilatory equivalents.¹¹ Patients were encouraged to exercise to a respiratory exchange ratio (ie, $\dot{V}_{CO_2}/\dot{V}O_2$) ≥ 1.09 .

Heart Rate Response to Exercise

Typically, the age-predicted maximum heart rate follows a linear regression equation, eg, 200 minus age in years. The problem with simply dividing peak heart rate by age-predicted maximum heart rate is that this value is significantly confounded by effects of age, resting heart rate, and most importantly, physical fitness.¹²

Wilkoff has described a method for describing the exercise heart rate response that takes advantage of the linear relation between exercise heart rate and metabolic work.¹³ Before exercise, a person has a certain metabolic reserve which is the difference between his peak oxygen consumption (or exercise capacity) and his rest oxygen consumption, typically 3.5 mL · kg⁻¹ · min⁻¹, or 1 metabolic equivalent (MET). As exercise progresses, that metabolic reserve is used up. Analogously, at rest there is a potential heart rate reserve, which is the difference between the peak attainable heart rate (as estimated, for example, by 220 minus age) and the resting heart rate. As exercise progresses heart rate reserve (HRR), like the metabolic reserve, is used up as well.

Thus, during any given stage of exercise, the percent metabolic reserve (MR) used can be expressed as:

$$\%MR \text{ used} = \frac{(\text{MET}_{s_{\text{stage}}} - \text{MET}_{s_{\text{rest}}})}{(\text{MET}_{s_{\text{peak}}} - \text{MET}_{s_{\text{rest}}})} \times 100$$

TABLE 2. Baseline Characteristics of Heart Failure Patients According to Value of Peak \dot{V}_E/\dot{V}_{CO_2}

Characteristic	\dot{V}_E/\dot{V}_{CO_2} Normal (<44.7)	\dot{V}_E/\dot{V}_{CO_2} Abnormal (≥ 44.7)
Age, y	50±11	56±9
Female	108 (31)	26 (22)
Coronary artery disease	107 (30)	56 (47)
Smoking	81 (23)	35 (30)
Diabetes	67 (19)	21 (18)
Hypertension	131 (38)	43 (36)
Lipid lowering therapy	63 (18)	12 (10)
Digoxin	277 (79)	102 (86)
ACE inhibitor	298 (85)	105 (89)
Diuretic	269 (76)	104 (88)
Ca-channel blocker	26 (7.4)	3 (2.5)
Resting systolic blood pressure, mm Hg	113±18	105±16
Resting diastolic blood pressure, mm Hg	76±11	74±10
Resting heart rate, bpm	83±17	86±15
Atrial fibrillation	21 (7.0)	8 (6.6)
Ejection fraction, %	21±8	18±7

Values in parentheses are percentages. ACE indicates angiotensin converting enzyme.

In an analogous fashion, the percent HRR used at any given stage of exercise is:

$$\%HRR \text{ used} = \frac{(\text{HR}_{\text{stage}} - \text{HR}_{\text{rest}})}{(220 - \text{age} - \text{HR}_{\text{rest}})} \times 100$$

In a group of healthy, nonhospitalized adults, a plot of heart rate reserve used to metabolic reserve used (% HRR used/% MR used) revealed a tight linear relationship with a slope of ≈ 1 and a 95% CI of 0.8 to 1.3.¹³ This chronotropic index accounts for age, resting heart rate, and functional capacity, and its value is independent of the stage of exercise considered or the protocol used.^{12,13} For the current study, peak exercise values were used.

End Points

The primary end point was death due to any cause; patients who underwent transplantation were censored on their transplant date.

TABLE 3. Exercise Characteristics of Heart Failure Patients According to the Value of Peak \dot{V}_E/\dot{V}_{CO_2}

Characteristic	\dot{V}_E/\dot{V}_{CO_2} Normal (<44.7)	\dot{V}_E/\dot{V}_{CO_2} Abnormal (≥ 44.7)
Peak $\dot{V}O_2$, mL · kg ⁻¹ · min ⁻¹	20±6	13±3
$\dot{V}O_2$ AT, mL · kg ⁻¹ · min ⁻¹	14±7	10±3
Peak respiratory exchange ratio	1.14±0.1	1.14±0.1
Peak heart rate, bpm	148±25	130±20
Peak systolic blood pressure, mm Hg	147±31	119±25
Chronotropic index	0.76±0.3	0.55±0.2
Peak \dot{V}_E , L/min	66±21	61±16
Peak respiratory rate, bpm	37±8	40±8
Resting \dot{V}_E/\dot{V}_{CO_2} *	42±6	52±7
AT \dot{V}_E/\dot{V}_{CO_2} *	34±5	47±7

$\dot{V}O_2$ AT indicates oxygen consumption at anaerobic threshold; \dot{V}_E , minute ventilation; \dot{V}_{CO_2} , carbon dioxide production; and peak $\dot{V}O_2$, peak oxygen consumption.

*Among patients where anaerobic threshold could be determined (n=406).

TABLE 4. Univariate Predictors of Death (n=71) Among Heart Failure Patients

Variable	Baseline Mortality*, %	Relative Risk (95% CI)	χ^2	P
High \dot{V}_E/\dot{V}_{CO_2} (≥ 44.7)	10	3.96 (2.48–6.31)	33	<0.0001
Low chronotropic index (≤ 0.51)	11	2.82 (1.76–4.50)	18	<0.0001
Low peak $\dot{V}O_2$ (≤ 13.9)	11	2.72 (1.70–4.35)	17	<0.0001
Low resting SBP (≤ 98 mm Hg)	12	2.10 (1.31–3.36)	10	0.0019
Low ejection fraction ($\leq 15\%$)	12	2.18 (1.32–3.59)	9	0.0022
Older age (≥ 61 y)	13	1.97 (1.22–3.19)	8	0.0055
Female	18	0.49 (0.26–0.92)	5	0.03
Coronary artery disease	13	1.57 (0.98–2.51)	4	0.06
Diabetes	14	1.51 (0.88–2.57)	3	0.133
Smoker	14	1.42 (0.86–2.35)	2	0.17
Shorter stature (≤ 167 cm)	16	0.69 (0.39–1.24)	2	0.22
Hypertension	14	1.30 (0.82–2.09)	1	0.27
High resting heart rate (≥ 96 bpm)	15	0.93 (0.55–1.59)	<1	0.80
Low weight (≤ 71 kg)	16	0.93 (0.54–1.61)	<1	0.81

SBP indicates blood pressure. Relative risks and CIs were derived from univariate Cox regression analyses.

*Mortality rate when risk factor absent.

Vital status was assessed by (1) interrogation of the hospital information system, (2) phone calls to patients, next of kin, or primary physicians, and (3) search of the social security master files.¹⁴ Vital status was confirmed in >98% of patients.

Statistical Analyses

Cut-off values for high \dot{V}_E/\dot{V}_{CO_2} , low chronotropic index, low peak $\dot{V}O_2$, low ejection fraction, short stature, low body weight, resting tachycardia, and low resting blood pressure were based on 75th or 25th percentiles as appropriate. The 75th and 25th percentile values were derived from the heart failure cohort. For descriptive purposes, baseline and exercise characteristics were divided according to normal or abnormally high \dot{V}_E/\dot{V}_{CO_2} . Variables thought to be related to death were analyzed using the Kaplan-Meier approach with formal testing by the log-rank test and univariate Cox regression analyses. After confirming the validity of the proportional hazard assumption, multivariate Cox regression models were used to assess the importance of \dot{V}_E/\dot{V}_{CO_2} , chronotropic index, peak $\dot{V}O_2$, and other possible predictors of death. Model construction was based on a stepwise approach with initial selection of covariates on the basis of results of

univariate analyses. The key variables of interest, namely \dot{V}_E/\dot{V}_{CO_2} , chronotropic index, and peak $\dot{V}O_2$, were assessed using both categorical and continuous approaches; for continuous approaches, logarithmic and inverse transformations were analyzed and found not to improve prediction of death. To avoid model overfitting, no more than 1 covariate per 10 outcome events were considered in regression models.

The ventilatory response to exercise is dependent on ventilatory drive, physiological dead space, and patient motivation to drive exercise beyond the anaerobic threshold. In order to eliminate potential confounding from the last factor, supplementary analyses were performed relating values of \dot{V}_E/\dot{V}_{CO_2} at rest and at anaerobic threshold. These analyses were confined to the 406 patients in whom anaerobic threshold could be determined. Pearson correlation analyses were used to assess the association between peak and submaximal values.

To analyze the association of peak \dot{V}_E/\dot{V}_{CO_2} and mortality in a continuous manner, a wholly parametric approach was used.¹⁵ One phase of constant hazard was identified indicating that an exponential model worked well. Modeling of peak \dot{V}_E/\dot{V}_{CO_2} and mortality included testing of logarithmic, threshold, inverse, and quadratic transformations after inspection of log odds of risk across quintiles of peak \dot{V}_E/\dot{V}_{CO_2} . A plot of estimated 18-month survivals for different conditions was constructed along with one standard error confidence limits.

All analyses were performed using the SAS 6.12 system (SAS, Inc). Statistical comparisons were considered significant for probability value ≤ 0.01 . Parametric hazards analyses were performed using PROC HAZARD and PROC HAZPRED (available from ftp://uabcvsr.cvsr.uab.edu).

Results

Baseline Characteristics

There were 470 heart failure patients eligible for analyses (72% men, age 52 ± 11 years, ejection fraction $21 \pm 8\%$, median peak $\dot{V}O_2$ $17.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ with 25th and 75th percentile 13.9 and $21.4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively). A respiratory exchange ratio of ≥ 1.09 was reached in 79% of the patients, whereas 90% reached a value of ≥ 1.02 . The majority of patients (65%) had a nonischemic cause of left ventricular dysfunction. Hypertension and atrial fibrillation

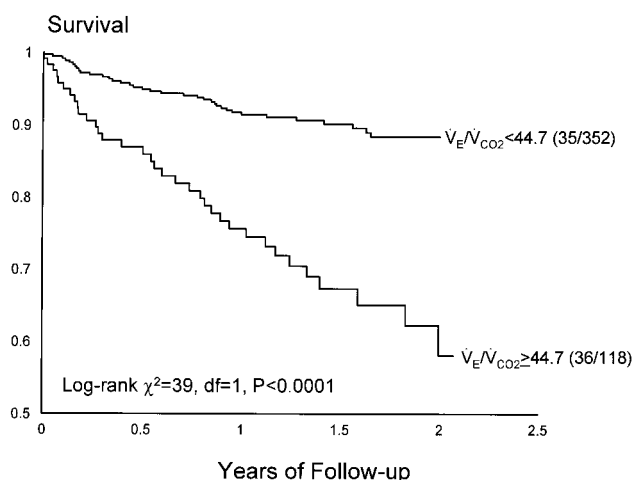


Figure 1. Kaplan-Meier plot relating survival to \dot{V}_E/\dot{V}_{CO_2} . For numbers in parentheses, numerators refer to number of deaths and denominators, number of patients within each subset.

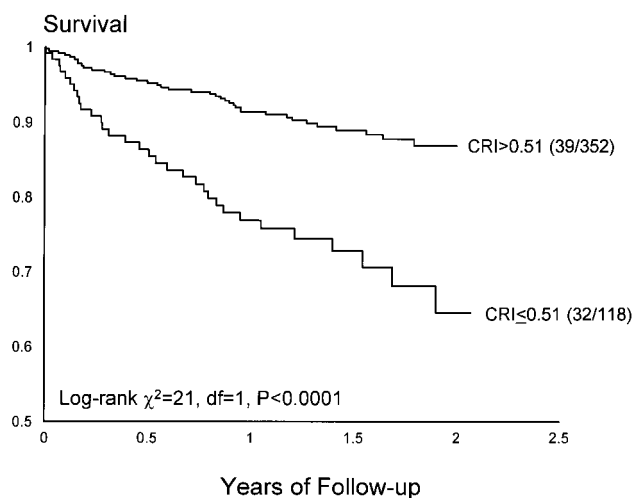


Figure 2. Kaplan-Meier plot relating survival to chronotropic index.

were present in 38% and 6% of patients, respectively. Most patients were receiving standard therapy with angiotensin-converting enzyme inhibitors (86%), digoxin (81%), and diuretics (79%). Only 6% of patients were taking calcium channel blockers.

Compared with 17 healthy controls (Table 1), the heart failure patients had markedly higher resting heart rate and peak \dot{V}_E/\dot{V}_{CO_2} and markedly lower peak $\dot{V}O_2$, peak heart rate, peak systolic blood pressure, and chronotropic index. Of note, the respiratory exchange ratios and the peak respiratory rates were similar in the 2 groups.

Baseline characteristics according to value of peak \dot{V}_E/\dot{V}_{CO_2} are summarized in Table 2. Patients who had an abnormally high \dot{V}_E/\dot{V}_{CO_2} were more likely to be older, have a history of coronary artery disease, and have lower resting systolic blood pressure, higher resting heart rate, and a lower ejection fraction. There were no marked differences between the 2 groups with respect to history of smoking, hypertension, diabetes, or atrial fibrillation.

Baseline exercise characteristics according to peak \dot{V}_E/\dot{V}_{CO_2} are summarized in Table 3. Patients with an abnormal \dot{V}_E/\dot{V}_{CO_2} had a lower exercise capacity (lower peak $\dot{V}O_2$ and $\dot{V}O_2$ at anaerobic threshold), a lower peak systolic blood pressure and heart rate, as well as a lower chronotropic index and lower peak \dot{V}_E . There was no difference in the respiratory exchange ratio between the 2 groups.

Correlation Analyses

Peak $\dot{V}O_2$ was found to have at least a moderate correlation with \dot{V}_E/\dot{V}_{CO_2} ($r = -0.64$) and chronotropic index ($r = 0.58$). The correlation was more modest between \dot{V}_E/\dot{V}_{CO_2} and chronotropic index ($r = -0.39$). Left ventricular ejection fraction had very weak correlations with \dot{V}_E/\dot{V}_{CO_2} ($r = -0.23$), chronotropic index ($r = 0.09$), and peak $\dot{V}O_2$ ($r = 0.15$).

Predictors of Mortality

Univariate predictors of death are found in Table 4. An abnormally high peak \dot{V}_E/\dot{V}_{CO_2} (≥ 44.7) was the strongest predictor of death. Analyses of the Kaplan-Meier survival curves (Figure 1) revealed a 1.5-year survival rate of 90% for

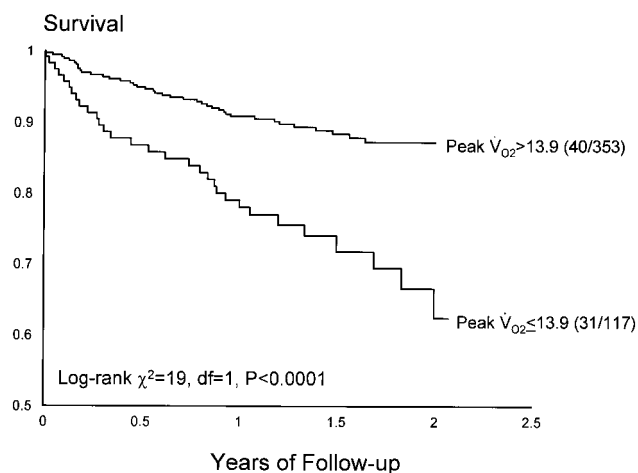


Figure 3. Kaplan-Meier plot relating survival to peak $\dot{V}O_2$.

those with a normal peak \dot{V}_E/\dot{V}_{CO_2} , compared with only 67% for those with an abnormal value. A low chronotropic index and a low peak $\dot{V}O_2$ also predicted higher mortality rates (Table 4, Figures 2 and 3). Resting systolic blood pressure, low ejection fraction, and older age were weaker predictors of death.

Combination of Risks and Mortality

When evaluating the significance of any combination of an abnormally high \dot{V}_E/\dot{V}_{CO_2} , low peak $\dot{V}O_2$, and low chronotropic index, an abnormally high \dot{V}_E/\dot{V}_{CO_2} combined with a low chronotropic index was associated with the highest risk of death (Figure 4). Combinations of an abnormally high \dot{V}_E/\dot{V}_{CO_2} and a low peak $\dot{V}O_2$ (Figure 5) and a low chronotropic index and a low peak $\dot{V}O_2$ (Figure 6) also identified groups at very high and relatively low risks for death.

Multivariate Analyses

Results of stepwise multivariate proportional hazards analyses are summarized in Table 5. After adjusting for low peak $\dot{V}O_2$, age, sex, history of coronary artery disease, and resting systolic blood pressure, only an abnormally high \dot{V}_E/\dot{V}_{CO_2} and a low chronotropic index remained independently pre-

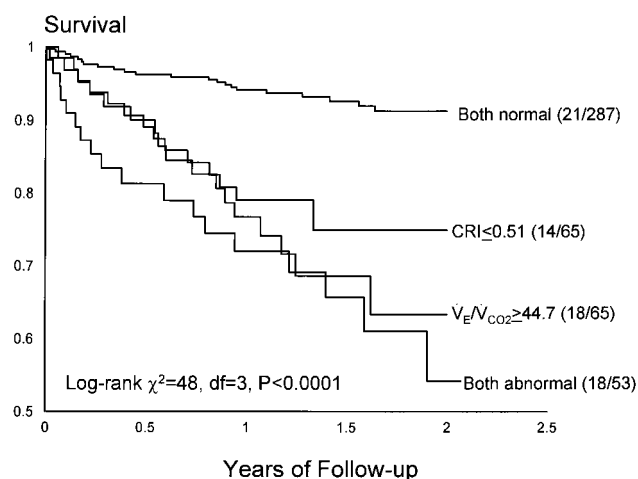


Figure 4. Kaplan-Meier plot relating survival to combination of \dot{V}_E/\dot{V}_{CO_2} and chronotropic index.

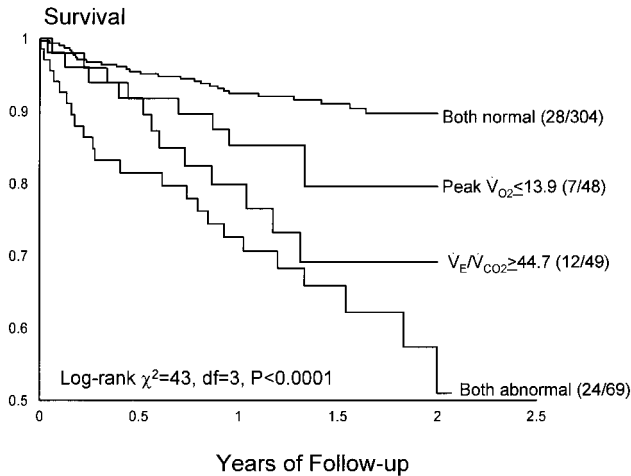


Figure 5. Kaplan-Meier plot relating survival to combination of \dot{V}_E/\dot{V}_{CO_2} and peak $\dot{V}O_2$.

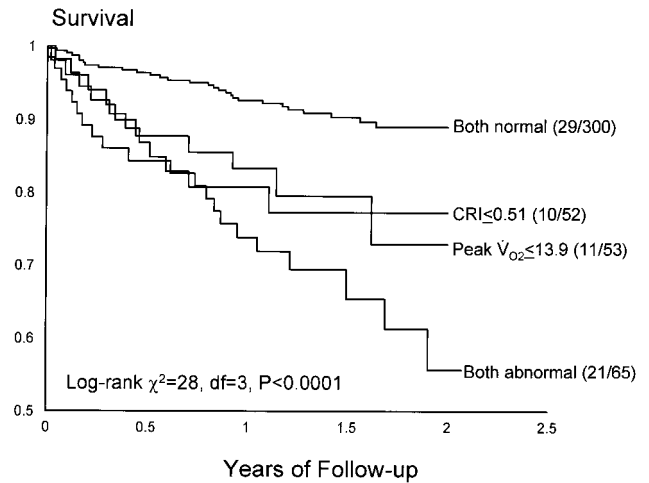


Figure 6. Kaplan-Meier plot relating survival to combination of chronotropic index and peak $\dot{V}O_2$.

dictive of death. When peak $\dot{V}O_2$ was forced into the regression model, again only a high \dot{V}_E/\dot{V}_{CO_2} and a low chronotropic index were predictive of death. When covariates were analyzed in a continuous manner, only \dot{V}_E/\dot{V}_{CO_2} , chronotropic index, and resting systolic blood pressure were predictive; peak $\dot{V}O_2$ was not associated with death.

When transplanted patients were excluded from the analyses, multivariate models yielded essentially identical results. There were no significant interactions found between any of the variables considered for prediction of mortality.

Associations of Resting and Submaximal \dot{V}_E/\dot{V}_{CO_2} With Mortality

Among the 406 patients for whom anaerobic threshold could be determined, resting and anaerobic threshold values of \dot{V}_E/\dot{V}_{CO_2} were higher when the peak value was abnormally high (Table 3). There was a strong correlation between peak and anaerobic threshold values ($r=0.86$) with a less strong correlation with resting values ($r=0.66$). Resting, anaerobic threshold, and peak values of \dot{V}_E/\dot{V}_{CO_2} were all associated with mortality (Table 6), with the anaerobic threshold value almost as strong a predictor as the peak value. After adjustment for potential confounders, the anaerobic threshold and peak values remained predictive of mortality (Table 6).

Peak \dot{V}_E/\dot{V}_{CO_2} as a Continuous Variable

When considered as a continuous variable, peak \dot{V}_E/\dot{V}_{CO_2} had a range of 15 to 84 with 5th, 25th, 50th, 75th, and 95th percentile values of 27, 33, 38, 45, and 58, respectively. A parametric model found that independent predictors of mortality included peak \dot{V}_E/\dot{V}_{CO_2} ($P=0.02$), resting systolic blood pressure ($P=0.02$), and male gender ($P=0.03$). Weaker predictors were chronotropic index ($P=0.06$) and peak $\dot{V}O_2$ (0.07). A plot of estimated 18-month survival according to values of peak \dot{V}_E/\dot{V}_{CO_2} and peak $\dot{V}O_2$ is shown in Figure 7. Of note, a threshold effect was noted whereby the mortality impact of peak \dot{V}_E/\dot{V}_{CO_2} becomes particularly marked at values exceeding 40 to 45.

Discussion

Principal Findings

Abnormal ventilatory and chronotropic responses to exercise were powerful and independent predictors of mortality. Al-

though both a high \dot{V}_E/\dot{V}_{CO_2} and a low chronotropic index were associated with a low peak $\dot{V}O_2$, in both univariate and multivariate analyses, these 2 values emerged as substantially stronger correlates of death.

There were 2 other findings of note. First, the value of \dot{V}_E/\dot{V}_{CO_2} obtained at submaximal exercise, namely at anaerobic threshold, was almost as strong an independent predictor of mortality as the peak value. Second, a parametric analysis of peak \dot{V}_E/\dot{V}_{CO_2} considered as a continuous variable revealed a threshold pattern, in which the mortality impact increased markedly at values exceeding 40 to 45.

Previous Findings

Several groups have reported that patients with severe heart failure manifest an impaired heart rate variability at rest¹⁶ and

TABLE 5. Multivariate Predictors of Death Among Heart Failure Patients: Results of Forward Cox Proportional Hazards Analyses

Characteristic	Relative Risk (95% CI)	χ^2	P
Model 1 (categorical variables)*			
High \dot{V}_E/\dot{V}_{CO_2} (≥ 44.7)	3.20 (1.95–5.26)	21	0.0001
Low chronotropic index (≤ 0.51)	1.94 (1.18–3.19)	7	0.009
Model 2 (continuous variables)†			
\dot{V}_E/\dot{V}_{CO_2}	1.43 (1.19–1.71)	15	0.0001
Chronotropic index	1.40 (1.07–1.79)	6	0.01
Resting SBP, mm Hg	1.40 (1.06–1.85)	6	0.02

*Covariates considered included high \dot{V}_E/\dot{V}_{CO_2} (≥ 44.7), low chronotropic index (≤ 0.51), low peak $\dot{V}O_2$ (≤ 13.9 mL · kg⁻¹ · min⁻¹), resting hypotension (≤ 98 mm Hg), older age (≥ 61 y), sex, and presence of coronary artery disease. Only high \dot{V}_E/\dot{V}_{CO_2} and low chronotropic index made it into the model. Low peak $\dot{V}O_2$ did not make it into the model.

†Covariates considered included \dot{V}_E/\dot{V}_{CO_2} , chronotropic index, peak $\dot{V}O_2$ (mL · kg⁻¹ · min⁻¹), resting systolic blood pressure (mm Hg), age (y), sex, and presence of coronary artery disease. Note that unlike model 1, the first 5 variables were considered in continuous rather than categorical terms. Only \dot{V}_E/\dot{V}_{CO_2} , low chronotropic index, and resting systolic blood pressure made it into the model. Peak $\dot{V}O_2$ did not make it into the model. Relative risks refer to a 1-SD increase of \dot{V}_E/\dot{V}_{CO_2} and 1-SD decreases of chronotropic index and resting systolic blood pressure.

TABLE 6. Resting, Submaximal, and Maximal \dot{V}_E/\dot{V}_{CO_2} and Mortality Among Patients Who Had an Anaerobic Threshold That Could Be Determined

\dot{V}_E/\dot{V}_{CO_2}	Relative Risk (95% CI)	χ^2	P
Unadjusted models*			
Rest	1.55 (1.23–1.94)	14	0.0002
Anaerobic threshold	1.83 (1.50–2.25)	34	<0.0001
Peak exercise	1.89 (1.54–2.32)	38	<0.0001
Adjusted models†			
Rest	1.21 (0.95–1.56)	2	>0.1
Anaerobic threshold	1.45 (1.10–1.90)	7	0.009
Peak exercise	1.53 (1.14–2.06)	8	0.005

*Results of univariate Cox regression analyses. Relative risks and CIs refer to 1-SD increases of \dot{V}_E/\dot{V}_{CO_2} at rest, anaerobic threshold, and peak exercise.

†Results of multivariate Cox regression analyses adjusted for age, sex, presence of ischemic heart disease, chronotropic index, and peak oxygen consumption.

blunted heart rate responses to exercise,⁸ both of which are thought to be reflective of underlying autonomic dysfunction.¹² Clark and Coats reported that chronotropic incompetence was evident in nearly 30% of heart failure patients they studied, but concluded it played a significant role in exercise intolerance in only a minority of these patients.¹⁷ Additionally, it has been shown that heart failure patients hyperventilate abnormally during exercise.¹⁸ More recently, the presence of a strong association between decreased resting heart rate variability and exercise hyperventilation has been used to argue that the latter is also a result of autonomic dysfunction.¹⁹

To date, peak $\dot{V}O_2$ has been one of the gold standards by which heart failure patients are risk stratified and is considered by many to be the key component of initial heart transplant evaluation.^{3,5,20–22} Recently, both an abnormally high \dot{V}_E/\dot{V}_{CO_2} and depressed heart rate variability have been reported to be associated with an increased risk of death in heart failure patients.^{6,7}

The current study extends on these previous reports in several important respects. First, we found that an abnormally high

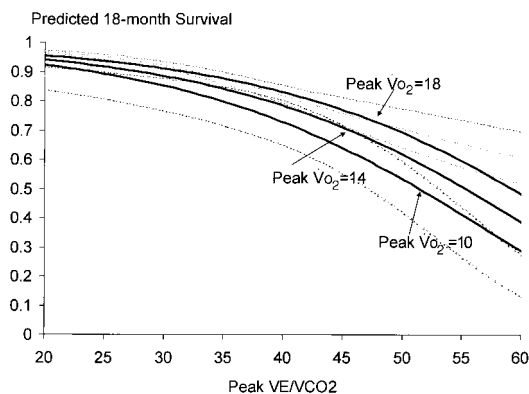


Figure 7. Plot of predicted 18-month survival according to peak \dot{V}_E/\dot{V}_{CO_2} and peak $\dot{V}O_2$, where peak \dot{V}_E/\dot{V}_{CO_2} is treated as a continuous variable. Curves are derived from parametric analyses in which only 1 phase of constant hazard was found. Dotted lines are 1 standard error confidence limits. Note the appearance of a threshold effect with a shoulder in the estimated survival curve apparent at a peak \dot{V}_E/\dot{V}_{CO_2} of 40 to 45.

\dot{V}_E/\dot{V}_{CO_2} predicts an increased risk of death among patients with severe heart failure to an even greater degree than a reduced peak $\dot{V}O_2$. Second, a low chronotropic index, a measure of exercise heart rate response which accounts for effects of age, resting heart rate, and functional capacity, was at least as strong a predictor of death as peak $\dot{V}O_2$. Third, when peak \dot{V}_E/\dot{V}_{CO_2} , chronotropic index, and peak $\dot{V}O_2$ were considered together, the ventilatory and chronotropic responses to exercise emerged as stronger and independent predictors of death. The independent predictive power of these 2 values indicate that they are not simply a function of lower workload achieved.

Possible Mechanisms

The mechanisms underlying an abnormally high \dot{V}_E/\dot{V}_{CO_2} in patients with heart failure are thought to be multifactorial and have been reported to include abnormalities among the following: central neurogenic drive, central chemoreceptors, cardiac mechanoreceptors, muscle ergoreceptors, anatomical and physiological dead space, and peripheral chemoreceptors.^{18,23,24} The \dot{V}_E/\dot{V}_{CO_2} value is also reported to be independent of motivation with little change in value at 30%, 60%, and 100% of exercise capacity.¹⁸ In the present study, the prognostic superiority of \dot{V}_E/\dot{V}_{CO_2} over peak $\dot{V}O_2$ therefore may reflect the ability of this value to exclude those patients with a falsely low peak $\dot{V}O_2$ secondary to a lack of motivation or peripheral skeletal muscle dysfunction. In this regard, it is noteworthy that anaerobic threshold values of \dot{V}_E/\dot{V}_{CO_2} were closely correlated with peak values and were almost as strongly predictive of death. Alternatively, it is possible that the underlying abnormalities of autonomic dysfunction associated with both abnormal ventilatory and chronotropic responses to exercise are distinct and more closely related to outcome.

It is noteworthy that peak respiratory rates in heart failure patients were similar to those of controls. This suggests that elevated levels of peak \dot{V}_E/\dot{V}_{CO_2} in patients with severe heart failure may be due more to increased dead space rather than to abnormalities of ventilatory drive. Thus, \dot{V}_E/\dot{V}_{CO_2} may be a better predictor of mortality as decreased cardiac output and elevated diastolic filling pressures may directly cause increased dead space in the form of interstitial edema and pulmonary endothelial dysfunction, whereas peak $\dot{V}O_2$ is a function of either central or peripheral abnormalities.

Limitations

The follow-up period for our study was relatively short; we are unable to comment on the effects of the ventilatory and chronotropic responses to exercise over >2 years of follow-up. Ejection fraction data were not obtained in a uniform manner among all patients; nonetheless, ejection fraction emerged as a relatively weaker predictor of outcome.

Another concern is that physicians would respond to low peak $\dot{V}O_2$ by listing patients for transplantation, thereby attenuating the association between peak $\dot{V}O_2$ and death. Peak \dot{V}_E/\dot{V}_{CO_2} values were not considered in clinical decision-making at the time these patients were evaluated. When we excluded the 46 patients who were censored because of transplantation, the associations relating ventilatory and chronotropic responses to mortality were unchanged.

Conclusions

An abnormally high \dot{V}_E/\dot{V}_{CO_2} and an abnormally low chronotropic index are both strong predictors of death among heart failure patients; their prognostic significance is independent of peak \dot{V}_{O_2} . Future research should focus on: (1) the influence of standard medical therapy (digoxin, ACE inhibitors, and diuretics), as well as, burgeoning therapies (β -adrenergic blockers, aldosterone inhibitors, and central active sympathoinhibitory agents) on chronotropic response and \dot{V}_E/\dot{V}_{CO_2} , and (2) how best to routinely incorporate chronotropic index and \dot{V}_E/\dot{V}_{CO_2} into heart failure staging and cardiac transplant evaluations.

References

- Robbins MA, O'Connell JB. Economic impact of heart failure. In: Rose EA, Stevenson LW, eds. *Management of End-Stage Heart Disease*. Philadelphia: Lippincott-Raven; 1998:3–13.
- Evens RW. Cardiac replacement: estimation of need, demand, and supply. In: Rose EA, Stevenson LW, eds. *Management of End-Stage Heart Disease*. Philadelphia: Lippincott-Raven; 1998:13–25.
- Myers J, Gullestad L. The role of exercise testing and gas-exchange measurement in the prognostic assessment of patients with heart failure. *Curr Opin Cardiol*. 1998;13:145–155.
- Francis GS. Determinants of prognosis in patients with heart failure. *J Heart Lung Transplant*. 1994;13:S113–116.
- Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, Fowler MB. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med*. 1998;129:286–293.
- Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJ. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 1997;29:1585–1590.
- Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JM, Fox KA. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart). *Circulation*. 1998;98:1510–1516.
- Colucci WS, Ribeiro JP, Rocco MB, Quigg RJ, Creager MA, Marsh JD, Gauthier DF, Hartley LH. Impaired chronotropic response to exercise in patients with congestive heart failure: role of postsynaptic beta-adrenergic desensitization. *Circulation*. 1989;80:314–323.
- The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) [see comments]. *Arch Intern Med*. 1993;153:154–183.
- Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60:2020–2027.
- Wasserman K. Breathing during exercise. *N Engl J Med*. 1978;298:780–785.
- Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation*. 1996;93:1520–1526.
- Wilkoff BL, Miller RE. Exercise testing for chronotropic assessment. *Cardiol Clin*. 1992;10:705–717.
- Curb JD, Ford CE, Pressel S, Palmer M, Babcock C, Hawkins CM. Ascertainment of vital status through the National Death Index and the Social Security Administration. *Am J Epidemiol*. 1985;121:754–766.
- Blackstone EH, Naftel DC, Turner ME. The decomposition of time-varying hazard into phases, each incorporating a separate stream on concomitant information. *J Am Stat Soc*. 1986;81:615–624.
- Wijbenga JA, Balk AH, Meij SH, Simoons ML, Malik M. Heart rate variability index in congestive heart failure: relation to clinical variables and prognosis. *Eur Heart J*. 1998;19:1719–1724.
- Clark AL, Coats AJ. Chronotropic incompetence in chronic heart failure. *Int J Cardiol*. 1995;49:225–231.
- Metra M, Dei Cas L, Panina G, Visioli O. Exercise hyperventilation chronic congestive heart failure, and its relation to functional capacity and hemodynamics [see comments]. *Am J Cardiol*. 1992;70:622–628.
- Ponikowski P, Chua TP, Piepoli M, Banasiak W, Anker SD, Szelemej R, Molenda W, Wrabec K, Capucci A, Coats AJ. Ventilatory response to exercise correlates with impaired heart rate variability in patients with chronic congestive heart failure. *Am J Cardiol*. 1998;82:338–344.
- Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778–786.
- Roul G, Moullichon ME, Bareiss P, Gries P, Sacrez J, Germain P, Mossard JM, Sacrez A. Exercise peak VO₂ determination in chronic heart failure: is it still of value? *Eur Heart J*. 1994;15:495–502.
- Stelken AM, Younis LT, Jennison SH, Miller DD, Miller LW, Shaw LJ, Kargl D, Chaitman BR. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. *J Am Coll Cardiol*. 1996;27:345–352.
- Reindl I, Wernecke KD, Opitz C, Wensel R, König D, Dengler T, Schimke I, Kleber FX. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J*. 1998;136:778–785.
- Clark AL, Chua TP, Coats AJ. Anatomical dead space, ventilatory pattern, and exercise capacity in chronic heart failure. *Br Heart J*. 1995;74:377–380.