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Prognostic Value of Cardiopulmonary Exercise Testing Using Percent Achieved of Predicted Peak Oxygen Uptake for Patients With Ischemic and Dilated Cardiomyopathy

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Objectives. We tested the hypothesis that percent achieved of predicted peak oxygen uptake (predicted $\dot{V}o_2max$) improves the prognostic accuracy of identifying high risk ambulatory patients with congestive heart failure considered for heart transplantation compared with absolute peak oxygen uptake ($\dot{V}o_2max$) in 181 patients with ischemic or dilated cardiomyopathy.

Background. Peak oxygen uptake during exercise has been shown to be a useful prognostic measurement to risk stratify patients with heart failure. The prognostic value of percent predicted $\dot{V}o_2max$ has not been assessed in these patients.

Methods. We retrospectively studied 181 ambulatory patients referred to the Saint Louis University Heart Failure Unit. Clinical, hemodynamic (137 patients) and coronary angiographic (145 patients) data were recorded, and all patients underwent symptom-limited cardiopulmonary exercise.

Results. During a mean follow-up period of 12 ± 6 months, 26 patients died, and 18 were listed as Status 1 priority for heart transplantation. The actuarial 1- and 2-year survival of the 89 patients who achieved ≤50% predicted $\dot{V}o_2max$ was 74% and 43%, respectively, compared with 98% and 90% in the 92 who achieved >50% predicted $\dot{V}o_2max$ ($p = 0.001$). Multivariable analysis selected ≤50% predicted $\dot{V}o_2max$ as the most significant predictor of cardiac death ($p = 0.007$) and cardiac death or Status 1 priority ($p = 0.0005$).

Conclusions. Percent achieved of predicted $\dot{V}o_2max$ provides important information that can be used to risk stratify ambulatory patients with heart failure with ischemic or dilated etiology that exceeds that provided by measurement of $\dot{V}o_2max$ alone. Patients who achieve >50% predicted $\dot{V}o_2max$ have an excellent short-term prognosis when treated medically, and heart transplantation can be safely deferred.

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Congestive heart failure is the leading diagnosis and cause of cardiovascular morbidity and mortality reported in recent years, with 1 to 2 million Americans affected (1). Despite significant advances in medical therapy and the use of angiotensin-converting enzyme inhibitor drugs, the survival of patients with moderate to severe congestive heart failure remains limited (2,3). Heart transplantation enhances survival in selected patients who have severely depressed left ventricular ejection fraction, with an 80% to 90% 1-year survival (4), significantly better than survival of historic control patients on optimal medical therapy (3,5,6). This has led to increased referrals to heart transplantation programs. However, the limited number of heart donors has increased the interval preceding transplantation, adversely influencing patient outcome (7). Several clinical, hemodynamic and exercise criteria have been proposed to identify high risk patients referred for heart transplantation (8–11). Peak exercise oxygen uptake ($\dot{V}o_2max$) <14 ml/kg per min is one exercise variable reported to predict mortality in patients with congestive heart failure with a 1-year survival of ~70%, significantly less than patients with exercise capacity >14 ml/kg per min (12).

Peak oxygen uptake is influenced by age, gender and body weight (13–18). The use of an exercise variable that adjusts for these factors may further improve the predictive accuracy of the $\dot{V}o_2max$ variable in the risk stratification process. Dilated cardiomyopathy is reported to have a better outcome than ischemic cardiomyopathy (5); however, the predictive value of cardiopulmonary exercise testing in these two patient subsets is not known. Therefore, we tested the hypotheses that 1) the use of the percent achieved of predicted $\dot{V}o_2max$, which accounts for age, gender and weight, enhances the risk stratification of ambulatory patients evaluated for heart transplantation compared with the use of absolute $\dot{V}o_2max$ alone; 2) the determination of percent predicted $\dot{V}o_2max$ and $\dot{V}o_2max$ are predictive of outcome events whether the etiology is ischemic cardiomyopathy or nonischemic dilated cardiomyopathy.

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Methods

Between April 1991 and June 1993, 181 consecutive ambulatory patients referred to the Heart Failure Program at Saint Louis University Health Sciences Center were evaluated (146 men, 35 women; mean [±SD] age 49 ± 10 years, range 21 to 68 years). The etiology of heart failure was coronary artery disease in 94 patients (52%) and dilated cardiomyopathy in 87 (48%) (idiopathic in 79, valvular in 5, congenital in 3). Previous myocardial infarction was reported in 81 patients (45%); 56 (31%) had history of hypertension; 31 (17%) had history of diabetes mellitus; and 105 (58%) had a history of smoking. All patients were in New York Heart Association functional classes II to III. Rest left ventricular ejection fraction was determined from left ventriculography or radionuclide angiography during the initial evaluation. Rest baseline hemodynamic data were obtained from right heart catheterization using Swan-Ganz catheters; cardiac output was determined by thermodilution technique.

Cardiopulmonary exercise testing. Symptom-limited cardiopulmonary exercise testing with respiratory gas exchange analysis was performed in 181 patients after written informed consent had been obtained. The modified Bruce protocol was used in 144 patients (80%), and the modified Asymptomatic Cardiac Ischemic Pilot (19) or modified Naughton protocol was used in the remaining 37 (20%). Patients with rest or crescendo angina pectoris were excluded. All patients with ischemic etiology were not candidates for revascularization. Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise and for 5 min into the recovery phase while blood pressures were measured using a standard cuff sphygmomanometer. Levels of mixed expired oxygen, carbon dioxide and ventilation were determined at rest and every 30 s using a Medical Graphics Corporation 2001 or $Cardio_2$ metabolic cart. Anaerobic threshold was defined as the $\dot{V}o_2$ at which expired carbon dioxide increased nonlinearly relative to oxygen consumption (V-slope) (20). The $\dot{V}o_2$max was defined as the highest $\dot{V}o_2$ rate observed during exercise.

Age- and gender-adjusted predicted $\dot{V}o_2$ was determined using the treadmill equations of Wasserman et al. (21), Jones et al. (22) and Bruce et al. (17) (see Appendix). The equations of Wasserman et al. (21) adjust for age, gender and weight and were used in all analyses.

Follow-up. All patients were followed up by the Heart Failure Unit at Saint Louis University Health Sciences Center, and data from clinic visits, medical records review or telephone interview were recorded. Cardiac deaths within 24 h of acute symptoms heralded by abrupt loss of consciousness were considered sudden, whereas those resulting from progressive symptomatic or hemodynamic deterioration were classified as progressive heart failure. Status 1 patients were defined as those patients who required intensive care unit admission and prolonged inotropic or mechanical cardiovascular support. *Cardiac-related events* were defined as cardiac death or the composite end point of cardiac death or Status 1 transplant priority.

Statistical analysis. Intergroup differences among clinical, hemodynamic and exercise variables were compared using unpaired *t* tests or chi-square analysis where appropriate. A p value <0.05 was considered statistically significant. A Cox proportional hazards model was used to measure the impact of clinical history and test results on time to cardiac event. Separate analyses were performed for the end point of cardiac death and cardiac death or change to Status 1 transplant priority. The cardiac event was coded as a binary event, with time to follow-up coded in months. Univariate analysis of baseline clinical, hemodynamic, angiographic and exercise variables was performed for the end points of cardiac death and cardiac death or Status 1 transplant priority. Multivariable regression analyses were performed on significant univariate predictors with $p < 0.2$ (23). Variables examined were ≤50% predicted $\dot{V}o_2$max, $\dot{V}o_2$max ≤14 ml/kg per min, history of myocardial infarction, male gender, functional class, smoking history and triple conventional medical therapy. Model-overfitting procedures were examined, that is, plots for the effect of influential cases and ratio of outcome events to number of independent variables (24). The proportional hazards assumption was satisfied for each regression model.

Receiver operating characteristic (ROC) curves (True Epistat, Version 5.0, Epistat Services) were constructed by plotting true positive rates (sensitivity) against false positive rates (1 − specificity) to compare discriminatory accuracy for survival and event-free survival for percent predicted $\dot{V}o_2$max among the equations of Wasserman et al. (21), Jones et al. (22) and Bruce et al. (17) and $\dot{V}o_2$max. The ROC curves were compared using the z statistic (25). The area under the ROC curve is a measure of the discriminatory accuracy of a variable in predicting outcome. A test with a high sensitivity and specificity will produce a curve shifted up and to the left compared to a test providing random estimates that will produce a 45° line. The area under the curve can range from 1 to 0, with 1 being perfect discrimination, 0.5 having no more discrimination than random chance and 0 being perfect incorrect discrimination.

Results

The clinical characteristics and hemodynamic and exercise data of the study patients are presented in Table 1. The mean percent predicted $\dot{V}o_2$max for all patients was 54 ± 19%. The mean $\dot{V}o_2$max was 16.3 ± 5.9 ml/kg per min. Anaerobic threshold could not be determined in 16 patients; peak respiratory exchange ratio (r) was >1.0 in these patients. There were no complications as a result of the exercise test procedure.

After 12 ± 6 months of follow-up, 44 patients (24%) experienced an event (cardiac death, Status 1). Of 26 patients who died, 12 had a sudden cardiac death, and 14 died of progressive heart failure. Twenty deaths occurred in patients with coronary artery disease. Thirty-five patients received a heart transplant. Eighteen patients were listed as Status 1, and 17 were listed as Status 2 priority for heart transplantation. The

Table 1. Clinical Characteristics and Hemodynamic and Exercise Data of 181 Patients With Congestive Heart Failure and Coronary Artery Disease or Dilated Cardiomyopathy

	All Pts (n = 181)	Etiology: CAD (n = 94)	Etiology: DCM (n = 87)	p Value
Age (yr)	49 ± 10	53 ± 8	44 ± 11	<0.0001
Gender				
Male	146 (81)	85 (90)	61 (70)	0.0005
Female	35 (19)	9 (10)	26 (30)	
NYHA functional class				
II	60 (33)	25 (27)	35 (40)	NS
III	121 (67)	69 (73)	52 (60)	NS
LVEF (%)	23 ± 9	23 ± 8	23 ± 10	NS
PCWP (mm Hg)	22 ± 9	22 ± 9	21 ± 9	NS
CI (liters/min per m^2)	2.4 ± 0.6	2.5 ± 0.6	2.2 ± 0.6	0.02
%PP$\dot{V}O_2$	54 ± 19	47 ± 15	61 ± 20	<0.0001
P$\dot{V}O_2$ (ml/kg per min)	16.3 ± 5.9	14.4 ± 4.5	18.4 ± 6.5	<0.0001
CO_2 production (liters/min)	1.6 ± 0.7	1.4 ± 4.5	1.7 ± 0.8	0.0008
Ventilation (liters/min)	64 ± 20	62 ± 17	66 ± 22	NS
Respiratory exchange ratio	1.15 ± 0.12	1.16 ± 0.13	1.14 ± 0.11	NS
Follow-up (mo)	12 ± 6	12 ± 6	11 ± 7	NS
Death	26 (14)	20 (21)	6 (7)	0.006
Death or Status 1	44 (24)	28 (30)	16 (18)	NS

Data presented are mean value ± SD or number (%) of patients (Pts). CAD = coronary artery disease; CHF = congestive heart failure; CI = cardiac index; CO_2 = carbon dioxide; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; %PP$\dot{V}O_2$ = percent achieved of predicted peak oxygen uptake (Wasserman et al. [21] formula); P$\dot{V}O_2$ = peak oxygen uptake.

clinical and hemodynamic characteristics between survivors and nonsurvivors are summarized in Table 2.

Comparison of cardiopulmonary exercise variables between nonsurvivors and survivors is displayed in Table 3. Nonsurvivors achieved a lower percent predicted $\dot{V}O_2$max (38 ± 10% vs. 57 ± 18%, $p < 0.0001$) and lower $\dot{V}O_2$max (12 ± 4 vs. 17 ± 6, $p < 0.0001$) than survivors.

Table 2. Clinical and Hemodynamic Characteristics of Nonsurviving and Surviving Patients With Congestive Heart Failure

	Nonsurvivors (n = 26)	Survivors (n = 155)	p Value
Age (yr)	51 ± 10	48 ± 10	NS
Male	25 (96)	121 (78)	0.03
LVEF (%) (145 pts)	23 ± 7	23 ± 9	NS
PCWP (mm Hg)	26 ± 9	21 ± 8	0.01
MAP (mm Hg)	81 ± 8	84 ± 10	NS
RA (mm Hg)	10 ± 6	9 ± 6	NS
NYHA functional class			
II	3 (12)	57 (37)	0.04
III	23 (88)	98 (63)	0.04
CAD	20 (77)	74 (48)	0.006
MI	19 (73)	62 (40)	0.001
Smoking	21 (81)	83 (54)	0.01
Race (white)	21 (81)	137 (88)	NS
ACE inhibitor	25 (96)	137 (88)	NS
Digitalis	23 (88)	117 (75)	NS
Diuretic	24 (92)	126 (81)	NS
Triple therapy*	21 (81)	86 (55)	0.03

*Angiotensin-converting enzyme (ACE) inhibitor, digitalis and diuretic drug combined medical therapy. Data presented are mean value ± SD or number (%) of patients (pts). MAP = mean arterial pressure; MI = myocardial infarction. RA = right atrial pressure; other abbreviations as in Table 1.

Multivariable models. Multivariable models to predict cardiac death and cardiac death or Status 1 were run to examine important baseline and exercise variables (Table 4). The only independent predictor of cardiac death was ≤50% predicted $\dot{V}O_2$max ($p = 0.007$); ≤50% predicted $\dot{V}O_2$max ($p = 0.0005$) and functional class ($p = 0.04$) were independent predictors of cardiac events.

Table 3. Comparison of Cardiopulmonary Exercise Testing Variables in Nonsurvivors and Survivors

	Nonsurvivors (n = 26)	Survivors (n = 155)	p Value
%PP$\dot{V}O_2$	38 ± 10	57 ± 18	<0.0001
P$\dot{V}O_2$ (ml/kg per min)	12 ± 4	17 ± 6	<0.0001
AT (ml/kg per min)	9.4 ± 2.4	12.5 ± 3.7	0.0002
Exercise duration (min)*	4.6 ± 2.1	6.3 ± 2.3	0.001
≤50% PP$\dot{V}O_2$	24 (92)	65 (42)	<0.0001
P$\dot{V}O_2$ ≤14 ml/kg per min	20 (77)	50 (32)	<0.0001
CO_2 production (liters/min)	1.2 ± 0.5	1.6 ± 0.7	0.003
Ventilation (liters/min)	62 ± 18	64 ± 20	NS
Respiratory exchange ratio	1.19 ± 0.1	1.15 ± 0.1	NS
%PMHR	80 ± 9	85 ± 13	NS
Peak systolic BP (mm Hg)	117 ± 20	137 ± 31	0.003

*144 patients performed modified Bruce protocol. Data presented are mean ± SD or number (%) of patients. AT = anaerobic threshold; BP = blood pressure; %PMHR = percent of predicted maximal heart rate; other abbreviations as in Table 1.

Table 4. Multivariable Models for Death and Death or Status 1 According to Known Prognostic High Risk Variables

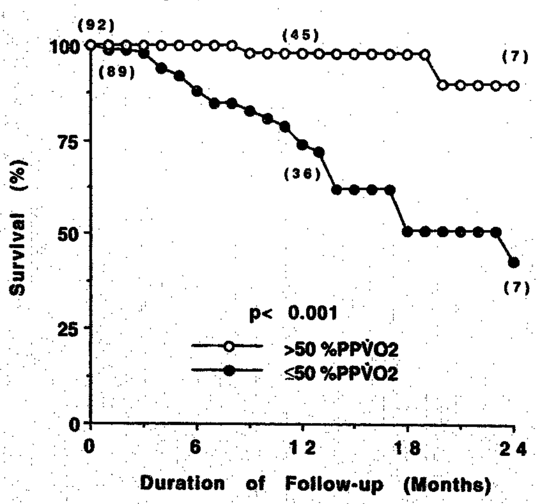
	Step No.	Beta Coefficient	SE	p Value
Death				
≤50 %PP$\dot{V}O_2$	1	2.16	0.8	0.007
P$\dot{V}O_2$ ≤14 ml/kg per min	2	0.85	0.5	0.09
Male gender	3	0.66	0.52	0.2
MI	4	0.19	0.23	0.43
NYHA functional class	5	0.14	0.36	0.68
Death or Status 1				
≤50 %PP$\dot{V}O_2$	1	1.62	0.46	0.0005
NYHA functional class	2	1.12	0.55	0.04
Male gender	3	0.76	0.61	0.22
Smoking history	4	0.33	0.35	0.34
Triple therapy	5	0.19	0.38	0.61
MI	6	0.11	0.33	0.73
P$\dot{V}O_2$ ≤14 ml/kg per min	7	0.12	0.38	0.76

Abbreviations as in Tables 1 and 2.

Survival was assessed using ≤50% and >50% predicted $\dot{V}O_2$max as a cut point. The 89 patients who achieved ≤50% predicted $\dot{V}O_2$max had a significantly worse survival than the 92 patients who achieved >50% predicted $\dot{V}O_2$max ($p = 0.001$) (Fig. 1). When survival of the 92 heart failure patients who achieved >50% predicted $\dot{V}O_2$max was compared with that of 35 patients who underwent heart transplantation, the 2-year survival rates were 90% and 89%, respectively (p = NS). Similar survival rates were observed when patients were stratified using $\dot{V}O_2$max ≤14 (n = 70) and >14 ml/kg per min (n = 111) ($p = 0.001$). Separate analyses for the combined end point of cardiac death or Status 1 revealed a greater event rate in patients unable to achieve ≤50% predicted $\dot{V}O_2$max ($p < 0.0001$) (Fig. 2). The results were similar using a cut point of ≤14 and >14 ml/kg per min ($p < 0.0001$). Although both percent predicted $\dot{V}O_2$max and $\dot{V}O_2$max were significant predictors of cardiac events, the percent predicted $\dot{V}O_2$max predicted 10 more events (4 cardiac death, 6 Status 1) than $\dot{V}O_2$max (n = 38 vs. n = 28).

Diagnostic accuracy of cardiopulmonary exercise testing. The discriminatory accuracy using the cut point of 50% predicted $\dot{V}O_2$max for the equation of Wasserman et al. (21) was compared with that obtained using the Jones (22) and Bruce (17) equations (Table 5). The Wasserman (21) equation had slightly greater diagnostic accuracy and a greater area under the ROC curve than both other equations. The difference was not statistically significant. The equation of Wasser-

Figure 1. Survival curves comparing patients achieving >50% (preserved exercise capacity) with those achieving ≤50% (reduced exercise capacity) predicted peak oxygen uptake (PPVO2). **Numbers in parentheses** = number of patients at risk.



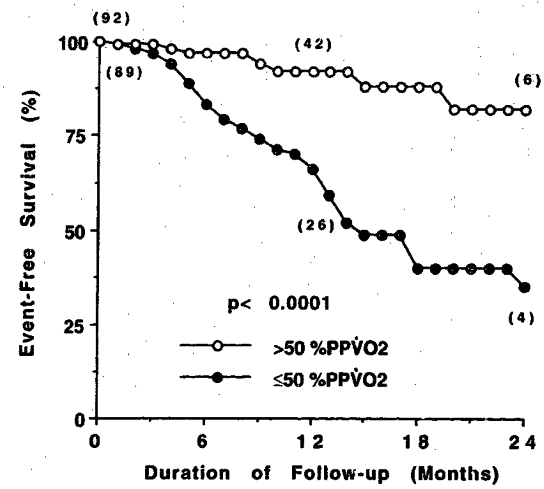


Figure 2. Event-free survival (death or Status 1) curves comparing patients achieving >50% (preserved exercise capacity) with those achieving ≤50% (reduced exercise capacity) predicted peak oxygen uptake (PPVO2). **Numbers in parentheses** = number of patients at risk.

Table 5. Area Under Receiver Operating Characteristic Curve for Predicted Maximal Oxygen Uptake Equations for Death and Death or Status 1

Equation	ROC Area	Z Score	SE	p Value (vs. 0.5 ROC area)
Death				
Wasserman et al. (21)	0.82	8.58	0.04	<0.001
Bruce et al. (17)	0.79	6.16	0.05	<0.001
Jones et al. (22)	0.77	5.55	0.05	<0.001
Death or Status 1				
Wasserman et al. (21)	0.78	7.60	0.04	<0.001
Bruce et al. (17)	0.75	6.26	0.04	<0.001
Jones et al. (22)	0.75	6.21	0.04	<0.001

ROC = receiver operating characteristic curve.

Table 6. Sensitivity and Specificity for Percent Predicted Maximal Oxygen Uptake Cut Points in Equations* for Death or Status 1

	30%	40%	50%	60%
Sensitivity	11	55	86	93
Specificity	95	84	63	41

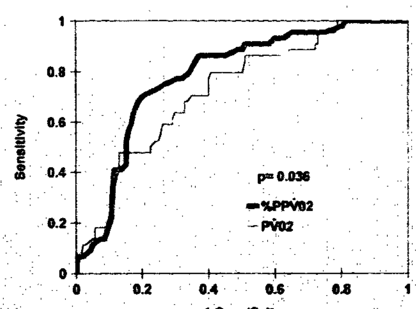
*Wasserman et al. (21).

man et al. (21) was used in all subsequent analyses. The sensitivity and specificity of various percentage predicted $\dot{V}O_2$max cut points for the combined end points of cardiac death or Status 1 are illustrated in Table 6. The optimal cut point for percent predicted $\dot{V}O_2$max was 50%. The sensitivity to predict cardiac death for ≤50% predicted $\dot{V}O_2$max and $\dot{V}O_2$max ≤14 was 92% and 77%, respectively, and specificity was 58% and 68%. Similarly, the sensitivity for ≤50% predicted $\dot{V}O_2$max was higher than $\dot{V}O_2$max ≤14 when the combined end points of cardiac death or Status 1 were analyzed (86% vs. 68%), with similar specificity (63% vs. 69%).

The overall discriminatory accuracy using ROC analysis for percent predicted $\dot{V}O_2$max (0.78) was significantly greater than that for $\dot{V}O_2$max (0.72) ($p = 0.036$) for cardiac-related events (Fig. 3). The difference was not significant for cardiac death (0.82 vs. 0.78, $p = 0.15$).

Analysis according to heart failure type. Separate univariate and Cox multivariable analyses of the 94 patients with coronary artery disease and 87 patients with dilated cardiomyopathy were performed to examine the impact of etiology on outcome. In the 94 patients with coronary artery disease etiology, ≤50% predicted $\dot{V}O_2$max, $\dot{V}O_2$max ≤14 and triple conventional medical therapy were significant univariate predictors ($p < 0.2$) (23) of both cardiac death and cardiac death or Status 1. When these variables were entered into a multivariable model, ≤50% predicted $\dot{V}O_2$max was the only remaining independent predictor of cardiac death ($p = 0.04$) or any cardiac-related event ($p = 0.02$). The 20 patients with coronary artery disease who died had a significantly lower percent

Figure 3. Receiver-operating characteristic (ROC) curves for 1-year event-free survival (death or Status 1). The area under the ROC curve for percent predicted peak oxygen uptake (%PPVO2) indicates significantly improved discriminatory accuracy compared with that for peak oxygen uptake (PVO2) (0.78 vs. 0.72, p = 0.036).



predicted $\dot{V}O_2$max (38 ± 10% vs. 50 ± 15%, $p = 0.001$) and lower $\dot{V}O_2$max (12 ± 4.3 ml/kg per min vs. 15 ± 4.4 ml/kg per min, $p = 0.006$) than the 74 survivors.

When the 87 patients with dilated cardiomyopathy etiology were examined, ≤50% predicted $\dot{V}O_2$max, $\dot{V}O_2$max ≤14 and functional class were the only significant univariate predictors for the combined end point of cardiac death or Status 1. When these variables were entered into a multivariable model, ≤50% predicted $\dot{V}O_2$max was the only remaining independent predictor ($p = 0.02$). The six patients with dilated cardiomyopathy who died had a significantly lower percent predicted $\dot{V}O_2$max (36 ± 9% vs. 63 ± 20%, $p = 0.002$) and lower $\dot{V}O_2$max (12.5 ± 1.9 ml/kg per min vs. 18.9 ± 6.5 ml/kg per min, $p = 0.02$) than survivors. The differences were similar when the combined end point of cardiac death or Status 1 priority was analyzed.

Discussion

The incidence of congestive heart failure is increasing despite an observed decline in coronary artery disease mortality (1,26). The median survival of patients with severe congestive heart failure is 2 to 3 years (27). Risk stratification of ambulatory congestive heart failure patients is primarily based on subjective measures such as clinical and functional assessment and rest hemodynamic data. The use of exercise tolerance evaluation in these patients provides an objective method to identify patients at higher risk of cardiac death and provides long-term prognostic information. The data are useful in selecting patients who could potentially benefit from heart transplantation (12).

Our data show that the use of cardiopulmonary exercise testing and determination of the percent achieved of predicted $\dot{V}O_2$max is a highly accurate predictor both in identifying patients at risk for future cardiac events (cardiac death or Status 1) and in identifying low risk patients who can be followed up clinically and maintained on medical therapy with relatively low mortality or morbidity. Our data confirm earlier results on the value of $\dot{V}O_2$max as a useful predictor of mortality and morbidity (5,8,12). However, percent predicted $\dot{V}O_2$max and the cut point ≤50% predicted $\dot{V}O_2$max are more sensitive in detecting events then the use of absolute $\dot{V}O_2$max, which does not adjust for age, weight or gender.

Previous studies. Cohn et al. (28) reported in the Department of Veterans Affairs Cooperative Vasodilator-Heart Failure Trials (V-HeFT I,II) that ejection fraction, cardiothoracic ratio and $\dot{V}O_2$max were independent predictors of all-cause mortality. When $\dot{V}O_2$max was ≤14.5 ml/kg per min, survival rates were significantly less than in patients with $\dot{V}O_2$max >14.5 ml/kg per min. In the V-HeFT I trial, $\dot{V}O_2$max only added significant independent prognostic information in the patient subset with a median ejection fraction >0.28. In both V-HeFT I ($n = 642$) and V-HeFT II trials ($n = 804$), the worst survival rates were observed in men with a left ventricular ejection fraction ≤0.28 and $\dot{V}O_2$max ≤14.5 ml/kg per min.

Mancini et al. (12) reported that a $\dot{V}O_2$max of 14 ml/kg per min was the best discriminatory variable to predict cardiac death after 11 ± 9 months in 122 patients referred for cardiac transplantation evaluation. Patients with $\dot{V}O_2max$ <14 ml/kg per min who were accepted for transplantation had a 1-year survival of 70% compared to 1- and 2-year survival of 94% and 84% in patients exceeding 14 ml/kg per min. The results are comparable to our observations using percent predicted $\dot{V}O_2max$ with patients achieving ≤50% predicted $\dot{V}O_2max$ having a 1- and 2-year survival of 74% and 43% versus 1- and 2-year survival of 98% and 90% in patients who achieved >50% predicted $\dot{V}O_2max$. The latter group had survival at 1 year similar to 35 patients who underwent heart transplantation. Likoff et al. (5) studied 201 patients with congestive heart failure with a mean follow-up of 10.8 ± 9 months and reported that patients with $\dot{V}O_2max$ ≤13 ml/kg per min had a substantially higher mortality rate than the 15% 1-year mortality in patients who exceeded 13 ml/kg per min.

Parameshwar et al. (8) reported on 127 patients with chronic heart failure who underwent cardiopulmonary exercise testing with 14.6 months of follow-up; total and event-free survival in patients with $\dot{V}O_2max$ <13.7 ml/kg per min was ~70% and 45% compared with ~85% and 60% in patients with $\dot{V}O_2max$ >13.7 ml/kg per min.

Selection and value of percent achieved of predicted $\dot{V}O_2max$. We selected 50% to enhance the sensitivity of predicting occurrence of cardiac events, a desirable feature of any screening test. The percent achieved of predicted $\dot{V}O_2max$ was the strongest predictor for cardiac death and cardiac death or Status 1 listing by multivariable analysis.

The data indicate that correction for factors that inherently affect $\dot{V}O_2max$ during exercise using the equation of Wasserman et al. (21), which accounts for age, gender and body weight, enhances the predictive accuracy of cardiopulmonary exercise testing in risk stratification of ambulatory patients with congestive heart failure, whether the etiology is secondary to ischemic heart disease or dilated cardiomyopathy. Similar results can be achieved with other formulas that adjust for age and gender only (17,22). Although we examined only three formulas to derive percent predicted $\dot{V}O_2max$ in this study, other equations can also be used to derive percent predicted $\dot{V}O_2max$ (29,30).

Comparison with other predictors. The predictive accuracy of clinical and hemodynamic variables was tested for their prognostic value in detecting future cardiac events. Functional class was the only significant clinical variable in multivariable analysis (Table 4). The clinical findings are at variance with other studies that report right atrial pressure >12 mm Hg (31), plasma sodium <138 mmol/liter (8) and left ventricular ejection fraction <17% (8) as significant multivariable predictors of death. Griffin et al. (32) reported on 49 patients with chronic congestive heart failure who underwent rest and exercise hemodynamic evaluation. The 1-year mortality was 33%. Rest pulmonary artery wedge pressure and peak exercise stroke work index were the only independent mortality predictors. Differences in exercise duration or $\dot{V}O_2max$ achieved between survivors and nonsurvivors were not significant. The number of patients in this series was small, and a type II error cannot be excluded. Pulmonary capillary wedge pressure was a univariate predictor in our series but was not selected after exercise results were entered into the model. The type of exercise performed (bicycle exercise) and the inclusion of patients with functional class IV heart failure in the study by Griffin et al. (32) (25% of participants) may also explain the differences observed.

In patients with congestive heart failure, coronary artery disease adversely affects prognosis (33). Thus, exercise outcome predictors such as percent predicted $\dot{V}O_2max$ or $\dot{V}O_2max$ may potentially be influenced by the type of patients with congestive heart failure selected for study. In the SOLVD trial (34), $\dot{V}O_2max$ did not differ between subjects with ischemic (n = 139) and nonischemic heart disease (n = 25); $\dot{V}O_2max$ did correlate significantly with age and gender. In our series of 94 patients with ischemic cardiomyopathy and 87 patients with nonischemic dilated cardiomyopathy, percent predicted $\dot{V}O_2max$ was significantly different between the two types of cardiomyopathy and was a useful variable in predicting outcome in both groups. The magnitude of prognostic separation was greater in the ischemic cardiomyopathy group.

Study limitations. The study cohort represents a large group of patients with congestive heart failure. Approximately half of the study cohort had ischemic cardiomyopathy, and the remainder had nonischemic dilated cardiomyopathy. The inclusion of the two different types of cardiomyopathy could have influenced the results. However, both patient groups share many similarities in their clinical, hemodynamic and therapeutic characteristics at the time of exercise testing, and we have shown the prognostic utility of cardiopulmonary exercise testing in both groups. The small number of cardiac deaths (n = 6; 7%) in the 87 patients with dilated cardiomyopathy precludes an in-depth prognostic assessment of this subgroup. Additional prospective studies with a larger series of patients with dilated cardiomyopathy are needed to substantiate the prognostic value of percent predicted $\dot{V}O_2max$ in this cohort.

The use of previously published data regarding age-, gender- and weight-adjusted $\dot{V}O_2max$ as a control value to derive the percent predicted oxygen uptake rate may not be the optimal method to determine the degree of exercise capacity impairment. However, the formulas are derived from large cross-sectional studies and represent a normal population, which we believe justifies the use of these data to represent a hypothetical control group. We tested our hypotheses for percent predicted $\dot{V}O_2max$ using other published predicted $\dot{V}O_2max$ formulas (17,22) and found that the results were not significantly influenced by choice of reference group.

We did not study a large group of women (n = 35) in our study, and the small number of events observed (n = 3) precludes firm conclusions regarding impact of gender on survival.

A potential limitation is the use of different exercise protocols in this study. However, analysis of the 144 patients who performed cardiopulmonary testing using the modified Bruce protocol gave similar results to patients who performed a non-Bruce protocol. The protocols used were compared in our laboratory in normal subjects and in patients with coronary artery disease (19). Peak oxygen uptake rate values were similar regardless of exercise protocol used.

Clinical implications. The present report extends previous observations of the significant predictive value of cardiopulmonary exercise testing in the risk stratification of patients with severe congestive heart failure. The use of ≤50% predicted $\dot{V}O_2$max provides prognostic information additional to the absolute $\dot{V}O_2$max and can eliminate the potential influence of factors such as age, gender, and weight on the predictive accuracy of the test. Our data demonstrate that patients who receive optimal medical therapy and have preserved exercise capacity can continue to be followed up clinically and undergo serial cardiopulmonary exercise testing to determine the optimal time and potentially prevent adverse outcomes, although this hypothesis needs to be tested prospectively. This approach can assist in decreasing the waiting time for patients awaiting heart transplantation by optimizing the selection process.

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Appendix

Determination of Age- and Gender-Adjusted Predicted Maximal Oxygen Consumption

Equations of Wasserman et al. (21). To relate normal weight to height the following equation was utilized: W = 0.79H − 60.7 for men and W = 0.79H − 68.2 for women, where W = weight in kilograms, and H = height in centimeters (17). If a patient's actual weight was at or below normal, the weight and age were used to predict maximal oxygen uptake ($\dot{V}O_2$max) (ml/min):

$$\text{Men: } W \times (56.36 - 0.413 \times \text{Age});$$

$$\text{Women: } W \times (44.37 - 0.413 \times \text{Age}).$$

If a patient was overweight, his or her "normalized" weight was integrated to predict $\dot{V}O_2$max (ml/min):

$$\text{Men: } (0.79 \times H - 60.7) \times (56.36 - 0.413 \times \text{Age});$$

$$\text{Women: } (0.79 \times H - 68.2) \times (44.37 - 0.413 \times \text{Age}).$$

Equations of Jones et al. (22). Gender and age were used to predict $\dot{V}O_2$max (liters/min):

$$\text{Men: } 4.2 - 0.032 \times \text{Age};$$

$$\text{Women: } 2.6 - 0.014 \times \text{Age}.$$

Equations of Bruce et al. (17). Gender and age were used to predict $\dot{V}O_2$max (ml/kg per min):

$$\text{Sedentary men: } 57.8 - 0.445 \times \text{Age};$$

$$\text{Sedentary women: } 41.2 - 0.343 \times \text{Age}.$$

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