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Peak Exercise Oxygen Consumption in Chronic Heart Failure: Toward Efficient Use in the Individual Patient

CRISTINA OPASICH, MD,*† GIAN DOMENICO PINNA, MS,† MARCO BOBBIO, MD,†
MASSIMO SISTI,† BRUNELLA DEMICHELIS, MD,† ORESTE FEBO, MD,*†
GIOVANNI FORNI, MD,*† ROBERTO RICCARDI, MD,*† P. GIORGIO RICCARDI, MD,*†
SOCCORSO CAPOMOLLA, MD,*† FRANCO COBELLI, MD,*†
LUIGI TAVAZZI, MD, FESC, FACC*†

Montescano (Pavia) and Turin, Italy

Objectives. **This study sought to 1) assess the short-, medium- and long-term prognostic power of peak oxygen consumption ($\dot{V}O_2$) in patients with heart failure; 2) verify the consistency of a nonmeasurable anaerobic threshold (AT) as a criterion of nonapplicability of peak $\dot{V}O_2$; 3) develop simple rules for the efficient use of peak $\dot{V}O_2$ in individualized prognostic stratification and clinical decision making.**

Background. **Peak $\dot{V}O_2$, when AT is identified, is among the indicators for heart transplant eligibility. However, in clinical practice the application of defined peak $\dot{V}O_2$ cutoff values to all patients could be inappropriate and misleading.**

Methods. **Six hundred fifty-three patients consecutively considered for eligibility for heart transplantation were followed up. Outcomes (cardiac death and urgent transplantation) were determined when all survivors had a minimum of 6 months of follow-up.**

Results. **Contraindication to the exercise test identified very high risk patients. The relatively small sample of women did not allow inferences to be drawn. In men, peak $\dot{V}O_2$ stratified into three levels (≤10, 10 to 18 and >18 ml/kg per min) identified groups at high, medium and low risk, respectively. The prognostic power of peak $\dot{V}O_2$ ≤10 ml/kg per min was maintained even when the AT was not detected. In patients in New York Heart Association functional class III or IV, peak $\dot{V}O_2$ did not have prognostic power. In patients in functional class I or II, peak $\dot{V}O_2$ stratification was prognostically valuable, but less so at 6 than at 12 or 24 months. Age did not influence peak $\dot{V}O_2$ prognostic stratification.**

Conclusions. **A contraindication to exercise testing should be considered a priority for listing patients for heart transplantation. Only in less symptomatic male patients does a peak $\dot{V}O_2$ ≤10 ml/kg per min identify short-, medium- and long-term high risk groups. A peak $\dot{V}O_2$ >18 ml/kg per min implies good prognosis with medical therapy.**

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In patients with chronic heart failure (HF), peak oxygen consumption ($\dot{V}O_2$), defined as the oxygen uptake at the maximal level of tolerated exercise, is a descriptive indicator with both prognostic power and decisional implications. A continuous variable, peak $\dot{V}O_2$ has been categorized by many investigators (1–11) for practical purposes, and the prognostic power of the various $\dot{V}O_2$ cutoff points (10, 12, 14, 16 and 18 ml/kg per min) has been repeatedly confirmed in published reports (1–11). In a study considered the cornerstone of the validation of the prognostic power of peak $\dot{V}O_2$, Mancini et al. (2) found that patients with a peak $\dot{V}O_2$ ≤10 ml/kg per min had the worst prognosis. The other cutoff values proposed for risk stratification were >10 to 14, >14 to 18 and >18 ml/kg per min. As a decisional indicator, peak $\dot{V}O_2$ appears in the first statement of the 24th Bethesda Conference (12) and in several other reports and statements as an indicator for heart transplant eligibility (2,13–19).

Peak $\dot{V}O_2$ should be considered only after the anaerobic threshold (AT) is detected, thus guaranteeing nearly maximal exercise performance. Mancini et al. (2), for instance, included in their survival analysis only patients whose AT could be identified for at least one of two exercise tests. However, in daily clinical practice, AT goes undetected in a large proportion of patients with a low peak $\dot{V}O_2$.

Despite such drawbacks, published studies have brought about both increasing use of cardiopulmonary exercise (CPX) testing in clinical practice and a simplistic application of defined peak $\dot{V}O_2$ cutoff values to all patients with chronic HF. Intuitively, such a generalized application holds the risk of inappropriateness or wide approximation.

The present study was conceived with the aim of reconsidering and elucidating major issues regarding the use of peak

From the *Salvatore Maugeri Foundation, Institute of Care and Scientific Research, Medical Center of Montescano (Pavia); and †Heart Failure Unit, Department of Biomedical Engineering and Department of Cardiology, University of Molinette Hospital, Turin, Italy.

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Address for correspondence: Dr. Cristina Opasich, Centro Medico di Montescano, Via per Montescano, 27040 Montescano (Pavia), Italy.

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Abbreviations and Acronyms

AT = anaerobic threshold
CI = confidence interval
CPX = cardiopulmonary exercise
HF = heart failure
$\dot{V}O_2$ = oxygen consumption

$\dot{V}O_2$ as a routine prognostic and decisional indicator in chronic HF. We intended to 1) verify the clinical applicability of the stratification suggested by Mancini et al. (2) in a large group of patients with moderate to severe chronic HF, consecutively considered for eligibility for heart transplantation; 2) verify the need for exclusion from peak $\dot{V}O_2$ prognostic stratification of those patients without a determinable AT; 3) compare the short- (6 months), medium- (12 months) and long-term (24 months) prognostic power of peak $\dot{V}O_2$; and 4) develop simple rules, based on some common clinical indicators, for using peak $\dot{V}O_2$ in individualized prognostic stratification and clinical decision making.

Methods

Patients. All patients with chronic HF and a left ventricular ejection fraction <40%, admitted for assessment or reassessment of indications for heart transplantation at the Heart Failure Unit of Montescano Medical Center or the Cardiological Department of Molinette Hospital of Turin from March 1992 to October 1995, were enrolled in the study.

On admission, all patients were given individualized therapy, which generally included angiotensin-converting enzyme inhibitors, vasodilators (nitroprusside, isosorbide dinitrate, hydralazine), digoxin, diuretic drugs, inotropic drugs (dopamine, dobutamine, enoximone) when needed and, in the absence of contraindications, antiacoagulants (international normalized ratio 2 to 3) or antiplatelet agents. At the time of recruitment, beta-adrenergic blocking agents were not yet considered routine therapy.

After therapeutic optimization, when patients were clinically stable, a functional evaluation was performed that included two-dimensional echocardiography; right heart catheterization, performed with a Swan-Ganz catheter for thermodilution, introduced through the internal jugular vein (Seldinger technique); and CPX testing, carried out on a treadmill with a modified Naughton protocol (20) and with simultaneous monitoring of respiratory gases by a CAD/NET System 2001 Medical Graphics analyzer. The AT was defined as one or more of the following: 1) the point at which the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) was minimal, followed by a progressive increase; or 2) the point after which the respiratory gas exchange ratio exceeded the rest respiratory gas exchange ratio; or 3) the point after which a nonlinear increase in minute ventilation occurred relative to carbon dioxide consumption. The peak $\dot{V}O_2$ cutoff values used were those proposed by Mancini et al. (2): ≤10, >10 to 14, >14 to 18 and >18 ml/kg per min.

Contraindications to CPX testing were symptomatic congestion at rest and the reappearance of rest symptoms after weaning from vasodilator or inotropic infusion treatment. Admission to the heart transplantation waiting list followed the current guidelines (12); absolute and relative contraindications were considered according to standard practice (12).

All patients were closely followed up by means of clinical examination and other tests (echocardiography, CPX). All surviving patients had a minimum of 6 months of follow-up.

Cardiac events. Sudden death (if unexpected, occurring in or out of the hospital within 1 h after the onset of, or change in, symptoms or during sleep in a patient who was symptomatically stable during the 24 h before death); progressive HF-related death; other cardiac-related death, including acute myocardial infarction and pulmonary embolism; and urgent transplantation (in Status I patients) were considered cardiac events.

Prognostic variables. To individualize the use of the prognostic and decisional power of peak $\dot{V}O_2$, three descriptive clinical indicators commonly used in clinical practice were considered: gender, age and New York Heart Association functional class.

Statistical analysis. All patients capable of performing the CPX test were initially subclassified by gender. Within the male group, survival analysis was performed separately for subjects in whom the AT was detected and in those in whom it was not. This analysis was carried out by stratifying patients according to the cutoff points of Mancini et al. (2) and estimating corresponding survival functions by the Kaplan-Meier method. Data from patients who survived until the end of the follow-up period, died of noncardiac-related causes or underwent transplantation (except for Status I patients) were treated as "censored" observations. Survival curves were compared by the log-rank test. Besides allowing verification of the robustness of the criteria of Mancini et al. (2) in a large group of patients, this analysis also allowed the prognostic stratification power of peak $\dot{V}O_2$ to be tested in patients without a detected AT. The result was the identification of a subgroup of patients, with or without a detected AT, for whom peak $\dot{V}O_2$ had a proven prognostic value. To refine this identification process on the basis of the chosen clinical indicators, these patients were then subclassified by age (≤55 vs. >55 years), and survival analysis was again performed to identify a further subgroup, if existing, in which peak $\dot{V}O_2$ had a clear prognostic value. Finally, the same procedure was repeated after classifying patients by functional class (I to II vs. III to IV). The overall procedural tree is summarized in Figure 1. In the final subgroup, identification of the relative risk of each peak $\dot{V}O_2$ cutoff was estimated by Cox proportional hazards analysis (peak $\dot{V}O_2$ cutoff was used as the explanatory variable in the model), and the survival experience was further examined over the first 6 months, 1 year and 2 years by the Kaplan-Meier method.

Because of the small sample size of the women who

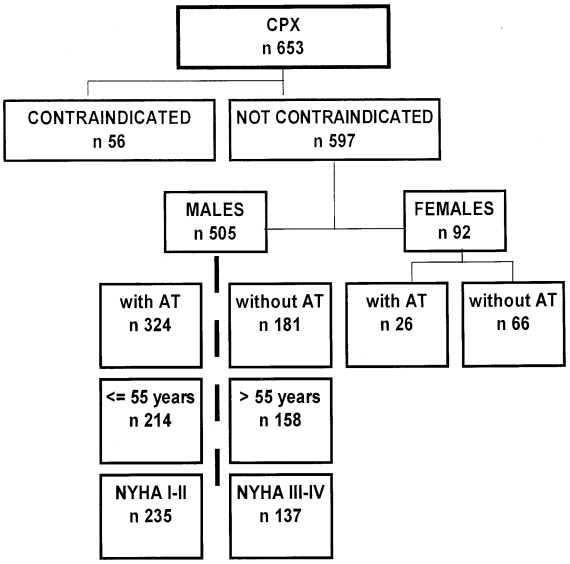


Figure 1. Grouping procedure followed in the study. The two age groups (≤55 and >55 years) and New York Heart Association (NYHA) functional class groups (I or II vs. III or IV) were derived from 324 patients with and 48 without a detectable AT and peak $\dot{V}O_2$ ≤10 ml/kg per min (see text for details).

performed the CPX test, survival analysis in this subgroup was not carried out.

Results are expressed as mean value ± SD. A probability value <0.05 was considered statistically significant. Statistical analysis was performed with the SAS/STAT version 6.10 statistical package (SAS Institute Inc.).

Results

Patients. The clinical characteristics of the 653 patients enrolled in the study are shown in Table 1. The average follow-up period was 498.8 ± 381 days (median 375). No patient was lost to follow-up. Fourteen patients died of noncardiac causes. Fifty-six patients (43 men) could not perform the CPX test because of clinical cardiac contraindications (20 of 24 patients in functional class IV were in this group). A cardiac event (cardiac death or heart transplantation in Status I patients) occurred in 77% of these patients, and in 70% (30 patients) within 100 days after the evaluation.

Female patients. Ninety-two of 105 female patients performed the CPX test (55 in functional class I or II, 37 in functional class III). Twenty-six patients of these 92 patients died of cardiac causes and 1 of a noncardiac cause. Twenty-five patients underwent heart transplantation, of whom 12 were in Status I. In all, 38 events (cardiac death and heart transplantation in Status I patients) occurred (Table 2).

During the exercise test, the AT was detected in only 26 patients and was not detected in 66. Because of the small number of patients in both subgroups, survival analysis was not carried out.

Male patients. In the male group, 505 of 548 patients performed the CPX test. Among these 505 patients, 126 (25%) died of cardiac causes and 11 (2.2%) of noncardiac causes; 93 (18.4%) underwent heart transplantation (24 were Status I). In all, 150 events occurred (Table 2).

During the exercise test, the AT was detected in 324 patients (64%). The survival curves for these patients according to the stratification of Mancini et al. (2) are shown in Figure 2. A peak $\dot{V}O_2$ ≤10 ml/kg per min identified patients with the worst prognosis (13 [59%] of 22 with a cardiac event),

Table 1. Clinical Characteristics of 653 Study Patients

Age (yr)	52.1 ± 9.0
Men/women	548/105
Etiology	
Dilated cardiomyopathy	315 (48.2%)
Coronary ischemic disease	250 (38.2%)
Valvular disease	56 (8.6%)
Other	32 (5%)
Disease duration (mo)	46.1 ± 8.6
NYHA functional class at evaluation	
I	57 (9%)
II	339 (52%)
III	233 (36%)
IV	24 (3%)
LVEF (%)	24 ± 7.7
Hemodynamic pattern (n = 520)	
Pulmonary wedge pressure (mm Hg)	20.1 ± 9.9
Right atrial pressure (mm Hg)	6.2 ± 4.8
Cardiac index (liters/min per m^2)	2.2 ± 0.5
CPX test (n = 597 [505 men, 92 women])	
Duration (min)	10.5 ± 4.9
Peak $\dot{V}O_2$ (ml/kg per min)	14.7 ± 5.4
Peak $\dot{V}O_2$ cutoff (% men/women)	
≤10 ml/kg per min	13.9%/33.7%
>10–14 ml/kg per min	33.3%/46.7%
>14–18 ml/kg per min	29.3%/9.8%
>18 ml/kg per min	23.6%/9.8%
AT (ml O_2/kg per min) detected in 354 patients (324 men, 26 women)	13.3 ± 4.3
Stop for fatigue	382 (64%)
Stop for dyspnea	101 (17%)
Other reasons	118 (19%)

Data presented are mean value ± SD or number (%) of patients, unless otherwise indicated. CPX = cardiopulmonary exercise; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; $\dot{V}O_2$ = oxygen uptake.

Table 2. Cardiac Events and Status at Follow-Up (mean 498.8 ± 381 days)

Event	Men (n = 548) [no. (%) of pts]	Women (n = 105) [no. (%) of pts]
Death due to progressive HF	84 (15%)	17 (16%)
Sudden death	51 (9%)	8 (8%)
Other cardiac death	14 (2.5%)	1 (1%)
Noncardiac death	13 (2.5%)	1 (1%)
Tx status II	75 (14%)	13 (12%)
Tx status I	34 (6%)	12 (11%)
Survivors free of Tx	277 (51%)	53 (50.5%)

HF = heart failure; pts = patients; Tx = transplantation.

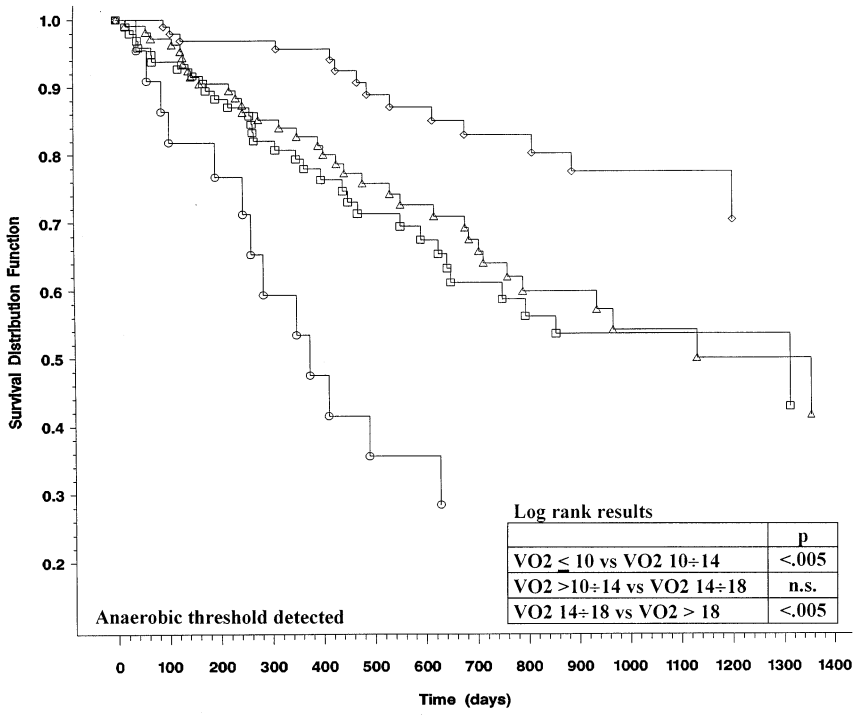


Figure 2. Survival curves for patients grouped according to the cutoff values of Mancini et al. (2). All patients had an identifiable AT. **Circles** = patients with a peak $\dot{V}O_2$ ≤10 ml/kg per min; **squares** = patients with a peak $\dot{V}O_2$ >10 to 14 ml/kg per min; **triangles** = patients with a peak $\dot{V}O_2$ >14 to 18 ml/kg per min; **diamonds** = patients with a peak $\dot{V}O_2$ >18 ml/kg per min.

whereas a peak $\dot{V}O_2$ >18 ml/kg per min identified patients with the best prognosis (14 [15%] of 96 with a cardiac event). No differences were found between survival of patients in the two intermediate groups (32 of 98 with a peak $\dot{V}O_2$ >10 to 14 ml/kg per min and 35 of 108 with a peak $\dot{V}O_2$ >14 to 18 ml/kg per min had a cardiac event, p = 0.66). We also repeated the analysis using a narrower stratification (10 to 12.5, 12.5 to 15, 15 to 17.5, 17.5 to 20, >20 ml/kg per min), but survival curves of patients with a peak $\dot{V}O_2$ in the range 10 to 17.5 ml/kg per min again did not differ.

Because of the similarity of the survival curves of patients with a peak $\dot{V}O_2$ 10 to 14 and 14 to 18 ml/kg per min, we considered these patients as a single group. The cardiac event rates of the three resulting groups (patients with a peak $\dot{V}O_2$ ≤10, 10 to 18, >18 ml/kg per min) were 62%, 33% and 15%, respectively. Death due to heart failure and Status I at the time of transplantation accounted for 62%, 59% and 50% of all cardiac events in the three groups, respectively, showing a homogeneous stratification power of peak $\dot{V}O_2$ when only these end points were considered.

The AT was not identified in 48 of the male patients (69%) with a peak $\dot{V}O_2$ ≤10 ml/kg per min, 70 (42%) with a peak $\dot{V}O_2$ >10 to 14 ml/kg per min, 40 (27%) with a peak $\dot{V}O_2$ >14 to 18 ml/kg per min and 23 (19%) with a peak $\dot{V}O_2$ >18 ml/kg per min. There was no significant difference between the survival curves for patients with a peak $\dot{V}O_2$ >10 to 14, >14 to 18 and >18 ml/kg per min (Fig. 3) for a cardiac event rate of 29%, 23% and 22% of 70, 40 and 23 subjects in each group, respectively. However, the survival of patients with a peak $\dot{V}O_2$ ≤10 ml/kg per min (22 [46%] of 48 patients with a cardiac event) was markedly worse (p = 0.007), indicating a high predictive power of this peak $\dot{V}O_2$ level. When the survival curve of this subgroup of patients was compared with that of the corresponding subgroup with the same peak $\dot{V}O_2$ but a measurable AT, substantial overlap of the two subgroups was seen (p = 0.52). For this reason, all 324 patients with a detectable AT and 48 patients with an undetected AT but with a peak $\dot{V}O_2$ ≤10 ml/kg per min were considered as a single group (372 patients in all) in further analyses.

In this group of patients the survival of older (n = 158) and younger (n = 214) subjects within the same peak $\dot{V}O_2$ cutoff value was very similar (p > 0.5 for all comparisons) (Fig. 4). The incidence of cardiac events was also comparable (Table 3). For this reason, in the further analysis we did not consider age groups separately.

When survival according to functional class at the time of evaluation (235 patients in functional class I or II vs. 137 patients in functional class III or IV) (Table 3, Fig. 5) was analyzed, different results were found depending on the value of this clinical indicator. Peak $\dot{V}O_2$ cutoff values discriminated well between low, medium and high risk patients in functional class I or II, with mortality rates of 12%, 28% and 45%, respectively (p = 0.0005). The risk ratio was 2.5 (95% confidence interval [CI] 1.2 to 5) between peak $\dot{V}O_2$ 10 to 18 and <10 ml/kg per min and 1.9 (95% CI 1.0 to 3.9) between peak $\dot{V}O_2$ >18 and 10 to 18 ml/kg per min. In contrast, for patients in functional class III or IV, all peak $\dot{V}O_2$ curves intersected each other, and the log-rank test was not significant (p = 0.15).

In the identified subgroup of patients in whom peak $\dot{V}O_2$ was a significant prognostic indicator (235 men in functional class I or II), we verified the prognostic power of this marker for short-, medium- and long-term outcome. The percent of

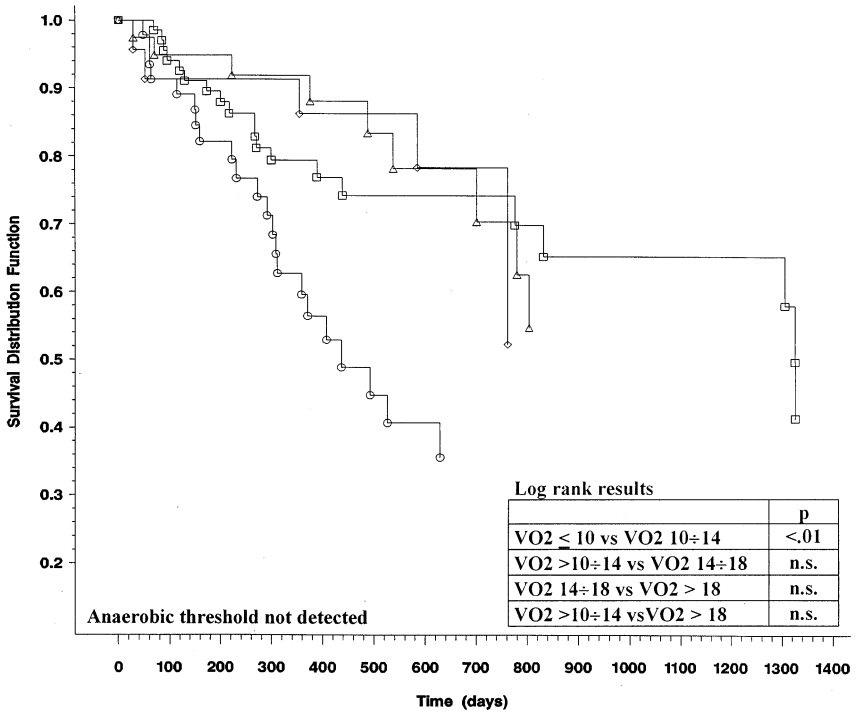


Figure 3. Survival curves for patients grouped according to the cutoff values of Mancini et al. (2); no patient had an identifiable AT. Symbols as in Figure 2.

event-free subjects at 6 months and 1 and 2 years is shown in Table 4. It can be seen that a peak $\dot{V}O_2$ ≤10 ml/kg per min has a prognostic power that persists over time, with a mortality rate of 18% within 6 months, 36% within 1 year and 45% within 2 years. A peak $\dot{V}O_2$ 10 to 18 ml/kg per min identified patients with a poorer medium-term outcome than those with a peak $\dot{V}O_2$ >18 ml/kg per min, who had the best prognosis up to 2 years.

Discussion

Peak $\dot{V}O_2$ has become an integral part of prognostic stratification and evaluation for heart transplantation in patients with chronic HF (2,13–19). However, validation of its clinical applicability in a large population is still lacking, and the simplistic (now widespread) use of its cutoff values in all patients with moderate to severe chronic HF as a clinical tool in decision making for heart transplantation might be inappropriate.

In the present study, we verified the prognostic value of peak $\dot{V}O_2$ stratification, originally proposed by Mancini et al. (2), in a large group of patients with moderate to severe chronic HF consecutively considered for candidacy for heart transplantation. We sought to exploit the information provided by a few simple clinical indicators to apply peak $\dot{V}O_2$ cutoff values more efficiently in the individual patient.

Contraindication to CPX testing. The present study verified that the presence of a clinical contraindication to performing the CPX test, despite optimized medical treatment, is the simplest and strongest negative prognostic indicator. This result confirms those previously demonstrated after acute myocardial infarction (21), after lung cancer resection (22) and in advanced HF (23).

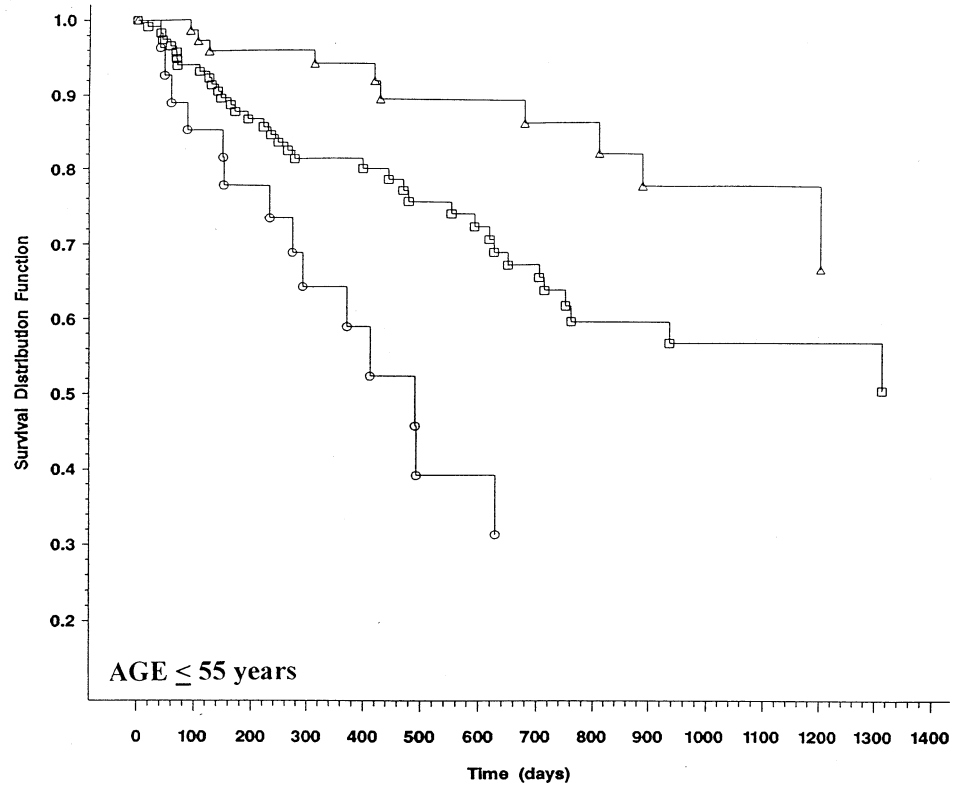
By identifying patients with a high probability of an unfavorable short-term outcome, the inability to perform an exercise test is also a decisional indicator in the process of eligibility for heart transplantation or ventricular assistance device implantation. Accordingly, this indicator should be added to the selection criteria for listing candidates with advanced HF and for timing heart transplantation.

Prognostic power of the peak $\dot{V}O_2$ with and without detection of the AT. In patients able to perform an exercise test, the peak $\dot{V}O_2$ cutoff points proposed by Mancini et al. (2) were partially confirmed in our large cohort. A peak $\dot{V}O_2$ ≤10 ml/kg per min identifies high risk patients, and a peak $\dot{V}O_2$ >18 ml/kg

Table 3. Cardiac Event Rates According to Peak Oxygen Uptake, Age and Functional Class in Male Patients

Peak $\dot{V}O_2$	Age		NYHA	
	≤55 yr	>55 yr	I/II	III/IV
<10 ml/kg per min				
No. of patients	29	41	22	48
Cardiac event rate	48%	51%	45%	52%
10–18 ml/kg per min				
No. of patients	115	91	127	79
Cardiac event rate	30%	35%	28%	39%
>18 ml/kg per min				
No. of patients	70	26	86	10
Cardiac event rate	14%	15%	12%	40%

Abbreviations as in Table 1.



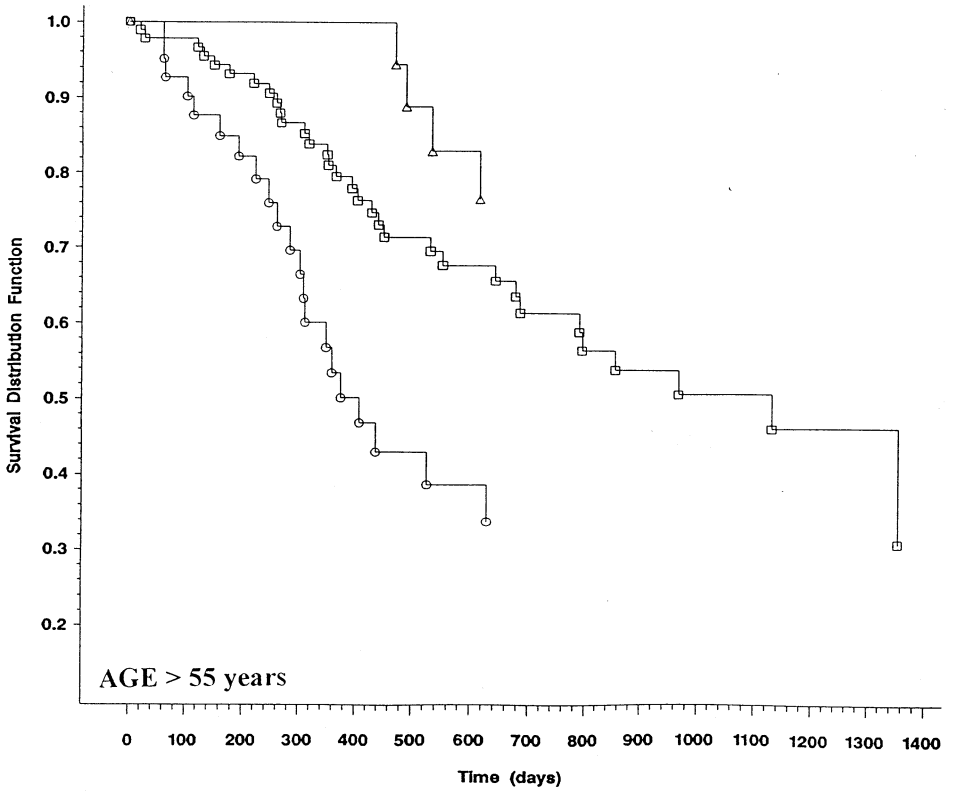


Figure 4. Survival curves for patients grouped according to peak $\dot{V}O_2$ and age. **Circles** = patients with a peak $\dot{V}O_2$ ≤10 ml/kg per min; **squares** = patients with a detectable AT and a peak $\dot{V}O_2$ 10 to 18 ml/kg per min; **triangles** = patients with a detectable AT and a peak $\dot{V}O_2$ >18 ml/kg per min.

per min identifies low risk patients; however, all other values in between these cutoff values define a gray area of medium risk patients, without any further possible stratification. This result confirms the observations of Kao et al. (24) in 178 patients with the same characteristics as ours. Moreover, our results do not confirm the prognostic and decisional value of the "magic

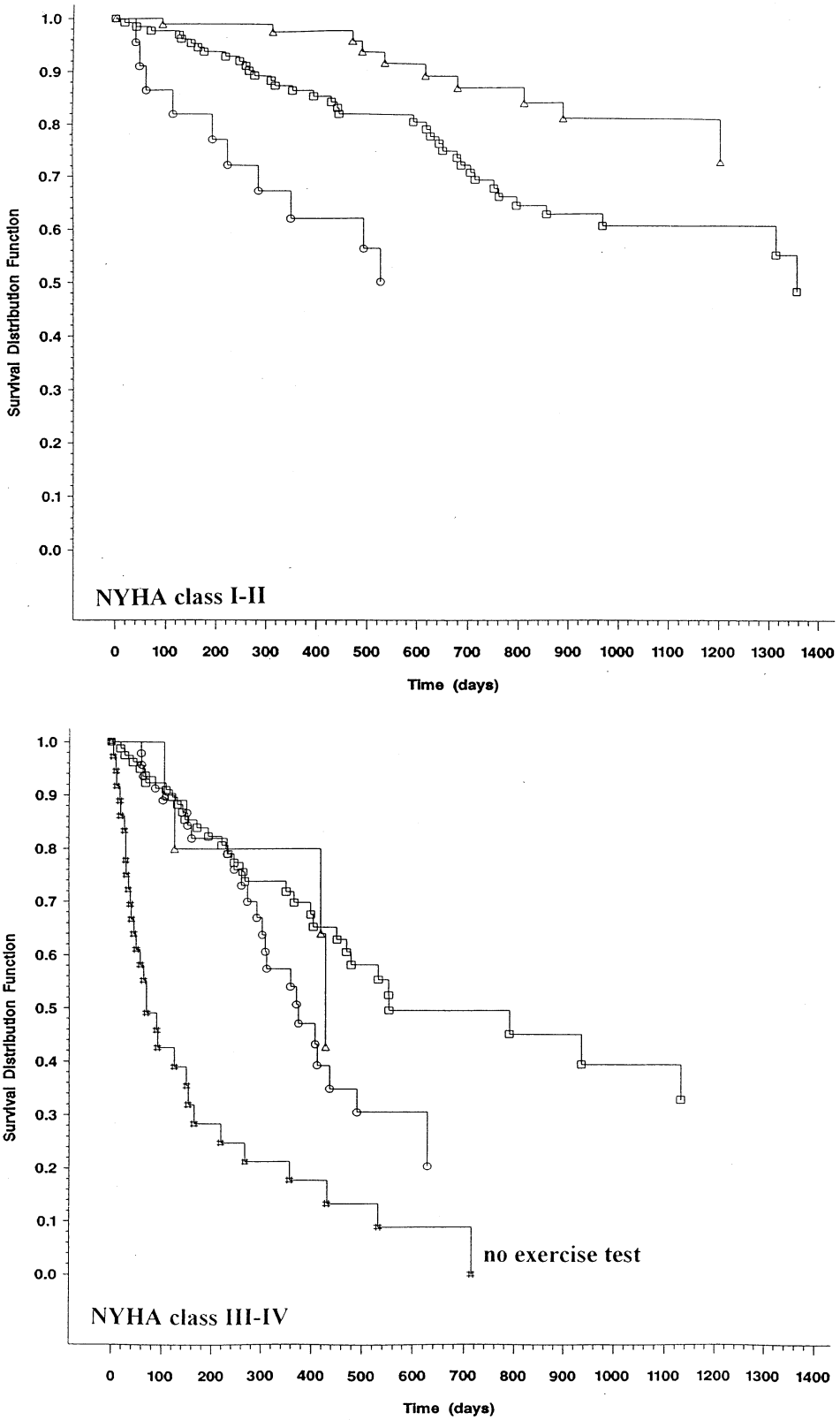


Figure 5. Survival curves for patients grouped according to peak $\dot{V}O_2$ and New York Heart Association (NYHA) functional class. **Hash marks** = patients with contraindications to exercise testing; other symbols as in Figure 4.

number" of 14 ml/kg per min of peak $\dot{V}O_2$ previously proposed (5); for 10 to 18 ml/kg per min, such a cutoff point does not discriminate patients at different risk.

In the Mancini et al. study (2), peak $\dot{V}O_2$ had prognostic power provided that the AT was reached. When we performed a survival analysis in the subgroup of our patients in whom the

Table 4. Percent of Event-Free Male Patients in Functional Class I or II According to Peak Oxygen Uptake

	Peak $\dot{V}O_2$ (ml/kg per min)		
Follow-Up Visit	≤10	10–18	>18
6 mo	82%	94%	99%
1 yr	64%	87%	98%
2 yr	54%	77%	92%

$\dot{V}O_2$ = oxygen uptake.

AT was not detected, we found that identification of the AT did not influence the prognostic power of a peak $\dot{V}O_2$ ≤10 ml/kg per min. The low level of symptom appearance is probably a valuable indicator of abnormal metabolic response to exercise and replaces the information of the low level of AT. This result has important practical implications because the AT is not detectable in the great majority of the patients with a peak $\dot{V}O_2$ ≤10 ml/kg per min (25–27) (Table 1) and, if reached, the AT is hard to identify by noninvasive methods. Thus, the other "magic number," peak $\dot{V}O_2$ 10 ml/kg per min should be taken into account in the prognostic stratification of and decision making for patients with chronic HF, without the constraint of AT detection. In contrast, for all other patients without a detectable AT and a peak $\dot{V}O_2$ >10 ml/kg per min, the peak $\dot{V}O_2$ value does not provide prognostic information. In these patients, a repeat exercise test is advisable.

Prognostic power of peak $\dot{V}O_2$ in the individual patient. To individualize the use of peak $\dot{V}O_2$ as a prognostic and decisional marker, gender, age and clinical severity were considered in the survival analysis. The first variable used to subgroup patients was gender, in accordance with published suggestions (19,28) of the limited prognostic power of peak $\dot{V}O_2$ in women with HF and the poor informative results of exercise testing previously seen in women with coronary disease (29–32). Although our group of female transplant candidates is, to our knowledge, the largest to be evaluated with exercise testing, the sample size achieved was considered inadequate for a reliable survival analysis to be performed. However, a major finding was that women, compared with men, comprise both a higher proportion of patients with low exercise capacity and good prognosis and a lower proportion with a detectable AT.

In male patients grouped according to age (≤55 vs. >55 years), no differences were seen in the prognostic power of peak $\dot{V}O_2$ cutoff values. This result could be explained in part by the absence of very elderly subjects among our transplant candidates and in part by the observation that the strength of the prognostic power of peak $\dot{V}O_2$ is concentrated at its lowest and highest values (≤10 and >18 ml/kg per min), which are far more influenced by severity of functional limitations than by age.

The prognostic power of peak $\dot{V}O_2$ was confirmed only in patients in functional class I or II. Although the cardiac events rate was higher in patients in functional class III or IV, survival curves corresponding to the three peak $\dot{V}O_2$ strata were not significantly different. Thus, peak $\dot{V}O_2$ shows less prognostic sensitivity in those patients for whom decisional contributions are most needed.

Short-, medium- and long-term prognostic power of peak $\dot{V}O_2$. *In summary*, we found that peak $\dot{V}O_2$ provides prognostic information in male patients with moderate to severe HF, who are between 30 and 70 years old and are in functional class I or II after optimal therapy. A peak $\dot{V}O_2$ >18 ml/kg per min maintains its predictive power of a good outcome for at least 2 years. Thus, in these patients, repetition of the CPX test for prognostic reasons might not be necessary throughout this period. A peak $\dot{V}O_2$ ≤10 ml/kg per min shows a prognostic power that is strong in the short term and is maintained over time.

Toward the efficient use of peak $\dot{V}O_2$ in the individual patient. The prognostic and decisional (evaluation for heart transplantation) value of peak $\dot{V}O_2$ is summarized in Figure 6, which may also be viewed as a flowchart for the efficient use of

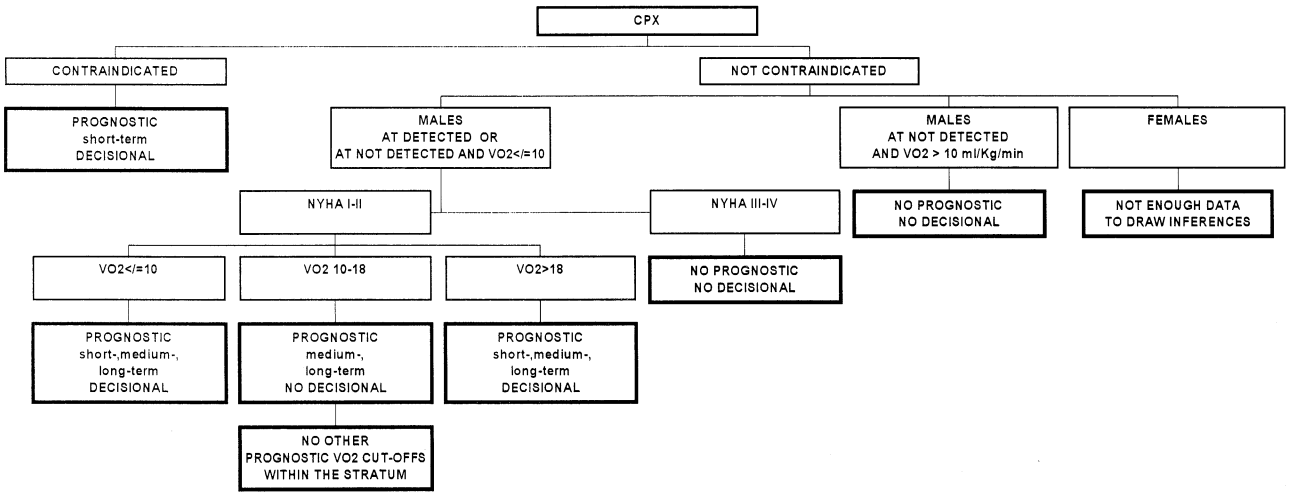


Figure 6. Flowchart for efficient use of a cardiopulmonary exercise test results in the individual patient with moderate to severe chronic HF. NYHA = New York Heart Association.

CPX test results in individual patients. A clear contraindication to exercise testing is both a prognostic and a decisional indicator: The patient is at very high risk, and aggressive treatment (i.e., urgent heart transplantation, ventricular assistance) should be considered. When the CPX test is not contraindicated and the patient is a woman, the current view is that peak $\dot{V}O_2$ has little value for prognostic stratification and decision making; however, larger studies are needed to confirm this current provisional policy.

For male patients, CPX test results should be taken into consideration in all subjects with a detectable AT and in those who reach a peak $\dot{V}O_2$ ≤10 ml/kg per min without an evident AT.

In patients in functional class III or IV, peak $\dot{V}O_2$ is neither prognostic nor decisional. Our data are partially in contrast with the results of Stevenson et al. (23), who showed that among exercising patients in an advanced functional class, the threshold of 10 ml/kg per min was the only cutoff value that identified a higher risk group. Currently, most heart transplantation centers rely heavily on peak $\dot{V}O_2$ evaluation to decide which patients with advanced HF should be considered for heart transplantation (12,18). We believe that this decision should rely more on other indicators of prognosis, such as contraindication to exercise testing and exhausted therapeutic alternatives.

Male patients 30 to 70 years old, in functional class I or II after optimal therapy and with a peak $\dot{V}O_2$ ≤10 ml/kg per min have a cardiac event probability higher than all other patients in functional class I or II and similar to that of patients in functional class III or IV. Hence, in these patients peak $\dot{V}O_2$ is a powerful decisional indicator for transplantation (and priority), whereas the simple evaluation of symptoms could be misleading. These data are in agreement with those of Aaronson et al. (33), who showed that among ambulatory patients referred for heart transplantation, peak $\dot{V}O_2$ alone gave a satisfactory prognostic discrimination.

A patient with a peak $\dot{V}O_2$ >18 ml/kg per min, has a good long-term prognosis. In this case, peak $\dot{V}O_2$ is also decisional, making any aggressive treatment or close follow-up unnecessary.

Finally, patients with a peak $\dot{V}O_2$ in the range 10 to 18 ml/kg per min fall into a gray (and unfortunately very large) prognostic region, and peak $\dot{V}O_2$ does not provide information on which decisions can be made. In such patients, further data should be collected to improve prognostic capability and to address decision making (e.g., serial cardiopulmonary exercise tests, other exercise/recovery indexes [34,35]), evaluation of responses to other therapy, other diagnostic tests [36]).

Conclusions. The results of the present study suggest that the decision to list patients with advanced HF for heart transplantation should rely not only on peak $\dot{V}O_2$ but on other indicators of prognosis as well. Contraindication to exercise testing appears to be a powerful short-term unfavorable prognostic indicator. Only among less symptomatic male patients able to exercise is peak $\dot{V}O_2$ a valuable prognostic indicator for decision making in that it can identify low and high risk subjects and thus offer a practical operative contribution for nearly 20% of all patients with moderate to severe chronic HF. For transplantation, only a peak $\dot{V}O_2$ ≤10 ml/kg per min is a definite decisional indicator, with or without AT. These considerations, together with the lack of prognostic power of peak $\dot{V}O_2$ in patients in a functional class III or IV, limit its role in clinical practice.

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