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Heart Failure

Effects of Gender on Peak Oxygen Consumption and the Timing of Cardiac Transplantation

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OBJECTIVES This study examines the gender effects on peak exercise oxygen consumption (VO_2) and survival in heart failure (HF) patients and their implications for cardiac transplantation.

BACKGROUND The predictive value of peak VO_2 in women HF patients is poorly established but is one of the indicators used to optimally time cardiac transplantation in women.

METHODS A total of 594 ambulatory HF patients (mean age 52 ± 12 years, 28% women, mean left ventricular ejection fraction 26 ± 12%, 73% on beta-blocker) underwent symptom-limited exercise tests with breath-by-breath expired gas analyses using ramped treadmill protocols. Kaplan-Meier survival curves were generated for each gender and compared using log-rank tests.

RESULTS Women had a significantly lower peak VO_2 than men (14.0 ± 4.9 ml/kg/min vs. 16.6 ± 7.1 ml/kg/min; $p < 0.0001$), despite being younger (48.9 ± 11.5 years vs. 53.2 ± 12.4 years; $p < 0.0001$) and having a higher left ventricular ejection fraction (29 ± 13% vs. 25 ± 11%; $p < 0.0003$). However, the one-year transplant-free survival was significantly lower for men than for women (81% vs. 94%, $p < 0.0001$), a finding seen across each Weber class. Cox regression analyses confirmed the protective effects of female gender on transplant-free survival when controlling for peak VO_2, age, race, beta-blocker use, and type of cardiomyopathy. The peak VO_2 associated with 85% one-year transplant-free survival was significantly higher in men than in women (11.5 vs. 10.0 ml/kg/min).

CONCLUSIONS Women had a significantly lower peak VO_2 than men, but had better survival at all levels of exercise capacity. The current practice of uniform application of peak VO_2 as an aid to determine cardiac transplantation timing should be re-examined. (J Am Coll Cardiol 2006; 47:2237–42) © 2006 by the American College of Cardiology Foundation

Peak oxygen consumption (VO_2) is a reliable predictor of survival in patients with advanced heart failure (HF) (1–7). Consequently, peak VO_2 is used for determining the timing of cardiac transplantation (3–7). Mancini et al. (3) showed that patients with a peak $VO_2 \leq 14$ ml/kg/min had poor outcomes and benefit from cardiac transplantation. However, this and other major studies examining the use of peak VO_2 as a predictor of outcomes in HF evaluated few women (3–7). As peak VO_2 is influenced by age, gender, muscle mass, motivation, and pulmonary status (8,9), it is unclear whether peak VO_2 values provide the same prognostic information in women.

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Despite their under-representation in HF trials, women constitute a significant proportion of cardiac transplant recipients in the U.S. United Network for Organ Sharing data reveal that in 2003, 26% of cardiac transplant recipients were women. Because peak VO_2 has not been validated in female HF patients, it is possible that its use in evaluating women leads to premature cardiac transplantation. Because there is a relative shortage of donor organs (10) and post-transplantation survival is limited, it is of the utmost importance that organs are allocated as appropriately as possible.

Given several gender-based differences in the pathophysiology and progression of HF (11–15), it is apparent that HF management, including the application of peak VO_2, should be customized for the patient population being treated (5–9,16–18). Here we describe a large and diverse population of ambulatory HF patients and their performance on cardiopulmonary exercise testing to delineate the prognostic value of peak VO_2 in women patients.

METHODS

Patient population. A total of 726 patients underwent 1,028 cardiopulmonary exercise tests between July 2000 and December 2003 at the University of Pennsylvania's Heart Failure and Transplant Ambulatory Care Center to evaluate functional capacity, HF management, and transplantation timing. Patient demographics, co-existing conditions, and medications were prospectively recorded before each test;

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Abbreviations and Acronyms

HF = heart failure
LVEF = left ventricular ejection fraction
OHT = orthotopic heart transplant
RER = respiratory exchange ratio
Vo_2 = oxygen consumption

whereas left ventricular ejection fraction (LVEF) and patient outcomes were retrospectively determined from medical records.

Patients were included in this analysis if they had a LVEF ≤45% as measured by echocardiography, left ventriculogram, or nuclear imaging. For patients with multiple Vo_2 tests during the study period, only the first test was used for analysis.

End points for this study were death and orthotopic heart transplantation (OHT) from the date of study until June 30, 2004. Whenever possible, the date of patient death, as documented in patient records or in the Social Security Death Index, was used. However, in the event that the exact date of death was unknown, the midpoint between the date of last contact and the date when the death was reported was used. The OHT date was obtained from the University of Pennsylvania's transplant database.

This analysis of clinical Vo_2 studies was approved by the University of Pennsylvania's Institutional Review Board.

Cardiopulmonary exercise testing. All patients underwent symptom-limited cardiopulmonary exercise testing using a ramped treadmill protocol with breath-by-breath expired gas analysis using a computerized metabolic cart (Sensormedics Vmax 29, Yorba Linda, California). Three different protocols were used for testing based on the patient's self-reported symptom class, as has been published elsewhere (19). Studies were interpreted by a single reader (A. K.). The anaerobic threshold was determined by the V-slope method (20).

Statistical analysis. Kaplan-Meier analyses were used to assess survival. Data from different patient populations were compared using log-rank testing. We stratified patients according to the Weber classification (class A: peak Vo_2 >20 ml/kg/min; class B: peak Vo_2 >16 to ≤20 ml/kg/min; class C: peak Vo_2 >10 to ≤16 ml/kg/min; class D: peak Vo_2 ≤10 ml/kg/min) to determine whether Weber classes are predictive of survival in each gender (21). To determine a cut-off peak Vo_2 value when cardiac transplantation would

Table 1. Baseline Patient Characteristics of Men Versus Women

Characteristics	Overall, n (%) (n = 594)	Men, n (%) (n = 427)	Women, n (%) (n = 167)	p Value
Age (yrs)	52 ± 12	53 ± 12	49 ± 11	<0.0002
LVEF (%)	26 ± 12	25 ± 11	29 ± 13	<0.001
Body mass index	29 ± 5	29 ± 5	29 ± 7	NS
Race				<0.05
White	453 (76)	338 (79)	115 (69)	
Black	127 (21)	78 (18)	49 (29)	
Hispanic	7 (1)	5 (1)	2 (1)	
Asian	7 (1)	6 (1)	1 (1)	
Etiology of HF				<0.001
Idiopathic	319 (54)	206 (48)	113 (68)	
Ischemic	206 (35)	181 (43)	25 (15)	
Valvular	28 (5)	21 (5)	7 (4)	
Other	41 (7)	19 (4)	22 (13)	
Therapies				
Beta-blockers	431 (73)	311 (73)	120 (72)	NS
ACE inhibitors	455 (77)	332 (78)	123 (74)	NS
ARBs	97 (16)	61 (14)	36 (22)	<0.05
Aspirin	241 (41)	184 (43)	57 (34)	<0.05
Calcium channel blockers	35 (6)	22 (5)	13 (8)	NS
Digoxin	421 (71)	306 (72)	115 (69)	NS
Diuretics	424 (72)	300 (70)	124 (74)	NS
Spironolactone	60 (10)	40 (9)	20 (12)	NS
Lipid-lowering medications	171 (29)	135 (32)	36 (22)	<0.03
Nitrates	53 (9)	45 (11)	8 (5)	<0.05
ICD	77 (13)	68 (16)	9 (5)	<0.0006
Comorbidities				
Hypertension	195 (33)	150 (35)	45 (27)	NS
Diabetes	137 (23)	111 (26)	26 (16)	<0.01
Lung disease (asthma/COPD)	41 (7)	28 (7)	13 (8)	NS
Atrial fibrillation	68 (11)	63 (15)	5 (3)	<0.001

Plus-minus values are mean ± standard deviation. NS = p > 0.05.
ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; COPD = chronic obstructive pulmonary disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

Table 2. Exercise Parameters

	Study Population	Men	Women	p Value
Baseline $\dot{V}O_2$ (ml/kg/min)	2.8 ± 0.4	2.8 ± 0.4	2.6 ± 0.4	<0.0001
Peak $\dot{V}O_2$ (ml/kg/min)	15.9 ± 6.7	16.6 ± 7.1	14.0 ± 4.9	<0.0001
Resting HR (beats/min)	77 ± 14	76 ± 14	80 ± 15	<0.002
Peak HR (beats/min)	132 ± 28	130 ± 29	135 ± 25	<0.04
Resting SBP (mm Hg)	112 ± 18	113 ± 18	109 ± 16	<0.03
Peak SBP (mm Hg)	139 ± 28	140 ± 28	136 ± 26	NS
Resting DBP (mm Hg)	71 ± 11	71 ± 11	70 ± 11	NS
Peak DBP (mm Hg)	77 ± 14	77 ± 13	76 ± 14	NS
Peak RER	1.09 ± 0.11	1.11 ± 0.11	1.05 ± 0.10	<0.0001
Number reaching AT, n (%)	449 (76%)	338 (79%)	111 (66%)	<0.01
Perceived exertion at peak (Borg scale)	17.5 ± 2.1	17.4 ± 2.0	17.7 ± 2.2	NS

Plus-minus values are mean ± standard deviation. NS = p > 0.05.
AT = anaerobic threshold; DBP = diastolic blood pressure; HR = heart rate; RER = respiratory exchange ratio; SBP = systolic blood pressure; $\dot{V}O_2$ = oxygen consumption.

be appropriate, linear regression analysis was used, plotting survival against peak $\dot{V}O_2$. The peak $\dot{V}O_2$ value corresponding to an 85% one-year transplant-free survival was then determined. All analyses were performed using SAS software version 8 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient population. Of the 726 patients reviewed, 594 patients met our inclusion criteria, of whom 427 (72%) were men and 167 (28%) were women. The etiology of HF was ischemic in 206 patients (35%) and non-ischemic in 388 (65%); 431 (73%) patients were receiving beta-blockers, 455 (77%) an angiotensin-converting enzyme inhibitor, and 97 (16%) an angiotensin II receptor blocker.

T1 A higher percentage of women than men were black (29% vs. 18%, $p < 0.05$) (Table 1). On average, women were younger than men (mean age 49 ± 11 years vs. 53 ± 12 years, $p < 0.0002$) and had a higher LVEF (29 ± 13% vs. 25 ± 11%; $p < 0.001$). The etiology of HF was significantly different between the genders, with 15% of women and 43% of men having an ischemic cardiomyopathy ($p < 0.001$). This may explain the lower percentage of women on aspirin (34% vs. 43%, $p < 0.05$), lipid lowering medications (22% vs. 32%, $p < 0.03$), and nitrates (5% vs. 11%, $p < 0.05$).

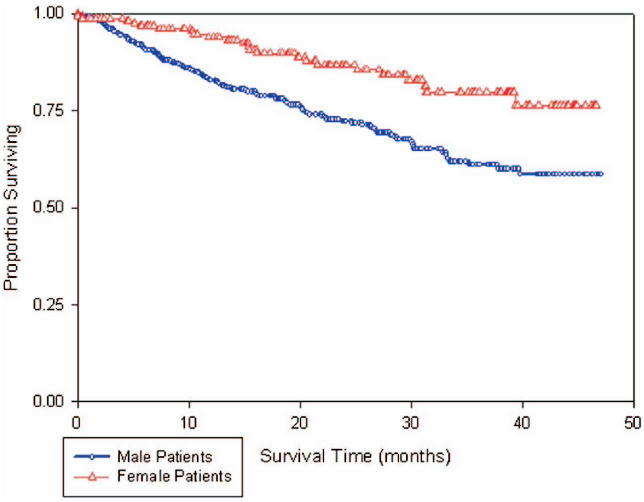

Figure 1. Patient survival across genders. Kaplan-Meier curves comparing survival in male and female heart failure patients. Using a log-rank test, the difference between the curves is significant with $p < 0.0001$.

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Cardiopulmonary exercise test results. The mean peak $\dot{V}O_2$ in our study group was 15.9 ± 6.7 ml/kg/min (Table 2), with a peak respiratory exchange ratio (RER) of 1.09 ± 0.11. As shown in Table 2, women had a lower peak $\dot{V}O_2$ than men (14.0 ± 4.9 ml/kg/min vs. 16.6 ± 7.1 ml/kg/min; $p < 0.0001$) (Fig. 1). A lower percentage of women reached anaerobic threshold than men (66% vs. 79%; $p < 0.01$), and peak RER was lower in women (1.05 ± 0.10 vs. 1.11 ± 0.11; $p < 0.0001$). However, the peak Borg Scale of Perceived Exertion was similar between genders (17.7 ± 2.2 vs 17.4 ± 2.0, p = NS). Linear regression analysis confirmed that the observed differences in peak $\dot{V}O_2$ were independent of race, LVEF, body mass index, HF etiology, beta-blocker use, RER, and history of hypertension, diabetes, atrial fibrillation, and lung disease. Stratified analysis by achievement of anaerobic threshold did not alter the results. T2 F1

Survival data. During the study period, 69 patients died and 70 received an OHT. The median transplant-free survival was 18.4 months, with an 85% one-year transplant-free survival (Table 3). Survival was significantly different between men and women in our population (Fig. 1). Women were found to have a median transplant-free survival of 22.2 months and a 94% one-year transplant-free survival, whereas men had a median survival of 17.4 months and an 81% one-year transplant-free survival (Table 3). T3

Furthermore, when stratifying patients using the Weber classification (21), we found that Weber class accurately predicted survival in the entire study group (Fig. 2), as well as in each gender (Fig. 3). However, Weber class had less predictive power in women than men because women in F2 F3

Table 3. Patient Population Outcomes

	Overall	Men	Women
Deaths	69	55	14
Transplants	70	61	9
Deaths and transplants	139	116	23
% 1-yr transplant-free survival	85%	81%	94%

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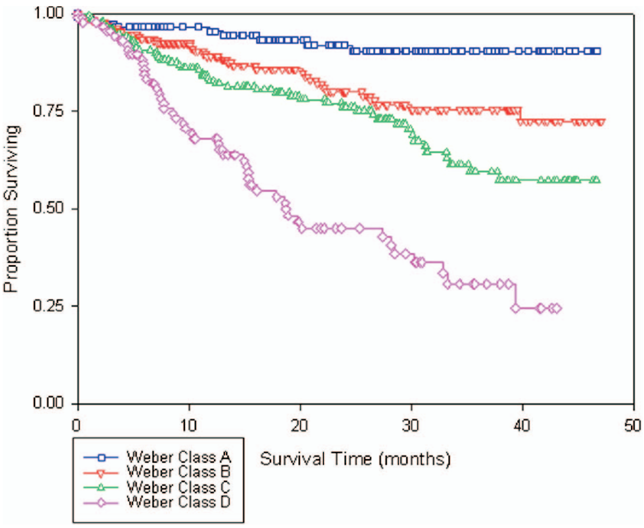

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Figure 2. Weber class predicts patient survival. Kaplan-Meier curves comparing survival in patients across Weber classes. Using a log-rank test, the difference between the curves is significant with $p < 0.0001$.

Table 4. One-Year Transplant-Free Survival by Weber Class

Weber Class	Overall (n)	Men (n)	Women (n)
A	96% (120)	95% (102)	99% (18)
B	91% (201)	90% (150)	95% (51)
C	83% (179)	77% (114)	95% (65)
D	70% (92)	59% (59)	84% (33)

class A, B, and C had similar survival (Fig. 3). As seen in
T4 Table 4, one-year transplant-free survival was significantly worse in men than in women across all Weber classes ($p < 0.0001$). Cox regression analyses confirmed that the observed protective effects of female gender on transplant-free survival persisted despite controlling for peak VO_2, age, race, beta-blocker use, HF etiology, RER, and history of hypertension, diabetes, atrial fibrillation, and lung disease, whereas younger age, higher peak VO_2, higher LVEF, female gender, and history of hypertension were all protective. Taken together, these data suggest that at any peak VO_2 value, women have a better survival than men.

Because more men achieved anaerobic threshold compared with women, we repeated our analyses stratified by achievement of anaerobic threshold. This did not alter the results, although the models including those who achieved anaerobic threshold or an RER >1.1 were more predictive.

Because one-year post-transplantation survival is 85% (United Network for Organ Sharing), we determined a cut-off value of VO_2, which corresponds to 85% one-year survival. Overall, a peak VO_2 value of 11.2 ml/kg/min corresponded to an 85% one-year survival, but this value was significantly lower in women than in men (10.0 vs. 11.5 ml/kg/min; $p < 0.001$).

DISCUSSION

Over the last decade, peak VO_2 has been an important determinant of the appropriate timing of cardiac transplantation. In the landmark study by Mancini et al. (3), patients with a peak $VO_2 \leq 14$ ml/kg/min were found to have a poor prognosis and were deemed appropriate for cardiac transplantation. The applicability of this cut off value for peak VO_2 to the general population, however, has been called into question because only 19 of 122 patients in the Mancini study were women (3). To date, no study evaluating peak VO_2 has included enough women to delineate the prognostic value of peak VO_2 in this population (5,6,8,9).

The natural history of HF is different in women and men. In women, HF develops later in life, and is more often attributable to hypertension and less frequently to coronary

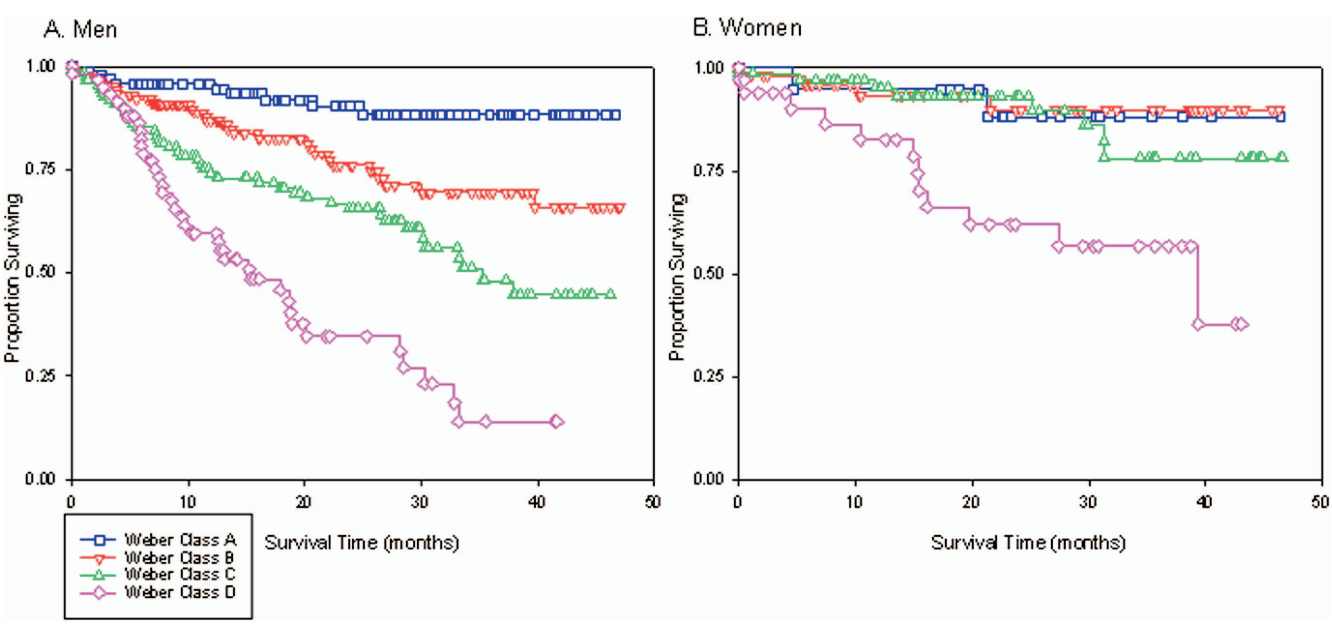

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Figure 3. Predictive value of Weber classes in men and women. Kaplan-Meier curves comparing survival in male **(A)** and female **(B)** heart failure patients across Weber classes. Using a log-rank test, difference between curves is significant with $p < 0.0001$.

disease (11–13). Additionally, women with non-ischemic cardiomyopathy have better survival than men (11–15). Despite their improved survival, women with HF are more symptomatic and have more hospital admissions (13,16–18,22). Given these gender-based differences in the pathophysiology and progression of HF and the relative paucity of data on cardiopulmonary exercise testing in women, we describe a large, diverse population of ambulatory HF patients to help define the gender effects on functional capacity in HF patients.

We found that women with HF have a lower peak Vo_2 than men, despite controlling for race, body mass index, LVEF, beta-blocker use, RER, achievement of anaerobic threshold, and HF etiology. This gender-based difference is well established in normal subjects and is thought to be attributable to smaller muscle mass, lower baseline metabolic rate, and lower hemoglobin levels in women (17,22,23). However, we found that despite their lower peak Vo_2 levels, women have longer survival times than men.

A number of previous studies have shown that women with HF have better survival than men (3,11,14,15). The current study confirms such observations despite a lower peak Vo_2 in women and confirms the finding by Aaronson and Mancini (9) that the prognostic value of peak Vo_2 is less accurate in women. Here, women of Weber functional classes A, B, and C have no significant difference in their survival. In contrast, men with HF had a gradual reduction in survival with each increase in Weber class. These data suggest a threshold in the progression of disease in women, after which survival decreases dramatically.

Given this survival pattern, we attempted to find the point at which one-year transplant-free survival in women drops below 85%, corresponding to expected one-year post-transplantation survival. We found that women do not reach this point until their peak Vo_2 is below 10 ml/kg/min. Thus, it seems that female HF patients may not gain a survival advantage from cardiac transplantation until their peak Vo_2 is $<$10 ml/kg/min, significantly lower than the more recently suggested 12 ml/kg/min in patients on beta-blockers (7). On the other hand, men with a peak Vo_2 $>$11.5 ml/kg/min have better survival than their post-transplantation counterparts, a value comparable to the 12 ml/kg/min proposed by Peterson et al. (7).

Study limitations. Our study is limited because it is a retrospective analysis of a prospectively collected database. Consequently, our results require confirmation by a prospective, randomized clinical trial. Additionally, there were a number of differences in the baseline characteristics of the gender groups studied here. Although these differences were corrected statistically, it is not possible to control for all differences, known or unknown, which could explain our results. Because such discrepancies likely reflect differences in the pathophysiology of HF between men and women, we anticipate that any study evaluating gender and HF will encounter similar limitations.

Additionally, the observed discrepancy in peak Vo_2 between men and women may be seen if the groups are presenting at different stages of HF. However, given that women in our study were younger, had a higher LVEF, and had better survival, yet lower peak Vo_2 values, this possibility seems unlikely. Our database did not contain adequate information on the number of patients with an intraventricular conduction delay or those treated with cardiac resynchronization therapy, both of which can affect peak Vo_2 (24). Thus, our results could be explained by a disproportionate incidence of intraventricular conduction delay or number of biventricular pacemakers in one of the gender groups. Moreover, it is important to note that serial cardiopulmonary exercise testing may add significant information to a patient's clinical evaluation, whereas this study evaluated the use of a single cardiopulmonary exercise test. Lastly, because recent findings have suggested a strong prognostic value to the minute ventilation–carbon dioxide production relationship (V_E/V_{CO_2} slope), future studies should evaluate whether this parameter may correct for the observed gender differences in HF patients (25).

Conclusions. We found that women with HF have lower peak Vo_2 values than men. Despite this, women with HF had better survival than men. These results suggest that different thresholds for peak Vo_2 by gender may be necessary for heart transplantation timing. It seems that cardiac transplantation in the current era may be deferred in female HF patients until their peak Vo_2 is $<$10 ml/kg/min, as opposed to 11.5 ml/kg/min in men. The current practice of uniformly applying peak Vo_2 as an aid for determining the optimal timing of cardiac transplantation should be re-examined.

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