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The Incremental Prognostic Importance of Body Fat Adjusted Peak Oxygen Consumption in Chronic Heart Failure

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OBJECTIVES We sought to assess whether the adjustment of peak oxygen consumption ($PkVO_2$) to lean body mass would yield a more accurate discriminator of outcomes in the chronic heart failure population.

BACKGROUND Peak oxygen consumption is traditionally used to risk stratify patients with congestive heart failure (CHF) and to time cardiac transplantation. There is, however, considerable variability in body fat content, which represents metabolically inactive mass.

METHODS In 225 consecutive patients with CHF, the percentage of body fat was determined by the sum of skinfolds technique. All underwent CPX using a ramping treadmill protocol. Mean follow-up duration was 18.9 ± 11.3 months.

RESULTS There were 14 cardiovascular deaths and 15 transplants. Peak oxygen consumption lean, both as a continuous variable and using a cutoff of ≤19 ml/kg/min, was a better predictor of outcome than unadjusted $PkVO_2$ ($p = 0.003$ vs. 0.027 for the continuous variables and $p = 0.0006$ vs. 0.055 for ≤19 ml/kg/min and ≤14 ml/kg/min unadjusted body weight, respectively). Using partial correlation index R statistics, the Cox model using $PkVO_2$ lean ≤19 ml/kg/min, in addition to age and etiology of CHF as covariates, yielded the strongest predictive relationship to the combined end point (chi-square value 24.32). Especially in the obese patients and in women, there was considerably better correlation of $PkVO_2$ lean with outcome than the unadjusted $PkVO_2$.

CONCLUSIONS The adjustment of $PkVO_2$ to lean body mass increases the prognostic value of cardiopulmonary stress testing in the evaluation of patients with chronic heart failure. The use of <19 ml O_2/kg of lean body mass/min as a cutoff in $PkVO_2$ should be used for timing transplantation, particularly in women and the obese. (J Am Coll Cardiol 2000;36:2126–31) © 2000 by the American College of Cardiology

As the treatment armamentarium in heart failure becomes increasingly complex and diverse, clinical strategies, based on functional capacity, to effectively triage patients with systolic heart failure into distinct prognostic subgroups are necessary. Peak oxygen uptake ($PkVO_2$) measured during exercise not only allows accurate evaluation of exercise capacity, but also has been shown to be a strong independent predictor of survival in chronic heart failure (1,2). Initially, Mancini and colleagues (3) demonstrated that a $PkVO_2$ of >14 ml/kg/min identified a low-risk cohort of patients. The survival of these patients was not improved by transplantation, and Mancini et al. (3) recommended that a $PkVO_2$ of 14 ml/kg/min be used as a discriminator for those being considered for transplantation. Subsequently, investigators have sought further refinements in this particular criterion, and other gas exchange variables have been evaluated for their predictive strengths, including percent predicted $PkVO_2$ (4,5), peak systolic blood pressure (6) and ventilation/carbon dioxide production ratio (7). The investigators demonstrated variability with regard to each parameter's predictive strength.

Peak oxygen uptake is traditionally corrected for total body weight and is reported in milliliters per kilogram of body weight per minute (ml/kg/min). Body fat, however, can represent a significant portion of total body weight, and it consumes essentially no oxygen. Moreover, considerable variability in body composition is present across populations, including those manifesting heart failure. We reasoned that $PkVO_2$ corrected for lean body mass (LBM) would reflect a more accurate picture of cardiopulmonary function during exercise and could serve as a better discriminator of clinical outcome than standard weight and relative predictive measures. The purpose of our investigation was threefold: first, to assess the predictive strength of $PkVO_2$ adjusted to LBM ($PkVO_2$ lean) in determining clinical outcomes in patients with moderate to severe chronic systolic heart failure; second, to stratify patients with systolic heart failure into high- and low-risk groups based on the value of $PkVO_2$ lean and third, to define specific subpopulations, particularly women and the obese, that may merit mandatory application of this prognostic criterion.

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Abbreviations and Acronyms

AT	=	Anaerobic Threshold
CHF	=	Congestive Heart Failure
LBM	=	Lean Body Mass
MVV	=	Maximal Voluntary Ventilation
NPP	=	Negative Predictive Value
NYHA	=	New York Heart Association
$PkVO_2$	=	peak oxygen consumption
PPV	=	Positive Predictive Value
TX	=	Urgent Transplantation
VE	=	Maximal Minute Ventilation
VO_2	=	Oxygen Consumption

METHODS

Patients. We prospectively studied 225 consecutive ambulatory patients with chronic systolic heart failure who were referred for cardiopulmonary exercise testing as part of a comprehensive heart failure evaluation between November 1995 and December 1998. The average age of the 45 women and 180 men was 54 ± 12 years (range 19 to 85 years). All patients had heart failure for at least six months and were on stable doses of their medications with no exacerbation of symptoms or need for intravenous inotropic support for a duration of four weeks before assessment. Patients were excluded if they exhibited severe peripheral vascular disease, low threshold angina or had orthopedic limitations preventing them from exercise testing. The baseline demographic and clinical characteristics are shown in Table 1.

Cardiopulmonary exercise testing. The research protocol was approved by the institutional review board, and informed consent was obtained from all patients who were then exercised maximally on a treadmill using an individually tailored ramping protocol designed to yield a test duration of between 8 and 12 min. Patients were encouraged to exercise until symptoms of chest discomfort or dyspnea were intolerable. Breath-to-breath online gas analysis was performed using a MedGraphics CPXID metabolic cart (St. Paul, Minnesota). Incremental data including minute ventilation, oxygen consumption (VO_2) and carbon dioxide production were collected every 15 s.

Body fat assessment. The percentage of body fat was determined by the skinfold technique using the average of three skinfolds (thigh, chest and abdomen in men; thigh, triceps and suprailium in women) (8). Skinfolds were measured in the fasting state in the morning before exercise by a single observer.

Cardiopulmonary parameters. From the above data, maximal VO_2, anaerobic threshold (AT) and respiratory exchange ratio were calculated as previously described (9). Peak VO_2 was determined as the highest oxygen uptake observed during the test. Anaerobic threshold was defined as the VO_2 at which expired carbon dioxide increased nonlinearly relative to VO_2 (V-slope method). Predicted maximum VO_2 was determined using the revised regression equations of Wasserman et al. (9), which take gender, age and obesity into consideration. Peak VO_2 lean was defined as the VO_2 corrected for LBM [LBM = actual body weight × (1− % body fat/100)] in milliliters of oxygen per kilogram of LBM per minute.

Table 1. Clinical and Exercise Characteristics of the Study Population (n = 225)

Clinical Characteristics	Data (Mean ± SD)
Age (yrs)	54.3 ± 12.2
Gender, male (%)	183 (80%)
Weight (kg)	89 ± 19
Body mass index (kg/m^2)	28.9 ± 5.4
Obese (≥30 kg/m^2)	83 (37%)
% fat	25.9 ± 7.6
Lean weight (kg)	67.3 ± 14.1
Etiology: ischemic	132 (58.1%)
Nonischemic	93 (41.9%)
Left ventricular ejection fraction, %	23 ± 13
NYHA class	2.4 ± 0.6
Medications, %	
Lanoxin	83%
Diuretics	82%
Angiotension-converting enzyme inhibitors or angiotensin-blockers	95%
Beta-blockers	31%
Exercise Characteristics	
Resting heart rate, beats/min	81 ± 16
Peak heart rate, beats/min	126 ± 24
Rest systolic pressure, mm Hg	129 ± 19
Peak systolic pressure, mm Hg	147 ± 29
Anaerobic threshold, ml/kg/min	12.7 ± 4.1
$PkVO_2$, ml/kg/min	16 ± 5.9
$PkVO_2$ lean, ml/kg/min	21.2 ± 7.4
% of predicted $PkVO_2$	69.2 ± 22.6

NYHA = New York Heart Association; $PkVO_2$ = peak oxygen consumption; SD = standard deviation.

Outcome measures. All patients were followed at the Ochsner Cardiomyopathy and Heart Transplantation Center, and outcome data were prospectively collected from medical records or interviews. The principal outcomes assessed included the composite end point of death due to cardiovascular causes and need for urgent cardiac transplantation. Listing for transplant was done by committee consensus based primarily on $PkVO_2$ but also in concert with other clinical, metabolic and hemodynamic variables.

Statistical analysis. Continuous variables are expressed as mean ± 1 standard deviation. Discrete variables are shown as percentages. Categorical variables were compared using the likelihood ratio chi-square test. With continuous variables, group means were compared with the unpaired Student *t* test or Wilcoxon rank sum test if the variable did not hold the normality assumption. Diagnostic test analysis was performed to calculate sensitivity, specificity, likelihood ratios, positive predictive values and negative predictive values for $PkVO_2$ using a cut-off of 14 ml/kg/min and $PkVO_2$ lean using a cutoff of 19 ml/kg/min (Table 2).

Table 2. Diagnostic Tests Analysis

Precision Estimates	PkVO$_2$ < 14 (ml/min/kg)	PkVO$_2$ Lean <19 (ml/min/kg)	p Value
Sensitivity	63.6%	72.3%	
Specificity	56%	59.3%	
Likelihood ratio:			
For positive test	1.45 (1.01 to 2.08)	1.78 (1.30 to 2.45)	
For negative test	0.65 (0.37 to 1.15)	0.46 (0.23 to 0.92)	
PPV	16.9%	20.1%	
NPP	91.7%	93.9%	
Kappa	0.09	0.15	0.04
AUC	0.58	0.67	0.0001

AUC = area under the curve; NPP = negative predictive value; PkVO$_2$ = peak oxygen consumption; PPV = positive predictive value.

19 ml/kg/min was determined by using receiver operator characteristic curve analysis. We also compared the two tests evaluated against the same "gold standard" in the same sample with Kappa indexes and using the area under the curve.

Bivariate analysis was performed with PkVO$_2$ as: 1) continuous absolute variable, 2) adjusted to LBM and 3) as percent of predicted. Cutoffs of 14 ml/kg/min, 50% predicted PkVO$_2$ and 19 ml/kg/min of PkVO$_2$ lean (derived from the median tendency of the data) were also used to categorize the results.

Cox proportional hazard regression analysis was performed to determine the independent predictors of event-free survival. Variables showing significance at an alpha level of 0.15 in bivariate analysis and age were included. Six models were then built using the PkVO$_2$ variables and other variables showing at least marginal predictive value ($p < 0.15$) on stepwise analysis.

Partial correlation index R statistics were used to compare the power of the individual variables within and between the six models. The assumption of proportional hazard was also assessed graphically. The results are shown as relative (or hazard) risks and their respective 95% confidence intervals. All tests were two-sided, and p values <5% were considered significant.

Survival curves were also constructed using the Kaplan-Meier product limit method and were compared with the log-rank test. Analysis of covariance was also performed to assess the differences in clinical and PkVO$_2$ parameters as well as in outcomes across the gender line and between obese and nonobese patients.

All calculations were performed using JMP software version 3.2.2 (SAS Institute, Inc., Cary, North Carolina) and PEPI version 3.00 (USD, Inc., Stone Mountain, Georgia).

RESULTS

Study population. Table 1 depicts the baseline clinical and exercise characteristics of the study population. The median follow-up duration was 19.5 months (range 2 to 40.4 months and mean 18.9 ± 11.3 months) during which time there were 29 cardiac events (14 cardiovascular deaths and 15 urgent transplants). Only two patients were lost to follow-up.

Table 2 demonstrates the superior diagnostic characteristics of the proposed lean PkVO$_2$ cutoff of 19 ml/kg/min.

The clinical and exercise characteristics of the event-free survivors and patients who reached the combined end point of cardiac death or transplant are shown in Tables 3 and 4.

The etiology of cardiomyopathy and percent body fat were significantly different between event-free survivors and those who reached the combined end point. The lean body weight, maximum minute ventilation and maximum voluntary ventilation were comparable between both groups and so were heart rate and systolic blood pressure at rest, AT and peak exercise.

Cardiopulmonary predictors. Anaerobic threshold ($p = 0.03$), percent of predicted PkVO$_2$ ($p = 0.0016$) and unadjusted and lean PkVO$_2$ ($p = 0.02$ and 0.003, respectively) were significant predictors of cardiac mortality and transplantation. Unadjusted and lean PkVO$_2$ were also

Table 3. Univariate Analysis of Clinical Characteristics Between Survivors and Those Reaching the Combined End Points

Clinical characteristics	Survivors (n = 196)	Death/TX (n = 29)	p Value
Age (yrs)	54 ± 12	54 ± 13.3	NS
Weight (kg)	90 ± 18.8	85.6 ± 20.7	NS
Body mass index (kg/m^2)	29.1 ± 5.4	27.7 ± 5	NS
% obese	52.6	37.9	NS
% fat	26.4 ± 7.6	22.6 ± 6.7	0.018
Lean body weight (kg)	67.3 ± 13.9	66.6 ± 15.4	NS
Gender: female	38 (19.6%)	4 (13.8%)	NS
male	156 (80.4%)	25 (86.2%)	
CHF etiology			0.0015
ischemic	72 (37.7%)	20 (69%)	
nonischemic	119 (62.3%)	9 (31%)	
NYHA classification I	19	1	0.029
II	84	8	
III	85	20	
Mean NYHA class, unit	2.3 ± 0.6	2.7 ± 0.5	0.001
Left ventricular ejection fraction, %	25 ± 13	20 ± 9	NS
Left ventricular end-diastolic diameter, cm	6.0 ± 1.2	6.4 ± 0.8	0.07

CHF = congestive heart failure; NYHA = New York Heart Association; TX = urgent transplantation.

Table 4. Univariate Analysis of Exercise Characteristics Between Survivors and Those Reaching the Combined End Point

Exercise Characteristics	Survivors (n = 196)	Death/TX (n = 29)	p Value
Maximal voluntary ventilation, L/min	97.3 ± 38.9	94.9 ± 35.2	NS
Maximum minute ventilation, L/min	50.8 ± 18.2	54.6 ± 34.7	NS
Rest heart rate (beats/min)	86	80	NS
Peak heart rate (beats/min)	130 ± 25	124 ± 23	NS
Rest systolic pressure (mm Hg)	130 ± 19	127 ± 19	NS
Peak systolic pressure (mm Hg)	151 ± 30	143 ± 29	NS
Anaerobic threshold (ml/kg/min)	12.9 ± 4.1	10.9 ± 3.1	0.03
$PkVO_2$ (ml/kg/min)	16.3 ± 6	13.8 ± 4.4	0.027
$PkVO_2$ lean (ml/kg/min)	21.7 ± 7.6	17.5 ± 5	0.003
% predicted VO_2	70.9 ± 23.1	57 ± 14.4	0.0016
$PkVO_2$ ≤14 ml/kg/min, number (%)	77 (39.7%)	17 (58.6%)	0.055
% pred. VO_2 ≤50, number (%)	37 (19.1%)	10 (34.5%)	0.07
$PkVO_2$ lean ≤19 ml/kg/min, number (%)	75 (38.7%)	21 (72.4%)	0.0006

$PkVO_2$ = peak oxygen consumption.

significantly predictive of cardiac mortality alone ($p = 0.04$ and 0.035, respectively). Whereas categorical cutoffs of a percentage of predicted VO_2 ≤50 and $PkVO_2$ ≤14 ml/kg/min showed a trend towards significance in our population, a $PkVO_2$ lean ≤19 ml/kg/min correlated best with the combined end point ($p = 0.0006$).

In partial correlation index R analysis the use of $PkVO_2$ lean ≤19 ml/kg/min yielded the strongest predictive model for the combined end point (Table 5). Both models using the adjusted maximal VO_2 were more predictive than the unadjusted models. It is noteworthy that the percent of predicted peak VO_2 as a continuous variable resulted in a stronger model than a cutoff of <50% of predicted. We then categorized our population using both the conventional and the proposed body fat adjusted cutoffs and analyzed on a univariate basis the clinical, exercise and outcome data of the resulting groups. There was a more significant difference in outcomes when the lean $PkVO_2$ cutoff was used.

Survival analysis. Figure 1 shows the Kaplan-Meier survival curves using a $PkVO_2$ of 14 ml/kg/min and a $PkVO_2$ lean of 19 ml/kg/min to categorize our study population. At 12 months patients with a $PkVO_2$ lean ≤19 ml/kg/min had a survival of 80% as compared with 98% for those whose values were >19 ml/kg/min.

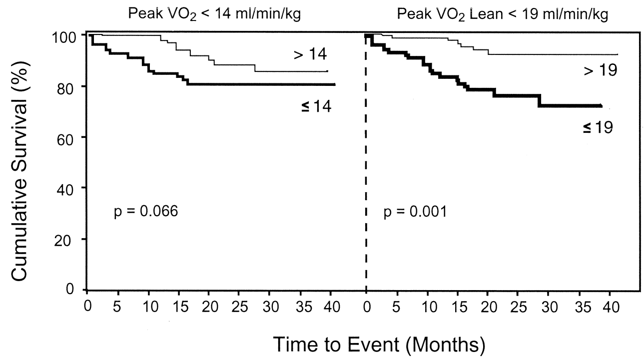

Figure 1. Kaplan-Meier survival curves using both $PkVO_2$ of 14 ml/kg/min and $PkVO_2$ lean of 19 ml/kg/min as cutoffs showing a stronger prognostic value to the fat-adjusted $PkVO_2$ by log-rank testing. $PkVO_2$ = peak oxygen consumption; $PkVO_2$ lean = peak oxygen consumption adjusted to lean body mass; VO_2 = oxygen consumption.

Discordant variable analysis. Further examination of patients demonstrating discordant cardiopulmonary variables (for example, $PkVO_2$ >14 ml/kg/min but $PkVO_2$ lean ≤19 ml/kg/min or vice versa) found 18 patients that showed discordant $PkVO_2$ levels. None of the eight patients that had a $PkVO_2$ ≤14 ml/kg/min and an adjusted $PkVO_2$ >19 ml/kg/min reached any of the outcomes. It is noteworthy that this group was composed of mostly obese (6 of 8) women (5 of 8). On the other hand, of the 10 patients with the opposite discordance ($PkVO_2$ >14 ml/kg/min but $PkVO_2$ lean ≤19 ml/kg/min), 4 had major events, including 2 who required urgent cardiac transplantation and 2 who died of progressive heart failure. This analysis exemplifies the incremental prognostic value provided by body fat adjusted $PkVO_2$ when the "standard" clinical cutoffs of $PkVO_2$ fail to segregate risk.

Subgroup analysis: women and obesity. Women (n = 45, 20% of the whole group) were more likely to have nonischemic disease (73% vs. 56%, $p = 0.02$), a lower total body weight (mean of 78.6 ± 20.7 vs. 92.2 ± 19.2 kg, $p < 0.0001$) but a higher percentage of body fat (34.1 ± 8.3% vs. 24 ± 6%, $p < 0.0001$) as compared with men. They achieved a lower unadjusted $PkVO_2$ level (13.5 ± 5.2 vs. 16.2 ± 5.8 ml/kg/min, $p = 0.0002$) but no statistical difference when $PkVO_2$ lean was used (18.8 ± 7.6 vs. 20.4 ± 7.5 ml/kg/min, $p = 0.11$). There was no difference in outcome between both groups (13.2% of women died or underwent transplantation compared with 18.8% of men, $p = 0.4$) and, therefore, body fat adjusted VO_2 (lean) was a

Table 5. Cox Proportional Hazard Model Comparisons, Including Age and Etiology of Cardiomyopathy

Models	Chi-square	RR	95% CI	p Value
$PkVO_2$ lean ≤19 ml/kg/min	24.32	0.24	0.1–0.58	<0.0001
% predicted $PkVO_2$	21.53	0.97	0.95–0.99	<0.0001
$PkVO_2$ lean	20.53	0.91	0.85–0.98	0.0001
$PkVO_2$	17.17	0.91	0.84–1	0.0007
$PkVO_2$ ≤14 ml/kg/min	16.38	2.22	1.02–4.8	0.0009
% predicted $PkVO_2$ <50	15.65	0.47	0.22–1.03	0.0013

CI = confidence interval; $PkVO_2$ = peak oxygen consumption; RR = relative risk.

better discriminator of clinical outcome than unadjusted values.

Obese patients (body mass index $\geq$ 30 kg/m^2), which consisted of 83 patients or 37% of the cohort, showed statistically lower AT (11.5 $\pm$ 3.5 vs. 12.7 $\pm$ 4.2 ml/kg/min, $p = 0.03$) and unadjusted $PkVO_2$ levels (14.4 $\pm$ 4.7 vs. 16.5 $\pm$ 6.1 ml/kg/min, $p = 0.04$) yet similar $PkVO_2$ lean levels (19.3 $\pm$ 6.7 vs. 20.5 $\pm$ 7.9 ml/kg/min, $p = 0.2$). There was no statistical difference in outcome, with 10% of obese patients reaching one of the end points compared with 17.8% of the nonobese patients ($p = 0.1$), indicating the more accurate stratification of prognosis provided by body fat adjusted VO_2.

On the other hand, lean men accounted for 48% (n = 108) of the study cohort. In this group, $PkVO_2$ lean was still a slightly better predictor of the risk of major cardiovascular events than unadjusted $PkVO_2$ ($p = 0.03$ and 0.08, respectively).

DISCUSSION

Study findings. The results of our prospective investigation demonstrate that, in ambulatory patients with chronic systolic heart failure, the simple adjustment of $PkVO_2$ to lean body weight provides much greater prognostic strength than the traditionally reported standard of $PkVO_2$ per kilogram of total body weight. Furthermore, a value of $PkVO_2$ lean of $\leq$19 ml/kg/min provides the best discriminator of adverse outcome, yielding a survival of 80% and 68% at 12 and 36 months, respectively. Additionally, we identified women and obese patient subgroups with a higher percent body fat in which using $PkVO_2$ lean may be particularly beneficial compared with unadjusted $PkVO_2$ determinations.

Aerobic capacity and prognosis. Peak oxygen uptake, normalized for total body weight, is a powerful short-term prognostic parameter in patients with chronic heart failure and has been used successfully to guide candidate selection for heart transplantation. In the Veterans Administration Heart Failure Trials (VHeFT I and II), a $PkVO_2$ $<$14.5 ml/kg/min predicted an increased mortality from 11.6% to 18.4% in patients with ejection fractions $<$28% when compared with values $>$14.5 ml/kg/min (10). Mancini et al. (3) reported in a study of 114 patients with severe heart failure that 94% of patients with a weight adjusted $PkVO_2$ higher than 14 ml/kg/min were alive at 1 year, and 84% were alive at 2 years. This good prognosis allowed the safe deferral of heart transplantation in the near term in those with $PkVO_2$ values $>$14 ml/kg/min. Aaronson and Mancini (3,11), and then our group, found that the percent of predicted maximum VO_2 was a better prognosticator than $PkVO_2$ in women with chronic heart failure, a population with traditionally higher values of percent body fat. The percent of predicted $PkVO_2$ has also been suggested as an additional prognostic variable, particularly for patients who have $PkVO_2$ $<$14 ml/kg/min (5,12). The discrepancy across the gender line as well as the known contribution of body fat changes in VO_2 led us to examine the effect of lean weight adjusted $PkVO_2$ on the overall prognostic power of peak aerobic capacity.

Rationale of body fat adjusted $PkVO_2$. Body fat represents metabolically inactive mass, and, as a percentage of total body weight, is highly variable across populations. The observed increase in body fat that occurs with aging has been shown to contribute to the age-related decline in $PkVO_2$ reported in men and women (13). Drinkwater et al. (14) found that, despite a gradual increase in body weight over 2 decades, the $PkVO_2$ of a group of very active women did not decline (14). In a study of 56 healthy subjects, Buskirk et al. (15) found that LBM correlated better with peak VO_2 than did total body weight. We previously studied the impact of reducing body fat during exercise training on the observed improvement in $PkVO_2$ after aerobic conditioning and found that the decrease in body fat overestimated the true increase in peak aerobic capacity (16). We suggested the use of a "corrected" peak VO_2 adjusted for LBM in order to assess the true effect of exercise conditioning, especially in subgroups with a higher percent body fat (17). Using the sum of three skinfold thicknesses as described by Jackson and Pollock (18,19), the body density can be calculated and the percent of body fat derived (8,18–20). This method was chosen from a large number of other well-validated methods because its application can be easily adopted by the exercise laboratory and the requirement of fewer measurements while maintaining a high level of accuracy (21–23).

Prognostic utility. We compared the proposed $PkVO_2$ lean to the established unadjusted value to determine their respective prognostic strengths for the outcomes of death and urgent transplantation. By multivariate analysis using the combined end point of cardiac death or urgent transplantation, we have demonstrated that $PkVO_2$ adjusted to LBM refines the weight adjusted peak aerobic capacity and provides a variable with greater prognostic discrimination than previously described, particularly in women and the obese. Thus, using a $PkVO_2$ lean $>$19 ml/kg/min as a prognostic threshold, rather than the traditional cutoff point of $PkVO_2$ of 14 ml/kg/min, provides a more comprehensive and accurate prognostic variable across the entire heterogeneous population of chronic heart failure. Furthermore, $PkVO_2$ lean adjusted for body fat, therefore, allows determination of prognosis in the specific subpopulations of women and the obese with greater predictive confidence.

Study limitations. Although the "gold standard" method for body fat assessment (underwater weighing) was not employed, the method of sum of several skinfold thicknesses proposed by Jackson and Pollock (16) was chosen. Several studies have shown that anthropometric techniques, in particular those using the skinfold fat thickness, provide excellent correlation with underwater weighing (8). The generalized equations used have been validated and have been widely used because of the smaller number of measurements required. It is noteworthy, however, that this estimate is less accurate at the extremes of age and weight (8).

In this study, as in others assessing the prognostic value of cardiopulmonary stress testing in heart failure, there is unavoidable referral bias towards transplantation after cardiopulmonary assessment. This may have been reduced, but not abolished, by the use of urgent transplantation rather than a listing as status I (4,5) as a cardiac end point.

Conclusions. As Buskirk wrote in 1957, "It is concluded that when VO_2 is used to examine the performance of the respiratory-cardiovascular system, the values should be expressed as VO_2 per kilogram of fat-free weight" (15). This investigation confirms the incremental prognostic predictive capability of adjustment of the $PkVO_2$ achieved to lean body weight in ambulatory chronic systolic heart failure. It also provides evidence that this cardiopulmonary exercise parameter offers the best risk stratification across the heterogeneous systolic heart failure cohort including women and the obese.

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