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Determining the Preferred Percent-Predicted Equation for Peak Oxygen Consumption in Patients With Heart Failure

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***Background*—**Peak oxygen consumption (VO_2) is routinely assessed in patients with heart failure undergoing cardiopulmonary exercise testing. The purpose of the present investigation was to determine the prognostic ability of several established peak VO_2 prediction equations in a large heart failure cohort.

***Methods and Results*—**One thousand one hundred sixty-five subjects (70% males; age, 57.0±13.8 years; ischemic etiology, 43%) diagnosed with heart failure underwent cardiopulmonary exercise testing. Percent-predicted peak VO_2 was calculated according to normative values proposed by Wasserman and Hansen (equation), Jones et al (equation), the Cooper Clinic (below low fitness threshold), a Veteran's Administration male referral data set (4 equations), and the St James Take Heart Project for women (equation). The prognostic significance of percent-predicted VO_2 values derived from the 2 latter, sex-specific equations were assessed collectively. There were 179 major cardiac events (117 deaths, 44 heart transplantations, and 18 left ventricular assist device implantations) during the 2-year tracking period (annual event rate, 10%). Measured peak VO_2 and all percent-predicted peak VO_2 calculations were significant univariate predictors of adverse events ($\chi^2 \geq 31.9$, $P<0.001$) and added prognostic value to ventilatory efficiency (VE/VCO_2 slope), the strongest cardiopulmonary exercise testing predictor of adverse events ($\chi^2=150.7$, $P<0.001$), in a multivariate regression. The Wasserman/Hansen prediction equation provided optimal prognostic information.

***Conclusions*—**Actual peak VO_2 and the percent-predicted models included in this analysis all were significant predictors of adverse events. It seems that the percent-predicted peak VO_2 value derived from the Wasserman/Hansen equations may outperform other expressions of this cardiopulmonary exercise testing variable. **(*Circ Heart Fail*. 2009;2:113-120.)**

Key Words: exercise ■ heart failure ■ prognosis ■ ventilation

Peak oxygen consumption (VO_2) is a clinically accepted and important variable in the prognostic evaluation of patients with heart failure (HF) undergoing cardiopulmonary exercise testing (CPX).[1] The actual value of peak VO_2, typically expressed relative to body weight, is the most common approach to reporting aerobic capacity in apparently healthy individuals and different patient populations, including HF.[2] Reporting peak VO_2 as a percent-predicted value has also been advocated. Moreover, a number of different approaches to estimating normal aerobic capacity are readily available.[3–9] These prediction equations have used various independent variables such as height, weight, and mode of exercise but the inclusion of age and consideration of sex is a shared commonality.

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The body of evidence demonstrating the prognostic utility of the actual peak VO_2 value is robust; collectively, these investigations have included thousands of patients and hundreds of adverse events, consistently demonstrating the ability of this CPX variable to identify those patients with HF at increased risk for poor outcomes.[10] A limited number of investigations have also examined the prognostic value of percent-predicted peak VO_2 in patients with HF with mixed results. For example, using 2 different prediction equations, Aaronson and Mancini[11] found neither percent-predicted peak VO_2 value was a superior prognostic marker compared with the actual value in 272 patients with HF. However, using

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Table 1. Baseline and Pharmacotherapy Characteristics

	All Patients (n=1165)	Event Free (n=986)	Major Cardiac Event (n=179)
Baseline characteristics			
Age, years	57.0±13.8	57.0±13.7	57.0±14.1
Sex (M/F), %	70/30	69/31	75/25
Race, (white/black/other), %	76/23/1	76/23/1	78/21/1
Etiology, ischemia/nonischemia	43/57	42/58	50/50*
NYHA class	2.5±0.61	2.4270.60	2.9270.55†
Resting heart rate, beats per minute	75.1±13.4	74.8±13.2	77.0±14.4
LVEF, %	31.4±14.0	32.7±14.1	24.4±11.6†
Therapy distribution, %			
ACE inhibitor	72	72	73
Diuretic	75	73	87†
β-blocker	67	67	65

M/F indicates male/female; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme.
*$P<0.05$.
†$P<0.01$.

one equation, Stelken et al[12] reported percent-predicted peak VO_2 was superior to the actual value in predicting mortality in a separate group of 181 patients with HF.

We are unaware of any investigation that has simultaneously compared the prognostic utility of the most commonly used peak VO_2 prediction equations with each other and the actual aerobic capacity value in a large HF cohort undergoing CPX within the past 10 years. Moreover, a prognostic comparison of percent-predicted VO_2 values to other important CPX measures, such as ventilatory efficiency, has not been performed. The purpose of the present investigation was to address these issues in an effort to determine the clinical relevance of expressing peak VO_2 relative to a normative value in patients with HF.

Methods

This study was a multicenter analysis including patients with HF from the CPX laboratories at San Paolo Hospital (Milan, Italy), Wake Forest University Baptist Medical Center (Winston-Salem, NC), LeBauer Cardiovascular Research Foundation (Greensboro, NC) Veteran's Administration (VA) Palo Alto Health Care System (Palo Alto, Calif), and Virginia Commonwealth University (Richmond, Va). A total of 1165 patients with chronic HF were included. Inclusion criteria consisted of a diagnosis of HF[13] and evidence of left ventricular dysfunction by 2D echocardiography obtained within 1 month of data collection. All subjects completed a written informed consent and institutional review board approval was obtained at each institution. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

CPX Procedure and Data Collection

Symptom-limited CPX was performed on all subjects and pharmacological therapy was maintained during exercise testing. Conservative ramping protocols were used at all centers. Ventilatory expired gas analysis was performed using a metabolic cart at all 5 centers (Medgraphics CPX-D and Ultima, Minneapolis, Minn; Sensormedics Vmax29, Yorba Linda, Calif; or Parvomedics TrueOne 2400,

Table 2. CPX Test Data and Percent-Predicted Peak VO_2 Calculations*

	All Patients (n=1165)	Event Free (n=986)	Major Cardiac Event (n=179)
Mode of exercise (treadmill/ergometer), %	57/43	57/43	55/45
Peak VO_2, mL/kg per min	15.3±5.6	15.9±5.6	12.0±4.0†
VE/VCO_2 slope	35.9±9.5	34.7±8.6	42.8±11.6†
Peak RER	1.09±0.14	1.09±0.14	1.09±0.14
Maximal heart rate, beats per minute	125.9±22.8	128.0±22.1	114.3±22.7†
Wasserman/Hansen, %	59.4±22.5	62.1±22.2	45.0±18.3†
Jones, %	65.6±30.8	68.5±31.2	49.1±22.0†
VA-A/St James, %	57.2±20.4	59.5±20.2	44.8±16.7†
VA-B/St James, %	55.2±19.9	57.4±19.6	43.4±16.8†
VA-C/St James, %	62.4±25.9	64.8±26.0	49.5±21.2†
VA-D/St James, %	51.5±18.9	53.5±18.7	40.4±16.5†
Cooper Clinic, %	55.4±18.9	57.6±18.6	43.6±15.7†

RER indicates respiratory exchange ratio.
*With the exception of VA-B/St James versus Cooper Clinic ($P=0.35$), all other percent-predicted values significantly different from one another for the overall group ($P<0.001$).
†No event versus adverse event subgroups, $P<0.01$.

Table 3. ROC Curve Analysis

	ROC Curve Area (95% CI)	Optimal Threshold, %	Sensitivity/ Specificity	Hazard Ratio (95% CI)*	P
Wasserman/Hansen	0.74 (0.71 to 0.78)†	<47	74/59	4.0 (3.0 to 5.4)	<0.001
Jones	0.73 (0.69 to 0.77)‡	<51	73/60	4.0 (2.9 to 5.3)	<0.001
VA-A/St James	0.72 (0.69 to 0.76)‡	<47	70/60	3.6 (2.6 to 4.8)	<0.001
VA-B/St James	0.72 (0.68 to 0.76)§	<46	70/61	3.5 (2.6 to 4.7)	<0.001
VA-C/St James	0.69 (0.64 to 0.73)	<50	67/62	3.3 (2.5 to 4.4)	<0.001
VA-D/St James	0.71 (0.67 to 0.75)	<43	68/62	3.4 (2.5 to 4.6)	<0.001
Cooper Clinic	0.73 (0.70 to 0.78)‡	<47	70/62	3.5 (2.6 to 4.8)	<0.001

*Hazard ratios generated from univariate Cox regression using optimal threshold value.
†Significantly greater than VA-C/St James ($P<0.01$) and VA-D/St. James ($P<0.05$).
‡Significantly greater than VA-C/St James ($P<0.01$).
§Significantly greater than VA-C/St James ($P<0.05$).

Sandy, Utah). Before each test, the equipment was calibrated in standard fashion using reference gases and a 3-L syringe. Standard 12-lead electrocardiograms were monitored throughout exercise; blood pressure was measured using a standard cuff sphygmomanometer. Heart rate at rest and maximal exercise were obtained from the ECG. Heart rate recovery at 1 minute was the difference between heart rate at peak exercise and 1-minute post. All subjects performed an active cool-down, at the initial workload of the exercise protocol, for at least 1 minute after the cessation of exercise. Minute ventilation (VE), oxygen uptake (VO_2), carbon dioxide output (VCO_2), and end-tidal carbon dioxide production ($P_{ET}CO_2$) were acquired breath-by-breath, and averaged over 10-second intervals. Resting $P_{ET}CO_2$ was expressed as a 2-minute averaged value in millimeter of mercury. Peak VO_2 and peak respiratory exchange ratio were expressed as the highest 10-second averaged samples obtained during the exercise test. VE and VCO_2 values, acquired from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, Wash) to calculate the VE/VCO_2 slope via least squares linear regression (y=mx+b, m=slope).[14,15] The oxygen uptake efficiency slope was also determined via least squares linear regression (VO_2=a $\log_{10}$VE+b)[16] by spreadsheet software (Microsoft Excel, Seattle, Wash) using all of the exercise data. Percent-predicted peak VO_2 was calculated according to normative values proposed by Wasserman and Hansen[4,5] (1 of 6 equations according to sex and bodyweight), Jones et al (equation),[3] the Cooper Clinic (below low fitness threshold),[8,9] a VA male referral data set (4 equations; A to D),[6] and the St James Take Heart Project for women (equation).[7] The prognostic significance of percent-predicted VO_2 values derived from the 2 latter, sex-specific prediction equations were assessed collectively (VA A to D/St James).

End Points

Subjects were followed for major cardiac events (mortality, left ventricular assist device implantation, heart transplantation) via hospital and outpatient medical chart review for a maximum of 2 years at all centers. Any death with a cardiac-related discharge diagnosis was considered an event. Clinicians conducting the exercise test were not involved in decisions regarding cause of death or heart transplant/left ventricular assist device implantation.

Statistical Analysis

All continuous data are reported as mean±SD. Unpaired t testing assessed differences in continuous baseline and CPX variables between those subjects experienceing an event and those who were event free. χ^2 analysis assessed differences in the distributions of HF etiology, gender, race, and pharmacological management between these groups. One-way ANOVA compared differences in the percent-predicted peak VO_2 values according to the various equations in the overall group. A mixed-model 2-way ANOVA assessed differences between percent-predicted peak VO_2 values (within subject factors) according to adverse event status (between subject factors). When a significant difference between percent-predicted peak VO_2 values was detected, post hoc analysis was performed by multiple paired testing with a Bonferroni correction ($P<0.007$ [0.05/7]). Receiver operating characteristic (ROC) curves were constructed for the prognostic classification schemes of all percent-predicted peak VO_2 values. A z test was used to assess for significance of differences among areas under the ROC curve for the prognostic models.[17] Univariate Cox regression analysis assessed the prognostic value of percent-predicted peak VO_2 calculations for cardiac mortality alone and in subgroups according to sex, mode of exercise (treadmill versus lower extremity ergometer), peak respiratory exchange ratio (<versus ≥1.05), and age (<versus ≥50 years old). Separate multivariate Cox regression analyses (forward stepwise method, entry, and removal values 0.10 and 0.05, respectively) then assessed the combined prognostic value of the VE/VCO_2 slope and each expression of peak VO_2 (actual and percent-predicted values). Multivariate Cox regression analysis was also used to assess the prognostic value of the VE/VCO_2 slope, peak VO_2 expressions, and an expanded list of baseline variables including age, HF etiology, left ventricular ejection fraction, and New York Heart Association (NYHA) class. For the peak VO_2 expression demonstrating the highest prognostic value in the expanded multivariate Cox regression, Kaplan–Meier analysis was performed including all variables retained in that particular regression. The log-rank test determined statistical significance of the Kaplan–Meier analysis. With the exception of post hoc testing for the mixed-model, 2-way ANOVA, all statistical tests with a probability value <0.05 were considered significant.

Results

There were 179 major cardiac events (117 deaths, 44 heart transplantations, and 18 left ventricular assist device implantations) during the 2-year tracking period (annual event rate, 10%). Baseline characteristics for the overall group as well as subgroups according to adverse event status are listed in Table 1. The percentages of subjects with an ischemic HF etiology and prescribed a diuretic were significantly higher in subjects experienceing a major cardiac event. In addition, mean NYHA class was significantly higher whereas left ventricular ejection fraction was significantly lower in the major cardiac event subgroup.

CPX results for the overall group and subgroups according to adverse event status are listed in Table 2. In the overall group, all percent-predicted peak VO_2 values were signifi-

Table 4. Prognostic Value of Percent-Predicted V_{O_2} According to Relevant Subgroups*

	Cardiac Mortality Alone	Sex		Mode of Exercise	
	All subjects (n=1165; 117 Events)	Male (n=813; 134 Events)	Female (n=352; 45 Events)	Treadmill (n=665; 98 Events)	LE Ergometer (n=419; 81 Events)
Wasserman/Hansen	33.8, $P<0.001$	84.7, $P<0.001$	11.5, $P=0.001$	75.9, $P<0.001$	23.7, $P<0.001$
Jones	28.3, $P<0.001$	53.4, $P<0.001$	8.6, $P=0.003$	42.2, $P<0.001$	21.8, $P<0.001$
VA-A/St James	30.3, $P<0.001$	88.8, $P<0.001$	7.6, $P=0.006$†	76.8, $P<0.001$	14.7, $P<0.001$
VA-B/St James	27.4, $P<0.001$	82.8, $P<0.001$		76.8, $P<0.001$	13.5, $P<0.001$
VA-C/St James	16.6, $P<0.001$	59.8, $P<0.001$		60.6, $P<0.001$	5.8, $P=0.016$
VA-D/St James	25.1, $P<0.001$	76.4, $P<0.001$		74.5, $P<0.001$	13.7, $P<0.001$
Cooper clinic	31.6, $P<0.001$	82.1, $P<0.001$	8.1, $P=0.004$	73.7, $P<0.001$	19.2, $P<0.001$

RER indicates respiratory exchange ratio; LE, lower extremity.
*Univariate Cox regression analysis results reported as χ^2 and respective P value.
†Same St James female equation used for VA-A to VA-D.

cantly different, with the exception of values derived from the VA-B/St James and Cooper clinic equations. Aside from mode of exercise characteristics and peak respiratory exchange ratio, all variables of interest were significantly different according to adverse event status. Peak V_{O_2}, maximal heart rate, and all percent-predicted peak V_{O_2} calculations were significantly lower whereas the VE/V_{CO_2} slope was significantly higher in subjects experienceing a major cardiac event. Moreover, all percent-predicted peak V_{O_2} calculations were significantly different between those with and without a major event. Resting $P_{ET}CO_2$, the oxygen uptake efficiency slope, and heart rate recovery at 1 minute data were available in 737 (major events, 120), 452 (major events, 62), and 612 (major events, 82) subjects, respectively. For these subgroups, resting $P_{ET}CO_2$ (34.3±4.5 versus 32.5±4.5 mm Hg), the oxygen uptake efficiency slope (1.8±0.9 versus 1.3±0.6), and heart rate recovery at 1 minute (19.2±11.8 versus 12.0±9.6 beats per minute) were all significantly higher ($P<0.001$) in subjects who did not experience a major cardiac event.

ROC curve analysis results for the different peak V_{O_2} prediction equations is listed in Table 3. All prognostic classification schemes were statistically significant. With the exception of the VA-D/St James equation, all optimal threshold values were within 5% points. The area under the ROC curve was greatest for the Wasserman/Hansen equation, although statistical significance in ROC areas was only reached in comparison between the VA-C and VA-D/St James equations. The Jones, Cooper Clinic, VA-A/St James, and VA-B/St James equations also demonstrated a significantly greater area under the ROC curve compared with VA-C/St James equation. All other area under the ROC curve comparisons did not reach statistical significance.

Table 4 lists the prognostic value of percent-predicted V_{O_2} values according to cardiac mortality as the only end point

Table 5. Multivariate Cox Regression Analyses for the Combination of VE/V_{CO_2} Slope and Different Aerobic Capacity Expressions*

Variable	χ^2	Residual χ^2	P
VE/V_{CO_2} slope	150.7		<0.001
Peak V_{O_2}		32.9† (univariate χ^2=75.1, $P<0.001$)	<0.001
Wasserman/Hansen‡		52.3† (univariate χ^2=96.9, $P<0.001$)	<0.001
Jones		42.9† (univariate χ^2=62.8, $P<0.001$)	<0.001
VA-A/St James		43.0† (univariate χ^2=86.9, $P<0.001$)	<0.001
VA-B/St James		43.0† (univariate χ^2=84.3, $P<0.001$)	<0.001
VA-C/St James		31.9† (univariate χ^2=58.9, $P<0.001$)	<0.001
VA-D/St James		42.8† (univariate χ^2=81.3, $P<0.001$)	<0.001
Cooper Clinic		42.9† (univariate χ^2=90.4, $P<0.001$)	<0.001

*Multivariate regression run total of eight separate times: VE/V_{CO_2} slope plus each aerobic capacity expression.
†Retained in multivariate regression.
‡Highest residual χ^2.

Table 6. Multivariate Cox Regression Analysis Using Actual Peak V_{O_2} and Percent-Predicted Peak V_{O_2} Using the Wasserman/Hansen Equation

Variable	χ^2	Residual χ^2	P
Actual peak V_{O_2}			
VE/V_{CO_2} slope	150.7		<0.001
NYHA class*		28.5	<0.001
Left ventricular ejection fraction*		26.7	<0.001
Peak VO_2*		8.1	0.005
HF etiology		1.7	0.20
Age		0.44	0.51
Percent-predicted peak V_{O_2}			
VE/VCO_2 slope	150.7		<0.001
Wasserman/Hansen Equation*		28.1	<0.001
Left ventricular ejection fraction*		14.8	<0.001
NYHA Class*		13.0	<0.001
HF etiology		2.4	0.12
Age		0.81	0.37

NYHA indicates New York Heart Association; HF, heart failure.
*Retained in multivariate regression.

Table 4. Continued

Subject Effort		Age	
Peak RER ≤1.05 (n=486; 76 Events)	Peak RER >1.05 (n=576; 103 Events)	<50 Years Old (n=314; 42 Events)	≥50 Years Old (n=851; 137 Events)
31.3, $P<0.001$	66.3, $P<0.001$	23.5, $P<0.001$	78.5, $P<0.001$
15.7, $P<0.001$	48.9, $P<0.001$	7.9, $P=0.005$	67.8, $P<0.001$
23.8, $P<0.001$	65.2, $P<0.001$	20.1, $P<0.001$	71.8, $P<0.001$
22.8, $P<0.001$	64.0, $P<0.001$	21.2, $P<0.001$	71.4, $P<0.001$
16.7, $P<0.001$	43.6, $P<0.001$	21.6, $P<0.001$	51.1, $P<0.001$
21.2, $P<0.001$	62.9, $P<0.001$	21.1, $P<0.001$	71.2, $P<0.001$
23.8, $P<0.001$	69.1, $P<0.001$	18.7, $P<0.001$	76.1, $P<0.001$

and sex, mode of exercise, exercise effort, and age-based subgroups. The ability of all percent-predicted V_{O_2} values to predict major adverse events remained statistically significant when cardiac mortality was considered the only end point and in all subgroup analyses.

Multivariate Cox regression analysis including the VE/V_{CO_2} slope and each expression of aerobic capacity is listed in Table 5. The VE/V_{CO_2} slope was the superior predictor of major cardiac events in each analysis whereas measured peak V_{O_2} and each percent-predicted peak V_{O_2} calculation added predictive value and were thus retained in the regression. The residual χ^2 value was greatest for the percent-predicted peak V_{O_2} value derived from the Wasserman/Hansen equation.

Two expanded multivariate Cox regression analyses that included the VE/V_{CO_2} slope, either measured peak V_{O_2} or percent-predicted peak V_{O_2} according the Wasserman/Hansen equation and key baseline characteristics are presented in Table 6. The VE/V_{CO_2} slope was again the superior prognostic marker in both assessments. Measured peak V_{O_2} and percent-predicted peak V_{O_2} according the Wasserman/Hansen equation were retained in the separate regression analyses in addition to NYHA class and left ventricular ejection fraction. On the basis of the residual χ^2 values, the Wasserman/Hansen equation provided superior predictive value compared with measured peak V_{O_2} and other consistent demographic variables.

The Jones (residual χ^2=10.8, P=0.001), VA-A/St James (residual χ^2=8.0, P=0.005), VA-B/St James (residual χ^2=7.9, P=0.005), VA-C/St James (residual χ^2=5.2, P=0.02), VA-D/St James (residual χ^2=8.0, P=0.005), and Cooper Clinic (residual χ^2=7.9, P=0.005) equations were all retained in the same expanded multivariate Cox regression depicted in online supplemental data. The residual χ^2 values were comparable with that found with measured peak V_{O_2} and below that provided by the Wasserman/Hansen equation. Moreover, as found with the analysis including measured peak V_{O_2}, the residual χ^2 values for left ventricular ejection fraction and NYHA class were higher (residual χ^2=12.2, $P<0.001$) in each of these latter scenarios.

Kaplan–Meier analysis curves are illustrated in the Figure. Dichotomous thresholds of < or ≥36.0, < or ≥47%, ≤ or >25%, and I/II versus III/IV were set for the VE/V_{CO_2} slope,[18] percent-predicted peak V_{O_2} according to the Wasserman/Hansen equation (determined by ROC curve analysis in the present investigation), left ventricular ejection fraction,[13] and the NYHA class, respectively. Using these thresholds, there was a significant difference in adverse event rates between subgroups according to the number of abnormal characteristics.

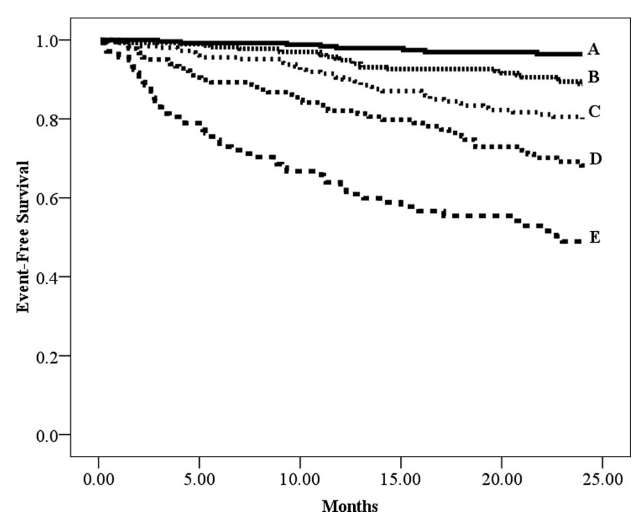

Figure. Kaplan–Meier analysis for combined VE/V_{CO_2} slope, percent-predicted peak V_{O_2}, left ventricular ejection fraction, and NYHA class thresholds.

Group	Characteristics*	Subjects Meeting Criteria	Major Cardiac Events	Percent Event Free, %
A	No abnormal values	271	8	97.0
B	1 Abnormal value	297	25	91.6
C	2 Abnormal values	269	42	84.4
D	3 Abnormal values	190	47	75.3
E	4 Abnormal values	138	57	58.7

Long rank: 171.8; $P<0.001$.
*Abnormal values:
- VE/V_{CO_2} slope: ≥36.0
- Percent-predicted peak V_{O_2}: <47%
- Left ventricular ejection fraction: ≤25%
- NYHA class: III/IV

Discussion

A number of equations designed to estimate the percentage of normal aerobic capacity achieved during exercise testing are presently available for clinical application. The present study demonstrates that several well-known methods for the determination of percent-predicted aerobic capacity: (1) provide values that are for the most part significantly different from one another, limiting the portability of a given equation to different populations of patients with HF; (2) are all prognostically significant in a large HF cohort from a univariate perspective; (3) are all prognostically significant when only cardiac mortality was considered as an end point; (4) all provide prognostic value in subgroups according to sex, mode of exercise, exercise effort and age; and (5) all provide additional prognostic value in a multivariate model including other clinically established exercise and resting variables.

In the prognostic comparison between equations, it seems the Wasserman/Hansen calculations provided better resolution, although differences in areas under the ROC curve were not significantly different compared with most other equations assessed. The potential value of the Wasserman/Hansen equations is more so apparent in the multivariate Cox regression analysis that included the VE/$\dot{V}CO_2$ slope and key resting variables (Tables 5 and 6). In these analyses, percent-predicted values derived from the Wasserman/Hansen approach possessed the highest univariate χ^2 value (compared with measured peak $\dot{V}O_2$ and other percent-predicted calculations), was retained in the multivariate regression and outperformed both left ventricular ejection fraction and NYHA class. Although measured peak $\dot{V}O_2$ and all other percent-predicted calculations were also retained in their respective multivariate Cox regression analyses, their added prognostic value was not as powerful as compared with that derived from inclusion of the Wasserman/Hansen equations. The findings of the present study are consistent with the previous investigation by Stelken et al[12] in that percent-predicted peak $\dot{V}O_2$ according to the Wasserman/Hansen equations prognostically outperformed an abbreviated list of other equations and measured peak $\dot{V}O_2$ in 181 patients with HF. Similalry, Osada et al[19] found percent-predicted peak $\dot{V}O_2$, again derived from the Wasserman/Hansen equations, prognostically outperformed measured peak $\dot{V}O_2$ in 500 patients with HF. Aaronson and Mancini,[11] however, found that the Wasserman/Hansen percent-predicted $\dot{V}O_2$ calculations and measured peak $\dot{V}O_2$ performed similarly in a HF cohort comprised of 272 patients. An advantage of the present investigation compared to these previous studies is the larger sample size, possibly lending more credence to our findings and supporting the previous investigations by Stelken et al[12] and Osada et al.[19]

Previous investigations[12,19] have solely used a percent-predicted peak $\dot{V}O_2$ threshold of 50% in their dichotomous prognostic assessments. Determination of this threshold seems to have been more arbitrary than the optimal sensitivity/specificity determination via ROC curve analysis. Despite differences in determination of the dichotomous threshold used in the current and previous investigations, the cut point was for the most part similar. This concordance of research indicates that patients with a percent-predicted $\dot{V}O_2$ value below ≈50% have poorer outcomes compared with those surpassing this threshold, although the optimal cut point may slightly deviate from 50% for a given predicted peak $\dot{V}O_2$ equation.

There is considerable variation in how presently available prediction equations are defined. Although all equations considered age and sex, the Wasserman/Hansen male/female equations have taken the greatest number of additional factors into consideration, including body weight (underweight/normal weight/overweight), mode of exercise (treadmill/lower extremity ergometer), and sedentary lifestyle. Moreover, the Wasserman/Hansen, Jones, VA-A, and VA-B equations, used peak $\dot{V}O_2$ determined by ventilatory expired gas analysis to develop their normative values. The VA-C, VA-D, St James, and Cooper Clinic equations all estimated aerobic capacity from treadmill speed/grade or exercise time. Given the differences in equation development, the improved prognostic utility of the Wasserman/Hansen equations may be the result of their ability to account for more explanatory variables and provide a truer depiction of aerobic capacity for an apparently healthy, but sedentary individual. It should be noted, however, that despite the potential limitations of the other prediction equations assessed in the present investigation, they all provided significant prognostic value both independently and in combination with clinically important variables.

It could be argued that the additional steps required for the Wasserman/Hansen equations are not worth the relatively modest increment gained in prognostic information. However, these equations are easily incorporated into the software packages that operate CPX systems. The percent-predicted peak $\dot{V}O_2$ value according to the Wasserman/Hansen equation can, therefore, be automatically generated by manually inputting age, sex, height, weight, and mode of exercise, a procedure which is already commonplace in preparation for a CPX. The ease by which all percent-predicted peak $\dot{V}O_2$ calculations are derived by presently available software packages eliminates the need for consideration of a given equations complexity.

There is a wealth of research supporting the prognostic strength of the VE/$\dot{V}CO_2$ slope in HF, which commonly outperforms measured peak $\dot{V}O_2$.[18,20–22] Although the prognostic value of the VE/$\dot{V}CO_2$ slope is gaining clinical recognition, peak $\dot{V}O_2$ continues to be the sole or primary CPX variable considered in the prognostic assessment of patients with HF undergoing this procedure. The results of the present study indicate measured or percent-predicted peak $\dot{V}O_2$ should continue to be considered as a secondary CPX variable, complimenting the insight gained from the VE/$\dot{V}CO_2$ slope. Irrespective of which variable provides the highest level of prognostic information, it seems clear from the recent literature that the ability to predict adverse events improves with multivariate modeling that includes CPX variables and key resting measures such as NYHA class and left ventricular ejection fraction.[21]

Subjects included in the present investigation were referred for CPX at their respective institution, creating the potential for selection bias. Caution must, therefore, be taken in extrapolating our findings to the population with

HF as a whole or to CPX laboratories assessing patients with HF with differing characteristics, such as, for example, younger individuals with a congenital heart defect being considered for transplantation. Moreover, although the overall number of subjects in the present investigation exceeded 1000, the majority were male. Although all percent-predicted VO_2 equations were prognostic in the female subgroup, particular caution should be taken in extrapolating our findings to the female population with HF. Given the heterogeneous nature of this disease process, future investigations should be performed in other HF cohorts to determine whether the prognostic value of percent-predicted peak VO_2 is universally applicable to this chronic disease population. Although peak VO_2 and the VE/VCO_2 slope are well established, other variables, such as resting $P_{ET}CO_2$,[23] the oxygen uptake efficiency slope,[24] and heart rate recovery at 1 minute[25] have demonstrated prognostic value. Although these variables were unfortunately not available for the entire cohort in the present investigation, subgroup analysis revealed all 3 demonstrated significantly better characteristics in subjects who did not experience a major cardiac event. In addition, peak VO_2 adjusted for body fat has demonstrated prognostic value in patients with HF.[26,27] Analysis of this expression of aerobic capacity could not be performed in the present study as body fat assessment was not performed in any of the subjects. Future research should be directed toward a more comprehensive multivariate survival analysis to determine all clinically relevant CPX variables and optimal expression.

In conclusion, variables obtained from CPX provide important prognostic insight in patients with HF. The findings of the present investigation further confirm the prognostic superiority of ventilatory efficiency (VE/VCO_2 slope) and suggest equations used to determine percent-predicted peak VO_2 provide similar and in some instances better predictive information compared with the measured value obtained from CPX. Although many laboratories conducting CPX in patients with HF report percent-predicted peak VO_2 values in their written report, they do not commonly consider its prognostic significance. Our results suggest that (1) peak VO_2 should be expressed as a percentage of the predicted normal value and this should be a routine part of the summary report, and (2) the Wasserman/Hansen equation is superior to other equations in terms of prognostic power in patients with HF.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Previous investigations have consistently demonstrated that cardiopulmonary exercise testing is a valuable tool in the clinical and prognostic assessment of patients with heart failure. Peak oxygen consumption (VO_2) is one of the primary variables obtained from such testing and is typically assessed as an actual value relative to body weight. A number of prediction equations have been developed to estimate normal aerobic capacity and are readily available to clinicians. While documenting a percent-predicted peak VO_2 value on the cardiopulmonary exercise testing report is typically advocated, it is frequently not afforded any consideration by clinicians assessing prognosis or weighing treatment options based on the exercise response. The present study demonstrates that the percent-predicted peak VO_2 value derived from several established equations provide prognostic value in patients with heart failure. In particular, the prediction equation established by Wasserman and Hansen seems to provide optimal prognostic value, potentially outperforming the predictive resolution obtained from the actual peak VO_2 value. This study may provide healthcare professionals performing cardiopulmonary exercise testing with important information regarding which peak VO_2 prediction equation to use and its potential clinical value in patients with heart failure. In conclusion, clinicians responsible for the interpretation of cardiopulmonary exercise testing data in patients with heart failure should consider the clinical utility of all information that is gained from this valuable assessment technique.

Supplemental Material

Table 1: Definition of Percent Predicted VO_2 Equations and Thresholds*

Wasserman/Hansen[£, α]	**Sedentary Male** **Step 1: Calculate** Cycle Factor = 50.72 – 0.372(age) Predicted weight: = 0.79(height) – 60.7 **Step 2: Classify weight** Measured weight </=/> predicted weight **Step 3: Select equation** Measured weight < Predicted weight Peak VO_2 (ml/min) = [(Predicted weight + Actual weight)/2] * cycle factor Measured weight = Predicted weight Peak VO_2 (ml/min) = Measured weight * cycle factor Measured weight > Predicted weight Peak VO_2 (ml/min) = (Predicted weight*cycle factor) + 6 * (Measured weight – predicted weight) **Step 4: Mode of exercise consideration** If treadmill used for test Multiply predicted VO_2 from step 3 * 1.11	**Sedentary Female** **Step 1: Calculate** Cycle Factor = 22.78 – 0.17(age) Predicted weight: = 0.65(height) – 42.8 **Step 2: Classify weight** Measured weight </=/> predicted weight **Step 3: Select equation** Measured weight < Predicted weight Peak VO_2 (ml/min) = [(Predicted weight + Actual weight +86)/2] * cycle factor Measured weight = Predicted weight Peak VO_2 (ml/min) = (Measured weight + 43) * cycle factor Measured weight > Predicted weight Peak VO_2 (ml/min) = (Predicted weight + 43) *cycle factor + 6 * (Measured weight – predicted weight) **Step 4: Mode of exercise consideration** If treadmill used for test Multiply predicted VO_2 from step 3 * 1.11
Jones[Ω, α]	**Males** Peak VO_2 (L/min) = 5.41(height) - 0.025(age) - 5.66	**Females** Peak VO_2 (L/min) = 3.01(height) - 0.017(age) - 2.56
VA (male only)	Predicted METs = A: 11.9-0.07(age)[β, α]; B: 14.7-0.11(age)[€, α]; C: 16.6-0.16(age)[β, ¥]; D: 18.5-0.15(age)[€, ¥]	
Saint James (women only)[¥]	Predicted METs = 14.7-0.13(age)	
Cooper Clinic[¥]	**Low Fitness Thresholds**	
	Males 20-39 years: ≤10.5 METs 40-49 years: ≤9.9 METs 50-59 years: ≤8.8 METs ≥60 years: ≤7.5 METs	**Females** 20-39 years: <8.2 METs 40-49 years: <7.6 METs 50-59 years: <6.7 METs ≥60 years: <5.8 METs

Legend for Table 1

* All equations expressed in original reported units. Converted to VO_2 in relative terms ($mlO_2 \bullet kg^{-1} \bullet min^{-1}$) to calculated percent-predicted value
    - 1 MET = 3.5 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$
    - VO_2 in L/min multiplied by 1000 for ml/min and then divided by body weight in kg to Convert to $mlO_2 \bullet kg^{-1} \bullet min^{-1}$

£ Height = cm and weight = kg
Ω Height = meters; weight = kg
β Equations derived from cohort subgroup to predict value for sedentary subjects
€ Equation derived from entire cohort; not accounting for physical activity patterns
α Peak VO_2 assessed by ventilatory expired gas analysis
¥ Peak VO_2 estimated from treadmill speed/grade