Prognostic usefulness of the functional aerobic reserve in patients with heart failure

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Background Peak oxygen consumption derived from cardiopulmonary exercise (CPX) testing provides important prognostic information in patients with heart failure (HF). The oxygen consumption at the ventilatory threshold (VT) has also been shown to be prognostic. However, the VT cannot always be detected in patients with HF. Other variables such as the difference between peak oxygen consumption and oxygen consumption at the VT (termed the *functional aerobic reserve* [FAR]) may also provide prognostic information. The purpose of this study was to determine the prognostic value of an undetectable VT and FAR.

Methods Eight hundred seventy-four patients with chronic, systolic HF (70% male, age 54 ± 14 years, ejection fraction 29% ± 12%) underwent CPX and were tracked for 2 years for major events (death, transplant, and left ventricular assist device implantation).

Results Patients were divided into 2 subgroups based on whether VT could be detected or not. There were 141 major events during the 2-year follow-up. Kaplan-Meier analysis for the 2 VT subgroups demonstrated worse prognoses for patients with a nondetectable VT versus those with a detectable VT ($P < .001$). Based on receiver operating characteristic curve analysis (FAR = 0 $mlO_2\ kg^{-1}\ min^{-1}$ for patients with undetectable VT), the optimal cut-point for FAR was ≤/>3 $mlO_2\ kg^{-1}\ min^{-1}$ (sensitivity/specificity 69%/60%). Cox regression analysis identified the FAR as a significant univariate predictor of risk and was retained in multivariate analysis.

Conclusion In conclusion, these data reveal that an undetectable VT and the FAR during CPX testing can provide useful prognostic information in patients with HF. (Am Heart J 2010;160:922-7.)

Peak oxygen consumption (VO_2pk) attained during a maximal cardiopulmonary exercise (CPX) test is a standard prognostic indicator for patients with heart failure (HF).[1] More recently, the ventilatory efficiency (VE/VCO_2) slope has also been found to be a powerful prognostic indicator, independent of VO_2pk, in the population with HF.[2-6] It has been proposed that other variables, such as VO_2 at the ventilatory threshold (VO_2VT),[7] may also provide prognostic information. However, the VT cannot be detected in up to 30% of patients with HF due to several factors, including exercise oscillatory ventilation, deconditioning, or early cessation of the exercise.[8]

Reflecting the onset of lactic acidosis, the VO_2VT is an important measure of submaximal exercise capacity and may be a better measure of the effect HF is having on a patient's activities of daily living than VO_2pk. Previous work has shown that a VO_2VT <11 $mlO_2\ kg^{-1}\ min^{-1}$ is an important dichotomous threshold for increased risk in patients with HF.[7,9] Furthermore, the likelihood of independent living in older populations is reduced when the VO_2pk is <18 $mlO_2\ kg^{-1}\ min^{-1}$.[10] Higher aerobic capacity is associated with greater aerobic reserve (exercise capacity above activities of daily living), and when aerobic capacity is reduced below the 18 $mlO_2\ kg^{-1}\ min^{-1}$ threshold, then the aerobic reserve may be reduced or eliminated. Many patients with HF have VO_2pks below the 18 $mlO_2\ kg^{-1}\ min^{-1}$ threshold and are likely to have the same limitation of a reduced aerobic reserve. Therefore, a variable that could be derived from the CPX test is the difference between the VO_2pk and the VO_2VT, or what we have termed the *functional aerobic reserve* (FAR).

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The primary purpose of the present study is to develop a prognostic model using FAR as a continuous variable that incorporates patients with an undetectable VT. Secondarily, we will determine the prognostic power of the FAR with that of VO_2pk and the VE/VCO_2 slope in patients with HF.

Methods

This study is a multicenter analysis including patients with HF from the CPX laboratories at San Paolo Hospital, Milan, Italy; Virginia Commonwealth University, Richmond, VA; and the LeBauer Cardiovascular Research Foundation, Greensboro, NC. A total of 874 patients with chronic, systolic HF and who were tested between May 13, 1997, and May 22, 2008, were included. Inclusion criteria consisted of a diagnosis of HF,[11] stable HF symptoms and medications for at least 1 month before exercise testing, and evidence of left ventricular systolic dysfunction by 2-dimensional echocardiography obtained within 1 month of exercise testing. Subjects were classified as having systolic HF if they presented with a left ventricular ejection fraction (EF) ≤45%. Subjects received routine follow-up care at the institutions included in this study. All subjects completed a written informed consent, and institutional review board approval was obtained at each institution.

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Symptom-limited CPX testing was performed on all patients using treadmill[12] or cycle ergometry[13] ramping protocols. A treadmill was the predominant mode of exercise used for testing in American centers, whereas a lower-extremity cycle ergometer was exclusively used in the European center. Ventilatory expired gas analysis was performed using a metabolic cart at all centers (Medgraphics CPX-D or ULTIMA PFX, Minneapolis, MN; Parvo Medics TrueOne 2400, Sandy, UT; or Sensormedics Vmax29, Yorba Linda, CA). Before each test, the equipment was calibrated in standard fashion using reference gases. In addition, each center routinely validated their metabolic exercise testing equipment by exercising a healthy subject at a submaximal steady rate to verify measured VO_2 matched estimated VO_2 from the workload.[14] Previous studies have demonstrated that optimal VO_2pk and VE/VCO_2 slope prognostic threshold values are similar irrespective of mode of exercise in patients with HF.[15] We therefore did not create subgroups based upon mode of exercise. Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least 5 minutes during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. VE, VO_2, VCO_2, and other CPX variables were acquired breath by breath and averaged over 10- or 15-second intervals. The VO_2VT was determined using the V-slope method.[16] Peak VO_2 and peak respiratory exchange ratio were expressed as the highest averaged samples obtained during the exercise test. VE and VCO_2 values, acquired from the initiation of exercise to peak, were input into a spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope). Previous work by our group and others has shown this method of calculating the VE/VCO_2 slope to be prognostically optimal.[17,18] The FAR was determined by subtraction of the VO_2VT from the VO_2pk.

Although it is common for patients without a detectable VT to be excluded from analysis,[7-9] several of the factors leading to an undetectable VT are also associated with advanced HF, including a significantly reduced VO_2pk and elevated VE/VCO_2 slope. Therefore, it is likely that these patients do not have much, if any, FAR. To include subjects without a detectable VT into the FAR analysis, FAR was set to 0 $mlO_2\ kg^{-1}\ min^{-1}$.

Using hospital and outpatient chart review, subjects were followed for major cardiac-related events (heart transplantation, left ventricular assist device implantation, and cardiac-related death) for 2 years after CPX testing. Any death with a cardiac-related discharge diagnosis was considered an event. Clinicians conducting the CPX testing were not involved in the decisions related to heart transplant, left ventricular assist device implant, or cause of death.

To test the premise that patients without a detectable VT were likely to have more advanced HF (thus justifying the approach of setting FAR to 0 $mlO_2\ kg^{-1}\ min^{-1}$ in this group), the patients were initially divided into 2 groups based on the whether the VT could be determined. Determination was made at each center by clinicians experienced with CPX testing and determining the VT using the V-slope method (P.C., R.A., J.M., M.G.). Subsequently, the patients were subdivided into 2 groups based on their FAR classification. All continuous data were reported as mean values ± SD and categorical data as percentages. One-way analysis of variance was used to assess differences in key continuous variables, whereas χ^2 analysis assessed differences in categorical variables among the VT and FAR subgroups. Tukey's honestly significant difference test was used to determine VT and FAR subgroups that were significantly different when the one-way analysis of variance P value was <.05. Kaplan-Meier analysis assessed survival characteristics of the VT and FAR subgroups. The log-rank test determined statistical significance for the Kaplan-Meier analysis. Univariate and multivariate Cox regression analysis was used to assess the prognostic value of FAR as well as key baseline and cardiopulmonary variables in the overall cohort. The following survival analyses were additionally performed in each FAR subgroup: (1) multivariate Cox regression analysis assessed the prognostic value of the VE/VCO_2 slope, VO_2pk, VO_2VT, FAR, age, EF, and HF etiology; (2) receiver operating characteristic curve (ROC) analysis was used to assess FAR classification schemes; and (3) Kaplan-Meier analysis assessed survival characteristics of the FAR according to optimal thresholds defined by ROC analysis. The log-rank test determined statistical significance of the Kaplan-Meier analysis. Statistical differences with a P value <.05 were considered significant.

Results

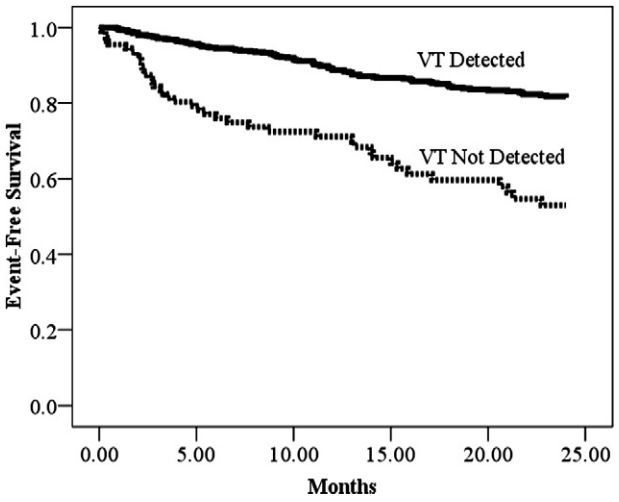
Overall group characteristics and subgroup comparisons between patients with a detectable VT (n = 762) and those with a nondetectable VT (n = 112) are listed in Table I. Baseline characteristics for patients without a detectable VT indicated they were more often male, more

Table I. Overall group baseline characteristics and CPX results and VT subgroup comparisons

Variable	All (n = 874)	No VT (n = 112)	VT (n = 762)
Age	54 ± 14	53 ± 15	55 ± 13
Gender (% male)*	70%	71%	61%
Body mass index	28.4 ± 6.0	29.2 ± 7.8	28.2 ± 5.6
Etiology (% ischemic)*	43%	33%	44%
NYHA class (% III/IV)†	50%	89%	45%
EF†	29% ± 12%	24% ± 12%	30% ± 12%
VO_2pk (mL kg^{-1} min^{-1})†	15.0 ± 5.3	10.7 ± 3.7	15.7 ± 5.2
Ventilatory efficiency slope†	36.5 ± 9.6	45.9 ± 13.1	35.1 ± 8.1
Respiratory exchange ratio†	1.09 ± 0.12	1.03 ± 0.16	1.10 ± 0.11
β-Blocker (% use)*	77%	86%	75%
Angiotensin-converting enzyme inhibitor (% use)	76%	78%	76%
Calcium channel blocker (% use)	7%	6%	7%
Diuretic (% use)†	72%	90%	70%

* $P < .05$.
† $P < .001$.

Figure 1



Kaplan-Meier analysis for the 2 VT subgroups. Log-rank = 47.1, $P <$ .001. *VT Detected,* Patients in whom the VT could be detected; *VT Not Detected,* patients in whom the VT could not be detected.

often had nonischemic etiology, almost all had New York Heart Association (NYHA) class III/IV symptoms, had lower EF, and more likely to be prescribed β-blockers and diuretics. Exercise results indicated that these patients also had much lower VO_2pk, lower respiratory exchange ratio (RER), and considerably higher VE/VCO_2 slope.

There were 141 major cardiac events (90 deaths, 35 transplants, 16 left ventricular assist device implants) during the 2-year follow-up. The annual event rate for the entire group was 10.4%. Kaplan-Meier analysis for the 2 subgroups is illustrated in Figure 1. Patients without a detectable VT had a significantly worse prognosis than those with a detectable VT (hazard ratio 3.3, 95% CI 2.3-4.8, $P < .001$).

Table II. Univariate Cox regression analysis and the ROC analysis for key CPX variables

Variable	χ^2	Hazard ratio (95% CI)	ROC curve area (95% CI)
Ventilatory efficiency slope	124.8	1.07 (1.05-1.08)	0.75 (0.70-0.79)
VO_2pk	63.7	0.84 (0.80-0.87)	0.72 (0.68-0.77)
Oxygen consumption at the VT	24.4	0.84 (0.78-0.90)	0.66 (0.60-0.72)
FAR	58.2	0.74 (0.68-0.80)	0.71 (0.66-0.75)

Table III. Baseline characteristics and CPX results for the 2 FAR subgroups

Variable	Low FAR (n = 314)	High FAR (n = 560)
Age*	56 ± 14	54 ± 13
Gender (% male)*	61%	74%
Body mass index	28.6 ± 6.7	28.2 ± 5.5
Etiology (% ischemic)	45%	42%
NYHA class (% III/IV)†	72%	38%
EF†	26% ± 12%	30% ± 12%
VO_2pk (mL kg^{-1} min^{-1})†	11.1 ± 3.5	17.2 ± 5.0
Ventilatory efficiency slope†	41.1 ± 11.4	33.9 ± 7.2
Oxygen consumption at the VT (mL kg^{-1} min^{-1})†	9.3 ± 3.0	11.6 ± 3.6
Respiratory exchange ratio†	1.06 ± 0.14	1.10 ± 0.11
β-Blocker (% use)*	81%	74%
Angiotensin-converting enzyme inhibitor (% use)	75%	78%
Calcium channel blocker (% use)	7%	7%
Diuretic (% use)†	81%	67%

* $P < .05$.
† $P < .001$.

Table II lists the results of the univariate Cox regression analysis and the ROC analysis for key CPX variables (VE/VCO_2 slope, VO_2pk, VO_2VT) and for FAR (where FAR was set to 0 mlO_2 kg^{-1} min^{-1} in those patients where VT could not be detected) in the overall group. Each of the variables is a significant univariate predictor of risk. Of these, VE/VCO_2 slope is the strongest overall predictor. The area under the ROC was significant for all variables, including FAR. The optimal prognostic cut-point for FAR was ≤/> 3 mlO_2 kg^{-1} min^{-1} (sensitivity/specificity 69%/60%, hazard ratio 3.1, 95% CI 2.2-4.4, $P < .001$) and was used to divide the patients into 2 FAR subgroups (low FAR ≤3 mlO_2 kg^{-1} min^{-1} [n = 314] and high FAR >3 mlO_2 kg^{-1} min^{-1} [n = 560]).

Baseline characteristics and CPX data for the 2 FAR subgroups are listed in Table III. Patients with low FAR were more likely female, to be considered NYHA class III/IV, have lower EF, and be more likely to be prescribed β-blockers and diuretics than the high FAR group. CPX results indicated the low FAR group had significantly

Table IV. Cox multivariate regression analysis

Variable	χ^2	*P*
Ventilatory efficiency slope	124.8	<.001
Variable	**Residual χ^2**	***P***
FAR	6.9	.008
VO_2pk	4.2	.04

lower VO_2pk, lower VO_2VT (those without a detectable VT excluded), lower RER, and higher VE/VCO_2 slope then the high FAR group.

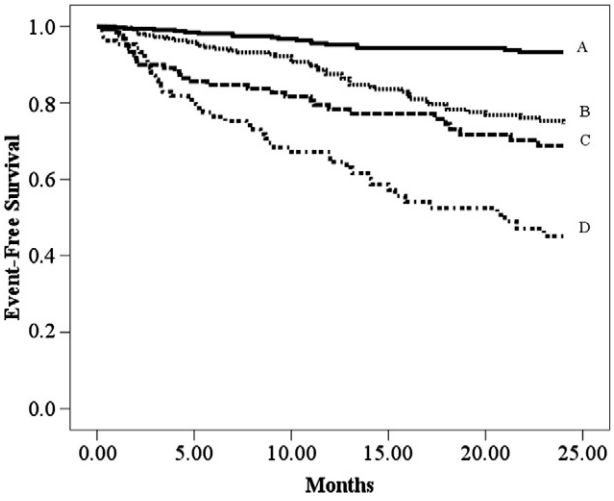
Cox multivariate regression analysis results for VE/VCO_2 slope, FAR, and VO_2pk are listed in Table IV. A forward stepwise method was used for the multivariate regression with entry and removal values set at 0.05 and 0.10, respectively. The VE/VCO_2 slope was the best overall predictor; FAR and VO_2pk were both retained in the analysis and were additive to the VE/VCO_2 slope.

When using the optimal cut-points of the VE/VCO_2 slope (</≥36), VO_2pk (≤/>10 mlO_2 kg^{-1} min^{-1}), and FAR (≤/>3 mlO_2 kg^{-1} min^{-1}) from the overall group, we developed a 4-tiered prognostic classification system, which is illustrated by the Kaplan-Meier survival curves in Figure 2. All favorable CPX responses (VE/VCO_2 slope <36, VO_2pk >10 mlO_2 kg^{-1} min^{-1}, and FAR >3 mlO_2 kg^{-1} min^{-1}) occurred in 359 patients (18 events, 95.0% survival rate). One and two abnormal responses occurred in 278 (47 events, 83.1% survival rate) and 129 (31 events, 76.0% survival rate) patients, respectively. All abnormal CPX responses occurred in 108 patients (45 events, 58.3% survival rate).

Discussion

The specific aims of this study were to determine the prognostic significance of the FAR (ie, the difference between the VO_2VT and VO_2pk) in patients with HF undergoing CPX testing and how this variable compares with other prognostic variables. We felt that because 13% of our sample was without a detectable VT, a percentage comparable to other investigations[7,8,19-21] and seemingly representative of worsening disease severity,[7,20] it was important to include these patients in the analysis of FAR. Because our results demonstrate that patients with HF in whom the VT could not be detected have significantly worse VO_2pk, VE/VCO_2 slope, and cardiac morbidity and mortality rates as compared to those in whom the VT was detected, we feel that setting FAR to 0 mlO_2 kg^{-1} min^{-1} for these patients was justified. In fact, subgroup analysis demonstrated that patients in the low FAR group (≤3.0 mlO_2 kg^{-1} min^{-1}) were found to have higher event rates than those in the higher FAR group. Moreover, the FAR provides additional prognostic information to more

Figure 2



Kaplan-Meier analysis of the 4-tiered prognostic classification system. (**A**) All favorable CPX responses; (**B**) 1 unfavorable CPX response; (**C**) 2 unfavorable CPX responses; (**D**) all 3 CPX responses unfavorable. Log-rank = 107.0, $P < .001$.

established indicators such as the VE/VCO_2 slope and VO_2pk. Although not reported in the results, we did perform the survival analysis of FAR only including patients with a detectable VT and found FAR to be a significant independent predictor of major cardiac events ($\chi^2 = 21.047$, $P < .0001$). To our knowledge, this is the first study to evaluate the magnitude of the difference between the VO_2pk and the VO_2VT or FAR.

In a study of 223 patients with HF, Gitt et al[7] reported that a VO_2VT of ≤11 mlO_2 kg^{-1} min^{-1} was a useful independent variable in identifying patients at high risk for early death and provided additional prognostic power to the VE/VCO_2 slope. Furthermore, in a smaller study of 45 patients with HF, Van Laethem et al[21] found the VO_2VT to be highly correlated with VO_2pk and was beneficial in identifying a subset of patients with HF at high risk for early death. However, in both of these studies, the researchers were not able to identify VT in a significant proportion of patients (8%[7] and 23%[21]), and these patients were excluded from many of the analyses.

It has been reported that the VT is not detectable in up to 30% of patients with HF tested.[8] Our data resulted in only 13% of the overall group without a detectable VT and are within the range previously reported.[7,8,19-21] It has been suggested that the detection of VT in patients with HF may be hindered by poor effort, significant deconditioning, abnormal breathing patterns (ie, oscillatory ventilation), and early onset of acidosis.[7,8] The novelty of FAR is that it is useful whether a VT is detected or not and allows for the evaluation of the VT as a continuous, rather then dichotomous (yes or no), variable.

Furthermore, when combined with other prognostic variables in a risk score, it can be helpful in differentiating between poor effort and pathophysiological limitations.

Researchers[10,22] have used continuous-scale physical functional performance tests that mimic tasks of daily living associated with independent living,[10] and aerobic reserve has defined as the difference between the VO_2pk and the VO_2 obtained during the continuous-scale physical functional performance tests.[22] The continuous-scale physical function performance tests measure the physical function in a multitude of tasks that are associated with activities for independent living; they have been measured to include tasks considered low work (ie, tying shoes or wrapping scarves) that are about 6.0 $mlO_2\ kg^{-1}\ min^{-1}$, moderate work (ie, making the bed or vacuuming) that are about 8.0 $mlO_2\ kg^{-1}\ min^{-1}$, and high work (ie, climbing stairs or grocery shopping) that are about 9.4 $mlO_2\ kg^{-1}\ min^{-1}$.[22] To some extent, those results support the notion of Gitt et al,[7] who suggested that a VO_2VT $\leq$11 $mlO_2\ kg^{-1}\ min^{-1}$ was associated with a higher risk in patients with HF. Furthermore, Arnett et al[22] concluded that a higher aerobic capacity results in a larger reserve, which creates a greater margin of safety and allows older adults to be more active throughout the day while remaining further below their maximum aerobic capacity. Our results suggest that the same may be true for patients with HF. That is, a higher FAR allows the patient to do more activities with a greater reserve and possibly less fatigue, whereas an individual with a low FAR is not only potentially going to be able to do less throughout the day, but they also experience more symptoms (as evidenced by 72% of the low FAR group reporting NYHA class III/IV symptoms).

There are some potential limitations to this study. First, although we used the V-slope method for determining the VT on all subjects, this measure is nevertheless subjective. However, all clinicians determining the VT were very experienced (combined 72 years, range 10-30 years) in making the determination using the V-slope method. Clinical guidelines recommend that VT should be visually determined by at least 1 experienced clinician.[23] For clinical studies, it has been recommended that up to 3 experienced observers should independently determine VT.[19] This recommendation is not only to reduce test-retest variability for clinical studies that involve some intervention but could also increase confidence (not precision) in the determination of VT clinically. However, we felt that using the single-clinician approach at each center was adequate and reflects current clinical practice. Second, we did not exclude any patients based on effort (RER), and all groups included patients above and below an RER of 1.10. Thus, any patient giving a truly submaximal effort could have influenced the results. Despite this, our results may be viewed as compelling and warranting further investigation. Lastly, our study sample was primarily middle-aged males. Therefore, these findings may not be applicable to other cohorts. Future research should be directed toward addressing these limitations.

In conclusion, FAR is a novel independent variable, which adds to the prognostic power of more common variables such as the VE/VCO_2 slope and VO_2pk in patients with HF. The value for FAR can be easily calculated as simply the difference between VO_2pk and VO_2VT. It is also more accessible to the clinician because it is derived from data collected during a routine CPX test versus the continuous-scale physical function performance tests. These data suggest that FAR has potential value as a functional and prognostic marker in patients with HF and that among patients with an intermediate risk VO_2pk, a low FAR may be a signal that more intensive intervention may be warranted.

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