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Does Peak Oxygen Pulse Complement Peak Oxygen Uptake in Risk Stratifying Patients with Heart Failure?

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Abstract

There is scarce information regarding the prognostic utility of peak exercise oxygen pulse (peak O₂ pulse), a surrogate for stroke volume, in patients with heart failure (HF). Between May 1994 and November 2007, 998 patients with HF underwent cardiopulmonary exercise testing. The ability of peak VO₂ and peak O₂ pulse to predict cardiac events was examined. Peak O₂ pulse was calculated by dividing peak VO₂ by heart rate at the time peak VO₂ was achieved, and was expressed in both milliliters per beat and as a percentage achieved of age-predicted. There were 212 cardiac events (176 deaths, 26 transplantations, and 10 LVAD implantations) over a mean of 28 ± 26 months follow-up. Peak VO₂ and age-predicted peak O₂ pulse were demonstrated by univariate and multivariate Cox regression analyses to be independent predictors of mortality (p<0.001). The optimal cut-points for peak VO₂ and age-predicted peak O₂ pulse (<14.3; 14.3 mL.kg⁻¹.min⁻¹ and <85%; 85%, respectively) were established by areas under the receiver-operating characteristic curves. Patients exhibiting abnormalities for both responses had 4.8 (95% CI; 2.7 – 8.5) and 6.7-fold (95% CI; 4.1 – 11.1) higher risks of mortality and cardiac events, respectively, than those whose responses were normal. Age-predicted peak O₂ pulse also predicted mortality among patients in the intermediate range of peak VO₂ (between 10 and 14 mL.kg⁻¹.min⁻¹). The 3-year mortality rate for patients in this range who had an age-predicted peak O₂

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pulse <85% was even slightly higher than those with a peak $\text{VO}_2 < 10.1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. In conclusion, age-predicted peak O_2 pulse was a strong and independent predictor of cardiac mortality and complemented peak VO_2 in predicting risk in patients with HF.

Keywords

peak oxygen pulse; exercise; heart failure; cardiovascular mortality

The exercise oxygen pulse (O_2 pulse), defined by dividing oxygen uptake (VO_2) by heart rate, combines the chronotropic and oxygen utilization responses to exercise and is often considered a surrogate for stroke volume^{1–4}. One of the hallmarks of heart failure (HF) is reduced maximal aerobic power, largely mediated by an impaired increase in stroke volume and thus a limited peak cardiac output, despite a preserved chronotropic response in many patients. Therefore, the rise in O_2 pulse relative to exercise intensity would be abnormal among patients with the most impaired ventricular response to exercise and should in theory be a strong predictor of outcomes. Although a few previous studies have investigated the prognostic utility of peak O_2 pulse in HF patients^{5,6}, conflicting results have been observed. In addition, to date, no studies have investigated the prognostic utility of age-predicted peak O_2 pulse in patients with HF. The aims of the present study were: 1) to investigate whether peak O_2 pulse and age-predicted peak O_2 pulse had prognostic value that complements peak oxygen uptake (peak VO_2); and 2) to determine the optimal application of age-predicted peak O_2 pulse in risk-stratifying HF patients who fall within the “intermediate” range of peak VO_2 (between 10 and 14 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Methods

This study was a multicenter analysis, including 998 patients with chronic HF (694 males), tested between 5/16/1994 and 11/7/2007. The subjects completed a written informed consent and institutional review board approval was obtained at each institution. More detailed information regarding patient selection, diagnostic criteria of HF and cardiopulmonary exercise testing (CPX) procedures and analyses have been published elsewhere^{7,8}. Peak O_2 pulse was calculated by dividing peak VO_2 by heart rate at the time peak VO_2 was achieved and was expressed in milliliters per beat. We also expressed peak O_2 pulse as a percentage of the age-predicted value achieved by dividing the age-predicted peak VO_2 by age-predicted peak heart rate. We used the Wasserman equation⁹ for predicted peak VO_2 since we recently observed that it outperformed other equations in terms of prognosis in a large HF cohort¹⁰.

The primary endpoint was cardiac mortality, defined as death directly resulting from failure of the cardiac system. A composite variable including cardiac-related mortality, hospitalization due to worsening HF, cardiac transplantation, and left ventricular assist device implantation (LVAD) was used as a secondary endpoint. Subjects were followed using the Social Security Death Index and hospital and outpatient medical chart review. Follow-up was performed by the HF program at each respective institution, providing a high likelihood that all major events were captured. Clinicians conducting the CPX were not involved in decisions regarding cause of death or heart transplantation/LVAD implantation.

NCSS statistical software (Kayesville, UT) was used to perform all analyses. All continuous data are reported as mean $\pm$ SD. Groups were categorized by peak VO_2 as $< 10 \text{ mL.kg}^{-1}.\text{min}^{-1}$, 10.1 to $14.2 \text{ mL.kg}^{-1}.\text{min}^{-1}$ and $> 14.3 \text{ mL.kg}^{-1}.\text{min}^{-1}$ (hereafter referred to as low, intermediate and high, respectively). One-way ANOVA was used to assess differences between continuous variables, followed by post-hoc analyses (Tukey), whereas χ^2 statistics was used to assess differences in categorical variables. ROC curve analysis was used to define optimal threshold values for each CPX response. The optimal threshold for peak VO_2 was $< 14.3 \text{ mL.kg}^{-1}.\text{min}^{-1}$ and the optimal threshold for age-predicted peak O_2 pulse was $< 85\%$. Age-adjusted Cox regression analysis was used to assess the independent prognostic value of left ventricular ejection fraction (LVEF), HF etiology (ischemic versus non-ischemic), peak VO_2 , peak O_2 pulse and percentage of age-predicted peak O_2 pulse. The Akaike Information Criterion (AIC) method was used to compare the predictive accuracy of the models¹¹. Collinearity was tested between peak VO_2 and peak O_2 pulse. Multivariate Cox regression analysis was used to assess the ability of peak VO_2 and percentage of age-predicted peak O_2 pulse to predict the aforementioned endpoints, with each expressed using the threshold value. Entry and removal p-values were set at 0.05 and 0.10, respectively. The multivariate Cox regression and AIC analyses were repeated after adjustments for LVEF, HF etiology and beta blocker use. Kaplan-Meier analysis was used to assess differences in cardiac-related deaths and events between subjects with normal and abnormal values for peak VO_2 and percentage of age-predicted O_2 pulse.

Results

Clinical characteristics and exercise test responses for the entire sample and peak VO_2 subgroups are shown in Table 1. Age, New York Heart Association functional class and use of diuretics were higher in those with a low peak VO_2 compared to those whose peak VO_2 was high. Among CPX results, RER was the only variable that was not significantly different among peak VO_2 sub-groups. There were 221 major cardiac events (176 deaths, 26 transplantations, and 10 LVAD implantations) over a mean 28 ± 26 months of follow-up. Predictors of cardiac events are shown in Table 2. By univariate analysis, except for HF etiology, all the variables in Table 2 were significant predictors of cardiac mortality and major events.

AIC weights demonstrated that the models including both peak VO_2 and age-predicted peak O_2 pulse had the highest predictive value. The model including both variables had a 55% probability of being the strongest model, compared to 33% and 12% probabilities when only peak VO_2 or only age-predicted peak O_2 pulse were included, respectively. The model including peak VO_2 and age-predicted peak O_2 pulse remained the most powerful after adjustments for beta blocker use and after applying different thresholds for high risk.

Table 3 presents relative risks associated with abnormal peak VO_2 , abnormal age-predicted peak O_2 pulse, and their combination. Patients with abnormalities in both responses had the highest risks for cardiac mortality and major events. Kaplan-Meier analyses for 3-year major cardiac events in patients with normal and abnormal peak VO_2 and age-predicted peak O_2 pulse responses and their combination are illustrated in Figure 1. Subjects with both an

abnormal age-predicted peak O_2 pulse and abnormal peak VO_2 had a 36% higher rate of cardiac events compared to those with normal responses.

Table 4 presents relative risks for major cardiac events associated with normal and abnormal age-predicted peak O_2 pulse responses and the pre-defined low, intermediate and high peak VO_2 groups. Patients in the intermediate peak VO_2 group with a normal age-predicted peak O_2 pulse ($\geq 85\%$) had an event risk that was similar to that among patients whose peak VO_2 was high. However, those in the intermediate peak VO_2 group with an abnormal age-predicted peak O_2 pulse ($<85\%$), had roughly the same event rate and mortality risk as those whose peak VO_2 was $<10 \text{ mL.kg}^{-1}.\text{min}^{-1}$.

Discussion

The current study comprised a typical heterogeneous group of patients with HF, including a mean peak VO_2 of $15 \text{ mL.kg}^{-1}.\text{min}^{-1}$, a mean LVEF of 32% and with 65% of subjects taking beta blockers. While the prognostic value of peak VO_2 and indices of ventilatory inefficiency have become well established, less is known about the additive predictive accuracy of age-predicted peak O_2 pulse. We addressed this issue using a model selection method designed to compare multiple candidate models, and determine which most accurately describes the data (the AIC weight). We observed that adding age-predicted peak O_2 pulse to the model with peak VO_2 provided the highest prediction of risk for mortality and composite cardiac events. It is also noteworthy that the highest risk was generated in the model that included peak VO_2 and age-predicted peak O_2 pulse together (Table 3). When both peak VO_2 and age-predicted peak O_2 pulse responses were abnormal, a greater than 4-fold risk of mortality and 6-fold risk of having an event were observed. The results were not influenced by LVEF, HF etiology or beta blocker use.

Since the landmark study by Mancini et al.¹², peak VO_2 has been considered a key criterion for risk-stratifying candidates for cardiac transplantation. Patients with a markedly reduced peak VO_2 ($<10 \text{ mL.kg}^{-1}.\text{min}^{-1}$) have been considered to be at the highest risk and therefore most likely to benefit from transplantation. However, the small survival differences observed between patients with peak VO_2 values ranging from 10 to $14 \text{ mL.kg}^{-1}.\text{min}^{-1}$ underscores the limitations of peak VO_2 among patients falling into this intermediate range. In the current study, patients in this range who had a low age-predicted peak O_2 pulse ($<85\%$) had a 3-year mortality rate comparable to those whose peak VO_2 was $<10 \text{ mL.kg}^{-1}.\text{min}^{-1}$ (43% vs. 40%, respectively). It is also noteworthy that the remaining 34% of patients in the intermediate peak VO_2 range with a normal age-predicted peak O_2 pulse ($\geq 85\%$), had the same three-year survival (77%) as those whose peak VO_2 was comparatively high ($\geq 14.3 \text{ mL.kg}^{-1}.\text{min}^{-1}$). Moreover, we observed that the relative risk (RR) of mortality among patients in the intermediate peak VO_2 range with a normal age-predicted peak O_2 pulse was not different (RR = 1.18, 95% confidence interval [CI] 0.84 – 2.24, $p = 0.66$) from those generally considered too well for transplantation (peak $VO_2 >14.3 \text{ mL.kg}^{-1}.\text{min}^{-1}$). In contrast, those with an abnormal age-predicted peak O_2 pulse had roughly the same RR as those considered strong candidates for transplantation (peak $VO_2 <10 \text{ mL.kg}^{-1}.\text{min}^{-1}$) (RR = 2.56, 95% CI 1.88 – 4.72, $p < 0.001$). These results were confirmed after adjustments for LVEF, etiology of HF, and beta blocker use.

There are several clinically relevant applications from the current study. Relative to some indices of ventilatory inefficiency (eg. the oxygen uptake efficiency slope [OUES] and oscillatory ventilation^{13–17}), for which more sophisticated calculations are required, peak O₂ pulse is a readily available CPX response that appears to strongly predict risk in HF. Aside from the advantage of having a large and heterogeneous cohort of HF patients, our study was novel in that we assessed the prognostic value of peak O₂ pulse expressed as a percentage of the age-predicted value. This approach has the advantage of considering the influence of body weight on the O₂ pulse response during exercise. In this context, Lavie and colleagues⁶ demonstrated that peak O₂ pulse, corrected for lean body mass, was the strongest independent predictor of event-free survival in patients with HF, performing better than peak VO₂. Although correcting for lean body mass has been recommended on theoretical grounds, CPX variables are conventionally corrected for total weight. Total weight is generally used because of convenience and due to the inherent limitations associated with estimating human body fat; this is particularly the case among older subjects in the extreme ranges of weight often seen in HF patients¹⁸.

O₂ pulse is a reflection of stroke volume and oxygen extraction that normally increases with incremental exercise. O₂ pulse will be reduced in any condition that reduces stroke volume (eg. left ventricular dysfunction secondary to ischemia) or conditions that reduce arterial O₂ content (anemia hypoxemia). Chronic HF presents a myriad of physiological abnormalities, including systolic dysfunction in which contractility is impaired, diastolic dysfunction in which ventricular stiffness impairs filling, a chronically dilated ventricle that limits pump function, or a combination of these. Regardless of the underlying mechanism, a lower peak O₂ pulse will reflect a more impaired cardiac output, largely mediated by a reduced stroke volume response to exercise and, as supported by the findings of the current study, an impaired O₂ pulse response to exercise is a strong predictor of cardiac events in patients with HF.

Our study was retrospective and has limitations inherent with any such study. In addition, the application of the age-predicted peak O₂ pulse cut-point in different HF populations is unknown. Future prospective studies should seek to determine the optimal application of age-predicted peak O₂ pulse in different subgroups of HF. In addition, the role that the age-predicted peak O₂ pulse plays in complementing other well established predictors of risk in HF, such as the VE/VCO₂ slope^{13,17}, OUES¹⁵ and resting and exercise end-tidal carbon dioxide partial pressures (PETCO₂)¹⁹ require further exploration.

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Figure 1.

Kaplan Meier analyses for 3-year major cardiac events with normal and abnormal peak VO_2 and age-predicted peak O_2 pulse responses and their combination. Group **A** - peak VO_2 $14.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ AND age-predicted peak O_2 pulse $\geq 85\%$; Group **B** - peak $\text{VO}_2 < 14.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ OR age-predicted peak O_2 pulse $< 85\%$; Group **C** - peak $\text{VO}_2 < 14.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ AND age-predicted peak O_2 pulse $< 85\%$.

Table 1 Clinical characteristics and exercise responses in overall and peak VO₂ groups

Variable	Overall group (n = 998)	Peak VO ₂ (mL.kg ⁻¹ .min ⁻¹)		
		> 14.3	10.1 – 14.2	< 10
Age (years)	58 ± 14	56 ± 14	59 ± 14 [*]	60 ± 14 [*]
Men	69.5%	80.0%	58.6% [*]	58.4% [*]
Left ventricular ejection fraction (%)	32 ± 14	32.7 ± 13.6	32.4 ± 15.2 [†]	28.5 ± 14.1 [*]
New York Heart Association Class (mean)	2.5 ± 0.7	2.2 ± 0.8	2.6 ± 0.6 ^{*†}	3.0 ± 0.6 [*]
Etiology (%ischemic)	40.5%	42.2%	37.1%	42.3%
Prescribed ACE inhibitor	73.0%	76.3%	68.6% [*]	71.8%
Prescribed diuretic	75.2%	67.4%	81.6% [*]	87.6% [*]
Prescribed beta-blocker	65.5%	65.9%	62.4%	71.1%
Peak VO ₂ (mL.kg ⁻¹ .min ⁻¹)	15.3 ± 5.5	19.4 ± 4.7	12.4 ± 1.2 ^{*†}	8.2 ± 1.3 [*]
Peak O ₂ pulse (mL.beat ⁻¹)	10.3 ± 4.4	12.4 ± 4.7	8.7 ± 2.5 ^{*†}	6.9 ± 2.3 [*]
Peak heart rate (bpm)	126 ± 23	134 ± 20	122 ± 19 ^{*†}	106 ± 21 [*]
Achieved predicted peak O ₂ pulse (%)	83.6 ± 34.6	92.0 ± 33.6	79.8 ± 33.2 ^{*†}	63.4 ± 28.3 [*]
Peak respiratory exchange ratio	1.08 ± 0.13	1.09 ± 0.13	1.07 ± 0.13	1.06 ± 0.14 [*]

^{*} $P < 0.05$ - Intermediate and low peak VO₂ versus high peak VO₂ group.

[†] $P < 0.05$ - Intermediate peak VO₂ versus low peak VO₂ group.

Table 2

Age-adjusted univariate analysis

Variable	Cardiac Mortality HR (95% CI)	P value	Major Events HR (95% CI)	P value
Left ventricular ejection fraction (%)	0.97 (0.95 – 0.98)	<0.001	0.94 (0.93 – 0.96)	<0.001
Etiology (ischemic)	1.29 (0.88 – 1.87)	0.18	1.19 (0.91 – 1.56)	0.21
Peak VO ₂ (mL.kg ⁻¹ .min ⁻¹)	0.91 (0.88 – 0.95)	<0.001	0.88 (0.86 – 0.91)	<0.001
Peak O ₂ pulse (mL.beat ⁻¹)	0.89 (0.84 – 0.94)	<0.001	0.88 (0.84 – 0.92)	<0.001
Achieved predicted peak O ₂ pulse (%) [*]	0.85 (0.78 – 0.91)	<0.001	0.83 (0.78 – 0.88)	<0.001

every 10% increment

Table 3

Relative risks associated with abnormal peak VO_2 and age-predicted peak O_2 pulse and their combination

Variable	Description	Cardiac Mortality HR (95% CI)	P value	Major Events HR (95% CI)	P value
Peak VO_2 14.2 and Predicted Peak O_2 pulse 85 %	All normal	1 (reference)	-	1 (reference)	-
Peak $\text{VO}_2 < 14.2$ or Predicted Peak O_2 pulse < 85 %	1 of 2 abnormal	2.31 (1.26 – 4.23)	0.006	2.91 (1.74 – 4.85)	< 0.001
Peak $\text{VO}_2 < 14.2$ and Predicted Peak O_2 pulse < 85 %	Both abnormal	4.76 (2.68 – 8.46)	< 0.001	6.74 (4.1 – 11.1)	< 0.001

Peak VO_2 is expressed in $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$

Table 4

Relative risks associated with peak VO_2 and age-predicted peak O_2 pulse responses.

Variable	Cardiac Mortality HR (95% CI)	<i>P</i> value	% Survival	Major Events HR (95% CI)	<i>P</i> value	% Event free
Peak VO_2 14.3	1 (reference)	-	77%	1 (reference)	-	85%
Peak $\text{VO}_2 > 10.1 < 14.3$ and Predicted Peak O_2 pulse 85 %	1.18 (0.56 – 2.51)	0.66	77%	1.38 (0.84 – 2.24)	0.19	78%
Peak $\text{VO}_2 > 10.1 < 14.3$ and Predicted Peak O_2 pulse < 85 %	2.56 (1.69 – 3.88)	<0.001	57%	2.82 (2.02 – 3.93)	<0.001	60%
Peak VO_2 10	2.98 (1.88 – 4.72)	<0.001	60%	3.94 (2.77 – 5.60)	<0.001	57%

Peak VO_2 is expressed in $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$