

Submaximal Cardiopulmonary Exercise Testing With Gas Exchange: An Emerging Method of Assessing Hospitalization Risk in Chronic Heart Failure

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An aging population, improved survival following myocardial infarction and an emphasis on prevention of sudden cardiac death have combined to increase heart failure hospitalizations by 174% over the past 30 years and there are now more than one million heart failure hospitalizations in the U.S. annually.¹ Despite improvements in the management of acute heart failure syndrome, post-discharge mortality and rehospitalization rates reach 10% to 20% and 20% to 30%, respectively, within three to six months,² increasing the demand on an already stressed healthcare system. This burgeoning healthcare problem has prompted recent investigation into methods to predict the risk of hospitalization in chronic heart failure.

Cardiopulmonary exercise testing (CPX) provides significant value in heart failure diagnosis, prognosis, and risk assessment. While peak oxygen consumption (pVO_2) is the most widely used variable in research and clinical settings, other variables, such as the relationship between minute ventilation (V_E) and carbon dioxide production (VCO_2) slope and the partial pressure of end-tidal CO_2 ($PetCO_2$), have emerged as providing prognostic information that is equal to, or in many cases better than, pVO_2 .³ Of significance is the observation that these variables are readily obtained using submaximal exercise,^{4,5} while a suboptimal effort may

provide a falsely lower pVO_2 values resulting in inaccurate assessment of clinical status and functional capacity.⁶ Recent studies have investigated the value of these submaximal exercise parameters in predicting hospitalization in the heart failure population.^{5,6,8}

In one study, Arena *et al.*⁸ enrolled 130 consecutive subjects with compensated heart failure who underwent symptom-limited cardiopulmonary exercise testing and were followed for cardiac-related mortality and hospitalization for one year. Cardiac related hospitalization was defined as a hospital admission directly related to cardiac dysfunction requiring in-patient care. There were eight cardiac related deaths and 44 hospitalizations over the one year tracking period.

Multivariate regression determined the ventilatory efficiency slope (V_E/VCO_2) was the strongest predictor of one-year cardiac-related events, with $PetCO_2$ at the anaerobic threshold (AT) and pVO_2 adding significant predictive value. Left ventricular ejection fraction (LVEF), NYHA class and heart failure etiology did not add additional value, and were removed from the regression. Optimal cut-off values for poorer prognosis were determined to be: V_E/VCO_2 slope, ≥ 34.4 ; $PetCO_2$ at AT, ≤ 36.1 mmHg; change in $PetCO_2$ from rest to AT, ≤ 1.8 mmHg; and pVO_2 , ≤ 14.2 mlO₂/kg/min. Kaplan-Meier analysis revealed results as shown in Table 1.

Table 1: Kaplan-Meier Analysis of Event Free Survival Characteristics at Threshold Values

Group	Characteristics	Subjects Meeting Criteria	Events	Percent Event Free
A	All three CPX variables normal	38	2	94.7
B	Two CPX variables normal	29	8	72.4
C	One CPX variable normal	28	13	53.6
D	All three CPX variables abnormal	35	29	17.1

From Arena, *et al.*⁸

These results confirmed an earlier study⁶ where it was determined that V_E/VCO_2 slope, $PetCO_2$ and pVO_2 were all predictive of 1-year cardiac related hospitalization, but V_E/VCO_2 provided the strongest

analysis, and NYHA class added prognostic value to V_E/VCO_2 and $PetCO_2$ in the multivariate analysis. Threshold values for resting $PetCO_2$ and V_E/VCO_2 slope are shown in Table 2.

Table 2: Kaplan-Meier Analysis for One-Year Cardiac-Related Events

Group	Characteristics	Subjects Meeting Criteria	Events	Percent Event Free
A	Resting $PetCO_2 > 33.0$ mmHg and V_E/VCO_2 slope < 34.4	48	4*	91.7%
B	Resting $PetCO_2 = 33.0$ mmHg or V_E/VCO_2 slope ≥ 34.4	33	15**	54.5%
C	Resting $PetCO_2 \leq 33.0$ mmHg and V_E/VCO_2 slope ≥ 34.4	40	31***	22.5%

*0 cardiac-related deaths, 4 hospitalizations; **2 cardiac-related deaths, 13 hospitalizations;

***7 cardiac-related deaths, 24 hospitalizations. From: Arena, et al.⁵

predictive value, followed by $PetCO_2$. Peak VO_2 was less predictive, in part because an exercise effort failing to reach maximal effort results in a falsely lower pVO_2 that could negatively impact patient assessment.

A separate study by the same investigators⁵ revealed that in 121 heart failure patients (age 49.3 ± 14.7 years; LVEF $28.4\% \pm 13.4\%$) V_E/VCO_2 and resting $PetCO_2$ emerged from multivariate analysis as predictive of cardiac-related events, including hospitalization, in the one year following CPX testing. Peak VO_2 , LVEF, body mass index, and β -blockade use were not significant predictors of outcome in the univariate Cox regression

The prognostic value of the ventilatory efficiency slope and $PetCO_2$ has been well elucidated in heart failure.^{7,8} The ability to use these parameters to effectively identify those patients at high risk for hospitalization may provide a basis for aggressive, appropriate interventions in an outpatient or patient management setting thereby reducing hospitalizations and helping to control healthcare costs. The combined results of the presented studies provide sufficient evidence to warrant further investigation in a hospital setting.

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