Cardiopulmonary Exercise Testing as a Diagnostic Tool for the Detection of Left-sided Pulmonary Hypertension in Heart Failure

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ABSTRACT

Background: Recently, it has become increasingly recognized that pulmonary hypertension (PH) is a particularly ominous consequence of left-sided heart failure (HF). The primary aim of this investigation was to assess the ability of key cardiopulmonary exercise testing (CPX) variables to detect elevated pulmonary pressures in a HF cohort.

Methods: This was a retrospective analysis of a prospectively collected database. Two hundred ninety-three subjects with HF (63 ± 10 years old, 79% male) underwent Doppler echocardiography to estimate resting pulmonary artery systolic pressure (PASP). Peak oxygen consumption (VO_2), the minute ventilation/carbon dioxide production (VE/VCO_2) slope, peak partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) and exercise oscillatory ventilation (EOV) were determined.

Results: Forty-six percent (n = 134) of the subjects presented with a PASP ≥40 mm Hg. A VE/VCO_2 slope </≥36.0 was the best predictor of a PASP ≥40 mm Hg (odds ratio [OR] 12.1, 95% confidence interval [CI] 6.8−21.4; $P < .001$). Peak $P_{ET}CO_2$ ≤34 mm Hg (OR 3.8, 95% CI 1.3−11.2; $P < .001$) and the presence of EOV (OR 3.2, 95% CI 1.8−5.8; $P < .001$) added significant diagnostic value.

Conclusions: Although CPX is an established prognostic assessment in the HF population, the results of the present investigation indicate that it may also have important diagnostic utility for PH. (*J Cardiac Fail 2013;19:461−467*)

Key Words: Ventilatory efficacy, pulmonary hemodynamics, diagnosis.

Despite advances in the clinical management of patients diagnosed with left-sided heart failure (HF), an overall poor prognosis for this chronic disease population persists. There are a number of pathophysiologic consequences stemming from HF which contribute to an often disconcerting prognostic outlook. In recent years, it has become increasingly recognized that secondary pulmonary hypertension (PH), resulting from left ventricular dysfunction, is a particularly ominous consequence of HF.[1−3] In this context, it would be important to identify cost-effective strategies that accurately detect elevated pulmonary pressures, prompting appropriate subsequent examination strategies, if necessary, and effectively gauge therapeutic efficacy.

Cardiopulmonary exercise testing (CPX) is a well established assessment in the HF population.[4] Most often, CPX is used to assess prognosis in HF patients being considered for heart transplantation as well as to provide an additional gauge of disease severity. The ability of ventilatory expired gas to reflect ventilation-perfusion abnormalities in the pulmonary system also creates the potential for CPX to be used as a diagnostic tool in patients with HF, specifically to identify those with PH. There is a growing body of literature that CPX effectively diagnoses elevated pulmonary pressures, prompting consideration of additional evaluation strategies to accurately identify the mechanism (ie, left-sided PH vs pulmonary arterial hypertension).[5−7] As such, CPX may have an added, currently underappreciated, value in the HF population, providing insight regarding pulmonary pressures that can be used to guide additional testing and therapies, especially as clinical research in this field evolves.[8,9]

Given the emerging importance of detecting PH in patients with HF and the already established role of CPX in this patient population, examination of this exertional assessment's ability to unmask elevated pulmonary pressure

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See page 466 for disclosure information.

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appears to be an important research endeavor. Therefore, the primary aim of the present investigation was to assess the ability of key CPX variables to diagnose elevated pulmonary pressure in an HF cohort. Given the established physiologic link between ventilatory gas exchange and ventilation-perfusion matching, we hypothesized that the ability of CPX to detect PH would be significant and thus demonstrate clinical utility.

Methods

Subjects

This was a retrospective analysis of a prospectively collected database. Two hundred ninety-three subjects (age 63 ± 10 years, 79% male) diagnosed with HF (left ventricular ejection fraction 36.0 ± 11.0%, 61% with ischemic etiology) were included in this analysis. Data from these subjects has been used in previous publications not pertaining to the present analysis.[10,11] All assessments were clinically indicated and performed as part of a comprehensive clinical HF examination. Echocardiography and tissue Doppler imaging (TDI) and exercise testing assessments were conducted within 48 hours of one another. All subjects were stable, in compensated HF, at the time of data collection, which was conducted on an outpatient basis. Inclusion criteria consisted of an earlier diagnosis of HF with evidence of left ventricular dysfunction confirmed by echocardiography. Each of the subjects signed written informed consent to have their clinical data used for research purposes and local Institutional Review Board approval was obtained for this analysis.

Echocardiography and TDI

An experienced echocardiographer performed the echocardiographic analysis by transthoracic echocardiography with the use of an IE33 Philips ultrasound unit (Andover, Maryland), equipped with software for TDI, using a 2.5−5.0-MHz probe (S5). Standard M-mode 2-dimensional Doppler blood flow measurements were performed according to the current American Society of Echocardiography Guidelines.[12]

Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography from the systolic right ventricular to right atrial pressure gradient with the use of the modified Bernoulli equation. Right atrial pressure (clinically assessed jugular venous pressure) was added to the calculated gradient to yield PASP. No subjects had significant right ventricular outflow tract obstruction.

CPX Procedures

Patients underwent an upright graded exercise test with the use of an electromagnetically braked cycle ergometer (Carnival 906900; Lode, The Netherlands). The workload was adjusted in a ramping fashion with the goal of achieving maximal effort within 8−10 minutes. The test protocol began with 2 minutes of unloaded cycling at 60 rpm, followed by a progressively increasing workload. Heart rate was continuously monitored by electrocardiography at rest and during exercise. Blood pressure was measured every 2 minutes and at peak exercise with a mercury sphygmomanometer. Respiratory gas analysis was carried out with a metabolic cart (Sensormedics Vmax29; Yorba Linda, California), which was calibrated with standard gases of known concentrations before each test. The pharmacologic regimen was maintained for all subjects during CPX.

Minute ventilation (VE, body temperature, atmospheric pressure saturated with water vapor), oxygen uptake (VO_2, standard temperature and pressure dry), and carbon dioxide output (VCO_2, standard temperature and pressure dry) were acquired breath by breath, averaged over 30 seconds, and printed in rolling averages every 10 seconds. Peak VO_2 and the peak respiratory exchange ratio (RER) were defined as the highest 30-second averaged value obtained during exercise. The partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was also obtained as a 30-second averaged value at peak exercise. Ten-second averaged VE and VCO_2 data, from the initiation of exercise to peak, were entered into spreadsheet software (Microsoft Excel; Bellevue, Washington) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$; m = slope). Evidence from different groups has convincingly shown this method of calculating the VE/VCO_2 slope provides optimal information on clinical status and disease severity.[13,14] The occurrence of exercise oscillatory ventilation (EOV) was defined as an oscillatory pattern at rest that persisted for ≥60% of the exercise test at an amplitude ≥15% of the average resting value.[15]

Test termination criteria consisted of patient request, ventricular tachycardia, ≥2.0 mm of horizontal or downsloping ST-segment depression, or a drop in systolic blood pressure ≥20 mm Hg during progressive exercise. A qualified exercise physiologist with physician supervision conducted each exercise test.

Statistical Analysis

A statistical software package (SPSS 19.0; Chicago, Illinois) was used to perform all of the analyses. Continuous and categoric data are reported as mean ± SD and as percentages, respectively. One-way analysis of variance (ANOVA) was used to compare key continuous variables between subgroups according to PASP quartiles. Chi-square testing was used to compare dichotomous data. ANOVA was also used to compare PASP values according to the 4-level Ventilatory[16] and Weber[17] classification systems. Tukey honestly significant difference was used to determine differences in subgroups when the 1-way ANOVA P value was $<.05$. Unpaired t testing was used to compare PASP according to the absence or presence of EOV and peak $P_{ET}CO_2$ ≤/>34 mm Hg. Receiver operating characteristic (ROC) curve analysis was used to assess the ability of the 4-level Ventilatory[16] and Weber[17] classification systems as well as the absence versus presence of EOV to identify subjects with a PASP ≥40 mm Hg, as well as PASP thresholds of ≥50 and ≥60 mm Hg. ROC curve analysis was also used to assess the ability of peak $P_{ET}CO_2$ to identify the aforementioned PASP thresholds and define the optimal dichotomous peak $P_{ET}CO_2$ threshold that identified subjects with a PASP ≥40 mm Hg with optimal sensitivity and specificity. Binary logistic regression assessed the univariate and multivariate (entry and removal thresholds .05 and .10, respectively) value of Ventilatory class I/II versus III/IV, Weber class A/B versus C/D, absence versus presence of EOV and peak $P_{ET}CO_2$ ≤/>34 mm Hg to identify subjects with a PASP ≥40 mm Hg. An a priori sample size was not calculated for this study. A P value of $<.05$ was considered to be statistically significant for all tests.

Results

Characteristics of key baseline and CPX variables according to PASP quartiles are listed in Table 1. In general, subjects with a higher PASP were older, had a higher New