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Peak Cardiac Power Output, Measured Noninvasively, Is a Powerful Predictor of Outcome in Chronic Heart Failure

Chim C. Lang, MD; Paula Karlin, BS; Jennifer Haythe, MD; Tiong K. Lim, MD; Donna M. Mancini, MD

Background—The cardiac output (CO) response to exercise and other invasively derived hemodynamic variables has been variably described to provide better prognostication than peak VO₂ in patients with chronic heart failure. Using noninvasive measurements of CO during exercise, we compared the prognostic value of peak CO and cardiac power to peak VO₂ in chronic heart failure patients.

Method and Results—One hundred seventy-one consecutive patients with chronic heart failure underwent symptom limited bicycle exercise with noninvasive estimation of CO using an inert gas rebreathing method. An accurate measure of peak CO was obtained in 148 patients (85% of patients; mean age, 53 ± 14 years; 80% male; left ventricular ejection fraction, 24 ± 12%; ischemic etiology, 34%). Peak cardiac power was derived from the product of the peak mean arterial blood pressure and CO divided by 451. End points consisted of death, urgent heart transplant, or left ventricular assist device implantation. Duration of follow-up averaged 337 ± 252 days (median, 295 days). Univariate and multivariate analysis were performed. The variables analyzed included peak VO₂, peak CO, peak cardiac power, VE/VCO₂ slope, and VO₂ at anaerobic threshold. Event-free survival for the entire cohort was 83% with 5 deaths, 4 left ventricular assist device implants, and 16 urgent transplants. Peak VO₂ was 12.9 ± 4.5 mL/kg per min, and peak cardiac power was 1.7 ± 0.9 W. Peak VO₂, peak CO, peak cardiac power, VE/VCO₂ slope, and VO₂ at anaerobic threshold were predictive of outcome on univariate analysis. On multivariate analysis, peak cardiac power and peak CO were predictive of outcome with peak cardiac power being the most powerful independent predictor of outcome (P = 0.01).

Conclusions—Peak cardiac power, measured noninvasively, is an independent predictor of outcome that can enhance the prognostic power of peak VO₂ in the evaluation of patients with heart failure. (Circ Heart Fail. 2009;2:33-38.)

Key Words: chronic heart failure ■ cardiac transplantation ■ peak VO₂ ■ cardiac output ■ exercise

Peak VO₂ has been shown to be an objective measure of functional capacity and a powerful independent prognostic index.¹,² Consequently, it has become a major criterion of selection for heart transplantation.³ It is hypothesized that peak VO₂ is an important prognostic factor as it provides an indirect measure for cardiac output (CO) as peak VO₂ is derived from the product of CO and arteriovenous difference in oxygen content (C(a–v) O₂) and thus an index of cardiac reserve of the chronic heart failure (CHF) patient.¹,⁴ However, peak VO₂ itself is also dependent on factors other than CO, such as muscle deconditioning, motivation, obesity, the age, and gender.⁵,⁶ These confounding factors may explain why some patients with CHF may have a favorable prognosis despite a low peak VO₂.⁷,⁸ Several previous studies have shown that invasive determination of the CO response to exercise via the thermodilution method in addition to the measurement of peak VO₂ enhances its discriminatory power.⁹,¹⁰ However, there are numerous concerns regarding invasively derived hemodynamic measurements during exercise including the complexity of the testing, bleeding, pneumothorax, arrhythmias, infection, and catheter dislodgement. In recent years, a number of noninvasive methods to measure CO have been described. Inert gas rebreathing is a novel noninvasive method to measure CO during exercise, which is a reliable, safe, and easily performed in patients with CHF.¹⁰,¹¹ The purpose of this study was to investigate whether noninvasive measurement of CO using the inert gas rebreathing method at peak exercise more accurately identifies patients who require listing for cardiac transplantation than peak VO₂.

Methods

Patients
One hundred seventy-one patients with stable CHF secondary to left ventricular dysfunction attending the CHF clinic at Columbia Presbyterian Medical Center underwent clinical assessment of their condition by cardiopulmonary exercise testing. Patients were excluded if they were unable to perform a familiarization test or if they...
had reduced exercise tolerance attributable to myocardial ischemia or noncardiac factors. All patients provided written informed consent to the participation of this study, which was approved by the local ethics committee. The authors of this manuscript 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.

**Cardiopulmonary Exercise Testing**

The method has previously been reported. In brief, patients were instructed on the breathing technique and performed at least 1 practice measurement before each test. The Innocor rebreathing system (Copenhagen, Denmark) uses an oxygen enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) from a 4-L prefilled anesthesia bag. Photo-acoustic analyzers measure gas concentrations over a 5-breath interval. Use of sulfur hexafluoride allowed us to measure the volume of the lungs, valve, and rebreathing bag. Nitrous oxide concentration decreases during the rebreathing maneuver, with a rate proportional to pulmonary blood flow. Three to four respiratory cycles were needed to obtain nitrous oxide washout. Absence of pulmonary shunt was defined as arterial oxygen saturation >98% by pulse oximetry. Patients performed a graded maximal bicycle exercise test using a mouthpiece connected to the Innocor breathing system. After 3 minutes of rest data, exercise began at a workload of 0 W and increased every 3 minutes by 25 W until symptom limited maximum. During exercise, tidal volume was progressively increased in the closed circuit to match the physiological increase. Patients were instructed to signal a 1-minute before peak exercise. Expired gas analysis was performed continuously throughout the test with the Innocor system. Metabolic measurements were made before and after rebreathing. CO measurements were made at the end of the rest period, at 25 W and at peak exercise. VO2, VCO2, and VE were measured on a breath-by-breath basis. Peak VO2 was defined as the highest value of VO2 achieved in the final 30 s of exercise VO2 at the anaerobic threshold was identified as the nadir of the ventilatory equivalent for VO2. The VE/VCO2 slope was calculated by linear regression fitting of the breath-by-breath values obtained below the anaerobic threshold. Mean arterial pressure was calculated from the standard equation, mean arterial pressure= (systolic pressure +2 x diastolic pressure)/3. Peak cardiac power was derived from the product of the peak mean arterial blood pressure and CO divided by 451. A peak pulmonary capillary wedge pressure of 25 mm Hg was imputed based on the median from prior invasive hemodynamic testing. Follow-up averaged 337±252 days (median, 295 days) and the end points consisted of death, urgent heart transplant, or left ventricular assisted device (LVAD) implantation.

**Statistical Analysis**

Categorical data are presented as numbers (percentages) and were compared using the χ2 test. Continuous data are presented as means±SD and compared using the Student t test. Differences in cardiopulmonary exercise variables among New York Heart Association (NYHA) functional classes were tested using 1-factorial ANOVA and the t test–based contrast statistics. The effects of known cardiopulmonary exercise testing variables on the outcome were examined using Cox proportional hazards regression analysis. The analysis of the data were performed in two stages. Initially the individual effects of cardiopulmonary exercise testing variables (peak VO2, peak CO, VO2 at anaerobic threshold, VE/VCO2, and peak cardiac power) were examined separately in a series of univariate analyses. Subsequently, the joint effect of the explanatory variables on the time to event was examined in a multivariable analysis. A forward stepwise selection procedure was used to retain only the statistically significant variables. As peak cardiac power was derived from the product of the peak mean arterial blood pressure and CO divided by 451, there is thus a strong correlation (coefficient=0.95, P<0.001) between peak cardiac power and peak CO. This is known as collinearity, and further check on collinearity diagnostics has confirmed this. Therefore, peak cardiac power and peak CO were entered separately into the multivariable model. The best cutoff for peak cardiac power to predict outcome was derived from the receiver operating curve. Survival was analyzed using Kaplan–Meier cumulative survival curves and compared using the log-rank test. A probability value ≤0.05 was considered significant. All analyses were done using SPSS version 12.

**Results**

Because of technical difficulties, CO was not obtained in 23 patients (13%). Most measurement failures resulted from too short an interval between rebreathing test measurements. The clinical characteristics of the study population with available CO measurements are shown in Table 1. Mean age (±SD) was 53±14 years; with 119 male patients (80%). Thirty-four percent of patients had CHF of ischemic etiology. Most patients were on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (88%) and β-blockers (91%). Peak VO2 was 12.9±4.5 mL/kg per min, peak CO was 7.3±2.9 L/min, VO2 at the anaerobic threshold was 8.7 mL/kg per min, and peak cardiac power was 1.7±0.9 W with a median of 1.5 W (Table 1). Differences between the cardiopulmonary exercise variables among different NYHA classes are shown in Table 2. This was significant for trend for all cardiopulmonary exercise variables (P<0.0001).

**Events**

Follow-up averaged 337±252 days (median, 295 days). There were a total of 25 events (5 deaths, 4 LVADs, and 16 urgent transplants). There were 3 elective cardiac transplants.
which were treated as censored observations. In patients with severe heart failure NYHA class 4, 5 of 23 required urgent heart transplantation and one required LVAD implantation. None of these patients died during follow-up. On the other hand, 4 died, 10 required urgent heart transplantation, and 3 underwent LVAD implantation in patients with NYHA class 3. However, the cumulative event free survival for the whole study population was 83% (Figure 1).

**Univariate and Multivariable Predictors of Outcome**

Univariate analysis demonstrated that, peak VO2, peak CO, peak cardiac power, VO2 at anaerobic threshold, and VE/VCO2 slope were significant predictors with their area under receiver operating curves (adjusted for age, sex, and body mass index) for the detection of outcome were 0.71, 0.71, 0.78, 0.71, and 0.75, respectively (Table 3). Multivariable analysis demonstrated that both peak CO and peak cardiac power were significant predictors of outcome after adjustment for age, gender, left ventricular ejection fraction (LVEF), NYHA class, heart rate, mean blood pressure, β-blocker, and angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment in this population (Table 4). Furthermore, multivariable Cox regression analysis after only including patients with peak VO2 <14 mL/kg per min demonstrates that CO is not a predictor whereas peak cardiac power still remains as a significant powerful predictor of outcome (Table 4). A receiver operating curve analysis revealed that a peak cardiac power value of 1.5 W provides the most discriminatory cutoff (Figure 2). The Kaplan–Meier survival curves for peak cardiac power greater and less than 1.5 W are shown in Figure 3. Event free survival was 94% versus 69% (P<0.0001) in those with and without a cardiac power of >1.5 W, respectively over a mean follow period of nearly 1 year.

**Discussion**

The key findings of this study was noninvasively measured peak CO and its derived parameters including peak cardiac power were better prognostic indicators than peak VO2 in a group of consecutive, ambulatory CHF patients.

These findings support the findings of previous studies that have used invasive techniques to derive cardiac work related performance to enhance the discriminatory power of peak VO2 measurement. Griffin et al were first to demonstrate that stroke work index at peak exercise dichotomized at 20 gm/m2 identified patients with a 3- to 5-fold higher mortality. Exercise duration and peak VO2 was not able to discriminate survivors from nonsurvivors. This was followed by the study of Roul et al who showed that hemodynamic data measured at rest were weak predictors but cardiac power output and stroke work index measured at peak exercise were very strong predictors. Chomsky et al in 185 patients with CHF found that the CO response to exercise was the most powerful predictor of survival in this study population according to both univariate and multivariate analyses. Several other investigators demonstrated that left ventricular stroke work and stroke work index were most predictive of survival. However, it remained unclear whether the risk of the catheter placement particularly for serial assessment was acceptable given that the data obtained only minimally and indirectly improved risk prognostication.

In 2001, Williams et al using noninvasive measurement of CO by CO2 rebreathing integrated with a standard exercise test showed that peak cardiac power was a stronger predictor than peak VO2. Patients with reduced VO2 (ie, peak <14 mL/min per kg) but with a peak cardiac power higher than the identified critical value of 1.96 W had an excellent prognosis with an 89% 4-year survival rate. However, it should be emphasized that Williams et al used the CO2 rebreathing method, which has a number of potential problems in the setting of exercise testing in patients with CHF. First, the CO2 rebreathing method, unlike the inert gas rebreathing method, requires 2 exercise tests. Second, at the required exercise situation (ie, above anaerobic threshold), lactic acidosis supervenes that will result in a buffering of H+ with the release of CO2 from HCO3-. Acidosis, therefore, has the effect of reducing the total CO2 concentration at a given Paco2 and the failure to take the pH into consideration could

| Table 2. The Cardiopulmonary Variables of Patients With Different NYHA Class |
|-------------------------------------------------|---------|---------|---------|---------|---------|
| Exercise Cardiopulmonary Variables | NYHA Class 1 (n=12) | NYHA Class 2 (n=38) | NYHA Class 3 (n=73) | NYHA Class 4 (n=23) |
| Peak VO2, mL/kg min | 21.4±6.3 | 15.7±3.1 | 11.6±2.1 | 8.1±1.9 |
| Peak cardiac output, L/min | 10.2±2.8 | 9.4±2.7 | 6.7±2.2 | 4.6±1.5 |
| VE/VCO2 slope | 25.5±8.5 | 30.9±7.7 | 34.2±9.7 | 45.4±15.8 |
| Peak cardiac power, Watt | 2.6±0.7 | 2.5±0.9 | 1.5±0.6 | 0.9±0.4 |
| VO2 at anaerobic threshold, mL/kg per min | 14.4±3.5 | 10.0±2.2 | 7.9±1.5 | 5.9±1.4 |

*Figure 1. Cumulative event free survival curve.*
from the product of peak VO2 and mean arterial pressure as an alternative to peak cardiac power, and have reported that it is an important prognostic indicator in patients with CHF than peak VO2. However, as mentioned earlier, peak VO2 may be influenced by factors other than CO such as muscle deconditioning and obesity. Therefore, a more reliable noninvasive measure of CO is required. Inert gas rebreathing with continuous analysis of respired gases has recently been shown to be a reliable, safe, and validated method for noninvasive measurements of CO including patients with CHF. In this study, we have demonstrated for the first time that peak CO and its derived variables determined by this simple and reliable inert gas rebreathing method may enhance the prognostic value of peak VO2 measurement. Thus, the potential indication of this noninvasive tool is to discriminate between patients whose main cause of exercise limitation and low peak VO2 is a poor CO response to exercise and those who are limited by peripheral factors, such as skeletal muscle deconditioning. This tool may therefore be useful in patients with a potential indication to heart transplantation and LVAD implantation and more generally, in patients with advanced chronic HF.

In this study, cardiac power output was found to be the best prognostic indicator. By incorporating both the pressure and flow domains of the cardiovascular system, cardiac power is an integrated measure of the cardiac hydraulic pumping capacity and it has been argued that it provides a comprehensive indicator of cardiac function. Cardiac power has been shown to be a powerful predictor of mortality in patients with acute cardiac diseases including cardiogenic shock.

It should be noted that submaximal measures such as O2 kinetics and ventilatory efficiency, which are not influenced by mechanical work, have been evaluated as prognostic markers. CO and derived variables may also potentially have prognostic value at submaximal exercise loads below the anaerobic threshold. In this study, we found VE/VCO2 slope to be a better predictor of outcome than peak VO2. VE/VCO2 slope >34 had been reported to be a more accurate prognostic index than peak VO2. Indeed, Arena et al have recently proposed that ventilatory data be used to guide therapy in patients with CHF. However, there is some concern regarding this strategy. In this regard, the group at Cleveland Clinic had prospectively analyzed data on 2015 patients, and found that the VE/VCO2 slope was not predictive of survival in patients with CHF.

**Limitations**

It should be emphasized that there are a number of limitations with our study. First, our group of patients is somewhat mixed and included patients with mild symptoms and slight impairment of the LVEF. Arguably, these patients do not represent a problem for prognostic stratification. A study limited to a higher risk group might have been more interesting as it would have been important in this group to discriminate whether the low peak VO2 is caused by inadequate cardiac output response to exercise or to physical deconditioning. A second limitation of this study was that there were only a few deaths in this cohort of optimally treated patients with CHF. Third, this was a single center study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>P for Hazard Ratio</th>
<th>Area Under ROC Curve* (95% CI)</th>
<th>P for Area Under ROC Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2, mL/kg per min</td>
<td>0.86 (0.77 to 0.97)</td>
<td>0.01</td>
<td>0.71 (0.60,0.82)</td>
<td>0.001</td>
</tr>
<tr>
<td>VO2 at AT, mL/kg per min</td>
<td>0.75 (0.60 to 0.94)</td>
<td>0.01</td>
<td>0.71 (0.59 to 0.82)</td>
<td>0.002</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>1.05 (1.02 to 1.08)</td>
<td>0.001</td>
<td>0.75 (0.65 to 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak CO, L/min</td>
<td>0.77 (0.64 to 0.93)</td>
<td>0.006</td>
<td>0.71 (0.60 to 0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak cardiac power, Watt</td>
<td>0.26 (0.13 to 0.55)</td>
<td>&lt;0.001</td>
<td>0.78 (0.67 to 0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AT indicates anaerobic threshold.

**Table 4. Multivariable Predictors of Outcome**

| Variables Entered into the Multivariable Cox Regression Model | All Patients (n=148) | | | | Patients With Peak VO2 <14 mL/kg per Min (n=97) | | | |
|--------------------------------------------------------------|----------------------|---|---|---|----------------------|---|---|
| | Independent Predictors | Hazard Ratio (CI) | P | Independent Predictors | Hazard Ratio (CI) | P |
| Peak CO, VE/VCO2, peak VO2 | Peak CO | 0.79* (0.63 to 0.99) | 0.04 | Nil | Nil | Nil |
| Peak cardiac power to VE/VCO2, Peak VO2 at AT | Peak cardiac power | 0.35* (0.15 to 0.82) | 0.01 | Peak cardiac power | 0.26* (0.08 to 0.84) | 0.03 |

AT indicates anaerobic threshold; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

After adjusted for age to gender to LVEF to NYHA to heart rate to mean blood pressure to p-blocker and angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment.
been adjusted for age, sex and body mass index. Cardiac power for the detection of outcome. ROC curve has determined a cutoff of 1.5 W.

Figure 3. Kaplan–Meier survival curve in patients with peak cardiac power using a cutoff of 1.5 W.

Figure 2. Receiver operating characteristic (ROC) curve of peak cardiac power for the detection of outcome. ROC curve has been adjusted for age, sex and body mass index.

study. Fourth, 13% of patients peak cardiac output measurements could not be made for technical reasons. Other newer noninvasive methods of measuring cardiac output may be more reliable.

Clinical Implications Do these findings call for the implementation of peak CO and cardiac power determination in the selection of heart transplant candidates? Clearly, the widespread clinical application of noninvasive determination peak CO and peak cardiac power in the evaluation of patients with CHF remains to be determined by a larger multicenter study with a longer follow-up of clinical events to fully determine its prognostic value. These parameters will also need to be compared with other predictive tools such as the Heart Failure Survival Score and Seattle Heart Failure Model.25,26

Disclosures

None.

References

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