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

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Background—The cardiac output (CO) response to exercise and other invasively derived hemodynamic variables has been variably described to provide better prognostication than peak VO_2 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 VO_2 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, $24 \pm 12\%$; 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 VO_2 , peak CO, peak cardiac power, VE/VCO_2 slope, and VO_2 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 VO_2 was 12.9 ± 4.5 mL/kg per min, and peak cardiac power was 1.7 ± 0.9 W. Peak VO_2 , peak CO, peak cardiac power, VE/VCO_2 slope, and VO_2 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 VO_2 in the evaluation of patients with heart failure. (*Circ Heart Fail.* 2009;2:33-38.)

Key Words: chronic heart failure ■ cardiac transplantation ■ peak VO_2 ■ cardiac output ■ exercise

Peak VO_2 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 VO_2 is an important prognostic factor as it provides an indirect measure for cardiac output (CO) as peak VO_2 is derived from the product of CO and arteriovenous difference in oxygen content ($C(a-v) \text{O}_2$) and thus an index of cardiac reserve of the chronic heart failure (CHF) patient.^{1,4} However, peak VO_2 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 VO_2 .^{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 VO_2 enhances its discriminatory power.^{8,9} 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 VO_2 .

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

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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.¹¹ 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 ≈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. $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ were measured on a breath-by-breath basis. Peak $\dot{V}O_2$ was defined as the highest value of $\dot{V}O_2$ achieved in the final 30 s of exercise. $\dot{V}O_2$ at the anaerobic threshold was identified as the nadir of the ventilatory equivalent for $\dot{V}O_2$. The $\dot{V}E/\dot{V}CO_2$ 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×diastolic pressure)/3. Peak cardiac power was derived from the product of the peak mean arterial blood pressure and CO divided by 451.¹² A peak pulmonary capillary wedge pressure of 25 mm Hg was imputed based on the median from prior invasive hemodynamic testing.¹³ 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 χ^2 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 $\dot{V}O_2$, peak CO, $\dot{V}O_2$ at anaerobic threshold, $\dot{V}E/\dot{V}CO_2$, and peak cardiac power) were examined separately in a series of univariate analysis. 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

Table 1. Patient Characteristics and Exercise Cardiopulmonary Variables

Patients Characteristics	
n	148
Age, y	53±14
Sex (male), %	119 (80)
Body mass index (BMI), kg/m ²	28±5
Resting mean BP, mm Hg	88±13
Resting heart rate, beats min ⁻¹	76±13
Ischemic cardiomyopathy, n (%)	51 (34)
LVEF, %	24±12
NYHA class, n (%)	
1	12 (8)
2	38 (27)
3	73 (49)
4	23 (16)
Medications	
Diuretic, n (%)	124 (90)
β-blocker, n (%)	127 (91)
ACE inhibitor, n (%)	101 (73)
A2 blocker, n (%)	23 (17)
Exercise cardiopulmonary variables	
Peak $\dot{V}O_2$, mL/kg per min	12.9±4.5
Peak cardiac output, L/min	7.3±2.9
$\dot{V}E/\dot{V}CO_2$ slope	34.4±11.4
Peak cardiac power, Watt	1.7±0.9
$\dot{V}O_2$ at anaerobic threshold, mL/kg per min	8.7±2.9

operating curve.¹⁴ 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 $\dot{V}O_2$ was 12.9±4.5 mL/kg per min, peak CO was 7.3±2.9 L/min, $\dot{V}O_2$ at the anaerobic threshold was 8.7 mL/kg per min, and mean 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,

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)	P by ANOVA
Peak VO_2 , mL/kg min	21.4±6.3	15.7±3.1	11.6±2.1	8.1±1.9	<0.0001
Peak cardiac output, L/min	10.2±2.8	9.4±2.7	6.7±2.2	4.6±1.5	<0.0001
VE/ CO_2 slope	25.5±8.5	30.9±7.7	34.3±9.7	45.4±15.8	<0.0001
Peak cardiac power, Watt	2.6±0.7	2.5±0.9	1.5±0.6	0.9±0.4	<0.0001
VO_2 at anaerobic threshold, mL/kg per min	14.4±3.5	10.0±2.2	7.9±1.5	5.9±1.4	<0.0001

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 VO_2 , peak CO, peak cardiac power, VO_2 at anaerobic threshold, and VE/ CO_2 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). Multivariate 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 $\text{VO}_2 < 14$ 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

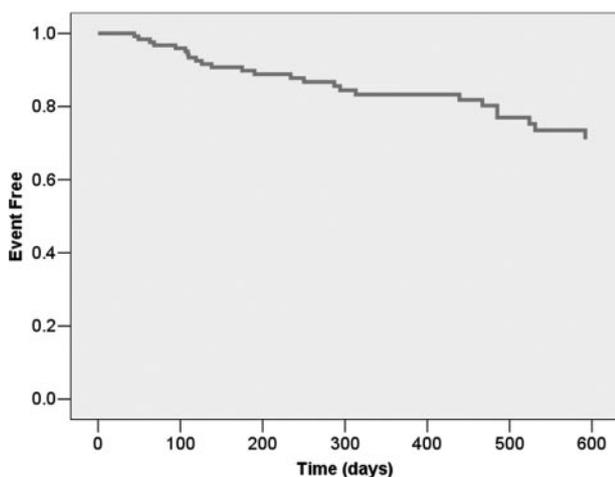
**Figure 1.** Cumulative event free survival curve.

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 VO_2 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 VO_2 measurement.^{8,9,12} Griffin et al¹⁵ 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 VO_2 was not able to discriminate survivors from nonsurvivors. This was followed by the study of Roul et al¹⁶ 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 al⁸ 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.¹² 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 al¹⁷ using noninvasive measurement of CO by CO_2 rebreathing integrated with a standard exercise test showed that peak cardiac power was a stronger predictor than peak VO_2 . Patients with reduced VO_2 (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 al¹⁷ used the CO_2 rebreathing method, which has a number of potential problems in the setting of exercise testing in patients with CHF.¹² First, the CO_2 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 CO_2 from HCO_3^- . Acidosis, therefore, has the effect of reducing the total CO_2 concentration at a given Paco_2 and the failure to take the pH into consideration could

Table 3. Univariate Predictors and Area Under the Receiver Operator Characteristic Curves (ROCs) of the Cardiopulmonary Exercise Variables for the Detection of Outcome

Cardiopulmonary Exercise Variables	Hazard Ratio (95% CI)	P for Hazard Ratio	Area Under ROC Curve* (95% CI)	P for Area Under ROC Curve
Peak VO_2 , mL/kg per min	0.86 (0.77 to 0.97)	0.01	0.71 (0.60,0.82)	0.001
VO_2 at AT, mL/kg per min	0.75 (0.60 to 0.94)	0.01	0.71 (0.59 to 0.82)	0.002
VE/VCO_2 slope	1.05 (1.02 to 1.08)	0.001	0.75 (0.65 to 0.85)	<0.001
Peak CO, L/min	0.77 (0.64 to 0.93)	0.006	0.71 (0.60 to 0.83)	0.001
Peak cardiac power, Watt	0.26 (0.13 to 0.55)	<0.001	0.78 (0.67 to 0.88)	<0.001

AT indicates anaerobic threshold.

*Area under ROC curve after adjusted for age, sex, and body mass index.

potentially cause an underestimation of CO by up to 50% at high levels of exercise. Finally, a problem with CO_2 rebreathing method is that for it to obtain reasonably fast equilibration with mixed venous CO_2 it is necessary to add high concentrations of CO_2 to the rebreathing mixture. Indeed, it is difficult to choose the right CO_2 concentration, and inhaled CO_2 occasionally causes discomfort to the patient with a strong feeling of suffocation. Consequently, Cohen-Solal et al¹⁸ have come up with the peak circulatory power, derived from the product of peak VO_2 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 VO_2 . However, as mentioned earlier, peak VO_2 may be influenced by factors other than CO such as muscle deconditioning and obesity.^{5,6} 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.^{10,11} 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 VO_2 measurement. Thus, the potential indication of this noninvasive tool is to discriminate between patients whose main cause of exercise limitation and low peak VO_2 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.¹⁹ Cardiac power has been shown to be powerful predictor of mortality in patients with acute cardiac diseases including cardiogenic shock.²⁰

It should be noted that submaximal measures such as O_2 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/VCO_2 slope to be a better predictor of outcome than peak VO_2 . VE/VCO_2 slope >34 had been reported to be a more accurate prognostic index than peak VO_2 .²¹ Indeed, Arena et al²² have recently proposed that ventilatory data be used to guide therapy in patients with CHF. However, there is some concern regarding this strategy.²³ In this regard, the group at Cleveland Clinic had prospectively analyzed data on 2015 patients, and found that the VE/VCO_2 slope was not predictive of survival in patients with CHF.²⁴

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 VO_2 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

Table 4. Multivariable Predictors of Outcome

Variables Entered into the Multivariable Cox Regression Model	All Patients (n=148)			Patients With Peak VO_2 <14 mL/kg per Min (n=97)		
	Independent Predictors	Hazard Ratio (CI)	P	Independent Predictors	Hazard Ratio (CI)	P
Peak CO, VE/VCO_2 , peak VO_2 , VO_2 at AT	Peak CO	0.79* (0.63 to 0.99)	0.04	Nil	Nil	Nil
Peak cardiac power to VE/VCO_2 , Peak VO_2 to VO_2 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 β -blocker and angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment.

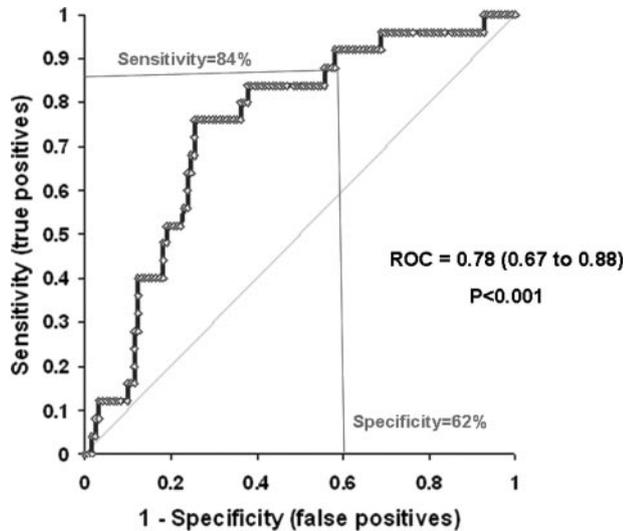


Figure 2. Receiver operating characteristic (ROC) curve of peak cardiac power for the detection of outcome. ROC curve has been adjusted for age, sex and body mass index.

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.

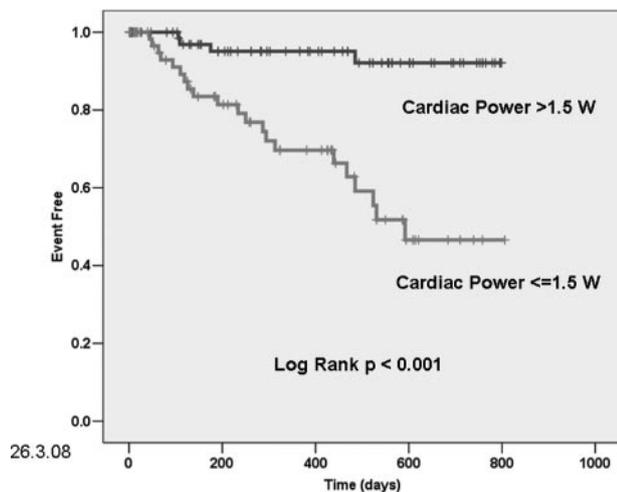


Figure 3. Kaplan-Meier survival curve in patients with peak cardiac power using a cutoff of 1.5 W.

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