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ORIGINAL PAPER

Peak Cardiac Power Measured Noninvasively With a Bioreactance Technique Is a Predictor of Adverse Outcomes in Patients With Advanced Heart Failure

Peak oxygen consumption (VO_2) during cardiopulmonary exercise testing (CPET) is a powerful predictor of survival, providing an indirect assessment of cardiac output (CO). Noninvasive indices of CO derived from bioreactance methodology would add significantly to peak VO_2 as a means of risk-stratifying patients with heart failure. In this study, 127 patients (53±14 years of age, 66% male) with heart failure and an average ejection fraction of 31%±15% underwent symptom-limited CPET using a bicycle ergometer while measuring CO noninvasively by a bioreactance technique. Peak cardiac power was derived from the product of the peak mean arterial blood pressure and CO divided by 451. Follow-up averaged 404±179 days (median, 366 days) to assess endpoints including death (n=3), heart transplant (n=10), or left ventricular assisted device implantation (n=2). Peak VO_2 and peak power had similar areas under the curve (0.77 and 0.76), which increased to 0.83 when combined. Kaplan-Meier cumulative survival curves demonstrated different outcomes in the subgroup with a VO_2 <14 mL/kg/min when stratified by a cardiac power above or below 1.5 W (92.2% vs 82.1% at 1 year and 81.6% vs 58.3% at last follow-up, P=.02 by log-rank test). Among patients with heart failure, peak cardiac power measured with bioreactance methodology and peak VO_2 had similar associations with adverse outcomes and peak power added independent prognostic information to peak VO_2 in those with advanced disease (eg, VO_2 <14 mL/kg/min). Congest Heart Fail. *2010;16:254–258.* ©*2010 Wiley Periodicals, Inc.*

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Cardiopulmonary exercise testing (CPET) has been the most widely used modality to risk-stratify patients with heart failure in order to determine prognosis. Among the variables obtained during CPET, peak oxygen consumption (VO_2) emerged as a powerful predictor of survival, as it provides an indirect assessment of the patient's cardiac reserve. It is generally thought that the reason peak VO_2 is such an important prognostic factor is that it is a surrogate for peak cardiac output (CO), which by most is considered the "true" measure of heart failure. Therefore, there are good reasons to hypothesize that CO would be an even stronger predictor than peak VO_2. This question has been addressed in a number of studies that have typically employed invasive hemodynamic monitoring.[1–8] These studies indicate that CO and derived variables do indeed contain independent prognostic information over and above what come from other parameters. More recent data have demonstrated that peak power (the product of peak exercise cardiac output and peak exercise blood pressure) had independent prognostic significance in addition to variables derived from CPET. [9]

A noninvasive method to quantify stroke volume and hence cardiac output during exercise that relies on bioreactance, a technique that analyzes the relative phase shift of an injected current to the thorax, has been developed and validated in various settings including patients with heart failure.[10–13] Accordingly, we sought to evaluate the hypothesis that additional noninvasive indices of cardiac output derived from bioreactance methodology would add significantly to peak VO_2 as a means of risk-stratifying patients with heart failure.

Methods

Study Participants. One hundred twenty-seven patients with chronic heart failure underwent CPET at the Center for Advanced Cardiac Care of Columbia University Medical Center in 2007–2008, along with a clinical assessment of their condition. They provided written informed consent for the use of their data in the analysis. Follow-up averaged 404±179 days (median, 366 days) and the endpoints consisted of death, heart transplant, or left ventricular assisted device (LVAD) implantation. The study 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.

CPET. Participants performed a graded maximal bicycle exercise test as described previously.[14] After 3 min of rest, the participant began to exercise at a workload of 0 W. The workload increased every 3 min by 25 W until symptom-limited maximum was obtained. Expired gas analysis was performed continuously throughout the test with a standard metabolic cart. Ventilatory oxygen uptake was measured and gas exchange data were acquired breath-by-breath and expressed in 10-s intervals of rolling 20- or 30-s averages. The peak VO_2 was the highest oxygen uptake achieved in the final 20 s of exercise. Twelve-lead electrocardiography was monitored continuously and recorded every minute. Systolic and diastolic blood pressures (SBP and DBP, respectively) were recorded manually at each stage of exercise throughout the test. Mean arterial pressure was estimated as DBP + (SBP – DBP) / 3. All participants were encouraged to provide a maximal effort.

NICOM. The Cheetah NICOM system (Cheetah Medical, Portland, OR) is a portable, noninvasive cardiac output monitoring device based on bioreactance cardiography. The NICOM technology, described in detail previously,[11,13,14] is based on an analysis of time-dependent relative phase shifts of an oscillating current that occur when traversing the thoracic cavity during each beat. The NICOM system comprises a radiofrequency generator for creating a high-frequency current that is injected across the thorax, 4 dual-electrode stickers that are used to establish electrical contact with the body, a receiving amplifier for recording the transthoracic voltage in response to the injected current, and circuitry for determining the relative phase shift between the injected current and the recorded voltage. Within each dual electrode sticker, one electrode is used for delivery of the high-frequency current and the other is used for measuring the resulting voltage. Signals are applied to and recorded from the left and right sides of the thorax; these signals are processed separately and averaged after digital processing. The relative phase shift between the input signal and the output signal, DF, in turn is due to instantaneous changes in blood flow through the thorax. Accordingly, the NICOM system noninvasively measures cardiac function parameters such as cardiac output, cardiac index, stroke volume, ventricular ejection time, and systemic vascular resistance on a beat by beat and average of 10 s basis. Peak exercise cardiac output was defined as the average of data in the last 20 s of exercise. Peak cardiac power was derived as the product of the mean arterial pressure and cardiac output at peak exercise divided by 451.

Statistical Analysis. Differences in demographic, clinical, laboratory, cardiopulmonary, and NICOM variables between participants who did and did not have events were compared by using the chi-square test for categorical data and using the Student's *t*-test for continuous data. To evaluate the clinical utility of peak VO_2 and peak cardiac power, we calculated the area under the receiver operating curve using logistic regression analysis individually and when combined. Event-free survival was determined using Kaplan–Meier cumulative survival curves and compared using the log-rank test among dichotomized participants based on previously determined values for peak VO_2 (14 mL/kg/min)[15] and for peak power (1.5).[9] A P value of $<.05$ was considered significant. All analyses were done using SAS 9.2 (SAS Institute, Cary, NC).

Results

Demographic and clinical characteristics are summarized in Table. The study included 127 middle-aged patients with moderate to advanced heart failure receiving standard medical therapy. Participants, on average, had reduced ejection fractions and severe limitations in exercise tolerance. A total of 15 events occurred during the course of the study including 3 deaths, placement of a LVAD in 2 patients, and 10 urgent transplants.

Differences in various demographic, clinical, and exercise parameters between participants with and without subsequent morbid events is shown in Table. Cardiopulmonary exercise variables including VO_2 at peak and at the anaerobic threshold differed between patients with and without events. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure both at rest and peak exercise were lower in patients with events compared with those without but heart rate did not differ between groups. All the parameters derived from noninvasive cardiac output monitoring including resting and peak cardiac output and cardiac power were lower among participants with subsequent events compared with those without.

The areas under the receiver operator characteristic (ROC) curves for peak VO_2 and peak power did not differ (0.77 and 0.76, respectively), and the area under the ROC was 0.83 when combined (Figure 1). Survival analysis (Figure 2), employing a cutpoint of 1.5 W for peak power[9] and 14 mL/kg/min for peak VO_2,[15] demonstrates that peak power added independent prognostic information in those participants with more advanced disease in that among patients with a peak VO_2 <14 mL/kg/min and peak power >1.5, event-free survival at 2 years was 80%, while in patients with peak VO_2 <14 mL/kg/min and peak power <1.5, event-free survival was 60% at 2 years. However, in patients with peak VO_2 >14 mL/kg/min, there were no events and thus peak power did not provide any incremental prognostic value in this population.

Discussion

The principal findings of this prospective cohort study are that noninvasive measures of cardiac output derived using bioreactance demonstrates significantly lower resting and peak cardiac output and cardiac power in persons with heart failure who subsequently had adverse outcomes. In addition, such measures

Table. Demographic and Clinical Characteristics of Study Population Stratified by Outcomes

Parameter	Overall (N=127)	With Event (N=15)	Without Event (N=112)	*P* Value
Demographic features				
Age, y	53±14	54±11	53±15	.9105
Sex, % male	66	40	69	.0388
BMI	30±9	29±13	30±8	.7947
Medications, %				
ACE inhibitor	57	40	60	.1705
ARB	18	21	18	.7183
β-Blocker	83	79	84	.6989
Statins	49	43	50	.7772
Aldosterone antagonists	37	79	32	.0020
Loop diuretic	62	67	62	1.000
Resting hemodynamics				
HR, beats/min	77±15	75±16	77±14	.7016
Systolic BP, mm Hg	114±19	97±8	116±19	.0003
Diastolic BP, mm Hg	71±10	65±7	71±11	.03667
Mean arterial pressure, mm Hg	92±13	81±6	94±13	.0004
Peak exercise hemodynamics				
HR, beats/min	111±25	106±21	113±26	.3157
Systolic BP, mm Hg	139±28	108±13	144±27	<.0001
Diastolic BP, mm Hg	78±13	70±10	79±12	.0144
Mean arterial pressure, mm Hg	109±18	88±11	111±17	<.001
Clinical features				
NYHA class	2.5±0.8	3.3±0.5	2.4±0.8	.0001
BNP, pg/mL	490±915	1065±710	423±915	.0268
Ejection fraction, %	31±15	24±15	32±15	.1346
Cardiopulmonary variables				
Resting VO_2, mL/kg/min	3.8±0.9	4.0±1.2	3.8±0.8	.3575
VO_2 at AT, mL/kg/min	8.8±3.1	6.3±1.4	9.2±3.1	.0014
Peak VO_2, mL/kg/min	13.2±4.8	9.6±2.5	13.7±4.9	.0019
RER	1.07±0.13	1.07±0.14	1.06±0.13	.8301
NICOM parameters				
Resting cardiac output, L/min	4.7±1.6	3.8±0.9	4.8±1.6	.0010
Peak cardiac output, L/min	10.7±5.2	7.7±2.7	11.1±5.3	.0243
Resting power, W	0.88±0.34	0.63±0.16	0.92±0.35	.0028
Peak power, W	2.32±1.3	1.46±0.6	2.41±1.3	.0118

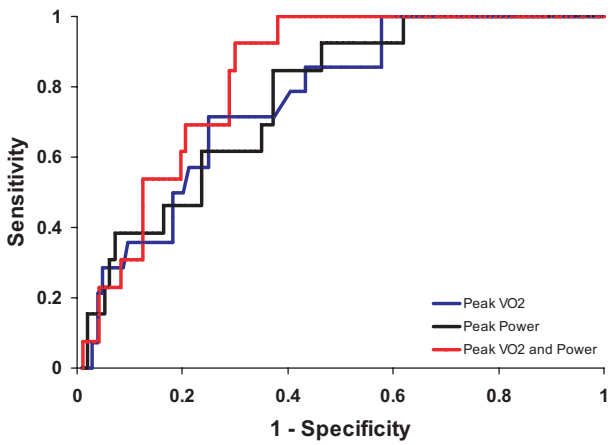

Figure 1. Receiver operating curves for peak oxygen consumption (VO_2) and peak cardiac power and their combination.

have similar associations with adverse outcomes as measures derived from CPET and have independent prognostic significance in patients with advanced heart failure, suggesting clinical utility.

Relevance to Previous Literature. Several studies have investigated the value of hemodynamic measurements during pharmacologically induced stress or exercise in patients with heart failure. The majority of these studies suggest that additional prognostic information can be obtained from assessment of cardiac output, left ventricular stroke work index, and other invasively obtained hemodynamic measures.[3–5] In addition, correlations between hemodynamic data (cardiac output and pulmonary wedge pressure) and peak VO_2 have been demonstrated to be variable.[2] These data suggest that hemodynamic information could be used in combination with cardiopulmonary exercise testing to improve risk stratification and determine transplant eligibility. Patients with a low VO_2 who can demonstrate appropriate cardiac function at peak exercise may not be listed for cardiac transplant, as the etiology for the low peak VO_2 may be the result of deconditioning, obesity, or other peripheral factors. Such conclusions were supported by data[6] in which the cardiac output response was

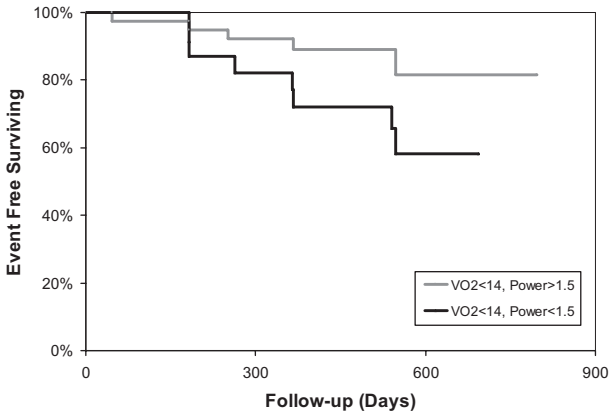

Figure 2. Kaplan-Meier survival analysis among participants with peak oxygen consumption (VO_2) <14 mL/kg/min stratified by peak power > or <1.5 W.

identified as the most powerful prognostic variable, with participants with a peak VO_2 of <14 mL/kg/min and a normal cardiac output response with exercise having a 1-year survival rate of 94%. Our data confirm these findings using a noninvasive technique to measure cardiac output, with a 1-year event-free survival of 92% in the cohort with a low peak VO_2 but normal cardiac power. Similarly, Metra and colleagues[7] noted that >40% of the patients with normal hemodynamic response had a peak VO_2 of <14 mL/min/kg. On this basis, they recommended to include hemodynamic measurements during exercise to avoid transplant in patients whose exercise limitation is due more to muscle deconditioning than pump failure.

Employing noninvasive methods, 2 studies have demonstrated the value of peak cardiac power in this regard. One that studied patients with mild heart failure (mean peak VO_2 of 23 mL/kg/min) used CO_2 rebreathing integrated with a standard CPET[8] and another[9] that studied persons with more advanced heart failure (mean peak VO_2 of 12.9 mL/kg/min) using a rebreathing technique during exercise testing. These modifications compared with previous studies are important because it is difficult to imagine that the complex procedure of invasive measurements could be implemented in the standard clinical exercise test on a large scale. Our data add to these latter studies and suggest that combining noninvasively derived hemodynamic data using bioreactance is feasible and potentially useful in risk stratification for patients with advanced heart failure.

Physiologic Importance of Peak Power. The previously cited studies[3–9,16] indicate that cardiac output and derived variables do indeed contain independent prognostic information over and above what come from other parameters derived from cardiopulmonary exercise testing. Thus, two patients could in principle have the same peak VO_2 values but quite different peak CO values due to variation in their arteriovenous oxygen difference and their conditioning status. It is unlikely that the prognoses of these patients are the same as demonstrated by these data. Ideally, treatment of these patients should be tailored to the underlying pathophysiologic mechanisms, with a focus on exercise training and cardiac rehabilitation for those patients with exercise limitations primarily due to muscle deconditioning.

Another potential advantage of the cardiac output data compared with VO_2 data is that the former may be of prognostic value at submaximal exercise. This is not the case for VO_2. At submaximal exercise, VO_2 is merely a consequence of the amount of mechanical work done and there is no difference between the patient with congestive heart failure and the healthy person. The difference becomes apparent when the anaerobic threshold is reached at a lower workload than in a healthy person. For cardiac output and variables that are derived from it, data at submaximal exercise might be valuable. Indeed, several studies have shown that cardiac output is lower than normal in patients with congestive heart failure, both systolic and diastolic,[1,2,17] in the entire exercise interval from rest to maximum workload. Recent data have suggested that using noninvasive measures of cardiac output at submaximal exercise does have prognostic significance when evaluated with another gas rebreathing technique.[18]

Potential Clinical Applications/Future Studies. Routine assessment of hemodynamic measurement of cardiac output during exercise is a difficult procedure that traditionally requires the insertion of a catheter into the pulmonary artery, which is associated with a non-negligible risk.[19,20] Whether this risk is amplified during exercise is unclear. It is probable that the combination of exercise and use of a Swan-Ganz catheter pose an added risk with increased potential for arrhythmias triggered by movement of the catheter and an increased risk of infection.

Few studies have examined the correlation between survival and data obtained through noninvasive hemodynamic measurements,[8,9] but findings suggest that these parameters have a strong predictive value. Just as important, these studies identified several patients who had a reduced peak VO_2 yet a cardiac output higher than the identified critical value, correlating to an excellent prognosis. These data, when coupled with the findings of the current study, suggest that the advent of new technologies that allow for noninvasive measurements of cardiac output may further refine this risk stratification process and make this approach more practical.

In addition, CPET requires relatively complex, difficult-to-maintain equipment that requires ongoing calibration and must be operated by highly trained technicians. As a result, such tests are typically only used in tertiary care centers. Thus, the clinically important information derived from CPET is not available for the evaluation and follow-up of most patients with heart failure followed

outside a specialized heart failure program. In contrast, the completely noninvasive bioreactance approach is simple to use and does not require complex maintenance, calibration, or training to use. If confirmed in larger studies, the data in the current study showing indistinguishable ROC curves between peak VO_2 and peak cardiac power suggest that noninvasively assessed peak power could be widely adopted into routine evaluation and follow-up in heart failure patients.

Limitations. This was a single-center study with a relatively small cohort of participants. The small and relatively heterogeneous sample included patients with mild symptoms (eg, New York Heart Association class II) and some with mild reductions in ejection fraction, who had a limited number of endpoints. Thus, our power to detect statistical differences was low. All the events occurred in participants with a VO_2 <14 mL/kg/min, prohibiting the determination of the value of peak power in those with less severe decrements in exercise capacity. However, data have demonstrated that the bioreactance technique can be performed in multicenter studies with the acquisition of high-quality data.[14] The NICOM system particularly has been demonstrated to have acceptable accuracy, precision, and responsiveness for CO monitoring when compared with invasive methods such as continuous thermodilution with a pulmonary artery catheter.[10,13,21–23] Moreover, the device works well in environments that are rich in electrical noise such as the experimental laboratory and the intensive care unit. Major factors that impact measurements of the NICOM system include patient movement and electrode placement and preparation. However, since NICOM detects phase shift–related changes rather than amplitude measures that are employed with bioimpedance devices, the measurements are less affected by factors such as temperature, obesity, and motion.

Conclusions

Cardiac output can be measured noninvasively at rest and during CPET in patients with heart failure being considered for cardiac replacement therapies including LVADs and cardiac transplant. The cardiac output can be coupled with exercise blood pressure to derive peak power, which has independent prognostic power among patients with advanced heart failure. Application of this approach to a larger cohort involving multiple centers seems warranted and, if useful, could significantly alter the approach for risk-stratifying patients with advanced heart failure for cardiac replacement therapy.

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