Review Article

# Prognostic Significance and Measurement of Exercise-Derived Hemodynamic Variables in Patients With Heart Failure

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**ABSTRACT**

The peak $VO_2$ is an important prognostic measurement in the evaluation of patients with heart failure and is used to monitor the progress of the condition, especially in selecting patients for cardiac transplantation. However, peak $VO_2$ may be influenced by noncardiac factors such as age, sex, motivation, anemia, and muscle deconditioning. These confounding factors may diminish somewhat the prognostic power of peak $VO_2$. Several groups have looked at exercise-derived variables beyond peak $VO_2$ to assess whether a more direct assessment of cardiac function, using exercise-derived hemodynamic variables, may yield more precise prognostic information than standard cardiopulmonary-derived data. This article reviews the evidence that cardiac work related to exercise may enhance the prognostic value of peak $VO_2$ in the evaluation of patients with heart failure and briefly discusses the available methods for measuring these parameters. (*J Cardiac Fail 2007;13:672−679*)

**Key Words:** Chronic heart failure, cardiac transplantation, exercise, cardiac output.

Despite continuing advances in the therapy of chronic heart failure (CHF), the mortality of this syndrome remains high. Heart transplantation, with 1-year survivals now exceeding 85%, has emerged as an important adjunct to medical therapy and has been considered the treatment of choice for patients with end-stage heart disease.[1,2] The resultant increase in referrals to heart transplantation centers has magnified the need for reliable prognostic markers as the gap widens between the number of potential transplant recipients and available donor organs.[3]

American Heart Association consensus reports have recommended that peak volume of oxygen utilization ($VO_2$) be used to help determine the timing of heart transplantation in ambulatory patients with CHF.[4] Specifically, it has been suggested that a peak exercise $VO_2$ level of less than or equal to 14 mL·min·kg be used as a key criterion for the acceptance of ambulatory patients for transplantation. This recommendation is based on several studies demonstrating that peak exercise $VO_2$ is a valuable prognostic marker in patients with CHF[5,6] and that transplantation can be safely deferred in patients with peak exercise $VO_2$ levels of more than 14 mL·min·kg. As will be discussed next, much research has focused on refining this parameter to identify patients at greatest risk. $VO_2$ is such a powerful predictor because it provides an indirect assessment of the cardiac reserve. With the advent of new technologies that greatly simplify the noninvasive measurement of cardiac output (CO) at rest and with exercise, it is time to readdress the prognostic value of CO and the hemodynamic response to exercise in patients with CHF and to review briefly the available methods that can measure hemodynamic parameters during an exercise stress test.

## Confounding Factors of Peak $VO_2$

The use of a specific peak exercise $VO_2$ level as a selection criterion for heart transplantation may have several potential confounding factors. In CHF, patients' peak exercise $VO_2$ can be influenced by comorbidities and noncardiac factors, such as muscle deconditioning, motivation, anemia,

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abnormal reflex response, and obesity.[7] Therefore, peak $VO_2$ is affected not only by the cardiac response to exercise as observed in healthy subjects but also by limited skeletal muscle mass and perfusion in patients with advanced CHF. Thus, it was recently argued by Mancini and LeJemtel[8] that the usefulness of peak $VO_2$ to predict prognosis in patients with CHF also results from an objective quantification of the derangements that the failing heart causes in the periphery. Not unexpectedly, patients with CHF with severe skeletal muscle wasting and low peak $VO_2$ have a worse prognosis than patients with little or no muscle wasting and moderately reduced peak $VO_2$. Nevertheless, it has been noted that the expected peak $VO_2$ varies according to the age and sex of the individual.[9] It has also been noted by several groups that there may be no statistical difference in survival between patients with peak exercise $VO_2$ levels of 10 to 14 mL·min·kg and patients with levels of 14 to 18 mL·min·kg.[10]

## Potential Prognostic Value of Ancillary Data During Cardiopulmonary Testing

Several groups have looked at exercise-derived variables other than peak $VO_2$ as predictors of outcomes, such as blood pressure response to exercise,[11] the slope of the ratio of minute ventilation to carbon dioxide production ($VE/VCO_2$), or its value at the anaerobic threshold[12] and oxygen kinetics in the post-exercise recovery phase.[13] It should be noted that these parameters, unlike $VO_2$, are not influenced by the mechanical work done during exercise testing but reflect alterations in the peripheries that are caused by the disease in CHF, which can in turn lead to the progression and symptomatology of CHF.

The use of the percent achieved of predicted peak $VO_2$ has been evaluated. Aaronson and Mancini[14] evaluated this parameter in 272 ambulatory patients with CHF and found that the overall model discrimination, as assessed by the area under the receiver operating curve (ROC), was not significantly improved with percent predicted peak $VO_2$ when compared with weight-adjusted peak $VO_2$ (0.71 vs. 0.66, $Z = 1.60$, $P = .11$). However, it could be argued that in absolute terms, there may be some value in percent predicted peak $VO_2$. If the absolute and relative improvement were determined, it could mean that the accuracy of the test was actually improved with percent predicted peak $VO_2$ from 32% (ie, ROC area under the curve [AUC] 0.50 = test not helpful; ROC AUC curve 1.00 = test perfect; therefore, ROC AUC of $0.16 = 0.16/0.50 \times 100 = 32\%$) to 44%. This is an increase in absolute accuracy of 12% or a relative increase of 37.5%. The prognostic value of percent predicted peak $VO_2$ was also investigated by Stelken and colleagues[15] in 137 patients with CHF; they found that the actuarial 2-year survival of patients who achieved 50% or less predicted peak $VO_2$ was 43% compared with 90% in patients who achieved greater than 50% predicted peak $VO_2$ ($P = .01$). Clearly, more work is needed in determining further the percent predicted peak $VO_2$.

With respect to other ventilatory variables that can be derived from respiratory gas exchange analysis that might have prognostic value in CHF, ventilatory efficiency has received the most attention.[16,17] Ventilatory efficiency is usually assessed by the $VE/VCO_2$ slope and depends on pulmonary hemodynamics, skeletal muscle ergoreceptor and peripheral chemoreceptor sensitivity, and heightened sympathetic activity. $VE/VCO_2$ slope greater than 34 has been reported to be a more accurate prognostic index than peak $VO_2$.[16,17] Arena and colleagues[18] proposed that ventilatory data be used to guide therapy in patients with CHF. However, there is some concern regarding this strategy.[18] In this regard, the group at Cleveland Clinic prospectively analyzed data on 2015 patients, arguably one of the largest dataset of cardiopulmonary exercise testing to date, and found that the $VE/VCO_2$ slope was not predictive of survival in patients with CHF.[19] Indeed, a low peak $VO_2$ may be an even more powerful predictor of mortality in patients receiving beta-blocker therapy than in those treated without beta-blocker therapy.

Statistical models that include peak $VO_2$ have also been developed. One such model,[20] the Heart Failure Survival Score (HFSS), is a multivariable predictive index that was developed from data on 80 clinical characteristics of 268 ambulatory patients with advanced CHF. The model was derived from the smallest number of noninvasive variables that could predict survival in a derivation sample, which was later validated in a second cohort of 223 patients. The final seven variables that were selected included different aspects of heart failure physiology: myocardial ischemia, resting heart rate, mean arterial blood pressure, ejection fraction, intraventricular conduction delay, peak $VO_2$, and serum sodium. The total HFSS was calculated by summing the individual variables with each variable weighed slightly differently. We validated this model and found that an HFSS of greater than 8.0 was associated with a 1-year event-free survival of 93% ± 2%, whereas an HFSS of 8.0 or less was associated with a 1-year event-free survival significantly less than expected with transplantation. We validated the predictive power of this model with sequential use and in the beta-blocker era.[21] However, it should be noted that most of these studies were performed largely in middle-aged men, in whom its predictive value seems to be excellent. Its predictive value in deconditioned obese individuals or those at the extreme of age is less certain. Furthermore, these variables are only indirectly related to cardiac function. Arguably, these variables can only be considered as markers of severity of organ failure. Consequently, direct means to improve these values need not necessarily indicate an improvement in cardiac function.

## Potential Arguments for Measuring the Hemodynamic Response to Exercise

It is generally thought that the reason for peak $VO_2$ to be such an important prognostic factor is that it is an indirect measure for CO and thus provides an index of cardiac reserve of the patients with CHF. However, as mentioned

earlier, it was argued by Mancini and LeJemtel[8] that the usefulness of peak $VO_2$ to predict prognosis might also be because it reflects the derangements that the failing heart causes in the periphery. However, because peak $VO_2$ is only an indirect measure of CO, there may be an argument that direct measurement of CO may be an even stronger predictor than peak $VO_2$. In recent years, there has been a growing interest in more refined indices of specific cardiac performance than peak $VO_2$, a measure that may depend in part on muscle function, $O_2$ delivery, blood distribution, and $O_2$ extraction capacity. Theoretically, hemodynamic data should add independent information to peak $VO_2$ because this parameter is the product of CO and arteriovenous difference in oxygen content (C[a-v]$O_2$):

$$\text{peak } VO_2 = \text{peak CO} \times \text{peak C(a-v)}O_2$$

Thus, two patients could in principle have the same peak $VO_2$ values, but different peak CO. A patient with pump failure with low peak $VO_2$ will have a low CO and a high C(a-v) $O_2$ at peak exercise, whereas another patient with severe muscle deconditioning might still have a low peak $VO_2$ but a normal peak CO and a low C(a-v) $O_2$ because of reduced ability of the muscle to extract oxygen.

Another potential advantage of CO data is that CO 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 will be little difference between the achieved $VO_2$ in the subject with CHF and the healthy subject. Differences in achieved $VO_2$ will only become apparent at the anaerobic threshold, which is reached at a lower workload in the subject with CHF than in the healthy subject. The achieved $VO_2$ at anaerobic threshold, which is reflective of CO at this point,[22] is a prognostic indicator in patients with CHF.[23] However, many patients with CHF undergoing cardiopulmonary exercise testing are unable to carry out maximal exercise and achieve anaerobic threshold. Consequently, submaximal measurements such $O_2$ kinetics and ventilatory efficiency during which are not influenced by mechanical work done at submaximal exercise have been evaluated as prognostic markers. CO and derived variables may also have prognostic value at submaximal exercise loads lower than the anaerobic threshold. Stringer et al.[24] and others[25,26] showed that patients with a lower cardiac reserve have a lower CO response throughout the entire exercise, including submaximal exercise. Therefore, there are good reasons to hypothesize that the CO response to exercise would be an even stronger prognostic predictor than peak $VO_2$

## Evidence of the Prognostic Value of Assessing the Hemodynamic Response to Exercise in Patients With Heart Failure

In 1986, Tan[27] published a study on 63 patients with severe heart failure. A series of hemodynamic parameters (cardiac index, stroke work index, pulmonary artery wedge pressure, and cardiac power output [CPO]) were measured at rest and under maximum stimulation with dobutamine using the thermodilution technique. The CPO was defined as the product of CO and the mean blood pressure. The patients were followed for 1 year after the initial test, during which time 23 of them died. Parameters measured at rest showed a considerable overlap between survivors and nonsurvivors, but with dobutamine stimulation there was an almost complete separation between survivors and nonsurvivors in cardiac index, CPO, and stroke work index. These results suggested that hemodynamic parameters obtained during dobutamine stimulation offered important discriminatory prognostic information when compared with resting values. The study did not allow comparison with the prognostic value of peak $VO_2$. The almost complete separation of data from survivors and nonsurvivors is interesting, but it should be noted that the nonsurvivors had heart failure at a very advanced stage and several of them completely lacked the ability to increase CO during dobutamine infusion.

The prognostic value of cardiac work-related performance over peak $VO_2$ was first shown by Griffin and colleagues,[28] who reported data on 49 patients with CHF at rest and during maximal exercise with an overall 1-year mortality rate of 33%. The results showed that stroke work index at peak exercise dichotomized at 20 g/$m^2$ identified patients with a three- to fivefold higher mortality compared with the remaining patients. Exercise duration and peak $VO_2$ did not discriminate survivors from nonsurvivors. This was followed by the study of Roul et al.,[29] who measured a large number of hemodynamic variables in rest and exercise in 50 patients. Patients of New York Heart Association (NYHA) class IV were excluded from the study because the poor prognosis of this group of patients was considered to be evident from the clinical data alone. This makes this study different from the other studies, which typically include approximately 25% of patients in NYHA class IV. Nevertheless, the study population had a 26% mortality over 21.2 ± 1.2 months. The study showed that hemodynamic data measured at rest were weak predictors, whereas CPO and stroke work index measured at peak exercise were strong predictors. The authors also showed that peak $VO_2$ was almost as powerful as CPO as a survival predictor, and because their setting required invasive CPO with the patients lying down, which was not always tolerated, they recommended peak $VO_2$ as an alternative to the hemodynamic measurements.

Wilson et al.[7] investigated the relationship between hemodynamic data (CO and pulmonary wedge pressure) and peak $VO_2$ in 64 patients with stable CHF listed for cardiac transplantation. The data showed no correlation between peak $VO_2$ and hemodynamic data recorded at all workloads in a 3-minute Naughton protocol. A significant portion of the patients (44%) had only mild or moderate hemodynamic dysfunction despite a peak $VO_2$ value less than the recommended limit for transplantation ($<14$ mL·kg·min). Conversely, 33% of patients with a peak $VO_2$ greater than 14 had severely impaired CO at peak exercise. Their conclusion was that invasive hemodynamic information

should be used in combination with $VO_2$ to determine transplant eligibility. Patients with a low $VO_2$ who can demonstrate appropriate cardiac function at peak exercise should not be listed, because the cause for the low $VO_2$ is probably the result of deconditioning, obesity, or other peripheral factors. The same researchers[30] studied a larger group of 185 patients in NYHA classes II, III, and IV with the same exclusion and inclusion criteria as in the prior study. Both $VO_2$ and CO were measured at rest and maximum exercise. The CO response to exercise was defined as normal or reduced. The normal CO response was derived from data previously reported by Higginbotham et al.,[31] who measured the CO response to upright exercise in healthy subjects and calculated a regression curve and 95% confidence limits for the relation between cardiac index and $VO_2$. Chomsky and colleagues[30] at Vanderbilt converted this regression curve to CO by multiplying the cardiac index by 1.8 $m^2$, an average body surface area. This conversion resulted in the following equation for the lower limit of normal for CO: $5 \times VO_2$ (L/min) + 3 L/min. The CO response to exercise was the most powerful predictor of survival in this study population according to both univariate and multivariate analyses. In patients with a reduced CO response, the overall 1-year survival was poor (72%). The additional finding of a peak $VO_2$ of less than or equal to 10 mL·min·kg in such patients identified a group with a particularly unfavorable prognosis (38% were alive at 1 year). In contrast, the overall 1-year survival of patients with a normal CO response was 95%, which is far superior to that expected after transplantation. The favorable prognosis of this group was evident regardless of the peak $VO_2$. This was particularly noteworthy in patients with a peak $VO_2$ of less than or equal to 14 mL·min·kg (1-year survival: 94%), a group who would be recommended for transplantation on the basis of the most recent American Heart Association consensus statement.[4] Although it was not statistically significant (P = .09), survivals did tend to be lower in patients with a reduced CO response and peak $VO_2$ less than 10 mL·min·kg.

The findings by Chomsky and his colleagues[30] were clearly provocative at the time and required further confirmation. Mancini et al.[32] repeated Wilson and colleagues'[7] protocol and found that peak $VO_2$ did correlate with peak CO. Multivariate analysis demonstrated that only left ventricular stroke work and stroke work index were predictive of survival. The inability to predict survival using either $VO_2$ or CO may have been the result of the small sample size (65 patients). Thus, it became 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. However, a larger study with the hemodynamic measurements was done by Metra et al.,[33] with the participation of 219 patients with CHF. Among the hemodynamic parameters, peak stroke work index was found to be the strongest predictor at both 1 and 2-year follow-ups. Although peak stroke work index was correlated to peak $VO_2$, the latter was a weaker predictor. They noted that more than 40% of the patients with normal hemodynamic response had a peak $VO_2$ of less than 14 mL·min·kg. On this basis, they recommended that hemodynamic measurements during exercise be used in heart failure evaluation to avoid transplantation in patients whose exercise limitation is due more to muscle deconditioning than to pump failure.

It should be noted that the above studies have largely been based on invasively derived parameters. In 2001, Williams et al.[34] published the first study on the correlation between survival and hemodynamic data obtained by noninvasive measurement of CO using $CO_2$ rebreathing integrated with a standard exercise test. This modification compared with previous studies is more important because it is difficult to imagine that the complex procedure of invasive measurements could be implemented in the standard clinical exercise test. A total of 219 patients with relatively mild heart failure (mean peak $VO_2$ 23 mL·min·kg) were studied. This study found that peak CPO was a stronger predictor than peak $VO_2$ with several patients with reduced $VO_2$ (ie, peak < 14 mL·min·kg) but with a peak CPO higher than the identified critical value of 1.96 watts. This group of patients had an excellent prognosis with an 89% 4-year survival. This same group of investigators recently reported on the extended follow-up of a cohort of patients (n = 219, 166 male, mean age 56 years) with a median duration of 8.6 years of follow-up. Survivals at 10 years in patients with good (> 8.1 L/min), moderate (≥5.8, < 8.1 L/min), or poor (≤5.8 L/min) CO reserve were 89%, 63%, and 36.1%, respectively ($P < .001$)[35] (Fig. 1).

By incorporating both the pressure and the flow domains of the cardiovascular system, CPO is an integrated measure of the cardiac hydraulic pumping capacity, and it has been

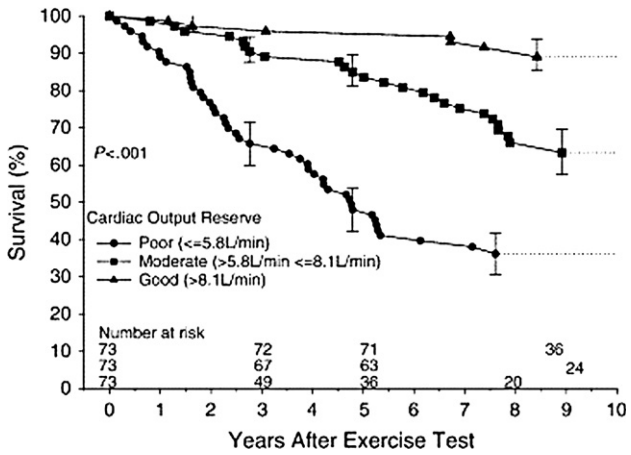


**Fig. 1.** Kaplan-Meier survival curves built on tertiles of CO reserve: good (> 8.1 L/min), moderate (≥5.8, < 8.1 L/min), or poor (≤5.8 L/min). Survivals at 10 years in patients with good (> 8.1 L/min), moderate (≥5.8, < 8.1 L/min), or poor (≤5.8 L/min) CO reserve were 89%, 63%, and 36.1%, respectively ($P < .001$). Williams SG, Jackson M, Cooke GA, et al. How do different indicators of cardiac pump function impact upon the long-term prognosis of patients with chronic heart failure. Am Heart J 2005;150:983.

argued that it provides a comprehensive indicator of cardiac function.[36] CPO has been shown to be a powerful predictor of mortality in patients with acute cardiac diseases, including cardiogenic shock.[37,38] Do these findings call for the implementation of CPO determination in all transplant evaluations of patients with heart failure? It should be emphasized that the equipment for the rebreathing $CO_2$ method of measuring CO is not widely available. There are also methodologic problems. CO is measured during a separate run at a work rate corresponding to the peak work rate in the preceding incremental test, and thus represents a high work load but not the true peak CPO, a target that still eludes us mainly because of the time taken to conduct the measurements. Further, CPO requires the measurement of mean arterial pressure, and this may be difficult during the cardiopulmonary exercise test. In an attempt to overcome some of these problems, Cohen-Solal and colleagues[39] proposed another index, the ''peak circulatory power,'' which is the product of the peak $VO_2$ and the last systolic arterial pressure measurement. It is therefore not as ''correct'' as CPO, but it has been argued that the information for its calculation is available from any cardiopulmonary exercise test without the need for special equipment. The value of the ''circulatory power'' was assessed by Cohen-Solal et al.[39] in a study involving 175 patients with heart failure during a 25 ± 10-month follow-up, which had a 16% mortality and 18% who underwent cardiac transplantation. Multivariate analysis demonstrated that the peak ''circulatory power'' ($\chi^2 = 19.9$, $P < .001$) was the only variable predictive of prognosis. When survival was analyzed in terms of quartiles of peak $VO_2$ or circulatory power, it seemed that prognosis was worse as peak $VO_2$ declined, but that circulatory power aids in selecting subgroups with particularly poor prognosis (those with both reduced peak $VO_2$ and reduced blood pressure). The authors did not compare the predictive value of circulatory power and CPO. The circulatory power represents the volume of $VO_2$ added to the mixed venous blood by the lungs and transferred to the systemic arterial circulation against a pressure gradient by the heart. Scharf et al.[40] approximated CPO by multiplying the predicted peak $VO_2$ with SBP; they called it ''exercise cardiac power'' and found it to be the most powerful predictor of mortality. An exercise cardiac power of less than 5000% mm Hg indicated a poor prognosis with a 1-year mortality rate of 37%, whereas only 2% of the patients with an exercise cardiac power of greater than 9000% mm Hg died during the first year. Williams and colleagues[41] examined the relationship between circulatory power and CPO in a cohort of 219 ambulatory patients with stable CHF and found a weak but statistically significant relation between circulatory power at rest and CPO at rest ($R = 0.48$, $P < .0001$). However, a stronger correlation was observed between the variables at peak exercise ($R = 0.84$, $P < .0001$). The results of many of the cited studies were obtained before the beta-blocker era and thus may not be typical for today's patients. In a recent report,[42] the Vanderbilt group reassessed the value of the CO response to exercise in the pre−beta-blocker era (n = 292) in patients with CHF in the current beta-blocker era (n = 203) and found that the CO response to exercise continued to provide additional prognostic information beyond peak $VO_2$ in both eras.

Table 1 summarizes the results of the nine cited studies, which include approximately 1200 patients with CHF. In the studies in which peak $VO_2$ was measured, it was shown that this parameter is significantly weaker in risk prediction than the hemodynamic parameters. In several of the studies, patient groups were identified with good hemodynamic responsiveness but with peak $VO_2$ less than 14 mL·min·kg. These patients were shown to have a considerably better prognosis than those with a poor hemodynamic response. We have not pooled the data largely because of different inclusion and exclusion criteria and differences in test protocols and observation times. Nevertheless, the qualitative conclusion seems to be in favor of including hemodynamic measurements as part of the exercise testing in the evaluation of transplant candidates.

## Methods for Measuring Cardiac Output

Methods of measuring CO, especially at peak exercise, are not straightforward. Invasively derived hemodynamic measurements during exercise raise serious concerns regarding risks and complexity of testing. Insertion of a catheter into the pulmonary artery may be associated with complications (eg, pneumothorax, local

**Table 1.** Prognostic Value of Hemodynamic Exercise Testing in Heart Failure

| Study | N | Measured Hemodynamic Parameter | Method Used | Cutoff Value | Better Predictor Than Peak $VO_2$ |
|---|---|---|---|---|---|
| Tan[27] | 63 | CPO and others | Thermodilution | 1 watt | NA |
| Griffin et al.[28] | 49 | Stroke work index and others | Thermodilution | 20 g × m/m$^2$ | Yes |
| Roul et al.[29] | 50 | CPO | Thermodilution | 2 watts | Yes |
| | | Stroke work index and others | Thermodilution | 39 g × m/m$^2$ | Yes |
| Chomsky et al.[30] | 185 | CO response | Thermodilution | CO = 5 × $VO_2$ + 3 | Yes |
| Mancini et al.[32] | 65 | CO response | Thermodilation | CO = 5 × $VO_2$ + 3 | No |
| | | Stroke work index | Thermodilution | | Yes |
| Metra et al.[33] | 219 | Stroke work index | Thermodilution | 30 g × m/m$^2$ | Yes |
| Williams et al.[34] | 219 | CPO | $CO_2$ rebreathing | 1.96 watts | Yes |
| Cohen-Solal et al.[39] | 175 | Circulatory power | Peak $VO_2$ and SBP | 3047 mm Hg mL·min·kg | Yes |
| Scharf et al.[40] | 154 | Exercise power capacity | % Peak $VO_2$ and SBP | 5000% mm Hg | Yes |
| | Total = 1179 | | | | |

NA, not available; $VO_2$, volume of oxygen utilization; CO, cardiac output; CPO, cardiac power output; SBP, systolic blood pressure.

pain, vasovagal reactions, atrioventricular blocks, and arrhythmias). During exercise, patients are tethered to the Swan-Ganz catheter, restricting movement and occasionally causing pain. The discomfort associated with an intravascular catheter may prevent patients from achieving their true maximum exercise capability. Movement during exercise can cause dislodgement of the catheter from its appropriate position, leading not only to erroneous measurements but also to potential increases of the risk of arrhythmias to the patient. Moreover, patients with CHF often have tricuspid insufficiency, which is made worse by exercise. The presence of tricuspid insufficiency decreases the accuracy of thermodilution output measurements.

### Noninvasive Measurement of CO During Exercise

**Impedance cardiography.** Impedance cardiography[43] uses changes in thoracic electrical impedance to measure thoracic fluid content, changes in the duration of cardiac ejection, and the velocity of blood flow within the aorta. However, the theory behind impedance cardiography makes several assumptions that may be questioned. The thorax is considered to be a cylinder filled with blood. During cardiac systole, it is assumed that the stroke volume is added to the volume of the blood filled cylinder and that this affects only the area of the cylinder (ie, expands the diameter of the cylinder and not the length). On the basis of this somewhat simplistic assumption, the electrical impedance is expected to be reduced by an amount directly proportional to the stroke volume. Thus, the electrical impedance in the thorax is reasoned to be proportional to the blood volume in the thorax, and this volume increases by an amount equal to the stroke volume. Thereafter, CO is derived by multiplying the heart rate with the change in the impedance signal and a calibration factor. Given the complexity of the anatomy and physiology of the human body, it is difficult to reason with the simplistic assumption that is applied with this technique. It is difficult to validate and assess the quantitative significance of the derivation from this model. Nevertheless, the technique has become increasingly popular over the past 10 years largely because of its ease of use.[44] With respect to reproducibility, mean absolute percent changes in intraday hemodynamic measures were reported to be less than 8%.[45] A previous meta-analysis of 34 published studies[46] on impedance cardiography showed mean coefficients of correlation that ranged from 0.65 to 0.83 with large individual variations. Recently, the PREDICT trial[47] showed that impedance cardiography may help identify patients with CHF who are at risk of decompensation. With respect to the method's utility during exercise, it should be noted that it is generally not recommended for use in exercise because of the sensitivity to electrical noise. However, there have been reports with encouraging results of its use during exercise.[48,49] The primary advantage of impedance cardiography is that no patient cooperation is required and that it provides beat-by-beat data. The disadvantages are that the method rests largely on an empirical basis and that existing validation data are rather inconclusive. Its use during cardiopulmonary exercise testing in patients with CHF has yet to be fully defined.

### Rebreathing Methods

**$CO_2$ rebreathing methods.** The $CO_2$ methods are based on the indirect Fick principle, using mass conservation for $CO_2$. The principle is called ''indirect'' because the blood concentrations of $CO_2$ in mixed venous and arterial blood are estimated indirectly rather than being measured directly in the blood, as in the direct Fick method. There are many variations of the same theme, but fundamentally the $CO_2$ methods are rebreathing or breath-hold (prolonged expiration) methods.[50] Only full $CO_2$ rebreathing methods have been used in exercise testing, including in patients with CHF.[34]

The $CO_2$ methods have a number of significant advantages when compared with impedance cardiography. They are truly analytic in nature, that is, the algorithms are derived solely from a plausible gas exchange model with no need of empirical corrections or calibrations. The difficulty with $CO_2$ rebreathing methods is that they are dependent on the estimation of the a-v difference in $CO_2$ content from alveolar $CO_2$ partial pressures. The difference is obtained by two almost independent estimations of arterial and mixed venous $CO_2$ contents. Small independent errors in estimated values of either will lead to a relatively large error in the difference. The estimation of arterial and mixed venous $CO_2$ contents from the $CO_2$ partial pressure profile in the respired air is uncertain because the relationship between $CO_2$ partial pressure and $CO_2$ content in blood depends on a number of factors that vary from patient to patient (eg, hemoglobin concentration, temperature, acid-base status, and blood oxygenation). This uncertainty combined with the tendency to large errors in the a-v difference is probably the main cause of occasionally unrealistic CO values when $CO_2$ methods are used. Sun and colleagues[51] also highlighted a problem during exercise and cast doubt on the widely accepted assumption[52] that $Paco_2$ is linearly related to $CO_2$ concentration over a broad physiologic range. During heavy exercise in both healthy subjects and those with cardiac disease, lactic acidosis supervenes resulting 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 it has been calculated that the failure to take the pH into consideration could potentially cause an underestimation of CO by up to 50% at high levels of exercise. Finally, a problem with $CO_2$ rebreathing methods is that to obtain reasonably fast equilibration with mixed venous $CO_2$ it is necessary to add high concentrations of $CO_2$ to the rebreathing mixture. 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.

**Foreign gas rebreathing methods.** With the foreign gas methods it is somewhat easier to estimate the three terms in the Fick equation than with the $CO_2$ methods. The blood-soluble gas is the substance to which the equation of mass conservation is applied. Because a foreign gas is used, the mixed venous content of this gas is zero. As for $CO_2$, the arterial partial pressure is taken to be equal to the alveolar partial pressure. The conversion from partial pressure to content in the blood is simple, because the gas has no chemical interaction with the blood. Content is linearly dependent on partial pressure. The blood insoluble gas is used to measure the lung volume, which is required to calculate CO. Foreign gas methods require accurate measurement of two foreign gases in low concentrations. The most recent technologically advanced analyzers outperform mass spectrometers by a factor of 20 in terms of signal-to-noise ratio, allowing the use of such low gas concentrations that previous problems of disagreeable taste and smell of the inert gases have vanished.

The foreign gas rebreathing method has been validated in both healthy subjects and patients with various diseases.[53,54] The reproducibility of this method during exercise testing in patients with CHF has been reported with an interday coefficient of variation of 10.8%.[54] In that study, data were obtained in 20 patients with CHF during cardiopulmonary exercise testing.[55] CO measured with foreign gas rebreathing was compared with CO obtained

with direct Fick and thermodilution from rest to maximum workload, and the foreign gas rebreathing method was reported to agree better with direct Fick than the thermodilution method. We recently performed 92 consecutive bicycle exercise tests in 88 patients with HF by using the Innocor system.[56] Patients were able to rapidly learn the rebreathing technique and easily integrate it into the exercise protocol, and 86% of the tests had successful measurement of both metabolic and CO data. Resting CO increased from 3.5 ± 1.1 L/min at rest to 7.2 ± 2.7 L/min with peak exercise. Peak $VO_2$ averaged 12.6 ± 4.7 mL·kg·min. Peak $VO_2$ and peak CO had a significant linear correlation ($r = 0.64$; $P < .0001$). In general, gas-exchange methods ($CO_2$ and foreign gas methods) tend to be less accurate in patients with advanced stages of pulmonary disease. These patients have difficulties breathing the necessary minimum volume, which, if combined with significant ventilation inhomogeneity, causes inadequate gas mixing. Another disadvantage of the gas-exchange methods is that they require patient cooperation, which can be difficult to achieve in elderly and anxious patients.

It is fair to say that at this time there is no ideal method for determining CO or $CPO_{max}$ during exercise in patients with CHF. This largely depends on each clinician's decision about how much tradeoff between the accuracy of the method and the ease of measurement is acceptable. In general, impedance cardiography is easy to use, but there are some concerns about its use during exercise. On the other hand, rebreathing methods require patients to learn the rebreathing technique. In addition, the theoretic maximal value for CO or CPO is only obtained when all the cardiac measurements and settings (loading conditions, heart rate) are optimized and precisely obtained. Perfect optimization of these settings is in practice unattainable because compromises are inevitable (eg, patient ability to cope with the device, patient discomfort). Therefore, measurements made in practice are at best only an approximation of the true CO or CPO.

## Conclusions

Over the years, there have been many indicators found to be predictive of prognosis in CHF. They can broadly be divided into those that are surrogates of outcomes of CHF and those that are direct indicators of cardiac dysfunction. The former category includes serum urea and plasma brain natriuretic peptide. The variables belonging to the latter category are those in which improvement may lead directly to an improvement of the condition. Because the cardiac work related to exercise (eg, CO and CPO response to exercise) has been found to be not only a predictor of prognosis but also an indicator of cardiac function that correlates with exercise, this more likely belongs to the latter category of prognostic indicators. Cotter and colleagues[36] suggested that there could be a hierarchy of precision of these exercise measures, with the most indirect measures, such as NYHA functional class, exercise duration, and 6-minute walking distance, at the lower end of the hierarchy; peak $VO_2$ and submaximal measures such as $VE/VCO_2$ slope in the middle of the hierarchy; and the direct measures of cardiac reserve, such as CPOmax or its derivatives, being the most predictive.[36] However, it should be noted that the clinical usefulness of peak $VO_2$ was established by a large body of data acquired over two decades and is now widely used in many centers. These exercise parameters could be used to enhance the prognostic discriminatory power of peak $VO_2$. Questions remain regarding the reality of a ''maximal'' exercise test performed with invasive measurements and the safety of performing invasive tests in these groups of frail patients. Although noninvasive methods of assessing CO are available and increasingly easier to use, the available data have largely come from single centers with special interest in exercise physiology. Therefore, the widespread clinical application of assessment of cardiac work related to exercise in the evaluation of patients with CHF is still to be determined by larger clinical trials.

## References


1. Bennet LE, Keck BM, Hertz MI, Trulock EP, Taylor DO. Worldwide thoracic organ transplantation: a report from the UNOS/ISHLT international registry for thoracic organ transplantation. Clin Transpl 2001;25−40.
2. Edwards NM, Rajasinghe HA, John R, Chen JM, Itescu S, Mancini DM. Cardiac transplantation in over 1000 patients: a single institution experience from Columbia University. Clin Transpl 1999;249−61.
3. Stevenson LW, Warner SL, Steimle AE, et al. The impending crisis awaiting cardiac transplantation: modeling a solution based on selection. Circulation 1994;89:450−7.
4. Costanzo MR, Augustine S, Bourge R, et al. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Circulation 1995;92:3593−612.
5. Szlachcic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 1985;55:1037−42.
6. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778−6.
7. Wilson JR, Rayos G, Yeoh TK, Gothard P. Dissociation between peak exercise oxygen consumption and hemodynamic dysfunction in potential heart transplant candidates. J Am Coll Cardiol 1995;26:429−35.
8. Mancini D, LeJemtel TH. Is ventilatory classification preferable to peak oxygen consumption for risk stratification in heart failure? Circulation 2007;115:2376−8.
9. Becklake MR, Frank H, Dagenais GR, Ostiguy GL, Guzman CA. Influence of age and sex on exercise cardiac output. J Appl Physiol 1965; 20:938−47.
10. Stevenson LW, Couper G, Natterson B, et al. Target heart failure populations for newer therapies. Circulation 1995;92(Suppl II):II-174−81.
11. Osada N, Chaitman BR, Miller LW, et al. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise considered for heart transplantation. J Am Coll Cardiol 1998;31:577−82.
12. Robbins M, Francis G, Pashkow F, et al. Ventilatory and heart rate responses to exercise. Better predictors of mortality then peak oxygen consumption. Circulation 1999;100:2411−7.
13. Cohen-Solal A, Laperche T, Morvan D, Geneves M, Caviezel B, Gourgon R. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Analysis with gas exchange measurements and NMR spectroscopy. Circulation 1995;91:2924−32.
14. Aaronson KD, Mancini DM. Is percentage of predicted maximal exercise oxygen consumption a better predictor of survival than peak exercise oxygen consumption for patients with severe heart failure. J Heart Lung Transplant 1995;14:981−9.

15. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol 1996;27:345−52.
16. Kleber F, Vietzke G, Wernecke K, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation 2000;103: 967−72.
17. Gitt A, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 2002;106:3079−84.
18. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. Circulation 2007;115: 2410−7.
19. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving B-blockers. Circulation 2005;111:2313−8.
20. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660−7.
21. Lund LH, Aaronson KD, Mancini DM. Predicting survival in ambulatory patients with severe heart failure on beta-blocker therapy. Am J Cardiol 2003;92:1350−4.
22. Agostoni PG, Wasserman K, Perego GB, et al. Non-invasive measurement of stroke volume during exercise in heart failure patients. Clin Sci (Lond) 2000;98:545−51.
23. Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 2002;106:3079−84.
24. Stringer WW, Hansen JE, Wasserrman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. J Appl Physiol 1997;82:908−12.
25. Sulivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Circulation 1989;80:769−81.
26. Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic heart failure. Am J Cardiol 1985;55:22A−31A.
27. Tan LB. Cardiac pumping capability and prognosis in heart failure. Lancet 1986;ii:1360−3.
28. Griffin BP, Shah PK, Ferguson J, Rubin SA. Incremental prognostic value of exercise hemodynamic variables in chronic congestive heart failure secondary to coronary artery disease or to dilated cardiomyopathy. Am J Cardiol 1991;67:848−53.
29. Roul G, Moulichon ME, Bareiss P, et al. Prognostic factors of chronic heart failure in NYHA class II or III: value of invasive exercise hemodynamic data. Eur Heart J 1995;16:1387−98.
30. Chomsky DB, Lang CC, Rayos GH, et al. Hemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. Circulation 1996;94:3176−83.
31. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. Circ Res 1986;58:281−91.
32. Mancini D, Katz SD, Donchez L, Aaronson K. Coupling of hemodynamic measurements with oxygen consumption during exercise does not improve risk stratification in patients with heart failure. Circulation 1996;94:2492−6.
33. Metra M, Faggiano P, D'Aloia A, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. J Am Coll Cardiol 1999;33:943−50.
34. Williams SG, Cooke GA, Wright DJ, et al. Peak exercise cardiac output: a direct indicator of cardiac function strongly predictive of prognosis in chronic heart failure. Eur Heart J 2001;22:1496−503.
35. Williams SG, Jackson M, Cooke GA, et al. How do different indicators of cardiac pump function impact upon the long-term prognosis of patients with chronic heart failure. Am Heart J 2005;150:983.
36. Cotter G, Williams SG, Vered Z, Tan LB. Role of cardiac power in heart failure. Curr Opin Cardiol 2003;18:215−22.
37. Mendoza DD, Cooper HA, Panza JA. Cardiac power output predicts mortality across a broad spectrum of patients with acute cardiac diseases. Am Heart J 2007;153:366−70.
38. Fincke R, Hochman JS, Lowe AM, et al. For the SHOCK Investigators. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol 2004;44:340−8.
39. Cohen-Solal A, Tabet J, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. Eur Heart J 2002;23:806−14.
40. Scharf C, Merz T, Kioski W, et al. Noninvasive assessment of cardiac pumping capacity during exercise predicts prognosis in patients with congestive heart failure. Chest 2002;122:1333−9.
41. Williams SG, Tzeng BH, Barker D, Tan LB. Comparison and relation of indirect and direct dynamic indexes of cardiac pumping capacity in chronic heart failure. Am J Cardiol 2005;96:1149−50.
42. Butler J, Khadim G, Khalid A, et al. Cardiac output response to exercise and mortality in the beta-blocker era of heart failure therapy. Circulation 2004;110:605.
43. Moshkowitz Y, Kaluski E, Milo O, et al. Recent developments in cardiac output determination by bioimpedance: comparison with invasive cardiac output and potential cardiovascular application. Curr Opin Cardiol 2004;19:229−37.
44. Yancy C, Abraham WT. Noninvasive hemodynamic monitoring in heart failure: utilization of impedance cardiography. Congest Heart Fail 2003;9:241−50.
45. Treister N, Wagner K, Jansen PR. Reproducibility of impedance cardiography parameters in outpatients with clinically stable coronary artery disease. Am J Hypertens 2005;18:44S−50S.
46. Fuller HD. The validity of cardiac output measurement by thoracic impedance cardiography: a meta analysis. Clin Invest Med 1992;15: 103−12.
47. Packer M, Abraham WT, Mehra MR, et al. For the PREDICT Investigators. Utility of impedance cardiography for the identification of short-term risk of clinical decompensation in stable patients with chronic heart failure. J Am Coll Cardiol 2006;47:2245−52.
48. Scherhag A, Kaden JJ, Kentschke E, Sueselbeck T, Borggrefe M. Comparison of impedance cardiography and thermodilution-derived measurements of stroke volume and cardiac output at rest and during exercise testing. Cardiovasc Drugs Ther 2005;19:141−7.
49. Belardinelli R, Ciampani N, Costantini C, Blandini A, Purcaro A. Comparison of impedance cardiography with thermodilution and direct Fick methods for non-invasive measurements of stroke volume and cardiac output during incremental exercise in patients with ischemic cardiomyopathy. Am J Cardiol 1996;77:1293−301.
50. Defares JG. Determination of $pvCO_2$ from the exponential $CO_2$ rise during rebreathing. J Appl Physiol 1958;13:159−64.
51. Sun XG, Hansen JE, Stringer WW, et al. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. J Appl Physiol 2001;90:1798−810.
52. McHardy GJR. The relationship between the differences in pressure and content of carbon dioxide in arterial and venous blood. Clin Sci 1967;32:299−309.
53. Gabrielsen A, Videbaek R, Schou M, Damgaard M, Kastrup J, Norsk P. Non-invasive measurement of cardiac output in heart failure patients using a new foreign gas rebreathing technique. Clin Sci 2002; 102:247−52.
54. Kallay M, Hyde RW, Smith RJ, Schreiner BF. Cardiac output by rebreathing in patients with cardiopulmonary diseases. J Appl Physiol 1987;63:201−10.
55. Agostoni P, Cattadori G, Apostolo A, et al. Non-invasive measurement of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. J Am Coll Cardiol 2005;46:1779−81.
56. Lang C, Karlin P, Haythe J, Tsao L, Mancini D. Ease of non-invasive measurement of cardiac output coupled with peak VO2 determination at rest and during exercise in patients with heart failure. Am J Cardiol 2007;99:404−5.