Cardiopulmonary Exercise Testing

How Do We Differentiate the Cause of Dyspnea?

Richard V. Milani, MD; Carl J. Lavie, MD; Mandeep R. Mehra, MD

Case report: A 54-year-old man is referred for dyspnea on exertion. He has a history of type II diabetes and 35 pack-years of smoking. He suffered an anterior myocardial infarction 14 months ago, and on recent echocardiography was found to have an ejection fraction of 25%. Since his myocardial infarction, he has quit smoking and has gained an additional 27 pounds. He admits to a sedentary lifestyle and has recently tried to initiate an exercise program in an effort to lose weight. His current body mass index is 33.4 kg/m^2. He denies orthopnea but does have progressive lower-extremity edema.

What is the primary cause of his dyspnea? Is it ventilatory or circulatory? Obesity or deconditioning? What is the prognosis for his ischemic cardiomyopathy? What would be the appropriate diagnostic study to obtain these answers?

Background

Exercise stress testing is commonly used in clinical practice to evaluate the presence and severity of coronary ischemia. A significant enhancement of clinical information available during exercise can be obtained by concurrent measurement of respiratory gas exchange via use of a metabolic cart. This modality of stress testing has been called cardiopulmonary stress testing (CPX). This article will update the cardiovascular clinician on the utility of CPX in the modern cardiovascular practice.

A major function of the cardiovascular system is gas exchange, supplying O_2 and other fuels to working muscles, as well as removal of CO_2 and other metabolites. The heart, lungs, and pulmonary and systemic circulations form a single circuit for exchange of respiratory gases between the environment and the cells of the body.[1,2] Under steady-state conditions, respiratory oxygen uptake ($\dot{V}O_2$) and carbon dioxide outflow ($\dot{V}CO_2$) measured at the mouth are equivalent to oxygen utilization ($\dot{Q}O_2$) and carbon dioxide production ($\dot{Q}CO_2$) occurring in the cell, thus "external respiration" equals "internal respiration." CPX directly measures $\dot{V}O_2$, $\dot{V}CO_2$, and air flow (minute ventilation [$\dot{V}E$], tidal volume, and respiratory rate) on a breath-by-breath basis using a nonrebreathing valve connected to a metabolic cart. Samples of expired air are typically assessed every 15 seconds, and real-time data are expressed in both a tabular and graphic format. Additionally, oxygen saturation using finger or ear oximetry is monitored and recorded. From these data, numerous clinically relevant metabolic parameters can be derived (Table 1). The abbreviations used subsequently are explained in Table 1.

Metabolic Derangements in Disease

Metabolic derangements can occur at multiple sites within the circuitry of gas exchange, including the consumers at the muscle mitochondria, the transporters within the circulatory system, to the exchangers at the site of ventilation (Figure 1). Knowledge of site and extent of metabolic dysfunction can have a wide application in clinical medicine (Table 2).

CPX provides an ideal modality for the evaluation of patients presenting with exertional dyspnea and fatigue, at which time the clinician is faced with a breadth of differential diagnoses ranging from circulatory impairment to deconditioning. Standard diagnostic studies may not identify the true cause because circulatory and ventilatory reserves cannot be assessed from indices

From the Department of Cardiology, Ochsner Clinic Foundation, New Orleans, La.
Correspondence to Richard V. Milani, MD, Ochsner Heart and Vascular Institute, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121. E-mail rmilani@ochsner.org
(*Circulation.* 2004;110:e27-e31.)

***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000136811.45524.2F**

TABLE 1. Metabolic Parameters Measured or Derived From CPX

- **Peak oxygen uptake ($PkV̇O_2$):** The highest $V̇O_2$ achieved during the CPX and generally occurs at or near peak exercise. Reported as a weight-adjusted parameter in mL/kg per minute.
- **Maximal oxygen uptake ($V̇O_2max$):** The value achieved when $V̇O_2$ remains stable despite a progressive increase in the intensity of exercise. This is synonymous with peak aerobic capacity.
- **Breathing reserve (BR):** The reserve capacity of the ventilatory system, calculated as 1 minus the ratio of peak exercise minute ventilation ($V̇E$) to maximal voluntary ventilation. A normal value would be ≥30%.
- **Anaerobic threshold (AT):** The highest oxygen uptake attained without a sustained increase in blood lactate concentration and lactate/pyruvate ratio. Reported as a weight-adjusted parameter in mL/kg per minute.
- **Respiratory exchange ratio (RER):** Related but not equivalent to its cellular counterpart, the respiratory quotient, and is defined as the ratio of $V̇CO_2$ to $V̇O_2$.
- **Oxygen saturation (SpO_2):** The percentage of hemoglobin that is saturated with oxygen. Typically measured by pulse oximetry.
- **O_2 pulse:** The amount of O_2 consumed from the volume of blood delivered to tissues by each heartbeat; is calculated as: O_2 pulse=$V̇O_2$/heart rate.
- **Ventilation/carbon dioxide production ratio ($V̇E/V̇CO_2$):** Also known as the ventilatory equivalent for CO_2, this represents a respiratory control function that reflects chemoreceptor sensitivity, acid-base balance, and ventilatory efficiency.
- **Peak $V̇O_2$lean:** The peak oxygen uptake adjusted for lean body mass. Reported as a lean body weight–adjusted parameter in mL/kg per minute.

of resting cardiac and pulmonary function.[3] By virtue of obtaining gas exchange data under the provocation of exercise, CPX can discriminate among many subtle and often overlapping etiologies.

Etiology of Dyspnea

Using the algorithm provided in Figure 2, a peak oxygen uptake ($PkV̇O_2$) <85% of that predicted by age and gender is considered to be low, and a normal anaerobic threshold (AT) is generally closer to 60% of the predicted $PkV̇O_2$. For purposes of classification, an AT <40% of the predicted peak $V̇O_2$ is considered pathologically reduced and indicative of circulatory insufficiency. A breathing reserve (BR) <30% would indicate ventilatory impairment, especially when accompanied by oxygen desaturation with exercise, although a BR of 20% to 30% is deemed a borderline value. CPX is very useful in dyspneic patients with combined cardiac and pulmonary diseases who may have a reduction in both AT and BR, the more dominant of which may indicate the primary cause of the patient's functional limitation. A respiratory exchange ratio (RER) of <1.1 (particularly <1.0) in the absence of other metabolic abnormalities suggests poor effort, anxiety, or mild disease. Finally, this type of evaluation can be helpful in patients being evaluated for employment disability.

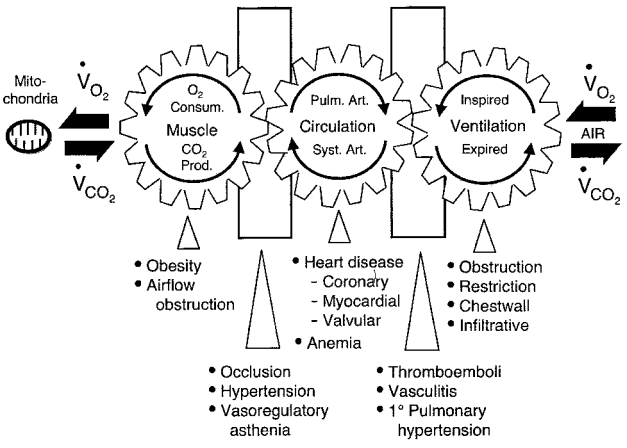

Figure 1. Derangements of gas exchange in disease. The gears represent the functional interdependence of the physiological components of the system. Reproduced with permission from Wasserman et al.[2]

Heart Failure Prognosis

From a clinical standpoint, probably the greatest utilization of CPX has been in the evaluation of patients with advanced systolic heart failure, in which CPX has gained widespread use by virtue of its superior prognostic capabilities in these patients. In the Veterans Administration Heart Failure Trial (V-HeFT), the mortality rate of patients with a $V̇O_2max$ ≤14.5 mL/kg per minute was double that of patients whose $V̇O_2max$ exceeded this value, a finding more significant than the drug treatment effect being studied.[4] In a separate investigation of heart failure patients referred for cardiac transplantation, Mancini et al[5] found that $PkV̇O_2$ was the single best predictor of survival. Moreover, transplantation could be safely deferred in patients whose $PkV̇O_2$ was >14 mL/kg per minute, where their survival exceeded that of patients undergoing heart transplantation. As a result of these seminal studies, CPX remains a pivotal modality in initial evaluation of patients with advanced heart failure, especially those who are considered for heart transplantation. The commonly used Weber-Janicki classification of exercise capacity in heart failure is provided in Table 3.[6]

Although a $PkV̇O_2$ cutoff of 14 mL/kg per minute remains an important prognostic discriminator in heart failure patients, our laboratory and others have described disparities in its

TABLE 2. Indications for CPX

- Evaluation for exertional dyspnea
- Development of an exercise prescription
- Direct measurement of $Pk\dot{V}O_2$ (functional capacity)
- Risk stratification and prognosis in heart failure
- Optimization of rate-adaptive pacemaker
- Congenital heart disease: determination of need for surgical repair and response to treatment
- Disability determination; worksite readiness
- Assess functional significance of regurgitant valvular heart disease

prognostic utility when evaluating patients with intermediate levels of $Pk\dot{V}O_2$ (between 10 and 18 mL/kg per minute) as well as in special populations such as women and obese patients.[7–9] Investigators have therefore sought to evaluate the predictive strength of other metabolic parameters in advanced heart failure, including percent predicted $Pk\dot{V}O_2$,[10] ventilation/carbon dioxide production ratio and slope,[11] oxygen consumption recovery,[12] and O_2 pulse.[13,14] Each investigation demonstrated variability with regard to each parameter's predictive strength. Moreover, a recent investigation suggests that the widespread use of β-blocker therapy in heart failure may require alteration of the $Pk\dot{V}O_2$ cutoff point of 14 mL/kg per minute to a lower value.[15]

A fundamental understanding of O_2 consumption may explain the disparate observations in women and obese patients. Although $Pk\dot{V}O_2$ is corrected for total body weight, body fat is "metabolically inert," consuming essentially no oxygen, and can represent a significant portion of total weight. Moreover, considerable variability in body composition is present across populations, including those with heart failure. We demonstrated that correcting $Pk\dot{V}O_2$ for lean body mass ($Pk\dot{V}O_2$lean) provides a more refined discriminator of outcome than traditionally reported total weight–adjusted values.[16] In heart failure patients, a $Pk\dot{V}O_2$lean cutoff of 19 mL/kg per minute provides a more robust discriminator than the total weight–adjusted figure of 14 mL/kg per minute. As such, we routinely assess body fat using the 3-site skinfold method before each CPX study to calculate lean body mass.[17] From a practical standpoint, this adds only 3 to 4 minutes to the time required to perform a CPX. Using the lean adjusted peak oxygen uptake, we eliminated previously observed disparities between genders, and between obese and nonobese patients, in predicting outcome in heart failure. We also reported the usefulness of peak O_2 pulse (cutoff value 10 mL/beat), especially when corrected for lean body mass (cutoff value 14 mL/beat), in predicting prognosis in patients with chronic systolic heart failure.[18]

Less commonly, clinicians need to evaluate heart failure patients who have very limited exercise tolerance resulting from low threshold angina or severe ventricular arrhythmias, in which an early exercise surrogate of $Pk\dot{V}O_2$ would be required for risk stratification. Our laboratory and others successfully used the pattern of $\dot{V}E/\dot{V}CO_2$ change during early exercise to predict $Pk\dot{V}O_2$ and subsequent outcome in such patients.[11,19,20] We found that a decrease in $\dot{V}E/\dot{V}CO_2$ of $<10\%$ early in exercise predicts a $Pk\dot{V}O_2$ of <14 mL/kg per minute and poor outcome in patients with heart failure.

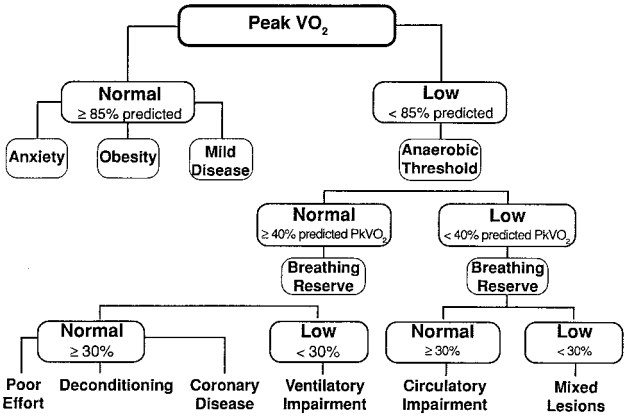

Figure 2. Flow chart for the differential diagnosis of exertional dyspnea and fatigue. Used with permission from Wasserman et al.[2]

Pitfalls in CPX Interpretation

In general, data obtained from CPX are reliable and reproducible, but as with any clinical modality, there may be pitfalls in collecting and interpreting metabolic data obtained during exercise. Among the most important requirements in performing CPX is a skilled technician who provides thorough instruction to patients before testing, as well as encouragement during exercise. The technician must be meticulous in monitoring data as they are acquired and be cognizant of system leaks (breathing around mouthpiece, nasal breathing, or sampling line leaks) in data acquisition.

$\dot{V}O_2$ is now a commonly used end point in various clinical investigations, particularly heart failure trials.[21–23] Changes in $Pk\dot{V}O_2$, therefore, may have important prognostic and therapeutic consequences.[24,25] An increase in $Pk\dot{V}O_2$ by as little as 1 mL/kg per minute can mean as much as a 69-second gain in treadmill exercise time, as well as improved cardiovascular outcomes.[24,26] In this context, however, it is important to remember that several factors, including effort, can influence the $Pk\dot{V}O_2$ value. Consequently, $Pk\dot{V}O_2$ may not always be the appropriate metabolic end point to evaluate the effects of a given intervention (Figure 3). Because $Pk\dot{V}O_2$ can be effort dependent, Pina and Karalis[27] demonstrated that AT rather than $Pk\dot{V}O_2$ was a more reproducible and effort-independent parameter in heart

TABLE 3. Functional Impairment During Incremental Treadmill Testing in Heart Failure: Weber-Janicki Classification*

Severity	Class	Peak $\dot{V}O_2$, mL/kg per minute	Anaerobic Threshold	Maximal Cardiac Index, L/min per m^2
None to mild	A	>20	>14	>8
Mild to moderate	B	16–20	11–14	6–8
Moderate to severe	C	10–16	8–11	4–6
Severe	D	6–10	5–8	2–4
Very severe	E	<6	<4	<2

*Data derived from Weber et al.[6]

failure patients undergoing serial testing. Therefore, AT and knowledge of RER must accompany $Pk\dot{V}O_2$ data when making clinical decisions, particularly with regard to results of therapeutic interventions.[28] In the less common event that AT is not achieved, an occurrence in up to 30% of our heart failure population, we successfully used the pattern of $\dot{V}E/\dot{V}CO_2$ change in early exercise to predict $Pk\dot{V}O_2$ and subsequent outcomes in such patients.[11,19,20]

Conclusions

Returning to our case study, the patient exercised for 9 minutes on an intermediate ramping protocol, stopping secondary to shortness of breath, achieving a peak heart rate of 149 bpm (90% of predicted). There were no electrocardiographic changes suggestive of ischemia. The principal metabolic data were as follows:

$Pk\dot{V}O_2$=19.2 mL/kg per minute (63% of predicted), measured metabolic equivalents =5.5
$Pk\dot{V}O_2$lean=30.33 mL/kg per minute (% body fat =36.7%)
AT=15.5 mL/kg per minute (51% of predicted)
BR=32%
Oxygen saturation at peak=98%
RER=1.13

On the basis of the interpretative schema in Figure 2, we conclude that this patient demonstrated an adequate effort (RER ≥1.1) with a low peak aerobic capacity ($Pk\dot{V}O_2$ 63% of predicted). The AT was normal, suggesting adequate circulatory status. Additionally, the BR and O_2 saturation at peak exercise were in the normal range, thereby excluding a ventilatory etiology to the patient's symptoms. Despite the underlying presence of a cardiomyopathy, the most likely explanation for the patient's symptoms is deconditioning, in large part due to the patient's obesity. The cardiopulmonary data suggest a very favorable prognosis for his cardiomyopathy. The patient's symptoms can be improved and possibly eliminated by enrollment into a structured conditioning program of exercise training.

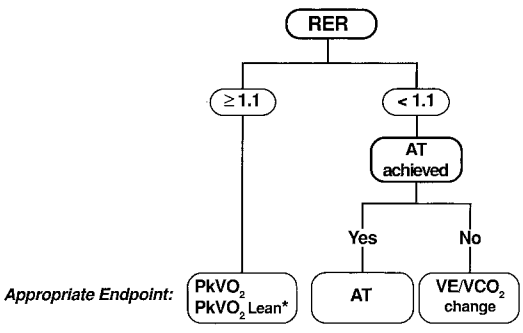

Figure 3. Metabolic endpoint to evaluate results of therapeutic interventions. (See Table 1 for abbreviations.) *, particularly useful in women and obese patients.

References

1. Weber KT, Janicki JS, Shroff SG, Likoff MJ. The cardiopulmonary unit: the body's gas transport system. *Clin Chest Med*. 1983;4: 101–110.
2. Wasserman K, Hansen J, Sue D, Casaburi R, Whipp B. *Principles of Exercise Testing and Interpretation*. Philadelphia, Pa: Lea & Febiger; 1999.
3. Neuberg GW, Friedman SH, Weiss MB, Herman MV. Cardiopulmonary exercise testing: the clinical value of gas exchange data. *Arch Intern Med*. 1988;148:2221–2226.
4. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991; 325:303–310.
5. 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;83:778–786.
6. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation*. 1982; 65:1213–1223.
7. Richards DR, Mehra MR, Ventura HO, Lavie CJ, Smart FW, Stapleton DD, Milani RV. Usefulness of peak oxygen consumption in predicting outcome of heart failure in women versus men. *Am J Cardiol*. 1997;80: 1236–1238.
8. Lavie CJ, Milani R, Mehra MR, Ventura HO, Messerli FH. Obesity, weight reduction and survival in heart failure. *J Am Coll Cardiol*. 2002;39:1563; author reply 2002; 39:1563–1564.
9. Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am J Cardiol*. 2003;91:891–894.
10. Stelken AM, Younis LT, Jennison SH, Miller DD, Miller LW, Shaw LJ, Kargl D, Chaitman BR. 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: 345–352.
11. Milani RV, Mehra MR, Reddy TK, Lavie CJ, Ventura HO. Ventilation/carbon dioxide production ratio in early exercise predicts poor functional capacity in congestive heart failure. *Heart*. 1996;76:393–396.
12. Robbins M, Francis G, Pashkow FJ, Snader CE, Hoercher K, Young JB, Lauer MS. Ventilatory and heart rate responses to exercise: better predictors of heart failure mortality than peak oxygen consumption. *Circulation*. 1999;100:2411–2417.
13. Cohen-Solal A, Barnier P, Pessione F, Seknadji P, Logeart D, Laperche T, Gourgon R. Comparison of the long-term prognostic value of peak exercise oxygen pulse and

peak oxygen uptake in patients with chronic heart failure. *Heart*. 1997;78:572–576.
14. Cohen-Solal A, Tabet JY, 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: 806–814.
15. Zugck C, Haunstetter A, Kruger C, Kell R, Schellberg D, Kubler W, Haass M. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. *J Am Coll Cardiol*. 2002;39:1615–1622.
16. Osman AF, Mehra MR, Lavie CJ, Nunez E, Milani RV. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. *J Am Coll Cardiol*. 2000;36:2126–2131.
17. Jackson AS, Pollock ML. Practical assessment of body composition. *Physician Sports Med*. 1985;13:76–90.
18. Lavie CJ, Milani RV, Mehra MR. Peak exercise oxygen pulse and prognosis in chronic heart failure. *Am J Cardiol*. 2004;93: 588–593.
19. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, Sperfeld A, Glaser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation*. 2000;101:2803–2809.
20. Koike A, Itoh H, Kato M, Sawada H, Aizawa T, Fu LT, Watanabe H. Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. *Chest*. 2002;121:1581–1588.
21. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation*. 2003;107:294–299.
22. Giannuzzi P, Temporelli PL, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) trial. *Circulation*. 2003;108:554–559.
23. Jaski BE, Lingle RJ, Kim J, Branch KR, Goldsmith R, Johnson MR, Lahpor JR, Icenogle TB, Pina I, Adamson R, Favrot LK, Dembitsky WP. Comparison of functional capacity in patients with end-stage heart failure following implantation of a left ventricular assist device versus heart transplantation: results of the experience with left ventricular assist device with exercise trial. *J Heart Lung Transplant*. 1999;18: 1031–1040.
24. Grigioni F, Barbieri A, Magnani G, Potena L, Coccolo F, Boriani G, Specchia S, Carigi S, Musuraca A, Zannoli R, Magelli C, Branzi A. Serial versus isolated assessment of clinical and instrumental parameters in heart failure: prognostic and therapeutic implications. *Am Heart J*. 2003;146:298–303.
25. Ventura HO, Mehra MR. Hippocrates and prognosis in heart failure: the challenge of static and dynamic measurements. *Am Heart J*. 2003;146:215–217.
26. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
27. Pina IL, Karalis DG. Comparison of four exercise protocols using anaerobic threshold measurement of functional capacity in congestive heart failure. *Am J Cardiol*. 1990;65: 1269–1271.
28. Mezzani A, Corra U, Bosimini E, Giordano A, Giannuzzi P. Contribution of peak respiratory exchange ratio to peak VO2 prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. *Am Heart J*. 2003;145:1102–1107.