

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



## **Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association**

Gary J. Balady, Ross Arena, Kathy Sietsema, Jonathan Myers, Lola Coke, Gerald F. Fletcher, Daniel Forman, Barry Franklin, Marco Guazzi, Martha Gulati, Steven J. Keteyian, Carl J. Lavie, Richard Macko, Donna Mancini, Richard V. Milani, on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease and Interdisciplinary Council on Quality of Care and Outcomes Research

*Circulation* 2010;122;191-225; originally published online Jun 28, 2010;

DOI: 10.1161/CIR.0b013e3181e52e69

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2010 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/122/2/191>

Subscriptions: Information about subscribing to *Circulation* is online at  
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:  
[journalpermissions@lww.com](mailto:journalpermissions@lww.com)

Reprints: Information about reprints can be found online at  
<http://www.lww.com/reprints>

## Clinician's Guide to Cardiopulmonary Exercise Testing in Adults

### A Scientific Statement From the American Heart Association

Gary J. Balady, MD, FAHA, Chair; Ross Arena, PhD, FAHA; Kathy Sietsema, MD; Jonathan Myers, PhD, FAHA; Lola Coke, RN, PhD; Gerald F. Fletcher, MD, FAHA; Daniel Forman, MD; Barry Franklin, PhD, FAHA; Marco Guazzi, MD, PhD; Martha Gulati, MD; Steven J. Keteyian, PhD; Carl J. Lavie, MD; Richard Macko, MD; Donna Mancini, MD; Richard V. Milani, MD, FAHA; on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; and Interdisciplinary Council on Quality of Care and Outcomes Research

Exercise testing remains a remarkably durable and versatile tool that provides valuable diagnostic and prognostic information regarding patients with cardiovascular and pulmonary disease. Exercise testing has been available for more than a half century and, like many other cardiovascular procedures, has evolved in its technology and scope. When combined with exercise testing, adjunctive imaging modalities offer greater diagnostic accuracy, additional information regarding cardiac structure and function, and additional prognostic information. Similarly, the addition of ventilatory gas exchange measurements during exercise testing provides a wide array of unique and clinically useful incremental information that heretofore has been poorly understood and underutilized by the practicing clinician. The reasons for this are many and include the requirement for additional equipment (cardiopulmonary exercise testing [CPX] systems), personnel who are proficient in the administration and interpretation of these tests, limited or absence of training of cardiovascular specialists and limited training by pulmonary specialists in this technique, and the lack of understanding of the value of CPX by practicing clinicians.

Modern CPX systems allow for the analysis of gas exchange at rest, during exercise, and during recovery and yield

breath-by-breath measures of oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ ), and ventilation ( $\dot{V}E$ ). These advanced computerized systems provide both simple and complex analyses of these data that are easy to retrieve and store, which makes CPX available for widespread use. These data can be readily integrated with standard variables measured during exercise testing, including heart rate, blood pressure, work rate, electrocardiography findings, and symptoms, to provide a comprehensive assessment of exercise tolerance and exercise responses. CPX can even be performed with adjunctive imaging modalities for additional diagnostic assessment. Hence, CPX offers the clinician the ability to obtain a wealth of information beyond standard exercise electrocardiography testing that when appropriately applied and interpreted can assist in the management of complex cardiovascular and pulmonary disease.

Although CPX has long been used in the assessment of athletic performance and in research venues, its burgeoning value in the clinical setting has prompted the American Heart Association to convene a writing group of experts in the field to generate this "Clinician's Guide to Cardiopulmonary Exercise Testing in Adults." The purpose of this document is to supplement existing exercise testing guidelines with a

---

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on March 24, 2010. A copy of the statement is available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the "topic list" link or the "chronological list" link (No. KB-0041). To purchase additional reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

The American Heart Association requests that this document be cited as follows: Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV; on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; and Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:191-225.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit <http://www.americanheart.org/presenter.jhtml?identifier=3023366>.

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <http://www.americanheart.org/presenter.jhtml?identifier=4431>. A link to the "Permission Request Form" appears on the right side of the page.

(*Circulation*. 2010;122:191-225.)

© 2010 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIR.0b013e3181e52e69

**Table 1. Abbreviations**

CO <sub>2</sub>	Carbon dioxide
CPX	Cardiopulmonary exercise testing
C(a-v) <sub>O<sub>2</sub></sub>	Arteriovenous oxygen difference
EOB	Exercise oscillatory breathing
F <sub>E</sub> CO <sub>2</sub>	Fraction of carbon dioxide in expired air
F <sub>E</sub> O <sub>2</sub>	Fraction of oxygen in expired air
FEV <sub>1</sub>	Forced expiratory volume in 1 second
MET	Metabolic equivalent
MVV	Maximum voluntary ventilation
O <sub>2</sub>	Oxygen
OUES	Oxygen-uptake efficiency slope
P <sub>ET</sub> CO <sub>2</sub>	Partial pressure of end-tidal carbon dioxide
P <sub>ET</sub> O <sub>2</sub>	Partial pressure of end-tidal oxygen
RER	Respiratory exchange ratio
$\dot{V}$ CO <sub>2</sub>	Carbon dioxide output
V <sub>D</sub>	Volume of dead space
$\dot{V}$ E	Minute ventilation
$\dot{V}$ E/ $\dot{V}$ CO <sub>2</sub>	Ventilatory equivalent of carbon dioxide
$\dot{V}$ E/ $\dot{V}$ O <sub>2</sub>	Ventilatory equivalent of oxygen
$\dot{V}$ O <sub>2</sub>	Oxygen uptake
VT	Ventilatory threshold

comprehensive overview of CPX. Accordingly, this “Clinician’s Guide” provides a summary and interpretation of the most relevant literature to address the following broad topic areas: (1) CPX technology; (2) key CPX variables and their clinical implications; (3) current clinical and emerging applications of CPX; and (4) interpretation and reporting of CPX test data. The recommendations made in the present document are based primarily on expert consensus interpretation of published data when available, because there are essentially no randomized trials to address diagnostic and prognostic applications of CPX. This “Clinician’s Guide” has been peer-reviewed by outside reviewers nominated by the American Heart Association and has been approved by the Science and Advisory Coordinating Committee of the American Heart Association. This “Clinician’s Guide” will be considered current unless the American Heart Association revises or withdraws it from distribution.

The abbreviations for selected terms used throughout this document appear in Table 1.

### Gas Exchange Physiology in Health and Disease

The ability to perform physical exercise is critically related to the cardiovascular system’s capacity to supply oxygen (O<sub>2</sub>) to the muscles and the pulmonary system’s ability to clear carbon dioxide (CO<sub>2</sub>) from the blood via the lungs. The cardiovascular and respiratory systems work together to provide both a delivery system (of O<sub>2</sub>) and a removal system (of CO<sub>2</sub>) from the tissues. There are 4 processes that occur to make this happen:

1. Pulmonary ventilation, or the movement of air into and out of the lungs;

2. Pulmonary diffusion, or the exchange of O<sub>2</sub> and CO<sub>2</sub> between the lungs and the blood;
3. Transport of O<sub>2</sub> and CO<sub>2</sub> in the blood;
4. Capillary gas exchange, or the exchange of O<sub>2</sub> and CO<sub>2</sub> between the capillary blood and the working muscle.

The first 2 processes are referred to as *external respiration* because they involve the movement of gases from the ambient air into the lungs and then the blood. The fourth step is commonly termed *internal respiration* because it involves gas exchange between the blood and the tissues. These 2 processes are linked by the circulatory system. CPX is valuable because taxing the mechanisms responsible for external and internal respiration by exercise can frequently reveal abnormalities not apparent at rest. In addition, typical pulmonary and cardiac function tests performed at rest cannot reliably determine exercise capacity or the particular mechanisms underlying exercise intolerance among individual subjects with cardiac or pulmonary disease.

The increase in oxygen uptake by the working muscles is facilitated most importantly by an increase in cardiac output (heart rate × stroke volume), which may increase to up to 6 times that at rest. Cardiac output is also redistributed away from nonactive tissues (eg, splanchnic and renal) to the skeletal muscles, which facilitates greater O<sub>2</sub> delivery. A concomitant increase in blood flow to the lungs occurs, both by the increase in cardiac output and by vasodilation of the pulmonary vessels. A greater extraction of O<sub>2</sub> from the blood also occurs as the blood perfuses the muscles, which results in a widening of the arteriovenous oxygen (a- $\dot{V}$ O<sub>2</sub>) difference.

In normal subjects, minute ventilation ( $\dot{V}$ E) increases in proportion to the increase in work rate. During inhalation, only part of the tidal volume of air reaches the alveoli, where gas exchange takes place in the lungs. The air that remains in the respiratory passages that does not participate in gas exchange is known as the dead space volume (V<sub>D</sub>). During exercise, dilation of the respiratory passages causes the V<sub>D</sub> to increase, but because tidal volume also increases, adequate alveolar ventilation, and therefore gas exchange, is maintained. This is termed *normal ventilation-perfusion matching*. Many disease states can alter the matching of ventilation to perfusion. For example, in many manifestations of pulmonary disease, exercise is limited by a higher than normal dead space, because there are fewer healthy tissues in the lungs with which gas exchange can take place. The increase in  $\dot{V}$ E during exercise must be matched by an increase in blood flow; that is, cardiac output must increase to appropriately match ventilation so that necessary gas exchange can occur. One of the hallmarks of chronic heart failure is an impaired cardiac output response to exercise; this can also lead to a mismatching of ventilation to perfusion, in which ventilation must increase disproportionately to the metabolic needs to compensate for inadequate perfusion. The degree to which ventilation is abnormally heightened during exercise is directly related to the severity of disease and is a strong marker of prognosis. The various expressions of this response and other causes of inefficient ventilation and their relation to prognosis are detailed in later sections of the present document.<sup>1</sup>

## Procedures for CPX

### Calibration of Gas Exchange Systems

Modern CPX systems contain rapidly responding O<sub>2</sub> and CO<sub>2</sub> sensors that allow for the calculation of oxygen uptake and carbon dioxide output at rest, during exercise, and during recovery, as frequently as breath by breath. Although manufacturers' recommendations vary considerably regarding calibration, all CPX systems should be calibrated immediately before each exercise test. This should include calibration of airflow, volumes, and both the O<sub>2</sub> and CO<sub>2</sub> analyzers. Gas analyzers and flow meters are prone to drift, which can lead to serious errors. Today, nearly all commercially available systems have convenient calibration procedures controlled by a microprocessor. Validation studies have been performed on many of the computerized systems.<sup>2-4</sup> Because ambient conditions affect the concentration of O<sub>2</sub> in the inspired air, temperature, barometric pressure, and humidity should be taken into account. Many modern CPX systems automatically quantify these conditions and make appropriate adjustments to calculate the inspired O<sub>2</sub> concentration. If this feature is not available, these atmospheric conditions should be measured by an external device and input into the CPX system. This should be done before every calibration of the system. A copy of the calibration report should be printed before each test and should be attached to the test report. Valid interpretation of test results is possible only if calibration values are appropriate. The test should not be performed if the system does not calibrate.

The following specific calibration procedures should be performed to ensure that valid data are obtained:

1. Room air (FiO<sub>2</sub>) should read 20.93±0.03% O<sub>2</sub> at 0% humidity; however, the precise fraction is dependent on humidity and should be adjusted accordingly. A calibration source that contains 100% nitrogen should read 0% O<sub>2</sub>. The analyzer should be checked further by simulating the fraction of expired O<sub>2</sub> (FEO<sub>2</sub>) during the test, that is, approximately 16% O<sub>2</sub>. Calibration gases should be used as provided by the system manufacturer. The exercise laboratory should be well ventilated to ensure a representative fraction of inspired O<sub>2</sub>; a small fan is helpful for this purpose.
2. The CO<sub>2</sub> analyzer should read a room air fraction of 0.03±0.02% and should not change when the 100% N<sub>2</sub> or 16% O<sub>2</sub> fractions are sampled from the calibration tanks. The CO<sub>2</sub> analyzer should be checked further by simulating the fraction of expired CO<sub>2</sub> (FECO<sub>2</sub>) during exercise, that is, approximately 4% CO<sub>2</sub>.
3. For breath-by-breath CPX systems in particular, it is also necessary to check the inherent response times of the analyzer and to precisely determine the transport delay between sampling point and analyzers. It is important that the system meet the specifications outlined by the manufacturer; this feature is available in most systems.
4. Measurement of ventilatory volume can now be easily achieved with 1 of several devices, including pneumotachometers, mass flow sensors, pitot tube flow meters, and turbine volume transducers. All can be validated before testing by ascertaining a stable baseline (0 L/min) and injecting a known volume (usually 3 or 4

L) from a syringe. It is preferable to perform several injections at different flow rates to ensure stability; the average error should be within ±3% of the known volume.<sup>5</sup>

### Software Considerations

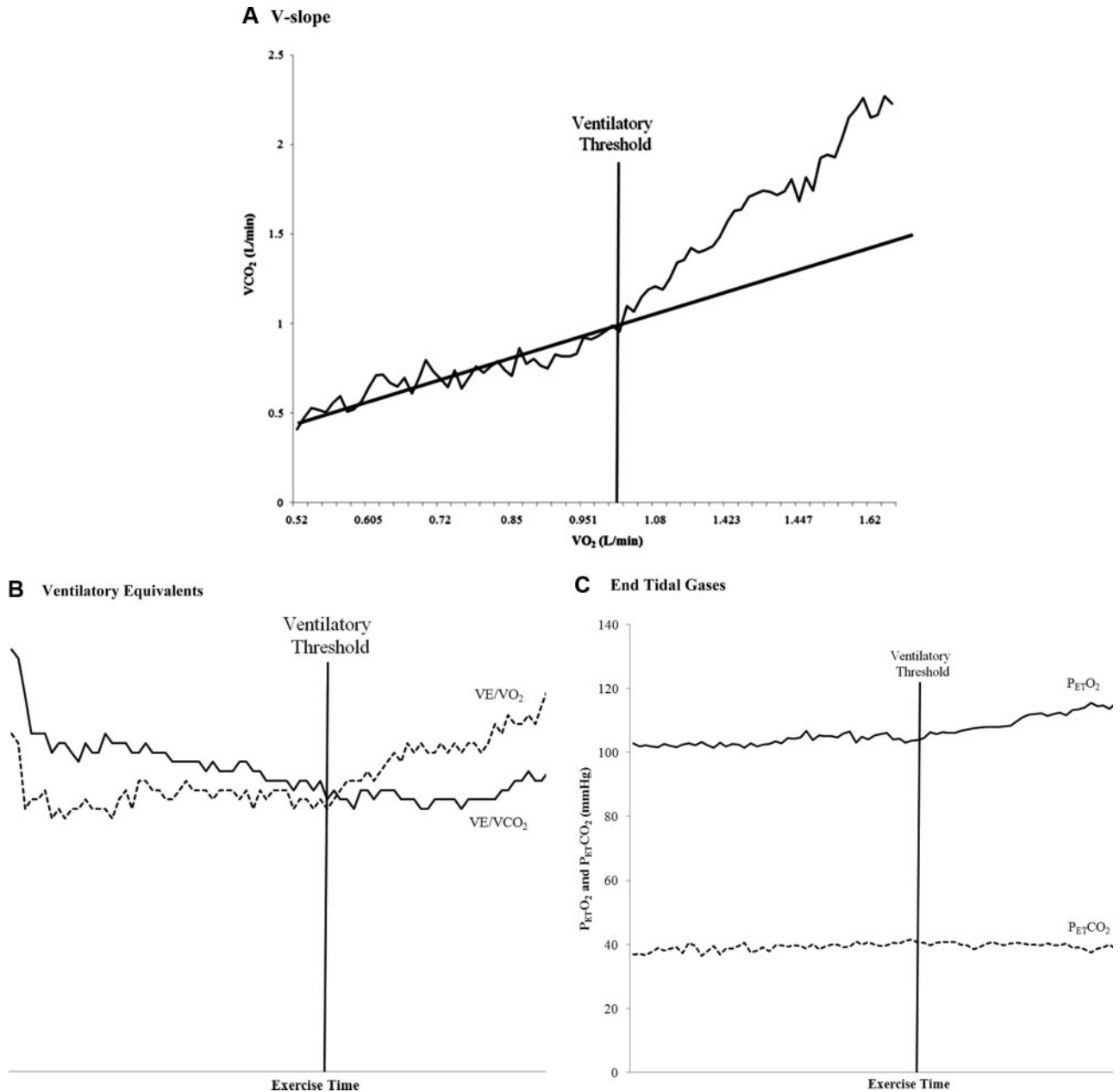
The many different CPX systems each have unique software for processing, analyzing, and displaying data. The software determines the type and amount of data extracted, the summary reports, data sampling and averaging, and graphical reports. Most systems permit the user to define the specific responses and the way in which they are displayed during the test and are summarized in test reports. These are important considerations because they can have a significant effect on the test results. Reporting of test results will be discussed in detail below (see Assessing and Reporting CPX Data). Patient characteristics used in the calculation of normal predicted values, including age, sex, and body size, are also generally entered into the CPX software. Equations for normal standards can vary widely, and population specificity should thus be considered when a patient's response is evaluated as a percentage of normal.

Modern CPX systems provide a wide variety of automated reports, data averaging and sampling techniques, calibration methods, and graphics. Although computerization has facilitated ease of use, it has also led to some confusion regarding which variables to consider and how the data should be expressed and interpreted. One important area in need of standardization is data sampling. Differences in sampling (eg, breath by breath, an averaged number of breaths, or time intervals such as 10, 15, or 30 seconds) can have a profound effect on test results. There is a need for consistency in this area that appropriately balances high precision but high variability (breath-by-breath method) with imprecision but low variability (long sampling intervals); therefore, for routine clinical use, if feasible, the averaging of data over 20- to 30-second intervals is generally sufficient to reduce the effect of random noise in breath-by-breath measurements. It is recommended that rolling 30-second averages be used that are printed frequently (eg, 10 seconds).<sup>6</sup> It is useful to display the key data in a time down format with rest, beginning of exercise, and peak exercise clearly defined. There are also an unlimited number of graphical choices, and on most systems, these can be specified by the user. As a minimum, a graphical display of the V-slope<sup>7</sup> and the  $\dot{V}_E/\dot{V}_{O_2}$  and  $\dot{V}_E/\dot{V}_{CO_2}$  responses with time should be printed to verify the ventilatory threshold (VT). Examples of these are presented in Figure 1 and will be discussed in detail below (see Variables From CPX and Their Physiological Implications).

Automated interpretation programs that provide diagnoses based on the CPX test results are common. These can be useful supplements to the test report but should not be relied on for making clinical decisions; any automated interpretation, including determination of VT, should be overread by an individual experienced in the applications of CPX.

### System Maintenance and Quality Control

It is important that validation of the CPX system be performed on a regular basis. Gas exchange measurements are



**Figure 1.** V-slope, ventilatory equivalents, and end-tidal methods for the detection of VT. See text for details.

highly reproducible within a given subject if testing methods are consistent. One method often used to validate a system's performance is to test laboratory staff members at a matched submaximal work rate on a periodic basis (perhaps every 4 to 6 months). It is recommended that several staff members participate in this process, each using a slightly different steady state submaximal work rate. As long as a subject is in a steady state (ie, a constant metabolic rate),  $\dot{V}O_2$  and other CPX variables should be reproducible. Four to 6 minutes of constant-load, low- to moderate-intensity exercise is required for most individuals to achieve a steady state. Acceptable limits of variation for  $\dot{V}O_2$ ,  $\dot{V}CO_2$ , and  $\dot{V}E$  for a given steady state work rate are shown in Table 2.<sup>8,9</sup> In addition to being reproducible,  $\dot{V}O_2$  should fall within an acceptable range when compared with estimated  $\dot{V}O_2$  based

on the external work rate. The recommended values for steady state work are best estimated with American College of Sports Medicine equations.<sup>10</sup> In this context, estimated  $\dot{V}O_2$  is only valid during steady state exercise;

**Table 2. Limits of Variation in Gas-Exchange Variables Obtained by Repeated Study of the Same Subject at a Given Submaximal Work Rate**

Variable	Variation, %
Oxygen uptake	±5.0
Carbon dioxide output	±6.0
Minute ventilation	±5.5
RER	±3.0

Data from Jones<sup>8</sup> and Wilmore et al.<sup>9</sup>

the inaccuracies of estimating  $\dot{V}O_2$  during progressive exercise are well documented.<sup>10,11</sup>

Even when appropriate calibration procedures are followed, modern automated CPX systems can provide results that appear to be accurate yet may be erroneous. Respiratory gas exchange simulators that calibrate CPX systems are available.<sup>12</sup> These systems involve injecting a precise gas mixture at various specified ventilation rates that can simulate rest and exercise at known ventilation,  $\dot{V}O_2$ , and  $\dot{V}CO_2$  rates. Although not necessary, simulators provide reference values for comparison with a CPX system and therefore can be helpful to ensure precision of a system. However, these systems do not perfectly simulate exercise conditions in humans, including variations in breathing patterns, temperature and humidity corrections, and other factors.

### Selection of Exercise Test Protocol

Assessment of exercise capacity typically is performed on a motorized treadmill or a stationary cycle ergometer. In the United States, however, treadmill exercise is generally the preferred modality. Furthermore, untrained subjects will usually terminate cycle exercise because of quadriceps fatigue at a  $\dot{V}O_2$  that is on average 10% to 20% below their treadmill peak  $\dot{V}O_2$ .<sup>13</sup> Cycle ergometry also requires subject cooperation in maintaining pedal speed at the desired level, usually  $\approx 60$  rpm, although modern ergometers that are electronically braked maintain a steady work rate at variable speeds. Several studies have demonstrated a consistent relationship between exercise capacity determined with a treadmill and a cycle ergometer, although the latter mode of exercise tends to produce a lower peak  $\dot{V}O_2$ .<sup>14,15</sup> Cycle ergometry may be preferred in subjects with gait or balance instability, severe obesity, or orthopedic limitations or when simultaneous cardiac imaging is planned. Although arm ergometry may be used to assess the exercise capacity of wheelchair athletes or other individuals with lower-limb disabilities, most persons cannot achieve work rates comparable to those obtained with leg exercise because of the smaller, often deconditioned muscle mass.<sup>16</sup>

The selection of an appropriate exercise test protocol for assessing exercise capacity is important. Exercise test protocols with large stage-to-stage increments in energy requirements generally have a weaker relationship between measured  $\dot{V}O_2$  and work rate. The Balke and Ware,<sup>17</sup> Naughton,<sup>18</sup> and individualized ramp protocols, which involve only modest increases in work rate per stage, are recommended for this reason. Ramp protocols typically involve increments in work rate at intervals of <10 to 60 seconds.<sup>19</sup> Regardless of the specific protocol chosen, the protocol should be tailored to the individual to yield a fatigue-limited exercise duration of  $\approx 8$  to 12 minutes. Even with exercise test protocols that use modest increases in work rate, results may still indicate a nonlinear relationship between  $\dot{V}O_2$  and work rate when test duration is <6 minutes. Conversely, when such protocols result in exercise durations >12 minutes, subjects may terminate exercise because of specific muscle fatigue or orthopedic factors rather than cardiopulmonary end points. In instances in which there is an expectation of >12 minutes of exercise, a test protocol that uses a more progressive ap-

proach to increasing work rate, for example, the Bruce protocol,<sup>20</sup> should be considered. Finally, minimal or no handrail support should be encouraged when possible during treadmill exercise testing, because handrail support reduces the work performed at any given level and alters the relationship between  $\dot{V}O_2$  and work rate.

### Level of Supervision, Monitoring Issues, and Risk of Adverse Events

Major complications of exercise testing include death, myocardial infarction, arrhythmia, hemodynamic instability, and orthopedic injury. Fortunately, adverse events are rare during properly supervised tests. Among large series of subjects with and without known disease, serious complications (including myocardial infarction and other events requiring hospitalization) have been reported to occur in <1 to as many as 5 per 10 000 tests, and death has occurred in  $\approx 0.5$  per 10 000 tests,<sup>21–23</sup> although the incidence of adverse events varies depending on the study population. The safety of CPX was evaluated among 2037 subjects who completed 4411 CPX in the HF-ACTION study (Heart Failure: A Controlled Trial Investigating Outcomes of exercise traiNing). There were no deaths, and the rate of nonfatal major cardiovascular events was <0.5 per 1000 tests.<sup>24</sup> Although the event rate is relatively low regardless of the patient population studied, complications resulting from exercise testing do occur. Consequently, it is essential that exercise test supervisory personnel be familiar with the clinical indications for the use of such testing, as well as the signs and symptoms of and clinical responses to adverse events, to minimize patient risk. The American College of Cardiology/American Heart Association clinical competence statement on stress testing outlines a series of cognitive skills necessary for performance, supervision, and interpretation of exercise tests.<sup>21</sup> A detailed description of medical supervision and risk stratification for exercise testing is provided elsewhere.<sup>6</sup>

General methodological guidelines for exercise testing laboratories are available.<sup>6</sup> Electrocardiographic monitoring of heart rate with multiple-lead electrocardiographic waveforms should be continuous throughout exercise and for at least 6 minutes into recovery for diagnostic testing in patients with suspected disease. It must be recognized that activity-compatible torso electrodes may produce significant changes in electrocardiography morphology compared with standard limb leads. Consequently, the former cannot be used as a substitute for, or for comparison with, the standard resting 12-lead electrocardiogram (ECG).<sup>25</sup> Blood pressure should be measured periodically throughout the test, at least at every 2 to 3 minutes and more frequently in some high-risk patients, as well as in recovery during electrocardiographic monitoring. Symptoms, rating of perceived exertion, and dyspnea should be assessed and quantified during and after exercise. When testing patients with implantable cardiac defibrillators, the exercise test personnel should obtain information regarding the programmed implantable cardiac defibrillator settings before beginning the test. The peak heart rate during the test should be kept below the heart rate at which the implantable cardiac defibrillator is programmed to discharge.

### Reimbursement Coding for CPX

Tests performed in a CPX laboratory are reimbursable by the Centers for Medicare and Medicaid Services and many private-pay insurance companies. Reimbursement for CPX is billed with Current Procedural Terminology (CPT-4) codes developed by the American Medical Association<sup>26</sup> for specific cardiac and pulmonary testing and any adjunct procedures (eg, arterial blood gases) that are performed. All of these tests must be supported with medical necessity using International Classification of Diseases, Ninth Revision<sup>27</sup> diagnostic codes. In addition, the Centers for Medicare and Medicaid Services monitors coding using the Correct Coding Initiative<sup>28</sup> to ensure that correct coding is used to minimize improper billing and payment from Medicare Part B.

CPX tests are coded as either simple or complex. This is determined by the equipment used, variables being measured, and whether additional tests are performed during the procedure. In all cases, specific documentation in the medical record is necessary to provide support for the test and any needed adjunct procedures. Simple pulmonary testing (CPT code 94620) is performed as a telemetry- (3-lead or 12-lead ECG) and pulse oximetry-monitored treadmill, bicycle ergometer, or 6-minute walk test. This test does not require that a physician be present physically, but they must provide general supervision and control of the test. Complex pulmonary testing (CPT code 94621) is performed as a simple pulmonary test with the addition of the metabolic cart to measure  $\dot{V}O_2$  and  $\dot{V}CO_2$ . This test requires direct physician presence and supervision during the entire test. Testing for oxygen uptake and expired gas analysis, including  $CO_2$  output and  $O_2$  percentage, may be obtained and is reimbursable with CPT code 94681. Additional tests such as arterial blood gas measurements have their own CPT codes, which must be included along with the primary test code. These codes include arterial puncture (36600) or arterial catheterization (36620) and blood gas analyzer for blood processing (82803).

The CPT code for a cardiac stress test is 93015. If both diagnostic pulmonary and cardiac measurements are performed during the same test, CPT code 93018 is added to either the simple or complex pulmonary testing codes as performed. The Correct Coding Initiative bundles a series of CPT codes together when procedures are typically performed together. For example, spirometry codes (94010, 94060, and 94070) are typically bundled with pulmonary testing codes 94620 and 94621. During a simple pulmonary test, spirometry may be performed at baseline and after exercise, but it is not an essential requirement, so it cannot be bundled with the CPT code 93015.<sup>29</sup> Separate interpretive reports of cardiac and pulmonary results must be generated, and each code must be linked to an International Classification of Diseases, Ninth Revision diagnostic code; there must be specific documentation of need for the test in the medical record. Table 3 lists the common Correct Coding Initiative codes for procedures commonly performed in the CPX laboratory.

**Table 3. Correct Coding Initiative Codes Used in CPX Laboratories**

CCI Code	Test or Procedure
94620	Simple stress pulmonary test
94621	Complex stress pulmonary test
94761	Pulse oximetry with multiple determinations
93015	Cardiac stress test
93018	Cardiac measurements during a pulmonary test
94010	Simple spirometry without bronchodilator
94060	Read and interpret a pulmonary function test
94070	Spirometry with postexposure bronchospasm
94681	Oxygen uptake, expired gas analysis ( $CO_2$ output, % $O_2$ )
36600	Arterial puncture
36620	Arterial catheterization
82803	Blood gas analyzer for blood processing

CCI indicates Common Coding Initiative.

### Variables From CPX and Their Physiological Implications

#### Standard Measures

##### *Maximal Aerobic Capacity: $\dot{V}O_{2max}$ or Peak $\dot{V}O_2$*

Maximal  $\dot{V}O_2$  ( $\dot{V}O_{2max}$ ) is an important measurement because it is considered to be the metric that defines the limits of the cardiopulmonary system. It is defined by the Fick equation as the product of cardiac output and arteriovenous oxygen difference [ $C(a-v)O_2$ ] at peak exercise:

$$\dot{V}O_{2max} = (HR \times SV) \times [C(a-v)O_2],$$

where HR is heart rate and SV is stroke volume. Although  $\dot{V}O_{2max}$  is measured in liters of oxygen per minute, it is usually expressed in milliliters of oxygen per kilogram of body weight per minute to facilitate intersubject comparisons. This is important, because a larger person will have a higher  $\dot{V}O_{2max}$  based simply on a larger body weight, and the expression of  $\dot{V}O_2$  in  $mL \cdot kg^{-1} \cdot min^{-1}$  normalizes for body weight. In addition, exercise capacity, particularly when estimated from the work rate achieved rather than as directly measured  $\dot{V}O_2$ , is frequently expressed in metabolic equivalents (METs).

The terms *functional capacity*, *exercise capacity*, and *exercise tolerance* are generally considered synonymous and imply that a maximal exercise test has been performed and a maximal effort has been given by the individual. However, these terms are also occasionally used to express an individual's capacity to perform submaximal activities using 1 of a variety of tests (eg, 6-minute walk tests), and therefore, to avoid confusion, the type of exercise evaluation should be described specifically. A distinction should also be made between estimated and directly measured  $\dot{V}O_2$ . The latter is more precise but requires CPX. Reference equations for normal standards should be specific as to whether  $\dot{V}O_2$  was measured or estimated, because estimated values require several assumptions and tend to overpredict  $\dot{V}O_2$ . Reference equations should also be specific as to whether the test was

performed on a treadmill or cycle ergometer, because exercise capacity is typically 10% to 20% higher on a treadmill.<sup>13</sup>

The measurement of  $\dot{V}O_{2max}$  implies that an individual's physiological limit has been reached (also termed *maximal aerobic capacity*). True  $\dot{V}O_{2max}$  (physiological  $\dot{V}O_{2max}$ ) has historically been defined by a plateau in  $\dot{V}O_2$  between the final 2 exercise work rates and requires that maximal effort be achieved and sustained for a specified period. Because this determination is subjective, can be difficult to define, and is rarely observed when patients with cardiovascular or pulmonary disease are tested, the term *peak  $\dot{V}O_2$*  is more commonly used clinically to express exercise capacity. Conversely, the term  *$\dot{V}O_{2max}$*  is more often used to describe exercise capacity in apparently healthy individuals, in whom achievement of a maximal physiological response is more likely.

### Ventilatory Threshold

Because most activities of daily living do not require maximal effort, a widely used submaximal index of exercise capacity is the anaerobic or ventilatory threshold (VT). The term VT indicates this physiological event is assessed by ventilatory expired gas, defined by the exercise level at which  $\dot{V}_E$  begins to increase exponentially relative to the increase in  $\dot{V}O_2$ . VT is thought to be a reflection of anaerobic threshold, the latter of which is based on the concept that at a given work rate, oxygen supply to the muscle does not meet the oxygen requirements. This imbalance increases the dependence on anaerobic glycolysis for energy output, with lactate as a final metabolic byproduct (lactate threshold).<sup>30</sup> An increase in  $\dot{V}_E$  is required to eliminate the excess  $CO_2$  produced during the conversion of lactic acid to lactate. Whether muscle hypoxia is the major stimulus for increased lactate production remains controversial, and methodologies used to detect anaerobic threshold are not universally accepted.<sup>31</sup> Thus, although the terms *anaerobic*, *ventilatory*, and *lactate thresholds* are commonly used interchangeably, they should be considered different but related events. Throughout this statement, the clinical term *ventilatory threshold* (VT) will be used.

Although VT usually occurs at approximately 45% to 65% of measured peak or maximal  $\dot{V}O_2$  in healthy untrained subjects,<sup>32</sup> it generally occurs at a higher percentage of exercise capacity in endurance-trained individuals.<sup>33</sup> Moreover, high test-retest reliability has been demonstrated for VT in both apparently healthy<sup>34</sup> and chronic disease<sup>35</sup> cohorts. However, the ability to detect VT may be lower in patients with heart failure,<sup>35</sup> perhaps secondary to ventilatory abnormalities<sup>36</sup> and a greater likelihood of submaximal effort during CPX. Additionally, the mode used for CPX, typically a treadmill or lower-extremity ergometer, potentially impacts the VT response for a given individual.<sup>37</sup> Therefore, when VT is used to prescribe exercise intensity, the same mode should be used for both testing and training, as discussed further in the section on Exercise Prescription. Exercise training has been shown to increase  $\dot{V}O_2$  at the VT to a degree that is similar to that for peak or maximal  $\dot{V}O_2$  (typically 10% to 25% for previously sedentary individuals); thus, it is an important response to document clinically. Several methods have been proposed for determination of VT; however, no universal agreement exists regarding which is best. The 3

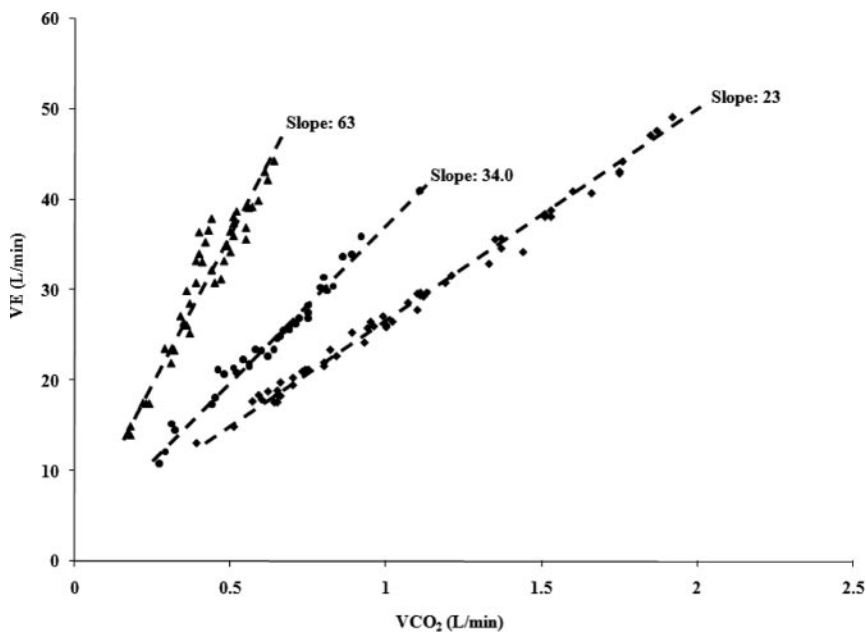
most common definitions of the VT are the following: (1) The departure of  $\dot{V}O_2$  from a line of identity drawn through a plot of  $\dot{V}CO_2$  versus  $\dot{V}O_2$ , often called the V-slope method; (2) the point at which a systematic increase in the ventilatory equivalent for oxygen ( $\dot{V}_E/\dot{V}O_2$ ) occurs without an increase in the ventilatory equivalent for carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ ); and (3) the point at which a systematic rise in end-tidal oxygen pressure ( $P_{ET}O_2$ ) occurs without a decrease in the end-tidal carbon dioxide pressure ( $P_{ET}CO_2$ ).<sup>38</sup>

Detection of VT by the V-slope, ventilatory equivalents, and end-tidal pressure methods is illustrated in Figures 1A through 1C, respectively. The graphs generated depict averaged data from an actual subject. When determined visually, these methods on average result in VT values at a similar percentage of peak or maximal  $\dot{V}O_2$ .<sup>39</sup> The assessment of all 3 of the aforementioned VT detection techniques in combination may result in an improved approximation of anaerobic threshold detected by blood lactate.<sup>40</sup> Although modern equipment that measures metabolic parameters usually quantifies this point automatically by use of 1 of several published or empirical algorithms, it should be validated visually by an experienced reviewer. The confidence in determining the VT may be increased by having 2 or 3 experienced observers independently calculate this point.<sup>39</sup> VT should be reported in absolute terms ( $mL \cdot kg^{-1} \cdot min^{-1}$ ) and may also be reported as a percentage of peak  $\dot{V}O_2$ .

### Peak Respiratory Exchange Ratio

Achievement of at least 85% of age-predicted maximal heart rate is a well-recognized indicator of sufficient subject effort during a CPX. The maximal heart rate response to exercise, however, possesses wide variability ( $\pm 12$  beats per minute) in the general population, which negatively impacts the ability to gauge subject effort by their heart rate response alone. The widespread use of  $\beta$ -blocking agents in the heart failure population further complicates this issue by significantly blunting the maximal heart rate response in a disparate manner, negating the validity of the age-predicted maximal heart rate equation (220 minus age). The respiratory exchange ratio (RER), defined as the ratio between  $\dot{V}CO_2$  and  $\dot{V}O_2$ , obtained exclusively from ventilatory expired gas analysis, obviates the need to assess heart rate in determining subject effort. With the progression to higher exercise intensities, lactic acid buffering contributes to  $\dot{V}CO_2$  output, which increases the numerator at a faster rate than the denominator. This physiological response to exercise is consistent in apparently healthy subjects and all patient populations, which makes peak RER the most accurate and reliable gauge of subject effort. A peak RER of  $\geq 1.10$  is generally considered an indication of excellent subject effort during CPX, but it is not an indication to stop the test. Achievement of a peak RER  $< 1.00$  in a CPX that is terminated by subject request, absent any electrocardiographic or hemodynamic abnormalities, generally reflects submaximal cardiovascular effort but may be seen in those with a pulmonary limitation to exercise. Previous research indicates caution should be taken in the use of peak  $\dot{V}O_2$  for prognostic purposes in the presence of a low peak RER.<sup>41</sup> Assessment of peak RER is also of great importance during interventional trials when an investigator





**Figure 2.** Examples of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope during exercise. Three different slopes are shown with their respective values. In patients with heart failure, chronic obstructive pulmonary disease, and pulmonary hypertension, disease severity continues to increase as  $\dot{V}_E/\dot{V}_{CO_2}$  response extends beyond the normal threshold (ie, <30), with values >60 being reported. See text for details.

attempts to demonstrate comparable subject effort among serial exercise tests. A significant change in exercise capacity during follow-up testing with similar peak RER values provides strong support for the assertion that observed changes are secondary to the intervention used, given similar test conditions and protocols. The ability to determine peak RER, which provides a highly accurate account of variability in subject effort, is an important reason that the incorporation of CPX should be strongly considered for interventional trials with a functional end point. Although most subjects attain VT at an RER  $\geq 1.0$ , VT can occasionally be detected in subjects who achieve an RER <1.0, given that VT is detected somewhere in the RER range of 0.8 to 0.99.

#### Minute Ventilation–Carbon Dioxide Output Relationship

Ventilatory efficiency can be assessed by evaluation of the rise in minute ventilation ( $\dot{V}_E$ ) relative to work rate,  $\dot{V}_{O_2}$ , or  $\dot{V}_{CO_2}$ . The most widely studied index of ventilatory efficiency is the  $\dot{V}_E/\dot{V}_{CO_2}$  slope. Other indices of ventilatory efficiency are discussed below (see Appendix 1). The relationship between  $\dot{V}_E$  and  $\dot{V}_{CO_2}$  during exercise is tightly coupled, because the former is modulated by the metabolic and anaerobic production of the latter. The  $\dot{V}_E/\dot{V}_{CO_2}$  relationship is most often expressed as a slope value, calculated by linear regression ( $y=mx+b$ ,  $b$ =slope). Moreover, calculation of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope with all exercise data obtained from a progressive exercise test (initiation to peak effort) appears to provide additional clinical information compared with submaximal calculations (ie, those that use linear data points before the steepening associated with ventilatory compensation for metabolic acidosis).<sup>42,43</sup> Although the former method affords optimal clinical information, the latter submaximal calculations have also demonstrated diagnostic/prognostic value.<sup>44</sup> Irrespective of the calculation technique used, a  $\dot{V}_E/\dot{V}_{CO_2}$  relationship <30 is considered normal without modification for age and sex.<sup>45</sup> Values observed in certain patient populations, such as those with heart failure, pulmo-

nary hypertension, and chronic obstructive pulmonary disease, can far exceed this normal threshold, with values >60 in patients with advanced disease severity.<sup>46–48</sup> Three examples of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope obtained during exercise (1 normal, 2 abnormal) are illustrated in Figure 2. Lastly, it appears the  $\dot{V}_E/\dot{V}_{CO_2}$  relationship demonstrates high test-retest reliability,<sup>35,49</sup> and unlike exercise capacity, the slope derivation of this variable appears to be uninfluenced by mode of exercise<sup>50</sup> or aggressiveness of the testing protocol.<sup>51</sup>

Studies of the mechanisms responsible for elevated  $\dot{V}_E/\dot{V}_{CO_2}$  in chronic heart failure suggest that it is multifactorial. Centrally, an elevated  $\dot{V}_E/\dot{V}_{CO_2}$  response has been associated with increased ventilation-perfusion mismatching (adequate ventilation and poor perfusion).<sup>52,53</sup> It also demonstrates a significant relationship with abnormally elevated chemoreceptor and ergoreceptor sensitivity, both of which contribute to an exaggerated ventilatory response to exercise. Additionally, an abnormal  $\dot{V}_E/\dot{V}_{CO_2}$  response has been significantly correlated with decreased cardiac output, elevated pulmonary pressures, decreased alveolar-capillary membrane conductance, and diminished heart rate variability.<sup>44</sup> There are no investigations that comprehensively quantify the degree to which each of the aforementioned pathophysiological phenomena independently account for the abnormal  $\dot{V}_E/\dot{V}_{CO_2}$  response observed in heart failure. From a clinical perspective, healthcare professionals should view an abnormal  $\dot{V}_E/\dot{V}_{CO_2}$  response as a reflection of systemic disease severity in this patient population. Assessment of the pathophysiological mechanism for an abnormal  $\dot{V}_E/\dot{V}_{CO_2}$  response has also been performed in patients with pulmonary hypertension, which is discussed in greater detail in a separate section below (see Emerging Applications of CPX). Similar to patients with heart failure, it appears that ventilation-perfusion abnormalities (adequate ventilation and poor perfusion) are a likely culprit for an elevated  $\dot{V}_E/\dot{V}_{CO_2}$  response.<sup>46,54</sup> Moreover, in patients with pulmonary hypertension, disease severity continues to increase as  $\dot{V}_E/\dot{V}_{CO_2}$  response extends beyond the

normal threshold (ie,  $<30$ ), with values  $>60$  being reported.<sup>55</sup> In patients with chronic lung diseases, high  $\dot{V}_E/\dot{V}_{CO_2}$  is attributed to the effects of increased physiological dead space and ventilation-perfusion inequalities that are present at rest and during exercise.<sup>56</sup>

#### **Pulmonary Function Testing and Pulse Oximetry**

Tests of lung mechanics performed before exercise provide a context for assessments of the normalcy of the pattern of breathing and the likelihood that lung mechanics are limiting to exercise function. Simple spirometry is performed before exercise to determine vital capacity, the forced expiratory volume in 1 second ( $FEV_1$ ), and inspiratory capacity. The maximum voluntary ventilation (MVV) can be calculated either directly from a 12- or 15-second maneuver of deep and rapid breathing as the corresponding minute volume or indirectly as  $FEV_1 \times 40$ . Standards for the performance and interpretation of spirometry are available from the European Respiratory Society<sup>57,58</sup> and American Thoracic Society.<sup>58,59</sup> The *exercise breathing reserve* refers to how closely  $\dot{V}_E$  approaches MVV during exercise and has been expressed in various forms. When calculated as  $(1 - [\text{peak } \dot{V}_E/\text{MVV}])$ , it is typically  $\geq 0.20$  in healthy nonathletes. Tidal volume normally increases during exercise but remains less than inspiratory capacity. When exercise testing is performed to identify the presence of exercise-induced asthma, spirometry is measured periodically over the 30 minutes after a 6- to 8-minute bout of high-intensity exercise. A decrease in  $FEV_1$  in the postexercise recovery period of 15% or more compared with before exercise is the most widely used criterion for identifying exercise-induced bronchoconstriction. Timing and performance of postexercise spirometry, design of the exercise protocol to provoke airway reactivity, and the relative sensitivity and specificity of exercise and other bronchial provocation procedures are reviewed in detail elsewhere.<sup>59,60</sup>

Pulse oximeters rely on differential absorption of varying wavelengths of light to noninvasively estimate the proportion of arterial capillary hemoglobin in the oxygenated form. A large number of pulse oximeters are available with variable accuracy and bias compared with CO-oximeter analysis of arterial blood samples.<sup>55,61,62</sup> Motion artifact and poor capillary perfusion are recognized sources of error in signals during exercise and tend to cause small underestimates of true oxygen saturation, particularly with use of a fingertip probe. Inaccurate pulse rate readings identify some, but not all, unreliable oximeter signals. Accuracy rates reported for individual instruments are often in the range of  $\pm 2\%$  to  $3\%$ , and wider confidence limits are not unusual, particularly in the range of  $O_2$  saturation  $<85\%$ . These confidence limits for estimated oxygen saturation represent large ranges for the corresponding values of partial pressure of  $O_2$  in arterial blood ( $PaO_2$ ). Precise measures of oxygenation therefore require arterial blood sampling for direct measurement of  $PaO_2$  and calculation of the alveolar-arterial oxygen gradient  $[P(A-a)O_2]$ . Pulse oximeters provide a general estimate of oxygenation for safety monitoring and are widely used to identify trends during exercise. A decrease of  $>5\%$  in the pulse oximeter estimate of arterial saturation during clinical CPX protocols is suggestive of abnormal exercise-induced

hypoxemia,<sup>5</sup> and if this is an unexpected finding, confirmation by analysis of arterial blood may be indicated. Some laboratories use oximeter findings of desaturation to less than 80% or 85% as an indication to discontinue exercise tests. Because of imprecision in exercise pulse oximetry and differences in the significance of hypoxemia between different clinical populations, any such criteria are arbitrary and require integration with clinical judgment.

Endurance athletes with high cardiovascular capacity can utilize more of their lung capacity than less fit individuals and may reach ventilatory limits at peak exercise, as reflected in a low or absent breathing reserve. True arterial desaturation of 5% to 10% from baseline can also occur in fit healthy individuals during sustained heavy-intensity exercise as a result of diffusion limitation due to rapid pulmonary vascular transit time associated with very high cardiac output.<sup>63</sup> Thus, although these findings indicate attainment of limits of capacity of certain aspects of the pulmonary system, they do not always indicate pathology.

#### **Additional Measures and Related Technologies**

Appendix 1 presents a discussion of complex gas exchange variables and related technologies that provide an advanced and more detailed assessment of cardiorespiratory status beyond what is used routinely in clinical practice. These measures are most often used in the research setting, and their clinical validity has not yet been fully established. They are presented to provide the reader with a comprehensive overview of CPX, because such measures have the potential to emerge in the clinical arena in the coming years.

### **Combined CPX Responses as Part of the Comprehensive Clinical and Exercise Evaluation**

The present overview of CPX focuses principally on the unique attributes and challenges of gas exchange assessments in association with exercise provocation; however, CPX testing also integrates standard measures of electrocardiography exercise stress testing with gas exchange assessment, which contributes to a more comprehensive evaluation. Electrocardiographic criteria (heart rate dynamics, arrhythmia, ST changes, and conduction disease), hemodynamics, and symptoms are all important exercise-related measures that complement and expand on the gas exchange indices. The variables presented in this section are discussed in greater detail in the American Heart Association's scientific statement entitled "Exercise Standards for Testing and Training."<sup>64</sup>

#### **Exercise-ECG Data**

##### **Heart Rate**

The immediate response of the cardiovascular system to exercise is an increased heart rate due to decreased vagal tone and increased sympathetic outflow. During dynamic exercise, heart rate increases linearly with work rate and  $\dot{V}O_2$ , but the slope and magnitude of heart rate acceleration are influenced by age, deconditioning, body position, type of exercise, and various states of health and therapy, including heart transplant. *Chronotropic incompetence*, defined as either failure to achieve 85% of the age-predicted maximal heart rate or a low

chronotropic index (heart rate adjusted to the MET level), is associated with increased mortality risk in patients with known cardiovascular disease,<sup>65</sup> although this assessment is confounded by the use of  $\beta$ -blockers and other heart rate-limiting medications.

#### **Heart Rate Recovery**

Heart rate recovery refers to the deceleration of the heart rate in early exercise recovery in association with vagal tone reactivation. Cole et al<sup>66</sup> initially demonstrated the utility of heart rate recovery to predict mortality in patients with coronary artery disease (CAD), but subsequent analyses have demonstrated similar physiological relationships and prognostic risks in patients with heart failure.<sup>67–70</sup> Other literature demonstrates the prognostic power of heart rate recovery in heart failure in combination with cardiopulmonary indices.<sup>71</sup> In contrast to chronotropic assessment, heart rate recovery remains prognostically important even among patients using  $\beta$ -blockers.

#### **Arrhythmia**

Assessment for arrhythmia is important and particularly helpful in assessing the heart failure population that is frequently referred for CPX. Heightened catecholamine tone, hypokalemia, and increased inflammatory cytokines such as interleukin 6 contribute to the likelihood of ventricular arrhythmias.<sup>72</sup> Furthermore, intrinsic myocardial morphological features associated with systolic and diastolic heart failure (left ventricular dilation, left ventricular hypertrophy, and scarring) increase susceptibility to ventricular ectopic activity, especially in the context of diuretics, digoxin, and other proarrhythmic therapies. Significant ventricular ectopic activity during exercise and recovery have been associated with increased mortality.<sup>73,74</sup> Paroxysmal atrial fibrillation and supraventricular tachycardia with exercise are rare.

#### **Ischemic Electrocardiography Changes**

ST-segment depression is the most common manifestation of exercise-induced myocardial ischemia. The standard criterion for this abnormal response is horizontal or downsloping ST-segment depression of  $\geq 0.10$  mV (1 mm) for 80 ms; however, downsloping ST-segment depressions are more specific than horizontal or upsloping depressions. In the presence of marked baseline abnormalities, exercise-induced ST-segment depression is less specific for myocardial ischemia. Other factors related to the probability and severity of CAD include the degree, time of appearance, duration, and number of leads with ST-segment depression. Severity of CAD is also related to the time of appearance of ischemic ST-segment shifts. The lower the work rate and rate-pressure product at which it occurs, the worse the prognosis and the more likely the presence of multivessel disease. The duration of ST depression in the recovery phase is also related to the severity of CAD. Exercise-induced elevation may occur in an infarct territory where Q waves are present or in a noninfarct territory. The development of  $\geq 0.10$  mV of J-point elevation that remains persistently elevated 60 ms after the J point in 3 consecutive beats with a stable baseline is considered an abnormal response. In subjects without prior myocardial infarction (ie, no Q waves on the resting ECG), ST-segment

elevation during exercise frequently localizes the site of severe transient ischemia that results from significant proximal disease or spasm.

#### **Blood Pressure**

Hemodynamic responses to exercise also vary depending on cardiac output and peripheral resistance. Systolic blood pressure usually rises with increasing work rates, particularly due to a rise in cardiac output. In contrast, diastolic blood pressure usually remains the same or decreases moderately with exercise. An inadequate rise ( $< 20$  to 30 mm Hg) or fall in systolic blood pressure from resting levels may result from aortic outflow obstruction, severe left ventricular dysfunction, myocardial ischemia, and certain types of medication s (eg,  $\beta$ -blockers). As a general standard, exercise-induced hypotension is associated with a poor prognosis and should raise emergent consideration of significant cardiac disease, including left-main or 3-vessel CAD; however, subjects without clinically significant heart disease can also exhibit exercise-induced hypotension due to dehydration, antihypertensive therapy, or even the direct effects of prolonged high-intensity exercise. In recovery, precipitous drops in systolic blood pressure may also occur due to a delayed postexercise increase in systemic vascular resistance to match the reduced cardiac output.

#### **Symptoms With Exercise**

Although assessment of symptoms is of key value in interpreting exercise performance, the subjective quality of symptoms can detract from objective, reproducible, and sensitive assessments. Personality, mood, culture, and idiosyncratic vacillations, as well as cognition, literacy, and socioeconomic factors, are among the factors that have an impact on these measures.

#### **Exercise Intensity and Dyspnea**

The subjective rating of exercise intensity is generally considered a reliable indicator of relative fatigue. The 6-to-20 Borg scale of perceived exertion has been demonstrated to be useful in quantifying these feelings.<sup>75</sup> The Borg scale assists the clinician in quantifying fatigue and intensity as exercise treadmill time advances. In general, a Borg scale  $> 18$  suggests that the patient has performed maximal exercise, and values  $> 15$  to 16 suggest that the VT has been exceeded. The Borg scale of perceived exertion was modified to a 1-to-10 scale for dyspnea assessment, which has been demonstrated to correlate with aerobic stress and blood lactate levels. Recent data demonstrate that among patients with heart failure, the termination of an exercise test primarily because of dyspnea is associated with an increased incidence of cardiac-related events and poorer CPX markers than those tests that are limited by fatigue.<sup>76</sup> Another major instrument used to quantify symptoms during CPX is the Visual Analog Scale. Typically, this scale is presented to the patient on a page, and the patient is asked to mark a point along the line that correlates to the magnitude of symptoms.<sup>77,78</sup>

#### **Chest Discomfort**

Chest discomfort assessment during exercise testing has been demonstrated to be a useful criterion for diagnosis and

prognosis, particularly in combination with other exercise testing variables. The Duke treadmill score provides an important example of chest pain assessed in combination with electrocardiography waveforms and exercise tolerance as a means to standardize and enhance interpretation of this exercise-related complaint.<sup>79</sup>

## Clinical Applications of CPX

### Heart Failure

#### *Systolic Dysfunction*

Reduced exercise capacity is the cardinal symptom of chronic heart failure. Exercise capacity traditionally has been assessed in heart failure by the New York Heart Association criteria. Such assessment is both subjective and insensitive. The 6-minute walk test (ie, the distance walked over a period of 6 minutes) is less subjective than the New York Heart Association functional class but still can be heavily influenced by the patient's and/or tester's motivation. Additionally, the results of the 6-minute walk test cannot estimate how close the patient is to his or her maximal capacity. Determination of peak  $\dot{V}O_2$  during a maximal symptom-limited treadmill or bicycle CPX is the most objective method to assess exercise capacity in heart failure patients. By determining the VT, the physician can assess how close the patient is to achieving his or her maximal effort. However, among patients with heart failure, VT is not always identifiable. Thus, CPX has gained widespread application in the functional assessment of patients with heart failure. It is a useful test to determine the severity of the disease and to help to determine whether heart failure is the cause of exercise limitation (American College of Cardiology/American Heart Association recommendation Class IIa, Level of Evidence C),<sup>80</sup> provide important prognostic information and identify candidates for cardiac transplantation or other advanced treatments (American College of Cardiology/American Heart Association Recommendation Class IIa, Level of Evidence B)<sup>80</sup>; facilitate the exercise prescription (American College of Cardiology/American Heart Association Recommendation Class I, Level of Evidence C)<sup>80</sup>; and assess the efficacy of new drugs and devices.

Peak  $\dot{V}O_2$  has been shown to predict prognosis in patients with heart failure in many studies.<sup>81–83</sup> In a prospective study of 114 ambulatory patients with heart failure referred for cardiac transplantation, a  $\dot{V}O_2$  of  $<14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  was used as a criterion for acceptance for cardiac transplantation.<sup>84</sup> One-year survival was 94% in patients with a  $\dot{V}O_2 >14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Accepted transplant candidates with a  $\dot{V}O_2 <14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  had a 1-year survival of 70%, whereas patients with a significant comorbidity and reduced  $\dot{V}O_2$  had a 1-year survival of 47%. This approach permitted the identification of candidates for whom transplantation could be deferred safely. However, there are several limitations to this approach. First, peak  $\dot{V}O_2$  is a continuous variable. Use of statistical methods such as stratum-specific ratios to identify a clear threshold below which the relative risk of an adverse event will increase precipitously have yielded a linear relationship of  $\dot{V}O_2$  to outcome without clear thresholds.<sup>85</sup> Second, peak exercise  $\dot{V}O_2$  can be influenced by

noncardiac factors such as muscle mass and deconditioning, age, sex, and obesity. Analysis of peak  $\dot{V}O_2$  normalized by a predicted maximum based on age, obesity, and sex has been performed to determine whether better prognostication can be achieved with use of a percent of predicted values. Some investigators have suggested the superiority of this approach, although others have shown no clear benefit. This is due in part to the observation that the cohorts studied are generally composed of middle-aged men, for whom agreements between the predictive equations and measured values are highest.<sup>86,87</sup> Its predictive value in women, deconditioned obese individuals, or those at the extreme of age is less certain.

The use of  $\dot{V}O_2$  in special heart failure populations such as women and the elderly has been described recently. In a study by Elmariah et al,<sup>88</sup> peak  $\dot{V}O_2$  identified those women with the worst prognosis, although the overall survival of women was significantly better than that of their male counterparts. These findings were confirmed by Green et al<sup>89</sup> and Hsich et al.<sup>90</sup> Exercise testing is used sparingly in geriatric populations, but several recent studies have also demonstrated the predictive value of peak  $\dot{V}O_2$  in this population.<sup>91,92</sup>

Serial measurements of peak  $\dot{V}O_2$  have also been shown to effectively identify patients in a low-risk category over time.<sup>93</sup> This is particularly important, because the therapies for cardiac diseases continue to evolve and improve. Exercise tolerance as measured with CPX in patients with heart failure can be divided into 4 classes based on peak  $\dot{V}O_2$  and VT<sup>94</sup> and has been used to identify those with the poorest prognosis, who should be considered for heart transplantation. However, the latter classification system was proposed more than 20 years ago. Over the past 2 decades, significant advances have been made in the treatment of heart failure. In particular, the use of  $\beta$ -blockade has had a significant impact on long-term survival without significantly improving peak  $\dot{V}O_2$ . Whether  $\dot{V}O_2$  retained its predictive power in the  $\beta$ -blocker era has been the subject of several reports.<sup>95–97</sup> Consistent across the reports was the sustained utility of this parameter in predicting survival. Cohorts dichotomized by threshold values of above and below  $14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  or above and below  $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in patients taking  $\beta$ -blockers demonstrated that  $\dot{V}O_2$  retained its predictive value. The survival for patients taking  $\beta$ -blocking agents shifted up but nevertheless diverged according to peak  $\dot{V}O_2$ . With the improved survival conferred by this therapy, a cut point lower than  $14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for referral or listing for cardiac transplantation appears warranted.<sup>97</sup> Recent data also suggest that reporting peak  $\dot{V}O_2$  as a percentage of that predicted by the Wasserman equation may have additional prognostic importance.<sup>98</sup>

Peak  $\dot{V}O_2$  is typically corrected for total weight and is reported in  $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Body fat, however, can represent a significant portion of total body weight, but it has little perfusion and consumes minimal oxygen. Considerable variability in body composition is present across populations, including those with heart failure. A few studies have demonstrated that correction of  $\dot{V}O_2$  for lean body mass may provide a better estimation of prognosis<sup>99,100</sup> than uncorrected values; however, these observations need to be confirmed by additional studies.

During CPX, many variables are collected that also confer prognostic information. The ventilatory response to exercise most frequently measured by the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, as discussed above (see Minute Ventilation–Carbon Dioxide Output Relationship), has been found by several investigators to be even more predictive of outcome than peak  $\dot{V}_{O_2}$ .<sup>101–104</sup> Unlike peak  $\dot{V}_{O_2}$ , the  $\dot{V}_E/\dot{V}_{CO_2}$  relation does not require a maximal effort. Similar to peak  $\dot{V}_{O_2}$ , it is a continuous variable with no absolute cut point; however, the most commonly cited dichotomous threshold for the  $\dot{V}_E/\dot{V}_{CO_2}$  slope is  $>34$ .<sup>44</sup> Two studies have evaluated the prognostic characteristics of the  $\dot{V}_E/\dot{V}_{CO_2}$  slope in combination with peak  $\dot{V}_{O_2}$  using a 4-level classification.<sup>101,104,105</sup> These studies found that mortality risk increases progressively as the  $\dot{V}_E/\dot{V}_{CO_2}$  slope increases from normal (ie,  $<30$ ) to  $>40$ . On the basis of the available literature on this topic, heart failure patients with a peak  $\dot{V}_{O_2} < 10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  or a  $\dot{V}_E/\dot{V}_{CO_2}$  slope  $>40$  should be considered to be in the highest-risk category, and patients with both of these characteristics have a particularly poor prognosis. In patients with a preserved exercise capacity, a  $\dot{V}_E/\dot{V}_{CO_2}$  slope  $>40$  remains a strong indicator of poor prognosis given the independent prognostic value of ventilatory inefficiency.

Although less well studied, several other parameters that are discussed elsewhere in this “Clinician’s Guide” (blood pressure response to exercise, heart rate recovery, VT, exercise oscillatory ventilation, and oxygen recovery kinetics after exercise)<sup>106,107</sup> have been evaluated in patients with heart failure. Advances in technology now permit measurement of cardiac output with inert gas–rebreathing techniques (Appendix 1), and recent studies suggest that cardiac power measurements (eg, peak cardiac output  $\times$  mean arterial pressure) may offer enhanced prognostic information beyond peak  $\dot{V}_{O_2}$ , but these results need to be confirmed.<sup>108</sup>

Statistical models that include peak  $\dot{V}_{O_2}$  have also been developed<sup>109</sup> but are not yet used clinically and remain a promising area for future research. One such model, the Heart Failure Survival Score, is a multivariable predictive index that was developed from data on 80 clinical characteristics of 268 ambulatory patients with advanced heart failure. The final model included 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 7 variables included different aspects of heart failure physiology: Presence or absence of CAD, resting heart rate, mean arterial blood pressure, left ventricular ejection fraction, presence or absence of intraventricular conduction delay, peak  $\dot{V}_{O_2}$ , and serum sodium. The total Heart Failure Survival Score is the absolute value of the sum of the products of individual variables with each Cox proportional coefficient. A Heart Failure Survival Score  $>8.1$  was associated with a 1-year event-free survival of  $93 \pm 2\%$ , whereas lower scores were associated with a 1-year event-free survival that was significantly less than expected with transplantation.<sup>109</sup>

Many studies have demonstrated significant improvement in peak  $\dot{V}_{O_2}$  after exercise training among patients with heart failure.<sup>110</sup> Although exercise testing without CPX can provide information on changes in treadmill time, peak work rate, and estimated MET levels, CPX can provide more accurate

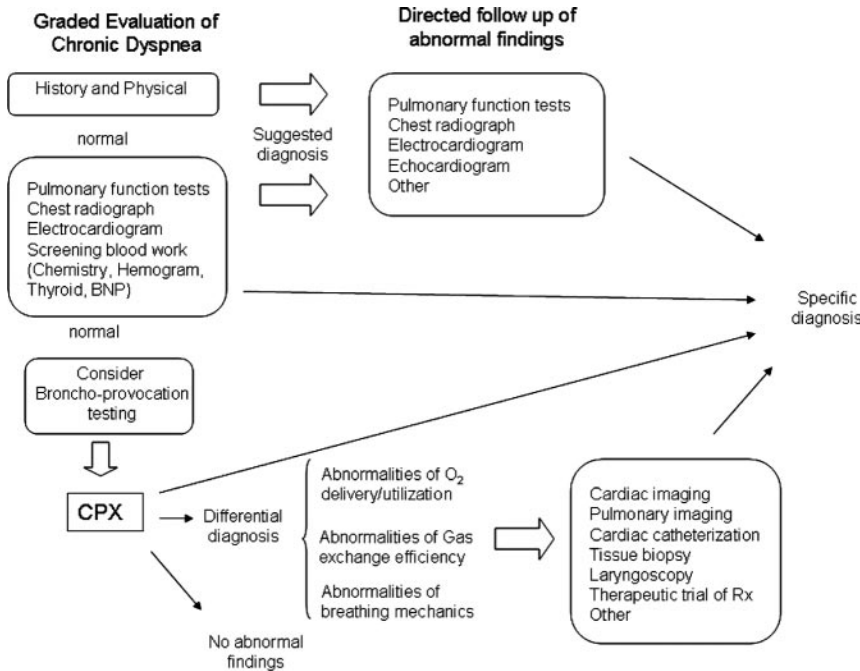
measures of change (or lack of change) that are not limited by the inaccuracies posed by handrail support or stride length. CPX can also provide data on VT, which is an important submaximal measure of exercise tolerance that is not as subject to patient effort as peak  $\dot{V}_{O_2}$ , exercise time, or estimated METs. Whether changes in peak  $\dot{V}_{O_2}$  translate to improved prognosis among patients with systolic heart failure is an important question that was addressed by the Heart Failure–ACTION trial.<sup>111</sup> This study was limited because of high levels of nonadherence to the prescribed exercise, and hence, only modest changes in peak  $\dot{V}_{O_2}$  were seen. Although the primary end point of a reduction in all-cause mortality and heart failure hospitalizations was not reached, after prespecified adjustment for highly prognostic predictors of the primary end point, exercise training was associated with modest significant reductions for both all-cause mortality or hospitalization and cardiovascular mortality or heart failure hospitalization.

#### **Heart Failure With Normal Ejection Fraction**

Although the majority of literature supporting the value of CPX in patients with heart failure has been performed in cohorts with systolic dysfunction, initial investigations demonstrate that CPX has promise in the evaluation of patients who have heart failure and normal ejection fraction (diastolic dysfunction). Patients with heart failure resulting from either systolic or diastolic dysfunction appear to have the same degree of impaired aerobic capacity.<sup>112,113</sup> The oxygen-uptake efficiency slope (OUES; Appendix 1) likewise appears to be comparably reduced in systolic and diastolic dysfunction and is significantly lower than in healthy subjects.<sup>114</sup> Ventilatory efficiency, expressed as the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, appears to be lower in heart failure patients with diastolic compared with systolic dysfunction.<sup>115,116</sup> In subjects diagnosed with hypertrophic cardiomyopathy, Arena et al<sup>117</sup> demonstrated that peak  $\dot{V}_{O_2}$  and  $\dot{V}_E/\dot{V}_{CO_2}$  at peak exercise were both significantly correlated with resting pulmonary hemodynamics. An abnormal response effectively identified subjects with pulmonary hypertension. Lastly, initial investigations indicate the  $\dot{V}_E/\dot{V}_{CO_2}$  slope, exercise oscillatory breathing (EOB; Appendix 1), and peak  $\dot{V}_{O_2}$  may be significant predictors of adverse events in heart failure patients with diastolic dysfunction, with the 2 former CPX variables providing superior prognostic value compared with the latter.<sup>115,118</sup> Although initial findings are promising, additional research is required before definitive conclusions can be drawn regarding the clinical value of CPX in patients with diastolic dysfunction.

#### **Unexplained Dyspnea**

Dyspnea on exertion is a common clinical complaint, the cause of which is usually readily determined by history, physical examination, and basic screening tests performed at rest, including ECG, spirometry, hemogram, serum chemistries, and chest radiograph. A common use of CPX is the assessment of patients with dyspnea unexplained by such an initial evaluation (Figure 3).<sup>5,119,120</sup> Although cardiovascular and pulmonary disorders are found to account for the majority of cases of chronic dyspnea, processes that present with this symptom are diverse; hence, the patient population



**Figure 3.** Use of CPX in the clinical evaluation of chronic dyspnea. Graded evaluation of the patient with dyspnea begins with a history and physical examination, which usually suggests a diagnosis that can be confirmed with appropriate follow-up tests. When no diagnosis is suggested by history and physical, selected noninvasive screening tests of cardiac and pulmonary function and laboratory analyses are recommended. Broncho provocation testing may be part of this screening in patients with a compatible history or risk profile. If these evaluations are nondiagnostic, dyspnea is classified as “unexplained.” CPX may either identify a specific diagnosis or restrict the broad differential diagnosis for unexplained dyspnea by categorizing abnormalities as typical of oxygen delivery (cardiovascular), oxygen utilization (peripheral nerve/muscle), or ventilatory disorders. Appropriate follow-up tests can be selected on the basis of these findings and the clinical context. In some proportion of cases, no abnormalities are found. BNP indicates brain natriuretic peptide; Rx, treatment.

undergoing exercise testing for evaluation of dyspnea includes individuals with a wide range of neuromuscular, hormonal, myopathic, metabolic, and psychogenic conditions as well.<sup>121–123</sup>

Interpretative algorithms have been proposed to identify patterns of findings typical of the various conditions that cause dyspnea on standard exercise testing protocols.<sup>57,124,125</sup> Examples of specific diagnoses that can be made by this approach include exercise-induced arrhythmias, chronotropic incompetence, myocardial ischemia, and hyperventilation syndromes. In some additional cases, establishment of specific diagnoses is possible if the test protocol is modified to detect particular conditions suspected on clinical grounds. Examples of this are the identification of exercise-induced bronchoconstriction by use of a test protocol of brief, high-intensity exercise with postexercise measurements of FEV<sub>1</sub><sup>59</sup> and the identification of exercise-induced laryngeal dysfunction by analysis of exercise flow-volume loops or direct laryngoscopy. Although unique diagnoses are thus possible with CPX, test results often serve to distinguish broadly between normal and abnormal exercise capacity and between cardiovascular and ventilatory patterns of exercise limitation.<sup>126,127</sup> These distinctions direct the individual workup toward the limiting organ system or provide a rational basis for curtailing further diagnostic studies, as shown in Table 4 and Figures 3 and 4. In either case, in addition to informing the diagnostic plan, the test also provides an objective measure of exercise capacity that quantifies the severity of the underlying condition.

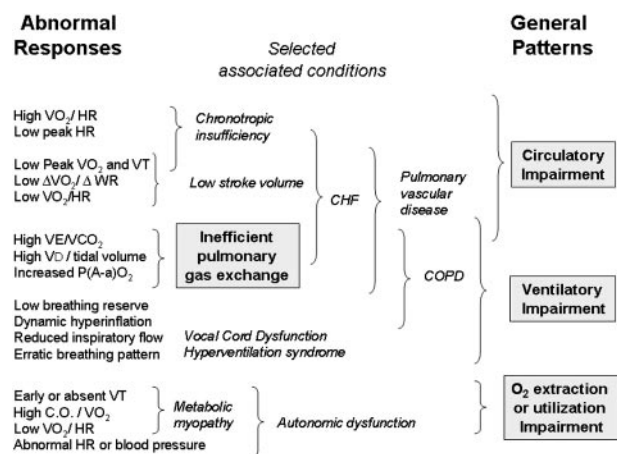
Cardiovascular disorders are characterized by findings related to impaired ability to deliver oxygen at the rate required of the exercise work rate. Peak  $\dot{V}O_2$  and VT are typically low, and  $\Delta\dot{V}O_2/\Delta$  work rate (Appendix 1,  $\dot{V}O_2$ /Work-Rate Relationship) during the incremental phase of exercise may be reduced below the normal slope of 10 mL · min<sup>-1</sup> · W<sup>-1</sup>.<sup>128</sup> This latter variable is more confidently

assessed by cycle ergometry than by treadmill walking because of the better precision of the work-rate measure. During incremental exercise, a shallow slope in this relationship is due to accumulation of an abnormal oxygen deficit rather than increased efficiency of skeletal muscle metabolism, so an associated finding is a delay in the rate of recovery of  $\dot{V}O_2$  toward baseline after exercise.<sup>106</sup> The recovery rate is not as well standardized as other exercise variables but has potential to facilitate identification of abnormal  $\dot{V}O_2$  responses independent of accurate work-rate measures (Appendix 1,  $\dot{V}O_2$  Kinetics During Exercise and Recovery). In addition to these findings, reduced cardiac stroke volume results in a steep increase in heart rate relative to  $\dot{V}O_2$ . Peak values of  $\dot{V}O_2$ /heart rate are thus low and may be reached early in exercise. The converse is expected in the setting of isolated chronotropic impairment, which results in a shallow

**Table 4. Findings From CPX Characteristic of Typical Cardiovascular (Chronic Heart Failure) and Pulmonary (Obstructive Airways Disease) Causes of Exercise Impairment**

	Cardiovascular	Pulmonary
Peak $\dot{V}O_2$	Reduced	Reduced
Ventilatory threshold	Reduced	Normal or reduced
$\Delta\dot{V}O_2/\Delta$ WR	Often reduced	Normal
Peak HR	May be reduced	May be reduced
Peak $\dot{V}O_2$ /HR	Often reduced	May be reduced
Breathing reserve, 1 – (peak $\dot{V}E$ /MVV)	>20%	<15%
Postexercise FEV <sub>1</sub>	Unchanged from rest	May decrease compared with rest
Pao <sub>2</sub> or Sao <sub>2</sub>	Normal	Often reduced
VD/tidal volume or $\dot{V}E/\dot{V}CO_2$	May be elevated	Often elevated

WR indicates work rate; HR, heart rate; and VD, dead space.



**Figure 4.** Abnormal patterns of responses from CPX characteristic of disorders that cause dyspnea. Profiles are shown of abnormal findings characteristic of general categories (shaded boxes) of impairment and typical of selected conditions within those categories (italicized). Impairment in oxygen delivery due to circulatory disorders and in oxygen extraction due to muscle disorders or distributive impairment results in abnormalities of variables related to  $\dot{V}O_2$ . Exercise limitation due to lung disease is reflected in variables related to ventilation and gas exchange efficiency. Gas exchange inefficiency is also characteristic of some cardiovascular diseases, most notably pulmonary vascular disorders. HR indicates heart rate; WR, work rate; C.O., cardiac output; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; and VT, ventilatory threshold.

increase in heart rate relative to  $\dot{V}O_2$  and an above-average  $\dot{V}O_2$ /heart rate at peak exercise. Arterial oxygenation is usually normal in cardiovascular disorders, with the exception of pulmonary vascular diseases or complex congenital heart diseases.

A cardiovascular pattern of  $\dot{V}O_2$  responses may alternatively represent impaired oxygen utilization due to defects in skeletal muscle glycolytic or mitochondrial oxidative function<sup>129</sup> or due to maldistribution of cardiac output caused by autonomic failure. These conditions are characterized by hyperdynamic cardiovascular responses to exercise due to an inability to normally widen the  $[C(a-v)O_2]$ . Measurement of exercise cardiac output is uniquely useful for distinguishing these from cardiovascular disorders by the demonstration of high rather than low values of cardiac output relative to  $\dot{V}O_2$ . Although far less common than cardiovascular disease, mitochondrial myopathies are increasingly recognized among conditions that cause exercise intolerance, accounting for an estimated 8% of 1 series of patients referred to a tertiary center for evaluation of unexplained dyspnea,<sup>130</sup> as discussed in detail below (see CPX in Patients With Skeletal Muscle Fiber and Mitochondrial Myopathy).

Ventilatory limitation is most commonly identified in terms of reduction in the breathing reserve due to peak  $\dot{V}E$  being a high proportion of MVV. Although usually 20% or more in nonathletes at the end of an incremental test, breathing reserve varies widely in healthy persons (see Pulmonary Function Testing and Pulse Oximetry). A value of 15% approximates the lower 95% confidence limit for normal populations,<sup>5</sup> although athletes (because of high exercise capacity) and the elderly (because of low MVV) may have

values below this in the absence of disease. Advances in the understanding of exercise breathing mechanics are expanding the definition of ventilatory limitation to include more individualized analysis of the tidal breath volume and flow patterns. With isolated pulmonary dysfunction, peak  $\dot{V}O_2$  is low because of ventilatory limitation that occurs before attainment of cardiovascular limits. Peak heart rate is thus low. VT may be normal if the patient can exercise to a sufficiently high level, and the relationships between  $\dot{V}O_2$  and work rate and between  $\dot{V}O_2$  and heart rate are normal up to the levels of exercise attained. Abnormalities of pulmonary gas exchange efficiency due to mismatch of pulmonary ventilation and perfusion ( $\dot{V}:\dot{Q}$ ) are typical of both obstructive and interstitial lung diseases. The presence of high  $\dot{V}:\dot{Q}$  regions results in an increased effective dead space fraction of the breath ( $V_D$ /tidal volume) as calculated from the modified Bohr equation with arterial  $PCO_2$  and gas exchange data,<sup>124</sup> as discussed elsewhere (Appendix 1, Ventilatory Dead Space/Tidal-Volume Ratio). Regions of low  $\dot{V}:\dot{Q}$  result in arterial hypoxemia, reflected in low  $PaO_2$  and an increased  $P(A-a)O_2$ . In the absence of arterial blood sampling, high  $V_D$ /tidal volume may be inferred from high  $\dot{V}E/\dot{V}CO_2$  and hypoxemia from noninvasive pulse oximetry. A decrease in pulse oximeter saturation by  $>5\%$  is commonly used as an indication of pulmonary limitation to exercise. Resting pulmonary function tests are imprecise in predicting the presence or severity of gas exchange abnormalities during exercise.<sup>57</sup>

These broad distinctions are not invariant and do not account for all possible patterns of findings. Of particular note, chronic lung disease of any form can induce changes in the pulmonary circulation that can constrain hemodynamic responses to exercise. Conversely, moderate to severe chronic heart failure and pulmonary vascular diseases both cause abnormalities of gas efficiency that are normally characteristic of lung diseases. Mixed patterns of responses are thus common, which reflects the presence of secondary effects of the underlying disorders or comorbid conditions. Interpretation of exercise responses must be informed by the clinical context and other relevant data (Figure 4).

### CPX in Patients With Skeletal Muscle Fiber and Mitochondrial Myopathy

Aerobic functional performance requires integrated cardiovascular, pulmonary, and skeletal muscle physiology. Abnormal function in any 1 of these systems diminishes peak  $\dot{V}O_2$  and increases ventilatory equivalents.<sup>131–137</sup> Although these abnormal indices provide important quantifications, they do not distinguish between underlying physiological components. Diagnostic ambiguity is often further exacerbated by deconditioning. In addition to changes in central cardiac and pulmonary physiology in heart failure, intrinsic changes in skeletal muscle fibers and mitochondrial function limit aerobic potential. Skeletal muscle typically atrophies, and remaining myocytes tend to be disproportionately anaerobic subtypes that less efficiently utilize the oxygen they receive.<sup>133,138,139</sup> A so-called heart failure myopathy often precedes classic New York Heart Association symptoms and has been associated with underlying inflammation and related changes in skeletal muscle molecular signaling patterns.<sup>140</sup>

Similarly, primary mitochondrial myopathy results from a wide range of genetic defects and can compromise the exercise capacity even among those with normal cardiac and pulmonary capacity.<sup>141–144</sup>

CPX can be modified to increase diagnostic resolution of skeletal muscle abnormalities, particularly mitochondrial myopathy. A slope derived from change in cardiac output ( $\Delta Q$ ; y-axis) and change in  $\dot{V}O_2$  ( $\Delta\dot{V}O_2$ ; x-axis) during progressive exercise can be calculated.<sup>143</sup> Patients with primary mitochondrial myopathies are unable to adequately utilize oxygen for oxidative phosphorylation; instead, lactic acid accumulates early in exercise, which leads to exaggerated circulatory and ventilatory responses. These abnormalities are manifest in early fatigue and a significantly increased  $\Delta Q/\Delta\dot{V}O_2$  slope with exercise ( $\Delta Q/\Delta\dot{V}O_2$  slope  $\approx 15$  L/min in mitochondrial myopathy versus 5 L/min patients in healthy control subjects). Thus, a constellation of low peak  $\dot{V}O_2$  in conjunction with an abnormally elevated  $\dot{V}E/\dot{V}O_2$  ratio and high  $\Delta Q/\Delta\dot{V}O_2$  slope should raise consideration of peripheral myopathy and consideration of further testing, such as muscle biopsy.

Although heart failure patients and patients with primary mitochondrial myopathy endure similar functional declines as a result of peripheral skeletal muscle abnormalities,  $\Delta Q/\Delta\dot{V}O_2$  does not provide the same diagnostic utility in heart failure. By definition, systolic and diastolic heart failure entail reduced cardiac output, such that the  $\Delta Q/\Delta\dot{V}O_2$  slope more typically falls with exercise in this population. Although the  $\Delta Q/\Delta\dot{V}O_2$  slope increases in those with mitochondrial myopathy, the cardiac limitations of heart failure undercut the utility of this variable to identify skeletal muscle myopathy among heart failure patients.

## Exercise Prescription

### Cardiac Disease

The CPX can be used for derivation of an exercise prescription, but this is most often done by use of heart rates from the standard exercise ECG test. The CPX, however, can provide additional information in certain individuals, ie, those with dyspnea out of context with physical activity, psychological/motivational issues, and certain musculoskeletal disabilities. By determining the VT, a precise training work rate that includes  $\dot{V}O_2$  level and specific heart rate range can be identified. A peak RER  $\geq 1.10$  is an indicator of maximal effort, and a prescription for exercise can be designated at less than maximal for the individual patient.<sup>145</sup> However, there are no data to demonstrate the superiority of the CPX method over the standard heart rate method of prescribing exercise training intensity. A rating of perceived exertion can also be used to further refine the training intensity and assist the patient in self-monitoring during exercise training and the performance of other physical activities. Levels of exercise intensity based on rating of perceived exertion, heart rate reserve (peak heart rate minus resting heart rate), or  $\dot{V}O_2$  reserve (peak  $\dot{V}O_2$  minus resting  $\dot{V}O_2$ ) are as follows<sup>20</sup>:

Light intensity: Rating of perceived exertion  $< 12$ ;  $< 40\%$  of heart rate reserve+resting heart rate;  $< 40\%$   $\dot{V}O_2$  reserve+resting  $\dot{V}O_2$ .

Moderate intensity: Rating of perceived exertion 12 to 13; 40% to  $< 60\%$  of heart rate reserve+resting heart rate; 40% to  $< 60\%$   $\dot{V}O_2$  reserve+resting  $\dot{V}O_2$ .

Vigorous intensity: Rating of perceived exertion 14 to 16;  $\geq 60\%$  of heart rate reserve+resting heart rate;  $\geq 60\%$   $\dot{V}O_2$  reserve+resting  $\dot{V}O_2$ .

Moderate-intensity exercise is generally prescribed. Activities in general can progress over time as tolerance is demonstrated by the patient. After safe levels are established, duration may be increased as appropriate, and intensity may be increased as heart rate response to exercise decreases with training. In the presence of myocardial ischemia, heart rate and work rate should be below the threshold of ischemia (angina or significant ST-segment depression on testing). In general, this should be 10 beats per minute below the heart rate at which the abnormality occurs. Special considerations in prescriptive exercise include the elderly, heart failure, heart transplantation, after coronary surgery, after percutaneous coronary intervention, use of pacemakers and defibrillators, diabetes, hypertension, peripheral artery disease, and other special medical conditions. These are discussed in detail elsewhere.<sup>64</sup>

### Stroke

Stroke is a leading cause of disability that may produce marked cardiovascular deconditioning, which in turn worsens exercise capacity and cardiometabolic risk factor profiles. Fitness levels after even mild- to moderate-severity stroke can be up to half normal, thus compromising ability to meet the 2-fold elevated oxygen demands of a hemiparetic gait.<sup>146</sup> A sedentary lifestyle along with structural-metabolic abnormalities in hemiparetic limb muscle, including atrophy, increased intramuscular area fat, elevated tumor necrosis factor expression, and shift to fast-twitch muscle molecular phenotype, propagate insulin resistance. Hence, impaired glucose tolerance or type 2 diabetes mellitus is reported in  $\geq 75\%$  of hemiparetic stroke survivors, which in turn predicts a 2- to 3-fold increased risk of recurrent cerebrovascular events.

Although conventional rehabilitation does not systematically provide an adequate exercise stimulus to reverse deconditioning, evidence-based exercise models have emerged over the past decade that offer to improve fitness, health, and functionality after stroke. Customized exercise stress tests and submaximal and peak-effort exercise protocols with CPX are proven reliable in gait-impaired subjects with overground walking velocities as low as 0.11 m/s.<sup>147</sup> Randomized studies using these protocols reveal a variety of training modalities, including modified cycle ergometry, treadmill, structured exercise classes, and aquatic therapy, that can improve fitness by a range of 8% to 23% ( $\Delta\% \dot{V}O_2$  peak) in the subacute and chronic stroke recovery period.<sup>148,149</sup> Task-oriented training models that emphasize repetitive locomotor or mobility exercises appear more efficacious in improving ambulatory function, even years after a stroke, by mediating brain plasticity.<sup>150</sup> Furthermore, treadmill training reduces the steady state oxygen demands of hemiparetic gait patterning, which may enable daily-mobility functions to be performed at a lower percentage of peak exercise capacity. Randomized studies further show that 6 months of progressive aerobic



training improves indices of insulin sensitivity and glucose tolerance to reverse impaired glucose tolerance or type 2 diabetes mellitus classification in 58% of cases.<sup>151</sup> Although further studies are needed to optimize exercise models to improve fitness and motor function, medically supervised aerobic exercise is emerging as a health-promoting option in long-term care after stroke.

## Disability Assessment

### *Cardiovascular Disease and Stroke*

Exercise testing may be useful in the determination of disability from cardiovascular disease and stroke because it can provide an objective assessment of exercise capacity; however, performance of exercise testing to fatigue is subject to individual effort. CPX can be helpful because it can provide additional information to gauge whether effort was maximal ( $RER > 1.10$ ). However, standard treadmill or cycle exercise tests may not simulate conditions for a given work task, because many tests involve prolonged submaximal effort that involves both upper- and lower-body movement. Although CPX has the potential to provide objective measures of task-related energy expenditure and associated cardiopulmonary responses, the data on the use of CPX for this purpose are scarce.

### *Pulmonary Disease*

Severe impairment in resting pulmonary function measures is accepted as evidence of disability due to lung disease, but it is recognized that functional impairment may be poorly predicted by resting studies. Published guides for determination of impairment due to lung disease recommend measurement of peak  $\dot{V}O_2$  when symptoms are judged to be disproportionately high relative to the degree of pulmonary function abnormality. In the American Medical Association's *Guides to the Evaluation of Permanent Impairment*,<sup>152</sup> impairment due to pulmonary dysfunction is rated either on the basis of measures of resting pulmonary function or exercise capacity. Impairment is graded as very severe when vital capacity is  $<50\%$  of predicted,  $FEV_1$  or carbon monoxide diffusing capacity is  $<45\%$  of predicted, or peak  $\dot{V}O_2$  is  $<15 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ . Among patients undergoing exercise testing for evaluation of impairment due to lung disease, high rates of comorbid cardiovascular disease have been identified,<sup>153,154</sup> so that attribution of symptoms and impairment is one of the purposes of exercise testing in this context.

## Emerging Applications of CPX

The following section provides a brief overview of emerging applications of CPX. In each case, the available data are not adequate to provide a consensus opinion on whether these applications can or should be used clinically. They are presented here to provide a comprehensive overview of potential uses of CPX, but in each case, more data are needed.

### **Adults With Congenital Heart Disease**

A small but growing body of literature has emerged over the past 2 decades regarding the use and value of CPX in adults with congenital heart disease (ACHD). Previous reports were limited to case reports or small case series of patients with a

specific type of ACHD. More recent larger comparative series of adults with various forms of ACHD demonstrate that because ACHD is heterogenous, so are the responses to CPX.<sup>155–157</sup> However, a common theme is evident: Patients with ACHD have reduced exercise capacity as measured by CPX compared with healthy adults,<sup>155,157</sup> and the spectrum of exercise impairment is broadly related to the underlying ACHD condition. These studies demonstrate that exercise capacity is limited even among asymptomatic patients<sup>157</sup> and that self-estimated physical functioning is a poor predictor of measured exercise capacity.<sup>158</sup> Moreover, there is an excessive ventilatory response to exercise across the diagnostic spectrum of ACHD as measured by  $\dot{V}E/\dot{V}CO_2$  slope. Cyanosis appears to be a strong stimulus for increased  $\dot{V}E/\dot{V}CO_2$  slope irrespective of the presence of pulmonary hypertension.<sup>156</sup> Importantly, CPX appears to provide important prognostic information among patients with ACHD. Peak  $\dot{V}O_2$  is an important predictor of those at risk for hospitalization or death.<sup>157</sup> Among patients with noncyanotic ACHD, a  $\dot{V}E/\dot{V}CO_2$  slope  $\geq 38$  is associated with a 10-fold increased risk of mortality.<sup>156</sup> Additionally, peak circulatory power (peak  $\dot{V}O_2$  multiplied by peak mean arterial pressure) has been found to predict mortality among patients with varying diagnoses of ACHD.<sup>159</sup> In summary, these data provide strong evidence that CPX can provide useful objective information regarding exercise tolerance and prognosis among patients with ACHD. Potential additional applications of CPX among these patients include assessment of exercise tolerance before and after therapeutic surgical and medical interventions, including exercise training programs.

### **Pulmonary Resection**

Pulmonary resection is most commonly performed for curative intent in localized lung cancer. Because of the poor prognosis of lung cancer that is treated nonoperatively, the focus of the evaluation is to avoid excluding patients from potentially curative procedures. Exercise capacity is predictive of perioperative morbidity and mortality related to resectional surgery and is recommended as part of the stepwise assessment of patients' physiological reserve.<sup>160</sup> Peak  $\dot{V}O_2$  values above  $15 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  predict no increase in operative risk for pneumonectomy or lobectomy compared with the lowest-risk patients, even for patients whose resting pulmonary function or predicted postoperative pulmonary function is poor.<sup>161</sup> Lower peak  $\dot{V}O_2$  values, particularly  $<10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ , are associated with increased operative risk, which can be factored into the overall risk-benefit assessment in selecting the type and extent of treatment appropriate for individual patients.<sup>160</sup> Exercise testing is an integral part of the selection and preparation of candidates for lung volume reduction surgery as treatment for severe emphysema.<sup>162</sup> The National Emphysema Treatment Trial<sup>163</sup> used exercise testing for design of preoperative rehabilitation of surgical candidates and found peak exercise work rate to be one of the key variables that identified the subset of patients who benefitted from the procedure. The role of other variables from CPX for surgical decision making in this setting needs further study.

## Pulmonary Hypertension

Pulmonary arterial hypertension occurs commonly in cardiopulmonary diseases and is defined by the National Institute of Health Registry as a mean pulmonary artery pressure of >25 mm Hg at rest or 30 mm Hg during exercise in the absence of pulmonary venous hypertension.<sup>164</sup> CPX has been used safely in patients with advanced respiratory diseases, including pulmonary arterial hypertension, for the following indications: Prognostic assessment; evaluation of impairment and disability; evaluation and monitoring of responses to various treatment modalities; evaluation for the presence of a patent foramen ovale and right-to-left shunting; development of an exercise prescription for pulmonary rehabilitation; and evaluation of patients for lung or heart-lung transplantation.<sup>5,55</sup> However, CPX confers some mortality risk in patients with pulmonary arterial hypertension and is contraindicated if syncope, serious arrhythmias, or acute right-sided heart failure is present.<sup>5</sup>

In chronic pulmonary arterial hypertension, the  $\dot{V}O_2$ max provides an index of disease severity; it is lower in patients with a high total pulmonary vascular resistance and lower cardiac index and is highly correlated with the amount of functional pulmonary vascular bed.<sup>55,120</sup> One of the leading causes of pulmonary arterial hypertension is chronic lung disease, and CPX has been used to separate lung disease patients with and without pulmonary arterial hypertension; in those with pulmonary arterial hypertension, a significantly reduced ventilatory efficiency is noted, along with a lower rest and exercise arterial oxygen saturation.<sup>48</sup> In patients with primary pulmonary arterial hypertension, the percent of predicted  $\dot{V}O_2$  achieved correlates significantly with mean pulmonary artery pressure; the  $P_{ET}CO_2$  values at rest, at VT, and at peak  $\dot{V}O_2$  are proportionately reduced as the percent of predicted peak  $\dot{V}O_2$  decreases and mean pulmonary artery pressure increases.<sup>46</sup> Also in patients with primary pulmonary arterial hypertension, CPX has been used to determine right-to-left exercise-induced shunting.<sup>165</sup> In fact, an abrupt and sustained increase in  $P_{ET}O_2$  with a simultaneous decrease in  $P_{ET}CO_2$ , an abrupt and sustained increase in the RER, and an associated decline in pulse oximetry saturation each has a reported sensitivity, specificity, and positive and negative predictive values in the range of 90% to 96% for predicting patent foramen ovale and shunting. In patients with severe primary pulmonary arterial hypertension, the  $\dot{V}E/\dot{V}CO_2$  ratio correlates significantly with pulmonary vascular resistance but not with mean pulmonary artery pressure or cardiac index.<sup>166</sup> Finally, CPX has been used to estimate survival in pulmonary hypertension, although typically, this has been done by use of the 6-minute walk distance.<sup>55,166,167</sup>

## Ischemic Heart Disease

Although it provides valuable prognostic assessment in patients with CAD, CPX can may be helpful in the diagnosis of exercise-induced myocardial ischemia, albeit the data are limited.<sup>168–172</sup> In addition to providing continuous electrocardiographic evaluation of ST-segment changes, CPX can detect subtle changes in stroke volume that accompany ischemia-induced left ventricular dysfunction. The normal physiological response to progressive exercise is a continu-

ously increasing  $O_2$  pulse, a linear increase in  $\dot{V}O_2$  versus work rate, and a linear increase in heart rate versus  $\dot{V}O_2$  until peak values are reached. The development of myocardial ischemia during exercise can lead to loss of augmentation of stroke volume, which is demonstrated as flattening of the  $O_2$ -pulse response to exercise. With a 2-variable model based on  $O_2$ -pulse–flattening duration and  $\Delta\dot{V}O_2/\Delta$ work rate slope, the diagnostic accuracy of standard electrocardiography stress testing versus CPX was compared in 202 consecutive patients with documented CAD,<sup>171</sup> with a reported a sensitivity of 46% and specificity of 66% for standard electrocardiography-based stress testing compared with 87% and 74%, respectively, for CPX. However, it is important to understand that these abnormal responses not only are seen in patients with myocardial ischemia but can be seen in many other conditions that might impair cardiac output during exercise.

## Evaluation of Cardiac Pacemaker Function

CPX is increasingly being used in the evaluation of pacemaker technology, particularly rate-responsive pacemakers and biventricular pacemakers. Rate-responsive pacemakers use activity and/or metabolic sensors that can monitor QT interval, right ventricular temperature, respiration, and peak endocardial acceleration. They can generate heart rates that are theoretically appropriate, at rest and during effort, for patients with chronotropic incompetence due to sick sinus syndrome or advanced atrioventricular block.<sup>173,174</sup>

Because the chronotropic control of the working sinus node is difficult to imitate, cardiologists must evaluate the rate-response pacing rate adequately, tailoring rate-response settings for many patients. This is typically performed by use of protocols based on activities of daily living, followed by an evaluation of the pacing rate through Holter monitoring. These simple and empirical measures are generally adequate for most individuals, particularly older or less active patients or those without significant hemodynamic compromise. Those patients, however, who are young or more physically active, as well as those with hemodynamic compromise, may require optimization of rate-response settings, including adjustment of the atrioventricular delay, by use of more accurate and reproducible methods such as CPX.<sup>175–178</sup> In this regard, investigators have reported the use of several metabolic parameters derived from CPX as clinical end points in the assessment of patients with rate-responsive pacemakers. Adjustments of the atrioventricular delay and rate-response settings have been reported to increase peak  $\dot{V}O_2$ , VT, and  $O_2$  pulse.<sup>179–181</sup> Similarly, CPX has been used to verify the efficacy of cardiac resynchronization therapy via biventricular pacing in patients with wide-QRS-complex heart failure.<sup>80</sup> The underlying basis of cardiac resynchronization therapy is to improve cardiac efficiency by synchronizing the timing of global left ventricular depolarization, thus improving mechanical contractility and reducing mitral regurgitation.<sup>182</sup> Peak  $\dot{V}O_2$ , VT,  $O_2$  pulse, and  $\dot{V}E/\dot{V}CO_2$  ratio have all been reported to improve significantly after cardiac resynchronization therapy and are standard measures used in clinical trials to assess the efficacy of this therapy.<sup>80,183</sup>

### Arrhythmias

Only limited data are available regarding the role of CPX in the evaluation of cardiac arrhythmias; this is almost entirely related to the effect of atrial fibrillation on exercise capacity in patients with heart failure. In a small study of 111 patients with heart failure, 18 patients with atrial fibrillation had a 20% lower peak  $\dot{V}O_2$  than those without atrial fibrillation.<sup>184</sup> In a much larger study of 942 heart failure patients, including 180 with atrial fibrillation, lower values for peak  $\dot{V}O_2$ ,  $O_2$  pulse, and  $\dot{V}CO_2$  were all independent predictors of the presence of atrial fibrillation.<sup>185</sup> In patients with atrial fibrillation and heart failure,  $\dot{V}O_2$  was higher at VT but lower at peak exercise. Likewise, in small studies of patients without heart failure, atrial fibrillation was associated with worsening of peak  $\dot{V}O_2$ , endothelial function, exercise ventilatory efficiency, and muscle ergoreflex contribution to ventilation.<sup>186–188</sup> In general, these parameters improve with cardioversion but not with rate control alone and worsen again after relapse of atrial fibrillation.<sup>186–189</sup>

### Bariatric Surgery

Recently, investigators extended the application of CPX to evaluate whether there is a relationship between complications after bariatric surgery and preoperative exercise capacity.<sup>190</sup> These data have clinical relevance because the number of bariatric surgeries performed in the United States has risen from 12 775 in 1998 to an estimated 140 000 operations in 2005. Such procedures, however, are not without risk.<sup>191</sup> Although there are no specific recommendations for the medical preoperative evaluation for morbidly obese patients undergoing bariatric surgery, current American Heart Association/American College of Cardiology guidelines<sup>192</sup> state that an assessment of exercise capacity, when possible, can be useful in the evaluation process for noncardiac surgery. McCullough and associates<sup>190</sup> evaluated directly measured exercise capacity in 109 patients before laparoscopic Roux-en-Y gastric bypass surgery. The primary composite complication rate, defined as death, unstable angina, myocardial infarction, venous thromboembolism (deep vein thrombosis or pulmonary embolism), renal failure, or stroke, occurred in 6 (16.2%) of 37 patients and 2 (2.8%) of 72 patients whose peak  $\dot{V}O_2$  was  $<15.8$  and  $\geq 15.8$   $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , respectively. Hospital lengths of stay and 30-day readmission rates were highest in the lowest tertile of peak  $\dot{V}O_2$ , which averaged  $13.7 \pm 2.1$   $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Multivariate analysis that adjusted for age, body mass index, and sex found that peak  $\dot{V}O_2$  was a significant predictor of complications. Collectively, these findings suggest an inverse relationship between exercise capacity and complications after bariatric surgery, which highlights the potential application of such data in risk stratification of this growing patient population. However, further data are needed.

### Assessing and Reporting CPX Data

In addition to the 3% to 4% biological variability that is intrinsic to CPX in most patient groups, a criticism of some parameters derived from CPX is that peak data can be influenced by both subject effort and differences in test conduct. The latter refers, in part, to differences between 1

test supervisor and another relative to the determination of symptom-limited maximal effort or achievement of prespecified criteria for test termination. As stated in the section on Procedures for CPX, parameters to help the test supervisor identify a true peak effort are well established, and the uniform application of these criteria over time by test supervisors should favorably contribute to the acquisition of true peak data. After ensuring appropriate calibration of CPX equipment, it remains the responsibility of those conducting the test and interpreting test results to be sure the data reflect valid information. Therefore, after the patient has been connected to the CPX system and while he or she is at seated rest before testing, the following variables should be assessed to help ensure that the data appear physiological:

- $F_{iO_2}$  (ie, oxygen content in room air) should be  $20.93\% \pm 0.5\%$ .
- With the subject sitting comfortably before testing,
- relative  $\dot{V}O_2$  is between 2.5 and 4.5  $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;
- RER is 0.8 to 1.0; however, it is not uncommon to see values for this parameter above 1.0 at rest, which reflects increased ventilation that is likely due to pretest apprehension and/or breathing irregularities.

During each test, the CPX data should be assessed continually to be sure that  $\dot{V}O_2$ ,  $\dot{V}E$ , and RER are increasing in a manner that is commensurate with the magnitude of the increases in external exercise work rates. To facilitate determination of this during real time, the CPX system should be set up in a manner that displays the data in a rolling breath-average format as described above (see Procedures for CPX). This smoothes out the typically sporadic unaveraged data, which can be difficult to interpret. The supervising staff should be familiar with the expected oxygen demands and physiological responses for a given work rate or stage of a protocol and should watch for sporadic changes (from normal to very low) in  $\dot{V}O_2$ ,  $\dot{V}E$ , RER, or respiratory rate, any and all of which might suggest an air leak at the mouthpiece/face mask or through an ineffective seal from nose clips.

A final report should be generated that (1) describes the reason for the test and what type of test was completed (eg, modality, protocol); (2) summarizes the patient's demographic information, the clinical and physiological responses to exercise (eg, duration, symptoms, reason for stopping), and whether according to the data available, the patient attained a maximal effort; and (3) avoids the use of the terms positive or negative. The report should conclude with a list of final impressions or recommendations that concisely and specifically respond to the reason the test was ordered. The final report should identify normal and abnormal responses, as well as put into perspective the impact or importance of these findings. Examples are as follows: For patients with heart failure, it should identify those with severe functional limitations and poor prognosis (peak  $\dot{V}O_2 < 10$   $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and  $\dot{V}E/\dot{V}CO_2$  slope  $>40$ ); for patients being evaluated for unexplained dyspnea, the report should specify the likely cause of the symptom (ie, cardiac, pulmonary, deconditioning, or other); for patients being evaluated for disability, the report should (1) identify peak exercise capacity (eg, peak

**Table 5. Normal/Abnormal Values and CPX**

	Heart Rate (% of Age Predicted)	$\dot{V}O_2$		$\dot{V}E/\dot{V}CO_2$ Slope
		Absolute	% of Age Predicted	
Apparently healthy people				
• Normal	$\geq 85$	Within 95% CI	NA	25
• Abnormal	$< 85$	NA	NA	NA
Systolic heart failure				
• Severely limited/high risk	NA	$< 10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ if treated with $\beta$ -blockade $< 14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ if not treated with $\beta$ -blockade;	$< 50$	$\geq 34$

CI indicates confidence interval; NA, not applicable.

$\dot{V}O_2$  and measured METs), (2) cite references to tables that provide estimated energy expenditure (in METs) for many occupational and leisure activities,<sup>193</sup> and (3) perhaps provide patient-specific examples of occupational and leisure activities that might be tolerated safely.

A suggested list of the recommended and optional parameters to include in a CPX final report is summarized in Table 6 of Appendix 2. Although graphs and figures are often used by those conducting or supervising a CPX test or interpreting test results, it is not necessary to include such elements in the final report. An example of a CPX test final report is shown in Table 7 in Appendix 2. Information that quantitatively and qualitatively compares a patient's test results to normative databases can be helpful (Table 5). In all cases, when possible, data should be reported in the context of published data from the same reference population using the same exercise modality. Table 8 and Figure 9 in Appendix 2 compare sample reports for 2 women of the same age who have been evaluated for different reasons (heart failure and dyspnea on exertion).

Similar considerations as noted above (see Heart Failure: Systolic Dysfunction) for obese patients apply to the use of predicting equations for calculation of normal reference values. Regression analyses of normal subjects usually show weight to be a positive factor in determining peak  $\dot{V}O_2$ , but unreasonably high predicted values may result when the same equations are applied to very obese subjects using their actual weights. Similarly, equations derived from athletic populations will predict higher  $\dot{V}O_2$  values than typical of healthy but sedentary individuals. Predicting equations should be selected and applied with an appreciation of the reference group and any systematic differences between those subjects and the laboratory's clinical population. Several databases exist for the comparison of a patient's test results to existing normative data, but each is associated with certain strengths and limitations.<sup>124,194–196</sup> For measured peak  $\dot{V}O_2$  and its expression as a percent of predicted in patients with heart failure, Arena et al<sup>98</sup> evaluated 4 different common equation sets and showed that the Wasserman/Hansen<sup>124,196</sup> equation set was superior to the other equations relative to its prognostic power.

### Future Research

This "Clinician's Guide" presents detailed discussions of the many variables that can be derived from CPX and how they

may be applied in the diagnostic and prognostic assessment of patients with heart failure and unexplained dyspnea, as well as many emerging applications. It remains to be studied whether data derived from CPX provide sufficient incremental information over that provided by exercise testing without gas analysis when used in conjunction with other clinical variables. That is, does CPX testing reclassify individuals into different prognostic groups over and above standard testing? This issue has been raised by a recent study that demonstrated that treadmill exercise time provided prognostic information in patients with heart failure, even when accounting for peak measured  $\dot{V}O_2$  during CPX.<sup>197</sup> From these data, the authors suggest that exercise treadmill testing may be useful as an initial prognostic screening test when CPX is not readily available. Whether CPX data beyond peak  $\dot{V}O_2$  (eg, VT,  $\dot{V}E/\dot{V}CO_2$  slope) provide additional discriminatory prognostic information in this context was not evaluated and needs to be studied. Finally, further studies are needed to evaluate the utility of the many CPX variables presented in Appendix 1 in patients with heart failure, unexplained dyspnea, and the growing number of other conditions in which CPX has been studied (see Emerging Applications of CPX).

### Summary of Key Points

- CPX offers the clinician the ability to obtain a wealth of information beyond standard exercise testing that, when appropriately applied and interpreted, can assist in the management of complex cardiovascular and pulmonary disease.
- The recommendations made in the present document are based primarily on expert consensus interpretation of published data when available, because there are essentially no randomized trials to address diagnostic and prognostic applications of CPX.
- CPX systems must be properly maintained and calibrated to ensure that high-quality data are provided.
- CPX test protocol selection is important to optimize the data that are derived from the test. Protocols that involve small to modest work-rate increments per stage (eg, ramp, Naughton, and Balke) maintain a greater relationship between  $\dot{V}O_2$  and work rate than do those protocols with larger work-rate increments.

- CPX test supervision, monitoring, and interpretation should be performed by competent personnel as recommended in established exercise testing guidelines.<sup>21</sup>
- Use of correct CPX billing codes coupled with correct diagnostic codes is important to obtain appropriate reimbursement for the services provided.
- Several important variables derived from CPX provide useful diagnostic and prognostic information. Peak  $\dot{V}O_2$ , VT, RER,  $\dot{V}E/\dot{V}CO_2$  slope,  $\dot{V}E/MVV$ , and oxygen saturation are the most commonly used clinically.
- Integration of CPX test data with exercise-ECG test data provides optimal comprehensive use of CPX. Electrocardiographic criteria (heart rate dynamics, arrhythmia, ST-segment changes, and conduction disease), hemodynamics, and symptoms are all important exercise-related measures that complement and expand on the gas exchange indices.
- Related technologies used during CPX, such as the noninvasive determination of cardiac output or flow-volume loops, may provide useful diagnostic and prognostic information in selected patients.
- CPX in clinical populations has been well studied and appears most useful in the evaluation of patients with heart failure and those with unexplained dyspnea. Other uses include the assessment of patients with mitochondrial myopathies, development of the exercise prescription in patients with cardiovascular disease or stroke, and the assessment of disability in patients with cardiac or pulmonary disease.
- Emerging and less well studied applications of CPX include the evaluation of patients with adult congenital heart disease, pulmonary hypertension, cardiac arrhythmias and pacemakers, and ischemic heart disease and the preoperative assessment of patients undergoing pulmonary resection or bariatric surgery.
- Assessment of CPX data should be done to ensure its validity before a final report is generated.
- A final report should describe the reason for the test and what type of test was completed (eg, modality, protocol); summarize the patient's demographics and clinical and physiological responses to exercise (eg, duration, symptoms, reason for stopping); and avoid the use of terms positive or negative. The report should conclude with a list of final impressions or recommendations that concisely and specifically respond to the reason the test was ordered.
- Future studies are needed to rigorously evaluate whether CPX provides additional discriminatory diagnostic and prognostic value over and above that provided by standard exercise tests and other clinical variables. More studies are needed to assess the increasing number of variables that can be derived from CPX, as well as their utility in many conditions that affect the cardiovascular and pulmonary systems.

## Appendix 1

### Additional Measures and Related Technologies

#### Oxygen Uptake Efficiency Slope

Without alteration of the data obtained from CPX, the relationship between  $\dot{V}E$  and  $\dot{V}O_2$  is exponential, which obviates the ability to derive a slope value by linear regression. Baba et al<sup>198</sup> developed a

technique named the OUES that logarithmically transforms  $\dot{V}E$  data in liters per minute (plotted on the x-axis), thereby creating a linear relationship with  $\dot{V}O_2$ , expressed in milliliters per minutes or liters per minute (plotted on the y-axis, where  $(\dot{V}O_2 = a \log_{10} \dot{V}E + b)$ ). Given the tight linear relationship the OUES creates between  $\dot{V}E$  and  $\dot{V}O_2$  throughout a progressive exercise test,<sup>199</sup> this calculation has been advanced as a measurement that requires only submaximal effort and reflects the integrated function and health of the pulmonary, cardiovascular, and skeletal muscle systems.<sup>200</sup> Because previous investigations have used different units to calculate the  $\dot{V}O_2$  portion (liters versus milliliters per minute),<sup>199,201</sup> there is no universally accepted expression of the OUES. Slope values are expressed in the thousands ( $\approx 1000$  to  $4000$ ) and single digits ( $\approx 1$  to  $4$ ) when  $\dot{V}O_2$  is expressed in milliliter-per-minute and liter-per-minute units, respectively. In contrast to the  $\dot{V}E/\dot{V}CO_2$  slope, a higher OUES portends a more favorable response and improved physiological function. Follow-up research by Baba et al<sup>202</sup> demonstrated high test-retest reliability for the OUES in apparently healthy subjects.

Compared with other CPX variables such as peak  $\dot{V}O_2$  and the  $\dot{V}E/\dot{V}CO_2$  relationship, scientific analysis of the OUES is limited. Previous investigations have found that the OUES is strongly correlated with  $\dot{V}O_{2max}$ ,<sup>200,203</sup> reflects varying degrees of cardiovascular health/disease,<sup>199</sup> and may possess prognostic value.<sup>201</sup> With respect to the latter, the prognostic value of the OUES over the  $\dot{V}E/\dot{V}CO_2$  slope or other CPX variables remains unclear.<sup>204,205</sup> There do not appear to be any investigations that have attempted to account for the pathophysiological mechanisms that lead to a diminished OUES. Although the OUES has now been available for more than 10 years, its incorporation into the software packages that operate CPX carts is not standard; therefore, data from a CPX must be exported into other spreadsheet software packages to calculate the OUES.

#### Partial Pressure of End-Tidal Carbon Dioxide

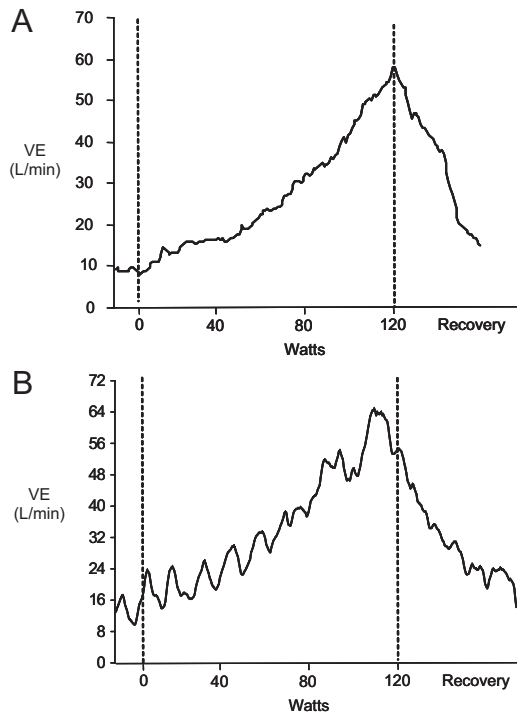
The  $P_{ET}O_2$  is easily derived and commonly reported at rest, VT, and peak exercise in mm Hg units by the software packages that operate CPX carts. Normal resting values range between 36 and 44 mm Hg, increase between 3 and 8 mm Hg from rest to VT, and then decrease as an individual approaches maximal exertion.<sup>124</sup> The limited available research on  $P_{ET}CO_2$  reliability demonstrates minimal test-retest variability for the resting expression of this variable.<sup>206</sup> Caution is required in interpreting values measured from a particular patient, because they may be confounded by factors such as acute hyperventilation, increased dead space due to emphysema or other lung diseases, or rapid shallow breathing patterns, all of which will reduce the  $P_{ET}CO_2$  independently of cardiac function.

Numerous investigations have demonstrated a significant relationship between resting  $P_{ET}CO_2$  and cardiac output.<sup>207,208</sup> The  $P_{ET}CO_2$  obtained during exercise has also been correlated with cardiac output in patients with heart failure<sup>209</sup> and can reflect disease severity in this population. Resting and peak exercise  $P_{ET}CO_2$ , as well as the highest increase from rest during a progressive CPX, all demonstrate independent prognostic value in patients with heart failure.<sup>205,210,211</sup>

In patients with pulmonary hypertension, resting, VT, and peak exercise  $P_{ET}CO_2$  are significantly correlated with pulmonary pressures and can thus provide a noninvasive reflection of disease severity. CPX may also aid in the detection of exercise-induced right-to-left shunting. With the following gas exchange measures and the resting echocardiogram as the reference, the sensitivity, specificity, positive and negative predictive values, and accuracy have been reported to be between 90% and 96%: (1) An abrupt and sustained increase in  $P_{ET}O_2$  with a simultaneous sustained decrease in  $P_{ET}CO_2$ ; (2) an abrupt and sustained increase in the RER; and (3) an associated decline in pulse oximetry saturation.<sup>165</sup>

#### Ventilatory Pattern During Exercise

$\dot{V}E$  progressively increases during exercise. Over time, 2 inflection points may be identified in the slope of  $\dot{V}E$  relative to  $\dot{V}O_2$  or work rate. The first change in slope occurs at work rates when the VT is exceeded. Above this point,  $\dot{V}CO_2$  begins to increase more steeply than  $\dot{V}O_2$  because of an additional amount of  $CO_2$  generated by  $HCO_3^-$  buffering of lactic acid. During this period of isocapnic



**Figure 5.** Examples of a linear (A) and oscillatory (B)  $\dot{V}_E$  increase over incremental work rate. EOB is a pathological phenomenon that comprises a regular waxing and waning of ventilation (hyperpnea and hypopnea) associated with changes in arterial  $O_2$  and  $CO_2$  tension. Abnormal cyclic oscillations during exercise occur with a variable length and amplitude (B) and are compared with the normal linear pattern (A).

buffering,  $\dot{V}_E$  retains a linear relation with  $\dot{V}_{CO_2}$ , so the  $\dot{V}_E/\dot{V}_{CO_2}$  ratio remains stable, but the  $\dot{V}_E/\dot{V}_{O_2}$  ratio increases. This discordant behavior in  $\dot{V}_E/\dot{V}_{CO_2}$  versus  $\dot{V}_E/\dot{V}_{O_2}$  ratios provides an additional gas exchange method for the identification of the VT (Figure 1B). After the isocapnic buffering period, the  $\dot{V}_E$  steepness further increases, which reflects a compensation for the development of exercise-induced metabolic acidosis. This results in an inflection in the slope of  $\dot{V}_E$  as a function of  $\dot{V}_{CO_2}$ , as well as a further increase in  $\dot{V}_E$  versus  $\dot{V}_{O_2}$  or work rate.

In some heart failure patients, the  $\dot{V}_E$  response to exercise is challenged in that a peculiar EOB pattern (Figure 5) may develop. EOB is a pathological phenomenon that consists of a regular waxing and waning of ventilation (hyperpnea and hypopnea) associated with changes in arterial  $O_2$  and  $CO_2$  tension.<sup>44,212</sup> Cyclic oscillations during exercise occur with a variable length and amplitude and may persist for the entire exercise duration or disappear at intermediate or higher work rates. Although definitive criteria for EOB definition are yet to be established, a persistence of EOB pattern for at least 60% of exercise at an amplitude  $\geq 15\%$  of the average resting value has been adopted by most recent studies as indicative of abnormal oscillatory gas exchange kinetics.<sup>118,213,214</sup>

EOB prevalence across heart failure populations is not defined clearly, but it can range between 12% and 30%,<sup>215</sup> with a similar prevalence and clinical significance in either systolic or diastolic heart failure.<sup>118</sup> Remarkably, in heart failure patients, an oscillatory ventilatory pattern may also occur during sleep (central sleep apnea)<sup>216</sup> or during the awake state at rest (Cheyne-Stokes respiration).<sup>217</sup> EOB is not characterized by periods of apnea, which is more typically observed in both central sleep apnea and Cheyne-Stokes respiration. Nonetheless, ventilatory patterns may share similar mechanisms, and EOB may reflect a less severe form of central sleep apnea or Cheyne-Stokes respiration. Most heart failure patients with EOB also exhibit central sleep apnea, which suggests a tight

pathogenetic relationship between sleep-disordered breathing and cardiopulmonary response during exercise.<sup>215</sup>

The true pathophysiological origin of this phenomenon is complex and intriguing and appears to be the result of the deregulation of different mechanisms involved in the mechanical and neural feedback control of the cardiopulmonary system. A number of pathogenetic theories have been formulated.<sup>218–220</sup> Clinical interest in EOB is increasing because it may predict mortality either when used alone<sup>36,213</sup> or when combined with an increased  $\dot{V}_E/\dot{V}_{CO_2}$  slope.<sup>214</sup> In a recent evaluation of a series of 156 heart failure patients, EOB emerged as a strong predictor of sudden death mortality<sup>221</sup>; however, additional prospective studies are needed to confirm its prognostic utility.

### Ventilatory Dead Space/Tidal-Volume Ratio

The dead space (VD)/tidal-volume ratio is a CPX-derived variable that provides an estimate of ventilation-perfusion ratio homogeneity both at rest and during exercise. Alveolar ventilation is the theoretical ideal ventilation that participates in pulmonary gas exchange if alveolar ventilation-perfusion ratios of alveolar/capillary units are uniform. However, even in physiological conditions, the actual  $\dot{V}_E$  includes the conducting airways and alveolar units that may not be optimally perfused. The difference between alveolar ventilation and  $\dot{V}_E$  is the *physiological dead space*, which is normally one third of the tidal volume. During exercise, recruitment and distension of the pulmonary vascular bed allows for a decrease in VD/tidal-volume ratio, with the major decrement occurring at the initial stages of exercise. In healthy individuals, VD/tidal-volume ratio at rest is  $\approx 0.34$ ; it may decrease to 0.10 or less at peak exercise. In patients with various respiratory disorders<sup>124</sup> and in cardiac patients with left-sided pulmonary hypertension,<sup>222,223</sup> the VD/tidal-volume ratio does not decrease appropriately throughout exercise and requires a disproportionate increase in respiratory rate to overcome the increased dead space ventilation. VD/tidal volume is calculated with the following formula:

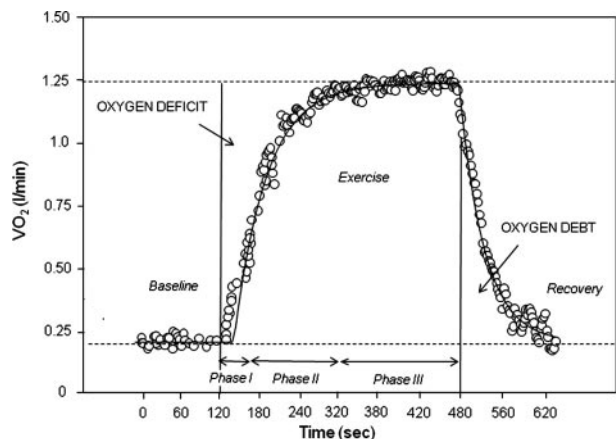
$$\text{VD/tidalvolume} = \left[ (\text{PaCO}_2 - \text{PECO}_2) / \text{PaCO}_2 \right] - (\text{VDapp/tidalvolume})$$

where  $\text{PaCO}_2$  is the arterial  $CO_2$  pressure,  $\text{PECO}_2$  is the partial pressure of  $CO_2$  in expired air, and VDapp is the apparatus dead space.

Ideally, VD/tidal-volume calculation requires direct measurement of arterial  $\text{PaCO}_2$  by arterial blood gas analysis; however, for practical reasons, especially during exertion,  $\text{PaCO}_2$  can be estimated noninvasively by use of  $\text{P}_{\text{ET}}\text{CO}_2$ . Jones et al<sup>224</sup> developed a formula for calculation of the  $\text{P}_{\text{JCO}_2}$ , an empirical equivalent of  $\text{PaCO}_2$  in healthy subjects. Both  $\text{P}_{\text{ET}}\text{CO}_2$  and  $\text{P}_{\text{JCO}_2}$  are incorporated in most CPX cart software for the noninvasive calculation of VD/tidal volume; however, the use of estimated  $\text{PaCO}_2$  may be less reliable in patients with cardiac or pulmonary disease.<sup>223,225</sup>

### $\dot{V}_{O_2}$ /Work-Rate Relationship

In physiological conditions, there is a linearity in the increase in  $\dot{V}_{O_2}$  over the rate of increase in work rate (WR;  $\Delta\dot{V}_{O_2}/\Delta\text{WR}$ ). The slope of this relationship is a function of the ability of exercising muscle to extract  $O_2$  and to provide aerobically generated adenosine triphosphate. In several reports obtained in healthy sedentary subjects, the slope for a linear ramp protocol test approximates  $10 \text{ mL } O_2 \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ , without a significant influence of age, sex, or height.<sup>124</sup> Although there may be many reasons for this slope to be reduced, a reduction in the  $\Delta\dot{V}_{O_2}/\Delta\text{WR}$  relationship most often indicates some failure of  $O_2$  transport. This may be seen in heart, peripheral arterial, and lung disease or in mitochondrial myopathy in which there is alteration in the cellular pathways involved in  $O_2$  utilization. In cardiac patients, a shallow exercise  $\Delta\dot{V}_{O_2}/\Delta\text{WR}$  may be associated with the development of myocardial ischemia<sup>170</sup> and an increased risk of death.<sup>226</sup>



**Figure 6.**  $\dot{V}O_2$  kinetics.  $\dot{V}O_2$  kinetics as a function of time during a constant work rate, moderate-intensity level of exercise in a healthy subject, depicting phase I (cardiodynamic), phase II (cell respiration), and phase III (steady state). Black line shows monoexponential fitting of the entire  $\dot{V}O_2$  on-response. The  $O_2$  deficit is the area between steady state  $\dot{V}O_2$  and the entire  $\dot{V}O_2$  on-response. The  $O_2$  debt is the area between steady state  $\dot{V}O_2$  and  $\dot{V}O_2$  recovery to baseline. See text for details.

### *O<sub>2</sub> Pulse Response During Exercise*

$O_2$  pulse is the ratio of  $\dot{V}O_2$  to heart rate and reflects the amount of  $O_2$  extracted per heart beat. The  $O_2$  pulse provides an estimate of left ventricular stroke-volume changes during exercise, assuming that the  $C(a-v)O_2$  is maximal and no anemia is present. During incremental exercise, the relative contribution of stroke volume to cardiac output is predominant during the initial and intermediate phases of exercise. Thus,  $O_2$  pulse has a typical hyperbolic profile, with a rapid rise during the initial stages of exercise and a slow approach to an asymptotic value at the end of exercise. A flattening or downward displacement of  $O_2$  pulse kinetics during progressive CPX very likely reflects a cardiogenic limitation to exercise or a peripheral vascular perfusion/extraction limitation to exercise performance. Although  $O_2$  pulse may be viewed as an attractive and reliable measure of stroke volume in normal subjects, some caution should be exercised in interpreting its clinical validity in patients in whom  $O_2$  extraction is not ideal or in those for whom the assumption of linearity between  $\dot{V}O_2$  and an increase in cardiac output during exercise may not reasonably be made.

### *$\dot{V}O_2$ Kinetics During Exercise and Recovery*

The  $\dot{V}O_2$  response within the first 60 to 120 seconds of exercise has been identified as the on-response. This is observed by examining  $\dot{V}O_2$  during a constant work rate. It is initially dominated by an increase in pulmonary blood flow (phase I or cardiodynamic phase), followed by a slower, monoexponential increase (phase II) that reflects muscle extraction of  $O_2$ . These are followed by a plateau in  $\dot{V}O_2$  (steady state) if the exercise level is below the VT (phase III; Figure 6). The lag in  $\dot{V}O_2$  seen before steady state is reached has been termed the  $O_2$  deficit. It is during this period that energy requirements are supplemented by anaerobic energy sources, such as high-energy phosphates (eg, phosphocreatine) and anaerobic glycolysis.<sup>124</sup> For this reason, lactic acid accumulation has been directly related to the duration of the on-response.<sup>227</sup> Thus, a prolonged on-response may contribute to exertional dyspnea and exercise intolerance. In healthy subjects, the speed of the on-response correlates with  $\dot{V}O_{2max}$  across a wide spectrum of exercise capacity.<sup>228,229</sup> In this respect, examination of the submaximal exercise response provides information that may be more clinically relevant in that most daily activities are submaximal in nature. The  $O_2$  kinetics on-response is calculated as the time constant ( $\tau$ ) by use of the following monoexponential equation:

$$\dot{V}O_2(t) = \dot{V}O_2(b) + A(1 - e^{-t/\tau})$$

where  $\dot{V}O_2(t)$  is the increase in  $O_2$  above the baseline at any time  $t$ ;  $\dot{V}O_2(b)$  is the baseline  $\dot{V}O_2$  at resting steady state;  $A$  is the amplitude of the  $\dot{V}O_2$  response (the difference between the  $\dot{V}O_2$  values at rest and during steady state exercise); and  $\tau$  is the time constant of the response that corresponds to 63% of the  $\Delta\dot{V}O_2$ . A prolonged  $\tau$  response has been observed in patients with heart failure.<sup>230–232</sup>

$\dot{V}O_2$  kinetics during the recovery phase of exercise (Figure 6) has emerged as an interesting variable that may be assessed during CPX.<sup>106</sup> Recovery  $\dot{V}O_2$  kinetics correlate with the recovery of energy stores in the active muscles and reflect the rate of recovery of phosphocreatine levels, as well as blood and tissue  $O_2$  stores after exercise.<sup>233</sup> In healthy subjects,  $\dot{V}O_2$  declines rapidly after exercise and is not affected by work rate. In heart failure patients, a delay in  $\dot{V}O_2$  recovery has been identified clearly. This is explained primarily by a slower rate of replenishment of energy stores in exercising skeletal muscles.<sup>106</sup> Moreover, a blunted cardiac output response during exercise together with a longer circulating transit time between the exercising muscle and the lungs may further account for the prolonged  $O_2$  kinetics.<sup>234</sup> Heart failure interventions aimed at improving endothelial function, peripheral circulation, and cardiac output have been shown to improve  $\dot{V}O_2$  recovery kinetics.<sup>235</sup> Finally, in cardiac patients with moderately reduced exercise capacity,  $\dot{V}O_2$  recovery kinetics may provide prognostic information.<sup>236</sup> However, prolonged  $\dot{V}O_2$  kinetics are not specific to heart failure patients and may occur whenever  $O_2$  transport or  $O_2$  utilization by the exercising muscles is impaired, such as in anemia, hypoxia, peripheral artery disease, muscle deconditioning, and myopathies.

### *Noninvasive Determination of Cardiac Output*

Although peak  $\dot{V}O_2$  is a powerful independent prognostic indicator and an indirect measure of cardiac output, it can be influenced by numerous confounding variables (eg, age, sex, motivation, obesity, deconditioning, and localized muscle fatigue).<sup>237</sup> This may explain why some candidates for cardiac transplantation have favorable prognoses despite low peak  $\dot{V}O_2$ .<sup>238</sup> Because somatic  $\dot{V}O_2$  is the product of heart rate, stroke volume, and arteriovenous oxygen difference ( $C[a-v]O_2$ ), several studies now suggest that the noninvasive determination of cardiac output may enhance the prognostic power of peak  $\dot{V}O_2$ .<sup>238,239</sup> Accordingly, 2 patients could in principle have identical, low peak  $\dot{V}O_2$  values but different peak cardiac output.<sup>240</sup>

A given patient with severe left ventricular dysfunction may have a reduced cardiac output and a high  $C(a-v)O_2$  at peak exercise; conversely, a severely deconditioned patient may have a relatively normal peak cardiac output and a low  $C(a-v)O_2$  because of peripheral limitations. Reduced oxygen extraction by skeletal muscle may be attributed to a variety of factors, including anemia; decreased muscle mass; decreases in muscle capillary density, myoglobin content, mitochondrial mass, or oxidative enzymes; or combinations thereof.

Another potential advantage of the use of concomitant cardiac output data is that it may be of prognostic value at submaximal exercise, including work rates below the anaerobic threshold.<sup>241</sup> A review of 9 previous studies that included nearly 1200 patients with congestive heart failure found that directly measured peak  $\dot{V}O_2$  was a significantly weaker prognostic variable than the associated hemodynamic correlates (eg, stroke work index and cardiac output).<sup>240</sup> In several of the studies, patient subsets with good hemodynamic responsiveness and reduced exercise capacity ( $<14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) fared better than their peak  $\dot{V}O_2$ -matched counterparts with a poor hemodynamic response. Other recent reports have demonstrated that peak cardiac output can be measured noninvasively and provides an independent predictor of outcome that can enhance the prognostic utility of peak  $\dot{V}O_2$ .<sup>108,242</sup> Other potential applications of exercise cardiac output measures include the identification of hyperdynamic states due to impaired peripheral oxygen extraction. The finding of abnormally high cardiac output relative to  $\dot{V}O_2$  in certain myopathic and autonomic abnormalities provides a rationale for the use of exercise cardiac output measures in the identification of these conditions (see CPX in Patients With Skeletal Muscle Fiber and Mitochondrial Myopathy). Although the Fick and

thermodilution methods remain the gold standards for the measurement of cardiac output,<sup>243</sup> several rebreathing methods that use CPX are available.

### CO<sub>2</sub> Rebreathing Methods

The term *indirect Fick* is used to describe the method in which blood concentrations of CO<sub>2</sub> in mixed venous and arterial blood are estimated indirectly from their partial pressure in the gas phase, with CO<sub>2</sub> as the indicator gas, to determine cardiac output:

$$\text{Cardiac output} = \frac{\text{somatic CO}_2 \text{ output}}{\text{veno-arterial CO}_2 \text{ difference}}$$

With the lungs acting as a tonometer, 2 approaches have been used for the measurement of mixed venous PCO<sub>2</sub> during exercise: Rebreathing from a rubber bag that contains a low concentration of CO<sub>2</sub>, and the equilibration method, which uses a bag that contains a high concentration of CO<sub>2</sub> in oxygen. The mixed venous CO<sub>2</sub> content is determined from the CO<sub>2</sub> tension, which can be estimated from the CO<sub>2</sub> tension curve as it gradually increases toward a limit during rebreathing of a known gas mixture (eg, 5% CO<sub>2</sub> and 95% O<sub>2</sub>). End-tidal CO<sub>2</sub> is taken as a measure of CO<sub>2</sub> partial pressure in alveolar gas and is representative of arterial blood CO<sub>2</sub>. Carbon dioxide output is determined from the expired air sample.

The difficulty with CO<sub>2</sub> rebreathing methods during exercise is that they require subject cooperation, which may be difficult to achieve in some patients.<sup>240</sup> Moreover, high concentrations of inhaled CO<sub>2</sub> may cause lightheadedness, feelings of suffocation, or both. Others emphasize that the accuracy of the CO<sub>2</sub> rebreathing technique may be compromised by numerous potential confounding variables and underlying assumptions<sup>244</sup> and that large errors can occur in patients with advanced pulmonary disease.<sup>240</sup>

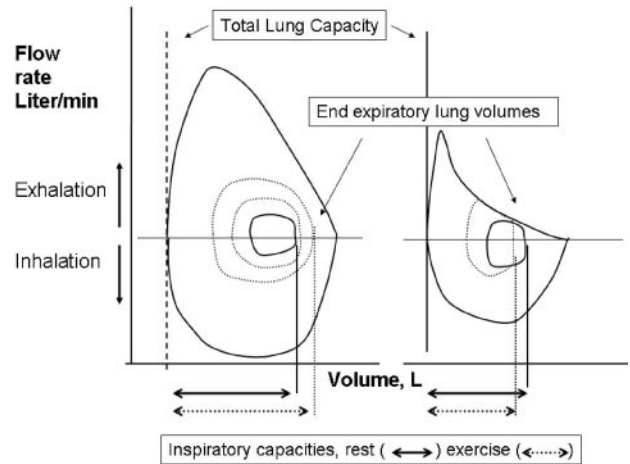
### Foreign Gas Rebreathing Methods

Foreign gas methods that use a soluble inspired gas such as acetylene or nitrous oxide have been shown to be a reliable and safe method for the noninvasive assessment of cardiac output during CPX. With this methodology, the mixed venous content of the gas is zero, and arterial partial pressure is assumed to be the same as in end-tidal air.<sup>240</sup> A new device that uses the inert gas rebreathing technique during exercise was described recently in patients with heart failure.<sup>242,245</sup> Although the measurement of foreign gases in low concentration has traditionally relied on the respiratory mass spectrometer, recent studies suggest that newer technology (ie, a portable infrared absorption spectrometer) may facilitate noninvasive cardiac output monitoring with the foreign gas uptake method in clinical, field, and point-of-care settings.<sup>246</sup>

The reproducibility of rebreathing methods for determination of cardiac output during exercise testing in patients with and without heart failure has been reported previously (coefficient of variation 7% to 11%).<sup>240,241,245</sup> Collectively, these data suggest that the prognostic value of CPX may be enhanced by the noninvasive determination of cardiac output in patients with heart failure. However, additional research is needed before it can be recommended that noninvasive cardiac output become standard practice in clinical CPX.

### Flow-Volume Loops

Many commercially available instruments provide the capability to record inspiratory and expiratory volumes and flow rates of individual breaths during exercise in the form of flow-volume loops to supplement the basic breathing mechanics information represented



**Figure 7.** Flow-volume loops. Spontaneous tidal flow-volume loops at rest (inner solid lines) and exercise (dotted lines) and maximal flow-volume loops measured before exercise (outer solid lines) for a normal subject (left) and a patient with chronic obstructive pulmonary disease (right). Tidal flow-volume loops are positioned within the maximal loops by periodic measurement of inspiratory capacity ( $\leftrightarrow$ ) during exercise. On the left, the normal subject increases tidal volume (x-axis) without reaching maximal flow rates and with stable or increased inspiratory capacity (arrows). In contrast, on the right, the patient with chronic obstructive pulmonary disease attains maximal expiratory flow rates during spontaneous breaths and needs to increase end-expiratory lung volume, as inferred from a decrease in inspiratory capacity.

by tidal volume and breathing frequency. Analyses of these measures focus on the identification of expiratory airflow limitation and changes in operational lung volumes that occur during exercise (Figure 7). *Expiratory flow limitation* refers to the attainment of the patient's maximal flow rates during spontaneous breathing and is identified by comparison of tidal flow-volume loops with the patient's maximal loop measured before exercise. Accurate alignment of the loops on the volume axis requires knowledge of any changes that occur in end-expiratory lung volume during exercise relative to rest, which are inferred from changes in inspiratory capacity (volume of full inspiration from the end-expiratory volume) determined periodically during the exercise test. An increase in end-expiratory lung volume relative to the resting volume is referred to as *dynamic hyperinflation*; the proportion of a breath that corresponds to the patient's maximal flow rates has been proposed as an index of ventilatory limitation. Details of the performance and analysis of these measures are reviewed elsewhere.<sup>247</sup>

Flow limitation and dynamic hyperinflation have been studied most extensively in patients with chronic obstructive pulmonary disease. In this group, dynamic hyperinflation can result in patients breathing at lung volumes that approach total lung capacity (Figure 7), and this has been demonstrated to be a key determinant of dyspnea and exercise intolerance.<sup>248</sup> The associated changes in breathing mechanics can constitute ventilatory limitation to exercise in a subset of chronic obstructive pulmonary disease patients who, by conventional measures based on maximal voluntary ventilation, might appear to have an adequate breathing reserve. Although flow limitation and changes in lung volumes occur in a number of other clinical populations, including patients with chronic heart failure,<sup>249</sup> athletes,<sup>4</sup> and the elderly,<sup>250</sup> their significance and influence on exercise performance in these groups are not as well characterized. These analyses are therefore not routine in the testing of unselected patients.



## Appendix 2

Table 6. Variables to Include in CPX Test Report

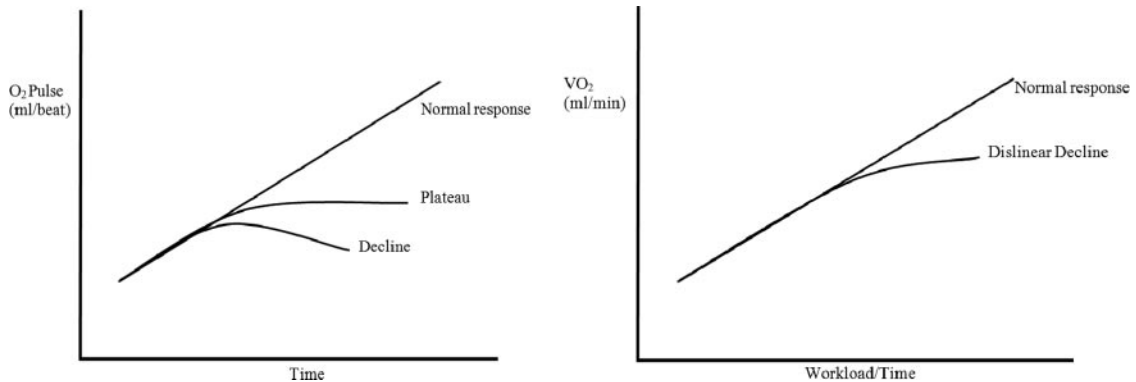
Variable	Indication for Testing							
	Normal, Apparently Healthy	Chronic Heart Failure	Unexplained Dyspnea	Exercise Prescription		Disability Assessment		
				CVD	Stroke	Cardiac	Pulmonary	Stroke
Heart rate (per min)								
Rest (seated)	R	R	R	R	R	R	R	R
Peak	R	R	R	R	R	R	R	R
Peak expressed as % of predicted	R	R	R	R	R	R	R	R
At ischemic or angina threshold	R	O	O	R		R		
At 1 minute of recovery	R	R	R	O		O		
Blood pressure (mm Hg)								
Rest (seated)	R	R	R	R	R	R	R	R
Peak	R	R	R	R	R	R	R	R
Test protocol	R	R	R	R	R	R	R	R
Test duration (min)	R	R	R	R	R	R	R	R
Work rate at peak (W or kg · m <sup>-1</sup> · min <sup>-1</sup> for cycle or speed/grade for treadmill)	R	R	R	R	R	R	R	R
Reason for test termination	R	R	R	R	R	R	R	R
Peak (RPE)	O	O	O	O	O	O	O	O
Peak $\dot{V}O_2$ (L/min)	R	R	R	R	R	R	R	R
Peak $\dot{V}O_2$ expressed as % of predicted	R	R	R	O	O	R	R	R
Peak $\dot{V}O_2$ (mL · kg <sup>-1</sup> · min <sup>-1</sup> )	R	R	R	R	R	R	R	R
Measured METs	O	O	O	R	O	R	R	R
VT (mL O <sub>2</sub> · kg <sup>-1</sup> · min <sup>-1</sup> )		R	R	O	O	O	O	O
VT at $\dot{V}O_2$ expressed as a percent of peak $\dot{V}O_2$		R	R	O	O	O	O	O
Peak RER	R	R	R	R	R	R	R	R
Peak ventilation (L/min)	O	O	R	O	O	O	R	O
Peak respiratory rate (per min)	O	O	R	O	O	O	R	O
$\dot{V}E/\dot{V}CO_2$ slope		R	R					
Breathing reserve (%)		O	R				R	
Oxygen pulse (mL/beat)		O	O				O	
Oxygen saturation (%)			R				R	

CVD indicates cardiovascular disease; R, recommended measure; O, optional measure; and RPE, rating of perceived exertion.

**Table 7. Expanded CPX Sample Report**

Aerobic Capacity	
Peak $\dot{V}O_2$ (mL O <sub>2</sub> · kg <sup>-1</sup> · min <sup>-1</sup> ) ____ (%predicted ____)	
Peak measured METs ____	
$\dot{V}O_2$ @ ventilatory threshold ____ ( ____ % of peak $\dot{V}O_2$ )	
Peak RER ____	
Ventilatory efficiency	Pulmonary function
$\dot{V}_E/\dot{V}CO_2$ slope ____	FVC: Pre ____ Post ____
$\dot{V}_E/\dot{V}CO_2$ nadir ____	FEV <sub>1</sub> : Pre ____ Post ____
(%predicted ____)	FEV <sub>1</sub> /FVC: Pre ____ Post ____
$\dot{V}_E/\dot{V}CO_2$ @ VT ____	FEF <sub>25-75</sub> : Pre ____ Post ____
Oscillatory ventilation: Yes ____ No ____	PEF: Pre ____ Post ____
OUES (L/min) ____	$\dot{V}_E/MVV$ ____
(%predicted ____)	(Note: Document maximal postexercise change)
P <sub>ET</sub> CO <sub>2</sub>	
Resting P <sub>ET</sub> CO <sub>2</sub> (mm Hg) ____	
Highest P <sub>ET</sub> CO <sub>2</sub> during exercise (mm Hg) ____ (change from rest ____)	
P <sub>ET</sub> CO <sub>2</sub> at peak exercise (mm Hg) ____	
Oxygen pulse	
Resting O <sub>2</sub> pulse (mL/beat) ____	
O <sub>2</sub> pulse at peak exercise (mL/beat) ____	

Pre indicates before CPX; Post, after CPX; FEF<sub>25-75</sub>, forced midexpiratory flow rate; FVC, forced vital capacity; and PEF, peak expiratory flow rate.

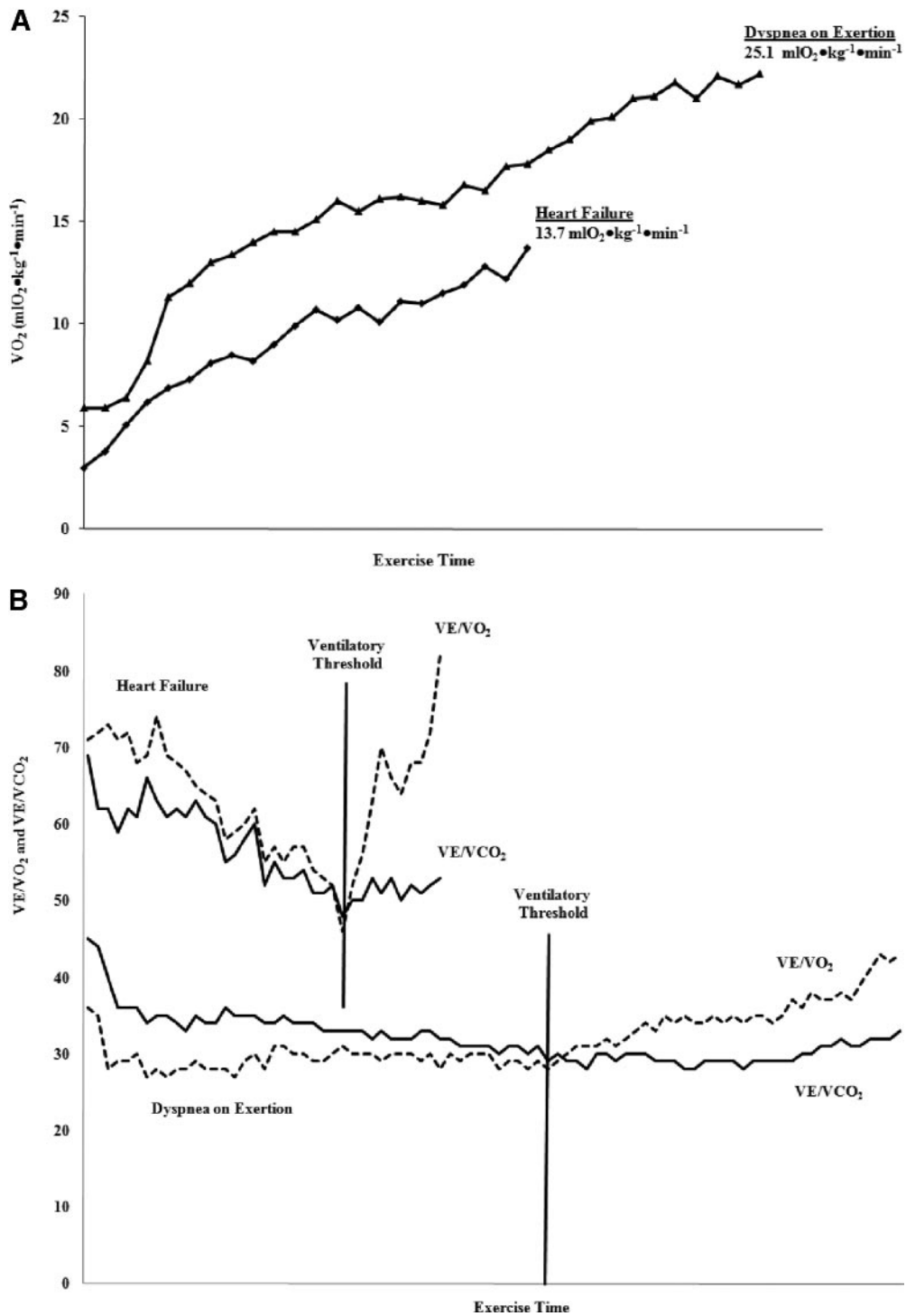


**Figure 8.** Graphical responses (circle one).

**Table 8. Heart Failure and Dyspnea on Exertion: Case Comparison**

Reason for Test	Heart Failure	Dyspnea on Exertion
Baseline characteristics	35-year-old female Normal body weight	35-year-old female Normal body weight
Relevant past medical history	3-year history of idiopathic heart failure Resting left ventricular ejection fraction 15%	2-year history of unexplained dyspnea on exertion Normal cardiac and pulmonary function
Aerobic capacity	Peak $\dot{V}O_2$ : 13.7 mL O <sub>2</sub> kg <sup>-1</sup> · min <sup>-1</sup> 45% of predicted for age/sex	Peak $\dot{V}O_2$ : 25.1 mL O <sub>2</sub> kg <sup>-1</sup> · min <sup>-1</sup> 83% of predicted for age/sex
Peak RER	1.14	1.18
Submaximal exercise tolerance	$\dot{V}O_2$ at VT: 8.5 mL O <sub>2</sub> kg <sup>-1</sup> · min <sup>-1</sup>	$\dot{V}O_2$ at VT: 14.0 mL O <sub>2</sub> kg <sup>-1</sup> · min <sup>-1</sup>
Ventilatory efficiency	Abnormally elevated $\dot{V}E/\dot{V}CO_2$ slope	Normal $\dot{V}E/\dot{V}CO_2$ slope
Additional pulmonary function testing	No change in PEF after exercise compared with baseline	30% reduction in PEF after exercise compared with baseline
Breathing reserve	$(1 - \dot{V}E/MVV) > 20\%$ and within normal limits	$(1 - \dot{V}E/MVV) < 20\%$ and abnormally reduced
Electrocardiography	Occasional ventricular ectopy Maximal heart rate=122 bpm (66% of predicted) on a $\beta$ -blocker	No abnormalities detected Maximal heart rate=176 bpm (95% of predicted)
Hemodynamics	Blood pressure at rest: 110/60 mm Hg Blood pressure at maximal exercise: 140/68 mm Hg	Blood pressure at rest: 118/72 mm Hg Blood pressure at maximal exercise: 180/66 mm Hg
Subjective symptoms	Maximal perceived exertion: 16/20 Maximal dyspnea: 3/4 Reason for stopping: dyspnea	Maximal perceived exertion: 16/20 Maximal dyspnea: 4/4 Reason for stopping: dyspnea
Interpretation	Severely diminished aerobic capacity and abnormal ventilatory efficiency; consistent with moderate to severe heart failure pathophysiology	Mildly diminished aerobic capacity; changes in pulmonary function after exercise and abnormally reduced breathing reserve are consistent with exercise-induced bronchospasm

PEF indicates peak expiratory flow rate; bpm, beats per minute.



**Figure 9.** A through C, Heart failure and dyspnea on exertion: case comparison. Comparison of graphical responses that would accompany the sample reports for a woman with heart failure and a woman with dyspnea on exertion as presented in Table 8. A,  $\dot{V}O_2$  during CPX; B, determination of ventilatory threshold with  $\dot{V}E/\dot{V}CO_2$  and  $\dot{V}E/\dot{V}O_2$  during CPX; and C (next page),  $\dot{V}E/\dot{V}CO_2$  slope during CPX.

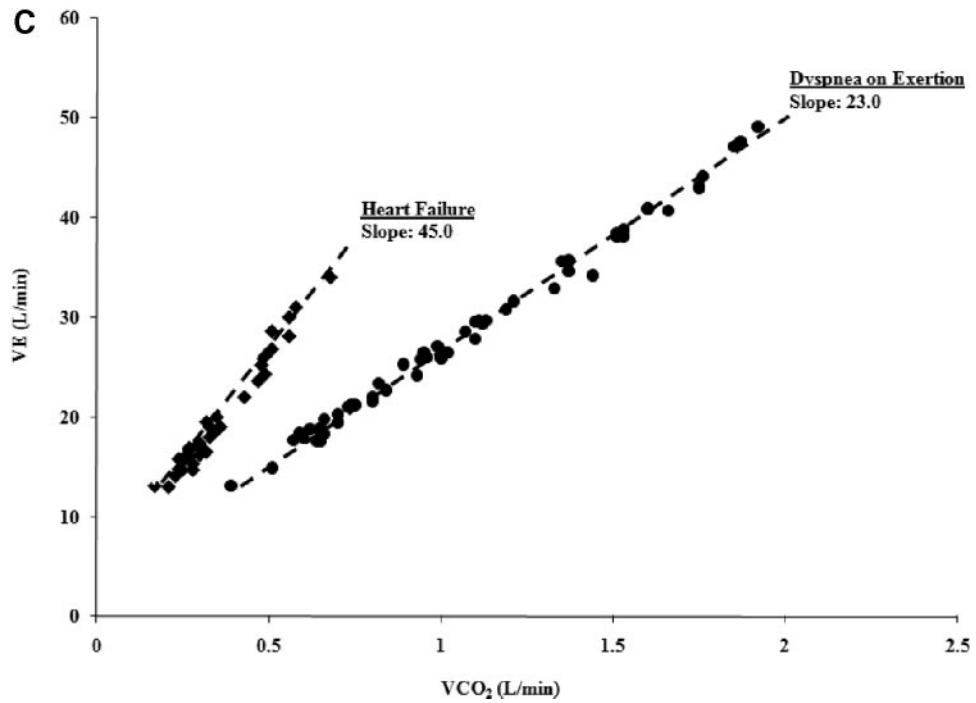


Figure 9 (Continued).

## Disclosures

## Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Gary J. Ross Arena	Boston University Virginia Commonwealth University	None	None	None	None	None	None
Lola Coke	Rush University College of Nursing	None	None	None	None	None	None
Gerald F. Fletcher	Mayo Clinic, Jacksonville, Fla	None	None	None	None	None	None
Daniel Forman	Brigham and Women's Hospital	NHLBI†; NIH*; VA†	None	None	None	None	None
Barry Franklin	William Beaumont Hospital	None	None	None	None	None	None
Marco Guazzi	San Paolo Hospital, Milano, Italy	None	None	None	None	None	None
Martha Gulati	Northwestern University	None	None	None	None	None	None
Steven J. Keteyian	Henry Ford Hospital	NIH†	None	None	None	None	Manuscript Writing Consultant, Duke Clinical Research Institute†
Carl J. Lavie	Ochsner Health System	None	None	None	None	None	None
Richard Macko	University of Maryland School of Medicine and Baltimore VA Medical Center	National Institute on Aging—Claude D. Pepper Center†; PI on VA Exercise and Robotics Center of Excellence†	Associate Director of Research—Baltimore VA Geriatrics Research Education and Clinical Center†	None	None	National Stroke Association Advisory Board*	None
Donna Mancini	Columbia University	None	None	None	None	None	None
Richard V. Milani	Ochsner Medical Center	None	None	None	None	None	None
Jonathan Myers	VA Palo Alto Health Care System	None	None	None	None	None	None
Kathy Sietsema	Harbor-UCLA Medical Center	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Bernard Chaitman	St Louis University Health Sciences Center	None	None	None	None	None	None	None
Victor Froelicher	Stanford University	None	None	None	None	None	None	None
Michael Lauer	NHLBI	None	None	None	None	None	None	None
Barry J. Maron	Minneapolis Heart Institute Foundation	None	None	None	None	None	None	None
Lori Mosca	New York Presbyterian Hospital	None	None	None	None	None	None	None
Bunny Pozehl	University of Nebraska Medical Center	None	None	None	None	None	None	None
Ray Squires	Mayo Clinic	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

## References

- Myers JN. *Essentials of Cardiopulmonary Exercise Testing*. Champaign, Ill: Human Kinetics; 1996.
- Crouter SE, Antczak A, Hudak JR, DellaValle DM, Haas JD. Accuracy and reliability of the ParvoMedics TrueOne 2400 and MedGraphics VO2000 metabolic systems. *Eur J Appl Physiol*. 2006;98:139–151.
- Carter J, Jeukendrup AE. Validity and reliability of three commercially available breath-by-breath respiratory systems. *Eur J Appl Physiol*. 2002;86:435–441.
- Foss Ø, Hallén J. Validity and stability of a computerized metabolic system with mixing chamber. *Int J Sports Med*. 2005;26:569–575.
- American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing [published correction appears in *Am J Respir Crit Care Med*. 2003;167:1451–1452]. *Am J Respir Crit Care Med*. 2003;167:211–277.
- Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, Balady GJ; American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention of the Council on Clinical Cardiology, the Council on Nutrition, Physical Activity, and Metabolism, and the Council on Cardiovascular Nursing. Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association. *Circulation*. 2009;119:3144–3161.
- Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60:2020–2027.
- Quality control in exercise studies. In: Jones NL. *Clinical Exercise Testing*. Philadelphia, Pa: Saunders; 1997:164–166.
- Wilmore JH, Stanforth PR, Turley KR, Gagnon J, Daw EW, Leon AS, Rao DC, Skinner JS, Bouchard C. Reproducibility of cardiovascular, respiratory, and metabolic responses to submaximal exercise: the HERITAGE Family Study. *Med Sci Sports Exerc*. 1998;30:259–265.
- American College of Sports Medicine. *ACSM's Metabolic Calculations Handbook*. Baltimore, Md: Lippincott Williams & Wilkins; 2006.
- Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, Fletcher G. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation*. 2007;116:329–343.
- Huszczuk A, Whipp BJ, Wasserman K. A respiratory gas exchange simulator for routine calibration in metabolic studies. *Eur Respir J*. 1990;3:465–468.
- Miyamura M, Honda Y. Oxygen intake and cardiac output during maximal treadmill and bicycle exercise. *J Appl Physiol*. 1972;32:185–188.
- Williford HN, Sport K, Wang N, Olson MS, Blessing D. The prediction of fitness levels of United States Air Force officers: validation of cycle ergometry. *Mil Med*. 1994;159:175–178.
- Lockwood PA, Yoder JE, Deuster PA. Comparison and cross-validation of cycle ergometry estimates of  $\dot{V}O_{2max}$ . *Med Sci Sports Exerc*. 1997;29:1513–1520.
- Foster C, Pollock ML, Rod JL, Dymond DS, Wible G, Schmidt DH. Evaluation of functional capacity during exercise radionuclide angiography. *Cardiology*. 1983;70:85–93.
- Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. *U S Armed Forces Med J*. 1959;10:675–688.
- Naughton J, Balke B, Nagle F. Refinements in method of evaluation and physical conditioning before and after myocardial infarction. *Am J Cardiol*. 1964;14:837–843.
- Swain DP, Abernathy KS, Smith CS, Lee SJ, Bunn SA. Target heart rates for the development of cardiorespiratory fitness. *Med Sci Sports Exerc*. 1994;26:112–116.
- American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2010:286–299.
- Rodgers GP, Ayanian JZ, Balady G, Beasley JW, Brown KA, Gervino EV, Paridon S, Quinones M, Schlant RC, Winters WL Jr, Achord JL, Boone AW, Hirshfeld JW Jr, Lorell BH, Rodgers GP, Tracy CM, Weitz HH. American College of Cardiology/American Heart Association Clinical Competence statement on stress testing: a report of the American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Task Force on Clinical Competence. *J Am Coll Cardiol*. 2000;36:1441–1453.
- Stuart RJ Jr, Ellestad MH. National survey of exercise stress testing facilities. *Chest*. 1980;77:94–97.
- Gibbons LW, Mitchell TL, Gonzalez V. The safety of exercise testing. *Prim Care*. 1994;21:611–629.
- Keteyian SJ, Isaac D, Thadani U, Roy BA, Bensimhon DR, McKelvie R, Russell SD, Hellkamp AS, Kraus WE; HF-ACTION Investigators. Safety of symptom-limited cardiopulmonary exercise testing in patients with chronic heart failure due to severe left ventricular systolic dysfunction. *Am Heart J*. 2009;158:S72–S77.
- Pahlm O, Haisty WK Jr, Edenbrandt L, Wagner NB, Sevilla DC, Selvester RH, Wagner GS. Evaluation of changes in standard electrocardiographic QRS waveforms recorded from activity-compatible proximal limb lead positions. *Am J Cardiol*. 1992;69:253–257.
- American Medical Association. CPT-4 procedure codes. Available at: [https://catalog.ama-assn.org/Catalog/cpt/cpt\\_search.jsp](https://catalog.ama-assn.org/Catalog/cpt/cpt_search.jsp). Accessed May 27, 2010.
- Centers for Disease Control. International Classification of Diseases. Available at: <https://www.cms.gov/ICD9ProviderDiagnosticCodes/>. Accessed May 27, 2010.
- Department of Health and Human Services. Medicare's National Correct Coding Initiative. Report No. OEI-03-02-00770. Available at: <http://oig.hhs.gov/oei/reports/oei-03-02-00770.pdf>. Accessed December 20, 2008.
- Diamond E. Developing a cardiopulmonary exercise testing laboratory. *Chest*. 2007;132:2000–2007.
- Wasserman K, Beaver WL, Whipp BJ. Gas exchange theory and the lactic acidosis (anaerobic) threshold. *Circulation*. 1990;81(suppl):II-14–II-30.
- Myers J, Ashley E. Dangerous curves: a perspective on exercise, lactate, and the anaerobic threshold. *Chest*. 1997;111:787–795.
- Davis JA, Vodak P, Wilmore JH, Vodak J, Kurtz P. Anaerobic threshold and maximal aerobic power for three modes of exercise. *J Appl Physiol*. 1976;41:544–550.
- Jones AM, Carter H. The effect of endurance training on parameters of aerobic fitness. *Sports Med*. 2000;29:373–386.
- Amann M, Subudhi AW, Walker J, Eisenman P, Shultz B, Foster C. An evaluation of the predictive validity and reliability of ventilatory threshold. *Med Sci Sports Exerc*. 2004;36:1716–1722.
- Bensimhon DR, Leifer ES, Ellis SJ, Fleg JL, Keteyian SJ, Piña IL, Kitzman DW, McKelvie RS, Kraus WE, Forman DE, Kao AJ, Whellan DJ, O'Connor CM, Russell SD; HF-ACTION Trial Investigators. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training). *Am J Cardiol*. 2008;102:712–717.
- Corrà U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJ, Giannuzzi P. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest*. 2002;121:1572–1580.
- Hansen D, Dendale P, Berger J, Meeusen R. Low agreement of ventilatory threshold between training modes in cardiac patients. *Eur J Appl Physiol*. 2007;101:547–554.
- Santos EL, Giannella-Neto A. Comparison of computerized methods for detecting the ventilatory thresholds. *Eur J Appl Physiol*. 2004;93:315–324.
- Shimizu M, Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Froelicher VF. The ventilatory threshold: method, protocol, and evaluator agreement. *Am Heart J*. 1991;122:509–516.
- Gaskill SE, Ruby BC, Walker AJ, Sanchez OA, Serfass RC, Leon AS. Validity and reliability of combining three methods to determine ventilatory threshold. *Med Sci Sports Exerc*. 2001;33:1841–1848.
- Mezzani A, Corra U, Bosimini E, Giordano A, Giannuzzi P. Contribution of peak respiratory exchange ratio to peak  $\dot{V}O_{2}$  prognostic reliability in patients with chronic heart failure and severely reduced exercise capacity. *Am Heart J*. 2003;145:1102–1107.
- Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Technical considerations related to the minute ventilation/carbon dioxide output slope in patients with heart failure. *Chest*. 2003;124:720–727.
- Ingle L, Goode K, Carroll S, Sloan R, Boyes C, Cleland JG, Clark AL. Prognostic value of the  $\dot{V}E/\dot{V}CO_{2}$  slope calculated from different time intervals in patients with suspected heart failure. *Int J Cardiol*. 2007;118:350–355.
- Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev*. 2008;13:245–269.
- Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med*. 2002;166:1443–1448.
- Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal  $PCO_{2}$  abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest*. 2005;127:1637–1646.

47. Ponikowski P, Chua TP, Piepoli M, Banasiak W, Anker SD, Szelemej R, Molenda W, Wrabec K, Capucci A, Coats AJ. Ventilatory response to exercise correlates with impaired heart rate variability in patients with chronic congestive heart failure. *Am J Cardiol.* 1998;82:338–344.
48. Holverda S, Bogaard HJ, Groepenhoff H, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Cardiopulmonary exercise test characteristics in patients with chronic obstructive pulmonary disease and associated pulmonary hypertension. *Respiration.* 2008;76:160–167.
49. Lehmann G, Kölling K. Reproducibility of cardiopulmonary exercise parameters in patients with valvular heart disease. *Chest.* 1996;110:685–692.
50. Maeder MT, Wolber T, Ammann P, Myers J, Brunner-La Rocca HP, Hack D, Riesen W, Rickli H. Cardiopulmonary exercise testing in mild heart failure: impact of the mode of exercise on established prognostic predictors. *Cardiology.* 2008;110:135–141.
51. Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R, Bussotti M, Wasserman K. Work-rate affects cardiopulmonary exercise test results in heart failure. *Eur J Heart Fail.* 2005;7:498–504.
52. Uren NG, Davies SW, Agnew JE, Irwin AG, Jordan SL, Hinson AJ, Lipkin DP. Reduction of mismatch of global ventilation and perfusion on exercise is related to exercise capacity in chronic heart failure. *Br Heart J.* 1993;70:241–246.
53. Wada O, Asanoi H, Miyagi K, Ishizaka S, Kameyama T, Seto H, Sasayama S. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J.* 1993;125:790–798.
54. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation.* 2001;104:429–435.
55. Arena R, Lavie CJ, Milanie RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary hypertension: an evidence-based review. *J Heart Lung Transplant.* 2010;29:159–173.
56. Wagner PD. Ventilation-perfusion matching during exercise. *Chest.* 1992;101:192S–198S.
57. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. *Eur Respir J.* 1997;10:2662–2689.
58. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J.* 2005;26:319–338.
59. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. Guidelines for methacholine and exercise challenge testing—1999: this official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med.* 2000;161:309–329.
60. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlén B, DiMaria G, Foresi A, Hargreave FE, Holgate ST, Inman M, Lötvall J, Magnussen H, Polosa R, Postma DS, Riedler J; ERS Task Force. Indirect airway challenges. *Eur Respir J.* 2003;21:1050–1068.
61. Yamaya Y, Bogaard HJ, Wagner PD, Niizeki K, Hopkins SR. Validity of pulse oximetry during maximal exercise in normoxia, hypoxia, and hyperoxia. *J Appl Physiol.* 2002;92:162–168.
62. Mengelkoch LJ, Martin D, Lawler J. A review of the principles of pulse oximetry and accuracy of pulse oximeter estimates during exercise. *Phys Ther.* 1994;74:40–49.
63. Hopkins SR. Exercise induced arterial hypoxemia: the role of ventilation-perfusion inequality and pulmonary diffusion limitation. *Adv Exp Med Biol.* 2006;588:17–30.
64. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation.* 2001;104:1694–1740.
65. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise: prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation.* 1996;93:1520–1526.
66. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med.* 1999;341:1351–1357.
67. Lipinski MJ, Vetrovec GW, Gorelik D, Froelicher VF. The importance of heart rate recovery in patients with heart failure or left ventricular systolic dysfunction. *J Card Fail.* 2005;11:624–630.
68. Nanas S, Anastasiou-Nana M, Dimopoulos S, Sakellariou D, Alexopoulos G, Kapsimalakou S, Papazoglou P, Tsolakis E, Papazachou O, Roussos C, Nanas J. Early heart rate recovery after exercise predicts mortality in patients with chronic heart failure. *Int J Cardiol.* 2006;110:393–400.
69. Bilsel T, Terzi S, Akbulut T, Sayar N, Hobikoglu G, Yesilcimen K. Abnormal heart rate recovery immediately after cardiopulmonary exercise testing in heart failure patients. *Int Heart J.* 2006;47:431–440.
70. Kubrychtova V, Olson TP, Bailey KR, Thapa P, Allison TG, Johnson BD. Heart rate recovery and prognosis in heart failure patients. *Eur J Appl Physiol.* 2009;105:37–45.
71. Arena R, Guazzi M, Myers J, Peberdy MA. Prognostic value of heart rate recovery in patients with heart failure. *Am Heart J.* 2006;151:851.e7–851.e-13.
72. Streitner F, Kuschyk J, Veltmann C, Brueckmann M, Streitner I, Brade J, Neumaier M, Bertsch T, Schumacher B, Borggrete M, Wolpert C. Prospective study of interleukin-6 and the risk of malignant ventricular tachyarrhythmia in ICD-recipients: a pilot study. *Cytokine.* 2007;40:30–34.
73. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death [published correction appears in *N Engl J Med.* 2003;348:1508]. *N Engl J Med.* 2003;348:781–790.
74. O'Neill JO, Young JB, Pothier CE, Lauer MS. Severe frequent ventricular ectopy after exercise as a predictor of death in patients with heart failure. *J Am Coll Cardiol.* 2004;44:820–826.
75. Noble BJ. Clinical applications of perceived exertion. *Med Sci Sports Exerc.* 1982;14:406–411.
76. Chase P, Arena R, Myers J, Abella J, Peberdy MA, Guazzi M, Kenjale A, Bensimhon D. Prognostic usefulness of dyspnea versus fatigue as reason for exercise test termination in patients with heart failure. *Am J Cardiol.* 2008;102:879–882.
77. Wilson RC, Jones PW. A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clin Sci (Lond).* 1989;76:277–282.
78. Neely G, Ljunggren G, Sylvén C, Borg G. Comparison between the Visual Analogue Scale (VAS) and the Category Ratio Scale (CR-10) for the evaluation of leg exertion. *Int J Sports Med.* 1992;13:133–136.
79. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med.* 1991;325:849–853.
80. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure) [published correction appears in *J Am Coll Cardiol.* 2006;47:1503–1505]. *J Am Coll Cardiol.* 2005;46:e1–e82.
81. Szałachciński 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;55:1037–1042.
82. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol.* 1987;59:634–638.
83. Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure: the V-HeFT VA Cooperative Studies Group. *Circulation.* 1993;87(suppl):V-15–V-16.
84. Mancini DM, Eisen H, Kusssmaul 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.
85. Aaronson K, Chen T, Mancini DM. Demonstration of the continuous nature of peak  $\dot{V}O_2$  for predicting survival in ambulatory patients evaluated for transplant. *J Heart Lung Transplant.* 1996;15:S66. Abstract.
86. 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? [published correction appears in *J Heart Lung Transplant.* 1996;15:106–107]. *J Heart Lung Transplant.* 1995;14:981–989.
87. 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.
88. Elmariah S, Goldberg LR, Allen MT, Kao A. Effects of gender on peak oxygen consumption and the timing of cardiac transplantation. *J Am Coll Cardiol*. 2006;47:2237–2242.
  89. Green P, Lund LH, Mancini D. Comparison of peak exercise oxygen consumption and the Heart Failure Survival Score for predicting prognosis in women versus men. *Am J Cardiol*. 2007;99:399–403.
  90. Hsieh E, Chadalavada S, Krishnaswamy G, Starling RC, Pothier CE, Blackstone EH, Lauer MS. Long-term prognostic value of peak oxygen consumption in women versus men with heart failure and severely impaired left ventricular systolic function. *Am J Cardiol*. 2007;100:291–295.
  91. Davies LC, Francis DP, Piepoli M, Scott AC, Ponikowski P, Coats AJ. Chronic heart failure in the elderly: value of cardiopulmonary exercise testing in risk stratification. *Heart*. 2000;83:147–151.
  92. Parikh MN, Lund LH, Goda A, Mancini D. Usefulness of peak exercise oxygen consumption and the Heart Failure Survival Score to predict survival in patients >65 years of age with heart failure. *Am J Cardiol*. 2009;103:998–1002.
  93. Lund LH, Aaronson KD, Mancini DM. Validation of peak exercise oxygen consumption and the Heart Failure Survival Score for serial risk stratification in advanced heart failure. *Am J Cardiol*. 2005;95:734–741.
  94. Weber KT, Janicki JS, McElroy PA. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. *Circulation*. 1987;76(part 2):V-140–V-145.
  95. Lund LH, Aaronson KD, Mancini DM. Predicting survival in ambulatory patients with severe heart failure on beta-blocker therapy. *Am J Cardiol*. 2003;92:1350–1354.
  96. Koelling TM, Joseph S, Aaronson KD. Heart failure survival score continues to predict clinical outcomes in patients with heart failure receiving beta-blockers. *J Heart Lung Transplant*. 2004;23:1414–1422.
  97. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving  $\beta$ -blockers. *Circulation*. 2005;111:2313–2318.
  98. Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Moore B, Kitzman D, Peberdy MA, Bensimhon D, Chase P, Forman D, West E, Guazzi M. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail*. 2009;2:113–120.
  99. 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.
  100. Ciccoira M, Davos CH, Francis DP, Doehner W, Zanolla L, Franceschini L, Piepoli MF, Coats AJ, Zardini P, Poole-Wilson PA, Anker SD. Prediction of mortality in chronic heart failure from peak oxygen consumption adjusted for either body weight or lean tissue. *J Card Fail*. 2004;10:421–426.
  101. Osada N, Chaitman BR, Miller LW, Yip D, Cishek MB, Wolford TL, Donohue TJ. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. *J Am Coll Cardiol*. 1998;31:577–582.
  102. 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.
  103. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, Sperfeld A, Gläser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation*. 2000;101:2803–2809.
  104. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007;115:2410–2417.
  105. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, Coats AJ. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO<sub>2</sub> slope and peak VO<sub>2</sub>. *Eur Heart J*. 2000;21:154–161.
  106. 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;91:2924–2932.
  107. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, Schneider S, Schwarz A, Senges J. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation*. 2002;106:3079–3084.
  108. Lang CC, Karlin P, Haythe J, Lim TK, Mancini DM. Peak cardiac power output, measured noninvasively, is a powerful predictor of outcome in chronic heart failure. *Circ Heart Fail*. 2009;2:33–38.
  109. 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;95:2660–2667.
  110. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN, Sullivan MJ. Exercise and heart failure: a statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation*. 2003;107:1210–1225.
  111. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–1450.
  112. Brubaker PH, Marburger CT, Morgan TM, Fray B, Kitzman DW. Exercise responses of elderly patients with diastolic versus systolic heart failure. *Med Sci Sports Exerc*. 2003;35:1477–1485.
  113. Farr MJ, Lang CC, Lamanca JJ, Zile MR, Francis G, Tavazzi L, Gaasch WH, St John Sutton M, Itoh H, Mancini D; MCC-135 GO1 Investigators. Cardiopulmonary exercise variables in diastolic versus systolic heart failure. *Am J Cardiol*. 2008;102:203–206.
  114. Arena R, Brubaker P, Moore B, Kitzman D. The oxygen uptake efficiency slope is reduced in older patients with heart failure and a normal ejection fraction. *Int J Cardiol*. Published online before print January 26, 2009. doi:10.1016/j.ijcard.2008.12.143. Available at: <http://www.sciencedirect.com>. Accessed May 27, 2010.
  115. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol*. 2005;46:1883–1890.
  116. Moore B, Brubaker PH, Stewart KP, Kitzman DW. VE/VCO<sub>2</sub> slope in older heart failure patients with normal versus reduced ejection fraction compared with age-matched healthy controls. *J Card Fail*. 2007;13:259–262.
  117. Arena R, Owens DS, Arevalo J, Smith K, Mohiddin SA, McAreavey D, Ullisny KL, Tripodi D, Fananapazir L, Plehn JF. Ventilatory efficiency and resting hemodynamics in hypertrophic cardiomyopathy. *Med Sci Sports Exerc*. 2008;40:799–805.
  118. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J*. 2008;29:2751–2759.
  119. Waraich S, Sietsema KE. Clinical cardiopulmonary exercise testing: patient and referral characteristics. *J Cardiopulm Rehabil Prev*. 2007;27:400–406.
  120. Janicki JS, Weber KT, Likoff MJ, Fishman AP. Exercise testing to evaluate patients with pulmonary vascular disease. *Am Rev Respir Dis*. 1984;129:S93–S95.
  121. Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. *Chest*. 1994;105:168–174.
  122. DePaso WJ, Winterbauer RH, Lusk JA, Dreis DF, Springmeyer SC. Chronic dyspnea unexplained by history, physical examination, chest roentgenogram, and spirometry: analysis of a seven-year experience. *Chest*. 1991;100:1293–1299.
  123. Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. *Arch Intern Med*. 1989;149:2277–2282.
  124. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004.
  125. Weisman IM, Zeballos RJ. An integrated approach to the interpretation of cardiopulmonary exercise testing. *Clin Chest Med*. 1994;15:421–445.
  126. Palange P, Carlone S, Forte S, Galassetti P, Serra P. Cardiopulmonary exercise testing in the evaluation of patients with ventilatory vs circulatory causes of reduced exercise tolerance. *Chest*. 1994;105:1122–1126.
  127. ERS Task Force, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, O'Donnell DE, Puente-Maestu L, Schols AM, Singh S, Whipp BJ. Recommendations on the use of exercise testing in clinical practice. *Eur Respir J*. 2007;29:185–209.
  128. Hansen JE, Sue DY, Oren A, Wasserman K. Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *Am J Cardiol*. 1987;59:669–674.

129. Haller RG, Lewis SF. Pathophysiology of exercise performance in muscle disease. *Med Sci Sports Exerc.* 1984;16:456–459.
130. Flaherty KR, Wald J, Weisman IM, Zeballos RJ, Schork MA, Blaivas M, Rubenfire M, Martinez FJ. Unexplained exertional limitation: characterization of patients with a mitochondrial myopathy. *Am J Respir Crit Care Med.* 2001;164:425–432.
131. Tanabe Y, Nakagawa I, Ito E, Suzuki K. Hemodynamic basis of the reduced oxygen uptake relative to work rate during incremental exercise in patients with chronic heart failure. *Int J Cardiol.* 2002;83:57–62.
132. Duscha BD, Kraus WE, Keteyian SJ, Sullivan MJ, Green HJ, Schachar FH, Phippen AM, Brawner CA, Blank JM, Annex BH. Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II–III chronic heart failure independent of other peripheral alterations. *J Am Coll Cardiol.* 1999;33:1956–1963.
133. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L, Adams V, Riede U, Schuler G. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* 1997;29:1067–1073.
134. Mettauer B, Zoll J, Garnier A, Ventura-Clapier R. Heart failure: a model of cardiac and skeletal muscle energetic failure. *Pflugers Arch.* 2006;452:653–666.
135. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure: muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation.* 1989;80:769–781.
136. Papazachou O, Anastasiou-Nana M, Sakellariou D, Tassiou A, Dimopoulos S, Venetsanakis N, Maroulidis G, Drakos S, Roussos C, Nanas S. Pulmonary function at peak exercise in patients with chronic heart failure. *Int J Cardiol.* 2007;118:28–35.
137. Agostoni P, Bussotti M, Cattadori G, Margutti E, Contini M, Muratori M, Marenzi G, Fiorentini C. Gas diffusion and alveolar-capillary unit in chronic heart failure. *Eur Heart J.* 2006;27:2538–2543.
138. Marin-García J, Goldenthal MJ, Moe GW. Abnormal cardiac and skeletal muscle mitochondrial function in pacing-induced cardiac failure. *Cardiovasc Res.* 2001;52:103–110.
139. Duscha BD, Schulze PC, Robbins JL, Forman DE. Implications of chronic heart failure on peripheral vasculature and skeletal muscle before and after exercise training. *Heart Fail Rev.* 2008;13:21–37.
140. Gielen S, Adams V, Möbius-Winkler S, Linke A, Erbs S, Yu J, Kempf W, Schubert A, Schuler G, Hambrecht R. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42:861–868.
141. Siciliano G, Volpi L, Piazza S, Ricci G, Mancuso M, Murri L. Functional diagnostics in mitochondrial diseases. *Biosci Rep.* 2007;27:53–67.
142. Jeppesen TD, Schwartz M, Olsen DB, Vissing J. Oxidative capacity correlates with muscle mutation load in mitochondrial myopathy. *Ann Neurol.* 2003;54:86–92.
143. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. *Brain.* 2003;126:413–423.
144. Taivassalo T, Haller RG. Exercise and training in mitochondrial myopathies. *Med Sci Sports Exerc.* 2005;37:2094–2101.
145. Arena R, Myers J, Guazzi M. The clinical significance of aerobic exercise testing and prescription: from apparently healthy to confirmed cardiovascular disease. *Am J Lifestyle Med.* 2008;2:519–536.
146. Macko RF, Ivey FM, Forrester LW. Task-oriented aerobic exercise in chronic hemiparetic stroke: training protocols and treatment effects. *Top Stroke Rehabil.* 2005;12:45–57.
147. Macko RF, Benvenuti F, Stanhope S, Macellari V, Taviani A, Nesi B, Weinrich M, Stuart M. Adaptive physical activity improves mobility function and quality of life in chronic hemiparesis. *J Rehabil Res Dev.* 2008;45:323–328.
148. Ivey FM, Macko RF. Prevention of deconditioning after stroke. In: Stein J, Harvey RL, Macko RF, Winstein CJ, Zorowitz RD, eds. *Stroke Recovery and Rehabilitation Textbook.* New York, NY: Demos Medical; 2009:387–404.
149. Fletcher BJ, Dunbar SB, Felner JM, Jensen BE, Almon L, Cotsonis G, Fletcher GF. Exercise testing and training in physically disabled men with clinical evidence of coronary artery disease. *Am J Cardiol.* 1994;73:170–174.
150. Luft AR, Macko RF, Forrester LW, Villagra F, Ivey F, Sorkin JD, Whitall J, McCombe-Waller S, Katzell L, Goldberg AP, Hanley DF. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke.* 2008;39:3341–3350.
151. Ivey FM, Ryan AS, Hafer-Macko CE, Goldberg AP, Macko RF. Treadmill aerobic training improves glucose tolerance and indices of insulin sensitivity in disabled stroke survivors: a preliminary report. *Stroke.* 2007;38:2752–2758.
152. American Medical Association. The pulmonary system. In: *Guides to the Evaluation of Permanent Impairment.* 6th ed. Chicago, Ill: American Medical Association; 2007.
153. Oren A, Sue DY, Hansen JE, Torrance DJ, Wasserman K. The role of exercise testing in impairment evaluation. *Am Rev Respir Dis.* 1987;135:230–235.
154. Agostoni P, Smith DD, Schoene RB, Robertson HT, Butler J. Evaluation of breathlessness in asbestos workers: results of exercise testing. *Am Rev Respir Dis.* 1987;135:812–816.
155. Fredriksen PM, Veldtman G, Hechter S, Therrien J, Chen A, Warsi MA, Freeman M, Liu P, Siu S, Thaulow E, Webb G. Aerobic capacity in adults with various congenital heart diseases. *Am J Cardiol.* 2001;87:310–314.
156. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, Li W, Uebing A, Bayne S, Wensel R, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation.* 2006;113:2796–2802.
157. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation.* 2005;112:828–835.
158. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. *Eur Heart J.* 2009;30:497–504.
159. Giardini A, Specchia S, Berton E, Sangiorgi D, Coutsoumbas G, Gargiulo G, Oppido G, Bonvicini M, Picchio FM. Strong and independent prognostic value of peak circulatory power in adults with congenital heart disease. *Am Heart J.* 2007;154:441–447.
160. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT; American College of Chest Physicians. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest.* 2007;132:161S–177S.
161. Loewen GM, Watson D, Kohman L, Herndon JE II, Shennib H, Kernstine K, Olak J, Mador MJ, Harpole D, Sugarbaker D, Green M; Cancer and Leukemia Group B. Preoperative exercise Vo<sub>2</sub> measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. *J Thorac Oncol.* 2007;2:619–625.
162. DeCamp MM Jr, Lipson D, Krasna M, Minai OA, McKenna RJ Jr, Thomashow BM. The evaluation and preparation of the patient for lung volume reduction surgery. *Proc Am Thorac Soc.* 2008;5:427–431.
163. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* 2003;348:2059–2073.
164. Rich S, Rabinovitch M. Diagnosis and treatment of secondary (non-category 1) pulmonary hypertension. *Circulation.* 2008;118:2190–2199.
165. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation.* 2002;105:54–60.
166. Ting H, Sun XG, Chuang ML, Lewis DA, Hansen JE, Wasserman K. A noninvasive assessment of pulmonary perfusion abnormality in patients with primary pulmonary hypertension. *Chest.* 2001;119:824–832.
167. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2000;161:487–492.
168. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shepherd RJ. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation.* 2002;106:666–671.
169. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, Shepherd RJ. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol.* 2003;42:2139–2143.
170. Chaundhry S, Arena R, Wasserman K, Hansen JE, Lewis GD, Myers J, Chronos N, Boden WE. Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing. *Am Heart J.* 2009;103:615–619.

171. Belardinelli R, Lacialaprice F, Carle F, Minnucci A, Cianci G, Perna G, D'Eusano G. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J*. 2003;24:1304–1313.
172. Bussotti M, Apostolo A, Andreini D, Palermo P, Contini M, Agostoni P. Cardiopulmonary evidence of exercise-induced silent ischaemia. *Eur J Cardiovasc Prev Rehabil*. 2006;13:249–253.
173. Greco EM, Guardini S, Ferrario M, Romano S. How to program rate responsive pacemakers. *Pacing Clin Electrophysiol*. 2000;23:165–173.
174. Duru F, Cho Y, Wilkoff BL, Cole CR, Adler S, Jensen DN, Strobel U, Radicke D, Candinas R. Rate responsive pacing using transthoracic impedance minute ventilation sensors: a multicenter study on calibration stability. *Pacing Clin Electrophysiol*. 2002;25:1679–1684.
175. Capucci A, Boriani G, Specchia S, Marinelli M, Santarelli A, Magnani B. Evaluation by cardiopulmonary exercise test of DDDR versus DDD pacing. *Pacing Clin Electrophysiol*. 1992;15:1908–1913.
176. Lemke B, Dryander SV, Jäger D, Machraoui A, MacCarter D, Barmeyer J. Aerobic capacity in rate modulated pacing. *Pacing Clin Electrophysiol*. 1992;15:1914–1918.
177. Lewalter T, Rickli H, MacCarter D, Schwartze P, Schimpf R, Schumacher B, Jung W, Candinas R, Lüderitz B. Oxygen uptake to work rate relation throughout peak exercise in normal subjects: relevance for rate adaptive pacemaker programming. *Pacing Clin Electrophysiol*. 1999;22:769–775.
178. Mathony U, Schmidt H, Gröger C, Francis DP, Konzag I, Müller-Werdan U, Werdan K, Syska J. Optimal maximum tracking rate of dual-chamber pacemakers required by children and young adults for a maximal cardiorespiratory performance. *Pacing Clin Electrophysiol*. 2005;28:378–383.
179. Alt EU, Schlegl MJ, Matula MM. Intrinsic heart rate response as a predictor of rate-adaptive pacing benefit. *Chest*. 1995;107:925–930.
180. Meine M, Achtelik M, Hexamer M, Kloppe A, Werner J, Trappe HJ. Assessment of the chronotropic response at the anaerobic threshold: an objective measure of chronotropic function. *Pacing Clin Electrophysiol*. 2000;23:1457–1467.
181. Page E, Defaye P, Bonnet JL, Durand C, Amblard A. Comparison of the cardiopulmonary response to exercise in recipients of dual sensor DDDR pacemakers versus a healthy control group. *Pacing Clin Electrophysiol*. 2003;26:239–243.
182. Madaric J, Vanderheyden M, Van Laethem C, Verhamme K, Feys A, Goethals M, Verstreken S, Geelen P, Penicka M, De Bruyne B, Bartunek J. Early and late effects of cardiac resynchronization therapy on exercise-induced mitral regurgitation: relationship with left ventricular dyssynchrony, remodelling and cardiopulmonary performance. *Eur Heart J*. 2007;28:2134–2141.
183. Strickberger SA, Conti J, Daoud EG, Havranek E, Mehra MR, Piña IL, Young J. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation*. 2005;111:2146–2150.
184. Pardaens K, Van Cleemput J, Vanhaecke J, Fagard RH. Atrial fibrillation is associated with a lower exercise capacity in male chronic heart failure patients. *Heart*. 1997;78:564–568.
185. Agostoni P, Emdin M, Corrà U, Veglia F, Magri D, Tedesco CC, Berton E, Passino C, Bertella E, Re F, Mezzani A, Belardinelli R, Colombo C, La Gioia R, Vicenzi M, Giannoni A, Scutinio D, Giannuzzi P, Tondo C, Di Lenarda A, Sinagra G, Piepoli MF, Guazzi M. Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J*. 2008;29:2367–2372.
186. Guazzi M, Belletti S, Bianco E, Lenatti L, Guazzi MD. Endothelial dysfunction and exercise performance in lone atrial fibrillation or associated with hypertension or diabetes: different results with cardioversion. *Am J Physiol Heart Circ Physiol*. 2006;291:H921–H928.
187. Guazzi M, Belletti S, Tumminello G, Fiorentini C, Guazzi MD. Exercise hyperventilation, dyspnea sensation, and ergoreflex activation in lone atrial fibrillation. *Am J Physiol Heart Circ Physiol*. 2004;287:H2899–H2905.
188. Wozakowska-Kaplon B, Opolski G. Effects of sinus rhythm restoration in patients with persistent atrial fibrillation: a clinical, echocardiographic and hormonal study. *Int J Cardiol*. 2004;96:171–176.
189. Lok NS, Lau CP. Oxygen uptake kinetics and cardiopulmonary performance in lone atrial fibrillation and the effects of sotalol. *Chest*. 1997;111:934–940.
190. McCullough PA, Gallagher MJ, Dejong AT, Sandberg KR, Trivax JE, Alexander D, Kasturi G, Jafri SM, Krause KR, Chengelis DL, Moy J, Franklin BA. Cardiorespiratory fitness and short-term complications after bariatric surgery. *Chest*. 2006;130:517–525.
191. Santry HP, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. *JAMA*. 2005;294:1909–1917.
192. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) [published correction appears in *Circulation*. 2006;113:e846]. *Circulation*. 2002;105:1257–1267.
193. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32:S498–S504.
194. Jones N. *Clinical Exercise Testing*. Philadelphia, Pa: Saunders; 1997.
195. Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol*. 1993;22:175–182.
196. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis*. 1984;129:S49–S55.
197. Hsieh E, Gorodeski EZ, Starling RC, Blackstone EH, Ishwaran H, Lauer MS. Importance of treadmill exercise time as an initial prognostic screening tool in patients with systolic left ventricular dysfunction. *Circulation*. 2009;119:3189–3197.
198. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, Nishibata K. Oxygen intake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relationship between oxygen consumption and minute ventilation during incremental exercise. *Nagoya J Med Sci*. 1996;59:55–62.
199. Van Laethem C, Bartunek J, Goethals M, Nellen P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J*. 2005;149:175–180.
200. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol*. 2000;36:194–201.
201. Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF, Francis DP. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J*. 2006;27:684–690.
202. Baba R, Kubo N, Morotome Y, Iwagaki S. Reproducibility of the oxygen uptake efficiency slope in normal healthy subjects. *J Sports Med Phys Fitness*. 1999;39:202–206.
203. Pogliaghi S, Dussin E, Tarperi C, Cevese A, Schena F. Calculation of oxygen uptake efficiency slope based on heart rate reserve end-points in healthy elderly subjects. *Eur J Appl Physiol*. 2007;101:691–696.
204. Arena R, Myers J, Hsu L, Peberdy MA, Pinkstaff S, Bensimhon D, Chase P, Vicenzi M, Guazzi M. The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. *J Card Fail*. 2007;13:462–469.
205. Myers J, Arena R, Dewey F, Bensimhon D, Abella J, Hsu L, Chase P, Guazzi M, Peberdy MA. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J*. 2008;156:1177–1183.
206. Arena R, Peberdy MA. Reliability of resting end-tidal carbon dioxide in chronic heart failure. *J Cardiopulm Rehabil*. 2005;25:177–180.
207. Jin X, Weil MH, Tang W, Povoas H, Pernat A, Xie J, Bisera J. End-tidal carbon dioxide as a noninvasive indicator of cardiac index during circulatory shock. *Crit Care Med*. 2000;28:2415–2419.
208. Isserles SA, Breen PH. Can changes in end-tidal PCO2 measure changes in cardiac output? *Anesth Analg*. 1991;73:808–814.
209. Matsumoto A, Itoh H, Eto Y, Kobayashi T, Kato M, Omata M, Watanabe H, Kato K, Momomura S. End-tidal CO2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol*. 2000;36:242–249.
210. Arena R, Guazzi M, Myers J. Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure. *Int J Cardiol*. 2007;117:103–108.
211. Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Moore B, Kitzman D, Peberdy MA, Bensimhon D, Chase P, Guazzi M. The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. *Am Heart J*. 2008;156:982–988.

212. Bradley TD. The ups and downs of periodic breathing: implications for mortality in heart failure. *J Am Coll Cardiol*. 2003;41:2182–2184.
213. Leite JJ, Mansur AJ, de Freitas HF, Chizola PR, Bocchi EA, Terra-Filho M, Neder JA, Lorenzi-Filho G. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol*. 2003;41:2175–2181.
214. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD; Gruppo di Studio Fisiologia dell'Esercizio, Cardiologia dello Sport e Riabilitazione Cardiovascolare of the Italian Society of Cardiology. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J*. 2007;153:859–867.
215. Ribeiro JP. Periodic breathing in heart failure: bridging the gap between the sleep laboratory and the exercise laboratory. *Circulation*. 2006;113:9–10.
216. Somers VK. Sleep: a new cardiovascular frontier [published correction appears in *N Engl J Med*. 2005;353:2523]. *N Engl J Med*. 2005;353:2070–2073.
217. Hanly P, Zuberi N, Gray R. Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure: relationship to arterial PCO<sub>2</sub>. *Chest*. 1993;104:1079–1084.
218. Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis*. 1992;145:776–781.
219. Francis DP, Willson K, Davies LC, Coats AJ, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. *Circulation*. 2000;102:2214–2221.
220. Ponikowski P, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, Coats AJ, Piepoli M. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation*. 1999;100:2418–2424.
221. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S, Pedretti R. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol*. 2007;50:299–308.
222. Myers J, Salleh A, Buchanan N, Smith D, Neutel J, Bowes E, Froelicher VF. Ventilatory mechanisms of exercise intolerance in chronic heart failure. *Am Heart J*. 1992;124:710–719.
223. Guazzi M, Marenzi G, Assanelli E, Perego GB, Cattadori G, Doria E, Agostoni PG. Evaluation of the dead space/tidal volume ratio in patients with chronic congestive heart failure. *J Card Fail*. 1995;1:401–408.
224. Jones NL, Robertson DG, Kane JW. Difference between end-tidal and arterial PCO<sub>2</sub> in exercise. *J Appl Physiol*. 1979;47:954–960.
225. Lewis DA, Sietsema KE, Casaburi R, Sue DY. Inaccuracy of noninvasive estimates of VD/VT in clinical exercise testing. *Chest*. 1994;106:1476–1480.
226. 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.
227. Barstow TJ, Casaburi R, Wasserman K. O<sub>2</sub> uptake kinetics and the O<sub>2</sub> deficit as related to exercise intensity and blood lactate. *J Appl Physiol*. 1993;75:755–762.
228. Hickson RC, Bomze HA, Hollozy JO. Faster adjustment of O<sub>2</sub> uptake to the energy requirement of exercise in the trained state. *J Appl Physiol*. 1978;44:877–881.
229. Powers SK, Dodd S, Beadle RE. Oxygen uptake kinetics in trained athletes differing in  $\dot{V}O_{2\max}$ . *Eur J Appl Physiol Occup Physiol*. 1985;54:306–308.
230. Sietsema KE, Ben-Dov I, Zhang YY, Sullivan C, Wasserman K. Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. *Chest*. 1994;105:1693–1700.
231. Sietsema KE, Cooper DM, Perloff JK, Rosove MH, Child JS, Canobbio MM, Whipp BJ, Wasserman K. Dynamics of oxygen uptake during exercise in adults with cyanotic congenital heart disease. *Circulation*. 1986;73:1137–1144.
232. Koike A, Yajima T, Adachi H, Shimizu N, Kano H, Sugimoto K, Niwa A, Marumo F, Hiroe M. Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. *Circulation*. 1995;91:1719–1724.
233. Harris RC, Edwards RH, Hultman E, Nordesjö LO, Ny Lind B, Sahlin K. The time course of phosphorylcreatine resynthesis during recovery of the quadriceps muscle in man. *Pflugers Arch*. 1976;367:137–142.
234. Barstow TJ, Lamarra N, Whipp BJ. Modulation of muscle and pulmonary O<sub>2</sub> uptakes by circulatory dynamics during exercise. *J Appl Physiol*. 1990;68:979–989.
235. Guazzi M, Tumminello G, Di Marco F, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. *J Am Coll Cardiol*. 2004;44:2339–2348.
236. de Groot P, Millaire A, Decoux E, Nugue O, Guimier P, Ducloux G. Kinetics of oxygen consumption during and after exercise in patients with dilated cardiomyopathy: new markers of exercise intolerance with clinical implications. *J Am Coll Cardiol*. 1996;28:168–175.
237. 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;26:429–435.
238. Chomsky DB, Lang CC, Rayos GH, Shyr Y, Yeoh TK, Pierson RN 3rd, Davis SF, Wilson JR. Hemodynamic exercise testing: a valuable tool in the selection of cardiac transplantation candidates. *Circulation*. 1996;94:3176–3183.
239. Metra M, Faggiano P, D'Aloia A, Nodari S, Gualeni A, Raccagni D, Dei Cas L. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. *J Am Coll Cardiol*. 1999;33:943–950.
240. Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. *J Card Fail*. 2007;13:672–679.
241. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol*. 1997;82:908–912.
242. Lang CC, Karlin P, Haythe J, Tsao L, Mancini DM. Ease of noninvasive measurement of cardiac output coupled with peak  $\dot{V}O_2$  determination at rest and during exercise in patients with heart failure. *Am J Cardiol*. 2007;99:404–405.
243. Grossman W. Blood flow measurement: cardiac output and vascular resistance. In: Baim D, ed. *Grossman's Cardiac Catheterization, Angiography, and Intervention*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2006:148–162.
244. Sun XG, Hansen JE, Stringer WW, Ting H, Wasserman K. Carbon dioxide pressure-concentration relationship in arterial and mixed venous blood during exercise. *J Appl Physiol*. 2001;90:1798–1810.
245. Agostoni P, Cattadori G, Apostolo A, Contini M, Palermo P, Marenzi G, Wasserman K. Noninvasive measurement of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. *J Am Coll Cardiol*. 2005;46:1779–1781.
246. Baum MM, Moss JA, Kumar S, Wagner PD. Non-invasive measurement of cardiac output: evaluation of new infrared absorption spectrometer. *Respir Physiol Neurobiol*. 2006;153:191–201.
247. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest*. 1999;116:488–503.
248. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2006;3:180–184.
249. Johnson BD, Beck KC, Olson LJ, O'Malley KA, Allison TG, Squires RW, Gau GT. Ventilatory constraints during exercise in patients with chronic heart failure. *Chest*. 2000;117:321–332.
250. Dempsey JA, McKenzie DC, Haverkamp HC, Eldridge MW. Update in the understanding of respiratory limitations to exercise performance in fit, active adults. *Chest*. 2008;134:613–622.

KEY WORDS: AHA Scientific Statements ■ diagnosis ■ exercise ■ heart failure ■ prognosis ■ exercise test ■ blood gas analysis