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How to interpret cardiopulmonary exercise tests

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Abstract

Exercise intolerance and related symptoms are cardinal manifestations of most cardiopulmonary disorders. Assessing the functional response with gas exchange analysis by cardiopulmonary exercise testing (CPX) is now the gold standard for thoroughly assessing the pathophysiological derangements behind these diseases. CPX provides an assessment of the integrative response involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems, which are not adequately reflected thorough the measurement of individual organ system function. Accordingly, CPX is now being used in a wide spectrum of clinical settings for evaluation of undiagnosed exercise intolerance, and the test's popularity is increasing due to recent statements and official documents that have provided simplified and easy-to-apply reports that may consistently help the practicing clinician with their interpretations and clinical directions. ■ *Heart Metab*. 2014;64:31–36

Keywords: cardiopulmonary exercise; oxygen consumption; ventilation inefficiency

Applications and use of exercise testing with gas exchange analysis, added to electrocardiogram (ECG) and blood pressure monitoring, have been expanding in recent years and is now part of routine clinical diagnostic studies.[1,2]

A growing appreciation for this test has been possible due to the development of rapidly responding electronic gas analyzers to replace the more demanding chemical methods for measuring respiratory gases and to the development of flow meters that can measure instantaneous flow and volume. This has greatly decreased the technical time, and therefore, the cost to do gas exchange measurements.[2] Test-to-test repeatability and high reliance of data recorded are other significant features that have contributed to a preferred use compared with other exercise testing modalities.[3] These tests are referred to as cardiopulmonary exercise tests (CPXs) because the cardiovascular and pulmonary systems are assessed when gas exchange is measured during exercise.

The purposes for which CPXs are currently being applied attest to its growing importance in cardiopulmonary medicine. This approach is useful in terms of assessing the mechanism of exercise intolerance, evaluating disability, making activity and training recommendations, quantifying responses to therapy, and predicting outcomes. Due to these distinctive features, CPX has received a particular amount of attention in recent years; numerous studies have adopted CPX variables as end points over the last decade, and the test, with all its features, is becoming more common in daily clinical practice.[1]

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Abbreviations

ATP: adenosine triphosphate; **CPX:** cardiopulmonary exercise test; **ECG:** electrocardiogram; **HR:** heart rate; **MVV:** maximum voluntary ventilation; **RER:** respiratory exchange rate; **$\dot{V}/\dot{Q}$:** ventilation/perfusion [ratio]; **$\dot{V}_E$:** ventilation; **$\dot{V}O_2$:** oxygen consumption; **WR:** work rate

The present review addresses how to broadly interpret CPX results and how data can be interpreted in cases of disorders of the heart and the lung. Therefore, a translation from pathophysiological bases to clinical implications is provided.

Mechanisms for exercise intolerance and cardiopulmonary exercise test diagnoses

Exercise necessitates an increase in gas transport between the air and the mitochondria. This vital physiological coupling occurs due to a correct matching between several systems; primarily the pulmonary, cardiovascular, and muscular systems. Exercise intolerance is caused by any disease state that disrupts the normal gas-exchange coupling between the external and internal ventilation.

The basic requirement to sustain muscular activity is an increase in cellular respiration for the production and regeneration of adenosine triphosphate (ATP). To support the increase in cellular respiration, there is a need for an increase in O_2 and CO_2 transport between the cells and the external airways. This increase must match the rate of cellular respiration except for the following: (i) transient lags allowed by the capacitance in the transport system; (ii) O_2 stores on the venous side of the circulation; and (iii) small stores of high-energy phosphate in the form of creatine phosphate in the myocytes.

There are a series of pathophysiological questions relevant for the clinician to ask when caring for patients with exercise intolerance due to dyspnea and/or fatigue. Primarily, the clinician should determine whether the metabolic demand for the given exercise is increased (ie, obesity), and if the exercise is limited by impaired O_2 flow (eg, cardiac, pulmonary, or peripheral disease, or an anemic condition), or impaired O_2 utilization (eg, muscle glycolytic problem or mitochondrial enzyme defect). Also relevant to the pathophysiology is whether there is an abnormal degree of ventilation perfusion ($\dot{V}/\dot{Q}$) ratio mismatching (ie, cardiac and pulmonary disease). Despite the complex pathophysiological interaction between biological systems during exercise, the simplified CPX approach for diagnostic standardization of exercise intolerance uses a nine-panel graphic array exemplified in *Figure 1* (normal healthy subject).

Panel 3. Oxygen consumption ($\dot{V}O_2$) vs work rate (WR) is the panel suggested to start with because it shows the true exercise performance by displaying $\dot{V}O_2$ at peak exercise that may differ from maximum $\dot{V}O_2$ ($\dot{V}O_2$max), where the percent predicted can be determined by appropriate reference equations.[4] This panel is also useful because it describes the pattern of increase in $\dot{V}O_2$, which may often be abnormal in patients with cardiovascular disorders depending on the specific pathophysiological condition. Linearity is a prerequisite for a normal response to exercise, and, in healthy subjects, the slope of $\dot{V}O_2$ increase over O_2 uptake is 10 mL/min/W.[5] After reviewing the plots in panel 3, the others are relevant to go into the pathophysiological state of coupling of the above mentioned main organ systems.

Panel 1. Minute ventilation ($\dot{V}_E$) vs WR. This linear relationship normally recognizes three patterns with the first change in slope corresponding to the switch to a prevalent anaerobic metabolism determining an increase in $\dot{V}_E$ for the augmented CO_2 release due to lactate tamponade and a second one close to exercise termination due to the ventilator compensatory response.

Panel 2. Heart rate (HR) and $\dot{V}O_2$/HR (O_2 pulse) vs WR. O_2 pulse is a surrogate measure of stroke volume considering $\dot{V}O_2$ as cardiac output (CO=stroke volume x HR) x arteriovenous oxygen difference ([a-v]O_2). Considering the C(a-v)O_2 difference content, O_2 pulse mirrors the stroke volume.

Panel 4. $\dot{V}_E$ vs $\dot{V}CO_2$. This is a linear relationship until compensation for metabolic acidosis. The slope of the linear part is steep when the exercise physiologic dead space/tidal volume ratio (V_{DS}/V_T) is increased.

Panel 5. HR vs $\dot{V}O_2$ and $\dot{V}CO_2$ vs $\dot{V}O_2$. HR increases linearly with $\dot{V}O_2$ to the predicted maximum in normal subjects. In patients with cardiac disease or pulmonary vascular disease, the increase may lose its linearity with HR increasing progressively, but more rapidly, than $\dot{V}O_2$. Up to the anaerobic threshold, $\dot{V}CO_2$ increases linearly with $\dot{V}O_2$ with a slope of one

or slightly less than one. Then, $\dot{V}CO_2$ increases more rapidly and the steepening of the slope depends on the rate of lactic acid buffering.

Panel 6. Ventilatory equivalent for O_2 and CO_2 ($\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}CO_2$) vs WR. $\dot{V}O_2$ decreases to a nadir at the anaerobic threshold, and $\dot{V}CO_2$ decreases to a nadir at the ventilatory compensatory point. Both values are high with pulmonary vascular occlusive disease.

Panel 7. VT vs $\dot{V}E$. The patients' vital capacity and inspiratory capacity (IC) are shown on the VT axis and measured maximum voluntary ventilation (MVV) is shown on the $\dot{V}E$ axis. With airflow limitation, maximal exercise $\dot{V}E$ approximates MVV. Thus, the breathing reserve ([MVV-$\dot{V}E$] at maximal exercise) is approximately zero. The breathing reserve cannot be predicted from resting pulmonary function measurements alone. With restrictive lung disease, VT may approximate the IC at low work rates and the respiratory rate may excessively increase.

Panel 8. Respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$). This usually starts at approximately

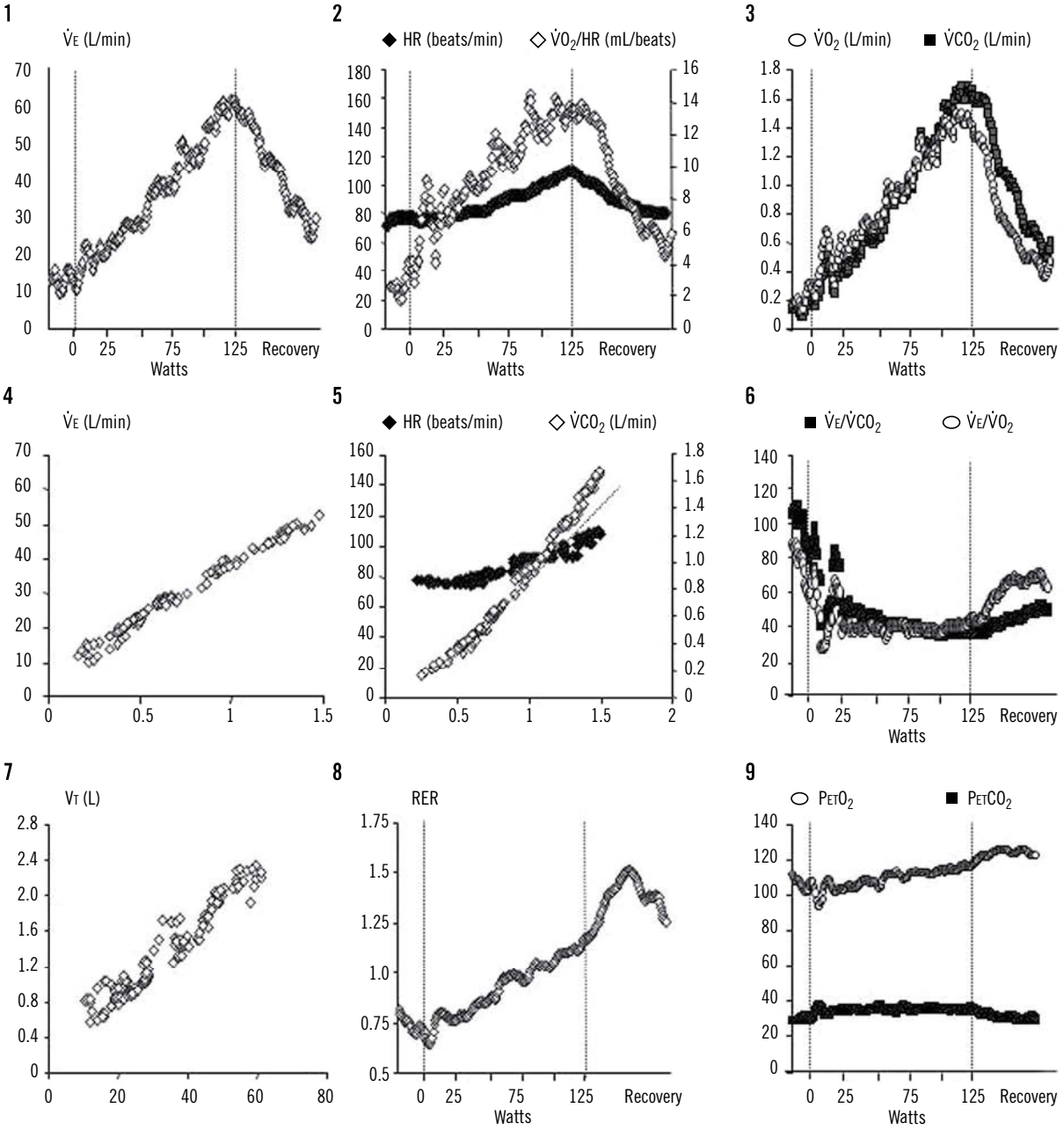

Fig. 1 *The nine-panel graphic array used in the CPX approach for diagnostic standardization of exercise intolerance uses.*
Abbreviations: *CPX, cardiopulmonary exercise testing; HR, heart rate; $\dot{V}E$, ventilation; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide consumption; VT, tidal volume; $P_{ET}O_2$, end-tidal oxygen tension; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide.*

0.8 and increases to above 1.0, which is above the anaerobic threshold. Acute hyperventilation at rest and initial exercise stages yields a RER>1.

Panel 9. End-tidal pressure of carbon dioxide ($P_{ET}CO_2$) and end-tidal oxygen tension ($P_{ET}CO_2$) vs WR. Low $P_{ET}CO_2$ reflects either hyperventilation or a high $\dot{V}/\dot{Q}$ mismatching. The RER signals if the hyperventilation is acute. Arterial blood gases or knowledge of plasma HCO_3- differentiates chronic hyperventilation from $\dot{V}/\dot{Q}$ mismatching.

The report in specific disorders

What is useful in heart failure and coronary artery disease?

In heart failure (HF), $\dot{V}O_2$ is markedly below the predicted normal value, and a major exercise limitation is a defect in cardiac output increase. Since cardiac output increases linearly with $\dot{V}O_2$ and $C(a\text{-}v)O_2$ is approximately maximal even in advanced HF, $\dot{V}O_2$ may be generally considered a valid surrogate of cardiac output. When cardiac output fails to increase appropriately, the relationship between $\dot{V}O_2$/WR decreases as WR increases. This change may be gradual (shallow) rather than abrupt like the change in $\dot{V}O_2$/WR slope (flattening) observed when the myocardium becomes ischemic.[1] In coronary artery disease, the occurrence of $\dot{V}O_2$/WR flattening is accompanied by a reduction in the slope of the O_2 pulse increase and may offer suitable clinical information in the clinical framework of coronary artery disease. In a report comparing sensitivity and specificity of CPX criteria with standard exercise-ECG criteria for diagnosis of cardiac ischemia, CPX provided a much higher sensitivity (87%) and specificity (74%) than standard ECG (46% and 66%, respectively).[6] When flattening and ECG abnormalities concur during the test, the ECG shows evidence of myocardial ischemia at work rates soon after the $\dot{V}O_2$/WR flattening.

Along with $\dot{V}O_2$, a series of ventilatory variables provide relevant insights in the data interpretation of cardiac patients, primarily, HF patients.[7] $\dot{V}E$ inefficiency is a typical manifestation that is conventionally defined by looking at the rate of increase in $\dot{V}E$ vs $\dot{V}CO_2$ (*Figure 1*, plot 6). This relationship is assessed as $\dot{V}E$ vs $\dot{V}CO_2$ or, less commonly, by the ratio at anaerobic threshold or at the nadir point of the ratio. The information obtained by these variables is not only diagnostic, but also especially useful in the clinical and prognostic assessment of patient follow-up. A 4 class $\dot{V}E$ severity classification has been identified and proposed[4] and is now suggested by statements from Balady et al and Guazzi et al as basic parts of the report in cardiac patients.[1,2]

The origin of an increased and inefficient ventilatory response to exercise is multifactorial and primarily reflects how left ventricular dysfunction may impair lung physiology and both central and peripheral ventilatory control.[7] For these latter peripheral mechanisms, main putative factors are an impaired chemoreflex sensitivity and regulation along with early developing acidosis.

High $\dot{V}E/\dot{V}CO_2$ slopes are observed in patients with moderate to severe forms of pulmonary hypertension, and end-tidal CO_2 is a determinant that becomes clinically and prognostically relevant.[8]

Another ventilatory abnormality peculiar to some HF patients is the pattern of oscillatory gas kinetics classified as exertional oscillatory ventilation (EOV), a pattern that resembles, in some instances, the occurrence of Cheyne-Stokes respiration during sleep.[9] This is an ominous sign of disease severity that is now recognized in up to 30% of symptomatic HF patients with a similar rate in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.[9]

What is useful in pulmonary lung diseases and arterial pulmonary hypertension?

Exercise limitation in patients with respiratory disease is complex, multifactorial, and may be difficult to establish and clearly quantitate. Ventilatory limiting factors include decreased ventilatory capacity (mostly due to mechanical factors; *Figure 1, plot 7*), abnormal gas exchange (ie, hypoxemia and increased VD/VT), and respiratory muscle dysfunction.

As for cardiac patients, the literature pertaining to patients with obstructive lung disease emphasizes the relevance of $\dot{V}O_2$ *(Figure 1, plot 3)* as a primary variable to be addressed[10] as a peak $\dot{V}O_2$<10 mL/min/kg portends a particularly poor prognosis (*Figure 1*, plot 3).[11]

The role of deconditioning in patients with chronic cardiopulmonary disease and in patients after heart, heart/lung, or lung transplantation has increased awareness of the role of peripheral limitation in

exercise performance and the importance of considering this as a contributing factor in their exercise limitation.

The prognostic ability of peak $\dot{V}O_2$ in patients with pulmonary disease has led the American College of Chest Physicians to recommend that CPX be used presurgically in lung resection candidates to assess postsurgical risk.[12] Initial evidence also indicates the $\dot{V}_E/\dot{V}CO_2$ slope is a significant postsurgical prognostic marker in patients with chronic obstructive pulmonary disease (COPD) undergoing lung resection *(Figure 1, plot 6)*.[13]

A key value of CPX in detecting potential pulmonary vascular limitation and the role of vasculopathy, or gauging disease severity once a diagnosis has been made, is the ability of this exercise approach to noninvasively quantify $\dot{V}/\dot{Q}$ abnormalities. Specifically, abnormalities in the $\dot{V}_E/\dot{V}CO_2$ slope and $P_{ET}CO_2$ *(Figure 1, plot 9)* are strongly suggestive of pulmonary vasculopathy whose etiology is either idiopathic or secondary pulmonary hypertension as a consequence of other primary conditions such as heart failure, hypertrophic cardiomyopathy, COPD, interstitial lung disease, or systemic connective tissue diseases.[14,15]

Universal cardiopulmonary exercise test report

In the recent joint European Association for Cardiovascular Prevention & Rehabilitation/American Heart Association statement on CPX application, a major goal has been to provide a universal report that may allow collecting all relevant CPX data in a concise and organized manner, which seems essential for meaningful data interpretation and clinical utilization. Specifically, the universal CPX reporting form *(Figure 2)* provides clinicians with the ability to collect relevant data that may subsequently be used for interpretation according to a patient's specific condition/test indication.

<table>
<tr><td colspan="3">Exercise modality: [ ] Treadmill [ ] Lower extremity ergometer</td></tr>
<tr><td colspan="3">Protocol:</td></tr>
<tr><td>Peak VO_2 (mL O_2•kg^{-1} min^{-1}) VO_2 at V_T (mL O_2•kg^{-1} min^{-1})</td><td>Per cent-predicted peak VO_2 (%)[a]
Peak RER</td><td>V_E/VCO_2 slope EOV [ ] Yes [ ] No</td></tr>
<tr><td>$P_{ET}CO_2$ (mmHg) Resting:
Increase during ET:</td><td>V_E/VO_2 at peak ET</td><td>$\Delta VQ/\Delta VO_2$[b]</td></tr>
<tr><td>V_E/MVV[c]</td><td>PEF (L/min): Pre-ET Post-ET</td><td></td></tr>
<tr><td colspan="3">O_2 pulse trajectory[d]
[ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline</td></tr>
<tr><td colspan="3">$\Delta VO_2/\Delta WR$ trajectory[d]
[ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline</td></tr>
<tr><td>Resting HR (b.p.m.)
Peak HR (b.p.m.)</td><td>Resting BP (mmHg)
Peak BP (mmHg)</td><td rowspan="2">Resting pulse oximetry (%)
Peak pulse oximetry (%)</td></tr>
<tr><td>Percent of age-predicted maximal HR[e] HRR at 1 min (beats)</td><td>Maximal workload
[ ] Treadmill speed/grade:
[ ] Cycler ergometer Watts:</td></tr>
<tr><td colspan="2">ECG criteria
[ ] No arrhythmias/ectopy/ST-segment changes
[ ] Arrhythmias/Ectopy/ST-segment changes: not exercise limiting
[ ] Arrhythmias/Ectopy/ST-segment changes: exercise limiting</td><td>ECG description</td></tr>
<tr><td colspan="3">Subjective symptoms (check box for primary termination criteria)
RPE [ ] Angina [ ] Dyspnoea [ ]</td></tr>
<tr><td colspan="3">Additional notes</td></tr>
</table>

Fig. 2 *Universal CPX report.*
Abbreviations: *$\Delta VQ/\Delta VO_2$, change in cardiac output/change in oxygen consumption; BP, blood pressure; CPX, cardiopulmonary exercise testing; $\Delta VO_2/\Delta W$, change in oxygen consumption/changes in Watts; ECG, electrocardiogram; EOV, exercise oscillatory ventilation; ET, exercise testing; HR, heart rate; HRR, heart rate recovery; MVV, maximal voluntary ventilation; O_2, oxygen; PEF, peak expiratory flow; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide production; RER, respiratory exchange ratio; RPE, rating of perceived exertion; V_E/MVV, peak minute ventilation/maximal voluntary ventilation; V_E/VCO_2, minute ventilation/carbon dioxide production; V_E/VO_2, minute ventilation/oxygen consumption; VO_2, oxygen consumption; V_T, ventilator threshold.*
[a]Use equations proposed by Wasserman. [b]Requires additional equipment to assess Q response to exercise through noninvasive rebreathing technique. [c]Directly measures MVV at baseline. [d]Requires O_2 pulse and $\Delta VO_2/\Delta WR$ plot from initiation of ET. If these variables required for assessment, electronically braked cycle ergometer should be used for testing. [e]Use equation: (peak HR/220-age) x 100.
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It should be noted that the CPX reporting form is primarily focused on the most common cardiovascular and pulmonary diseases. However, other reported variables may be relevant in conditions that are less frequent, but may still be a matter of useful investigation in the presence of exercise limitation (eg, mitochondrial myopathy and peripheral vascular disease).

Conclusions

Applications and use of CPX in the cardiology arena is increasing and is now included in the routine clinical diagnostic workup of patients with cardiopulmonary disorders. Data interpretation for diagnostic and prognostic purposes is based on physiological principles sustaining the matching between the external and internal ventilation and O_2 transport. The most recent statements and official documents have provided simplified easy-to-apply reports that may consistently help the practicing clinicians in their daily clinical practice. ■

REFERENCES

1. Balady GJ, Ades PA, Comoss P, et al. Core components of cardiac rehabilitation/secondary prevention programs: A statement for healthcare professionals from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2000;102:1069-1073.
2. Guazzi M, Adams V, Conraads V, et al; European Association for Cardiovascular Prevention & Rehabilitation; American Heart Association. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126:2261-2274.
3. Guazzi M. Reproducibility of cardiopulmonary exercise test variables: getting into an additional strength of the test. *Eur J Prev Cardiol*. 2014;21:442-444.
4. Arena R, Myers J, Abella J, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail*. 2009;2:113-120.
5. Wasserman K, Hansen JE, Sue DY, et al. *Principles of Exercise Testing and Interpretation*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
6. Belardinelli R, Lacalaprice F, Carle F, et al. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J*. 2003;24:1304-1313.
7. 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.
8. Guazzi M, Reina G, Tumminello G, Guazzi MD. Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO2 partial pressure. *Eur Heart J*. 2005;26:472-480.
9. Guazzi M. Treating exercise oscillatory ventilation in heart failure: the detail that may matter. *Eur Respir J*. 2012;40:1075-1077.
10. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med*. 2003;167:544-549.
11. Hiraga T, Maekura R, Okuda Y, et al. Prognostic predictors for survival in patients with COPD using cardiopulmonary exercise testing. *Clin Physiol Funct Imaging*. 2003;23:324-331.
12. 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.
13. Torchio R, Guglielmo M, Giardino R, et al. Exercise ventilatory inefficiency and mortality in patients with chronic obstructive pulmonary disease undergoing surgery for non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2010;38:14-19.
14. 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.
15. Glaser S, Noga O, Koch B, et al. Impact of pulmonary hypertension on gas exchange and exercise capacity in patients with pulmonary fibrosis. *Respir Med*. 2009;103:317-324.