Cardiopulmonary Exercise Testing in the Clinical Evaluation of Patients With Heart and Lung Disease

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Exercise tests are commonly used in clinical practice for both functional and diagnostic assessments. Many exercise tests are designed to produce a single measurement relevant to a specific clinical setting such as a timed walking distance as a measure of functional capacity in rehabilitation candidates or the presence of ECG changes consistent with myocardial ischemia in patients with chest pain. Cardiopulmonary exercise testing (CPX) measures a broader range of variables related to cardiorespiratory function, including expiratory ventilation ($\dot{V}_E$) and pulmonary gas exchange (oxygen uptake [$\dot{V}O_2$] and carbon dioxide output [$\dot{V}CO_2$]), along with the ECG and blood pressure, with the goal of quantitatively linking metabolic, cardiovascular, and pulmonary responses to exercise.[1–3] With increased availability of instruments for the facile measurement of exercise gas exchange, experience with CPX has expanded from clinical research applications to a broad range of clinical practice settings.[4]

Interpretation of CPX for clinical purposes includes comparison of data from individual patients with those from healthy and disease populations. Substantial data are available characterizing exercise responses of patients with certain common heart and lung diseases, providing a basis for using CPX to compare individual patients' impairment relative to others from the same populations. Diagnostic applications of CPX, eg, for evaluating unexplained dyspnea or exercise intolerance, also rely on a comparison of patients' data with those of patients with known diagnoses. In clinical practice, in contrast to much of the research related to specific disorders, patients frequently have multiple medical problems, confounding the assessment of impairment or the attribution of symptoms to one or another condition. Although there are few systematic analyses of the effects of coexistent conditions on exercise responses, an advantage of CPX compared with other forms of testing is the potential for gaining insight into these interactions. This review highlights CPX findings in selected clinical populations and the implication of these observations to the clinical evaluation of patients with heart and/or lung diseases.

Rationale and Terminology

To contract, skeletal muscle uses energy in the form of adenosine triphosphate, generated from oxidative metabolism of substrate, involving the consumption of O_2 and production of CO_2. Exchange of these gases in the muscle requires equivalent rates of exchange with the environment. Transport of gases between muscle and environment is mediated by the integrated function of multiple organ systems, any of which could become limiting to exercise if sufficiently impaired. The dependence of gas transport on large excursions in output of the heart and lungs makes disease of these organs particularly common causes of exercise intolerance.

The standard expression of capacity for endurance, or aerobic, exercise is the maximum $\dot{V}O_2$, reflecting the highest attainable rate of transport and use of oxygen. Peak $\dot{V}O_2$ reached during a symptom-limited incremental CPX protocol usually approximates maximal $\dot{V}O_2$[5] and is commonly expressed either indexed to body weight or as percent of an appropriate reference value. The significance of exercise capacity to health is well established and highlighted in a meta-analysis by Kodama et al,[6] comprising data of $>$100 000 subjects and $>$6000 events from 33 studies. In this analysis, each increment of 1 metabolic equivalent (3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) in peak $\dot{V}O_2$ (estimated from treadmill grade and speed) corresponded to 13% and 15% reductions in all-cause and cardiovascular mortality, respectively. The prognostic value of exercise capacity pertains to many disease populations as well and is the basis of a number of the clinical applications of CPX.

From the Fick expression for oxygen, $\dot{V}O_2 = Q \times [Cao_2 - Cv_{O_2}]$, where Q is cardiac output and $Cao_2 - Cv_{O_2}$ is the difference in oxygen content between arterial and venous blood, it is clear that $\dot{V}O_2$ is a function of cardiac output and therefore relevant to cardiac patients. Similarly, because abnormal lung mechanics limit the capacity for $\dot{V}_E$ in chronic lung disease, the peak exercise $\dot{V}_E$ is relevant to pulmonary patients. In addition, however, insight can be gained into the effect of disease on the integrated adaptation to exercise stress by examination of the relationships among $\dot{V}O_2$, $\dot{V}_E$, and other variables measured over the range of submaximal to peak exertion. For example, the lactate threshold, a marker of cardiovascular fitness and of endurance capacity, is evident in the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ during incremental exercise as the point where CO_2 generated from bicarbonate buffering of lactic acid accelerates $\dot{V}CO_2$ relative to $\dot{V}O_2$.

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Table 1. Commonly Measured Variables From Clinical CPX

Variable	Definition and Technical Considerations	Physiological Significance	Normal Response[7]	Clinical Relevance
$\dot{V}O_2$, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ or % of appropriately selected predicted value	Highest demonstrable $\dot{V}O_2$; "maximal" when there is objective evidence of true physiological limit; otherwise "peak"	Reflection of integrated function of pulmonary, cardiac, and skeletal muscle systems	Depends on age, sex, exercise habits, and genetic predisposition	Conventional expression of aerobic exercise capacity
	When derived from breath-by-breath data reported as 10–60-s average, depending on protocol: 10–20-s average if stages are ≤30 s; 30–60-s averages for 3-min stages	In health, response is indicative of capacity for delivery (cardiac) and use (muscle) of oxygen	Normal range is wide: from ≈80 to ≈15 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in an elite athlete and healthy 80-y-old woman, respectively	Measure of cardiovascular fitness in healthy persons Objective indicator of disease severity in certain chronic disease populations and of degree of impairment Prognostic in many chronic disease populations
V_T, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ or % of the predicted peak $\dot{V}O_2$	$\dot{V}O_2$ above which there is an accelerated rise in $\dot{V}_E$ and $\dot{V}CO_2$ relative to $\dot{V}O_2$	Defines the upper end of the range of moderate-intensity (sustainable) exercise	Normally averages ≈50%-65% of maximal/peak $\dot{V}O_2$	Responsive to aerobic training; is a measure of fitness
	Reflecting exhalation of CO_2 derived from the buffering of lactic acid	Closely related to lactate threshold; alternate term "anaerobic threshold" reflects dependence on oxygen delivery (Hb, F_{IO_2})	Higher with advanced age and endurance training	Can be used to set a highly individualized training intensity for exercise prescription
Peak RER	The ratio of $\dot{V}CO_2$ over VO_2 at maximal exercise	As exercise is continued above V_T, acceleration of $\dot{V}CO_2$ results in increasing RER	Peak RER ≥1.10 commonly used as indication of good effort on an incremental test	Good indicator of subject effort
	Averaging practices similar to peak $\dot{V}O_2$	Depends on baseline RER, rate of lactate accumulation, and extent of exercise above V_T		Valuable in determining intrasubject effort during serial testing (ie, pre- and postintervention)
Breathing reserve, %	Relationship between exercise $\dot{V}_E$ and maximal breathing capacity as estimated by the resting maximal voluntary ventilation (MVV)	Low breathing reserve is typical of chronic obstructive lung disease Low reserve also occurs in healthy subjects with high cardiovascular capacity	Normal nonathletes have reserves >20%, but variance is wide	May be insensitive to mechanical ventilatory constraints caused by differences in lung mechanics during exercise and during the MVV maneuver
	Values <15% suggest ventilatory limitation			
$\dot{V}_E/\dot{V}CO_2$ $\dot{V}_E$, l/min BTPS; $\dot{V}CO_2$, l/min STPD	Describes efficiency of pulmonary clearance of CO_2 during exercise	Reflects matching of pulmonary ventilation to perfusion	$\dot{V}_E/\dot{V}CO_2$ slope or submaximal ratio expressions are both typically <30	Index of disease severity in certain chronic disease populations
	Expressed as either a ratio (at nadir near V_T) or a slope over the range of incremental exercise	Indirectly reflects cardiac function secondary to the link between the cardiac and pulmonary systems	Values increase slightly with aging	Abnormalities may indicate pulmonary vascular disease
	For the ratio: averaging practices as for maximal/peak $\dot{V}O_2$			Prognostic in certain chronic disease populations
	For slope: $\dot{V}_E$ is the dependent variable; may include or exclude nonlinear data at near-maximal exercise, reflecting respiratory compensation for lactic acidosis			

(*Continued*)

Table 1. Continued

Variable	Definition and Technical Considerations	Physiological Significance	Normal Response[7]	Clinical Relevance
P_{ETCO_2}, mm Hg	Partial pressure of CO_2 at the end of a tidal breath exhalation	P_{ETCO_2} reflects both ventilation-perfusion matching in the lung and the level of arterial P_{CO_2}	Rest: 36–42 mm Hg	Indicator of disease severity in certain chronic disease populations
			Increases 3–8 mm Hg by V_T	Abnormalities may indicate pulmonary vascular disease
			Decreases from V_T to maximal exercise	Prognostic in certain chronic disease populations
				Low values can also reflect acute or chronic hyperventilation, which may be confirmed by arterial blood gas analysis
Oxygen pulse, mL O_2/beat	$\dot{V}_{O_2}$ divided by heart rate	Equals the product of stroke volume and arterial and venous oxygen content difference	Peak exercise values vary widely by the same factors that affect normal maximal $\dot{V}_{O_2}$ and heart rate	Prognostic in certain chronic disease populations
				A plateau at lower-than-expected value or decrease with increasing work rate suggests low or falling stroke volume
$\Delta\dot{V}_{O_2}/\Delta$WR, $mL \cdot min^{-1} \cdot W^{-1}$	Describes the relationship between $\dot{V}_{O_2}$ and work rate during exercise	For non–steady-state incremental tests, slope is affected by dynamics of cardiac and metabolic responses	Slope is linear with a normal value averaging 10 $mL \cdot min^{-1} \cdot W^{-1}$	Reduction in slope (throughout or during incremental test) reported in a wide range of cardiovascular diseases
	Slope is calculated over incremental portion of test with $\dot{V}_{O_2}$ as the dependent variable	If calculated from steady-state V_{O_2} measured at constant work rates, reflects metabolic and ergonomic efficiency		
	Changes in work rate are known more confidently for cycle tests; walking skill and handrail use can affect actual work rate on treadmill			
Spo_2	Estimated arterial hemoglobin saturation by noninvasive pulse oximetry	Exercise hypoxemia is common in many lung diseases and right-to-left shunt	Decrease by >5% suggests abnormal oxygenation	Prognostic value in some lung disease populations
	Accuracy and bias of measurements vary by device			
	Accuracy can be affected by perfusion, motion, and ambient light		May require verification by arterial blood analysis	

$\dot{V}_{O_2}$ indicates oxygen consumption; V_T, ventilatory threshold; $\dot{V}_E/\dot{V}_{CO_2}$, minute ventilation/carbon dioxide production relationship; P_{ETCO_2}, partial pressure of end-tidal carbon dioxide; $\Delta\dot{V}_{O_2}/\Delta$WR, $\dot{V}_{O_2}$/work rate relationship; Spo_2, oxyhemoglobin saturation; BTPS, body temperature and pressure saturated; STPD, standard temperature and pressure, dry; RER, respiratory exchange ratio; W, watts.

Identified this way, it is called the anaerobic, or ventilatory, threshold (V_T). The relationship between $\dot{V}_{O_2}$ and heart rate is also relevant to health and fitness in that it is related to the concomitant cardiac stroke volume (from the Fick relationship: $\dot{V}_{O_2}/HR = \text{stroke volume} \times Ca_{O_2} - Cv_{O_2}$). The $\dot{V}_E$ needed at any given metabolic rate is dependent on regional matching of pulmonary ventilation to perfusion ($\dot{V}/\dot{Q}$), so the $\dot{V}_E:\dot{V}_{CO_2}$ relationship during exercise is affected by disorders of pulmonary blood flow or airflow. A list of key CPX variables, many of which characterize these relationships, is provided in Table 1. Importantly, heart and lung diseases affect exercise responses to degrees that are often poorly predicted by resting measurements.

Methodology

Most widely used CPX protocols involve incremental exercise on either a treadmill or a cycle ergometer continued to

symptom limitation. Similar analyses apply to tests of either modality, although when comparing data from different sources, we should note that in most subjects, cycle tests result in peak $\dot{V}O_2$ and VT values that average ≈10% lower than treadmill tests.[8]

Carts that measure gas exchange from expired breath during exercise are widely available from commercial manufactures. Although technical specifications vary, basic components include a transducer to measure airflow rates and gas analyzers to measure partial pressures of O_2 and CO_2. Ventilation, $\dot{V}O_2$, and $\dot{V}CO_2$ may be calculated as frequently as breath by breath. Detailed discussions of methods and quality control are available in recent statements.[4,9]

Experience With CPX in Selected Patient Populations

Heart Failure

The relevance of CPX to patients with systolic heart failure (HF) is borne out in both the clinical and research settings by an extensive body of publications spanning >25 years.[10,11] Strong correlations are found between maximal cardiac output, peak $\dot{V}O_2$, and mortality risk.[12] In addition to being limited to a low peak value, $\dot{V}O_2$ may fail to increase normally relative to energy demands as work rate is increased ($\Delta\dot{V}O_2/\Delta WR$),[13] resulting in delayed postexercise recovery of $\dot{V}O_2$.[14] Peak heart rate and the rate of recovery of heart rate after exercise are also reduced.[15,16] In addition to diminished cardiovascular function, HF is associated with adverse effects on pulmonary and skeletal muscle function.[17] As extracardiac effects of chronic HF have gained attention, correlates of these have been identified in the response to CPX.

Exercise ventilation reflects adverse effects of HF on lung mechanics and diffusing capacity, augmented ventilatory drive, and the hemodynamic demands associated with the work of breathing.[18] Alterations in resting pulmonary function and $\dot{V}/\dot{Q}$ matching are manifest during exercise by inefficiency of gas exchange, obligating increased levels of ventilation relative to metabolic rate. This is reflected in a steep relationship between $\dot{V}E$ and $\dot{V}CO_2$ during incremental exercise, decreased partial pressure of end-tidal CO_2 ($PETCO_2$), and elevation of the ratio of ventilatory dead space to tidal volume.[19,20] A distinct oscillatory pattern of $\dot{V}E$ is evident in a subset of patients with HF that may persist from rest through all or part of exercise. The mechanism underlying this finding is debated, but it is associated with more severe HF and worse prognosis.[21]

Skeletal muscle changes in HF include reduced muscle mass and a selective loss of type I fibers having oxidative, fatigue-resistant characteristics compared with type IIa and IIb fibers, which are more dependent on glycolytic energy production. There are strong correlations between reduction in peak $\dot{V}O_2$ and reduction in muscle mass and in inspiratory muscle weakness.[22,23] Peripheral muscle changes in HF are postulated to result from chronic inflammation or other systemic factors and may be compounded by disuse atrophy. These changes contribute to early onset of lactic acidosis (low VT) during incremental exercise, identifying the restricted range of sustainable activity levels, and to delayed adjustment

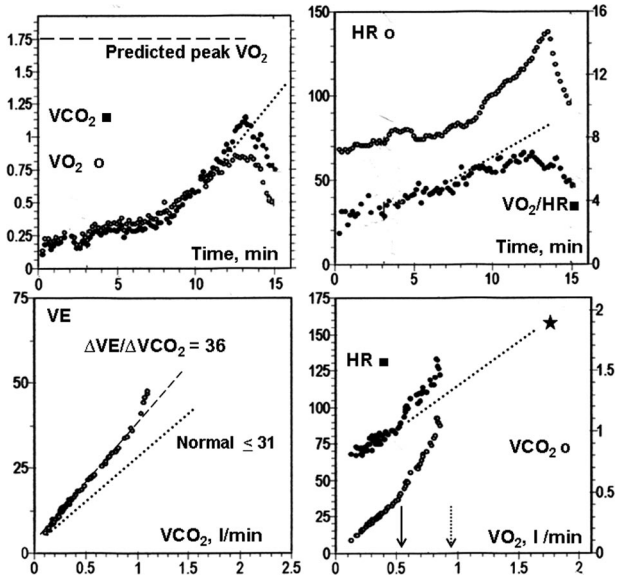

Figure 1. Selected variables measured during cycle ergometer CPX of a 57-year-old man (weight, 61 kg; height, 170 cm) with dilated cardiomyopathy illustrating findings typical of chronic heart failure. $\dot{V}O_2$ and $\dot{V}CO_2$ (top left) and heart rate (HR) and $\dot{V}O_2$/HR (top right) are shown as functions of time (3 minutes of rest, 3 minutes of unresisted cycling, then progressive increase in work rate by 10 W/min). During the final 2 minutes of exercise, the rates of increase of $\dot{V}O_2$ and $\dot{V}O_2$/HR decline relative to the normal responses (dotted lines) and plateau at peak values that are well below normal reference values.[7] The increase in ventilation ($\dot{V}E$) as a function of $\dot{V}CO_2$ (bottom left) is steeper than normal (dotted line). A plot of $\dot{V}CO_2$ as a function of $\dot{V}O_2$ (bottom right) identifies the ventilatory threshold (solid arrow), which is lower than predicted (dotted arrow). The slope of HR as a function of $\dot{V}O_2$ becomes steeper than normal (dotted line) at mid exercise, and neither value reaches predicted maximal values (star). This patient was not receiving β-blockers.

to changes in metabolic rate, manifest as prolonged $\dot{V}O_2$ kinetics at the start[24] and end[14] of exercise. Heightened response to peripheral muscle (ergo-receptor) stimulation of breathing is also reported[25,26] and contributes to the high $\dot{V}E$ response to exercise. Figure 1 illustrates some common findings during CPX in HF.

The CPX variables identified above do not identify a single discrete pathophysiological process as limiting in HF but rather reflect the systemic nature of the condition. Thus, they are readily obtainable measures of disease severity.

Congenital Heart Defects, Valve Disease, and Hypertrophic Cardiomyopathy

The role of routine CPX in the care for patients with congenital heart defects, valve disease, or hypertrophic cardiomyopathy is not established, but a burgeoning body of research suggests potential clinical value of CPX in these populations. Fredriksen et al[27] reported a significantly lower peak $\dot{V}O_2$ in patients with a wide range of conditions, including atrial septal defect, transposition of the great arteries corrected with the Mustard procedure, congenitally corrected transposition of the great arteries, tetralogy of Fallot, Ebstein anomaly, and modified Fontan procedure, compared with healthy control subjects across the adult lifespan. The $\dot{V}E/\dot{V}CO_2$ slope is also significantly higher in

subjects with congenital heart defects (≈30 to >70, depending on congenital defect) compared with healthy control subjects (≈25).[28] Although both the $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ appear to be significant predictors of mortality in noncyanotic congenital defects, the former variable appears to be superior, similar to findings in systolic HF. Surgical procedures to close atrial septal defects[29] or Fontan fenestrations[30] are reported to reduce the $\dot{V}E/\dot{V}CO_2$ slope significantly, whereas only the former procedure significantly increased peak $\dot{V}O_2$. Mitral valve stenosis is also associated with a lower peak $\dot{V}O_2$ and higher $\dot{V}E/\dot{V}CO_2$ slope. Surgical correction of mitral valve stenosis immediately (1 to 4 days) and significantly reduces the $\dot{V}E/\dot{V}CO_2$ slope, whereas a significant increase in peak $\dot{V}O_2$ is apparent several weeks after the procedure.[31,32] Lastly, subjects with hypertrophic cardiomyopathy also demonstrate lower peak $\dot{V}O_2$ and $PETCO_2$ and higher $\dot{V}E/\dot{V}CO_2$ slope or ratio, which correlate with central hemodynamic variables such as pulmonary pressure and left atrial volume.[33,34] Thus, there is increasing information available related to the effects of diverse structural heart diseases on responses that can be measured during clinical exercise testing. Available data indicate that CPX may reflect disease severity in patients with congenital heart defects, valve disease, and hypertrophic cardiomyopathy; reflect favorable responses to surgical interventions in patients with congenital and valve disease; and provide prognostic information in patients with congenital heart defects.

Left Ventricular Dysfunction Secondary to Myocardial Ischemia

The ECG-monitored exercise test has long been used as a first-line evaluation in subjects with suspected myocardial ischemia, albeit with well-established limitations in diagnostic accuracy.[11,35] Although CPX is not routinely used for this purpose, left ventricular dysfunction secondary to exercise-induced myocardial ischemia can be manifest in patterns of the $\dot{V}O_2$ response to exercise.[36] The relevant findings are a decrement in the normal linear increase in $\dot{V}O_2$ relative to work rate or a premature plateau or decline in the ratio of $\dot{V}O_2$/HR, reflecting defects in cardiac output and stroke volume, respectively. Although plateau of either $\dot{V}O_2$ or $\dot{V}O_2$/HR can occur normally late in exercise on attainment of maximal $\dot{V}O_2$, plateau of either variable at a level lower than the expected peak value can be viewed as abnormal. In one study of patients with known coronary disease, these findings had better sensitivity and specificity for exercise-induced ischemia than ECG findings alone.[37]

The validity of these observations is supported by quantitative relationships between the severity of the gas exchange abnormalities and the extent of myocardial ischemia and left ventricular dysfunction, as well as by the responsiveness of these variables to pharmacological and surgical interventions reducing the myocardial ischemic burden.[38,39] Additional data from broadly selected populations are required to define the effect of adding CPX variables on the sensitivity and specificity of exercise testing for the noninvasive detection of myocardial ischemia, how this compares with other evolving diagnostic methodologies, and the type of patient or clinical settings in which these measures are most likely to be useful. Regardless of whether gas exchange measures prove useful in routine testing for ischemic heart disease, recognition of these abnormalities in the course of CPX performed for other purposes may be clinically valuable.

Pulmonary Vascular Disease

Pulmonary vascular diseases impair exercise function through multiple mechanisms. Functional and structural changes in the pulmonary circulation disrupt normal $\dot{V}/\dot{Q}$ matching, with regions of high $\dot{V}/\dot{Q}$ increasing the ratio of physiological dead space to tidal volume and regions of low $\dot{V}/\dot{Q}$ increasing PAO_2 (*alveolar partial pressure of oxygen*)−Pao_2 (*partial pressure of oxygen in arterial blood*). In the absence of blood gas analyses, the noninvasive correlate of the ratio of high dead space to tidal volume is an increase in $\dot{V}E/\dot{V}CO_2$,[40] which is typical of primary or secondary pulmonary vascular disease of any cause. Increased pulmonary vascular resistance can also constrain right ventricular output, reducing systemic oxygen delivery. During CPX, this is reflected in abnormalities of $\dot{V}O_2$ similar to those seen in left-sided HF, including reduced peak $\dot{V}O_2$, $\dot{V}O_2$ at VT, and $\Delta\dot{V}O_2/\Delta WR$. These markers of impaired cardiovascular capacity, together with gas exchange inefficiency, in the absence of clinically evident cardiopulmonary diagnosis raise suspicion for pulmonary vascular disease. Among patients with unexplained exertional dyspnea, a $\dot{V}E/\dot{V}CO_2$ ≥60 and $PETCO_2$ ≤20 mm Hg at VT are highly suggestive of pulmonary hypertension.[41,42]

Among patients with established diagnoses of pulmonary hypertension, reduction in exercise $\dot{V}E/\dot{V}CO_2$ has been reported to be more sensitive than peak $\dot{V}O_2$ to improvements related to pharmacological therapy.[43] This suggests a potential role for CPX in titrating or selecting effective pulmonary hypertension medications, especially as these therapeutic options increase, although this remains to be systematically evaluated. Intra-atrial right-to-left shunting can occur in the setting of pulmonary hypertension if the foramen ovale is patent. The onset of right-to-left shunting during exercise is associated with an abrupt increase in $\dot{V}E$ relative to $\dot{V}O_2$ and $\dot{V}CO_2$, a corresponding increase in respiratory exchange ratio, and a reciprocal increase in $PETO_2$ and decrease in $PETCO_2$. These changes reflect the ventilatory response to a step change in the admixture of venous CO_2 and deoxygenated blood into the systemic arterial circuit.[44] Among patients with idiopathic pulmonary hypertension, this pattern of findings has high concordance with contrast echocardiography for identifying intra-atrial right-to-left shunting[45] and thus can help distinguish among mechanisms of hypoxemia in this population.

Chronic Obstructive Pulmonary Disease

The severity of chronic obstructive pulmonary disease (COPD) is graded by resting pulmonary function tests, but they may not accurately predict exercise impairment in individual patients. This is consistent with the recognition that exercise intolerance in COPD, as in HF, is multifactorial.[46–48] The most obvious mechanism for reduced exercise capacity in COPD is the inability to increase $\dot{V}E$ sufficiently to support higher levels of gas exchange (Figures 2 and 3). Ventilatory limitation has

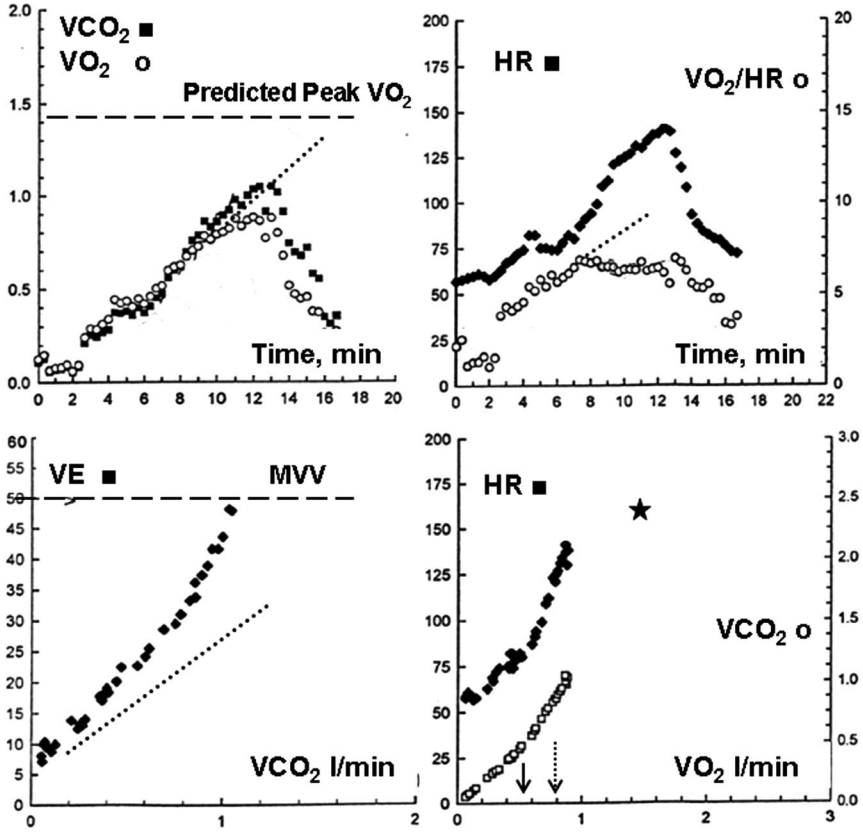

Figure 2. Selected variables measured during CPX of a 60-year-old woman (weight, 167 cm; height, 68 kg) with obstructive lung disease and lung cancer being evaluated for lung resection surgery. Exercise was terminated by leg fatigue, although CPX demonstrates ventilatory limitation and findings suggestive of myocardial ischemia. Test protocol and variables are as defined in Figure 1. Top, Abnormal decreases in the rates of increase of $\dot{V}O_2$ (left) and $\dot{V}O_2$/heart rate (HR; right) relative to the predicted patterns (dotted lines). The changes in slope coincided with development of 2 mm of ST-segment depression in multiple ECG leads (not shown) and with steepening of HR relative to $\dot{V}O_2$ (bottom right). The occurrence of the $\dot{V}O_2$ at VT early in exercise (solid arrow) contributes to the steep slope of $\dot{V}E/\dot{V}CO_2$ (bottom left), leading to attainment of the MVV, indicating ventilatory limitation. The ECG and gas exchange findings suggest the presence of myocardial ischemia, and the peak $\dot{V}O_2$ of 14 $mL \cdot min^{-1} \cdot kg^{-1}$ identifies an increased risk for perioperative morbidity/mortality.

been conventionally defined by breathing reserve of <15%; breathing reserve is the difference between maximal voluntary ventilation (MVV) and peak exercise $\dot{V}E$, expressed as a percent of MVV.[4]

In COPD, this results from the combined effects of a reduction in MVV and the inefficiency of gas exchange, which raises the requirement of $\dot{V}E$ at any given metabolic rate. Although encroachment of $\dot{V}E$ on MVV is strong evidence that breathing mechanics are limiting, it is not an invariant finding in pulmonary patients with dyspnea, and there is general consensus that additional criteria are needed to better define ventilatory limitation.[4] With COPD in particular, it is recognized that lung mechanics may change during exercise as a result of the development of dynamic hyperinflation. The latter refers to an increase in end-expiratory lung volume resulting from incomplete exhalation as breathing frequency and tidal volumes increase. In patients with COPD, hyperinflation has been shown to be closely tied to the severity of exertional dyspnea.[49] Dynamic hyperinflation can be identified by tracking changes in inspiratory capacity measured periodically during CPX.[50] Breath-by-breath recording of spontaneous breathes and inspiratory capacity maneuvers for this assessment are possible with many commercial CPX systems. This may be helpful diagnostically in the evaluation of patients whose symptoms seem disproportionate to the degree of resting airflow obstruction. Exercise hypoxemia can also contribute to exercise limitation in COPD documented by arterial blood analysis or noninvasive estimates of oxyhemoglobin saturation by pulse oximetry (Spo_2). Although less accurate than blood gases, a decrease in Spo_2 by >5% is generally considered abnormal, and sustained values <88% may justify oxygen therapy. Hypoxemia appears more pronounced in COPD during walking tests compared with cycling, so the former is recommended for determining need for oxygen therapy.[51] In addition to screening for hypoxemia, CPX may identify whether lung mechanics or another factor such as skeletal muscle weakness is the proximal cause of exercise limitation for tailoring rehabilitation interventions.

Interstitial Lung Diseases

A heterogeneous group of diseases result in distortion and fibrosis of the lung parenchyma, decreasing breathing capacity and impairing gas exchange. Abnormal gas exchange is most precisely identified by calculation of the ratio of physiological dead space to tidal volume and $P_{AO_2} - P_{aO_2}$ from arterial blood gas and expired gas analyses.[52] These can be the earliest detectable physiological abnormalities in chronic interstitial lung disease[53,54] and, although not specific to a particular disease, can provide supporting evidence for diagnostic or medicolegal investigations. In addition to reducing breathing capacity, there are multiple secondary effects of interstitial lung diseases on gas exchange, work of breathing, and the pulmonary circulation[55] such that CPX results often appear typical of cardiovascular limitation[56] as described above for pulmonary vascular disease, rather than demonstrating mechanical ventilatory limitation. Exercise hypoxemia may be marked in patients with advanced interstitial lung disease and cause exercise limitation. Both peak $\dot{V}O_2$[57,58] and the presence or degree of arterial hypoxemia

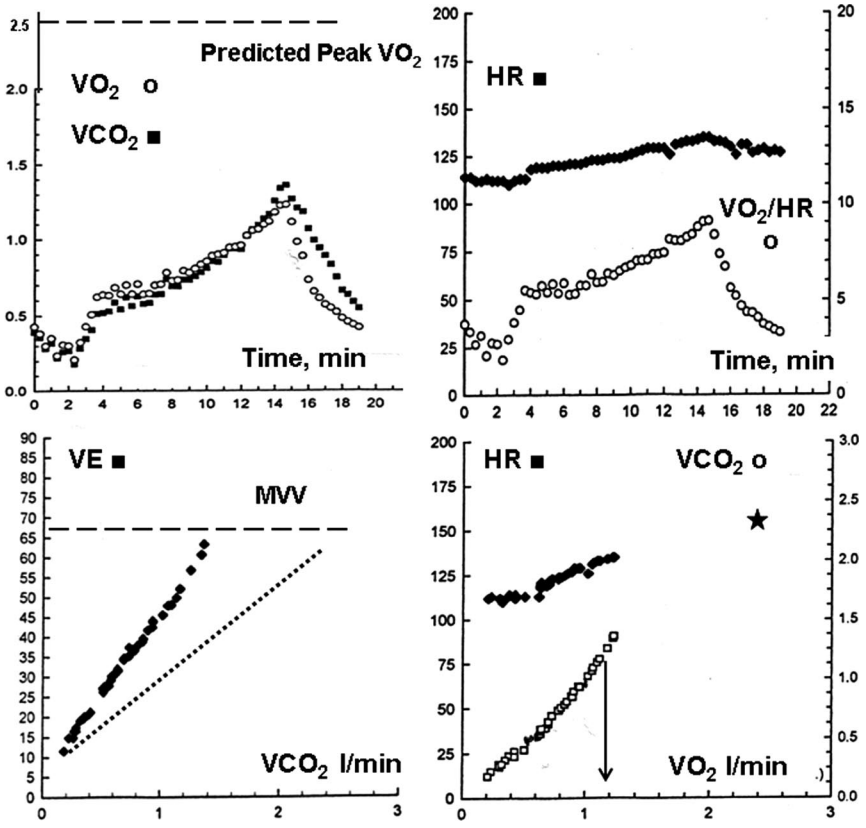

Figure 3. Selected variables measured during CPX of a 59-year-old man (weight, 80 kg; height, 172 cm) with moderate COPD evaluated for exertional symptoms disproportionate to his resting pulmonary function abnormalities. Findings illustrate clear ventilatory limitation occurring primarily because of high $\dot{V}_E$ requirements. Work rate increment was 15 W/min; otherwise, the protocol and variables are as defined in Figure 1. The increase in $\dot{V}_E$ relative to $\dot{V}_{CO_2}$ (bottom right) is steeper than the upper limit of normal (dotted line), and exercise is terminated when $\dot{V}_E$ reaches MVV. Exercise ends shortly after the patient exceeded the $\dot{V}_{O_2}$ at VT, (arrow, bottom right), which occurs at a normal level, so $\dot{V}_{O_2}$ at VT is a high percentage of peak $\dot{V}_{O_2}$. HR indicates heart rate.

during CPX[57] or 6-minute walk[59,60] are predictive of prognosis in certain interstitial diseases.

Application of CPX in the Clinical Care of Patients With Cardiopulmonary Diseases

The application of CPX to the care of patients with heart and lung diseases has been most extensively reported in the context of prognostic assessment of candidates for heart transplantation, certain other preoperative risk assessments, prerehabilitation evaluation, and diagnostic evaluation of unexplained exertional dyspnea.

Prognostic Assessment of Candidates for Transplantation or Other Major Interventions

The ability of CPX variables to predict adverse events in patients with systolic HF represents one if its clearest clinical utilities, particularly with respect to consideration of major interventions when accurate estimation of prognosis without the intervention is needed.[10] Since the demonstration by Mancini et al[61] that peak $\dot{V}_{O_2}$ identified patients for whom heart transplantation could be delayed without excess mortality, CPX has been incorporated into recommendations for the pretransplantation assessment of HF patients.[10] Subsequently additional variables from CPX have been identified as prognostic in this population, including the $\dot{V}_E/\dot{V}_{CO_2}$ slope, which appears to have superior prognostic power compared with peak $\dot{V}_{O_2}$. A multivariate approach further improves the ability to identify individuals at greatest risk.[12] Four-level classification systems have been developed for both peak $\dot{V}_{O_2}$[56] and, more recently, the $\dot{V}_E/\dot{V}_{CO_2}$ slope (Table 2).[62,63]

Prognosis appears to be most favorable for subjects with a $\dot{V}_E/\dot{V}_{CO_2}$ slope and peak $\dot{V}_{O_2}$ of <30 and >20 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, respectively. Conversely, patients with a $\dot{V}_E/\dot{V}_{CO_2}$ slope >45 and peak $\dot{V}_{O_2}$ <10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ appear to have a particularly poor prognosis. Intermediate values predict intermediate risk. It should be noted that both $\dot{V}_E/\dot{V}_{CO_2}$ slope and peak $\dot{V}_{O_2}$ maintain robust prognostic value in subjects receiving β-blocker therapy, although the improvement in prognosis associated with this treatment alters the absolute level of risk associated with a given exercise value.[64,65] Consistent with the normal variation in peak $\dot{V}_{O_2}$ by age and sex, it has been reported that a percent-predicted expression[66] or use of gender-specific[67,68] interpretations of peak $\dot{V}_{O_2}$ improves its prognostic accuracy.

Other CPX variables demonstrated to predict adverse events in patients with systolic HF include the P_{ETCO_2} at rest

Table 2. Weber and Ventilatory Classification Systems Used in Chronic Heart Failure

	Weber Class		Ventilatory Class	
Disease Severity		Peak $\dot{V}_{O_2}$ (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)		$\dot{V}_E/\dot{V}_{CO_2}$ Slope
Mild to none	A	>20	I	≤29.9
Mild to moderate	B	16–20	II	30.0–35.9
Moderate to severe	C	10–16	III	36.0–44.9
Severe	D	<10	IV	≥45.0

$\dot{V}_{O_2}$ indicates oxygen consumption; $\dot{V}_E/\dot{V}_{CO_2}$, minute ventilation/carbon dioxide production relationship.

and exercise,[69,70] the oxygen uptake efficiency slope[71] (ie, relationship between log-transformed $\dot{V}_E$ and $\dot{V}_{O_2}$), exercise oscillatory ventilation,[72] and heart rate recovery.[15] An expanded multivariate model including a number of these additional CPX variables may provide higher prognostic discrimination in patients with systolic HF.[73] In this model, the combined assessment of the $\dot{V}_E/\dot{V}_{CO_2}$ slope, heart rate recovery, oxygen uptake efficiency slope, resting P_{ETCO_2}, and peak $\dot{V}_{O_2}$ improved prediction of death or a composite end point of adverse events compared with individual variables. Additional research is needed to determine the utility of this or other models in predicting specific outcomes or in characterizing the risk profile of subsets of patients before advocating their use in decision making regarding the selection of patients for heart transplantation or other major interventions.

There are fewer data related to prognosis in patients with HF and preserved systolic function, but initial investigations indicate that CPX reflects disease severity[74,75] and provides prognostic information[76,77] in these patients as well. This is consistent with observations that exercise capacity correlates better with indexes of diastolic than systolic function among patients with systolic HF.[78] Future research is needed to refine the list of clinically accepted CPX variables serving as prognostic markers in patients with systolic HF and to determine their value in those with isolated diastolic dysfunction. Another relatively unexplored issue is the effect of comorbid conditions on the prognostic accuracy of the variables discussed above. Because pulmonary and pulmonary vascular diseases may independently influence the same variables used to assess prognosis in HF, this could either enhance the prognostic power of the findings if the added burden of disease contributes to outcome or alternatively contribute "noise" to the assessment.

The American Heart Association guidelines for exercise testing identify the use of CPX to assess the "response to therapy" as a Class I indication in assessment of patients with HF for transplantation.[11] Independently of the consideration of heart transplantation, CPX has been widely used to assess the efficacy of interventions for HF in clinical trials.[12,79] Using CPX to assess responses to interventions is less common in clinical practice. A robust body of literature demonstrates that variables such as $\dot{V}_E/\dot{V}_{CO_2}$ slope and/or peak $\dot{V}_{O_2}$ are responsive to improvement in function associated with pharmacological (β-blockade, inhibition of the renin-angiotensin-aldosterone axis, sildenafil), device (cardiac resynchronization therapy), and lifestyle (exercise training) interventions.[12,79] Given the reliability of CPX and its ability to objectively quantify disease severity and prognosis, this evaluation technique should provide meaningful information regarding clinical status and so appears reasonable before and after significant alterations in patients' management.

Fewer data are available on the use of CPX in decision making regarding lung compared with heart transplantation. Candidates for lung transplantation come from a number of distinct clinical populations, and the timing and priority for this procedure vary by underlying disease. Exercise capacity identifies mortality risk in a number of these populations, eg, COPD,[80] idiopathic pulmonary fibrosis,[81] and idiopathic pulmonary hypertension.[82] Most of the data related to exercise and mortality in these groups are based on the distance walked on a 6-minute walk test, which is incorporated into recommendations for transplant assessment for COPD, idiopathic pulmonary fibrosis, and idiopathic pulmonary hypertension put forth by the International Society of Heart and Lung Transplantation.[83] Whether variables derived from CPX would provide additive or improved discriminatory value relative to results of simpler exercise tests in patient selection for lung transplant has not been defined.

Exercise capacity is also predictive of perioperative morbidity and mortality for patients undergoing surgical resection of lung cancer. In contrast to the situation for transplantation, functional capacity may be expected to be reduced by lung resection procedures, so exercise testing is performed to identify whether physiological reserve is sufficiently high to tolerate the anticipated surgery[84,85] rather than sufficiently low to justify it. Physiological reserve can be evaluated a number of ways, ranging from simple walking or stair climbing to formal assessment of peak $\dot{V}_{O_2}$, which, in contrast to pulmonary function tests, reflect overall cardiac, pulmonary, and metabolic function (Figure 2). In general, peak $\dot{V}_{O_2}$ of >20 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ on incremental cycle ergometry is predictive of the ability to tolerate resection as large as pneumonectomy, whereas values <10 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ predict high risk for resection of any extent. Increased rates of complications and deaths are reported in various series for patients whose preoperative peak $\dot{V}_{O_2}$ is <12, 15, or 16 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$.[84,86,87] Because of the poor prognosis associated with unresected lung cancer, however, peak $\dot{V}_{O_2}$ values in this range may serve more for informing risk-benefit discussions or consideration of limited (eg, wedge) resections rather than absolutely precluding surgery. Indeed, it has been argued that CPX should be used more broadly, specifically to avoid excluding patients from potentially curative procedures on the basis of the demonstration that peak $\dot{V}_{O_2}$ >15 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ predicts a high likelihood of tolerating surgery even if pulmonary function values might be considered exclusionary by some algorithms.[87] Recent consensus statements differ somewhat regarding the use of CPX in operative assessments. The European Respiratory Society endorses exercise testing, preferably with peak $\dot{V}_{O_2}$, for any lung resection candidate with resting forced expiratory volume in 1 second (FEV_1) or diffusion capacity for carbon monoxide $<80\%$ of predicted.[88] The American College of Chest Physician's most recent guidelines recommend first calculating the expected postoperative FEV_1 and diffusion capacity for carbon monoxide values and performing CPX if either is $<40\%$.[85]

Cardiac and Pulmonary Rehabilitation

Exercise training is a core component of both cardiac[89] and pulmonary[90] rehabilitation programs. In addition to characterizing patients' limitations, prerehabilitation exercise testing is used to screen for adverse effects of exercise such as ischemia, arrhythmia, or hypoxemia and to develop a training prescription.[4,91] Although these goals do not necessarily require measurement of gas exchange, CPX can be uniquely helpful in designing training regimens that are effective and

tolerable. Aerobic exercise prescriptions ideally entails ≥30 minutes of moderate- to vigorous-intensity exercise several days per week.[92] Effectiveness of training is greatest if the intensity is high, ie, at or above the $\dot{V}O_2$ at $\dot{V}T$, but not so high as to be unsustainable, precluding adherence. Consistent with this, cardiac rehabilitation exercise typically targets heart rate or work rates that are 50% to 80% of measured peak.[89] In COPD, when peak capacity is truncated by ventilatory limitation, $\dot{V}O_2$ at VT may be an unusually high percentage of peak, as illustrated in Figure 3. Exercise training at a high percentage, eg, 80% to 90%, of maximum capacity is therefore commonly feasible and recommended for rehabilitation in this population.[93,94] Determining the $\dot{V}O_2$ at VT by CPX can thus aid individualized exercise prescriptions, although in practice, training levels are often approximated from peak heart rate or work rate and titrated to patients' tolerance.

Comorbid conditions are common among patients in rehabilitation programs and may have an important influence on outcomes. COPD is reported to have a prevalence of 4% to 27% among patients undergoing coronary bypass grafting[95] and 20% to 30% among patients with chronic HF.[96,97] Similarly, cardiovascular disease is common among patients with COPD.[98,99] The potential for coexistent heart and lung disease to have interactive effects on exercise tolerance is illustrated by data in Figure 2.

HF and COPD are both associated with changes in peripheral muscle,[100] and muscle function has been identified as an important factor in impairment in both of these groups.[101,102] Although this might suggest that patients with coexistent heart and lung disease would be particularly benefited by exercise rehabilitation, some data suggest that the presence and burden of comorbid conditions are predictive of ineffectiveness of exercise rehabilitation interventions.[99,103] Given the frequency of coexistent heart and lung disease and the implications this has for functional prognosis, there is remarkably little reported specifically about exercise responses in patients with mixed disease.[104] There is clearly a need to better define the interactive effects of coexistent heart and lung diseases on functional capacity and the most effective approaches to these patients in the rehabilitation setting.[105]

Diagnostic Evaluation of Patients With Dyspnea

Exercise testing is used in the evaluation of dyspnea, both for the targeted diagnosis of suspected exercise-induced asthma (EIA) and in the more comprehensive evaluation of the dyspneic patient with a broad differential diagnosis. Although exercise is less sensitive for eliciting nonspecific bronchial hyperreactivity than is methacholine inhalation, it is more specific than the latter for the diagnosis of EIA.[106] Testing to identify EIA is indicated in the setting of high-risk professions or sports that could be contraindicated by this finding, to support the use of medications for EIA in competitive athletes, or to assess the effectiveness of pharmacological therapy in established EIA. For this purpose, testing uses a brief high-intensity exercise stress rather than a graded protocol and includes serial spirometry.[107] Although measuring gas exchange is not essential in these tests, it is useful for documenting the physiological intensity of the exercise, particularly if the results are negative.

Table 3. Variables Commonly Used in CPX for Diagnostic Evaluations of Exercise Intolerance

Variables Reflecting Cardiovascular Function	Variables Reflecting Ventilatory Function	Variables Reflecting Pulmonary Gas Exchange Efficiency
Peak $\dot{V}o_2$	Breathing reserve	Ratio of physiological dead space to tidal volume
$\dot{V}o_2$ at VT	Tidal volume:breathing frequency relationships	$\dot{V}E/\dot{V}co_2$
$\Delta\dot{V}o_2/\Delta WR$	Inspiratory capacity and end-expiratory lung volume	Pao_2 and $PAo_2 - Pao_2$
$\dot{V}o_2/HR$	Pre- and postexercise spirometry	Spo_2 by pulse oximetry
ECG		
Blood pressure		

WR indicates work rate; HR, heart rate; $\dot{V}o_2$, maximal or peak oxygen consumption; VT, ventilatory threshold; $\dot{V}E/\dot{V}co_2$, minute ventilation/carbon dioxide production relationship; $\Delta\dot{V}o_2/\Delta WR$, $\dot{V}o_2$/work rate relationship; Spo_2, oxyhemoglobin saturation; PAO_2, Alveolar partial pressure of oxygen; PaO_2, partial pressure of oxygen in arterial blood. Measured values differing from reference values imply impairment in organ system function, which may or may not be limiting to overall performance. See text for definitions.

CPX is widely recommended for diagnostic evaluation of patients with chronic unexplained dyspnea.[4,108] In published series of such patients, most are eventually found to have either cardiac or pulmonary disorders,[109–111] but the spectrum of underlying conditions is wide and includes metabolic, endocrine, neurological, psychiatric, and gastrointestinal disorders, among others. CPX provides an objective measure of exercise capacity and allows analysis of patterns of response of $\dot{V}O_2$ and other variables to characterize the nature of exercise limitation. Diagnostic algorithms have been developed to compare test results with findings from normal subjects and from patients with known clinical diagnoses.[1,2] These analyses are dependent on the appropriateness of the reference values chosen for comparison and by the sensitivity and specificity of abnormal findings for particular disease states. Some exercise variables, including peak $\dot{V}O_2$ and $\dot{V}O_2$ at VT, have relatively wide ranges in healthy population because they vary by demographic factors and by physical training status.[112] Consistent with this, some find CPX to be insensitive for distinguishing between deconditioning and mild cardiovascular disease.[111] Other response patterns defined by CPX such as $\dot{V}E/\dot{V}CO_2$ and $\Delta\dot{V}O_2/\Delta WR$, on the other hand, have narrow confidence limits in healthy populations and are unaffected by fitness.[7,113,114] These are therefore useful for discriminating between normal and abnormal, although abnormalities are not necessarily specific to any single disease. For example, $\Delta\dot{V}O_2/\Delta WR$ can be reduced in a wide range of cardiovascular disorders.[13] Similarly, as discussed above, $\dot{V}E/\dot{V}CO_2$ may be elevated in any pulmonary, pulmonary vascular, or cardiac diseases that alter pulmonary $\dot{V}/\dot{Q}$. Hansen et al[115] have reported that despite qualitatively similar changes in $\dot{V}E/\dot{V}CO_2$, qualitative differences in the relation between mixed expired and end-tidal concentrations of CO_2 distinguish between the $\dot{V}/\dot{Q}$ derangements resulting from airflow disease and those caused by circulatory defects.

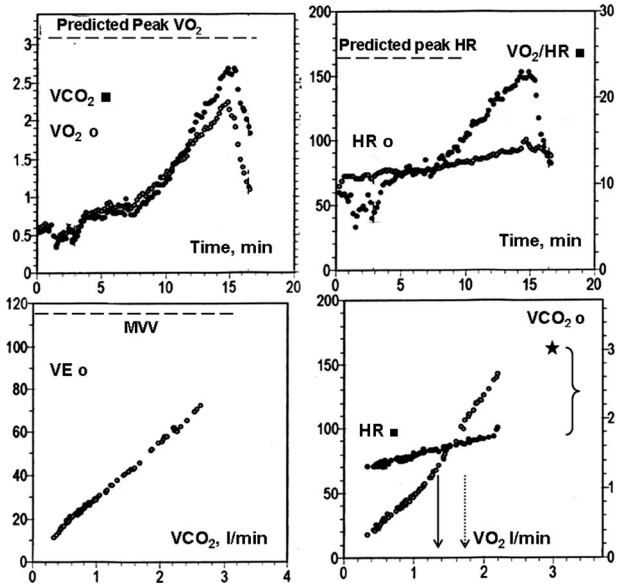

Figure 4. Selected variables from CPX performed to evaluate unexplained dyspnea in a 55-year-old man (weight, 168 kg; height, 185 cm) with asthma, diabetes mellitus, and obesity, illustrating findings of chronotropic insufficiency. Work rate increased by 20 W/min; otherwise, the protocol and variables are as defined in Figure 1. Exercise was limited by dyspnea without chest pain or ischemic ECG changes. Peak $\dot{V}O_2$ (top left) is below predicted. The $\dot{V}O_2$ at VT (solid arrow, bottom right) is at the lower limit of the normal range (average normal, dotted arrow) and occurred at the midpoint of the test, resulting in a peak gas exchange ratio (not shown) of 1.2, indicating good effort. The peak heart rate (HR) of 94 (top and bottom right) is far below predicted (bracket, bottom right). The slope of HR relative to $\dot{V}O_2$ is abnormally shallow over the entire range of exercise (bottom right), and peak $\dot{V}O_2$/HR (top right) is higher than predicted, implying a compensatory increase in stroke volume. The patient was not taking medications altering HR, so the findings reflect chronotropic insufficiency. The $\dot{V}E\dot{V}CO_2$ slope (bottom left) and postexercise spirometry (not shown) were normal.

Whether analyses of mixed expired CO_2 (readily derived from $\dot{V}E$ and $\dot{V}CO_2$ measures during CPX) can accurately identify mild degrees of circulatory or lung disease or reliably attribute symptoms among coexistent diseases in medically complex patients has not been explored.

Because many exercise abnormalities are not specific for discrete diseases, recommendations for the use of CPX in evaluation of dyspnea are often framed in terms of distinguishing between patterns of cardiovascular and pulmonary limitation for the purpose of directing further testing rather than in making specific diagnoses.[108] Variables commonly used for identifying patterns typical of cardiovascular, ventilatory, and gas exchange dysfunction are shown in Table 3. As noted however, primary cardiac and pulmonary conditions often have secondary effects on the other, and either can alter gas exchange efficiency. Designation of variables as purely cardiac or pulmonary is therefore overly simplistic. Indeed, a frequent motivation for diagnostic CPX is to identify the proximal cause of exercise limitation and effects of interacting organ system dysfunction in patients who have multiple known diagnoses with potential effects on exercise function.[116]

Some clinical conditions underlying dyspnea do result in sufficiently unique findings on a standard CPX protocol to make a precise diagnosis such as an exercise-induced arrhythmia or chronotropic incompetence, as illustrated in Figure 4. Although these particular diagnoses are defined by the ECG, demonstration of their physiological and functional significance may depend on concomitant findings in pulmonary gas exchange. Additional specific diagnoses may be made by CPX if the pretest clinical suspicion is sufficiently high to prompt inclusion of specialized measurements needed for their confirmation. Examples include assessment of changes in inspiratory capacity to identify dynamic hyperinflation resulting from airflow obstruction, laryngoscopy to identify exercise-induced laryngeal dysfunction, or serial spirometry for EIA.

Several small single-center series support the concept that CPX provides unique and valuable information in the evaluation of patients with dyspnea,[110,111,117,118] and it is widely advocated[4] and used[116] for this purpose. Although there are no large series defining the diagnostic accuracy or cost effectiveness of CPX in this context, it is reasonable to expect that it is most effective used early in the evaluation to help focus diagnostic testing in areas most likely to be revealing or to limit invasive diagnostic tests in patients, for example, whose findings are nonpathological and characteristic of uncomplicated obesity or deconditioning.

Summary

The aerobic exercise assessment provides a wealth of clinically valuable information in patients with cardiac or pulmonary diseases. The addition of ventilatory and gas exchange measurements to the ECG and blood pressure monitoring used in conventional exercise tests provides more precise determination of aerobic capacity and unique insight into the independent and coupled functions of the cardiovascular, pulmonary, and skeletal muscle systems. Currently, the most widely used applications of CPX are the evaluation of patients diagnosed with systolic HF, preoperative assessment of selected patient populations, and diagnostic evaluation of patients with dyspnea. With widespread availability of commercial instruments for readily measuring pulmonary gas exchange, exercise function is being characterized for an increasing number of patient populations and diverse clinical situations, with the potential that the use of CPX in clinical practice will continue to expand.

Disclosures

None.

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