

Cardiopulmonary Exercise Testing: Relevant But Underused

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Abstract: Cardiopulmonary exercise testing (CPX) is a relatively old technology, but has sustained relevance for many primary care clinical scenarios in which it is, ironically, rarely considered. Advancing computer technology has made CPX easier to administer and interpret at a time when our aging population is more prone to comorbidities and higher prevalence of nonspecific symptoms of exercise intolerance and dyspnea, for which CPX is particularly useful diagnostically and prognostically. These discrepancies in application are compounded by patterns in which CPX is often administered and interpreted by cardiology, pulmonary, or exercise specialists who limit their assessments to the priorities of their own discipline, thereby missing opportunities to distinguish symptom origins. When used properly, CPX enables the physician to assess fitness and uncover cardiopulmonary issues at earlier phases of work-up, which would therefore be especially useful for primary care physicians. In this article, we provide an overview of CPX principles and testing logistics, as well as some of the clinical contexts in which it can enhance patient care.

Keywords: cardiopulmonary exercise testing; functional capacity; diagnosis; prognosis

Introduction

Cardiopulmonary exercise testing (CPX) provides information regarding the body's response to exercise. Cardiovascular performance and ventilatory criteria are assessed during a progressive-intensity exercise stimulus to provide an integrated analysis of the physiologic responses required by the cardiovascular (CV) and respiratory systems to meet the metabolic demands of the skeletal muscle (ie, the primary consumers of oxygen [O₂] during exercise).^{1,2} This reflects a complex physiology rooted in basic cellular metabolic needs and the body's capacity to sustain them. Although CPX has become generally well established among cardiology, pulmonary, and sports medicine providers as a means to assess heart failure (HF), respiratory disease, or athletic capacity, many specialists administering CPX tend to organize the data and interpretations with emphasis on their own clinical priorities, often omitting more comprehensive assessments that may be useful in relation to primary care patients (ie, clinical scenarios in which diagnoses and pertinent physiology may not have been clear beforehand). For example, CPX can be used to clarify the etiology of exercise intolerance and unexplained dyspnea among the growing patient population with multiple chronic comorbidities, yet few primary care physicians routinely consider CPX for such common complaints. Therefore, in this review, we provide an overview of CPX principles and testing logistics, as well as some of the clinical contexts in which it can enhance patient care.

The fundamental premise of CPX is that assessment of inhaled O₂ and exhaled CO₂ gas exchange during physical stress provides perspective on the overall physiology of

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the body. The energy required to perform the mechanical work of exercise is derived from hydrolysis of adenosine triphosphate (ATP). Skeletal muscle stores very little ATP, and therefore sustained exercise requires that ATP be replenished rapidly through metabolism of fuels (fats and carbohydrates). Cardiopulmonary exercise testing reflects performance capacities of heart, lungs, vasculature (ie, respiration and circulation), and blood to sustain the O_2 delivery and removal of CO_2 that are critical for cellular homeostasis. If pathology is present that impedes functional capacity, CPX can assist in identifying which parts of the physiologic system are responsible.

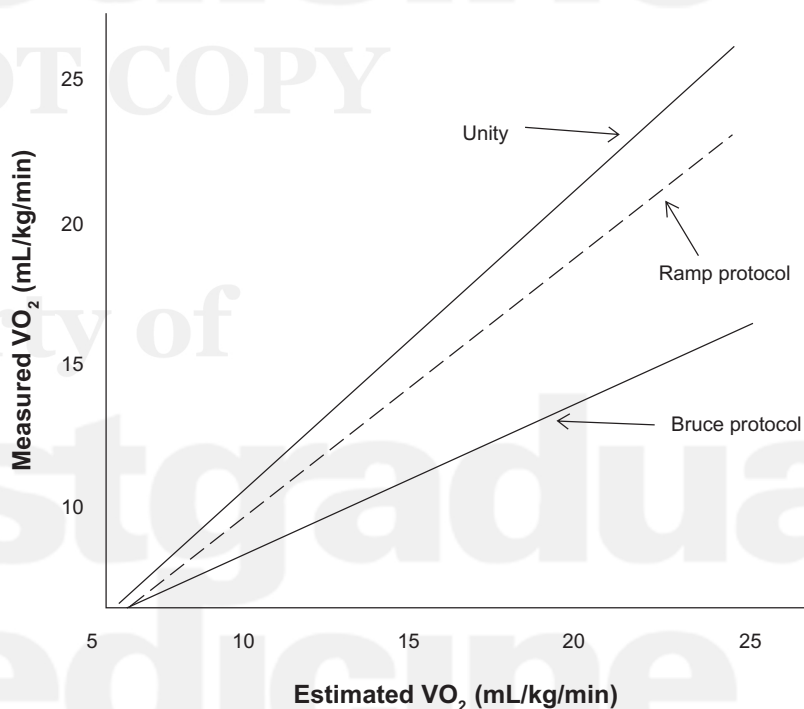
Functional Capacity

Functional capacity has been repeatedly demonstrated to be one of the most important measures provided by exercise testing.³⁻⁵ Despite these important implications, exercise quantification is often relatively simplistic (ie, usually expressed as tolerated time on a specific exercise protocol). Studies have demonstrated that familiarization, fluctuations in motivation, and the characteristics of protocols can confound such exercise assessments, leading many to question the value of exercise-based evaluations.

In comparison, functional-capacity assessments based on ventilatory gas exchange have significantly increased reliability, reproducibility, and clinical utility.⁶ Instead of time, the exercise measurements are based on metabolic function (ie, O_2 uptake per unit of time and related parameters of CV and respiratory performance). This provides a basis for a much more dependable assessment of function-based prognostic parameters and greater discrimination of physiological factors that cause functional limitations.⁷

The concept of measuring O_2 utilization of maximal oxygen uptake (VO_{2max}) with CPX is related to the concept of reporting metabolic equivalents (METs) from standard exercise testing protocols. However, METs provided during routine tests are only estimated using linear-regression equations, and are not based on patients with chronic conditions.⁸⁻¹⁰ Therefore, while 1 MET is, by definition, equivalent to an oxygen utilization of $3.5 \text{ mL}O_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, reliance on estimated METs significantly overestimates oxygen utilization (Figure 1). Using CPX to directly measure ventilatory inhaled and exhaled gases during exercise, and thereby determine the true VO_2 , provides a significantly more accurate quantification of functional capacity.

Figure 1. Slope of the relationship between measured and estimated oxygen uptake using the ramp and Bruce treadmill protocols in patients with heart failure. The unity line would be achieved if the predicted value were equal to the estimated value. These data demonstrate that measured maximal oxygen uptake (VO_2) is overpredicted by estimated values in exercise tests performed on patients with heart disease, particularly when using the Bruce protocol. In contrast to the Bruce protocol, exercise estimates achieved using a ramp protocol are much closer to the line of unity, highlighting that the choice of exercise protocol has a substantial impact on the accuracy with which VO_2 is estimated.



Gas Exchange Technology

The acquisition of VO_2 and related CPX variables requires the ability to measure 3 responses during inspiration and expiration: 1) the concentration of O_2 ; 2) the concentration of CO_2 ; and 3) a quantification of ventilation, usually the minute ventilation (VE), which refers to both tidal volume and respiratory rate. The exchange of O_2 and CO_2 are assessed while breathing room air through a mouthpiece and wearing a nose clip, or using a face mask that covers the nose and mouth simultaneously. Inhaled and exhaled gases are analyzed in real time using fast-responding, computer-linked analyzers. VO_2 can be described as the product of VE and the fraction of O_2 that has been utilized by the working muscle. A valid test interpretation is crucially dependent on the calibration of airflow and gases (O_2 and CO_2) that are performed immediately prior to testing. Modern commercially available systems have convenient calibration procedures controlled by a microprocessor that reduces the occurrence of errors.¹¹ The new CPX systems also adjust automatically for ambient conditions that affect the concentration of O_2 in the inspired air (ie, temperature, barometric pressure, and humidity).

Cardiac Responses to Exercise

Sustained exercise requires increased O_2 supply to meet metabolic needs. Normal exercise responses include increased systolic arterial pressure (normal response, 10 ± 2 mm Hg/MET) in association with reduced vascular resistance to facilitate increased muscle perfusion. Increased venous return to the heart, accelerated heart rate (HR), and increased systolic function increase cardiac output (CO). In healthy adults, adding upper-extremity work will increase CO even in someone who is already exercising at maximal lower extremity exercise,¹² highlighting that energy demands are the dominant determinant of CV responses. Among patients with CV disease, pathological limitations in CO are likely to restrict maximal exercise.

Systolic pump failure, diastolic filling abnormalities, and chronotropic incompetence are some of the cardiac factors that can diminish exercise performance. Peripheral pathophysiology is also relevant; HF-related vasoconstriction and skeletal muscle myopathy exacerbate functional limitations and decrease VO_2 .¹³ Thus, while it may initially seem counterintuitive that a ventilation index is a criterion for heart disease,¹⁴ peak VO_2 is a robust marker of CV performance.

Patterns of ventilation also correspond to cardiac function; advanced HF is associated with less-efficient breathing (ie, more rapid and shallow breathing character-

istics). Inefficient pulmonary gas exchange, intrinsic diaphragm muscle weakening, and abnormal peripheral skeletal muscle stimuli to the lungs are all factors that contribute to cardiac-based ventilatory abnormalities.¹⁵

Respiratory Responses to Exercise

Skeletal muscle metabolism during exercise leads to increased intramuscular CO_2 production. However, partial pressure of CO_2 in the blood is maintained constant in healthy adults by the homeostatic capacity to increase ventilation efficiently. Among adults with pulmonary disease, ventilatory limitation of exercise is more likely to occur such that VE is unable to keep pace with CO_2 production, resulting in hypercapnia.

When VE fails to keep pace with demand, partial pressure of arterial O_2 can also decrease; therefore, hypoxemia and arterial O_2 desaturation with exercise is more likely to occur in adults with pulmonary disease. Still, responses vary from person to person, with individual differences in pulmonary capillary perfusion, pulmonary dead space, respiratory drive, metabolism, and pulmonary pressures leading to a wide range of CPX abnormalities. Moreover, just as cardiac patients may have intrinsic skeletal muscle abnormalities that limit exercise capacity, pulmonary disease may also be associated with skeletal muscle myopathy, diminishing exercise capacity and increasing dyspnea due to intrinsic peripheral muscle dysfunction.

Technical Considerations Patient Referral

Absolute and relative contraindications to exercise testing have long been established by the American Heart Association, American College of Cardiology,¹⁶ American Thoracic Society, and American College of Chest Physicians.¹⁷ Unstable angina, uncontrolled arrhythmias, or severe aortic stenosis are unequivocal reasons that exercise provocation should be avoided or postponed until the patient's medical condition has been stabilized. However, relative contraindications for stress testing, such as moderate stenotic valvular disease, hypertrophic cardiomyopathy, and/or history of sudden death can usually be safely managed in laboratories staffed by appropriately trained health care professionals and overseen by a trained physician.¹⁸ In fact, CPX may be particularly useful in such circumstances, such as when the degree of exercise intolerance or dyspnea exceed what one might expect from moderate aortic stenosis, myopathy, or other cardiac pathology. It distinguishes the extent of exercise limitation attributable to cardiac etiology versus pulmonary etiology versus other sources. It is also important

to appreciate that clinical obstacles regarded as relative contraindications to exercise testing (eg, frailty or obesity) can usually be achieved by careful selection of the exercise modality (treadmill vs bicycle vs arm ergometer), intensity of testing, and appropriate testing supervision.

Generally, patients should abstain from ingesting caffeine for 12 hours and/or eating within 3 hours prior to CPX and come to the test in clothes suited for exercise. While food restrictions prior to exercise testing are a common source of concern for patients, eating limitations prior to CPX are generally much easier to achieve and tolerate than the relatively more rigid and prolonged fasting criteria required for nuclear perfusion stress testing. The goal in CPX is only to reduce food and caffeine effects on exercise performance, whereas food restrictions for nuclear perfusion scanning (eg, sestamibi or positron-emission tomography scans) are implemented to avoid blunting of the adenosine-induced coronary vasodilation by caffeine, and distortion to cardiac imaging that can result from digestion-induced blood flow to the stomach. Unfortunately, many patients arrive for stress tests wearing unsuitable clothing. Patients should therefore be instructed to wear comfortable clothes and footwear on the day of testing, and women should be encouraged to wear a sports bra. In most instances, patients undergo CPX while maintaining all routine medications, including beta-blockers.

Mode of Exercise: Treadmill Versus Cycle Ergometer

Assessment of functional capacity is usually performed on a motorized treadmill or a stationary lower extremity (cycle) ergometer. The treadmill is the most common exercise testing modality in the United States, whereas the cycle ergometer is the preferred modality in most European countries. Whether the treadmill or the cycle ergometer is better for testing has been a subject of much debate.¹⁹ Upright cycle ergometry may be preferred in subjects with gait or balance instability or orthopedic limitations. Although many obese patients might similarly benefit from a bicycle modality, this option is often limited by the fact that maximum weight restrictions on many commercially available cycle ergometers often preclude their use.

Although many assert that treadmill exercise is more natural and reflects greater overall muscle use, it is also frequently criticized because patients tend to rely on handrails, which confound assessments of work capacity. An advantage of gas exchange measurements over estimated METs is that directly measured ventilatory gases provide a more accurate assessment of exercise performance whether or not

a patient is using the handrails (ie, O_2 utilization will merely be lower in someone who leans on the handrails compared with someone who does not).

Although there is a consistent relationship between aerobic capacity determined with a treadmill and a cycle ergometer, ergometer-based exercise tends to produce a lower peak VO_2 , usually 10% to 20% less than the treadmill due to utilization of a smaller amount of muscle mass.^{6,20,21} Similarly, arm ergometry may be used to assess the aerobic capacity of individuals with lower-limb disabilities and peripheral arterial disease. However, tests performed with arm ergometry will usually correspond to even lower peak VO_2 because even less muscle mass is used.²² In general, any comparisons of performance to age-predicted normal values must be matched for exercise modality.²³ Serial exercise assessments should also be matched for modality. Likewise, it is important to interpret the results of a given test with sensitivity regarding the mode of the test, expecting that VO_2 on a cycle or arm ergometer will be relatively lower than VO_2 on a treadmill.

The work performed on a leg or arm ergometer is determined primarily from electronically controlled crankshaft resistance and is generally expressed in watts. The work performed on a treadmill depends on the speed and incline of the treadmill, the subject's body weight, and the extent to which he/she uses the handrails.

Exercise Protocols

There are several protocols that can be used with either a cycle ergometer or a treadmill. The type of protocol depends on the manner in which the work is applied: 1) progressive incremental (eg, every minute) or continuous ramp protocol; 2) multistage exercise protocol (increasing intensity every 3 minutes); or 3) constant work rate (same work rate for a given time period, usually for 5–30 minutes). For typical clinical exercise testing, the protocol should be tailored to the individual to achieve fatigue-limited exercise, with a duration of 8 to 12 minutes.⁶ When the test duration is < 6 minutes, results may indicate a nonlinear relationship between VO_2 and work rate. Conversely, when the exercise duration is > 12 minutes, subjects may terminate exercise because of specific muscle fatigue or orthopedic factors rather than cardiopulmonary endpoints.

A key point is that exercise intensity should ideally be tailored to the fitness and clinical circumstances of each patient, and ideal exercise times should be between 8 and 12 minutes regardless of the baseline fitness level. Therefore, selection of the modality and intensity of exercise is

particularly important in CPX. Some laboratories administer specific activity questionnaire tools to assess patients' exercise habits or typical symptoms during daily activities prior to exercise testing, and these can serve as a basis for individualized exercise testing protocols.^{24,25} At minimum, the patient should be queried with the objective to select a protocol (with respect to mode and intensity) matched to his/her capacities and limitations.

Common CPX Indices

Maximal O₂ Utilization

Maximal O₂ utilization (VO_{2max}) is a well-established measure of exercise performance which reflects the body's maximal oxygen utilization (Table 1). It is based on the Fick equation (the product of the CO and arteriovenous O₂ difference at peak exercise) and is a reliable and reproducible index that is influenced by CV or pulmonary disease, state of training or therapy, and/or degree of fitness. During a progressive exercise stimulus, VO₂ increases linearly in proportion to work. The measurement of VO_{2max} implies that an individual's physiologic limit has been reached. VO_{2max} has historically been defined by a plateau in VO₂ between the final 2 exercise work rates and requires that maximal effort be achieved and sustained for a specified period (Figure 2A). Although this is usually achievable by younger adults and/or those who exercise regularly, it is often not observed in individuals with pulmonary disease, HF, skeletal muscle myopathy, and/

or who are deconditioned. Therefore, the term peak VO₂ is more commonly used as the expression of an individual's exercise capacity (Figure 2B).

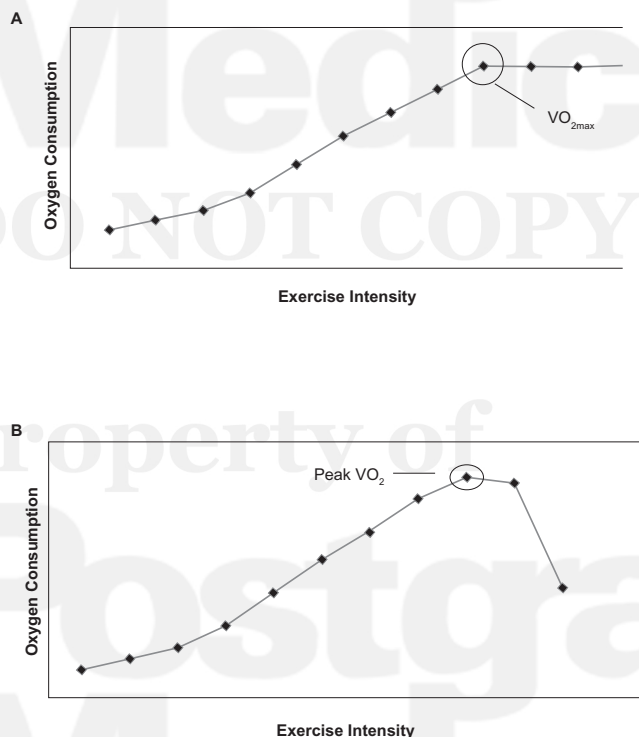
Peak VO₂ is an important measurement clinically because it is considered the metric that defines the limits of the cardiopulmonary system. Although commonly expressed in L/min, this value naturally increases as body mass increases. To better facilitate intersubject comparisons, peak VO₂ is commonly normalized for body weight and expressed as mL O₂·kg⁻¹·min⁻¹. However, the relationship between peak VO₂ and body weight is not linear, with inherent imprecision associated with weight-normalized values. Furthermore, adipose tissue consumes a relatively smaller amount of O₂ than muscle during exercise. Therefore, normalizing to body weight may also be misleading; obese patients often appear to have much lower cardiopulmonary capacities than is the case. Alternatively, peak VO₂ normalized to lean body mass may lead to improved prognostic value of the index,²⁶ but this is rarely done in routine clinical practice, probably because lean body mass is difficult to determine.

Peak VO₂ is often interpreted relative to age- and gender-matched standards. A variety of formulas have been developed as the basis of these standards,^{23,27} yet there is considerable variability between different calculated assessments, reflecting the complexity of VO₂ and differences in the populations from which different calculations were originally based.²⁸

Table 1. Key Ventilatory Variables to be Integrated as Part of a CPX Assessment

- **Peak VO₂:** Oxygen utilization (mL O₂·kg⁻¹·min⁻¹): A measure of aerobic capacity; normal values are influenced by age and sex.
- **VT:** VO₂ at the ventilatory threshold (mL O₂·kg⁻¹·min⁻¹): A measure of submaximal exercise tolerance.
- **Peak RER:** The ratio of exhaled CO₂ to inhaled O₂. Provides a means to quantify subject effort during CPX. An RER ≥ 1.00 indicates good effort and RER ≥ 1.10 indicates excellent effort.
- **VO₂/w (mL/min/w):** Characterizes the ability of exercising muscle to extract oxygen. A low VO₂/w relationship suggests cardiac or pulmonary impairment.
- **O₂ pulse (mL O₂/heart beat):** Approximates stroke volume.
- **PetCO₂:** End-tidal CO₂ or the level of CO₂ in the air exhaled from the body (measured in mm Hg). Reduced values indicate VQ mismatching, and is consistent with worsening cardiac or pulmonary disease severity, and worse prognosis.
- **VE (L O₂/min):** Ventilation (based on tidal volume and respiratory rate) during exercise. Peak VE can be assessed relative it can help determine if exercise intolerance or dyspnea relate to a pulmonary limitation.
- **VE/MVV:** Assessment of the maximum minute ventilation during exercise relative to maximum voluntary ventilation which is determined during PFTs at rest. The VE/MVV ratio is normally ≤ 80% (and consistent with the premise that the pulmonary system is not limiting the exercise capacity); a ratio > 80% suggests pulmonary limitation.
- **VE/VCO₂ slope:** Measurement of ventilatory efficiency (ie, minute ventilation relative to CO₂ exhalation). Whereas VE/VCO₂ slope is normally < 30, efficiency decreases with HF, intrinsic lung disease, and/or pulmonary hypertension, VE/VCO₂ slope increases in each instance.
- **Exercise oscillatory ventilation:** Oscillation ventilatory pattern that indicates poor prognosis in patients with heart failure.
- **Pulse oximetry (% O₂ saturation):** Decline in hemoglobin oxygenation levels < 90% indicative of diminished ability to adequately increase alveolar-pulmonary capillary oxygen transfer during exercise.

Figure 2A–B. **A)** O_2 consumption (VO_2) relative to exercise intensity (eg, watts on a bicycle or treadmill speed and incline). $\text{VO}_{2\text{max}}$ is identified as the level of greatest oxygen utilization in association with a physiologic plateau of capacity. **B)** Peak VO_2 is also used to identify oxygen utilization; while it may indicate the same O_2 utilization as $\text{VO}_{2\text{max}}$ in some, for others the capacity of achieving and sustaining a plateau of maximum O_2 utilization capacity may not be achievable. Therefore, many regard peak VO_2 is a more accurate characterization of maximum O_2 utilization that may be maximal, but also may be limited by other factors (eg, breathlessness, anxiety, deconditioning).



The respiratory exchange ratio ($\text{RER} = \text{VCO}_2/\text{VO}_2$) provides a physiological context to substantiate that a high exercise effort has been achieved. It helps validate that VO_2 is truly a peak exercise assessment, rather than an underestimate for someone who stopped because of poor motivation. When exercising, the metabolic demands of progressive exercise exceed the limits of ATP synthesis dependent on O_2 delivery, and metabolism shifts to greater reliance on anaerobic metabolism. Such a natural change in metabolism results in increased production of lactic acid in the muscle, which then diffuses out into the blood and increases CO_2 throughout the body. However, homeostasis is preserved because the elevated CO_2 is quickly eliminated from the body in the form of exhaled gas. Therefore, RER increases with exercise as exhaled CO_2 predictably increases; an RER of ≥ 1.10 is a criterion by which one can be highly confident that the peak VO_2 reflects a peak physiological workload. Consistently, when assessing peak VO_2 as a basis for prognosis, it is important to ascertain that the VO_2 is associated with a high RER (ie, a low VO_2 in the context of a low RER may be a significant underestimate of exercise capacity).²⁹ Similarly,

if using peak VO_2 to gauge utility of a particular therapeutic intervention, one must achieve high RER with CPX before and after the therapy to be sure performance changes reflect true benefit and not merely fluctuations in patient motivation.

If a patient requests that the CPX is stopped in a situation when his/her RER remains < 1 (and when there is no ECG or hemodynamic impairment), it may indicate poor patient effort. Nonetheless, clinical assessment is critical because peak exercise performance despite low RER may also reflect pulmonary disease, peripheral arterial disease, musculoskeletal impairment, and other factors that can fundamentally limit functional capacity.

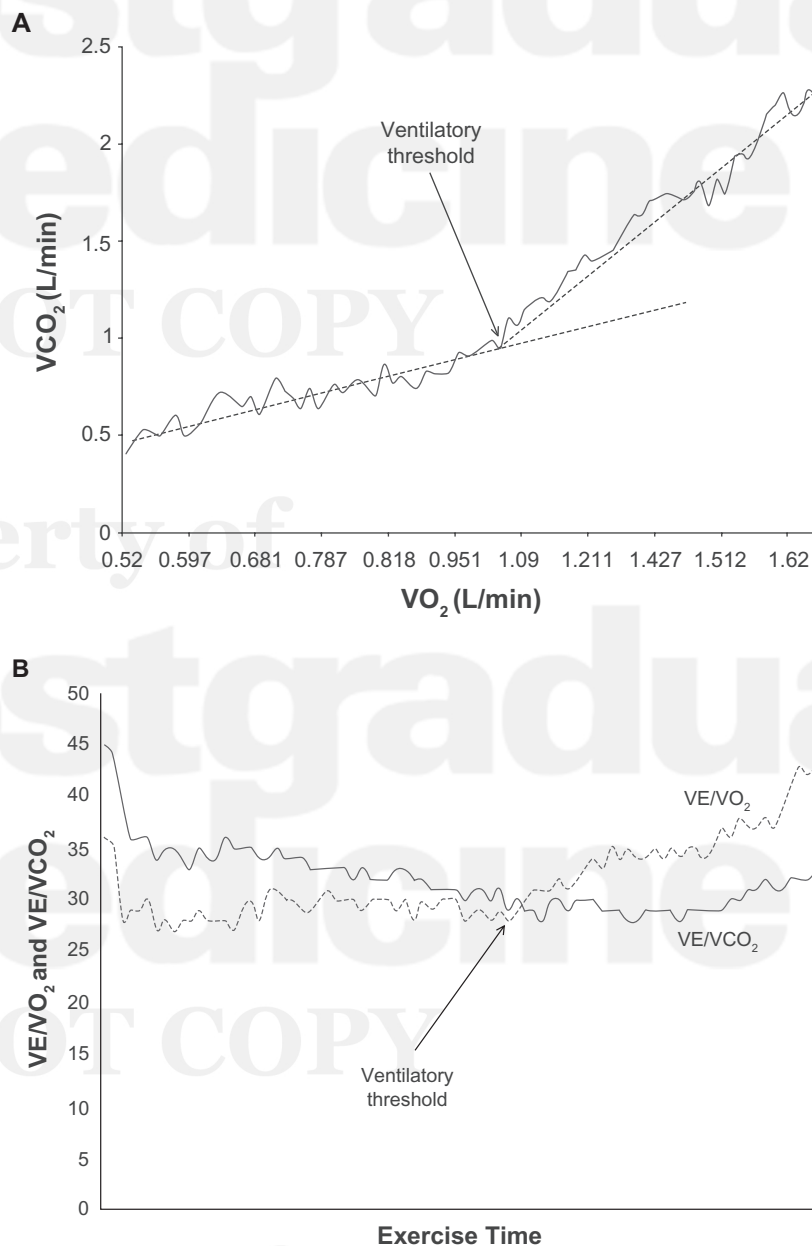
Whereas achieving a peak HR of at least 85% of age-predicted maximal HR is a well-recognized indicator of sufficient patient effort for assessing ischemia during exercise testing, this criterion is confounded by sinus node dysfunction, medications (especially beta-blockers), pacemakers, and other common clinical factors.³⁰ Moreover, the standard deviation of maximal HR is 10 to 12 $\text{beats}\cdot\text{min}^{-1}$, which creates a high degree of interindividual variability, irrespective of age, and which further weakens the ability of this measure to gauge exercise effort. In contrast, a high RER provides a more reliable means to assess high patient effort and related assessments of ischemia, prognosis, and other CV work-related parameters.

Anaerobic or Ventilatory Threshold

The point of nonlinear increase in VE during exercise demarcates the ventilatory threshold (VT), and constitutes a reliable, reproducible index of submaximal exercise intensity (Figure 3). The VT is related to the point at which anaerobic metabolism increases in exercising muscles to sustain work when aerobic metabolic capacity can no longer meet the physiologic demands, and the body shifts to anaerobic metabolism as an additional source of energy. The VE corresponds to these physiological shifts, as ventilation accelerates to counterbalance increases of CO_2 in the blood.

A key utility of VT is that it provides information at a submaximal level of exercise intensity (ie, it does not require a physiologically maximal exercise effort). Often, it is a more practical performance index for many patients who are too anxious or debilitated to exercise to a level of very high exercise, but who can still exercise to the point of breathlessness. The VT is also considered more consistent with a patient's ability to perform daily activities, especially because exercising beyond the VT for sustained periods eventually results in fatigue. The VT also provides a useful means to gauge functional benefits of therapy because most

Figure 3A–B. **A)** The ventilatory threshold (VT) is the point at which respirations increase to maintain PaCO₂ equilibrium despite rising lactic acid production in the exercising muscles. Most commonly VT is determined as the departure of VO₂ from a line of identity drawn through a plot of VCO₂ versus VO₂, often called the V-slope method. **B)** An alternate mechanism to ascertain VT is achieved through assessment of ventilator equivalent for oxygen (VE/VO₂) and ventilatory equivalent for carbon dioxide (VE/VCO₂); VT is the point at which VE/VO₂ increases without an increase in VE/VCO₂.



activities of daily living do not require maximal effort. The VT is often useful as a parameter on which to base an exercise prescription for patients with CV or pulmonary conditions that limit maximal exercise performance.^{31–33}

In some exercise laboratories, the term anaerobic threshold is used instead of VT, which may lead to some confusion. The term anaerobic threshold was originally premised on the physiology of accumulating lactic acid in exercising muscle; however, the nomenclature has typically shifted to VT because this is a better representation of the ventilatory

parameters actually being assessed using CPX. Similarly, overlap between the concepts of VT and RER may create some confusion because both relate to the physiology of increasing CO₂ with advancing exercise. Nonetheless, they are distinct concepts; RER is a ratio of VCO₂, and VO₂ and is primarily used to gauge exercise effort. The VT is a noninvasive, reliable, and reproducible diagnostic/prognostic marker that is based on ventilatory dynamics as exercise intensity progresses. The VT usually occurs at approximately 45% to 65% of peak VO₂ in healthy untrained subjects, and at a

relatively lower percentage of peak VO_2 among those with HF. However, VT can shift to a relatively higher percentage of peak VO_2 after exercise training and/or after specific types of HF therapy. Just as with peak VO_2 , high test–retest reliability has been demonstrated for VT in both healthy and chronic disease cohorts.³⁴

There are differing views regarding the optimal technique of determining VT. The most common method entails graphing values of VCO_2 versus VO_2 and is called the V-slope method. The VT is identified as the point where there is a shift in slope along a line of identity between these gas measurements (Figure 3A).²³ Alternatively, VT can be identified as the point at which there is a systematic increase in the curve characterizing ventilation relative to VO_2 (VE/VO_2) without an increase in the ventilatory equivalent for CO_2 (VE/VCO_2). These 2 relationships are typically displayed in association with one another (Figure 3B) to pinpoint the VT. If the V-slope cannot provide a reliable VT, it is common to review the VE/VO_2 and VE/VCO_2 curves to distinguish the VT.

VO_2 /Work Rate Relationship

In general, there is a linear relationship between increasing VO_2 and the work rate (watts) achieved. The slope of this relationship reflects the ability of exercising muscle to extract O_2 and to aerobically generate ATP. In general, a reduction ($< 10 \text{ mL}/\text{min}/\text{w}$) throughout the exercise test or an acute flattening at a given point during exercise in the $\Delta\text{VO}_2/\Delta\text{WR}$ relationship suggests the possibility of a problem in O_2 transport.²³ General reductions may be seen in heart and lung disease, and disease in peripheral arterial function and/or mitochondrial myopathy, in which there are alterations in the cellular pathways involved in O_2 utilization. Furthermore, a pattern of initial rise of the $\Delta\text{VO}_2/\Delta\text{WR}$ during exercise followed by abrupt flattening may reflect the onset of ischemia-induced left ventricular (LV) dysfunction in patients with coronary heart disease (CHD).³⁵ Because consistent and accurate quantification of workload during treadmill testing is complicated by underlying variability during treadmill protocols (eg, body weight and handrail holding), assessment of the $\Delta\text{VO}_2/\Delta\text{WR}$ relationship is typically confined to exercise tests using a cycle ergometer.

Oxygen Pulse

The O_2 pulse at peak exercise is calculated as the peak VO_2 divided by peak HR and expressed as mL O_2 per heart beat. Essentially, it is an index of stroke volume in association with O_2 extraction. Oxygen pulse tends to be reduced in

conditions that impair stroke volume during peak exercise. Patients with reduced CO, severe valvular disease, CHD, pulmonary vascular obstructive disease, chronic obstructive pulmonary disease (COPD), and hyperinflation typically have a low O_2 pulse.^{23,36,37}

However, among patients with depressed arterial O_2 concentration at peak exercise (eg, significant desaturation), O_2 pulse will underestimate stroke volume. Likewise, in conditions with abnormally elevated O_2 saturation (eg, polycythemia vera), O_2 pulse will overestimate stroke volume. It is also important to emphasize that stroke volume refers to forward-flowing blood only. It is not equivalent to the anatomic stroke volumes (end-diastolic volume minus systolic value) that are germane to comprehensive study of intracardiac flow dynamics (ie, O_2 pulse does not distinguish intracardiac flow dynamics attributable to valvular insufficiency and/or shunts). Therefore, while not a definitive means to assess LV function, O_2 pulse can be used to illuminate broader performance patterns, which can help identify unexpected issues as parts of comprehensive dyspnea assessments, preoperative evaluations, and other routine applications.

Minute Ventilation

In healthy adults, increasing exercise CO_2 production prompts increased ventilatory efficiency. Tidal volume increases, respiratory rate accelerates, and perfusion of the alveoli also improves. Through these mechanisms, the partial pressure of CO_2 in arterial blood (PaCO_2) is maintained at a constant level. In healthy individuals, there is more than sufficient minute VE capacity to maintain PaCO_2 at any achievable workload.

However, some gases in the respiratory passages leading to the lungs (and alveoli) do not participate in gas exchange (ie, the so-called dead space [V_D]). During exercise, dilation of the respiratory passages causes the V_D to increase, but because tidal volume also increases, adequate alveolar ventilation is maintained. Furthermore, it is critical that increases in VE be matched by increases in pulmonary blood flow and by expanded lung capacity (reserves of healthy lung architecture) for augmented gas exchange to occur.

Patients with bronchospasm, intrinsic lung disease, or HF will all experience interruptions to this vital physiology. Bronchospasm will constrict the vital capacity for bronchodilation that is essential for increased air flow. Lung disease will often lead to reduced alveoli for gas exchange to occur. Patients with HF have preserved lung parenchyma but reduced lung perfusion. The degree to which VE becomes abnormally heightened during exercise is directly related

to the severity of disease and is a strong marker of poor prognosis.³⁸

Breathing Reserve

Maximal voluntary ventilation (MVV) is a measure of maximal breathing performance that is usually assessed as the maximum air flow over 12 or 15 seconds in a subject who is at rest. Typically, MVV is approximated by multiplying the forced expiratory volume (FEV) (obtained during routine spirometry) by a factor of 40.¹⁷ This directly measured or approximated value of MVV is then compared with the maximum VE achieved during CPX. If the maximum exercise VE approaches the MVV, it distinguishes a ventilatory limitation to performance, which is commonly experienced by patients as severe shortness of breath. Whereas normal subjects rarely experience ventilatory limitations to exercise, many pulmonary patients have reduced MVV such that their VE are more likely to reach the MVV value during exercise.

Breathing reserve (BR) is the percentage of a subject's MVV that is not used at peak exercise:

$$BR = 100 (MVV - \text{peak VE})/MVV$$

The normal BR at peak exercise in healthy nonathletes is $\geq 20\%$. Patients with CV disease may have limited exercise tolerance and even dyspnea, but BR is usually normal. In contrast, patients whose exercise is limited by pulmonary disease will typically have low baseline MVVs, and little or no BR at peak exercise.

Minute Ventilation- CO_2 Output Relationship (The VE/VCO_2 Slope)

During a CPX, VE is modulated by the metabolic and anaerobic production of VCO_2 ; a close linear relationship exists between VE and VCO_2 . In particular disease states, VE can become relatively heightened in the $\text{VE}-\text{VCO}_2$ relationship. The slope of the relation between VCO_2 and VE during exercise (commonly termed the VE/VCO_2 slope) is used as an index of ventilatory efficiency. A VE/VCO_2 slope of < 30 is considered normal, irrespective of age and gender.³⁸ Values observed in pulmonary patients, such as those with pulmonary hypertension (PH), can far exceed this normal threshold, surpassing 60 in patients with advanced disease severity.³⁹

Similarly, a high VE/VCO_2 slope during exercise is a powerful prognostic marker of HF patients, with the degree of slope elevation reflecting disease severity.⁴⁰ Multiple factors contribute to the elevated VE/VCO_2 slope in HF, even in euvolemic patients, including reduced CO in response to

exercise, which leads to ventilation-perfusion mismatching in the lungs (adequate ventilation and poor perfusion) and higher V_D and dyspnea.⁴¹

In addition to these lung-cardiac factors, peripheral skeletal muscle acidosis contributes to dyspnea and exaggerated ventilatory responses both independently and as part of pulmonary and cardiac disease processes because of abnormal chemo- and ergoreceptor sensitivities.^{42,43}

Exercise Oscillatory Breathing

In some patients with HF, the ventilatory response to exercise is not only exaggerated (ie, with a high VE/VCO_2 slope) but may also exhibit a variable breathing pattern, known as exercise oscillatory breathing (EOB). Exercise oscillatory breathing is a pathological phenomenon characterized by alterations in tidal volume associated with changes in arterial O_2 and CO_2 tension.^{38,44} 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 have not been established, the presence of an EOB pattern lasting at least 60% of an exercise test at an amplitude of $\geq 15\%$ of the average resting value is regarded as a standard for presence of EOB.^{45,46} Exercise oscillatory breathing prevalence across HF populations ranges between 12% and 30%,⁴⁷ with similar prevalence and clinical significance in either systolic HF or HF with preserved ejection fraction.⁴⁸

The underlying cause of EOB likely relates to dysregulation of mechanisms involved in the mechanical and neural feedback control of the cardiopulmonary system, including increased peripheral chemoreceptor activity and impaired baroreflex sensitivity.⁴⁹ Interest in EOB has increased in recent years because it has been shown to predict mortality in HF patients, both as an independent index, and particularly in combination with other CPX indices.^{50,51}

Partial Pressure of End-Tidal CO_2

The partial pressure of end-tidal CO_2 (PetCO_2 , expressed in mm Hg) at rest and during exercise is another valuable marker of disease severity which has been demonstrated to be diagnostic for pulmonary disease as well as a predictor of HF prognosis. Normal resting PetCO_2 ranges between 36 and 44 mm Hg, approximating arterial PCO_2 . With exercise, PetCO_2 should normally increase 3 to 8 mm Hg from rest to VT, and then slightly decline at maximal exercise secondary to the anaerobically induced increase in VE.^{23,40,52} However, in the presence of pathological VE/perfusion mismatch, end-tidal air is derived disproportionately from alveoli with high VE/

perfusion ratios, leading to low end-tidal CO₂ concentrations. In fact, while PetCO₂ is usually greater than PaCO₂ in healthy exercising adults, this is reversed in the context of a significant VE/perfusion mismatch. Likewise, persistently low PetCO₂ throughout exercise is consistent with ventilation/perfusion mismatching and is seen in patients with emphysema or other lung diseases and/or rapid shallow breathing patterns. PetCO₂ is also low with chronic metabolic acidosis and right-to-left intracardiac shunts.

Low PetCO₂ and cardiac output have also been demonstrated to be strongly related.^{53,54} Increases in CO and pulmonary blood flow result in better perfusion of the alveoli and a rise in PetO₂. A PetCO₂ > 30 mm Hg is associated with a CO of > 4 L/min or a cardiac index of > 2 L/min. Low PetCO₂ indicates low CO and poor prognosis in HF, especially in association with other pertinent CPX indices.^{55,56}

Complementary Assessments Before and During CPX Pulmonary Function Testing

Pulmonary function testing (PFT) is completed at rest and provides an assessment of baseline pulmonary performance that complements analysis of dynamic ventilation indices during CPX. Tests of lung mechanics and flow, including forced vital capacity (FVC), FEV in 1 second (FEV₁), and MVV provide a context to assess exertional ventilation, helping discern whether basic lung mechanics are determining symptoms and/or limiting exercise performance (Table 2). Given that both cardiac and pulmonary abnormalities can similarly influence CPX ventilation variables, baseline PFTs help refine interpretation, with potential to distinguish pulmonary abnormalities that may be predominant, particularly in the circumstance of severe obstructive or restrictive patterns. Nonetheless, baseline PFTs are not always diagnostic of pulmonary pathology that may exist; the dynamic ventilatory

patterns of CPX increase sensitivity to detect pulmonary disease and are an important consideration for complete CPX analysis for the primary care patient.

Among the components of standard PFTs, FEV₁ and FVC provide an indication of the presence of COPD or restrictive lung disease. Most importantly, it is the degree of impairment of both variables that determines the constraints that may limit the performance of exercise in clinical lung disease. Standards for the performance and interpretation of spirometry are available from the European Respiratory Society and American Thoracic Society.^{57,58}

Flow-Volume Assessment During Exercise

Assessing flow-volume curves during exercise further complements PFTs and CPX breathing indices. Exercise provokes greater inspiratory and expiratory flows, tidal volume, and respiratory rate, and thereby creates an opportunity to assess the complex physiology of ventilatory demand in relation to mechanical lung performance.

Among healthy adults, end-expiratory lung volume (functional residual capacity) generally remains unchanged, as their lungs can increase ventilatory efficiency (through augmented tidal volume and flow). Healthy individuals typically reach only 50% to 70% of their maximal volitional inspiratory flow at rest, and can accommodate higher volumes during exercise as needed. However, in those with chronic airway obstruction, resting tidal flow may already be maximal. During exercise, these adults may be able to mount some increase in inspiratory flow. However, given their expiratory flow limitation some of the air inhaled will be trapped and the end-expiratory volume will increase, a condition referred to as dynamic hyperinflation or air trapping.⁵⁹

Arterial Oxygenation and O₂ Saturation During Exercise

In typical healthy adults, the partial pressure of O₂ in arterial blood (PaO₂) is usually well preserved during exercise. On the other hand, in patients with impaired ventilation/perfusion ratios (interstitial or obstructive lung disease) or physiological shunts, the development of hypoxia during exercise may be a prominent feature of abnormal pulmonary function.

In general, a > 5% decrease in the pulse oximeter estimate of arterial saturation during short duration clinical CPX protocols is suggestive of abnormal exercise-induced hypoxemia, consistent with symptomatic pulmonary disease.⁷ Nonetheless, O₂ desaturation is possible in elite athletes.

Table 2. Pulmonary Function Test Parameters Associated with Different Diagnoses

	COPD	Restrictive Disease	HF	Obesity
FVC	N--↓	↓	↓	N--↓
FEV ₁	↓	↓	↓	N--↓
FEV ₁ /FVC	↓	N--↑	N--↓	N--↓
MVV	↓	↓	↓	N--↓
RV	↑	↓	↑--N--↓	↑--N--↓
RV/TLC	↑	N--↑	↑--N--↓	↑--N--↓
DLCO	N--↓	N--↓	N--↓	N--↑

Endurance athletes with high CV capacity can demonstrate O_2 arterial desaturation (as much as 5%–10% from baseline) during sustained heavy intensity exercise. Thus, changes in arterial oxygenation do not always denote pathology.

In many CPX labs, pulse oximetry is used to monitor O_2 saturation during exercise. Pulse oximeters rely on differential absorption of varying wavelengths of light to noninvasively estimate the proportion of arterial capillary hemoglobin in the oxygenated form. These devices have generally been shown to provide reasonably accurate measures of O_2 saturation, with errors in the range of $\pm 2\%$ to 3% when compared with direct arterial blood samples. Nonetheless, technical limitations attributable to motion artifact and/or poor capillary perfusion can lead to false-positive desaturation data.

Therefore, assessing pre- and postexercise oxygenation with arterial blood gases (ABGs) provides superior assessment of O_2 . In addition to reliable measurement of PaO_2 , arterial blood gases also provide a full profile of $PaCO_2$, pH, and hemoglobin, further enhancing assessments. The early onset of acidosis during exercise in individuals found to be free of CV and/or pulmonary disease can, for example, also assist in detecting mitochondrial disease. Despite these obvious attributes, ABGs entail the discomfort and distress of arterial needle sticks such that many physicians opt to use them selectively.

Electrocardiogram

Electrocardiographic responses and HR are pertinent during exercise and recovery. Heart rate responses (chronotropic responses and HR recovery [HRR]), ischemic changes (ST elevation or depression), conduction disease, and arrhythmias are all important considerations that should be documented during exercise.^{60,61}

Heart Rate Reserve

Heart rate control is regulated by autonomic responses. Parasympathetic withdrawal and sympathetic activation⁶² work in combination to determine HR acceleration during exercise. Heart rate reserve is a measure of the rate at which HR decelerates over the minute(s) following exercise cessation, and relates primarily to vagal reactivation. A more rapid HRR is associated with good CV health and fitness. In contrast, impaired HRR is associated with higher all-cause and CV mortality, particularly due to increased likelihood of ventricular arrhythmias.⁶³ The prognostic power of HRR is even more evident when combined with CPX responses, such as peak VO_2 and the VE/VCO_2 slope.⁶⁴

Notably, HRR remains a sensitive predictor of risk even in subjects who are taking beta-blockers,⁶⁵ although very low maximum heart rates may diminish sensitivity to detect these physiological properties as a low maximum HR may diminish the magnitude of deceleration. An HRR of < 12 bpm at 1 minute post exercise is a commonly used standard for increased mortality risk.⁶⁶ Still, cutpoints may vary in relation to different populations, reflecting differences in autonomic tone and/or the effects of medications. Other factors affecting HRR include differences in position or timing during recovery. An HRR cutpoint of 18 bpm has been identified to distinguish risk in patients who are supine in recovery and a threshold of 22 bpm has been described for HR at 2 minutes of recovery.^{67,68}

Chronotropic Response to Exercise

Applying the Fick formula, O_2 utilization corresponds directly to CO (ie, the $VO_2 = CO \times$ differences in arterial and venous O_2 content). Because CO is determined by the product of HR and stroke volume, age- or disease-related changes in HR are significant factors that underlie differences in peak VO_2 . Maximal HR decreases with age due to immutable declines in β_1 sympathetic responsiveness such that normal peak HR is commonly estimated as $220 - \text{age}$ (in years). Disease-related changes in autonomic function can exacerbate age-related HR decrements. Normally, HR rises linearly in proportion to VO_2 during a progressive exercise test. Chronotropic incompetence (CI) is generally defined as failure to achieve 85% of the age-predicted maximal HR despite achieving a true maximal exercise effort.⁶⁹ However, some identify the CI diagnostic threshold as 80% of the age-related maximal HR,⁷⁰ and HR is also sometimes normalized to METs.⁷¹ Moreover, there is considerable interindividual variability associated with age-predicted HR, with a standard deviation of 10–12 beats·min⁻¹, and peak HR on a bicycle tends to be about 5% to 10% lower than peak HR on a treadmill.

However, despite such ambiguities of diagnosis and variability of responses, the implications of CI are strong; reduced maximum HR can reduce exercise performance, and this limitation has significant prognostic implications. The functional impact of CI is particularly significant for individuals with depressed stroke volumes. In such circumstances, exercise physiology depends primarily on increases in HR to augment CO. In patients with known CV disease, a low chronotropic response is associated with 2- to 5-fold increased mortality.^{69,72}

Prognostic relevance of chronotropic responses may vary in relation to clinical context. A relatively rapid rise in HR

during submaximal exercise can be due to deconditioning, prolonged bed rest, anemia, metabolic conditions, or other conditions that decrease vascular volume or peripheral resistance. In contrast, a low HR may occur due to medications (particularly beta-blockers), which confound chronotropic assessments. Although relatively low resting HR can result from exercise training (and high basal parasympathetic tone), HR should nevertheless be able to increase to age-predicted maximal levels during symptom-limited exercise.

Symptoms

Symptoms occurring during exercise testing (dyspnea, fatigue, and/or angina) are important to document because they have important diagnostic and prognostic applications. The presence and degree of these symptoms are integral parts of a comprehensive CPX assessment, especially because they can reflect neurologic or other physiological contributors to exercise limitations, as well as the possibility of significant emotion-related dynamics that determine performance.⁷³

Assessment of symptoms and investigation of the reasons for premature termination are important components of the clinical and prognostic follow-up. Symptoms are generally recorded at regular intervals throughout the exercise test. Quantification of exercise-associated intensity and dyspnea are usually quantified with validated scales. Either the original Borg scale,⁷⁴ which rates intensity on a scale of 6 to 20, or the revised nonlinear scale of 1 to 10 is appropriate as a subjective tool for assessing the effort a patient exerts during exercise testing. Simpler 1-to-4 scales are sometimes considered preferable to quantify symptoms of angina and dyspnea.¹⁸ Dyspnea may also be measured by means of a validated visual analog scale.⁷⁵

CPX in Clinical Applications

Heart Failure

Reduced exercise capacity is a cardinal symptom of HF, and CPX offers the advantage of quantifying exercise intolerance accurately and objectively, primarily as a basis of prognosis (Table 3). Cardiopulmonary exercise testing parameters can be assessed individually, but also provide an opportunity to be assessed in aggregate (ie, grouping peak VO_2 , VT, ventilatory efficiency [VE/VCO_2], EOB, and PetCO_2 , O_2 pulse, HRR, CI, and arrhythmias to refine estimates of prognosis). The synergistic quality of CPX indices is a key advantage over other functional assessments such as exercise duration, the 6-minute walk test, or New York Heart Association (NYHA) functional class. Cardiopulmonary exercise testing also provides advantages over more expensive diagnostic imag-

ing modalities that lack the critical dimension of functional capacity in the assessments they provide. Similarly, the fact that CPX variables are obtained during exercise provides superior evaluation relative to rest-based assessments.⁷

Most studies assessing the role of CPX have been performed in patients with systolic LV dysfunction. However, approximately 40% to 50% of HF patients have a preserved ejection fraction (HFPEF),⁷⁶⁻⁷⁸ particularly in the growing subpopulation of older HF patients, and there has been renewed focus on these patients in recent years. Several studies have focused on the prognostic applications of CPX in patients with HFPEF, and these studies indicate that these patients have similar aerobic capacity impairments as those with systolic dysfunction. Related analyses indicate that peak VO_2 , VE/VCO_2 slope, and EOB are all significant predictors of adverse events in patients with HFPEF. Likewise, just as with systolic dysfunction, the ventilatory parameters VE/VCO_2 slope and EOB have particularly strong predictive value for HFPEF.^{46,48}

Dyspnea Associated with HF

Cardiopulmonary exercise testing helps to better characterize the pathophysiological bases of dyspnea sensation and provides insightful clinical and prognostic implications.^{15,79} In chronic systolic HF, pulmonary mechanics show a typical restrictive pattern that contributes to an increased dead space to tidal volume (V_D/V_T) ratio at incremental levels of exercise. An increased V_D/V_T also has been linked to a high V/Q mismatching due to an impaired regional lung perfusion.^{80,81} In addition, increased exercise breathlessness is exacerbated by heightened peripheral afferent reflexes originating from skeletal muscle chemoreceptor hyperactivity.^{82,83} Despite these changes, breathing reserve at peak exercise is usually normal.

Additional CPX features of HF-associated dyspnea include high respiratory rate, a low PetCO_2 , and elevated VE/CO_2 slope. The elevated VE/VCO_2 slope is considered an important correlate of ventilatory inefficiency and is elevated in primary pulmonary diseases and PH. Although a growing number of cardiologists incorporate CPX as part of their management of HF patients, there are still gaps between pulmonary and cardiology assessments for dyspnea and exercise intolerance. It is not as likely that a cardiologist will consider PFTs, assessment of BR, flow volume loops, O_2 saturation, and other pulmonary assessments as part of the cardiac work-up. However, recent literature is calling attention to the prominent interplay between cardiac and pulmonary disease, and provide strong rationale for inclusion of both pulmonary and cardiac parameters in

Table 3. CPX Parameters Associated with Different Diagnoses

CPX Response	Deconditioning	Chronic Heart Failure	Pulmonary Disease	Pulmonary Hypertension	Mitochondrial Disease
Peak VO ₂	Decreased relative to age- and gender-matched standards	Decreased relative to age- and gender-matched standards < 10 mL/kg/min consistent with very poor prognosis	Decreased relative to age- and gender-matched standards	Decreased relative to age- and gender-matched standards	Decreased relative to age- and gender-matched standards
VT	Occurs early relative to peak VO ₂ (< 30% peak VO ₂)	Occurs early relative to Peak VO ₂ (< 30% peak VO ₂)	Normal (40%–60% peak VO ₂)	Normal (40%–60% peak VO ₂)	Normal (40%–60% peak VO ₂)
VO ₂ /Work rate	Normal	Reduced slope < 10	Reduced slope < 10	Reduced slope < 10	Reduced slope < 10
O ₂ pulse	Normal	Decreased	Normal	Normal	Normal
VE/VCO ₂ slope	Normal (20–30)	High (30–60)	High (30–60)	Particularly high (≥ 40)	Normal (20–30)
Breathing reserve	Normal	Normal	Decreased	Normal or decreased	Normal
O ₂ sat (Assessed by pulse oximetry or ABG)	Normal	Normal	Decreased	Normal or decreased	Normal
EOB	None	Can be present	Normal	Normal	Normal
PetCO ₂	Normal	Low	Low (30–40 mm Hg)	Particularly low (≥ 30 mm Hg)	Normal
VE/VO ₂ slope					High (> 100)
Δ Cardiac Output/Δ VO ₂				Normal (~5)	High (> 40)

basic clinical assessments of dyspnea.^{84,85} Such consideration seems even more apropos in the context of HFPEF, a disease common in the primary care patient population, and one in which overlap between cardiac and pulmonary factors is subtle and can rarely be delineated without such formal evaluation.

Pulmonary Disease

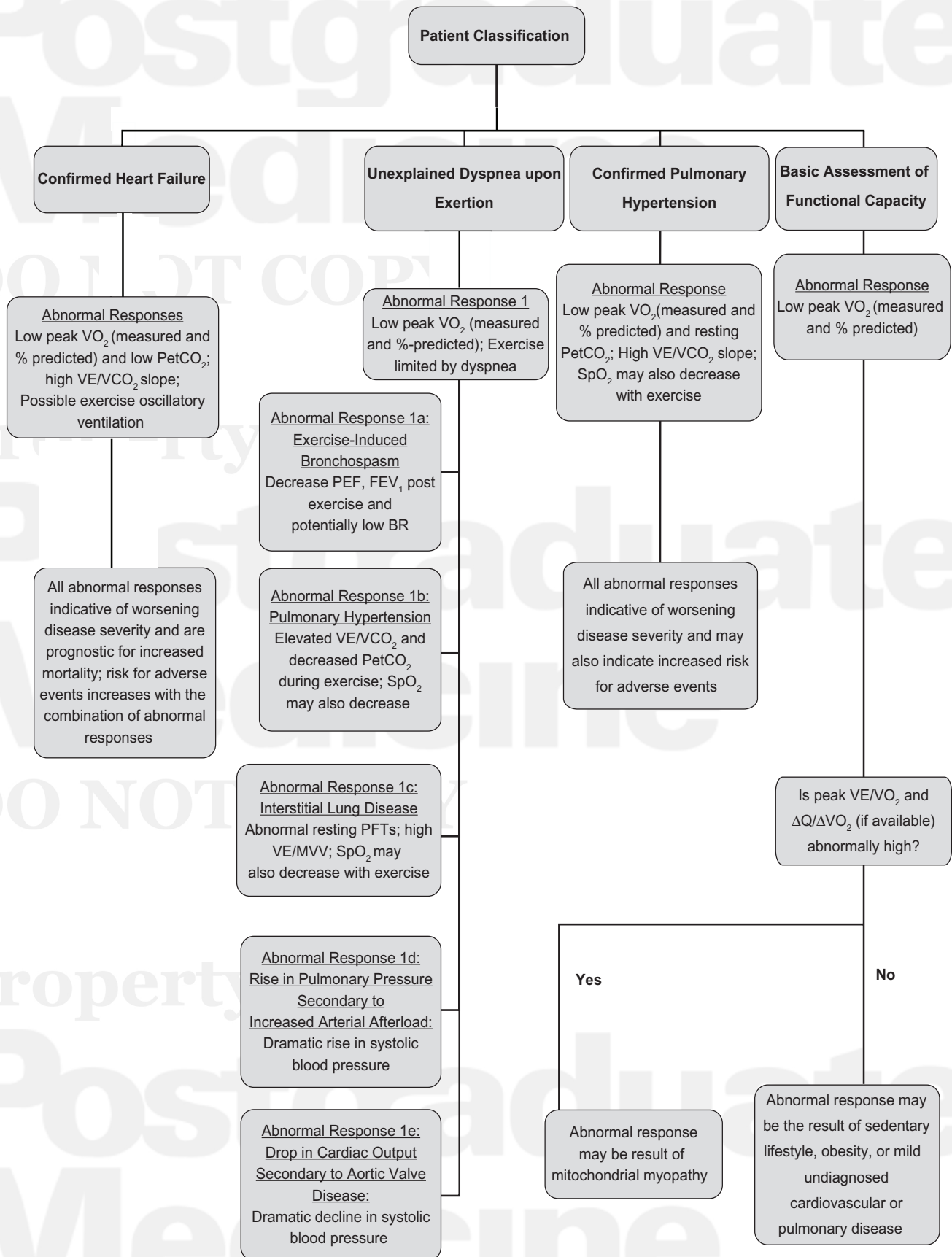
In COPD, peak VO₂ is also predictive of overall survival. Peak VO₂ is also a useful standard with which to gauge training intensity for a pulmonary rehabilitation program and as well as to assess therapeutic benefit after a training program. Likewise, measurement of oxygenation during exercise can be used to guide use of supplemental of oxygen.

The dynamic nature of CPX assessment can be particularly helpful in diagnosing pulmonary disease. Rapid, shallow ventilatory responses and early hypoxemia during CPX can help identify interstitial lung disease that was indistinguishable at rest. Likewise, PH may not be apparent with resting assessments (pulmonary function tests, electrocardiogram and chest roentgenogram can all appear normal), but CPX typically reveals some combina-

tion of low peak VO₂, high VE/VCO₂, low PetCO₂, early-onset tachycardia, and hypoxemia. High pulmonary artery pressures can be superimposed on underlying obstructive and restrictive pulmonary disease patterns, and CPX provides the discriminatory capacity to delineate these dynamic differences, particularly with disproportionate elevation of VE/VCO₂.^{38,86} It is important to consider an echocardiogram and/or right-sided heart catheterization when CPX indices are suggestive of PH in patients who remain short of breath in recovery.⁴³

Cardiopulmonary exercise testing is also used in the preoperative evaluation of patients with pulmonary disease. The degree of exercise limitation (low work capacity) is one of the most important determinants of inhomogeneous emphysema and severe airflow limitation that have been shown to be responsive to lung volume reduction surgery. Similarly, a low peak VO₂ has been shown to indicate a high risk of postoperative pulmonary complications and mortality in patients with lung cancer considered for lung resection. A poor exercise capacity is also characteristic of patients likely to benefit from lung transplantation. More recently, a high preoperative VE/VCO₂ slope was found

Figure 4. Cardiopulmonary parameters associated with different diagnoses.



to be a significant predictor of mortality in patients with COPD undergoing lung resection, even in the presence of an acceptable aerobic capacity ($> 15 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).⁸⁷

Dyspnea Associated with Pulmonary

Diseases

COPD

While the response to incremental exercise shows peculiar characteristics, the diagnosis of COPD is generally based on clinical history and spirometry. Nonetheless, CPX has gained an established role for the precise identification of the causes limiting exercise tolerance, especially when exertional symptoms are disproportionate to resting PFTs, and for the assessment of efficacy of various interventions (ie, oxygen supply, bronchodilators, physical rehabilitation, continuous positive airway pressure, and lung resection). In the majority of COPD patients, CPX reveals that dyspnea primarily occurs because of the combination of reduced ventilatory capacity and an increased ventilatory requirement.⁸⁸ Development of an increased ventilatory demand depends on dynamic hyperinflation related to the degree of expiratory flow limitation, the breathing pattern at a specific VE intensity, the shape of the maximal expiratory flow-volume loop, and the degree of resting lung hyperinflation and/or exercise-associated air trapping.⁵⁹ One of the most important recognized measures that help to identify patients with moderate-to-severe COPD limitation is a reduced VE/MVV (ie, $< 20\%$) and a decrease in pulse oximeter saturation by $> 5\%$.

Interstitial Lung Diseases

Cardiopulmonary exercise testing may be particularly useful in detecting exercise-induced ventilatory and gas exchange abnormalities early in the course of interstitial lung diseases (ILD) when resting lung function measurements are still normal. As in other pulmonary disorders, exercise intolerance is multifactorial, but restrictive mechanics and severe gas exchange derangement are primary contributors. Typical features are arterial desaturation and an elevated ventilatory requirement. Exercise ventilatory response patterns typical of ILD are reduced breathing reserve, increased VE/VCO₂ slope, and an abnormally high breathing frequency–low tidal volume pattern at any given level of VE. In patients with a clinical diagnosis of idiopathic pulmonary fibrosis, peak VO₂, VE/VCO₂ at peak exercise, and peak O₂ pulse have been shown to be strong predictors of survival.⁸⁹

Idiopathic Pulmonary Hypertension

In patients with chronic pulmonary vascular disease, such as idiopathic pulmonary hypertension (IPH), exercise tolerance is usually markedly reduced. The ventilatory gas exchange profile

of IPH patients is similar to that observed in HF with secondary PH as documented by a reduced peak VO₂, ratio of VO₂/watts, O₂ pulse, tidal volume, PetCO₂, an increased dead space ventilation, and elevated VE/VCO₂ slope.^{86,90} On exertion, these patients typically exhibit a severely increased VE and dyspnea sensation for low-level exercise due to a marked increase in vascular resistance and failure to perfuse ventilated lungs. Development of VE/CO mismatching can be documented by an increase in P(A-a)O₂. Another pathophysiological mechanism at work in these patients is an unfavorable right (pressure overload) to LV interaction that precipitates LV underfilling with a resultant decrease in CO and peripheral O₂ delivery. This leads to an early occurrence of metabolic acidosis and CO₂ production rate, providing an additional peripheral source to an increased VE requirement. In a significant percentage of patients with IPH, there is evidence of development of a right-to-left shunt through a patent foramen ovale, whose CPX correlates include an abrupt decrease in end-tidal CO₂ pressure and an increase in the respiratory exchange ratio.⁹¹

Exercise-Induced Bronchospasm

Exercise-induced bronchoconstriction may be detected by a brief, high-intensity exercise protocol with pre- and postexercise measurement of FEV₁. A $\geq 15\%$ reduction in FEV₁ after exercise termination (typically within the first 10 minutes of recovery) is indicative of exercise-induced bronchoconstriction.^{6, 92} Moreover, exercise-induced bronchoconstriction should be suspected in patients who develop wheezing, cough, chest tightness, or dyspnea during or shortly after exercise. If exercise-induced bronchoconstriction is suspected following CPX with PFTs, repeat testing after initiation of bronchodilator therapy is valuable in assessing improvement in symptoms, pulmonary function, and functional capacity.

Mitochondrial Myopathy

Although far less common than cardiopulmonary disorders, mitochondrial myopathies are still recognized as common determinants of exercise intolerance, accounting for approximately 8% in one series of patients referred to a tertiary center for evaluation of unexplained dyspnea.^{93–95} In particular, low peak VO₂ in conjunction with an abnormally elevated VE/VO₂ ratio should prompt consideration of intrinsic skeletal muscle abnormalities.

In this case, it is also particularly helpful to measure CO, which can be assessed in combination with CPX using complementary noninvasive technologies. There are a variety of techniques to assess CO noninvasively, but none

are to this point frequently incorporated in routine clinical CPX assessments. CO₂ rebreathing methods, for example, are employed in many research investigations, but it is a technique that requires significant subject cooperation and remains inherently cumbersome to measure. In contrast, a new device measures cardiac output using inhalation of a soluble inert gas (Innocor).⁹⁶ Measurement of the absorbed gas in the circulation using an infrared absorption spectrometer facilitates a convenient CO assessment.

Patients with primary mitochondrial myopathies are unable to adequately utilize O₂ for oxidative phosphorylation; instead, lactic acid accumulates early in exercise, which leads to exaggerated circulatory and ventilatory responses. These abnormalities manifest themselves as early fatigue. By determining changes in CO with exercise and assessing it relative to changes in VO₂, a diagnostic relationship is revealed. A significantly increased $\Delta\text{CO}/\Delta\text{VO}_2$ slope with exercise identifies those likely to have peripheral myopathy (≈ 15 vs ≈ 5 L/min patients in healthy controls). Therefore, high values of $\Delta\text{CO}/\Delta\text{VO}_2$ slope should prompt consideration of further testing, such as a muscle biopsy.

Although HF patients and patients with primary mitochondrial myopathy endure similar functional declines from peripheral skeletal muscle abnormalities, $\Delta\text{CO}/\Delta\text{VO}_2$ presents a very different profile in HF. By definition, systolic and diastolic HF have reduced CO, such that the $\Delta\text{CO}/\Delta\text{VO}_2$ slope would more typically decline with exercise.

Athletic and Disability Assessment

Cardiopulmonary exercise testing facilitates assessment of maximal performance and the effects of training or technique based on peak VO₂ and VT. Furthermore, CPX can be used to differentiate components of exercise performance with respect to aerobic metabolism versus anaerobic metabolism, such that training and/or performance can be analyzed from the perspective of the underlying metabolism. At workloads below the VT, blood lactate levels presumably remain low, and slow-twitch (type I) skeletal muscle fibers with high oxidative capacity are utilized to a greater degree. Such exercise can be sustained for prolonged periods, limited only by substrate availability and musculoskeletal trauma. On the other hand, competitive athletes improve performance by doing at least parts of several weekly workouts at levels above the VT, where blood lactate levels increase, and increased fast-twitch (II) fibers with low oxidative capacity are utilized.

Cardiopulmonary exercise testing can also differentiate low VO₂ from deconditioning versus circulatory impairment versus pulmonary impairment. Those with deconditioning will have a reduced peak VO₂, but normal RER, VT, hemodynamics, ECG, arterial saturation and BR. Those with respiratory impairment would more likely have one or more of the following: 1) abnormal PFTs, 2) low arterial CO₂, 3) arterial O₂ desaturation, and/or 4) insufficient BR. Those with cardiac etiology would be more likely to present with one or more of the following: 1) ischemia, 2) arrhythmia, 3) hemodynamic abnormalities, 4) a normal BR, and 5) impaired HR dynamics. Ventilatory inefficiency (ie, elevated VE/VCO₂ slope) may be present in primary cardiac, primary pulmonary or mixed pathophysiology.^{38,86} Occasionally, adults with no known pulmonary or cardiac disease demonstrate severely elevated VE/VCO₂ slopes with exercise (ie, 40s or greater) with work-up then leading to new diagnosis of PH and ventilation-perfusion abnormalities.

Consistently, CPX is useful for disability determination or similar situations when one wants to confirm that the subject has achieved his/her physiological peak exercise performance.⁹⁷ Whereas a patient might claim fatigue at any time during a standard ECG treadmill test, CPX helps determine if such fatigue is associated with a high RER and other measures of adequate performance. In other words, assessment of a good exercise effort can usually be corroborated by high RER, measurable VT, normal HR response, and perceived exertion scores. If these parameters are not achieved, it may be an indication of disease and/or deconditioning, but it may also indicate malingering or inadequate effort.

Conclusion

In a time of greater refinement of diagnosis and risk stratification, assessment of functional capacity adds an important perspective. Cardiopulmonary exercise testing is a powerful tool that facilitates functional assessment reliably and accurately, providing a critical enhancement of other diagnostic and prognostic tools. In this article, we provided a wide overview of the broad benefits of CPX assessment and the related rationale to utilize the full spectrum of CPX indices to achieve integrated assessments of lung, cardiac, and even muscle contributors to exercise performance. Although cardiologists, pulmonologists, sports providers, and other specialists have the benefit of a growing body of literature to base the applications of CPX, the test remains relatively underutilized by many

health care providers. Broader application of CPX and better integration of all its components seems certain to enhance precision of management choices, especially in the context of a growing population prone to comorbidities and related symptoms of dyspnea and exercise intolerance.

Conflict of Interest Statement

Daniel E. Forman, MD, Jonathan Myers, PhD, Carl J. Lavie, MD, Marco Guazzi, MD, PhD, Bartolome Celli, and Ross Arena, PhD disclose no conflicts of interest.

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