Chapter 5. Cardiopulmonary Exercise Testing

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Objectives:

- Provide a brief overview of normal exercise physiology and responses.
- Outline the clinical indications, utility, conduct, and interpretation of cardiopulmonary exercise testing.
- Highlight characteristic responses commonly demonstrated by patients with various symptoms and disorders frequently assessed by the pulmonologist.

Key words: cardiopulmonary exercise testing; exercise; interpretation; pulmonary function laboratory; pulmonary function testing

Synopsis:

Physical activity in the healthy human involves the active and effective integration of respiratory, cardiovascular, neuromuscular, and metabolic functions. Organs involved in these varied and important roles have sizeable reserve, with the consequence that clinical manifestations of a disease state or abnormality may not become readily apparent until the functional capacity of the organ(s) is markedly impaired. When this occurs, patients commonly experience the distressing, and often disabling, symptoms of shortness of breath with activity and exercise limitation. Cardiopulmonary exercise testing (CPET) allows the clinician to objectively evaluate these important functions and symptoms. Objective assessment and measurement of various parameters during exercise, which strategically places an increased physiologic demand on the functional reserve capacity of these organs, can also provide a sensitive method for the early detection of abnormal function and response(s). Exercise testing results parallel functional capacity and quality of life more closely than measurements obtained only at rest, and accurately predict important outcomes, such as mortality, in a variety of patients and clinical circumstances. While CPET has been previously viewed as being merely interesting (in the hands of a few individuals), it is now cemented into mainstream clinical practice. In view of these meaningful benefits, the conduct and interpretation of CPET is now an essential competency for practicing pulmonologists.

Normal Exercise Physiology

Normal exercise physiology must be appreciated for the appropriate interpretation of exercise responses in disease. While relevant principles of normal exercise physiology will be briefly summarized, a comprehensive review of this subject topic is beyond the intent of this course and syllabus. The reader is encouraged to consult more detailed appropriate source literature and documents on this topic (see "References").

To meet the expected metabolic demands of exercise, the respiratory and cardiovascular systems must be able to augment oxygen (O_2) delivery to the working skeletal muscles. Oxygen transport in the body depends on a series of linked mechanisms that can be schematically expressed as follows (and potential factors that may affect these mechanisms are shown in brackets, but these are not inclusive):

Inspired O_2
(altitude)
↓
Respiratory Ventilation
(alveolar ventilation, distribution)
↓
Respiratory Gas Exchange
(diffusion, ventilation perfusion)
↓
Arterial O_2
(oxygen capacity saturation)
↓
Cardiac Output
(stroke volume, cardiac frequency)
↓
Circulation and Muscle Blood Flow
(peripheral vascular resistance)
↓
O_2 Extraction
(capillary-tissue diffusion)
↓
Muscle O_2 Utilization → O_2 Stores
(respiratory enzymes)
↓
Venous O_2

Adapted from Jones.[1]

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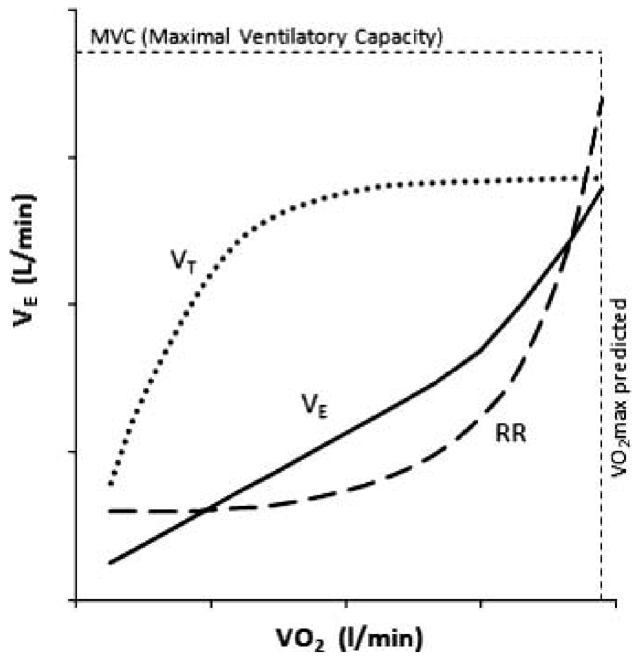

Figure 1. Respiratory system responses during exercise.

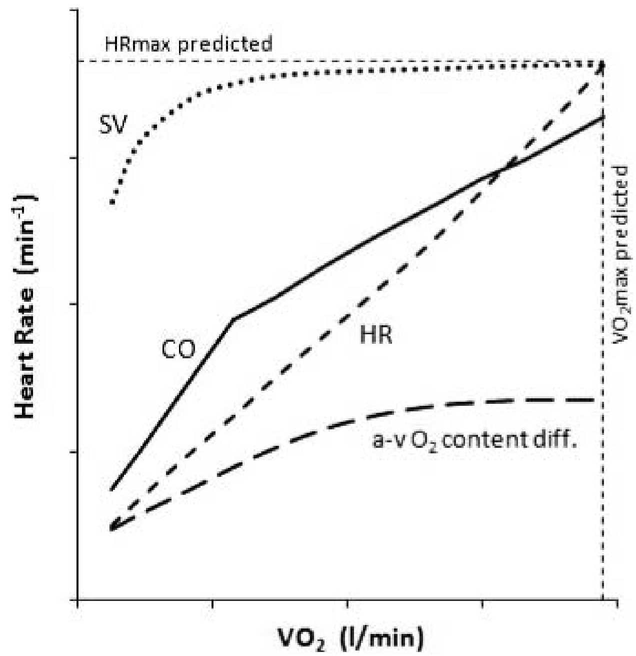

Figure 2. Cardiovascular system responses during exercise.

Similarly, the removal of CO_2, which is a byproduct of metabolism, can be expressed as:

CO_2 Production (aerobic, anaerobic)
↓ → CO_2 Stores
Muscle Blood Flow and Circulation
↓
Venous CO_2
↓
Venous Return
(cardiac output)
↓
Respiratory Gas Exchange
(ventilation-perfusion)
↓
Respiratory Ventilation
(alveolar ventilation, distribution)
↓
Expired CO_2

Adapted from Jones.[1]

Understanding the cardiorespiratory and metabolic responses to exercise is facilitated by close examination of the direct physiologic determinants of oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$), as depicted in the following equations. The cardiovascular responses are represented by rearrangement of the Fick equation:

$$\dot{V}O_2 = \dot{Q}T(CaO_2 - C\bar{v}O_2) \qquad (1)$$

or

$$\dot{V}O_2 = (HR \cdot SV)(CaO_2 - C\bar{v}O_2) \qquad (2)$$

where $\dot{Q}T$ is cardiac output, the product of stroke volume (SV) and heart rate (HR), and $CaO_2 - C\bar{v}O_2$ is the oxygen content difference between systemic arterial and mixed venous blood.

Meanwhile, when the inspired CO_2 concentration is negligible, the respiratory response to exercise can be represented by:

$$\dot{V}A = \frac{k \cdot \dot{V}CO_2}{PaCO_2} \qquad (3)$$

or

$$\dot{V}E = \frac{k \cdot \dot{V}CO_2}{PaCO_2}(1 - V_{DS}/V_T) \qquad (4)$$

where $\dot{V}E$ is minute ventilation, the sum of alveolar ventilation ($\dot{V}A$) and dead space ventilation ($\dot{V}DS$). $PaCO_2$ is arterial PCO_2 and V_{DS}/V_T is the ratio of physiologic dead space to tidal volume. These relationships are used to understand the ventilatory response during exercise, because $\dot{V}E$ and $\dot{V}A$ are associated more closely to $\dot{V}CO_2$ than to $\dot{V}O_2$.

The normal respiratory and cardiovascular system responses during exercise are shown in Figures 1 and 2.

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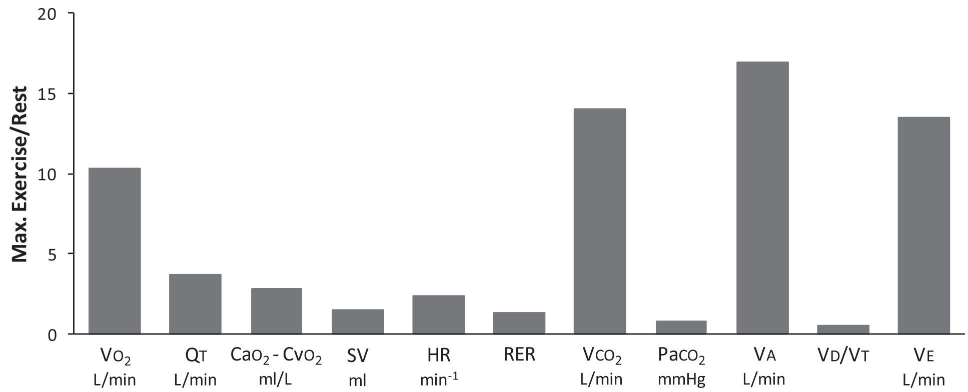

	V_{O_2} L/min	Q_T L/min	Ca_{O_2} - Cv_{O_2} ml/L	SV ml	HR min^{-1}	RER	V_{CO_2} L/min	Pa_{CO_2} mmHg	V_A L/min	V_D/V_T	V_E L/min
Rest	0.29	5.8	50	77	75	0.83	0.24	40	5.2	0.34	7.9
End	3.00	21.6	140	120	180	1.12	3.36	33	88	0.18	107

Figure 3. Relationship between resting and maximal exercise values in healthy humans. Adapted from Gallager.[2]

These relationships and equations also serve to illustrate and emphasize the integrative aspects of exercise, which result in the cumulative response being significantly greater than any individual contribution alone. For instance, oxygen supply in a fit athlete may increase to more than 20 times the resting oxygen consumption (ie, from 0.25 L/min at rest to more than 5.0 L/min at peak exercise). This net increase is not brought about by a 20-fold increase in any one mechanism, but rather is shared between mechanisms. For example, the increase in $\dot{V}_E$ during exercise occurs not only because of the typical hyperventilation (due to metabolic acidosis) at end-exercise, but also because of a fall in V_{DS}/V_T during exercise.

The fractional changes in various components of the cardiovascular and respiratory systems during exercise are summarized in Figure 3 (representative data from a population of healthy middle-aged men[2]).

These data illustrate the major demands placed on cardiorespiratory function during exercise and exemplify the significant reserve that exists to meet these increased demands of exercise. The demands are met by increases in ventilation (breathing frequency and tidal volume) and cardiac output (heart rate and stroke volume), as well as by redistribution of blood to the exercising muscles. In addition, dead space ventilation decreases as alveolar ventilation becomes more efficient. The oxygen uptake rises with increasing exercise, and in some fit and motivated individuals, reaches a plateau near end-exercise. Meanwhile, as carbon dioxide production continues, further fueled by anaerobic respiration and progressive increases in lactate production later in exercise, the respiratory exchange ratio rises in the healthy human. The peak oxygen uptake is usually determined by the capacity of the cardiovascular system to deliver oxygen to the working muscles. Except in well-trained athletes and perhaps the fit elderly, gas exchange remains well preserved during exercise, although the hyperventilation induced by lactic acid production typically results in a slight fall in the Pa_{CO_2} and a rise in Pa_{O_2} near the end of exercise.

Clinical Indications and Utility of CPET

The indications for CPET depend on the clinical setting and question(s) to be addressed. Shortness of breath with exercise and activity limitation are cardinal and common symptoms of dysfunction, and are, therefore, some of the most frequent reasons for testing in the clinical laboratory. CPET also has significant utility in distinguishing normal from abnormal responses, and in establishing cardiovascular from respiratory causes for activity limitation, or for symptoms.

Our understanding of the clinical utility of CPET is also increasing as further work is published demonstrating the prognostic value of exercise testing in various clinical settings.[1,3–5] Results from exercise testing have been shown to correlate with important clinical outcomes including mortality in normal humans, COPD, interstitial lung disease (ILD), cystic fibrosis,

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Table 1—*Clinical Indications for Cardiopulmonary Exercise Testing*

- Objective assessment of symptoms
- Evaluation of severity of impairment
- Appraisal of contributors to exercise limitation
- Early detection of disease or impairment
- Assessment of response to therapy
- Disability assessment
- Assessment/titration of supplemental O_2 therapy
- Identification of exercise-associated bronchoconstriction
- Preoperative risk and transplantation assessment

Adapted from Palange et al[4] and Weisman et al.[5]

pulmonary hypertension, solid organ transplant, ischemic heart disease, and chronic heart failure (CHF).

Generally accepted clinical indications for CPET are listed in Table 1.

CPET has been found to be particularly useful in the setting of preoperative assessment for major surgery and/or lung resection. The risk of death and complications associated with surgery in these instances tends to be higher in patients with a lower peak $\dot{V}O_2$. For lung cancer resection, patients with a peak $\dot{V}O_2 > 15$ mL/kg/min may undergo surgery with an acceptably low mortality risk.[6] However, reported operative mortality for patients with a peak $\dot{V}O_2$ of 10 to 15 mL/kg/min is approximately 8.3% (range, 0%–33%), and in patients with a peak $\dot{V}O_2 < 10$ mL/kg/min, the operative mortality is approximately 26% (range, 0%–50%).[6] A suggested algorithm for the determination of operative suitability and risk in the setting of lung resection surgery is shown in Figure 4.

CPET has also recently evolved into one of the most important tools for evaluating outcomes in chronic heart failure.[7,8] Compared to the healthy human, excessive ventilation during exercise is characteristic of patients with CHF. These abnormalities can be assessed during exercise by using various measurements, including the $\dot{V}E/\dot{V}CO_2$ at the anaerobic threshold or at end-exercise, the slope of $\dot{V}E$ vs $\dot{V}CO_2$, and with other derived variables between $\dot{V}E$ and $\dot{V}CO_2$.[7] The information garnered from CPET has been demonstrated to highly correlate with risks of hospitalization and mortality in this population.

Equipment, Conduct, and Measurements

A stationary cycle ergometer or a motorized treadmill is most commonly used for clinical testing. Both cycle ergometer and treadmill testing are appropriate, although the cycle ergometer is more frequently used. The cycle ergometer allows for a direct measurement of work rate, has less potential for artifact, and seems to be better tolerated by patients, particularly those with significant lower limb joint problems. Alternatively, the treadmill yields higher values for the peak $\dot{V}O_2$ (approximately 8%–12%), and is better accepted by fit normal subjects.

Specialized equipment is used for CPET. Similar to pulmonary function testing equipment, exercise testing equipment systems, whether mixing chamber or breath-by-breath, require meticulous calibration procedures to ensure measurements are and remain accurate and precise. In addition to daily calibration, routine physiologic calibration should be performed. This is best undertaken by a healthy staff member who exercises at several constant work rates for a specified duration while $\dot{V}E$, $\dot{V}O_2$, and $\dot{V}CO_2$ are measured. This might entail measurements after 4 to 6 min each at rest, at 50 W, and at 100 W. Values should remain consistent (less than 5% variation) with measurements collected previously under identical circumstances. If not, the cause of any discrepancy must be investigated and corrected.

Ventilatory measurements unique to CPET, as well as other commonly performed measurements, assessments, and derived variables are illustrated in Figure 5.

As evident in Figure 5, PaO_2 (arterial sampling) or arterial oxygen saturation (SaO_2) (pulse oximetry), work rate (cycle ergometer), blood pressure (cuff sphygmomanometer), heart rate/rhythm (electrocardiogram), and symptoms of shortness of breath and leg fatigue (modified Borg scale or visual analogue scale) are also measured. The reason(s) for stopping exercise should always be noted. Together these measurements allow for a comprehensive evaluation of behaviors during exercise, and for the determi-

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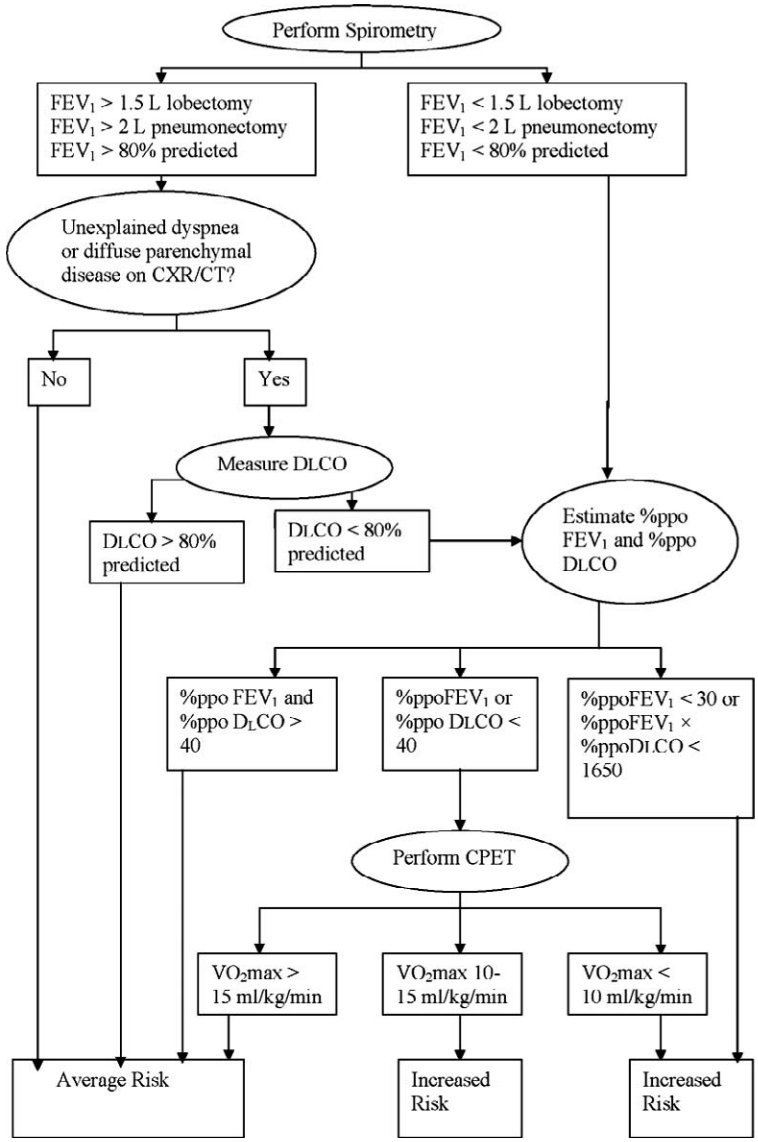

Figure 4. Preoperative assessment of perioperative risk for lung resection surgery.[6]

nation of various derived variables that provide additional information in the interpretation process.

The patient should wear comfortable clothes and shoes, and refrain from heavy activity or meals for 2 h before testing. All testing procedures should be explained, and informed consent obtained. A brief review of the clinical history and a physical examination should be performed. Baseline spirometry is measured, and the patient should be familiarized with the equipment before testing. If a cycle will be used, the seat and handlebars should be adjusted for comfort. In the case of a treadmill, the patient should be shown how to get on and off the moving belt comfortably and safely.

The choice of which test to perform largely depends on the clinical question being addressed. Maximal symptom-limited incremental protocols are most commonly performed. Endurance exercise protocols are often carried out in research trials to determine a treatment effect and may have clinical utility in the individual patient in assessing a response to an intervention. They are often completed at a constant work rate (typically approximately 75% of the maximal work rate) and continued until the patient is no longer able to exercise. Exercise challenge testing is frequently done to objectively assess for the presence of exercise-induced bronchoconstriction. The test is performed to illicit approximately 6 min of very intense exercise associated with

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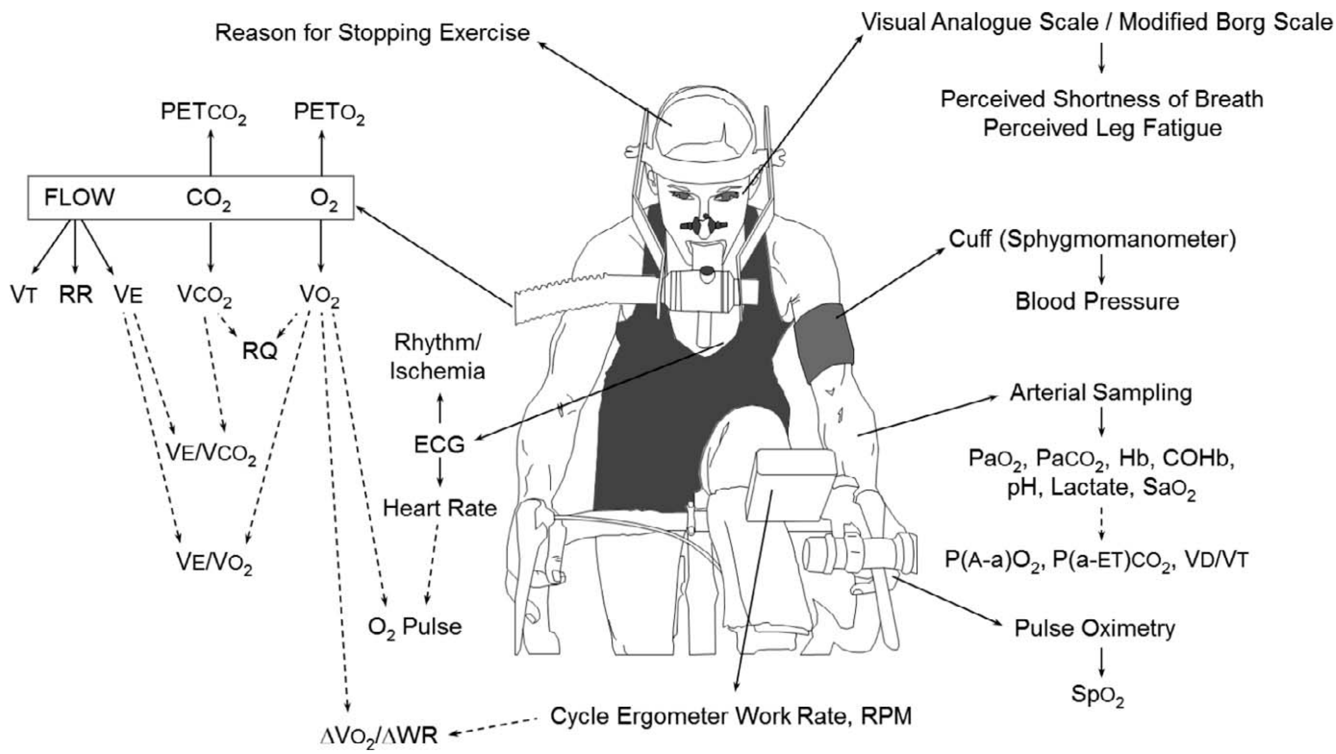

Figure 5. Measurements, assessments, and derived variables from CPET. Measured variables are denoted by solid lines, derived variables by dashed lines. Adapted with permission from photograph by Marco Quezada.

high levels of $\dot{V}_E$. Spirometry is then performed after exercise at frequent intervals (1, 5, 10, 15, 20, 30 min), with a drop in the FEV_1 of 10% to 12% indicating possible, and 15% probable, exercise-induced bronchoconstriction.[9] Readers are asked to consult referenced guideline statements for further information and detail regarding the conduct of this specialized testing.[5,9]

When assessing activity, the clinician has a number of varied options, including self-reported questionnaires, activity motion sensors, stair climbing or step-testing, timed walk tests, shuttle walk tests beyond CPET. The results obtained from pedometers and accelerometers correlate with disease severity.[10] The performance and conduct of the six-minute walk distance test will not be addressed in this chapter, but is discussed in more detail elsewhere.[11] However, timed walk tests (typically 6 or 12 min) are the standard "simple" test for assessing activity limitation. They are safe and practical, and tend to mimic activities of daily living. Their utility has been confirmed to improve with standardization, although they are susceptible to a training effect (similar to other tests). Their major limitation is that they provide restricted information regarding physiologic contributors and mechanisms of exercise limitation, and may demonstrate a ceiling effect because of a smaller magnitude of change in the healthy. Nonetheless, they have become embedded in our field because of the meaningful information they yield.[12,13]

Shuttle walk tests are emerging as another option in this setting, and recent reports[14,15] have validated their usefulness in detecting a treatment effect. The exercise intensity during testing is comparable to maximal tests on a cycle ergometer or treadmill, and the results correlate well with peak $\dot{V}O_2$. The obstacle to more widespread use at this time relates to a lack of familiarity. However, as further reports validating their utility are published, our understanding of the role of both incremental and endurance shuttle walk test protocols will mature.

While these tests do evaluate activity, CPET is the current gold standard for assessing exercise performance. It allows determination of mechanistic insights, recognition of coexistent and multiple exercise-limiting factors, and provides a thorough evaluation of respiratory responses and constraint. Both incremental and endurance protocols may be used, and the results from

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Table 2—*Contraindications to Cardiopulmonary Exercise Testing*

- Unstable angina or recent acute coronary syndrome
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Active endocarditis, myocarditis, or pericarditis
- Symptomatic, severe aortic stenosis
- Poorly or uncontrolled heart failure
- Acute pulmonary embolism or infarction
- Thrombosis of the lower limbs
- Suspected dissecting aortic aneurysm
- Uncontrolled asthma
- Pulmonary edema
- Significant hypoxemia

Table 3—*Indications for Terminating CPET in the Clinical Laboratory*

- Unstable angina or chest pain suggestive of myocardial ischemia
- ECG changes suggestive of ischemia, complex ectopy, or 2°/3° heart block
- Systolic blood pressure fall >20 mm Hg from highest value
- Systolic blood pressure >250 mm Hg, diastolic >120 mm Hg
- Desaturation to below 80%
- Sudden pallor or dizziness
- Mental confusion
- Signs of respiratory failure

Adapted from Weisman et al.[5]

endurance exercise testing have been found to be more responsive to a treatment effect than either incremental exercise or six-minute walk testing. If a thorough evaluation of exercise performance is required, particularly in patients with multiple comorbidities, CPET remains the testing method of choice.

CPET is safe, with the risk of death for patients approximating 2 to 5 per 100,000 exercise tests performed.[5] These risks can be minimized by a number of practical and common sense precautions:

1. Direct physician supervision (the importance cannot be overemphasized), and a thorough understanding of the contraindications to testing, as well as the indications for terminating exercise testing.
2. Appropriate cardiac and blood pressure monitoring.
3. Resuscitation equipment and expertise.
4. Accurate SaO_2 monitoring and availability of supplemental O_2.

Specific contraindications for testing are listed in Table 2. Indications for prematurely terminating CPET are listed in Table 3.

Variables Assessed During Exercise

While a discussion of individual measurements is presented, it is important to recognize that CPET involves their collective integration for interpretation. In many instances, specific individual measurements are of lesser importance—this is dictated by the clinical question being addressed and in part, by responses demonstrated by the patient during testing.

$\dot{V}O_2$

Oxygen uptake is determined by cellular O_2 demand and maximal O_2 transport (see "Normal Exercise Physiology"). It is typically presented together with work rate and increases nearly linearly as external work increases. The slope of this relationship reflects the efficiency of metabolic conversion of energy to work, and the mechanical efficiency of the musculoskeletal system. Values of 8.5 to 11.0 mL/min/W are normal for the $\Delta\dot{V}O_2/\Delta$work rate relationship, and are unaffected by age, height, or sex. While obese individuals may have an elevated ratio, the slope of that relationship remains normal.

As exercise progresses, $\dot{V}O_2$ increases until one or more of its determinants approach limitation (HR, SV, or tissue extraction), and the $\dot{V}O_2$/work rate may begin to plateau. This plateau has been used as the best evidence of $\dot{V}O_2$max, which is the gold standard used for assessing cardiorespiratory fitness. However, in the clinical setting, a plateau may not be reached, and the peak $\dot{V}O_2$ is often used for this purpose. The peak $\dot{V}O_2$ is often normalized for body size by dividing it by weight in kilograms. Unfortunately, normalization by body weight in obese individuals may provide a falsely low value. While using the lean body mass or height may be more desirable, there is no consensus on how best to account for body size.

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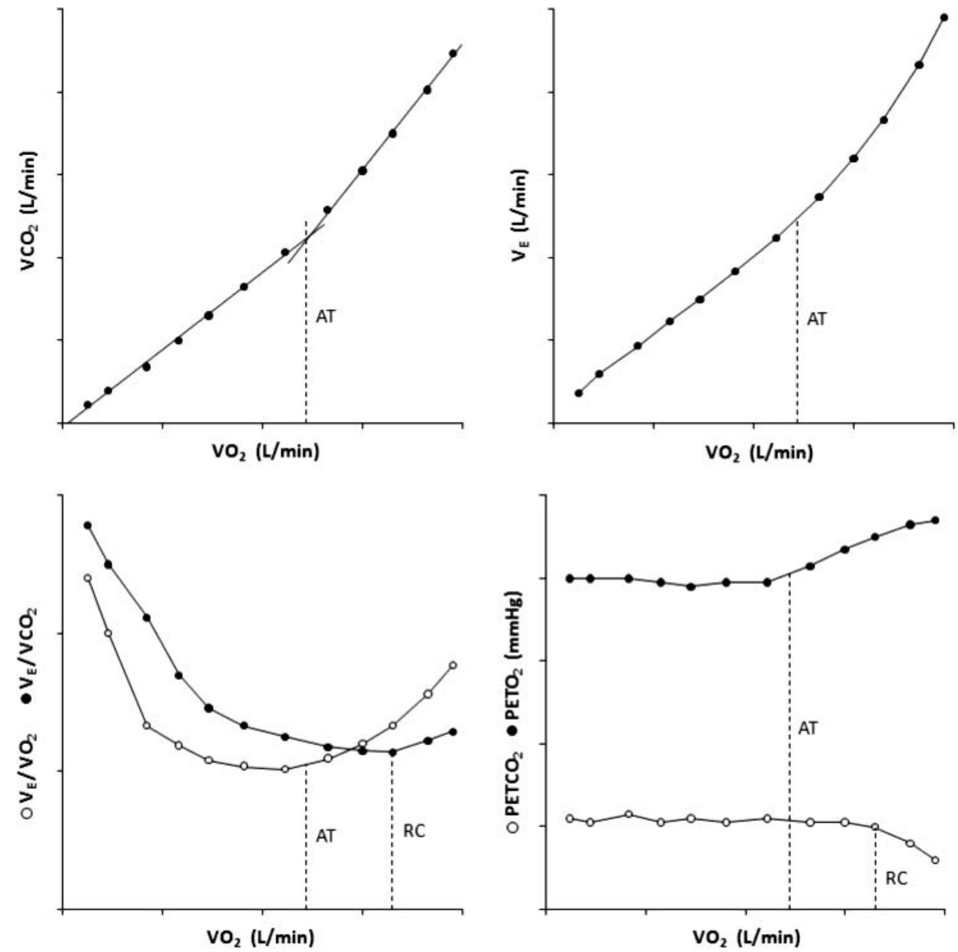

Figure 6. Noninvasive estimations of the anaerobic threshold.

A reduced peak $\dot{V}O_2$ is the starting point for interpretation, and underlying causes responsible for reduced exercise capacity are determined by inspecting the pattern of responses in other variables. The peak $\dot{V}O_2$ should be expressed as both an absolute value and also as a percentage of the predicted value.

$\dot{V}CO_2$

CO_2 output is determined by factors similar to $\dot{V}O_2$, but because CO_2 is more soluble, CO_2 output is more closely related to $\dot{V}E$ than to $\dot{V}O_2$. Importantly, the body uses CO_2 to compensate for acute metabolic acidosis, which contributes to the $\dot{V}CO_2$ vs work intensity relationship above the point of anaerobic metabolism.

Accurate measurement of the CO_2 output is important, as it serves in the calculation of several meaningful derived variables. Moreover, because $\dot{V}E$ is so closely related to $\dot{V}CO_2$, it is helpful to analyze $\dot{V}E$ in relation to $\dot{V}CO_2$.

Respiratory Exchange Ratio (RER)

The RER is the ratio of $\dot{V}CO_2/\dot{V}O_2$, which, under steady state conditions, approximates the respiratory quotient. An RER of 1.0 indicates metabolism by primarily carbohydrates; 0.7, by primarily fat; and 0.8, by primarily protein. Values above 1.0 may indicate carbohydrate metabolism, but also CO_2 derived from lactic acidosis or importantly, hyperventilation. The RER should be reported as a function of the $\dot{V}O_2$.

Anaerobic Threshold (AT)

The AT (often referred to as the lactate threshold, lactate anaerobic threshold, or gas exchange threshold) is considered an indicator of the onset of metabolic acidosis caused predominantly by increased arterial lactate during exercise. The AT should be expressed as a percentage of the peak $\dot{V}O_2$. In healthy individuals, the AT occurs at 50% to 60% peak $\dot{V}O_2$, with

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the range of normal being 40% to 80%. The AT is affected by the type of exercise (lower for arm vs leg exercise) and method of testing (lower for cycle vs treadmill testing). From a practical point of view, the AT denotes the upper limit of exercise intensity that can be accomplished aerobically, and exercise above the AT is associated with a progressive decrease in exercise tolerance.

Invasive methods for measuring the AT include arterial blood sampling of lactate or bicarbonate. There are various methods for estimating the AT noninvasively (Fig 6), including the ventilatory equivalents method ($\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, $PETO_2$, $PETCO_2$), and the V-slope method ($\dot{V}CO_2$ vs $\dot{V}O_2$). Confirmatory evidence is provided by noting the change in slope of the $\dot{V}E$ vs $\dot{V}O_2$ relationship, and when the RER approximates 1.

Like the peak $\dot{V}O_2$, a reduced AT is nonspecific and requires inspection of other variables to determine the underlying etiology of the reduction. Values below 40% may be witnessed with a wide variety of cardiovascular, respiratory, and musculoskeletal conditions. In some patients with severe respiratory limitation (for example, severe COPD), the AT cannot be determined noninvasively.

HR and HR-$\dot{V}O_2$

In healthy individuals, HR increases linearly with increasing exercise and $\dot{V}O_2$. Predicted maximal HR is often estimated by 220 − age, but this equation may underestimate maximal heart rate in the elderly. The difference between predicted maximal HR and the observed maximal HR is called the heart rate reserve. In healthy individuals, there is little or no heart rate reserve at end-exercise, and this suggests a maximal or near-maximal patient effort. Peak HR may be reduced in a variety of cardiovascular conditions (including with pharmacologic agents) or in a submaximal study, but if a patient achieves predicted maximal HR, it suggests that cardiovascular function contributed to exercise limitation. In this instance, examination of other variables (ie, $\dot{V}O_2$, AT) will assist in the determination of whether this observation was normal or abnormal.

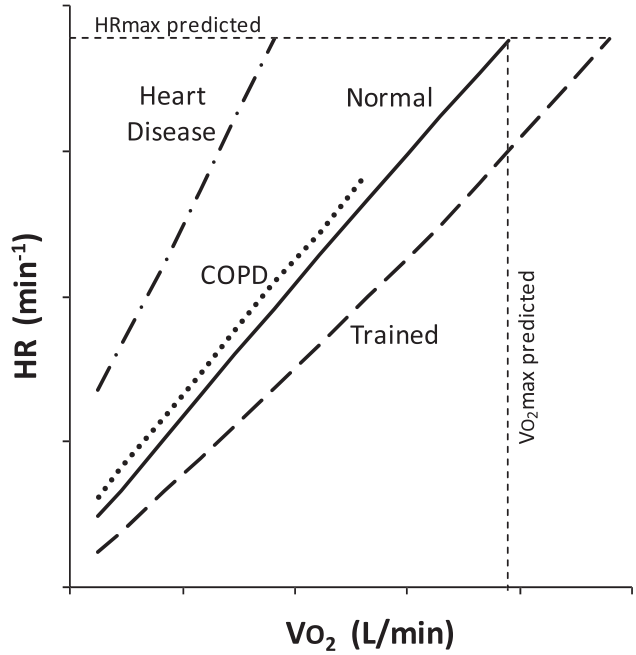

Figure 7. Cardiovascular responses during exercise in different clinical situations.

The slope of the HR-$\dot{V}O_2$ relationship is a function of SV, with the higher the SV, the lower the HR (Figs 2, 7). In patients with significant lung disease, the opposite may be seen, often reflecting deconditioning, mechanical ventilatory limitation, or potentially the hemodynamic consequences of dynamic hyperinflation.

Oxygen Pulse

The ratio of $\dot{V}O_2$ to HR is referred to as the O_2 pulse, and is often used as a correlate of stroke volume during exercise. While under ideal conditions this relationship generally holds true (Equations 1 and 2), in many settings the variable must be used with caution. The assumptions in the equations are not valid in the presence of significant desaturation, or with impaired skeletal muscle O_2 extraction. A low O_2 pulse may therefore not only reflect cardiovascular disease, but also deconditioning, early exercise termination due to respiratory factors, symptoms or submaximal effort, and/or the presence of arterial O_2 desaturation.

Blood Pressure

Systolic blood pressure typically rises progressively during exercise as $\dot{V}O_2$ increases, while

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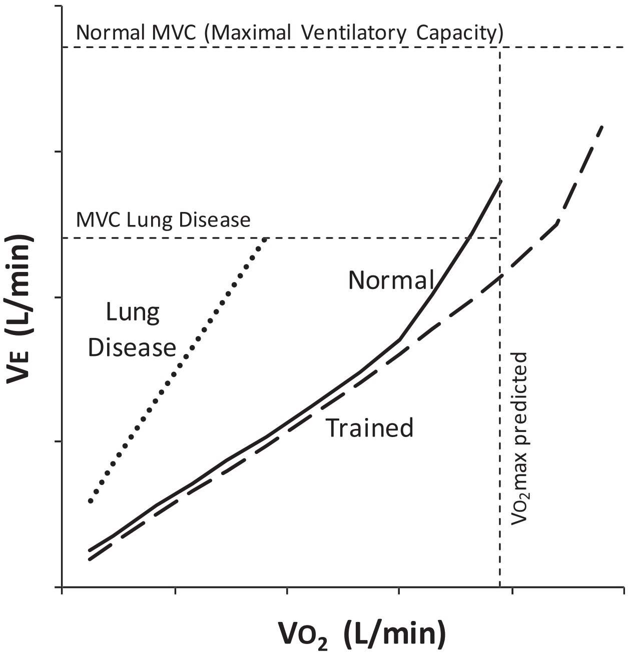

Figure 8. Respiratory responses during exercise in different clinical situations.

diastolic blood pressure typically increases only slightly or remains relatively unchanged. Abnormal patterns of response during exercise include an exaggerated rise, a reduced rise, or a fall. Exaggerated increases are seen with resting hypertension, but in those without a known diagnosis, may also predict the future onset of resting hypertension. A reduced rise may suggest underlying cardiovascular or sympathetic control abnormalities. A falling blood pressure during exercise is very serious, and an indication for immediate termination of the test. If this occurs, serious efforts to exclude heart failure, ischemia, or outflow tract obstruction should be undertaken.

Breathing Pattern and Ventilatory Responses During Exercise

The increase in $\dot{V}_E$ with exercise is accompanied by increases in both the depth and frequency of breathing (Fig 1). Increases in V_T are primarily responsible for the increase in $\dot{V}_E$ at low levels of exercise, but as exercise progresses, both V_T and respiratory rate increase. At 70% to 80% of peak exercise, increases in $\dot{V}_E$ are achieved primarily by increases in respiratory rate.

There are various methods used to estimate peak $\dot{V}_E$, including actual measurement of the maximal voluntary ventilation. Predicted maximal $\dot{V}_E$ may also be estimated with various equations, most commonly the $FEV_1 \times 37$–40. Unfortunately, none of these methods are perfect and there is a pressing need for enhancements in this area. The use of the maximal voluntary ventilation is limited by concerns about patient effort and repeatability, and with the unique breathing strategy adopted during the maneuver that does not parallel the strategy used during exercise. Equations are therefore most commonly used, but may be less suited for patients with neuromuscular disorders or respiratory muscle weakness. Despite these limitations and regardless of the method used, estimating the peak $\dot{V}_E$ has significant clinical utility and has withstood the test of time.

The terms *breathing* or *ventilatory reserve* are used to denote the relationship between predicted peak $\dot{V}_E$ and the actual measured peak $\dot{V}_E$, displayed both as an absolute value (in L) and as a percentage of the predicted peak $\dot{V}_E$. Patients with respiratory disease characteristically have reduced ventilatory capacity and increased ventilatory demand, resulting in reduced ventilatory reserve. Ventilatory demand is usually increased both at rest and during exercise in patients with COPD, ILD, and pulmonary vascular disease, for example due to ventilation-perfusion inequality and increased dead space ventilation, hypoxemia, and/or increased stimulation of lung receptors (which serves to increase ventilation). It is also dependent on other factors such as metabolic requirements, lactic acidosis, behavioral factors, deconditioning, body weight, and mode of testing. In most healthy adults, peak $\dot{V}_E$ at end-exercise approaches 70% of the maximal $\dot{V}_E$, although this percentage may be higher with increased fitness and with aging (Fig 8). In patients with significant respiratory disease and mechanical abnormalities, the patient's end-exercise $\dot{V}_E$ may reach or even exceed the predicted maximal peak $\dot{V}_E$. A plot of $\dot{V}_E$ vs either $\dot{V}CO_2$ or $\dot{V}O_2$ (see below) is acceptable for the graphical representation of ventilatory data.

An oscillatory breathing response during exercise may be seen in patients with CHF, and appears to be predictive of a poor outcome.[16,17]

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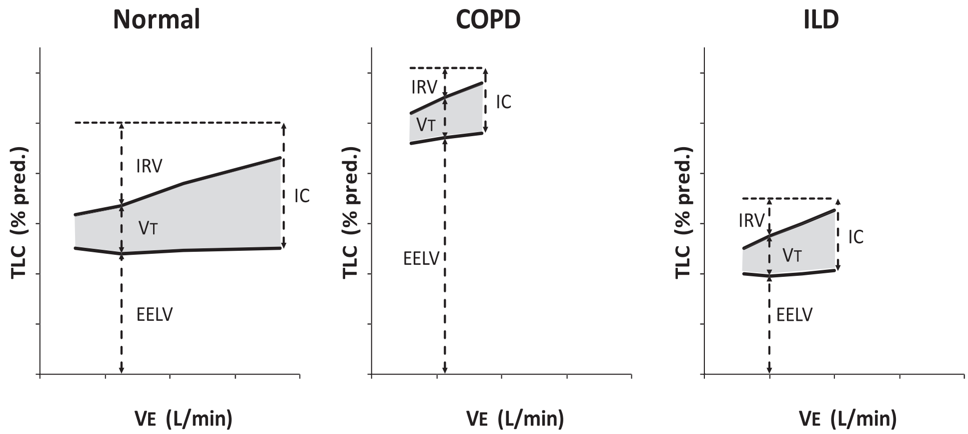

Figure 9. Behavior of operational lung volumes during exercise.

This pattern of cyclical fluctuations in $\dot{V}E$ of more than 30%, lasting between 40 and 140 s, is noted in as many as 50% of patients with significant CHF. Invasive hemodynamic monitoring has revealed that exercise oscillatory ventilation is related to reduced cardiac index and elevated filling pressures during exercise, and appears to reflect exercise-associated hemodynamic impairment in patients with CHF.[18]

Ventilatory Equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$

The ratio of $\dot{V}E$ to $\dot{V}O_2$ is called the ventilatory equivalent for O_2, and the ratio of $\dot{V}E$ to $\dot{V}CO_2$ is called ventilatory equivalent for CO_2. They are both related to V_{DS}/V_T, and are higher as V_{DS}/V_T increases. They also both increase with hyperventilation. Normal responses for these variables are shown in Figure 6 (bottom left). The initial increase in the $\dot{V}E/\dot{V}O_2$ (while the $\dot{V}E/\dot{V}CO_2$ has still not increased) that typically occurs in concert with metabolic acidosis is different from the pattern demonstrated with hyperventilation (attributable to anxiety, pain, or hypoxemia), whereby both the $\dot{V}E/\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ increase together. The subsequent increase in the $\dot{V}E/\dot{V}CO_2$ represents the respiratory compensation associated with a fall in the $PaCO_2$ and the $PETCO_2$.

The $\dot{V}E/\dot{V}CO_2$ is usually <34 at the AT, and usually <37–40 at end-exercise. Similarly, a peak $\dot{V}E/\dot{V}CO_2$ slope greater than 34 is also considered abnormal. Elevated values reflect either an increased V_{DS}/V_T or a low $PaCO_2$ from varied causes. A lack of an increase with exercise potentially reflects insensitivity to the stimulus of metabolic acidosis, an inability of the respiratory system to respond to that stimulus (ie, significant COPD), or physiologically submaximal exercise.

End-Tidal PO_2 ($PETO_2$) and PCO_2 ($PETCO_2$)

The characteristic response of these variables during exercise is shown in Figure 6 (bottom right). The period of increasing $PETO_2$ with relatively stable $PETCO_2$ has been termed *isocapnic buffering*. A high $\dot{V}E/\dot{V}CO_2$ without a corresponding fall in $PETCO_2$ suggests increased dead space ventilation, whereas a fall in $PETCO_2$ when the $\dot{V}E/\dot{V}CO_2$ is high suggests hyperventilation.

Flow-Volume Curves

While first reported in 1961, flow-volume curves during exercise were not adopted nor well studied until the 1990s. Since that time, our insight of their usefulness to better understand respiratory responses and symptoms during exercise has grown.[19] This greater understanding, coupled with advances in technology, has led to the routine analysis of flow-volume curves during exercise. The added value garnered from their use relates to their ability to provide information about the overall breathing strategy adopted by patients during exercise. They also enable an appreciation of the behavior of operational lung volumes, including the end-expiratory lung volume (derived from total lung capacity and the inspiratory capacity) and the

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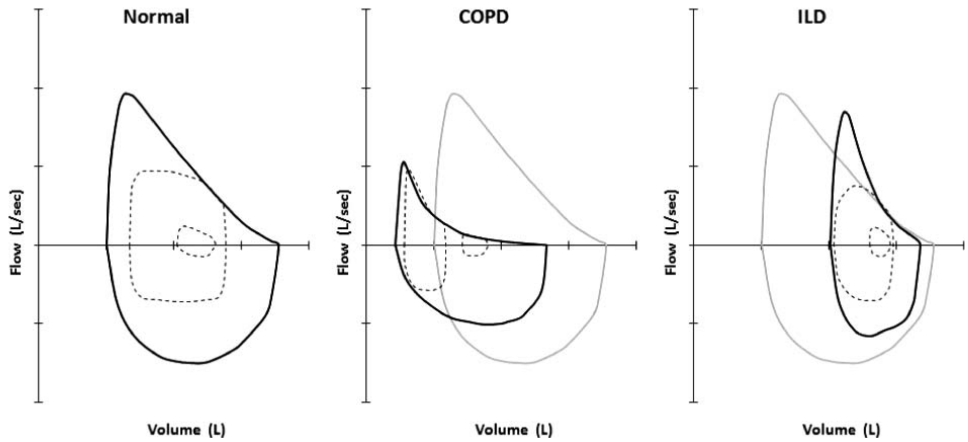

Figure 10. Maximal and tidal flow-volume curves at rest and during exercise.

end-inspiratory lung volume. Additionally, analysis of flow-volume curves provides an objective assessment of the presence and degree of flow limitation during exercise.

In patients with significant disease, there are a number of characteristic patterns of response in lung volumes that differ from healthy individuals (Fig 9, volume vs $\dot{V}_E$; Fig 10, flow vs volume). In addition to COPD and ILD, patients with significant obesity (see Fig 11 below) and central airway obstruction also demonstrate distinguishing responses.[20] Analysis of flow-volume curves during exercise is also useful in helping to assess a therapeutic response.[21,22]

In these examples, the end-expiratory lung volume, the inspiratory reserve volume, and the presence/absence of flow limitation serve to distinguish the various disease states from normal—these changes being unique and characteristic. The value of flow-volume curves during exercise is being further studied, and it is likely that additional indications and applications, such as using them to better estimate maximal ventilatory capacity, may be adopted.

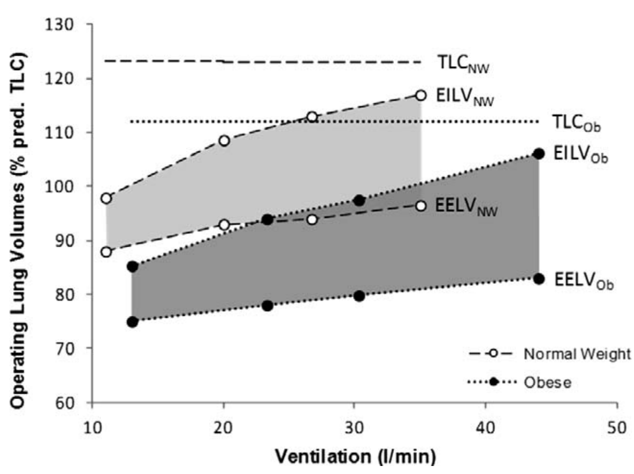

Figure 11. Operational lung volumes during exercise in obese and normal-weight patients with COPD. Adapted from Ora et al.[29]

Pa_{O_2}, Sa_{O_2}, and $P_{AO_2} - Pa_{O_2}$

Normal exercise responses are enabled by efficient gas exchange. Arterial hypoxemia is uncommon during exercise in healthy humans, but may occur in some elite or aging athletes during high-intensity exercise. Inefficient gas exchange is demonstrated by the alveolar-arterial P_{O_2} (P_{AO_2} – Pa_{O_2}) gradient and by the Pa_{O_2}. A significant widening of the gradient and fall in the Pa_{O_2} are abnormal, and most characteristic of ILD and significant right-to-left shunts, and in some patients with COPD and pulmonary vascular disease. A reduced Pa_{O_2} with a normal $P_{AO_2} - Pa_{O_2}$ may be seen in processes associated with abnormal respiratory control and in a hypoxic environment (ie, altitude), although the latter is rarely reproduced in the clinical laboratory. A reduced Pa_{O_2} with an abnormally widened $P_{AO_2} - Pa_{O_2}$ would suggest worsening $\dot{V}/\dot{Q}$ inequalities, right-to-left shunt, and/or diffusion limitation, potentially accompanied by a fall in the mixed venous P_{O_2}.

The $P_{AO_2} - Pa_{O_2}$ is normally $<$10 mm Hg at rest, but may normally increase to $>$20 mm Hg during exercise. Values $>$35 mm Hg are abnormal and indicate possible gas-exchange abnormalities. While occasionally a less-than-optimal substitute, oxygen saturation (Sa_{O_2}) determined by pulse oximetry is frequently used as an alternative to arterial blood gas sampling. In the healthy individ-

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ual, both the PaO_2 and the SaO_2 are not appreciably different during exercise when compared to rest.

Ratio of VDS/VT

The ratio of physiologic dead space to tidal volume is another index of gas exchange efficiency. An increase in V_{DS}/V_T represents an increased inefficiency of ventilation, which requires an increase in $\dot{V}_E$ to maintain $PaCO_2$. V_{DS}/V_T is highly dependent on the breathing pattern, as a rapid shallow breathing pattern increases V_{DS}/V_T without any other abnormalities.

The V_{DS}/V_T is calculated from the $PaCO_2$ and the P_{ECO_2} by using the following equation:

$$V_{DS}/V_T = \frac{(PaCO_2 - P_{ECO_2})}{PaCO_2} \quad (5)$$

where the P_{ECO_2} is the mixed expired CO_2 value of alveolar and dead space gas. It is obtained directly by collecting expired gas and measuring the CO_2 concentration. This can easily be done from a mixing chamber, or for breath-by-breath systems after determining the $\dot{V}_E/\dot{V}CO_2$ ratio. Approaches that substitute end-tidal PCO_2 for $PaCO_2$ yield unreliable results, particularly in disease, because pulmonary gas-exchange abnormalities in themselves affect the difference between $PaCO_2$ and P_{ETCO_2}.

At rest, the V_{DS}/V_T may normally be approximately 0.30, and fall to approximately 0.10 to 0.15 at end-exercise. Patients with respiratory disease may have at rest either normal or elevated values that fail to decrease normally during exercise. In some instances, the V_{DS}/V_T will increase during exercise in patients with significant disease. However, the V_{DS}/V_T is neither sensitive nor specific for lung disease, and thus an isolated abnormality should be interpreted with caution. This also emphasizes the importance of evaluating the patterns of response from a collection of variables rather than reacting to just a single measurement.

Symptoms During Exercise

Patients often report that breathlessness and/or leg fatigue limits their exercise, although other reasons such as musculoskeletal complaints and exhaustion are also reported. Objective evaluation of these endpoints is valuable, and the use of either a visual analogue scale[23] or a modified Borg scale[24] is recommended. These have shown to be repeatable and responsive, and are commonly used in clinical laboratories. The reproducibility of results obtained from these scales can be enhanced by providing a consistent set of written instructions to the patient before testing. As noted, the reason(s) for discontinuing exercise should be recorded. The value of these ratings is further enhanced when relationships such as $\dot{V}_E$ or work rate vs dyspnea or leg fatigue are examined, particularly in serial studies or after interventions.

Reference Values

The selection of appropriate reference values for use in interpreting CPET is essential. The reader is advised to consult source references[1,5,25] for guidance in selecting which reference values may be most appropriate for his or her specific clinical laboratory.

Reproducibility of CPET Results

Whenever serial testing is undertaken, for example to assess the response to therapy, the variability of the measurements during cardiopulmonary exercise testing must be considered before a beneficial, detrimental, or no effect can be concluded. The coefficient of variation (ratio of the standard deviation to the mean, expressed as a %) reported for serial measurements during maximal testing in the same subject are as follows (range of reported values listed):

$\dot{V}O_2$	3.0%–8.4%	$\dot{V}CO_2$	5.0%–9.6%
HR	1.4%–8.6%	$\dot{V}_E$	5.0%–12.3%
AT	9.2%–13.0%	Systolic BP	2.2%–6.7%
SaO_2	2.5%	Duration (work rate)	3.6%–13.8%

It should be understood that the variability depends on a number of factors, such as the population studied, the type of testing performed, and the specific variable examined. However, it appears reasonable to assume that differences in most measurements obtained during cardiopulmonary exercise testing should exceed approximately 12% to 20% in order to be considered clinically significant (ie, twice the coefficient of variation), and not due to inherent variability alone.

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Table 4—*Suggested Normal Values for Selected CPET Variables*

Variable	Normal Value
Peak $\dot{V}O_2$	>85% predicted
AT	>40% predicted peak $\dot{V}O_2$
Peak HR	>90% predicted peak HR
HR reserve	<15 beats/min
BP	<200/90 mm Hg
O_2 pulse ($\dot{V}O_2$/HR)	>80% predicted
Peak $\dot{V}E$	<85% (peak $\dot{V}E$/predicted peak $\dot{V}E$)
Ventilatory reserve	>11 L (predicted peak $\dot{V}E$ – peak $\dot{V}E$)
Respiratory rate	<60/min
$\dot{V}E/\dot{V}CO_2$	<34 at AT; <37–40 at end-exercise
V_{DS}/V_T	<0.30
PaO_2	>80 mm Hg
SaO_2 desaturation	<5%
P_{AO_2} - PaO_2	<35 mm Hg
Exercise-induced bronchoconstriction	<10% fall in FEV_1

Adapted from Weisman et al.[5]

Interpretation and Reporting of CPET

Interpretation of CPET begins with the requisition form. Requisition forms should be designed to encourage the requesting physician to provide as much clinical information as is reasonable to enable the interpretation to be valuable. This will enhance the ability of the reporting physician to provide the most meaningful interpretation possible from the available measured data.

There are a number of important fundamental questions that the reporting physician must address when interpreting cardiopulmonary exercise testing.[26] These include the following:

1. Are the results normal or abnormal?
2. How limited is the patient?
3. What factors are responsible for the limitation?
4. What abnormal patterns of response are demonstrated?
5. What clinical disorders may result in these patterns of response?

Determining whether a test is physiologically maximal is necessary in excluding potential underlying diseases or abnormalities. Useful indicators may include the following:

1. Plateau of peak $\dot{V}O_2$, or peak $\dot{V}O_2$ is achieved
2. Maximum work rate is achieved
3. HR or $\dot{V}E$ reaches predicted maximum
4. Respiratory exchange ratio >1.15
5. Blood lactate concentration >4 mM
6. Patient exhaustion

The clinician must also decide upon contributors to exercise limitation, and whether they are normal (ie, appropriate) or abnormal. Potential factors that may contribute to limit exercise include the following:

1. Cardiovascular function
2. Respiratory mechanics (and/or respiratory muscle function)
3. Arterial hypoxemia
4. Dyspnea
5. Unfitness/deconditioning
6. Musculoskeletal disorders, peripheral vascular disease
7. Other factors, for example, motivation, secondary gain, technical factors

While responses during exercise may vary in healthy individuals and the range of normal is quite broad, an understanding of "normalcy" and normal exercise physiology is essential for the recognition of disease. This understanding is essential for the appropriate interpretation of CPET. Suggested normal values for various measurements obtained during CPET are listed in Table 4.

In interpreting CPET, it is important to focus on what is most important, on patterns of responses during exercise, and the reason(s) for testing. This focus will ensure that a correct and meaningful interpretation will result. Current systems almost robotically produce a multitude of both graphical and numerical results. This abundance of "results," and an overreliance and overdependence on complicated algorithms, have contributed to confusion. They undermine the cardinal measurements and relationships, the fundamental importance of patient's symptoms during exercise, and the basic physiologic principles that help us to better understand and appreciate the role and benefit (as well as the limitations) of exercise testing in clinical practice. They also detract from the practical reality that, unlike in textbooks, guideline statements and/or the lecture hall, CPET is never ordered nor interpreted in isolation. It should be requested,

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Table 5—*Characteristic Patterns of Response During Exercise in Various Settings*

Variable	CHF	COPD	ILD	PVD	Deconditioned
Peak $\dot{V}O_2$	↓	↓	↓	↓	↓
AT	↓	V or indeterminate	↓	↓	↔ or ↓
Peak HR	V	↔ or ↓	↓	↔ or ↓	↔ or ↓
O_2 Pulse	↓	↔ or ↓	↔ or ↓	↓	↓
Peak $\dot{V}E$/MVV	↔ or ↓	↑	↔ or ↑	↔	↔
$\dot{V}E/\dot{V}CO_2$	↑	↑	↑	↑	↔
V_{DS}/V_T	↑	↑	↑	↑	↔
PaO_2	↔	V	↓	↓	↔
PAO_2 - PaO_2	↔	V	↑	↑	↔

MVV = maximal voluntary ventilation; PVD = pulmonary vascular disease; V = variable; ↓ = decreased; ↔ = unchanged from normal; ↑ = increased. Adapted from Palange et al,[4] Weisman et al,[5] Wasserman et al,[25] and Marciniuk and Gallagher.[27,28]

and its results translated within the context of all available clinical information from the patient, with the specific goal of addressing the question(s) being asked. CPET does not replace common sense—starting with the clinical assessment of the patient. For example, there are more appropriate methods than CPET to differentiate COPD from ILD. To aid in achieving this goal, the characteristic patterns of response during exercise, demonstrated in various disease states, are noted in Table 5. These values highlight the importance of understanding that no single measurement is diagnostic of any specific disease entity.

Some special clinical circumstances require comment. While obese individuals have well-documented impairments in respiratory function, obese patients with COPD may paradoxically have similar or better dyspnea scores during exercise and comparatively preserved (or improved) exercise capacity and peak $\dot{V}O_2$. These observations may be attributable to the finding that obese patients with COPD have lower operating lung volumes at rest and during exercise (Fig 11),[29] although further study is required to better understand these observations. Another unique setting becoming increasingly realized is when multiple comorbid conditions coexist, which may together act to further impair exercise capacity. For example, subjects with heart failure and coexistent COPD demonstrated a significantly lower maximal $\dot{V}O_2$, and a significantly higher $\dot{V}E/\dot{V}CO_2$ slope, as compared to otherwise comparable patients with heart failure.[30] Comorbidities in COPD are common and include osteoporosis and arthritis (50%–70%), depression (25%), ischemic heart disease (10%–23%), anemia (17%), diabetes (12%–13%), cerebrovascular disease (10%–14%), chronic renal failure (6%-11%), and chronic heart failure (5%–7%).[31] In these instances, interpretation should be partnered closely with the clinical setting and recognition of all potential comorbid conditions that could either alone or collectively affect exercise performance.

Summary

CPET typically involves the measurement of respiratory gas exchange (oxygen uptake [$\dot{V}O_2$], carbon dioxide output [$\dot{V}CO_2$], minute ventilation [$\dot{V}E$], and other variables) while monitoring the ECG, blood pressure, pulse oximetry (SaO_2), and perceived exertion (Borg Scale) during a maximal symptom-limited incremental exercise test on a cycle ergometer or on a treadmill. In some circumstances, a constant workload exercise test (based on maximal test results) may be performed. Measurement of arterial blood gases provides more detailed information on pulmonary gas exchange. Resting and exercise tidal flow-volume loops should also be monitored to accurately assess/understand the degree of ventilatory constraint.

CPET provides a global assessment of the integrative exercise responses, which are not adequately reflected by measurement of individual organ system function at rest—resting values cannot reliably predict exercise performance and functional capacity. CPET is safe, and comorbidities can be identified, while enhanced understanding and insight into various responses,

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including exercise limiting factors, is possible. Importantly, CPET promotes an integrative approach to assessing metabolic, ventilatory, and cardiac function and reserve. While technically more demanding than simpler tests, CPET provides measurement of the peak $\dot{V}O_2$ (and relationships involving the peak $\dot{V}O_2$), which remains the gold standard for assessing aerobic exercise capacity.

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References

1. Jones NL. *Clinical Exercise Testing*. 4th ed. Philadelphia, PA: Saunders; 1997.
2. Gallagher CG. Exercise and chronic obstructive pulmonary disease. *Med Clin N Am*. 1990;74(3): 619–641.
3. Palange P. The prognostic value of exercise testing. *Breathe*. 2009;5(3):229–234.
4. Palange P, Ward SA, Carlsen K-H, et al. Recommendations on the use of exercise testing in clinical practice–ERS Task Force. *Eur Respir J*. 2007;29(1):185–209.
5. Weisman IM, Beck K, Casaburi R, et al. American Thoracic Society/American College of Chest Physicians Joint Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med*. 2003; 167(2):211–277.
6. Colice G, Shafazan S, Griffin J, Keenan R, Bolliger C. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 suppl):161S–177S.
7. Sue DY. Excess ventilation during exercise and prognosis in chronic heart failure. *Am J Respir Crit Care Med*. 2011;183(10):1302–1310.
8. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic evaluation of diastolic heart failure. *JACC*. 2005; 46(10):1883–1890.
9. Crapo RO, Casaburi R, Coates AL, et al. ATS statement: guidelines for methacholine and exercise challenge testing–1999. *Am J Respir Crit Care Med*. 2000;161(1):309–329.
10. Trooster T, Sciurba F, Battaglia S, et al. Physical inactivity in patients with COPD: a controlled multi-center pilot-study. *Respir Med*. 2010;104(7): 1005–1011.
11. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–117.
12. Marciniuk DD, Butcher SJ, Reid JK, et al. The effects of helium-hyperoxia on 6-min walking distance in COPD: a randomized, controlled trial. *Chest*. 2007;131(6):1659–1665.
13. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005–1012.
14. Pepin V, Brodeur J, Lacasse Y, et al. 6-minute walking versus shuttle walking: responsiveness to bronchodilation in chronic obstructive pulmonary disease. *Thorax*. 2007;62(4):291–298.

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15. Brouillard D, Pepin V, Milot J, Lacasse Y, Maltais F. Endurance shuttle waling test: responsiveness to salmeterol in COPD. *Eur Respir J*. 2008;31(3): 579–584.
16. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J*. 2007;153(5): 859–867.
17. Sun XG, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *J Am Coll Cardiol*. 2010; 55(17):1814–1823.
18. Murphy RM, Shah RV, Malhotra R, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. *Circulation*. 2011;124(13):1442–1451.
19. Johnson BD, Weisman IM, Zeballos RJ, et al. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest*. 1999;116(2):488–503.
20. Babb TG. Mechanical ventilatory constraints in aging, lung disease, and obesity: perspectives and brief review. *Med Sci Sports Exerc*. 1999;31(1 suppl):S12–S22.
21. Maltais F, Marciniuk DD, Hernandez P, et al. Improvements in symptom-limited exercise performance over eight hours with once-daily Tiotropium in patients with COPD. *Chest*. 2005; 128(3):1168–1178.
22. O'Donnell DE, Sciurba F, Celli B, et al. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest*. 2006;130(3):647–656.
23. Gift AG. Visual analogue scales: measurement of subjective phenomena. *Nurs Res*. 1989;38(5): 286–288.
24. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14(5):377–381.
25. Wasserman K, Hansen JE, Sue DY, et al. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
26. Younes M. Interpretation of clinical exercise testing in respiratory disease. *Clin Chest Med*. 1984;5(1):189–206.
27. Marciniuk DD, Gallagher CG. Clinical exercise testing in interstitial lung disease. *Clin Chest Med*. 1994;15(2):287–303.
28. Marciniuk DD, Gallagher CG. Clinical exercise testing in chronic airflow limitation. *Med Clin N Am*. 1996;80(3):565–587.
29. Ora J, Laveneziana P, Ofir D, Deesomchok A, Webb KA, O'Donnell DE. Combined effects of obesity and chronic obstructive pulmonary disease on dyspnea and exercise tolerance. *Am J Respir Crit Care Med*. 2009;180(10):964–971.
30. Guazzi M, Myers J, Vicenzi M, et al. Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant chronic obstructive pulmonary disease. *Am Heart J*. 2010;160(5):900–905.
31. Patel AR, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med*. 2011;5(5): 647–662.

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Notes

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