INTRODUCTION
Sustained exercise requires tight integration of multiple physiologic systems including the cardiac, neuromuscular, and respiratory systems. Diseases affecting any of these systems can manifest as dyspnea or exercise limitation. In addition to other modalities commonly used in the assessment of patients with these complaints, cardiopulmonary exercise testing (CPET) provides a systematic means to assess exercise responses, unravel the different interacting components, and understand which system is contributing the most to the perceived limitation. Beyond this primary role, CPET has other important uses including (1) quantifying maximal exercise capacity and generating data that can be used to assess functional limitation, (2) prescribing appropriate rehabilitation and training regimens, and (3) guiding clinical decisions about fitness for planned procedures.

The goals of this chapter are to describe the application of CPET in clinical practice and assist the reader in understanding who would benefit from CPET and how it can be used to evaluate dyspnea and exercise limitation. Because CPET interpretation requires a solid understanding of the physiologic responses to exercise, the chapter begins with a review of exercise physiology that sets the foundation for the balance of the chapter. The review includes exercise responses in normal individuals and those with various forms of cardiopulmonary disease, including heart failure, chronic obstructive pulmonary disease (COPD), pulmonary vascular disease, interstitial lung diseases (ILDs), and adult congenital heart disease. The chapter then describes the primary indications and contraindications of CPET, reviews the various options for conducting exercise tests, and presents an approach to test interpretation. It concludes by describing alternative modalities for assessing exercise responses that are used in clinical practice.

PHYSIOLOGIC RESPONSES TO EXERCISE

EXERCISE AS A MULTISYSTEM PROCESS
The ability to perform vigorous aerobic exercise requires tight integration of multiple systems. The respiratory system serves as a ventilatory pump to move oxygen \( \text{O}_2 \) from the atmosphere to the alveoli, where it efficiently moves across the alveolar walls to bind to hemoglobin. The heart must then pump the oxygenated blood to the exercising muscles, which extract oxygen to support adenosine triphosphate generation and muscle contraction. Muscle activity leads to production of carbon dioxide \( \text{CO}_2 \), which must be delivered by the circulatory system to the lungs, where it diffuses across the alveolar walls and is eliminated via the ventilatory pump. The nervous system contributes at multiple stages in this process, providing important signals to increase ventilation and drive muscular contraction. All of these systems work in a highly coordinated manner to support exercise, and problems in one or more of these systems may manifest as dyspnea or exercise limitation.

NORMAL INDIVIDUALS
To appreciate changes in exercise performance associated with cardiopulmonary diseases, it is helpful to examine the normal physiologic responses to progressive exercise in four major areas—metabolic activity, hemodynamic responses, ventilatory responses, and gas exchange.

Metabolic Activity
Oxygen Consumption. Of all the parameters followed in clinical exercise testing, oxygen consumption, denoted as \( \text{VO}_2 \) (a volume per time, e.g., mL/min), is perhaps the most useful for assessing overall exercise capacity. In essence, \( \text{VO}_2 \) is the amount of fuel consumed in conducting work; the bigger or better the motor, the greater the maximum fuel consumption. To understand its utility in this regard, consider the determinants of \( \text{VO}_2 \) using the Fick equation:

\[
\dot{Q} = \frac{\dot{\text{V}}\text{O}_2}{\text{CaO}_2 - \text{CvO}_2}
\]

where \( \dot{Q} \) = cardiac output (mL/min), \( \text{CaO}_2 \) = arterial oxygen content (mL/dL), and \( \text{CvO}_2 \) = mixed venous oxygen content (mL/dL). Rearranging the relationship as follows,

\[
\dot{\text{V}}\text{O}_2 = \dot{Q}(\text{CaO}_2 - \text{CvO}_2)
\]
demonstrates that oxygen consumption is dependent on cardiac output; oxygen content, which is related to the
amount of hemoglobin and the partial pressure of oxygen; and the ability of the tissues to utilize oxygen. As a result, \( \dot{V}O_2 \) provides useful information about many of the systems necessary to perform sustained high-level exercise.

In addition to providing a sense of overall exercise capacity, the maximum oxygen consumption (\( \dot{V}O_{2\text{max}} \)) achieved during progressive exercise is particularly useful for assessing cardiac function. Given that the arteriovenous oxygen content difference at maximum exercise is largely the same in normal individuals and those with cardiac disease, the wide variation in \( \dot{V}O_{2\text{max}} \) across individuals is primarily determined by the variation in cardiac output. The greater the \( \dot{V}O_{2\text{max}} \), the greater an individual’s cardiac output and vice versa.

Oxygen consumption can also be used to estimate stroke volume at maximum exercise. To understand this, equation (2) can be rewritten:

\[
\dot{V}O_2 = HR \times SV(CaO_2 - C\bar{V}O_2)
\]

and then rearranged as:

\[
\frac{\dot{V}O_2}{HR} = SV \times (CaO_2 - C\bar{V}O_2)
\]

The constancy of the arteriovenous oxygen content difference across normal individuals at maximum exercise means that the term \( \dot{V}O_2/HR \), referred to as the oxygen pulse or \( O_2 \) pulse, can be used as a surrogate marker for stroke volume. The expected changes in normal individuals for this parameter, as well as cardiac output, are described as follows.

During progressive exercise to a symptom-limited maximum, \( \dot{V}O_2 \) increases linearly from resting values near 250 mL/min for an average-sized person until a plateau is reached at \( \dot{V}O_{2\text{max}} \). If a plateau is not identified, the term \( \dot{V}O_{2\text{peak}} \) is often applied instead to denote that it may not represent the individual’s potential maximum. In average sedentary individuals, \( \dot{V}O_{2\text{max}} \) is roughly 30 to 40 mL/kg/min at end-exercise, whereas fit athletes can attain values as high as 80 to 90 mL/kg/min. An individual’s \( \dot{V}O_{2\text{max}} \) is influenced by a variety of factors including age and gender, which are discussed further later. With intensive training, unfit subjects can increase \( \dot{V}O_{2\text{max}} \) by 15% to 25%, but it is not possible to raise \( \dot{V}O_{2\text{max}} \) from an average level to an elite level. What tends to improve with training is the efficiency of work and ability to sustain high levels of power output. Genetic factors also play an important role in determining an individual’s \( \dot{V}O_{2\text{max}} \) in the sedentary state, as well as in their response to training regimens. In clinical exercise testing, an individual’s \( \dot{V}O_{2\text{max}} \) is typically expressed in reference to what would be predicted for their age and gender on the basis of data from large population studies. Numerous reference values have been published, but methodologic issues limit the wide applicability of many of them. As with all reference values, the normal range is dependent on the population studied. For example, Hansen and colleagues used studies from ex-shipyard workers who tended to be primarily older men while Neder and colleagues randomly selected their subjects to include equal numbers of men and women uniformly drawn across ages 20 to 80.

Carbon Dioxide Output. With increasing work, carbon dioxide output (\( \dot{V}CO_2 \)) increases linearly from resting values, which are near 200 mL/min for an average-size person, at about the same rate as oxygen consumption. Above the ventilatory threshold, an important exercise time point described further later, the rate of \( CO_2 \) output steepens as bicarbonate buffering of increasing lactate production leads to \( CO_2 \) production beyond that generated by aerobic metabolism.

Respiratory Exchange Ratio. Defined as \( CO_2 \) production divided by oxygen uptake (\( \dot{V}CO_2/\dot{V}O_2 \)), the respiratory exchange ratio (R) remains largely stable between 0.8 and 0.9 in early to mid-exercise, with slight variation between individuals depending on the balance of dietary fats and carbohydrates. Just before and in the early stages of exercise, R can transiently increase due to anticipatory hyperventilation. Above the ventilatory threshold, \( VCO_2 \) increases markedly and R increases above 1.0. With cessation of exercise, \( \dot{V}O_2 \) decreases abruptly while \( VCO_2 \) remains elevated as tissue \( CO_2 \) stores continue to be eliminated. R can subsequently increase over 1 to 2 minutes to values as high as 1.3 to 1.5 before returning to baseline levels.

Ventilatory Thresholds. Normal individuals demonstrate a phenomenon termed the ventilatory threshold at about 50% to 60% of \( \dot{V}O_{2\text{max}} \), although there is considerable interindividual variability in the timing of this phenomenon. This threshold marks a critical point in progressive exercise where blood flow to the exercising muscle is no longer sufficient to meet metabolic demands and the individual is transitioning from light-moderate to moderate-high-intensity exercise. Alternatively referred to as the lactate threshold, gas exchange threshold, or anaerobic threshold, the phenomenon is usually related to an increase in lactic acid production and a decrease in pH, with considerable debate regarding the mechanisms for the increased lactate production and whether it happens suddenly or in a more continuous manner throughout exercise. As lactic acid dissociates, hydrogen ions are buffered by intracellular bicarbonate leading to further \( CO_2 \) generation beyond that associated with aerobic metabolism. This leads to a steep rise in the \( VCO_2 \) versus work relationship, as well as the \( VCO_2 \) versus \( \dot{V}O_2 \) relationship (Fig. 26-1). Identifying the change in slope of the latter relationship is referred to as the V-slope method and is a key step in CPET interpretation described later in this chapter.

With further increases in work beyond the ventilatory threshold, many individuals demonstrate a second ventilatory threshold, sometimes referred to as the respiratory compensation point, at which rising lactate concentrations cannot be buffered by intracellular bicarbonate, and minute ventilation (\( V\), which increases beyond that expected for the increase in \( VCO_2 \), thereby leading to a respiratory alkalosis. This point, which may not be visible in all individuals due to interindividual variation in ventilatory responses to metabolic acidosis, can be identified by finding threshold responses in several ventilatory parameters described further later.

Further information on how to identify various thresholds is provided in “Interpreting Cardiopulmonary Exercise Tests” later.
Cardiac Output. Cardiac output (mL/min), which can be either estimated from oxygen uptake using the Fick principle, measured invasively with a pulmonary artery catheter, or estimated noninvasively using inert gas rebreathing techniques, increases linearly with workload before reaching a plateau near peak exercise. The initial increase is a function of increasing stroke volume and heart rate, whereas the changes seen near peak exercise are driven primarily by increases in heart rate.

Heart Rate. Due initially to decreased vagal tone and later to increases in sympathetic activity, heart rate (beats/min) increases linearly with increasing oxygen consumption. The heart rate reserve, defined as the difference between the maximum predicted heart rate and the heart rate achieved at peak exercise, is typically small or nonexistent in normal individuals (<20 beats/min), but this parameter is difficult to use in exercise test interpretation due to significant variability in maximum heart rates in normal age-matched individuals. Another measure of heart rate response, also termed the heart rate reserve, is the difference between the resting and maximal heart rate. This review uses the former definition.

Pulmonary Artery Pressure. Pulmonary artery pressure rises only modestly with progressive exercise in normal individuals, due to recruitment and distention of the pulmonary vasculature and the subsequent decrease in pulmonary vascular resistance. There is interindividual variability in observed responses, with greater variability seen in older individuals. For physiologic implications of pulmonary vascular recruitment see Chapter 4.

Stroke Volume. Characterized during CPET by the O2 pulse (described earlier), stroke volume increases in early exercise before leveling off and possibly decreasing slightly at high levels of exercise. The initial increases are driven largely by mobilization of blood from lower extremity venous capacitance vessels, whereas later, smaller increases result from increased inotropic activity.

Systemic Blood Pressure. Due to increases in cardiac output and vascular resistance in the skin and renal and splanchnic circulations, systemic blood pressure (mm Hg) increases with progressive exercise. Although vasodilation in exercising muscle beds limits the rise in diastolic pressure, systolic pressure rises significantly, particularly following the ventilatory threshold, and may reach values over 200 mm Hg at peak exercise.

Ventilatory Responses

Minute Ventilation. Due to an increase in both the respiratory rate and tidal volume, minute ventilation (VE, mL/min) rises throughout exercise with large increases seen following the ventilatory threshold. The tidal volume plateaus at about 50% to 60% of vital capacity, after which further increases in VE are driven solely by increases in respiratory rate. At peak exercise, VE is typically less than 80% of the predicted maximum, as estimated by the maximum voluntary ventilation (MVV) or forced expiratory volume in 1 second (FEV1) × 40.

Ventilatory Equivalents for Oxygen and Carbon Dioxide. The ventilatory response can be expressed as a function of the amount of ventilation per liter of oxygen consumed (VE/VO2, unitless) or per liter of exhaled carbon dioxide (VE/VCO2, unitless). Both ratios remain relatively steady (~24 to 30) through early exercise as ventilation rises proportionately with VO2 and VCO2. Due to the large increases in VE noted earlier, both parameters rise following the ventilatory threshold, peaking at around 35 to 40, with slightly greater increases seen in the VE/VO2. Both parameters may be elevated in early exercise in highly fit or anxious individuals but typically return to the normal range as exercise progresses and reach their nadir just before the ventilatory threshold. The range of ventilatory equivalents seen across normal individuals reflects the variability in respiratory drives in the population.

Dead Space Fraction. Because of increased tidal volumes and recruitment of the pulmonary vasculature resulting from increased pulmonary blood flow, the dead space fraction (VD/VT, unitless) normally decreases from 0.3 to 0.4 at rest to less than 0.2 at peak exercise, with the lowest values seen in younger individuals.

Gas Exchange

Arterial and End-Tidal Partial Pressures of Carbon Dioxide. Despite increasing VCO2, the arterial (Paco2, mm Hg) and end-tidal partial pressure (PETCO2, mm Hg) of carbon dioxide remain near normal through early exercise due to the fact that alveolar ventilation rises proportionally with increasing VCO2. Low values may be seen in normal individuals who hyperventilate at the start of exercise, but these values typically normalize over the first few minutes of work. Following the ventilatory threshold, minute and alveolar ventilation rise out of proportion to the increase in VCO2, and, as a result, both arterial PCO2 and PETCO2 decrease so that both values are nearly always less than 40 mm Hg at VO2max.
Arterial and End-Tidal Partial Pressures of Oxygen and the Alveolar-Arterial Oxygen Difference. Below the ventilatory threshold, both the end-tidal partial pressure of oxygen (PETO2, mm Hg), which is used as a surrogate measure of alveolar oxygen tensions, and the arterial (PO2, mm Hg) remain in the normal range, as do both the arterial oxygen saturation (Sao2, %) and the alveolar-arterial oxygen difference ((A-a)PO2, mm Hg). As normal individuals pass their ventilatory threshold and approach maximum exercise, PETO2 increases due to alveolar ventilation that increases out of proportion to VO2.

While the alveolar PO2 increases, the arterial PO2 remains unchanged due to a lower CVO2 and normal physiologic shunting. As a result, the (A-a)PO2 increases slightly with heavy exercise. In a minority of highly fit individuals with high VO2max, arterial PO2 and arterial SO2 can decline in late exercise, a phenomenon referred to as exercise-induced arterial hypoxemia.

In CPET, the changes in many of the parameters described earlier can be identified from tabular data but are often best appreciated graphically using an approach developed by Wasserman and colleagues in which nine separate graphs are displayed in a standardized format. The exercise responses in normal individuals described earlier are depicted in this manner in Figure 26-2.

Changes with Age

Perhaps the most important change in exercise responses with aging is the decrease in maximum exercise capacity, which has been consistently reported in both cross-sectional and longitudinal studies. The expected rate of decline in VO2max is unclear because documented rates vary from as low as 0.28 mL/kg/min/yr to as high as 1.04 mL/kg/min/yr, with much of the variation attributable to differences in study design such as participant age, activity levels at the time of enrollment, and time intervals over which the study took place. Although some studies demonstrate a slower rate of decline in active individuals compared with sedentary individuals, others have reported no effect of activity level on age-related declines in VO2max. Training programs in older sedentary individuals may be able to reverse much of the age-related decline in VO2max, which accelerates in the later stages of life.

The etiology of the decrease in VO2max varies depending on the time period examined. Between 20 and 50 years of age the decline in VO2max is largely attributable to impaired peripheral oxygen extraction, whereas later changes relate to impaired peripheral extraction and decrements in maximum cardiac output due to an inability to raise stroke volume at maximum exercise. Impairment in peripheral extraction may be due to decreases in lean body mass, age-related changes in skeletal muscle, or blood flow distribution at peak-exercise; the decline in cardiac output may represent the increasing incidence of comorbid conditions affecting cardiac performance.

Gender Differences

Comparisons of exercise responses in men and women are difficult because the majority of studies of physiologic responses to exercise have been performed in men. The available evidence shows that women have the same qualitative responses to exercise as men but have lower VO2max, even after accounting for differences in lean body mass and training status. The mechanism for the observed differences remains unclear but may relate to differences in blood volume, heart size, hormonal and metabolic status, as well as autonomic nervous system regulation of the heart and vascular system. Although some studies report slower age-related rates of decline in VO2max in women compared with men, a recent large, cross-sectional study found no differences in this regard.

Ventilatory responses and gas exchange may also differ by gender, with some studies noting higher VE/VO2 and VEE/VO2 in women and others reporting higher (A-a) PO2 in fit women at high levels of oxygen consumption. At high exercise intensities, women may also rely more heavily than men on fat oxidation as a fuel source and, as a result, may have a lower respiratory exchange ratio.

Obesity

Obese individuals lacking underlying cardiac or pulmonary disease display VO2max lower than predicted for age and gender when expressed per kilogram of actual body weight but normal values when adjusted for ideal body weight. Because of the increased metabolic requirements resulting from their increased weight, however, several important differences are observed relative to nonobese individuals. VO2 for any given level of work is higher than in the nonobese, although the rate of change in oxygen consumption per given change in work rate (ΔVO2/ΔWR) remains the same. Obese individuals also have markedly increased VO2 when pedaling without resistance (unloaded pedaling) due to the energy demands of moving heavier legs against gravity that is not reflected in the work rate reported on the cycle ergometer.

Another consequence of the increased metabolic requirements is an increase in VE for a given work rate compared with the nonobese due to the added CO2 production from the additional tissues. This is typically achieved by increasing respiratory rate rather than tidal volume, which some data suggest is decreased during exercise relative to normal individuals, possibly due to the increased inspiratory load associated with extra chest wall soft tissue. Obese individuals also have difficulty decreasing end-expiratory lung volume during exercise, likely as a result of expiratory flow limitation and air trapping.

The presence and magnitude of observed differences in these parameters may be a function of the degree of obesity, with greater differences seen in heavier individuals. The presence or absence of comorbid conditions may also be important, as demonstrated by Vanhecke and colleagues, who showed that obese individuals (average body mass index 49 ± 9 kg/m2) with obstructive sleep apnea (OSA) have lower VO2max, increased systolic and diastolic blood pressure, and impaired heart rate recovery compared with obese patients lacking OSA.

INDIVIDUALS WITH UNDERLYING CARDIOPULMONARY DISEASE

The physiologic responses to exercise described earlier are altered by the presence of underlying cardiopulmonary disease with different responses seen depending on the particular disease process.
Heart Failure

As in normal individuals, maximum exercise in patients with heart failure is limited by the amount of blood that can be delivered to exercising muscle (i.e., they have a cardiac limitation to exercise). As a result, patients with heart failure demonstrate the same patterns of physiologic responses during progressive exercise to a symptom-limited maximum, albeit with significant differences in the magnitude of many of the observed responses.

The most important difference is the decrease in $\dot{V}O_2^{\text{max}}$, which does not vary in magnitude between patients with systolic or diastolic dysfunction, results from an inability to raise cardiac output adequately due to impaired stroke volume responses with progressive exercise, denoted by the decreased $\dot{V}O_2/HR$. The ventilatory threshold is still usually reached at 50% to 60% of $\dot{V}O_2^{\text{max}}$, but because $\dot{V}O_2^{\text{max}}$ is decreased, the threshold is at a lower $\dot{V}O_2$ compared with normal individuals.

Many patients with heart failure compensate for the decreased stroke volume with an increase in heart rate for any given level of work. As a result, the heart rate reserve
at peak exercise is usually small (<20 beats/min). There is considerable variability in these responses, however, with some patients manifesting an inability to raise heart rate with progressive exercise, a phenomenon referred to as *chronotropic incompetence*, that persists even following discontinuation of β-blockers.54 Patients with heart failure also may demonstrate an abnormal decline in heart rate on stopping exercise. In particular, heart rate recovery, which takes place as a result of reactivation of vagal tone55 and is defined as the difference between peak heart rate and heart rate 1 minute into the recovery period, is decreased compared with normal individuals.

Altered ventilatory responses have also been described in patients with heart failure including increased airway resistance,66 expiratory flow limitation at low work rates,57 and an increased ventilatory reserve due to the fact that they are not able to do as much work and therefore do not require a high VE. Perhaps the most important difference, however, is the increased ventilatory inefficiency in patients with moderate to severe systolic or diastolic dysfunction, as indicated by an increased VE/VCO2 at the ventilatory threshold or an increased slope of the relationship between these parameters (ΔVt/ΔVCO2).52,53 The most likely cause of this phenomenon is an increase in physiologic dead space due to impaired lung perfusion. Studies have shown, for example, that ventilatory inefficiency is related to abnormal pulmonary vascular tone58 or right ventricular dysfunction59 and actually improves following treatment with phosphodiesterase inhibitors and improvements in right ventricular function even when left ventricular function is unchanged.60 Abnormal peripheral and central chemoreceptor sensitivity may also play a role in augmenting ventilation above that necessary for a given level of CO2 production.61

Between 13% and 50% of patients with heart failure demonstrate another abnormal ventilatory response, referred to as *exercise oscillatory ventilation*, in which exercise ventilation is marked by periodicity similar to that seen in central sleep apnea.62-64 The mechanism for this is not clear but may relate to increased circulatory times, increased peripheral chemoreceptor sensitivity, increased ventilatory responses related to pulmonary congestion, and increased ergoreflex signaling (a peripheral reflex originating in skeletal muscle) related to muscle metabolic abnormalities.64 Exercise oscillatory ventilation may be a marker of reduced cardiac index both at rest and during exercise65 and may also improve following therapeutic interventions directed at the underlying heart failure such as treatment with sildenafil66 or an exercise training program.67 Despite these altered ventilatory responses, patients with heart failure have a normal (A-a)PO2 and do not develop hypoxemia during exercise even though pulmonary artery occlusion pressure is elevated.68,69

The pattern of exercise responses seen in patients with heart failure is displayed graphically in Figure 26-3.

### Pulmonary Vascular Disease (for discussion of clinical aspects of pulmonary vascular disease, see Chapter 58)

In many respects, patients with pulmonary vascular diseases such as *pulmonary arterial hypertension* (PAH) and chronic thromboembolic pulmonary hypertension demonstrate physiologic responses to progressive exercise similar to those seen in patients with heart failure. Relative to normal individuals, VO2max, peak work rate and VO2/HR are decreased while the ventilatory threshold is reached at a lower VO2. Similar to patients with heart failure, the observed decline in VO2max, which correlates inversely with mean pulmonary arterial pressure,70 is due to an inability to raise cardiac output in response to exercise. The decreased cardiac output in patients with pulmonary hypertension exists because the right ventricle is unable to adequately preload the left ventricle due to high pulmonary vascular resistance.71 The fact that treatment with a pulmonary vasodilator such as sildenafil over a several-month period leads to improvements in both VO2max and VO2/HR provides support for this concept.72

These patients also demonstrate abnormal ventilatory responses including increases in VE/VO2 and VE/VCO273,74 of greater magnitude than those seen in patients with heart failure of similar New York Heart Association (NYHA) functional class.73 This ventilatory inefficiency can be attributed to increased physiologic dead space, as well as increased peripheral chemoreceptor stimulation from exercise-induced hypoxemia, and improves following several months of treatment with sildenafil.74 Depending on the extent of vascular occlusion and subsequent differences in physiologic dead space, the degree of ventilatory inefficiency, as measured by ∆VE/∆VCO2, may vary in magnitude between classes of pulmonary vascular disease patients, with higher values seen in patients with chronic thromboembolic pulmonary hypertension compared with PAH.75

Aside from these similarities, an important difference between heart failure and pulmonary vascular disease is seen in the pulmonary artery pressure responses. Unlike in normal individuals or patients with heart failure where pulmonary artery pressure rises only modestly with increasing exercise, pulmonary vascular disease patients experience large rises in their pulmonary artery pressure with increasing blood flow due to impaired recruitment and distention of the pulmonary vasculature.77-79

Physiologic dead space also changes in a different manner. Whereas Vd/Vt decreases from 0.3 to 0.4 at rest to less than 0.2 at peak exercise in normal individuals and patients with heart failure, it decreases only mildly and may even increase in patients with pulmonary vascular disease.79 For example, Zhai and colleagues79 reported Vd/Vt of 0.42 ± 0.13 and 0.53 ± 0.08 at peak exercise in patients with PAH and chronic thromboembolic pulmonary hypertension, respectively. This response is abnormal because perfusion of many lung units does not increase proportionately with alveolar ventilation due to impaired recruitment and distention. In addition, if patients develop right-to-left shunt by opening a patent foramen ovale during exercise, mean expired CO2 decreases, leading to higher calculated Vd/Vt. As a result of the abnormal physiologic dead space, PETCO2 is decreased relative to normal individuals at all stages of exercise in proportion to the patient’s functional limitation.70

A final important difference is the fact that patients with pulmonary vascular disease develop hypoxemia with progressive exercise even in the absence of resting hypoxemia. For example, Deboeck and colleagues75 reported an oxygen saturation by pulse oximetry of 86 ± 2% at peak exercise in PAH patients compared with 96 ± 3% in patients with heart failure with similar NYHA functional class and D’Alonzo and colleagues79 reported a mean (A-a)PO2 of 45 ±
The findings noted earlier pertain to patients with PAH at rest. Recent work suggests that measurement of hemodynamic variables during exercise may identify an intermediate phenotype between healthy individuals and overt PAH in which individuals develop mean pulmonary artery pressure greater than 30 mm Hg during exercise. This group may represent an early form of PAH. Standardized protocols to guide clinical practice regarding these patients are lacking at this time.

The pattern of exercise responses seen in patients with pulmonary vascular disease is displayed graphically in Figure 26-4.
Interstitial Lung Diseases (for discussion of clinical aspects of interstitial lung diseases, see Chapters 63–66)

Patients with interstitial lung disease (ILD) manifest physiologic responses during progressive exercise similar to those seen in patients with pulmonary vascular disease. In particular, they demonstrate reduced \( \dot{V}O_2 \max \) and maximum work rate \((W_{\text{max}})\), increased \( \dot{V}E/\dot{V}O_2 \) and \( \dot{V}E/\dot{V}CO_2 \), reduced tidal volumes and increased respiratory rates, stable or increased \( Vd/VT \) at end-exercise, and hypoxemia with reduced arterial \( P_O2 \) and increased \( (A-a)P_O2 \). Although patients with ILD may not have a decreased \( \dot{V}O_2/HR \) and the ventilatory threshold may not be decreased relative to their \( \dot{V}O_2 \max \), these differences are usually not sufficient to distinguish between these two classes of patients on the basis of CPET alone and further studies such as pulmonary function tests (PFTs) and computed tomography (CT) imaging are necessary. Of note, when ILD develops in the setting of a collagen vascular disease, some of these responses can be observed before pulmonary involvement is evident on PFTs.\(^8^5\)

Debate exists regarding the underlying mechanism for the reduction in maximum exercise capacity. Hansen and

![Diagram](Image)
Wasserman, for example, demonstrated that abnormal cardiac function due to pulmonary vascular pathology was more important than respiratory system factors in limiting exercise while Marcinuik and colleagues used dead space loading during exercise to show that abnormal respiratory mechanics were the more important factor. Ventilatory equivalents are increased due to the increased dead space and the hypoxic ventilatory response, whereas exercise-induced hypoxemia, for which risk is increased in patients with a low diffusion capacity for carbon monoxide (DLCO) on PFTs, is due to a combination of ventilation-perfusion (VA/Q) inequality and diffusion limitation.

Because the term interstitial lung disease represents a heterogeneous group of disorders, the physiologic responses to exercise vary on the basis of the specific disease process. Wells and colleagues, for example, found increased dyspnea and hypoxemia in idiopathic pulmonary fibrosis compared with systemic sclerosis with ILD, while other studies have also shown worse hypoxemia, as well as increased pulmonary artery pressure responses in patients with idiopathic pulmonary fibrosis compared with sarcoidosis and other forms of ILD. The onset of pulmonary hypertension as a complication of ILD or an underlying systemic illness is associated with worse exercise tolerance, hypoxemia, and ventilatory inefficiency compared with otherwise similar patients with normal pulmonary artery pressures.

The pattern of exercise responses seen in patients with interstitial lung disease is displayed graphically in Figure 26-4.

Adult Congenital Heart Disease

With improvements in medical care, many patients with congenital heart disease are living into adulthood and the increasing use of CPET in disease management has enhanced the understanding of their physiologic responses to exercise. Similar to that seen in patients with heart failure, patients with congenital heart disease demonstrate reductions in VO2max, peak work rate, and maximum heart rate and increases in VE/VO2 compared with normal individuals. In contrast, however, many congenital heart disease patients develop hypoxemia at end-exercise. Given that many have coexisting pulmonary hypertension, one might also expect stable or increased Vd/Vt at end-exercise in many patients but this variable has not been reported in major series.

Owing to the diversity in the type and severity of congenital lesions, there is significant variability in the magnitude of observed changes in VO2max and VE/VO2 with the most serious abnormalities seen in those patients with Eisenmenger syndrome and complex lesions such as double-outlet ventricle or univentricular physiology. Patients with cyanosis and/or pulmonary hypertension also demonstrate greater reductions in these parameters when compared with patients lacking these problems. Importantly, functional impairment is not limited to those with significant lesions because even patients who are reportedly asymptomatic or those with mild lesions such as repaired coarctation of the aorta demonstrate decreased VO2max and increased VE/VO2 compared with normal individuals. Surgical repair is associated with improvements in exercise capacity, with the degree of improvement related in some cases to whether the abnormality is repaired when the patient is a child or an adult.

Although much of the decrement in exercise capacity in these patients is attributable to cardiac and pulmonary vascular dysfunction related to the underlying defect or its repair, some patients are also limited by abnormal respiratory mechanics. Up to 50% of patients who have undergone surgical repairs have findings suggestive of restriction on spirometry, perhaps due to their often multiple thoracotomies and sternotomies. Those with abnormal spirometry show worse exercise capacity and NYHA functional class compared with those with normal spirometry.

Chronic Obstructive Pulmonary Disease

(for clinical discussion, see Chapters 43 and 44)

Patients with mild COPD may actually have normal exercise capacity while patients with moderate to severe COPD demonstrate decrements in VO2max and peak work rate proportional to the severity of their disease as measured by Global Initiative for Obstructive Lung Disease (GOLD) stage. Beyond this decrease in exercise capacity, the pattern of physiologic responses to progressive exercise in COPD is different from that seen in patients with heart failure. Whereas exercise is limited in heart failure by an inability to deliver oxygen-rich blood to exercising muscles, patients with moderate-severe COPD are limited by altered respiratory mechanics; their ventilatory pump fails before the heart does.

The hallmark of ventilatory limitation in moderate to severe COPD is the fact that both arterial PCO2 and PETCO2 remain stable or increase at end-exercise due to an inability to raise minute and alveolar ventilation in response to increasing VCO2 and, when present, a metabolic acidosis. This phenomenon, which is present to a greater extent at higher GOLD stages of disease, results from mechanical constraints due to dynamic hyperinflation during exercise (discussed further later) and altered ventilation-perfusion relationships.

In addition, VE at peak exercise will be at or close to the maximum predicted ventilation as measured by the MVV or FEV1 × 40, a marked contrast from normal sedentary individuals and those with heart failure in whom VE/MVV is normally less than 75% to 80%. Ventilation is typically higher for any given work rate and is usually marked by a high respiratory rate, low tidal volume, higher end-expiratory volume, and lower inspiratory capacity compared with normal individuals. Still another manifestation of ventilatory limitation is the absence of a ventilatory threshold in most patients with severe disease. Although patients with mild disease may still develop a metabolic acidosi and even manifest a ventilatory threshold at lower levels of VO2 than normal individuals, patients with severe disease will not manifest such changes. Along with the fact that peak heart rate is typically well below the maximum predicted heart rate in severe disease, the absence of the ventilatory threshold is strongly indicative of the fact that the ventilatory pump is failing before the circulatory pump.

Perhaps the most important reason for these manifestations of ventilatory limitation is a phenomenon referred to as dynamic hyperinflation. Due to expiratory flow limitation that develops even at low-moderate levels of exercise,
patients with COPD must increase end-expiratory lung volumes and encroach on their inspiratory reserve volume in order to raise VE as metabolic activity increases (Fig. 26-5). The hyperinflation that results causes flattening of the diaphragm, which limits contractile strength, increases respiratory muscle fatigue, and causes increased dyspnea for any given level of ventilation. Interestingly, patients with dynamic hyperinflation have less locomotor muscle fatigue with exercise because the ventilatory pump fails before the nonrespiratory muscle groups face significant loads.

Dynamic hyperinflation also has significant hemodynamic effects, including alterations in cardiac preload and afterload that subsequently impair cardiac function and manifest as a decrease in VO2/HR. The magnitude of this problem inversely correlates with the increase in end-expiratory lung volumes, and improvement can be seen following interventions that decrease dynamic hyperinflation such as lung volume reduction surgery (LVRS). Impaired right ventricular function may also result from increased pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction and structural changes in the pulmonary circulation. In fact, in patients whose COPD is complicated by pulmonary hypertension (mean PAP  ≥ 40 mm Hg), impaired circulatory function is the primary factor limiting exercise rather than the ventilatory constraints. Some patients with COPD also manifest chronotropic incompetence, which may limit the cardiac response to exercise. The increased work of breathing may also contribute to exercise limitation by limiting blood flow to locomotor muscles.

Another important feature of progressive exercise in patients with COPD is the onset of hypoxemia with a widened (A-a)PO2. This problem correlates with reductions in diffusing capacity, more common when the COPD is due to emphysema rather than to chronic bronchitis, is more severe in patients with pulmonary hypertension, and is more prominent with walking as opposed to cycling. The predominant mechanism is VA/Q inequality, the effects of which are magnified by reductions in \( \text{VCO}_2 \) during exercise. Depending on the distribution of blood flow and ventilation, however, VA/Q inequality may actually improve during exercise, which accounts for the observation that some patients with COPD actually see improvement in arterial \( \text{PO}_2 \) during exercise testing.

The pattern of exercise responses seen in patients with ventilatory limitation due to COPD is displayed in Figure 26-6.

## CARDIOPULMONARY EXERCISE TESTING

### INDICATIONS AND CONTRAINDICATIONS

The indications for CPET sort into five general areas: determining the etiology of exercise limitation, assessing functional status, stratifying risk for surgery, prognosticating outcomes related to specific diseases, and creating individualized exercise prescriptions for rehabilitation programs. The list of indications for CPET (Table 26-1) is largely compiled from expert opinions, and the evidence for the utility of CPET varies by indication, each of which is reviewed later.

### Determining Etiology of Dyspnea and Exercise Limitation

**Evaluating Dyspnea.** Dyspnea with exercise is a subjective complaint that is the end result of various diseases. When the cause of dyspnea is not apparent from history, physical examination, laboratory testing (including a hemoglobin concentration and resting arterial blood gas), chest imaging, and PFTs, CPET can be used to quantify a patient’s exercise limitation and determine which system is limiting exercise. Although CPET on occasion can narrow the differential list down to a single limiting system, such as
in patients with chronotropic incompetence or myocardial ischemia, it is most useful in identifying the next best studies to pursue in making a definitive diagnosis.

The first step in using CPET to evaluate dyspnea is to determine if the patient’s subjective complaints and description of their limitations are appropriate for the degree of work they are able to perform. It is therefore imperative that the patient gives a maximal effort during the CPET. An arterial blood gas at the end of exercise can be helpful in this setting to determine if the individual gave a good effort, was ventilatory limited, had excess dead space, or was hyperventilating. It can also be helpful to use a dyspnea scale during a ramped exercise protocol to quantify and link a patient’s sense of dyspnea with the level of work being performed. It is also important to ask the patient if the CPET protocol reproduced the patient’s symptoms of dyspnea. This postexercise questioning often helps define the subjective complaints and narrow the differential diagnosis.

As described earlier, the pattern of response to exercise can be used to determine which system is limiting exercise and likely creating the sense of dyspnea. In a group of 50 patients referred for CPET with unexplained dyspnea, broad diagnoses of cardiac limitation, pulmonary limitation, obesity and/or deconditioning, and psychogenic dyspnea were identified.

Figure 26-6 COPD compared to normal. Nine-box plot demonstrating expected physiologic responses to exercise in patients with ventilatory limitation due to COPD (solid lines) compared with normal individuals (dotted lines). (Modified from Luks AM, Glenny RW, Robertson HT: Introduction to cardiopulmonary exercise testing. New York, 2013, Springer, Fig. 3-4.)
Table 26-1  Indications and Contraindications for Cardiopulmonary Exercise Testing

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| Determining the etiology of dyspnea and exercise limitation               | ABSOLUTE<br>Active myocardial ischemia (unstable angina, myocardial infarction within 30 days)<br>Acute heart failure exacerbation<br>Exercise-induced syncope<br>Uncontrolled arrhythmias<br>Severe aortic stenosis<br>Acute endocarditis, myocarditis, pericarditis<br>Acute aortic dissection or suspected dissecting aortic aneurysm<br>Acute pulmonary embolism or lower extremity deep venous thrombosis<br>Active COPD exacerbation or uncontrolled asthma<br>Active pulmonary edema<br>Oxygen saturation < 85% breathing air at rest<br>Acute respiratory failure<br>PRELATIVE<br>Severe pulmonary hypertension<br>Left main coronary artery stenosis<br>Moderate stenotic valve disease<br>Severe hypertension (SBP > 200 mm Hg, DBP > 120 mm Hg)<br>Hypertrophic cardiomyopathy<br>High-degree atrioventricular block<br>Severe electrolyte abnormalities<br>Tachyarrhythmias or bradycardiac<br>Advanced or complicated pregnancy<br>Implanted cardiac defibrillator that cannot be interrogated or temporarily reset due to inaccessibility of an individual qualified to do this (e.g., device manufacturer representative)<br>
| Evaluating dyspnea                                                        |                                                                                  |
| Evaluating exercise limitation                                            |                                                                                  |
| Evaluating combined cardiac and pulmonary disorders                      |                                                                                  |
| Diagnosing exercise-induced bronchoconstriction                          |                                                                                  |
| Assessing functional status and quantifying impairment                   |                                                                                  |
| Risk stratification                                                       |                                                                                  |
| Assessment for thoracic surgery                                          |                                                                                  |
| Evaluation for lung volume reduction surgery                             |                                                                                  |
| Assessment for major general surgery                                     |                                                                                  |
| Prognosticating outcomes                                                  |                                                                                  |
| Evaluation of heart failure and prognostication for transplantation       |                                                                                  |
| Assessment of adult congenital heart disease                             |                                                                                  |
| Assessment of pulmonary arterial hypertension                             |                                                                                  |
| Exercise prescriptions for rehabilitation programs                        |                                                                                  |

DBP, diastolic blood pressure; SBP, systemic blood pressure.

Table 26-2  Estimating $\dot{V}_{O_{2}}_{\text{max}}$ from the History

<table>
<thead>
<tr>
<th>Activity Limitations</th>
<th>Approximate $\dot{V}<em>{O</em>{2}}_{\text{max}}$ (mL/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participates in competitive sports with sustained activity like rowing, basketball, and soccer. Engages in regular endurance training. Tolerates sustained heavy labor well; can play recreational soccer or full-court basketball without slacking or run at an 8-minute/mile pace.</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Tolerates sustained heavy labor well; can play recreational soccer or full-court basketball.</td>
<td>35–40</td>
</tr>
<tr>
<td>Participates in recreational cross-country skiing or half-court basketball with minimal limitation.</td>
<td>30–35</td>
</tr>
<tr>
<td>Performs heavy labor with difficulty; downhill skiing somewhat limited by fatigue.</td>
<td>25–30</td>
</tr>
<tr>
<td>Heavy housework or yard work causes dyspnea; cannot play singles tennis.</td>
<td>20–25</td>
</tr>
<tr>
<td>Dyspnea with two flights of stairs at own pace; cannot play golf while carrying bag or pulling a cart.</td>
<td>17–20</td>
</tr>
<tr>
<td>Unable to vacuum average room or change sheets without rest.</td>
<td>14–17</td>
</tr>
<tr>
<td>Difficulty walking slowly with peers in shopping mall.</td>
<td>12–14</td>
</tr>
<tr>
<td>Dyspnea while brushing hair, dressing, showering.</td>
<td>&lt;12</td>
</tr>
</tbody>
</table>


**Evaluation of Exercise Limitation.** Patients presenting with exercise limitation rather than dyspnea as a complaint state that they just cannot perform the amount of work that they could do in the past. These complaints tend to be more vague and difficult to sort out by the usual history and standard studies. CPET is useful in this setting to quantify the amount of work that an individual can perform in a supervised test and compare it with what they say they can do during the activities of daily living. *Table 26-2* provides a rough estimate of the maximal oxygen consumption that correlates with the level of exercise a patient states he or she can perform.128 It is important to keep in mind that there is a broad spectrum of exercise capabilities across the normal population. Although an individual may have a “normal” exercise study as judged by the maximal oxygen consumption, the observed response for any individual may represent a significant decline in his or her exercise performance from a previous supranormal level.

**Evaluating Combined Cardiovascular and Pulmonary Disorders.** When individuals have underlying diseases in more than one system, CPET can help determine which system is primarily responsible for their exercise limitation and guide patient management. For example, in a patient with both aortic stenosis and COPD, CPET can help determine whether or not to proceed with valve repair. Were such a patient to be primarily limited by his or her ventilatory capacity, repairing the aortic valve may not be indicated, because following surgery the individual would still be significantly limited by his or her ventilatory
capacity. While assisting in identifying the primary limiting system, CPET cannot quantitatively partition the degree of limitation due to each of the affected systems.

**Diagnosing Exercise-Induced Bronchoconstriction.** CPET can be used to diagnose exercise-induced bronchoconstriction, a transient, reversible bronchoconstriction that develops during or after strenuous exercise, which is present in more than 10% of the general population and up to 90% of persons previously diagnosed with asthma. Although administration of inhaled bronchoprovocatory agents such as methacholine or mannitol can be used to make the diagnosis (see Chapter 25), exercise challenge using free running, treadmill, or cycle ergometry has been used to elicit exercise-induced bronchoconstriction since the 1970s and, along with eucapnic voluntary hyperventilation, is a more sensitive and specific testing modality. Exercise testing for this purpose requires specialized equipment, personnel, and the ability to exercise at 85% to 95% maximum heart rate with dry medical grade air and high flow rates (>100 L/min) and should be performed according to published guidelines.

Due to the logistical issues associated with exercise challenges, the International Olympic Committee Medical Commission recommends eucapnic voluntary hyperventilation as the initial testing modality followed by CPET if eucapnic voluntary hyperventilation is nondiagnostic.

**Assessing Functional Status and Degree of Impairment**

Quantitative measures of exercise capacity are also useful in determining eligibility for disability because static tests such as PFTs and cardiac ejection fraction by echocardiography do not correlate well with exercise capacity. For example, in a heterogeneous population of subjects, the variables FEV₁ and DLCO poorly predicted the maximal O₂ consumption, likely due to the fact that many individuals have cardiovascular limitations not captured by either of these PFT parameters. Despite these issues, the American Thoracic Society statement on the evaluation of impairment and disability states that impairment can be determined from standard pulmonary functions studies in most cases and that further testing with CPET may be helpful in selected situations. Importantly, quantifying impairment informs but does not define disability because disability assessment requires social, economic, environmental, and other input. Largely on the basis of empirical knowledge, rough estimates of the work that an individual should be able to perform have been proposed (Table 26-3).

**Risk Stratification**

**Risk Assessment for Thoracic Surgery.** A number of studies have looked at preoperative CPET to determine whether patient outcomes can be predicted on the basis of exercise capacity. Although the available studies have not used randomized, controlled designs and generally involve small numbers of patients from single centers, they do show an association between exercise capacity and clinical outcomes following major surgery. Drawing on this evidence, an expert panel of the American College of Chest Physicians devised an algorithm that incorporates CPET along with the Thoracic Revised Cardiac Risk Index.

<table>
<thead>
<tr>
<th>Table 26-3</th>
<th>Impairment Determined by Cardiopulmonary Exercise Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VO₂max (mL/kg/min)</strong></td>
<td><strong>Description of Work</strong></td>
</tr>
<tr>
<td>&gt;25</td>
<td>Capable of all but most physically demanding jobs</td>
</tr>
<tr>
<td>15–25</td>
<td>Able to work at the specific job that does not require frequent and extended work above 40% of maximum VO₂max</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Unable to perform most jobs</td>
</tr>
</tbody>
</table>


spirometry, DLCO, and performance on stair climbing or shuttle walk testing to guide selection of the appropriate therapeutic approach in lung cancer patients (Fig. 26-7). The general approach can probably be used as a foundation for any lung resection surgery. Patients who require CPET as part of this algorithm are deemed low risk (expected risk of mortality <1%) if the VO₂max is greater than 20 mL/kg/min or more than 75% of predicted. They are considered high risk (expected mortality >10%) if their VO₂max is less than 10 mL/kg/min or less than 35% of predicted. The expert panel gave this algorithm a strong recommendation on the basis of their experience, although it should be recognized there are no data demonstrating the utility of this approach or comparing it with other risk stratification algorithms that do not use CPET.

In addition to risk stratification, CPET provides a wealth of information that helps identify those systems responsible for reduced aerobic capacity. Once those systems are identified, corrections can be implemented to improve patient fitness and minimize surgical risk. Such steps might include, for example, coronary revascularization, medical treatment, or physical rehabilitation.

**Evaluation for Lung Volume Reduction Surgery.** The landmark National Emphysema Therapy Trial demonstrated that LVRS was clearly of benefit, but only for the subset of patients defined by their reduced exercise capacity, when using a modified but formalized exercise protocol. The study participants underwent a maximal CPET on a cycle ergometer while wearing a face mask delivering an FIO₂ of 0.30 and pedaling for 3 minutes without resistance, followed by progressive increases in work rate by 5 or 10 watts/min. Those patients with a low exercise capacity, here defined as less than 25 W for women and 40 W for men, were found to benefit from LVRS.

**Risk Assessment for Extrathoracic Surgery.** A number of studies have investigated the utility of performing CPET for risk stratification or identification of other comorbidities that could be addressed in the perioperative period. Such an approach has been investigated in a variety of groups undergoing major surgery including those undergoing abdominal-aortic repair, hepatic transplantation, upper gastrointestinal surgery, as well as elderly patients undergoing intra-abdominal surgery. Seven of the nine studies included in a review of this issue found higher mortality in patients with lower VO₂max. In one of the
Clinical Exercise Testing

A number of early studies documented a progressive decline in survival with decreasing VO₂max. More recent studies have shown similar relationships between VO₂max and mortality. Importantly, the inclusion of patients treated with β-blockers in recent series now suggests that a threshold of less than 14 mL/kg/min should be considered for heart transplantation. Most studies investigating the utility of VO₂max for prognostication in heart failure use the traditional weight normalized values (mL/kg/min), but due to the obesity “epidemic,” the reported oxygen consumption data may be inappropriately low and decisions for heart transplantation may be skewed toward the obese. Correcting VO₂ for lean body mass may improve prognostication.

Other CPET variables may be better predictive tools than VO₂max. For example, a series of studies show that VE/VCO₂ or the VE/VCO₂ slope is an accurate predictor of mortality and may improve predictive capabilities of models used to guide heart failure management. Although most of these studies identify a single threshold above which the VE/VCO₂ indicates a higher mortality in patients with heart failure, a more recent analysis by Arena and colleagues created four classes on the basis of the VE/VCO₂ slope and reported that event-free survival was significantly different across the four classes. When combined with the peak VO₂ at the ventilatory threshold measured preoperatively was used to determine the appropriate hospital location for postoperative care; a VO₂ less than 11 mL/kg/min was the cutoff in the postoperative intensive care unit and a marker of increased mortality. Despite this evidence, there are no prospective studies documenting survival benefit or cost-effectiveness for using CPET in this manner.

Prognosticating Clinical Outcomes

In normal subjects without specific diseases and in general among individuals with disease, survival is associated with a higher exercise capacity. However, interventional studies have not been conducted to determine whether training to improve VO₂max increases life expectancy. Some of the patient populations for whom VO₂max and other data derived from CPET provide prognostic information are described as follows.

Heart Failure. VO₂max is the most objective data available for assessing exercise capacity in individuals with heart failure. When the contribution of heart failure to exercise limitation is uncertain, the American College of Cardiology and the American Heart Association recommend CPET in patients presenting with heart failure to guide management and determine whether heart failure is the cause of exercise limitation. A number of early studies documented a progressive decline in survival with decreasing VO₂max. More recent studies have shown similar relationships between VO₂max and mortality. Importantly, the inclusion of patients treated with β-blockers in recent series now suggests that a threshold of less than 14 mL/kg/min should be considered for heart transplantation. Most studies investigating the utility of VO₂ for prognostication in heart failure use the traditional weight normalized values (mL/kg/min), but due to the obesity “epidemic,” the reported oxygen consumption data may be inappropriately low and decisions for heart transplantation may be skewed toward the obese. Correcting VO₂ for lean body mass may improve prognostication.

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Pulmonary Arterial Hypertension. Assessment of exercise capacity can also be used to assess prognosis and response to treatment in PAH patients. For example, Sun and colleagues\textsuperscript{74} found that peak work rate, \( \text{VO}_2 \text{max} \), ventilatory threshold, \( O_2 \) pulse, and slope of \( \text{VE}/\text{VCO}_2 \) were all correlated with NYHA class. Yasunobu and colleagues\textsuperscript{70} reported that \( \text{PETCO}_2 \) progressively decreased as the disease severity increased and directly correlated with changes in mean pulmonary artery pressure. Other studies have demonstrated a relationship between survival and \( \text{VO}_2 \text{max} \) and \( \text{VE}/\text{VCO}_2 \),\textsuperscript{197,198} and that persistent exercise-induced right-to-left shunt and poor ventilatory efficiency during serial assessments were highly predictive of poor outcomes in patients with PAH.\textsuperscript{195}

Although CPET is a safe\textsuperscript{74,199} and effective means to grade the severity of exercise limitation, assess prognosis, and measure response to therapy,\textsuperscript{200} the use of CPET is limited in most PAH trials due to a number of practical issues. Instead, most trials rely on the simple, less expensive, and reproducible 6-Minute Walk Test (6MWT, described in greater detail later), which, like CPET, provides prognostic information.\textsuperscript{201,202} Improvement in the 6MWT following therapeutic intervention may also be associated with a decrease in mortality,\textsuperscript{203,204} although not all studies have validated this finding.\textsuperscript{205}

Exercise Prescriptions for Cardiac and Pulmonary Rehabilitation Programs (for discussion of clinical aspects of rehabilitation, see Chapter 105)

Given that the intensity of aerobic exercise is linked to both the improvement in exercise capacity and the risk of adverse events during exercise, a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation stressed the importance of functional evaluation using exercise testing before starting an aerobic training program.\textsuperscript{10} Although there are many methods for creating individualized training programs, these guidelines propose that CPET be the gold standard for assessment and prescription of exercise intensity. The committee’s goal is to shift from a “range-based” to a “threshold-based” aerobic exercise intensity prescription to maximize the benefits obtainable by the use of aerobic exercise training in cardiac rehabilitation.\textsuperscript{10}

Similarly, the American Thoracic Society and the European Respiratory Society statement on pulmonary rehabilitation\textsuperscript{206} states that before initiating rehabilitation for COPD, CPET should be considered as part of a thorough assessment to identify factors contributing to exercise limitation, to determine the exercise prescription, and to evaluate safety by monitoring ECG and blood pressure for potential risks.\textsuperscript{207} Casaburi and colleagues,\textsuperscript{208} for example, have shown that high-intensity training programs (80% of \( W_{\text{max}} \) in the incremental test) are more effective than less intense programs (50% of \( W_{\text{max}} \)) in patients with COPD. In the absence of cardiovascular limitation, the training program in these individuals may begin at or above the intensity of the ventilatory threshold, with progressive increase in the limits of tolerance.\textsuperscript{208,209} In patients who cannot reach the ventilatory threshold during incremental testing, training can begin at a level closer to the maximum

\[ \text{VO}_2 \text{max} \]
intensity obtained. Using the ventilatory threshold as a landmark when it is reached or knowing that it has not been reached during standardized testing facilitates higher-intensity targets and more efficient training. From a practical standpoint, a formal CPET study may not be necessary to build a tailored exercise program and others have used variables obtained in the 6MWT, such as peak heart rate, to target exercise levels. Despite the expert opinions that CPET or 6MWT should be used to create individualized training programs, there are no data showing that the exercise prescription derived by these means improves quality of life or survival.

SAFETY CONSIDERATIONS AND CONTRAINDICATIONS TO CPET

Performing a CPET is not without risk, and the decision to conduct the test must reflect consideration of those risks relative to the benefits in terms of information gained. Multiple contemporary surveys indicate that the risks of complications that require hospitalization are low; the risk of serious arrhythmias, acute myocardial infarction, or sudden cardiac death during or immediately after an exercise test are less than 0.2%, 0.04%, and 0.01%, respectively. This estimate captures the risk for the entire population of individuals performing CPET and is likely to vary in a given patient on the basis of his or her underlying disease. Unfortunately, risk estimates are not available for every possible condition, and the clinician must use clinical judgment in assessing the risk and informing each individual.

Some diseases do carry significantly higher risks and represent absolute or relative contraindications to performing CPET (see Table 26-1). Patients with implantable cardiac defibrillators (ICDs) also require special attention. Documentation of the defibrillator settings should be reviewed before exercise to ensure that the peak heart rate during the test does not encroach on the rate at which the defibrillator is set to discharge. The defibrillator function should not be entirely disabled, however, as one needs maintain the ability to defibrillate patients who develop arrhythmias during the exercise test.

CONDUCTING EXERCISE TESTS

Exercise Equipment

A number of commercially available exercise monitoring systems allow breath-by-breath measurements of exhaled gases. The general components of these systems include an airflow transducer to measure the volumes of each inhalation and exhalation and rapid gas analyzers to measure the O2 and CO2 during inspiration and expiration. As technologies have improved, these components have become more reliable but still require strict and daily calibration tests to assure accurate data. Multiple resources are available with recommendations for calibration procedures and quality control. Gas exchange measurements during exercise should be reproducible, and therefore it is a good practice to have one or two individuals in the exercise laboratory perform monthly CPET to confirm that their data remain stable over time. Both maximal and submaximal tests can be used for this purpose because reproducible data are generated in either case.

Exercise Modalities and Protocols

Cycle Ergometer versus Treadmill. Functional capacity is usually assessed in CPET by having the individual exercise on a stationary cycle ergometer or motorized treadmill. Either modality can be used to elicit progressively increasing work rates in subjects. Progressive work is produced on the cycle ergometer by increases in the resistance to pedaling. Through electronic braking and sensors, it is possible to gauge the work being done by the individual and quantify work over time as a rate in watts (W). Progressive work is produced on the treadmill by increases in the grade and speed of the treadmill. Because arm movement and the uplift of body weight while walking/running on the treadmill add to the work being performed, work on a treadmill is more dependent on an individual’s weight and, as a result, is harder to quantify than with cycle ergometry, in which leg muscles do the vast majority of the work and the individual’s weight is supported by the bicycle. Treadmill work is measured relative to each individual’s resting energy expenditure and is typically expressed in terms of metabolic equivalents (METs). One MET represents the amount of oxygen consumed at rest and each successive stage achieved in a given treadmill protocol corresponds to a higher level of METS that can, in turn, be related to the individual’s oxygen consumption (1 MET = 3.5 mL O2/kg/min in the average adult). As discussed previously, oxygen consumption is also tightly linked with work rate on a cycle ergometer, with VO2 increasing at a rate of 10 mL/min/watt above the resting value. Hence watts and METs can be roughly compared through the shared VO2 and are dependent on the individual’s weight. Table 26-4 provides examples of watts, oxygen consumption, and METs for two individuals of different weights to give the reader a general idea of how these measures of work compare.

Both exercise modalities can impose progressively increasing work rates that provide a range of oxygen consumptions to identify exercise patterns described earlier in this chapter. The resistance and, therefore, watts in cycle ergometry can be increased in either a continuous or stepwise manner over time. Treadmill work rates are usually increased according to specific protocols such as the

| Table 26-4 | Comparison of Oxygen Consumption and Metabolic Equivalents (METs) at Different Levels of Work in Individuals of Different Weights |
|-------------|------------------------------------------------------------------------------------------------|-----------------|
|             | 70-kg PERSON | 100-kg PERSON |
| Watts       | VO2 (mL/min) | METs | VO2 (mL/min) | METs |
| 0 (rest)    | 250          | 1.0  | 350          | 1.0  |
| 25          | 500          | 2.0  | 600          | 1.7  |
| 50          | 750          | 3.1  | 850          | 2.4  |
| 100         | 1250         | 5.1  | 1350         | 3.9  |
| 200         | 2250         | 9.2  | 2350         | 6.7  |
| 300         | 3250         | 13.3 | 3350         | 9.6  |
| 400         | 4250         | 17.3 | 4350         | 12.4 |

VO2 increases at a rate of 10 mL/min/watt above the resting value. One MET represents the amount of oxygen consumed at rest.
Invasive Cardiopulmonary Exercise Testing. When competing comorbidities in a given patient make it difficult to determine the primary cause of exercise limitation, exercise with a right heart catheter can provide additional data to help (1) separate out the cardiac and pulmonary systems, (2) further differentiate the broad category of "cardiac limitation" as either right or left heart failure, and (3) identify a component of muscle deconditioning. The data available from the right heart catheter include mixed venous oxygen saturation and content, pulmonary artery pressure, pulmonary artery occlusion pressure, and thermodilution cardiac output. With increasing exercise to exhaustion in a normal individual, cardiac output should increase fourfold to fivefold, but the mean pulmonary arterial pressure should remain less than 30 mm Hg. In patients with left heart failure or pulmonary vascular disease, the mean pulmonary arterial pressure may increase above this level and, if associated with symptoms of dyspnea, may give a clue to underlying mechanisms. Pulmonary vascular resistance can be calculated to determine if elevated pulmonary artery pressures are due to left-sided heart failure or pulmonary vascular disease. Because intrathoracic pressure affects right-heart catheterization measurements, the pulmonary artery occlusion pressure must be measured at end-exhalation, which may be difficult to achieve without asking patients to temporarily alter their breathing patterns during measurements. Stroke volume can be calculated from the heart rate and cardiac output rather than assessed through a surrogate measure, the O2 pulse. Placement of an arterial line with the right heart catheter allows calculation of cardiac output using the Fick equation and determination of the arteriovenous oxygen content difference, with narrow values of the latter providing evidence of deconditioning as a cause of exercise limitation.

Noninvasive Estimates of Cardiac Output during CPET. A number of noninvasive commercial methods are also available for estimating the cardiac output during exercise. They rely on a variety of different technologies, including CO2 rebreathing, pulse contour analysis, chest bioelectrocardiography, and inert gas rebreathing. The technology that has been most rigorously evaluated in exercise is the inert gas rebreathing method. Although the available evidence indicates that these measurements are feasible and that cardiac output and VO2 are tightly correlated in both normal subjects and individuals with heart failure, their clinical utility remains unclear.

Indications for Arterial Blood Gases

Arterial blood gases provide additional data that assist in differentiating the causes of exercise limitation and dyspnea. In particular, they allow the determination of the (1) (A-a) PO2 to evaluate gas exchange; (2) arterial PCO2, as the gold standard for identifying ventilatory limitation; (3) VT/VT as an indicator of pulmonary vascular disease; and (4) base deficit as a surrogate for lactic acidosis. Arterial blood gases can be measured either once immediately following conclusion of the exercise test or at repeated intervals throughout the test. Both sampling methods permit determination of the dead space fraction at end-exercise while the latter method also allows one to roughly estimate the position of the ventilatory threshold. The latter approach requires an arterial line while a single needle puncture can be used for the former. The operator should be aware that arterial puncture following maximal exertion can cause a vagal reaction and hypotension, especially in younger subjects.
Clinical Exercise Testing

Figure 26-9  
A general approach to cardiopulmonary exercise test interpretation. Because data interpretation is highly dependent on the quality of the data, the initial steps involve ensuring there are no systematic data errors and that the patient gave a complete effort. Once this is done, the next tasks are to assess maximum exercise capacity and the cardiovascular, ventilatory, and gas exchange responses and then identify whether a ventilatory threshold is present and determine the primary system limiting exercise.

Assess Data Quality
- Resting $\dot{V}O_2 = 250\% - 300\%$ mL/min (may be higher in the obese)
- $\dot{V}O_2$ rises $\sim 10$ mL O$_2$/W
- $R$ between 0.8 and 0.9 at rest and over first one third of test
- Oxygen saturation data follows clear, nonchaotic trend

Did the Patient Give a Full Effort?
- Was patient diaphoretic at the end of the test?
- Did the patient have rise in blood pressure? Marked tachypnea?
- $R > 1.0$ at end-exercise and ventilatory threshold present (both may be absent in patients with ventilatory limitation)

Assess Maximum Exercise Capacity
- What is the $\dot{V}O_{2\text{max}}$?
- Compare the $\dot{V}O_{2\text{max}}$ to reference values
- What was the peak work rate?
- What was the limiting symptom (dyspnea, leg fatigue, other)?
- Did the test reproduce the symptoms present in daily life?

Assess Cardiovascular Response
- Resting heart rate
- Maximal heart rate
- Heart rate reserve
- Blood pressure response
- $O_2$ pulse
- Arrhythmia
- ST segment changes on ECG

Assess Ventilatory Response
- Peak respiratory rate
- Peak tidal volume
- Tidal volume recruitment
- Resting minute ventilation
- Peak minute ventilation
- Ventilatory reserve
- $\dot{V}E/\dot{V}O_2$
- $\dot{V}E/\dot{V}CO_2$

Assess Gas Exchange
- $SpO_2$
- $PETO_2$
- $PETCO_2$
- If ABGs collected:
  - $PaO_2$
  - $PaCO_2$
  - $(A-a)PO_2$
  - $V_D/V_T$

Assess for Presence of Ventilatory Threshold
- $\dot{V}CO_2$ vs. $\dot{V}O_2$
- $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ vs. Work
- $PETO_2$ and $PETCO_2$ vs. Work
- Lactic acidosis on ABG

Identify the Primary System Limiting Exercise
- Algorithm approach (see Figure 26-11) or
- Pattern recognition approach (see Table 26-5)

Figure 26-10  
A, Analysis of ventilatory equivalents to identify whether a ventilatory threshold is present. Following the increase in minute ventilation at the ventilatory threshold, ventilatory equivalents for oxygen ($\dot{V}E/\dot{V}O_2$, denoted in brown) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$, denoted in blue) begin a steady rise. The point at which each variable starts to rise is marked by an arrow in the respective colors. The start of the rise in $\dot{V}E/\dot{V}O_2$ is associated with the first ventilatory threshold and is expected to take place before the rise in $\dot{V}E/\dot{V}CO_2$. B, Using changes in end-tidal partial pressure of oxygen ($PETO_2$) and carbon dioxide ($PETCO_2$) to identify whether a ventilatory threshold is present. At the ventilatory threshold, minute ventilation ($VE$) increases out of proportion to the changes in oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). As a result, $PETO_2$ (denoted in brown) begins a steady rise (brown arrow), while $PETCO_2$ (denoted in blue) begins a steady decrease (blue arrow).
and colleagues,\textsuperscript{28} employs a binary tree algorithm and flow charts that direct the interpretation through a series of decision points to specific causes of exercise limitation. A simplified flow chart is shown in Figure 26-11 to demonstrate the concept. The advantages of this approach are that the decision points and values are well defined so that there is no ambiguity in the direction to branch in the flow chart. This strategy is probably easier to follow for the novice interpreter than the pattern recognition approach outlined later. The primary disadvantage is that the interpretation is entirely dependent on a single data point at each bifurcation. Any error in data collection or misinterpretation at one bifurcation can direct the interpretation down a wrong pathway and an incorrect diagnosis. A secondary disadvantage is that CPET interpretation by this method requires an extensive array of flow charts.

Identifying the Primary System Limiting Exercise: Algorithmic versus Pattern Recognition Approaches

Perhaps the most important aspect of CPET interpretation is identifying the primary reason for exercise limitation. One approach to this task, first introduced by Wasserman protocol, and the data collection system,\textsuperscript{6} and there is no evidence that any particular noninvasive method is superior to the others.\textsuperscript{225,226} This is not a critical issue in most CPET interpretations because the key question is whether or not the threshold is reached rather than when it is reached. When the specific \( \text{VO}_2 \) at the ventilatory threshold must be known, as in devising exercise prescriptions or training protocols, the key factor will be application of a consistent approach from test to test.

![Figure 26-11](https://example.com/fig26-11.png)

**Figure 26-11 Simplified flow chart demonstrating decision making in cardiopulmonary exercise test interpretation.** The decision tree begins at the top with the maximum oxygen consumption (\( \text{VO}_2\text{max} \)) compared with predicted values. ABG, arterial blood gas; AT, anaerobic threshold; CAD, coronary artery disease; ECG, electrocardiogram; MVV, maximum voluntary ventilation; (A-a)\( \text{PO}_2 \), alveolar-arterial oxygen difference; \( \text{Vd/VT} \), dead space fraction; \( \text{VE/VCO}_2 \), ventilatory equivalents for carbon dioxide. (Modified from Wasserman K, Hansen JE, Sue DY, et al: Principles of exercise testing and interpretation, ed 5. Philadelphia, 2012, Lippincott Williams & Wilkins.)
An alternative method is one of pattern recognition that uses the expected trends for multiple variables over the course of progressive exercise to identify the organ system limiting exercise. As discussed earlier, general disease categories such as heart failure, pulmonary vascular disease, or ventilatory insufficiency have expected patterns of exercise responses (Table 26-5). These patterns can be weighted by their relative specificity for each organ system and then examined in sum to suggest the most likely organ system limiting exercise. Patients with cardiac limitation, for example, will demonstrate a ventilatory threshold, a decreased PETCO$_2$ and arterial PCO$_2$, and an increased ventilatory/V$_{E}$/O$_{2}$ and ventilatory/V$_{E}$/CO$_{2}$ at end-exercise. Patients with pulmonary hypertension demonstrate many similar findings but will manifest hypoxemia and a fixed Vd/Vt in late exercise. Other temporal trends that are specific for an organ system failure can be seen with exercise but not regularly enough to warrant listing in Table 26-5. Patients with severe heart failure, for example, may have exercise oscillatory ventilation$^{64,65}$ that can be readily seen when the Vt is plotted as a function of time or work rate.

Because the various observations listed in Table 26-5 are not necessarily present in every patient, a useful approach in the pattern recognition method is to conceptualize it as a scale on which the different observations are blocks that are placed on the side of the scale representing the potential limiting pattern (Fig. 26-12). Each block may be of different size representing the relative weight placed on that particular factor. The presence or absence of a ventilatory threshold would be the biggest block in this method. The side of the scale with the greatest weight (number of blocks)

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**Table 26-5** Identifying the Pattern of Limitation on Cardiopulmonary Exercise Testing

<table>
<thead>
<tr>
<th>Observation</th>
<th>Cardiac</th>
<th>Pulmonary Vascular and Interstitial Lung Disease*</th>
<th>Ventilatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear ventilatory threshold</td>
<td>◯</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Plateau in O$_2$ pulse late in exercise</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>High Vt/VCO$_2$</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>High Vt/VO$_2$</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>VEmax far below maximum voluntary ventilation (MVV)</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Metabolic acidosis by arterial blood gas late in exercise</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Decreasing PETCO$_2$ late in exercise</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>R clearly rises above 1.0</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Stop exercising due to leg fatigue</td>
<td></td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Heart rate near predicted maximum late in exercise</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>ST changes on electrocardiography</td>
<td></td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Inappropriate blood pressure response</td>
<td></td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Increasing or unchanged Vd/Vt by arterial blood gas late in exercise</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Absent ventilatory threshold</td>
<td>◯</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Decrease in oxygen saturation</td>
<td></td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Heart rate far below predicted maximum late in exercise</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Increasing or unchanged PETCO$_2$ late in exercise</td>
<td>◯</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>PaCO$_2$ &gt; 40 mm Hg by arterial blood gas (end-exercise)</td>
<td>◯</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>VEmax near MVV</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Decreasing tidal volume</td>
<td>*</td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>R does not increase above 1.0</td>
<td></td>
<td>◯</td>
<td>◯</td>
</tr>
<tr>
<td>Stop exercising due to dyspnea</td>
<td></td>
<td>◯</td>
<td>◯</td>
</tr>
</tbody>
</table>

*Pulmonary vascular and interstitial lung diseases share many common features on CPET, and additional resting, such as echocardiography, pulmonary function testing, and imaging, is often necessary to distinguish between the two forms of disease.

Can be seen if “air trapping” affects cardiac function.

The size of the marker indicates the relative importance of the observation.

is most likely to be the limiting organ system. By being less dependent on single parameters to make a decision throughout a binary tree, pattern recognition may be less prone to misclassifications of the limiting organ system. The disadvantage of the pattern recognition approach is that it requires some expertise to recognize the patterns.

Each of these approaches to data interpretation has strengths and weaknesses, and neither has been demonstrated to be superior to the other. Regardless of the interpretation method used, the CPET data are more useful for determining the primary system limiting exercise and less effective at identifying the specific disease process at work.

**ALTERNATIVE METHODS OF ASSESSING EXERCISE PERFORMANCE**

In addition to the symptom-limited progressive work exercise test, there are several other means for assessing exercise responses in clinical practice.

**The 6-Minute Walk and Shuttle Walk Tests**

The 6MWT is a widely available, inexpensive, and reproducible submaximal exercise test during which subjects walk back and forth along a flat indoor course varying in length between 30 and 100 m for a period of 6 minutes under the supervision of a trained technician following a specified testing protocol. Individuals move at their own pace, can use supplemental oxygen, and, unlike in a cardiopulmonary exercise test, may stop to rest if necessary. The primary measurements obtained during the test include the distance walked, as well as heart rate, oxygen saturation, blood pressure, and subjective ratings of dyspnea and leg fatigue. The test is usually performed only once during a given testing period, although some have argued that addition of a second trial improves the yield of the study.

The 6MWT is used for two general purposes. The first of these is to monitor response to interventions or follow disease activity over time as demonstrated by the extensive use of the distance walked as an outcome in pulmonary hypertension and idiopathic pulmonary fibrosis trials, while the other is to assess patient prognosis. Studies done in patients with COPD, pulmonary hypertension, and idiopathic pulmonary fibrosis have shown relationships between the distance walked or development of hypoxemia during the test and outcomes such as mortality risk. Such information can be used to guide management decisions, such as when to list a patient for transplantation. Whether the distance walked is an adequate surrogate for VO$_{2\text{max}}$ remains unclear, however, because studies have reported varying degrees of correlation between these two variables. Importantly, due to the limited nature of the data available from the test, the 6MWT cannot be used to determine the etiology of exercise limitation. In addition, it is generally only relevant to patients or elderly individuals who are unable to maintain a normal or brisk walking pace and has little role in the assessment of exercise responses in fit individuals.

Use of the test for the purposes noted earlier requires recognition of several important issues. First, although reference values for normal individuals have been published, their utility is limited by the fact that test results vary on the basis of differences in testing methodology and the population under consideration. Second, subject performance can be affected by learning, verbal encouragement, and course layout, necessitating strict adherence to published guidelines for conducting the test. Finally, when using the 6MWT to assess response to therapy or change over time, clinicians must understand the minimal clinically important difference, the threshold at which a change in 6MWT is recognized as either important by the patient or associated with other outcomes. Minimal clinically important difference values have been published but vary depending on the patient population and outcome in question.

The Incremental Shuttle Walk Test (SWT) is a less widely used alternative to the 6MWT, which requires the patient to walk at a specified pace that increases over time until the individual can no longer maintain the pace or stops due to symptoms. Designed as a less invasive assessment of maximum exercise capacity, the test correlates reasonably well with VO$_{2\text{max}}$ and can be used to monitor responses to therapeutic interventions. Reference values for normal individuals are lacking, and its use is largely limited to following changes over time in a given patient or to making comparisons between patient groups.

More thorough reviews of the clinical utility and limitations of these tests are available elsewhere.

**Exercise Treadmill Testing**

In addition to its role in cardiopulmonary testing described earlier, exercise treadmill testing (ETT) is also commonly performed without exhaled gas collection. Because data collection is limited in such cases to assessment of symptoms, blood pressure, heart rate, oxygen saturation, electrocardiography, and exercise duration, ETT cannot be used to determine which system is limiting exercise but does provide information for assessing exercise responses and guiding management.

The primary use of ETT is to identify coronary artery disease in low- to intermediate-risk individuals capable of exercise who have normal baseline electrocardiograms (absence of left bundle branch block, left ventricular hypertrophy with any repolarization abnormalities, or ST segment depression). The test can be performed in the outpatient setting, as well as part of diagnostic protocols for low-risk patients admitted to chest pain units from the emergency department. Myocardial perfusion imaging is combined with ETT for patients with abnormal baseline electrocardiograms and is often necessary when evaluating female patients because the predictive capability of routine ETT is limited by the lower pretest probability of coronary artery disease (CAD) in this patient group.

Using the concept of metabolic equivalents (METS) rather than direct measurement of VO$_{2\text{max}}$, ETT can also be used to assess exercise capacity. Although this approach is less precise than measurements using exhaled gas collection, various studies have demonstrated its utility in patient assessment and prognostication. Higher exercise capacity on ETT is associated with less significant coronary artery disease on left heart catheterization, for example, while decrements in exercise capacity measured by ETT predict mortality in both men and women. Consideration of exercise capacity may also improve the predictive ability of risk models on the basis of traditional clinical CAD risk factors.
Other variables measured during ETT can also be related to mortality risk or the severity of coronary artery disease. For example, decreased heart rate recovery following exercise (<25 beats/min) is associated with increased risk of sudden death from myocardial infarction, whereas impaired heart rate response to increasing work rates is an independent predictor of mortality in asymptomatic women and impaired blood pressure responses are useful for identifying patients with three-vessel coronary disease. More complete reviews of the utility of ETT can be found elsewhere.

### Key Points

- The ability to perform sustained exercise requires tight integration of multiple systems. Disease within any of these systems can manifest as dyspnea during exertion or as exercise limitation.
- Assessment of maximal oxygen consumption provides valuable insight into maximum exercise capacity, as well as important aspects of cardiac function including cardiac output and stroke volume.
- Normal individuals demonstrate a characteristic pattern of responses to progressive exercise to a symptom-limited maximum. Characteristic patterns of deviation from these normal responses are seen in various disease states such as heart failure, pulmonary vascular disease, interstitial lung disease, and COPD.
- Cardiopulmonary exercise testing can be used to characterize the pattern of responses to progressive exercise and to identify the primary organ system limiting exercise capacity.

Beyond assessing exercise capacity, cardiopulmonary exercise testing can be used to gather prognostic information and guide management in certain patient groups, guide perioperative management in thoracic and other major surgical procedures, assess disability, and develop exercise prescriptions as part of rehabilitation programs.

### Complete reference list available at ExpertConsult.

### Key Readings

References


PART 2 • Diagnosis and Evaluation of Respiratory Disease


