

Cardiopulmonary Exercise Testing

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Objectives:

- To understand the physiologic mechanisms that support the increased metabolic rate during normal exercise
- To review how disease disrupts the coordinated function of several systems that support exercise function
- To review the indications for performing cardiopulmonary exercise testing
- To understand the measurements performed during cardiopulmonary exercise testing and their use in interpreting exercise tests
- To recognize the typical patterns seen during exercise in common conditions: cardiomyopathy, COPD, interstitial lung disease, pulmonary vascular disease, obesity, and the deconditioned state

Key words: anaerobic threshold; cardiopulmonary exercise testing; dead space fraction; peak or maximum oxygen consumption; ventilatory reserve

Pulmonary function tests (PFTs) performed at rest measure the mechanical and gas exchange physiology of the lung, and are reliable tools for diagnosis and management of respiratory disease. FEV₁ is used for rating severity because it is the resting pulmonary function variable that best correlates with exercise performance. However, the correlation coefficient is of only moderate magnitude, resulting in considerable variability in predicting an individual patient's exercise capacity. For some clinical questions, it is better to measure exercise performance directly. Exercise requires the coordinated function of several integrated systems: oxygen must flow from the environment to the lung, meet capillary blood in an appropriate ratio, then go to the left heart, to the peripheral circulation, and to the exercising muscles; carbon dioxide must flow back from the metabolizing muscles, via the venous system, to the right heart, through the pulmonary circulation, and back to the lung for elimination back to the environment.

Exercise testing assesses the integration of the whole system (peak oxygen consumption [$\dot{V}O_2$], anaerobic threshold [AT]) and allows an evaluation of which link in the system is causing exercise impairment. This allows statements regarding the

individual's global ability to perform exercise and clarify the organ system limiting exertion.

Exercise Testing Equipment

Exercise testing refers to a wide range of tests, including the cardiologist's treadmill-based Bruce protocol tests aimed at detecting cardiac ischemia, simple walking tests performed in a corridor, and the cardiopulmonary exercise tests (CPETs) that are the subject of this review. I will focus on the symptom-limited, incremental bicycle ergometry exercise test that is the test protocol used most by pulmonologists. This test involves a continuous ramped increase in work rate (or at 1-min increments), with the test continuing until the patient has symptoms (fatigue or dyspnea, most commonly) that cause him to believe he cannot continue to higher work rates. Since we often aim to clarify the mechanisms causing exercise limitation, the patient is exhorted to give a maximal effort. Tests may also be stopped due to significant tachyarrhythmia, ST-segment depression, or fall in systolic BP.

Equipment and Primary Measurements

Quantifiable Workload: Although the treadmill has the advantage of using the main exercise activity of interest (walking, running) and is used for most cardiac tests for ischemic heart disease, most pulmonary laboratories favor the bicycle ergometer. Its advantages include less body movement, resulting in less noisy data signals and an easily controlled, linear increase in work rate. In contrast, work rate on the treadmill, which depends on gait, grade, and speed, is less accurate, and a linear increment in work rate is not usually obtained.

ECG: The ECG is used for heart rate (HR), ST-segment depression, and arrhythmia detection.

Collection of Expired Gases: Most clinical laboratories use computerized systems that measure exhaled gases in breath-by-breath mode or, less commonly, using a mixing chamber (5- to 15-L baffled chamber). However, due to potential inaccuracies from

temporal misalignments of measurements, the American Thoracic Society (ATS)/American College of Chest Physicians guidelines recommend use of the Douglas bag method for quality control. In this latter system, all exhaled gases are collected in a large bag (similar to a meteorologic balloon). Volume is measured with a Tissot spirometer (a large-volume spirometer, approximately 100 L) and gas concentrations by a mass spectrometer. When using data from breath-by-breath or mixing chamber systems, the ATS/American College of Chest Physicians guidelines recommend 30- to 60-s intervals for data averaging to smooth out noise, although 20-s intervals may be acceptable in breath-by-breath systems.

In the commonly used commercial systems, the primary measurements are from a flowmeter, capnometer, and oximeter. From these three measurements, many ventilatory and gas exchange parameters are obtained. These include the following:

- Tidal volume (V_T) in milliliters or liters (V refers to volume, and $\dot{V}$ means flow, *ie*, first derivative of volume with respect to time; small capital letters represent gas phase variables, and lowercase letters represents blood phase variables).
- Minute volume or minute ventilation ($\dot{V}_E$) in liters per minute.
- Respiratory rate (RR [or breathing frequency]) in breaths per minute.
- Rate of carbon dioxide output ($\dot{V}_{CO_2}$) or elimination in liters per minute
- $\dot{V}_{O_2}$
- Respiratory exchange ratio (RER), which is the ratio of $\dot{V}_{CO_2}$ to $\dot{V}_{O_2}$ measured simultaneously based on gas exchange at the mouth. During steady state, the RER is equal to the respiratory quotient (RQ), representing $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at the tissue level. The RQ is difficult to measure and is not measured during clinical exercise testing.
- Ventilatory equivalents for CO_2 and O_2 ($\dot{V}_E/\dot{V}_{CO_2}$, $\dot{V}_E/\dot{V}_{O_2}$); these ratios are obtained by the division of these two parameters measured at the same time, literally the liters per minute of ventilation required per liter of $\dot{V}_{O_2}$ or $\dot{V}_{CO_2}$ (an “efficiency” ratio).

Pulse Oximetry: This is abbreviated as oxygen saturation measured by pulse oximetry (SpO_2), in contrast to arterial oxygen saturation (SaO_2). At

rest, these are accurate within 3% and may be less accurate during exercise. In patients with normal resting Pao_2 , significant changes in alveolar-arterial oxygen pressure gradient [$P(A-a)O_2$] may occur with exercise but little change in SpO_2 .

Arterial Catheterization: Blood gases, lactate (optional). Although noninvasive tests are done in most clinical situation, arterial blood samples are required to accurately measure gas exchange abnormalities during exercise. Pao_2 and $P(A-a)O_2$ assess oxygen exchange in the lung, and $Paco_2$ is needed for calculation of dead space fraction to assess the efficiency of CO_2 exchange (see later section). An alternative to arterial catheterization is measuring arterial blood gas levels at rest and near work rate maximum. Waiting until maximum exercise or immediately after exercise is not recommended, as the patient is struggling at this point, and values change rapidly in the recovery phase. The radial artery is the preferred sampling or catheterization site.

BP: Invasive or noninvasive measurement. Intra-arterial BP measurements are modestly higher than those done by auscultation, particularly the systolic pressure measurement. The normal BP response to exercise is an increase in systolic pressure; diastolic pressure is unchanged or slightly lower by auscultation but rises slightly with intra-arterial measurement.

Indications for CPETs

Unexplained Exertional Intolerance: Dyspnea or Fatigue

When routine clinical evaluation including history, physical examination, chest radiography, ECG, and resting PFTs do not provide an answer, CPETs are a useful tool for identifying diseases and factors contributing to the symptoms. CPETs may suggest deconditioning or cardiovascular, pulmonary, psychological, or myopathic processes as explanations. It can also clarify that responses are normal and alleviate patient and clinician concern.

Objective Assessment of Capacity/Impairment

When the patient’s symptoms do not match resting data, such as PFTs or echocardiography, or in disability evaluation, measurement of objective

exercise performance can be helpful. In disability assessment, CPETs combined with information about job-related energy and environmental conditions will lead to the most accurate rating of impairment/disability.

Establish Organ System-Limiting Exercise When Multiple Diagnoses Are Present

This can be particularly important when interventional procedures and surgery are being contemplated in patients with combined heart and lung disease. Establishing the relative importance of several pathophysiologic processes in limiting exercise performance may aid decision making about therapeutic options.

Preoperative Assessment Before Lung Resection

When resting PFT results indicate a high risk for lung resectional surgery, peak $\dot{V}O_2$ along with perfusion scan data help to assess operability and the extent of resection that can be tolerated. This may help stratify high-risk operative candidates into acceptable and unacceptable degrees of risk (see additional discussion in chapter on PFTs).

Diagnose Exercise-Induced Asthma

Bronchoprovocation testing is a simpler and more sensitive method for diagnosis of this condition, although some patients with exercise-induced bronchospasm will have negative methacholine challenge test results. The incremental protocol used for other conditions is not ideal for this diagnosis. A treadmill test performed at 80 to 90% of predicted HR with sequential posttest spirometry is the preferred exercise protocol for exercise-induced asthma (see chapter on PFTs for further discussion).

Identify Gas Exchange Abnormalities

Resting data are not sufficiently reliable to predict exercise oxygen desaturation. Exercise gas exchange abnormalities are more sensitive parameters than resting PFTs in patients with early or mild interstitial lung disease. Patients with COPD and normal or near-normal diffusion capacity of the lung for carbon monoxide (DLCO) almost never

lower their Pao_2 with exercise; conversely, many but not all patients with a DLCO <55% have exercise oxygen desaturation.

Titrate O_2 Flow During Exercise

O_2 prescription should indicate appropriate flow rates for rest, exercise, and sleep (sleep study not routinely performed). Exercise-induced hypoxemia may contribute to exercise intolerance.

Pulmonary Rehabilitation Prescription and Assessment of Response

Individually targeted programs can be based on peak $\dot{V}O_2$, AT, and presence of O_2 desaturation. Arrhythmias and coexisting cardiac disease can be identified. CPETs help determine the safety and optimal training intensity of pulmonary rehabilitation. The CPET is currently preferred over the standard or treadmill 6-min walk test (6MWT) for this purpose.

Transplant Referral and Prognosis

Functional status and prognosis best correlate with peak $\dot{V}O_2$. Peak $\dot{V}O_2$ <14 mL/kg is often used as a basis for referral for cardiac transplantation for patients with cardiomyopathy. Others have used a peak $\dot{V}O_2$ <50% in this setting, as it was the best predictor of cardiac death in multivariate analysis. Prognosis in cystic fibrosis is predicted by peak $\dot{V}O_2$ and may be useful for transplant decisions. The use of CPETs and other exercise tests for lung transplant decisions has not been standardized. Some have suggested that a 6MWT distance <400 m is helpful in choosing to list a patient for lung transplantation.

Assess Response to Therapy: Medical, Physical, Surgical

CPETs probably provide a more clinically meaningful objective end point measurement than resting PFTs for evaluation of new therapies. Constant work rate protocols and the 6MWT have also been used for these assessments. The latter is simpler to perform than the symptom-limited progressive exercise tolerance test. The former may be better at serial follow-up to assess response to

interventions. The preferred test in this setting is still controversial.

Patient Safety

Maximum, symptom-limited exercise testing is a relatively safe procedure. The risk of complications is related to the underlying disease. Rate of death is between 2 and 5 per 100,000 tests. Major cardiac events such as myocardial infarction and ventricular tachycardia have been estimated at 1.2 per 10,000 tests. Informed consent should be obtained prior to proceeding with the test. Resuscitation equipment should be immediately available.

Absolute Contraindications to CPETs

Absolute contraindications include acute myocardial infarction (prior 3 to 5 days); unstable angina; uncontrolled, symptomatic arrhythmias; syncope; active endocarditis; acute myocarditis or pericarditis; symptomatic severe aortic stenosis; uncontrolled heart failure; acute pulmonary embolism; thrombosis of lower extremities; suspected dissecting aneurysm; uncontrolled asthma; pulmonary edema; room air saturation <85% (can exercise with supplemental O₂); respiratory failure; and mental impairment leading to inability to cooperate.

Relative Contraindications to CPETs

Relative contraindications include left main coronary stenosis or equivalent; moderate stenotic valvular heart disease; severe untreated arterial hypertension at rest (>200 mm Hg systolic, >120 mm Hg diastolic), tachyarrhythmias or bradyarrhythmias; high-degree atrioventricular block; hypertrophic cardiomyopathy; significant pulmonary hypertension (although this can be done safely); advanced or complicated pregnancy; electrolyte abnormalities; and orthopedic impairment that compromises exercise performance.

External and Internal Measurements of Work

During an incremental exercise test, there is a steady, linear increase in external work rate performed by the patient. This is expressed in watts.

The internal metabolic work performed by the muscles is generally represented by the linear increase in $\dot{V}O_2$ with increasing work. Most of the metabolic work is accomplished by aerobic mechanisms (so O₂ is consumed), although increasing proportions of the work are done via anaerobic mechanisms later in exercise.

Determinants of O₂ Delivery at Rest and During Exercise

Modified Fick Equation

The systems supporting this steadily increasing work rate are explained by a rearrangement of the Fick equation (CO = cardiac output; $Cao_2 - C\bar{v}O_2$ = the arterial–mixed venous oxygen content difference):

$$CO = \frac{\dot{V}O_2}{Cao_2 - C\bar{v}O_2} \quad (\text{Fick equation})$$

The following is a rearrangement of the Fick equation (HR in beats per minute; SV = stroke volume in milliliters; Hb = hemoglobin concentration in grams per deciliter; 1.34 = oxygen-carrying capacity of Hb in milliliters of O₂/gram/deciliter of Hb; Sao_2 = arterial oxygen saturation; $S\bar{v}O_2$ = mixed venous oxygen saturation):

$$\dot{V}O_2 = CO \times (Cao_2 - C\bar{v}O_2) \quad [2]$$

$$\dot{V}O_2 = HR \times SV \times 1.34 \text{ Hb} (Sao_2 - S\bar{v}O_2) \quad [3]$$

From the rearranged Fick equation, we can see that increasing $\dot{V}O_2$ during steadily increasing exercise depends on the degree to which CO can increase. The maximum level of exercise, and the maximum $\dot{V}O_2$ ($\dot{V}O_{2\text{max}}$) are dependent on the maximum CO, the presence of anemia, the Sao_2 , and the degree to which the exercising muscles can extract oxygen and lower the $S\bar{v}O_2$ (manifested as $Cao_2 - C\bar{v}O_2$ in equation 2, or saturation difference in equation 3).

The Cardiac Pump

In plain terms, the maximum output of the heart pump is dependent on the amount of blood ejected per beat (SV) and the number of beats per minute: $CO = HR \times SV$. Viewed in this manner, in the normal individual peak exercise work level and $\dot{V}O_2$ occur when SV and HR reach their physiologic maxima.

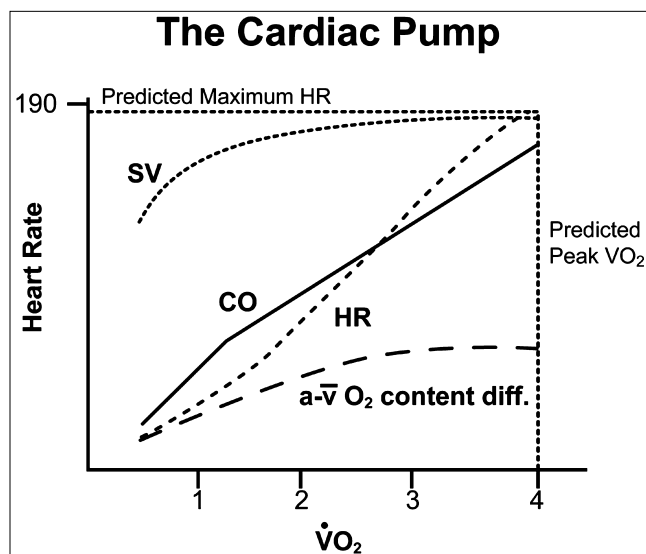


Figure 1. Normal exercise responses in a 30-year-old man. This graphic presentation of the rearranged Fick equation shows the contribution of SV, HR, and O₂ extraction in the tissues to the increased $\dot{V}O_2$ of progressive exercise loads.

Table 1. Determinants of Peak $\dot{V}O_2$ *

Condition	Peak $\dot{V}O_2 = (HR \times SV) \times (Cao_2 - C\bar{v}O_2)$
25-yr-old normal subject	$3.5 = (195 \times 112) \times (20 - 4)$
70-yr-old normal subject	$2.2 = (160^\dagger \times 100) \times (20 - 6^\dagger)$
Trained	$6.2 = (190 \times 205^\dagger) \times (20 - 4)$
Mitral stenosis	$1.4 = (190 \times 43^\dagger) \times (20 - 3)$
Arterial hypoxemia	$2.6 = (195 \times 112) \times (15^\dagger - 4)$

*From Dempsey (ATS 1998).

†Major difference from 25-year-old normal subject.

Changes in CO, HR, SV, and $Cao_2 - C\bar{v}O_2$ During Exercise

The role of these factors from the modified Fick equation is shown graphically in Figure 1. Note that CO linearly increases with workload or $\dot{V}O_2$. This is accomplished by an increase in HR and SV, although early in exercise this is accomplished predominantly by an increase in SV. O₂ extraction in the muscles increases to a maximum value in late exercise. The maximum extraction is approximately 75% of the arterial oxygen content (Cao_2) in healthy nonathletes. Table 1 shows how reduced aerobic capacity (peak $\dot{V}O_2$), relative to the young normal person, results from changes in various organs as represented by the modified Fick equation.

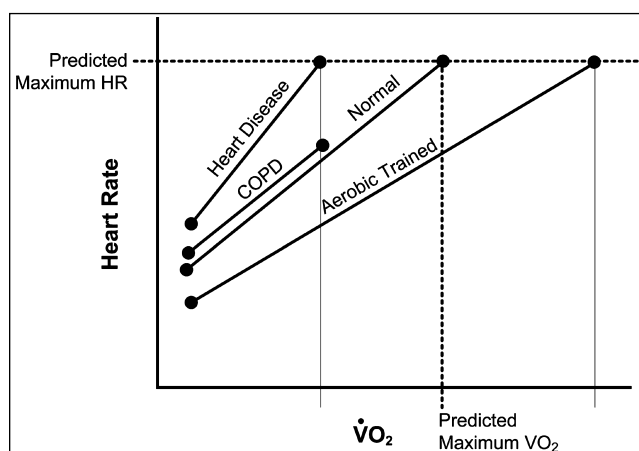


Figure 2. HR vs $\dot{V}O_2$ relationship during exercise.

Aging reduces the maximum HR and the ability of the muscles to extract O₂, and to a lesser extent the maximum-achieved SV. Training increases the SV, although increased extraction can be a factor. Cardiac disease, exemplified by mitral stenosis, reduces peak $\dot{V}O_2$ mostly due to reduction in SV. Lung disease resulting in hypoxemia decreases Sao_2 . Anemia and carboxyhemoglobinemia ("functional" anemia) would also reduce Sao_2 and reduce peak $\dot{V}O_2$.

The Relationship Between HR and $\dot{V}O_2$

HR and $\dot{V}O_2$ are easily measured during exercise testing performed with gas exchange measurements. The graphic evaluation of their relationship is a fundamental relationship examined during exercise (Fig 2). The predicted maximum HR is 220 minus age in years (alternate: $210 - [0.65 \times \text{age in years}]$). The former equation tends to underestimate maximal HR in older subjects. The predicted $\dot{V}O_{2\text{max}}$ is based on data in sedentary normal people, and is calculated from age, height, and sex. The normal person stops exercising because of fatigue symptoms when he or she has reached the peak HR. In Figure 2, a normal subject reached the predicted peak $\dot{V}O_2$ when the peak HR was reached. The patient with heart disease has a left-shifted and steeper-sloped curve. As a result of a limitation in SV, these patients need to meet the CO requirement for any level of work rate or $\dot{V}O_2$ by having a higher HR (relative tachycardia). As a result, they reach their peak HR sooner and stop exercising due to

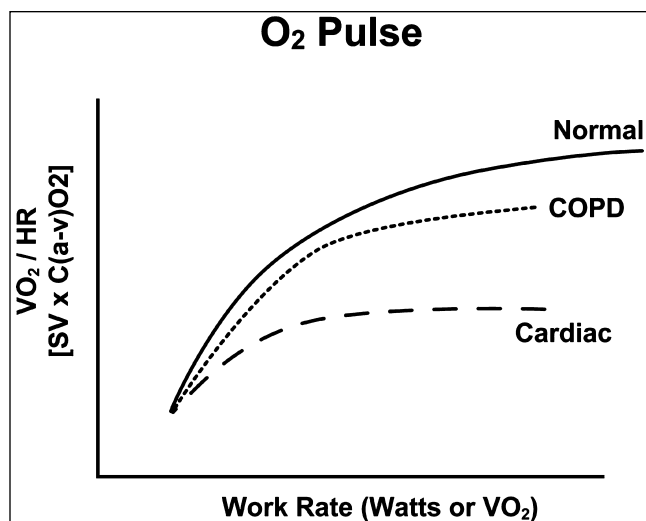


Figure 3. Relationship of $\dot{V}O_2$ pulse ($\dot{V}O_2/HR$) and work rate during exercise.

symptoms occurring at this below-normal exercise level. This is referred to as a reduced peak $\dot{V}O_2$. The aerobically trained person reaches an exercise-limiting HR at an above-predicted level because of higher SV and lower HR at any given level of $\dot{V}O_2$ or work rate.

O₂ Pulse

O_2 pulse is $\dot{V}O_2/HR$, obtained by dividing these two simultaneous measurements taken during exercise. It is literally the milliliters of O_2 consumed per beat, although it is often used (with some hedging) as a noninvasive surrogate for SV. A rearrangement of equation 3 explains the significance of the O_2 pulse: $\dot{V}O_2/HR = SV \times (Cao_2 - C\bar{v}O_2)$.

If we assume that Sao_2 is normal and that the $Cao_2 - C\bar{v}O_2$ progressively widens in a predictable manner, then differences from expected O_2 pulse will be due to abnormalities of SV. This is a fair assumption in normal people and patients with heart disease. Arterial hypoxemia, anemia, metabolic myopathies, and deconditioning (with reduced capability of the tissue to extract O_2 in the latter two) are exceptions because they affect the right side of the equation.

Figure 3 shows the relationship of O_2 pulse to increasing exercise work rate. It has the same shape as the SV graph. The cardiac patient (cardiomyopathy or valvular heart disease) has a low maximum SV with early plateau. The typical patient with COPD may have a slightly right-shifted curve. With

more severe COPD, it may approach the “cardiac” curve due to reduced SV (cor pulmonale, pulmonary hypertension, or hemodynamic effects of dynamic hyperinflation) or due to deconditioning. Interpreting a reduction in peak O_2 pulse as evidence of a cardiovascular limitation must be done with caution, and in the context of other exercise parameters.

AT

Most of the metabolic work performed by the muscles during exercise is done via aerobic mechanisms. There is workload above which a given person exceeds his or her or her physiologic capability to do most of the work aerobically, and incremental work rates result in progressive lactic acidosis in the blood due to anaerobic metabolism in muscle. This work rate is referred to as the lactate threshold or AT. This can be measured directly as accumulation of lactate or by the roughly equimolar decrease in bicarbonate in the blood. This has the disadvantage of requiring blood samples and can be done only intermittently. The shift into increasing anaerobic metabolism is a reflection of limitations in O_2 delivery or in muscle oxidative capacity, or both.

AT is regarded as an estimator of the onset of metabolic acidosis, predominantly due to rise of arterial lactate. It is reported as the $\dot{V}O_2$ at which this occurs, expressed as a percentage of the predicted value of exercise $\dot{V}O_{2max}$ for that subject.

The actual cause of the AT remains controversial, although roles for a deficiency of O_2 delivery and reduced muscle oxidative capacity both have support. It is likely that the processes underlying the AT vary by disease state. Although commonly reduced in cardiovascular diseases, it is not specific for any disease type.

Noninvasive Gas Exchange Method of Measuring AT

Noninvasive measurement of AT can be performed by analysis of gas exchange variables. The various parameters used all result from the buffering of lactic acid by bicarbonate, which results in $\dot{V}CO_2$ without $\dot{V}O_2$ and characteristic effects on gas exchange parameters.

Aerobic Metabolism: This is determined as follows: 1 mol of O_2 consumed results in 0.8 mol of CO_2 produced (assuming a normal RQ of 0.8).

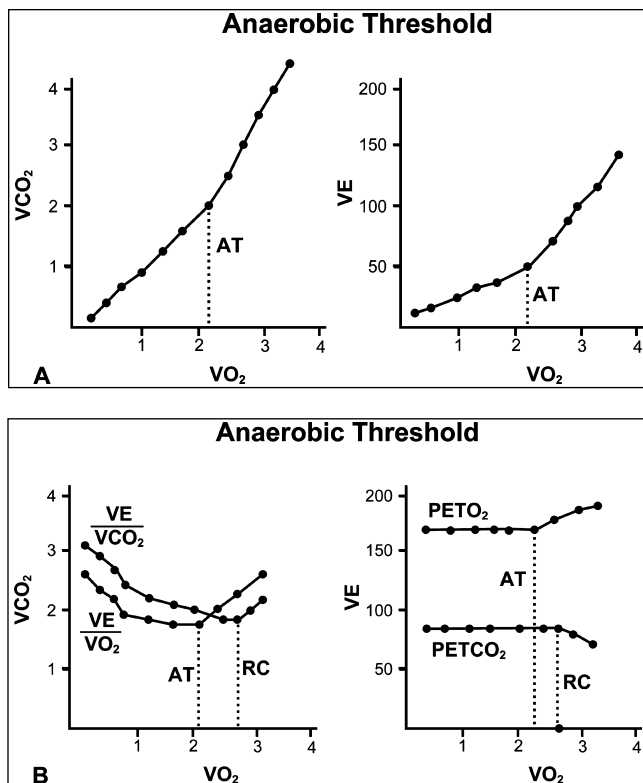


Figure 4. Graphs typically used to identify AT by gas exchange criteria. See text for details.

Anaerobic Metabolism: $[H^+] + [lactate^-] + [HCO_3^-] \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$. As lactate accumulates, progressively increasing amounts of CO_2 are generated from nonaerobic metabolic sources. This results in an increase in RER and a steepening in the slope of increase of $\dot{V}E$ to maintain a normal $Paco_2$ in the face of accelerating $\dot{V}CO_2$. AT is identified by inspection of several graphs (Fig 4).

V-Slope Method: In the left side of the upper panel of Fig 4, $\dot{V}CO_2$ is plotted against $\dot{V}O_2$. At exercise levels below AT, both $\dot{V}CO_2$ and $\dot{V}O_2$ increase linearly based on their linkage by aerobic metabolism. Above the AT, the additional source of CO_2 from bicarbonate buffering causes an upward inflection in slope of their relationship. This inflection identifies AT by the V-slope method.

Ventilatory Equivalents for CO_2 and O_2 : In the left side of the lower panel of Fig 4, $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ (ratios of these parameters measured at the same time in exercise) both decrease early in exercise as a result of the decrease in the physiologic dead space (V_D) to V_T ratio (mechanism explained below). At AT, the $\dot{V}E/\dot{V}O_2$ inflects upward since $\dot{V}E$ is driven upward by the sudden increase in $\dot{V}CO_2$ while $\dot{V}O_2$ continues to increase at its previous pace. At the

same time, the $\dot{V}E/\dot{V}CO_2$ ratio stays flat because the increase in $\dot{V}E$ is proportional to, and a consequence of, the acceleration in $\dot{V}CO_2$. This maintains the normality of $Paco_2$. Shortly thereafter, $\dot{V}E/\dot{V}CO_2$ also inflects upward, when the onset of frank metabolic acidosis causes respiratory compensation. At this "respiratory compensation" (RC) point, $\dot{V}E$ is increasing more rapidly than $\dot{V}CO_2$, which results in hypocapnia, *ie*, respiratory compensation for metabolic acidosis. This graph is particularly useful for identifying AT because of two features: (1) the nadir of $\dot{V}E/\dot{V}O_2$ is the AT; and (2) as the $\dot{V}E/\dot{V}O_2$ inflects upward, it crosses over the $\dot{V}E/\dot{V}CO_2$ because the latter remains flat, not inflected upward until the respiratory compensation point.

End-Tidal O_2 and CO_2 : The end-tidal O_2 ($PETO_2$) and end-tidal CO_2 ($PETCO_2$) can be measured at the mouthpiece by rapid response analyzers in "breath-by-breath" exercise systems. Because these gas pressures are measured at end-exhalation, they are not contaminated by gas from the anatomic dead space and represent "alveolar" gas. At AT, when ventilation inflects upward to eliminate the increased amount of CO_2 arriving at the alveolus, it has the indirect affect of enriching the alveolus as a reservoir of O_2 . This hyperventilation with respect to $\dot{V}O_2$ results in an increased alveolar pressure of O_2 , Pao_2 , and $PETO_2$. The AT is identified by the upward inflection of the $PETO_2$ curve, which occurs slightly before the downward deflection in $PETCO_2$ at the respiratory compensation (RC) point (Fig 4, lower right panel).

Graphic Identification of AT: It is useful to use the multiple graphic approaches simultaneously to confidently identify the AT. In addition, at the AT the RER will approximate 1.0, and one needs to avoid identifying an apparent AT by V-slope that is actually due to hyperventilation. Hyperventilation is indicated by an increase in the $\dot{V}E/\dot{V}CO_2$ and a decrease in $PETCO_2$.

Practical Correlates of AT and Peak $\dot{V}O_2$

From a functional standpoint, peak $\dot{V}O_2$ or $\dot{V}O_{2max}$ define the upper limits of exercise capacity for a person. This would represent the highest burst of exertion that could be performed for a short period. While *peak* and *maximal* $\dot{V}O_2$ are often used interchangeably, $\dot{V}O_{2max}$ is a peak $\dot{V}O_2$ that has been demonstrated to represent a plateau or

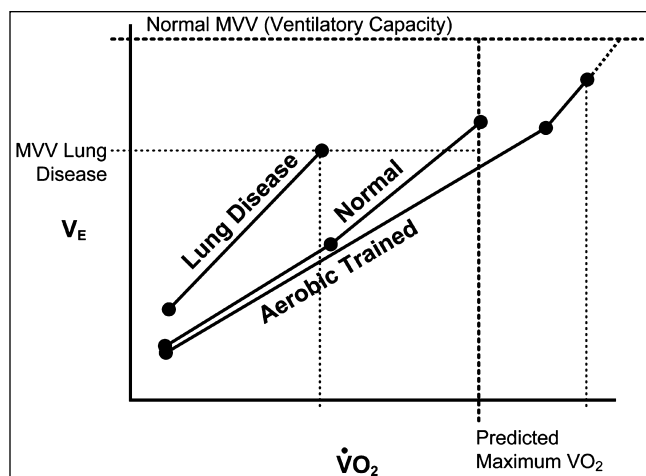


Figure 5. Exercise ventilatory responses: $\dot{V}_E$ vs $\dot{V}_{O_2}$. The normal subject has a ventilatory reserve. The lung disease subject has a reduced MVV and an increased ventilatory requirement, leading to early termination of exercise due to ventilatory limitation. Endurance-trained subjects can encroach on their ventilatory reserve, but this occurs at an above-normal exercise workload.

true physiologic maximum. This is shown by failure of $\dot{V}_{O_2}$ to increase further at higher external workloads. The AT defines the highest level of exercise that can be sustained for prolonged periods of time. Above this level, fatigue and discomfort set in (probably due to afferent signals from lactate production), such that exercise duration is more limited at these work levels. As such, the AT defines an important functional upper limit for sustained activity levels.

Ventilatory Limitation and Factors

The preceding discussion, which related peak $\dot{V}_{O_2}$ to the factors in the modified Fick equation, does not incorporate ventilation directly, and would seem to imply that ventilation is not a factor limiting $\dot{V}_{O_2}$. One reason is that the normal person is “overengineered” with respect to ventilation such that it does not play a role in limiting the maximal exercise level. The peak $\dot{V}_E$ achieved during maximal exercise is well below the maximum ability to ventilate, or maximum voluntary ventilation (MVV). In the normal individual, there is a ventilatory “reserve.”

These relationships are demonstrated graphically in Figure 5. Note that the normal person only reaches approximately 75% of MVV when reaching the predicted peak $\dot{V}_{O_2}$. Instead, normal people stop exercising after reaching the maximum achievable

HR (Fig 2) and typically report fatigue rather than dyspnea as the exercise-limiting symptom. The patient with lung disease has two interrelated problems that lead to ventilatory limitation. The ventilatory capacity is reduced. This is the maximal achievable ventilation, usually measured as the MVV, and it will be reduced in direct relation to the reduction in FEV₁ and FVC as measures of mechanical lung dysfunction. In addition, the patient with lung disease has an increased ventilatory requirement, shifting the curve upward and to the left. At any level of work, the patient needs a higher $\dot{V}_E$. This two-edged sword, a reduced ventilatory capacity and an increased ventilatory requirement, results in early termination of exercise, usually due to dyspnea.

The ventilatory requirement is high most commonly due to an increase in dead space, such that $\dot{V}_E$ must increase to maintain alveolar ventilation ($\dot{V}_A$). This is expressed in the following equation: $\dot{V}_E = \dot{V}_A + \dot{V}_D$ ($\dot{V}_D$ = dead space ventilation). An additional factor in some patients is hyperventilation due to exercise-induced arterial hypoxemia or afferent reflexes in interstitial lung disease.

The Ventilatory Pump

The output of the cardiac pump (CO, liters per minute) is the volume per beat (SV) and the number of beats per minute (HR). The ventilatory pump is analogous:

$$\dot{V}_E = V_T \times RR.$$

Another parallel between these two pumps is seen graphically in Figures 1 and 6. Early in exercise, $\dot{V}_E$ increases mostly due to increases in V_T . As V_T reaches approximately 50 to 60% of vital capacity (VC), it begins to plateau, and further increases in $\dot{V}_E$ are mostly due to increases in RR. Patients with restrictive impairment reach a larger percentage of their VC early in exercise and must increase $\dot{V}_E$ predominantly due to increases in RR. At end-exercise, they often exceed rates of 50 to 60 breaths/min; most normal subjects and patients with obstructive lung disease have a maximal exercise RR < 50 breaths/min.

Exercise Tidal Flow-Volume Loops

A new way to evaluate patients for ventilatory limitation is to measure tidal breathing at

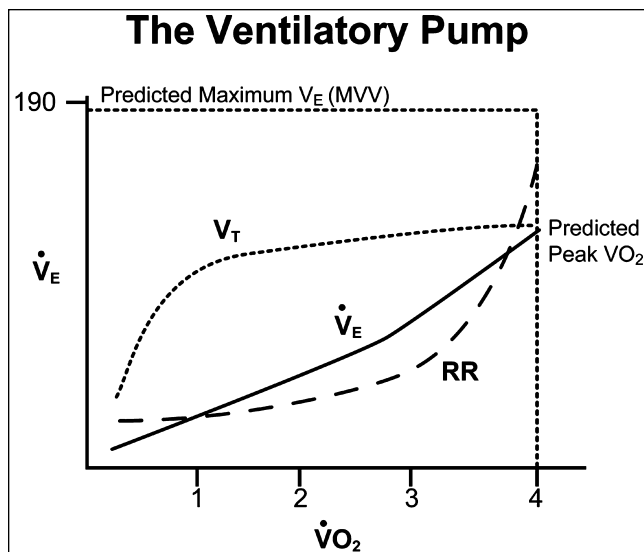


Figure 6. Normal ventilatory responses in a 30-year-old man: $\dot{V}_E$ vs $\dot{V}_{O_2}$ during an incremental exercise test. $\dot{V}_E$ increases mostly due to V_T increases early in exercise, mostly due to increase in RR later in exercise. There is a ventilatory reserve at maximum exercise. $\dot{V}_E$ inflects upward after the AT is reached.

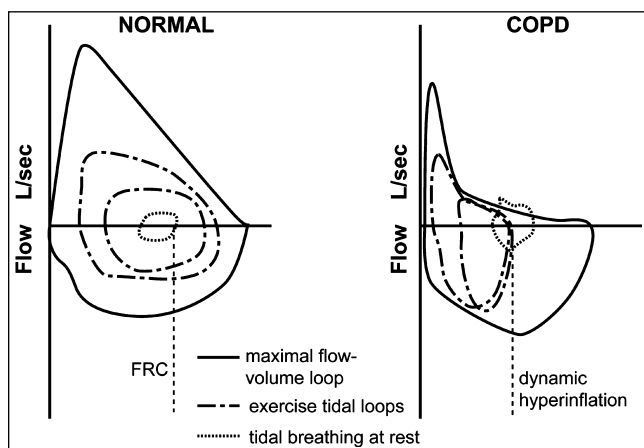


Figure 7. Tidal flow-volume loops measured during exercise can be placed within the maximal flow-volume loop, measured at rest, to identify the development of ventilatory limitation during exercise. This is seen as obliteration of flow and volume reserve.

rest and during exercise, and place these loops within the maximal flow-volume loop (Fig 7). With this technique, one can graphically inspect for inspiratory flow and volume limitation and expiratory flow and volume limitation during exercise. The normal subject has flow and volume reserve at rest and throughout exercise. Note that in health, V_T increases during exercise mostly due to increase in end-inspiratory lung volume, but also end-expiratory lung volume goes below resting

functional residual capacity (FRC), encroaching on expiratory reserve volume. By contrast, the patient with COPD has dynamic hyperinflation during exercise (end-expiratory lung volume is above resting FRC) and there is a lack of flow and volume reserve. This flow and volume limitation is seen as lack of space between the exercise loop and the maximal resting flow-volume loop. The lower expiratory flow on the maximum-effort resting flow-volume loop compared with the resting V_T is due to dynamic compression of the airways and lung during the forced effort.

Hypercapnia as a Measure of Ventilatory Limitation

P_{aCO_2} remains steady throughout exercise until the onset of lactic acidosis, at which point it decreases as respiratory compensation for metabolic acidosis. An increase in P_{aCO_2} (or P_{ETCO_2} when arterial blood gases are not measured) during exercise is abnormal. If AT was exceeded, failure to decrease these values is also abnormal. This inability of ventilation to keep up with increasing $\dot{V}_{CO_2}$ or compensate for lactic acidosis is important evidence of a ventilatory limitation.

Gas Exchange in the Lung

Pulmonary gas exchange is assessed by both dead space fraction and O_2 transfer parameters. Abnormalities causing an increase in high ventilation/perfusion ($\dot{V}/\dot{Q}$) ratios in the lung cause a high V_D/V_T ratio, since these areas are ventilated and poorly perfused or not perfused at all (pure alveolar dead space). Increases in the $P(A-a)O_2$ at rest are due to low $\dot{V}/\dot{Q}$ areas or shunt. During exercise, $P(A-a)O_2$ normally increases due $\dot{V}/\dot{Q}$ mismatching, O_2 diffusion limitation, and low $S\bar{v}O_2$.

Physiologic Dead Space

Dead space is also known as “wasted ventilation” because it represents ventilatory work done to bring air into parts of the system that do not lead to gas exchange. Total $\dot{V}_E$ is partitioned into two components: the portion participating in gas exchange ($\dot{V}_A$), and the portion going to dead space ($\dot{V}_D$). The fraction of each breath going to the dead space (V_D/V_T ratio) decreases from

approximately 0.30 at rest to 0.18 during maximal exercise. This is easy to remember as a change from approximately 1/3 to 1/5. The decrease is due to two factors: $\dot{V}_T$ increases during exercise; and perfusion of the upper lung zones increases during exercise as CO and pulmonary artery pressures increase, leading to a reduction in high $\dot{V}/\dot{Q}$ areas of the lung. V_D/V_T is calculated by the following formula, the dead space equation:

$$\frac{V_D}{V_T} = \frac{P_{aCO_2} - P_{E\bar{CO}_2}}{P_{aCO_2}}$$

P_{aCO_2}

This parameter requires measurement of an arterial blood sample and a measurement of $P_{E\bar{CO}_2}$, which is the average CO_2 concentration (actually partial pressure) of expired gases, measured easily by modern cardiopulmonary exercise systems. It is instructive to think of this as an efficiency equation. The closer $P_{E\bar{CO}_2}$ is to P_{aCO_2} , the more efficient the lung is as an “exhaust” or elimination system for CO_2 . Here are examples for clarification:

Example 1: A patient has a normal P_{aCO_2} of 40 mm Hg. If the average exhaled CO_2 concentration (or partial pressure), $P_{E\bar{CO}_2}$, is 30 mm Hg, then $V_D/V_T = (40 - 30)/40 = 10/40 = 0.25$. The dead space fraction is low, the amount of CO_2 in mixed-exhaled gas is high, and this lung is efficient at eliminating CO_2 .

Example 2: The P_{aCO_2} is again 40 mm Hg, but the $P_{E\bar{CO}_2}$ is 20 mm Hg. $V_D/V_T = (40 - 20)/40 = 20/40 = 0.5$. The dead space fraction is high, the amount of CO_2 in mixed-exhaled gas is low, and this lung is inefficient at eliminating CO_2 .

Ventilatory Equivalents for CO_2 —Noninvasive Surrogate for V_D/V_T : When arterial samples are not obtained, $\dot{V}_E/\dot{V}_{CO_2}$ provides information relevant to the estimation of V_D/V_T . Recall that the $\dot{V}_E/\dot{V}_{CO_2}$ is a noninvasive measurement provided by dividing these two measurements simultaneously obtained during exercise. The mass balance equation, as follows, is instructive:

$$P_{aCO_2} = K \cdot \frac{\dot{V}_{CO_2}}{\dot{V}_A} \approx \frac{\dot{V}_{CO_2}}{(\dot{V}_E - \dot{V}_D)} = \frac{\dot{V}_{CO_2}}{\dot{V}_E [1 - (V_D/V_T)]}$$

In plain English, this equation tells us that a person's arterial CO_2 concentration is a result of how much CO_2 is produced and how much CO_2 is eliminated. P_{aCO_2} remains unchanged if ventilation increases linearly with $\dot{V}_{CO_2}$. Only the ventilation going to

perfused lung ($\dot{V}_A$) eliminates CO_2 , rather than the total ventilation ($\dot{V}_E$). So the portion going to dead space is important. A rearrangement of the equation above gives you ventilatory equivalents for CO_2 :

$$\frac{\dot{V}_E}{\dot{V}_{CO_2}} = K \cdot \frac{1}{P_{aCO_2} [1 - (V_D/V_T)]}$$

This equation tells us that only two factors determine the value of $\dot{V}_E/\dot{V}_{CO_2}$: the level of P_{aCO_2} and V_D/V_T . If we know that a patient had a normal P_{aCO_2} (based on a resting arterial blood gas measurement), did not have an irregular breathing pattern during the exercise test, and did not have significant oxygen desaturation (likely to produce hyperventilation and hypocapnia), then we can assume that an elevated $\dot{V}_E/\dot{V}_{CO_2}$ is likely to represent an elevated dead space fraction. This parameter is usually examined at its nadir, near AT, since subsequent lactic acidosis-induced hypocapnia will drive the ratio upward and it no longer is a reliable index of dead space fraction. When examined near AT, the $\dot{V}_E/\dot{V}_{CO_2}$ should be approximately 29, with an upper limit of 34.

O_2 Transfer

During exercise, $P(A-a)O_2$ increases due to $\dot{V}/\dot{Q}$ mismatching, O_2 diffusion limitation, and low $S\bar{v}O_2$. Despite this widening of $P(A-a)O_2$ and steady increase in $\dot{V}O_2$ during exercise, P_{aO_2} usually remains essentially unchanged. Typically, P_{aO_2} increases slightly at high levels of exercise, although the $P(A-a)O_2$ also increases. While this may seem contradictory, it relates to a larger increase in alveolar pressure of O_2 in association with a falling P_{aCO_2} and increasing RER. A drop in maximum exercise P_{aO_2} has been demonstrated in endurance-trained athletes. While it is not always practical to place an arterial catheter to measure arterial blood gases, it is important to realize that Spo_2 at rest is accurate $\pm 3\%$, and likely less reliable during exercise. Obtaining an arterial sample by needle at near-maximal work rates is a practical alternative to an indwelling arterial catheter.

Identification of Maximal Effort

With experience, testing personnel's subjective assessment of maximal effort is quite reliable. The

objective evidence for a maximal (or near-maximal) test usually includes one of the following:

- Reached predicted maximum HR or $\dot{V}O_2$ max.
- Ventilatory limitation reached ($Paco_2$ increases or normal ventilatory reserve exceeded [$\dot{V}_E/MVV$ above approximately 0.85]).
- Significant lactic acidosis develops, based on a HCO_3^- drop at maximal exercise of 5 mEq/L, or $RER > 1.15$.

Indications for Exercise Termination

The patient should be verbally encouraged to give a maximal effort both before and during the test. Indications for terminating the exercise test include chest pain suggestive of ischemia; ischemic ECG changes; complex ectopy; second- or third-degree heart block; fall in systolic BP > 20 mm Hg; hypertension (> 250 mm Hg systolic, > 120 mm Hg diastolic); severe desaturation ($SpO_2 \leq 80\%$ when accompanied by symptoms and signs of severe hypoxemia); sudden pallor; loss of coordination; mental confusion; dizziness or faintness; and signs of respiratory failure. Reaching predicted HR or other parameters is not a reason to stop the test.

Perceptual Assessment of Symptom Intensity

Most subjects report their exercise-limiting symptom as breathlessness or leg discomfort. The main tools to measure the symptom intensity during exercise is the visual analog scale and the category ratio-10 scale developed by Borg. The visual analog scale is a 100-mm line displayed on paper, with descriptors anchoring the top and bottom (eg, no breathlessness and maximum breathlessness). The patient indicates a mark on this line, and the distance is measured from the bottom, enumerating the symptom intensity. By contrast, the category ratio-10 scale, often referred to as the Borg scale, uses nonlinear spacing of verbal descriptors of severity corresponding to specific numbers. The subject is asked to quantify symptom intensity at intervals during the test by indicating a number-descriptor pair. Changes in slope of response or response at a given work rate can be used to measure changes due to interventions, such as pulmonary rehabilitation or other treatments.

Interpretation of CPETs

Interpretation of CPETs is daunting, in part due to the plethora of data that are supplied by the computerized exercise systems. The data should be looked at graphically and numerically, as both approaches provide useful information. The numerical approach looks at maximum, or rest and maximum data, in relation to expected responses. In contrast, graphical data include submaximal data in showing a response over time. Table 2 lists the normal values and their ranges for major parameters used in interpretation of CPETs.

Method of Sequential Questions

- Is exercise capacity normal? $\dot{V}O_2$ max; maximum work rate.
- Is cardiovascular function normal? HR vs $\dot{V}O_2$ graph; O_2 pulse ($\dot{V}O_2/HR$); $\dot{V}O_2$ vs work rate.
- Is there early onset of metabolic acidosis? AT; lactate; bicarbonate.
- Is ventilatory function normal? $\dot{V}_E/MVV$; $MVV - \dot{V}_E$; maximum RR; increasing $Paco_2$; exercise and maximum flow-volume loop graphical analysis; V_T/VC .
- Is gas exchange normal? dead space: V_D/V_T ; $\dot{V}_E/\dot{V}CO_2$ at AT; oxygenation: Pao_2 ; $P(A-a)O_2$; SpO_2 .

Exercise Patterns in Common Diseases and Conditions

Major distinguishing features are shown in bold.

Heart Failure

- Exercise capacity is reduced: reduced $\dot{V}O_2$ max.
- **Cardiovascular responses are abnormal:** No HR reserve is present as a result of reaching predicted HR early in exercise. With increased severity, chronotropic incompetence develops, and HR reserve may be increased, although a steep slope of increase in HR defines an abnormal response. O_2 pulse has early plateau and low maximum value. AT has early onset.
- **Ventilatory limitation not present:** $\dot{V}_E/MVV$ is normal or low. $\dot{V}_E/\dot{V}CO_2$ at AT may be mildly

Table 2. Normal Values for Major CPET Parameters

Parameters (Unit)	Comments	Predicted	Range
Peak $\dot{V}O_2$ or $\dot{V}O_{2\max}$	Highest work rate, also expressed per kilogram (less useful)	Based on height, age, sex, habitual activity level ($\pm$ weight)	Lower limit = 83% of predicted
Maximum HR (beats/min)		220 – age in yr (alternate: 210 – 0.65 $\times$ age in yr)	$\pm$ 15 beats; >90% of predicted
HR reserve		Predicted maximum HR – observed = 0	$\pm$ 15 beats
O ₂ pulse ($\dot{V}O_2$ /HR) [mL/beat]	At high work loads with maximum SV and O ₂ extraction	Predicted peak $\dot{V}O_2$ /predicted maximum HR	>80% of predicted
AT (L/min $\dot{V}O_2$)	Lactic acid begins to accumulate	50 to 60% of predicted (not actual) $\dot{V}O_{2\max}$	>40% of predicted $\dot{V}O_{2\max}$
Systolic/diastolic BP, mm Hg Cuff			
Rest		125/80	
Near exercise maximum		200/90	<220/90
Intra-arterial			
Rest		140/85	
Near exercise maximum		205/100	
MVV, L/min	This parameter defines the upper “ceiling” of achievable ventilation	Indirect MVV: FEV ₁ $\times$ 40 (some use 35); direct MVV: performed at 60 breaths/min for 12 s	We use the higher of the directly and indirectly measured MVV
Ventilatory reserve, L/min	MVV – maximum exercise $\dot{V}_E$	38	>11
Ventilatory reserve, %	(Maximum $\dot{V}_E$ /MVV) $\times$ 100	72 $\pm$ 15%	<85%
Maximum RR, breaths/min		<50	<60
Ventilatory equivalents for CO ₂ and O ₂ at AT	A noninvasive index of dead space (unless hyperventilation is present)		
$\dot{V}_E/\dot{V}_{CO_2}$		25 (young); 30 (older)	<34
$\dot{V}_E/\dot{V}_{O_2}$		26.5	<31
V _D /V _T	Requires arterial sampling of Paco ₂		
Rest		.30 (approximately one third)	<.45
Maximum exercise		.18 (approximately one fifth)	<.20 (young); <.28 (<40 yr old); <.30 (>40 yr old)
Paco ₂ , mm Hg	Declines during heavy exercise due to lactic acidosis	Stable at 36 to 42; declining with heavy exercise	
Pao ₂ , mm Hg	Often increases slightly with heavy exercise; more sensitive than Spo ₂	>80; increasing slightly with heavy exercise	
P(A-a)O ₂ , mm Hg	Defines abnormalities of O ₂ transfer in the lung		
Rest		10 to 20	<20
Maximum exercise		15 to 30	<35
Sao ₂ or Spo ₂	Spo ₂ less reliable during exercise	>95%; no decrease throughout exercise	Drop of $\geq$ 4% with exercise
RER	$\dot{V}_{CO_2}/\dot{V}_{O_2}$ ratio		
Rest		0.8	0.6 to 1.0
Maximum exercise		1.21	1.1 to 1.3
Decline in HCO ₃ ⁻ , mmol/L	Due to lactic acidosis above AT	Maximum exercise: 6 (young), 4 (older)	Maximum exercise: 4 to 8 (young), 2 to 6 (older)

increased with increasing cardiac disease due to increased V_D/V_T (poor lung perfusion).

- **Gas exchange normal except for mild V_D/V_T abnormalities with increasing severity of heart disease.**

COPD

- Exercise capacity is reduced: reduced $\dot{V}O_{2\max}$.
- Cardiovascular responses are normal but understressed: HR reserve is increased (stop due to ventilatory limitation before maximum HR reached). AT is normal or indeterminate (may stop before reaching AT; others have blunted ventilatory responses limiting graphic interpretation). O_2 pulse is normal or slightly low. With superimposed deconditioning, AT and other cardiovascular responses may become borderline abnormal. With pulmonary hypertension and cor pulmonale, or severe exercise hypoxemia, AT can be frankly low with “cardiovascular disease” pattern as in cardiomyopathy (above). AT may be low from superimposed deconditioning.
- **Ventilatory limitation is the characteristic abnormality:** Peak $\dot{V}_E/MVV$ is increased (reduced or absent ventilatory reserve) and may be >1.0 in some. $\dot{V}_E/\dot{V}CO_2$ at AT is increased due to increased dead space fraction. Hypercapnia may develop, indicating ventilatory limitation (cannot keep up with the increased $\dot{V}CO_2$).
- **Gas exchange is abnormal:** At rest, V_D/V_T is elevated and less than normal reduction with exercise; Pao_2 and $P(A-a)O_2$ are abnormal. Oxygenation may worsen, be stable, or improve with exercise, although it is more likely to fall with exercise in moderate-to-severe COPD.

Interstitial Lung Disease

- Exercise capacity is reduced: reduced $\dot{V}O_{2\max}$.
- Cardiovascular responses are normal but understressed: see COPD above. However, with prominent pulmonary vascular component or pulmonary hypertension, “cardiovascular” patterns develop (as in cardiomyopathy above). Peak HR is usually reduced.

- **Ventilatory limitation is present:** High maximum $RR \geq 50$ breaths/min is present; $\dot{V}_E/MVV$ is increased (reduced or absent ventilatory reserve); $\dot{V}_E/\dot{V}CO_2$ is increased at AT due to increased V_D/V_T and low $Paco_2$ set point.
- **Gas exchange is abnormal:** V_D/V_T is elevated at rest and less than normal reduction with exercise. Pao_2 may be normal at rest, but progressively severe abnormalities in Pao_2 and $P(A-a)O_2$ are seen with exercise.

Pulmonary Vascular Disease

- Exercise capacity is reduced: reduced $\dot{V}O_{2\max}$.
- **Cardiovascular responses are abnormal** (same as in cardiomyopathy above): AT has early onset. There is no HR reserve as a result of reaching predicted HR early in exercise in association with a steep slope of increase in HR. If peak HR is slightly low, the slope will be steep. O_2 pulse has an early plateau and low maximum value.
- **Ventilatory limitation is not present:** Despite high $\dot{V}_E/\dot{V}CO_2$ at AT due to both high V_D/V_T and hyperventilation during exercise, the cardiovascular system limits exercise prior to reaching MVV; $\dot{V}_E/MVV$ is normal at peak exercise.
- **Gas exchange is the characteristic abnormality:** V_D/V_T is elevated at rest with only a small decrement with exercise, and may actually increase with exercise (obstructed vasculature leads to high $\dot{V}/\dot{Q}$ zones). Pao_2 and $P(A-a)O_2$ are abnormal at rest and are progressively abnormal during exercise.

Obesity

- **Decreased exercise capacity:** $\dot{V}O_{2\max}$ per kilogram is reduced but normal in liters per minute (based on ideal body weight). There is a high O_2 cost to perform external work ($\dot{V}O_2$ vs work rate in watts shifted up to left).
- Cardiovascular responses are normal.
- There is no ventilatory limitation based on normal ventilatory reserve ($\dot{V}_E/MVV$); this is reduced in some.
- Gas exchange responses are normal: those with low Pao_2 at rest improve with exercise (improved ventilation to bases of lung).

Deconditioned

- Exercise capacity is decreased: reduced $\dot{V}O_{2\max}$.
- **Cardiovascular responses are all borderline abnormal; improvement is seen with conditioning.** Echocardiographic findings are normal.
- AT is low normal or frankly low.
- Ventilatory abnormalities are not present.
- Gas exchange is normal at rest and with exercise.

Malingering/Poor Effort

- Exercise capacity is decreased: reduced $\dot{V}O_{2\max}$.
- **No physiologic limit to exercise is identified:** HR reserve is increased (predicted HR not achieved); ventilatory reserve is normal or increased (no ventilatory limitation); gas exchange is normal at rest and with exercise. RER is low at end-exercise.
- Breathing pattern is irregular or erratic, with hyperventilation and hypoventilation intermittently.

Psychogenic/Anxiety

- **Breathing patterns are nonphysiologic**, especially hyperventilation. If there is no arterial line, acute hyperventilation is noted by high RER (unloading excess CO_2 relative to $\dot{V}O_2$), high $\dot{V}_E/\dot{V}CO_2$, and low $PETCO_2$. An abrupt onset of “turned on” rapid, shallow breathing pattern may occur.

Metabolic Myopathy

Mitochondrial myopathy appears to be more common than previously thought. Patients may present with unexplained exertional limitation due to dyspnea, muscle fatigue, or myalgia. The pattern of response may overlap the cardiac or deconditioned pattern. Muscle biopsy confirms the diagnosis. Exercise training may improve exercise performance in this disorder.

- Exercise capacity is decreased: reduced $\dot{V}O_{2\max}$.

- **Hypercirculatory response:** Steep HR slope; slightly low O_2 pulse; AT low to normal, indeterminate, sometimes frankly low (reflects poor O_2 utilization in peripheral tissues).
- **Hyperventilatory response:** $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ are high at peak exercise and at 50% of $\dot{V}O_{2\max}$, but there is no strict ventilatory limitation based on $\dot{V}_E/MVV$ (mostly due to low V_T /high frequency pattern of breathing as a result of respiratory muscle weakness).
- **Gas exchange is essentially normal:** Pao_2 and $P(A-a)O_2$ are normal at rest and during exercise; V_D/V_T is normal at rest and decreases slightly less than usual, likely due to reduced peak intensity of exercise.

Illustrative Cases

See Table 2 for major parameters used during exercise testing for interpretation of normal and abnormal responses.

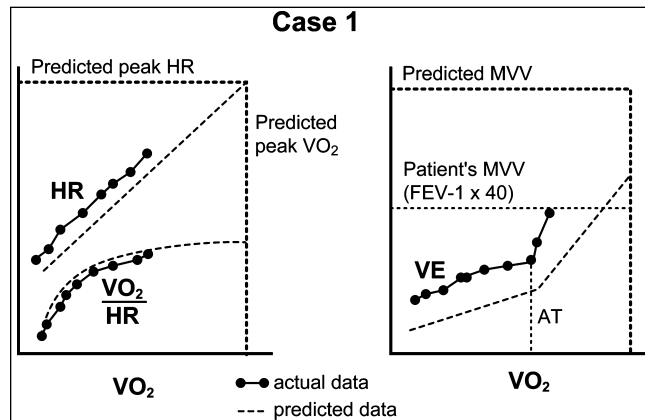
Case 1

A 69-year-old man has COPD, hypertension, and coronary artery disease. He underwent a CPET to clarify the major cause of exercise intolerance (Table 3). FEV_1 was 1.5 L (56% of predicted), FVC was 3.1 L (94% of predicted), FEV_1/FVC was 0.48 (predicted, 0.74), and DLCO adjusted for hemoglobin was 12 mL/min/mm Hg (52%). MVV was 52 L/min, and calculated MVV ($FEV_1 \times 40$) was 60 L/min. An echocardiogram showed mild left ventricular dysfunction. ECG findings were normal throughout exercise. See graphs in Figure 8 and Table 3. The patient stopped exercising due to dyspnea. No ECG abnormalities were noted.

Interpretation: This patient's exercise capacity is moderately reduced and is limited by COPD. Ventilatory limitation to exercise is demonstrated as shown by the two measures of ventilatory reserve: the $\dot{V}_E/MVV$ ratio (0.95), and the difference between MVV and maximal exercise $\dot{V}_E$ is 3 L/min. This is seen graphically on the $\dot{V}_E$ vs $\dot{V}O_2$ graph, which shows that the patient had no ventilatory reserve due to both a reduced MVV compared with the normal predicted MVV, and an increased ventilatory requirement (shifted up to the left) likely due to the increased dead space fraction. Although not present in this case, some patients with ventilatory limitation fail to

Table 3. Data for Case 1

Measurements	Predicted	Measured
Peak $\dot{V}O_2$, L/min	1.95	1.21 (62% of predicted)
HR maximum, beats/min	151	117 (71% of predicted)
HR reserve	0	34
Maximum O_2 pulse, mL/beat	12.9	10.9 (80% of predicted)
AT, L/min of $\dot{V}O_2$	1.13 (0.92, lower limit)	1.09 (56% of predicted)
Systolic/diastolic BP, mm Hg		
Rest	140/85	150/80
Exercise	205/100	200/90
Maximum $\dot{V}E$, L/min	(calculated MVV = 60)	57
Maximum $\dot{V}E$ /MVV	0.70 to 0.75 (0.87, upper limit)	0.95
Ventilatory reserve, L/m	>15	3
Maximum RR, breaths/min	<50	40
Pao_2 , mm Hg		
Rest	>80	83
Maximum exercise	>80	64
$P(A-a)O_2$, mm Hg		
Rest	<20	17
Maximum exercise	<35	54
$Paco_2$, mm Hg		
Rest	36 to 42	41
Maximum exercise	Lower after AT	35
V_D/V_T		
Rest	30	42
Maximum exercise	18	32
$\dot{V}E/\dot{V}CO_2$ at AT	<34	43

**Figure 8.** Case 1 data: HR and O_2 pulse ($\dot{V}O_2/HR$) vs $\dot{V}O_2$; $\dot{V}E$ vs $\dot{V}O_2$. AT and MVV are labeled.

lower their $Paco_2$ to compensate for lactic acidosis, or hypercapnia develops during exercise.

There was no suggestion of a cardiovascular limitation due to hypertension, cardiomyopathy, or ischemia. The patient had an increased HR reserve. The HR vs $\dot{V}O_2$ graph suggests a normal pattern of response (not shifted to the left and normal slope). The patient did not reach the maximum predicted HR because the ventilatory

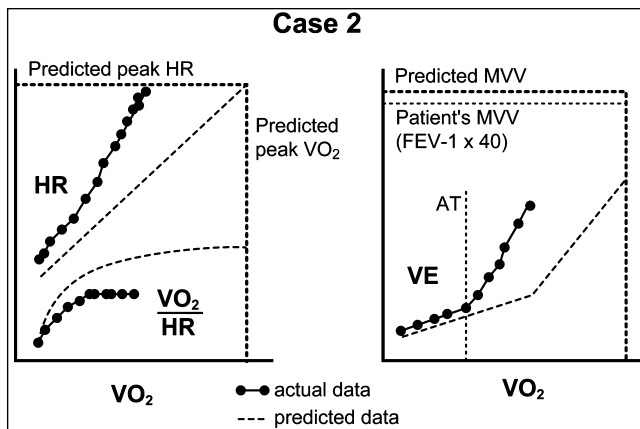
ceiling was reached before the cardiac system was limiting. The normal AT indicates lack of abnormal O_2 delivery due to cardiac disease. The low normal O_2 pulse is due to an understressed cardiovascular system rather than cardiac disease. The upward inflection of $\dot{V}E$ in the $\dot{V}E$ vs $\dot{V}CO_2$ graph represents AT, and occurs at a normal $\dot{V}O_2$ (compare the patient data with the predicted values). Although cardiac disease could cause increased dead space fraction, the reduction in Pao_2 and the widened $P(A-a)O_2$ with exercise are not consistent with cardiac disease.

Case 2

A 45-year-old man with known cardiomyopathy and obesity underwent a CPET for prognosis and cardiac transplant evaluation (Table 4). He had no lung disease and had normal resting PFT results. An echocardiogram showed severe global hypokinesis, and the nuclear left ventricular ejection fraction was 35%. His height was 170 cm (67 in), and his weight was 100 kg (220 lb). The patient stopped exercising due to leg and generalized

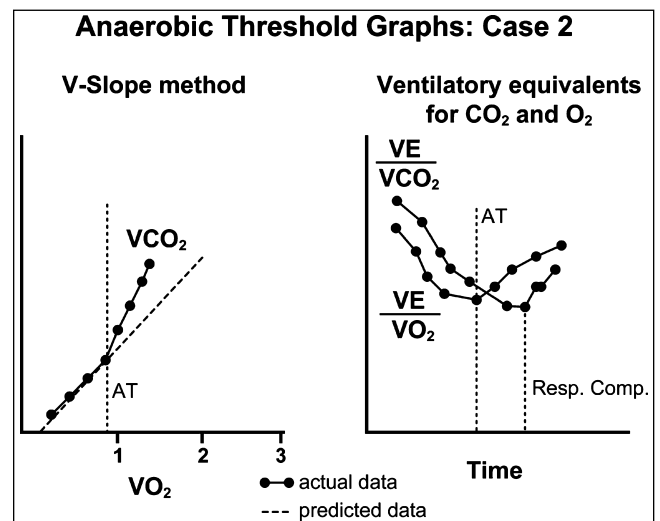
Table 4. Data for Case 2

Measurements	Predicted	Measured
Peak work rate, W	191	90 (47% of predicted)
Peak $\dot{V}O_2$, L/min	2.66	1.65 (62% of predicted)
Peak $\dot{V}O_2$ /kg	34.0	16.5 (49% of predicted)
HR maximum, beats/min	175	172 (98% of predicted)
HR reserve	0	3
O ₂ pulse, maximum, mL/beat	15.1	9.6 (64% of predicted)
AT, L/min of $\dot{V}O_2$	1.49 (lower limit, 1.17)	0.98 (37% or predicted $\dot{V}O_{2\max}$)
Maximum $\dot{V}E$, L/min	(MVV=130)	86
Maximum $\dot{V}E$ /MVV	0.70 to 0.75 (0.87, upper limit)	0.66
Ventilatory reserve, L/m	>15	44
RR maximum, beats/min	<50	34
Pao ₂ , mm Hg		
Rest	>80	68
Maximum exercise	>80	86
P(A-a)O ₂ , mm Hg		
Rest	<20	31
Maximum exercise	<35	30
Paco ₂ , mm Hg		
Rest	36 to 42	41
Maximum exercise	Lower after AT	34
V _D /V _T		
Rest	30	35
Maximum exercise	18	22
$\dot{V}E/\dot{V}O_2$ at AT	<34	31

**Figure 9.** Case 2 data: HR and O₂ pulse ($\dot{V}O_2/\text{HR}$) vs $\dot{V}O_2$; $\dot{V}E$ vs $\dot{V}O_2$. AT and MVV are labeled.

fatigue; dyspnea was present but was not an exercise-limiting symptom. ECG showed no arrhythmias or ST-T wave changes. See Figures 9 and 10 and the case 2 data in Table 4.

Interpretation: This patient has a severe reduction in exercise capacity due to cardiomyopathy and obesity. The peak external workload and aerobic capacity per kilogram (peak $\dot{V}O_2/\text{kg}$) are more severely reduced than the peak $\dot{V}O_2$. This difference

**Figure 10.** Case 2. Graphs for identifying AT. $\dot{V}CO_2$ vs $\dot{V}O_2$. Ventilatory equivalents for CO₂ and $\dot{V}O_2$ ($\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$). AT and the respiratory (Resp) compensation (comp) point for lactic acidosis are identified.

reflects the increased oxygen cost of movement due to obesity.

Evidence for a cardiac limitation includes reaching predicted HR (no HR reserve) at a low workload, reduced O₂ pulse, and reduced AT. Graphically, the

Table 5. Data for Case 3

Measurement	Predicted	Measured
Peak $\dot{V}O_2$, L/min	1.68	0.85 (51% of predicted)
HR maximum, beats/min	182	171 (94% of predicted)
HR reserve	0	11
Maximum O_2 pulse, mL/beat	9.2	5.0 (54% of predicted)
AT, L/min of $\dot{V}O_2$	0.97 (lower limit = 0.79)	0.65 (39% of predicted $\dot{V}O_{2max}$)
Maximum $\dot{V}E$, L/min	(calculated MVV = 96L/min)	62
Maximum $\dot{V}E$ /MVV	0.70 to 0.75 (<0.87)	0.65
Ventilatory reserve, L/m	>15	32
Maximum RR, beats/min	<50	40
Pao_2 , mm Hg		
Rest	>80	81
Maximum exercise	>80	56
$P(A-a)O_2$, mm Hg		
Rest	<20	24
Maximum exercise	<35	50
$Paco_2$, mm Hg		
Rest	36 to 42	36
Maximum exercise	Lower after AT	29
V_D/V_T		
Rest	0.30	0.35
Maximum exercise	0.18	0.38
$\dot{V}E/\dot{V}CO_2$ at AT	<34	42

HR vs $\dot{V}O_2$ graph shows upward displacement and a steep slope indicating a low SV. The O_2 pulse has an early plateau typical of cardiac disease. Early onset of AT is seen compared with the predicted value in the $\dot{V}E$ vs $\dot{V}O_2$ graph. AT is identified by the V-slope and ventilatory equivalents graphs in Figure 10.

There is no ventilatory limitation to exercise as shown by an increase in ventilatory reserve. The $\dot{V}E$ vs $\dot{V}O_2$ graph shows higher-than-expected $\dot{V}E$ at higher work rates due to early onset AT. This high ventilation relative to workload likely explains the symptom of dyspnea. However, there is a large ventilatory reserve at peak exercise. The drop in $Paco_2$ with exercise is evidence of lack of ventilatory limitation.

Pao_2 improves with exercise, as is seen in some obese subjects. Lack of worsening in Pao_2 and $P(A-a)O_2$ is the expected pattern in cardiomyopathy. Dead space fraction is in the higher range of normal at rest and at maximum exercise, although mild abnormalities can be seen as cardiomyopathy increases in severity.

Case 3

A 38-year-old woman underwent a CPET for unexplained exertional dyspnea and fatigue. Her

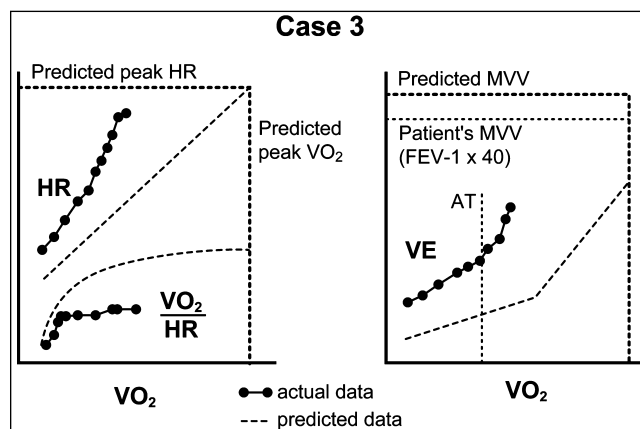


Figure 11. Case 3 data: HR and O_2 pulse ($\dot{V}O_2$ /HR) vs $\dot{V}O_2$; $\dot{V}E$ vs $\dot{V}O_2$. AT and MVV are labeled.

resting PFT results were normal except for a borderline low VC and DLCO. Her FEV₁ was 2.40 L. She stopped exercising due to both dyspnea and leg and global fatigue. Her height was 157 cm (62 in), and her weight was 60 kg (132 lb). ECG findings were normal. See Figure 11 and Table 5 for more data.

Interpretation: This patient has a severe reduction in exercise capacity in a pattern suggesting pulmonary vascular disease. There is a steep HR response, reaching near the predicted maximum at

Table 6. Differentiating Features*

Measurement	CHF	COPD	ILD	PVD	Obesity	Deconditioned	Poor Effort	Psych/Anx.
$\dot{V}O_2\text{max}$	↓	↓	↓	↓	↓ per kg normal L/m IBW	↓	↓	Normal, near normal
AT	↓	Normal, indet. ↓	Normal. ↓	↓	Normal	Normal, sl ↓	Normal	Abnormal breathing pattern especially hyperventilation; abrupt; onset rapid shallow breathing; ↑RER and $\dot{V}_E/\dot{V}CO_2$
Peak HR	(Normal) may be ↓	↓	↓	(Normal) may be ↓	Normal	Normal, sl ↓	↓	
O ₂ pulse	↓	Normal. ↓	Normal. ↓	↓	Normal	Normal, sl ↓	↓	
$\dot{V}_E/\text{MVV}$	Normal. ↓	↑	↑ Normal	Normal	Normal	Normal	↓	
V _D /V _T	Normal. ↑	↑	↑	↑	Normal	Normal	Normal	
Pao ₂	Normal	↓ varies	↓	↓	Normal ↑ if low	Normal	Normal	↑RER; end test erratic breathing
Other	Steep HR slope		Peak RR ≥ 50 beats/min		$\dot{V}O_2$ vs watts shift up to L	Improvement with rehab; Echocard wnl		

*Main distinguishing features are circled. Psych/Anx = psychiatric/anxiety; rehab = rehabilitation; IBW = ideal body weight; CHF = congestive heart failure; ILD = interstitial lung disease; PVD = pulmonary vascular disease.

a low work rate, reduced AT, and reduced O₂ pulse with early plateau (Fig 11). The pattern is similar to the cardiovascular disease pattern seen in case 2, but the severity of the gas exchange abnormalities makes cardiovascular disease other than pulmonary vascular disease unlikely. The gas exchange abnormalities include the significant drop in Pao₂, the widening of the P(A-a)O₂, and highly abnormal dead space fraction during exercise.

Ventilation is high throughout exercise as seen on the $\dot{V}_E$ vs $\dot{V}O_2$ graph, and high $\dot{V}_E/\dot{V}CO_2$ at AT. This is due to the high dead space fraction and mild hypocapnia, to a lesser extent. The lack of a ventilatory limitation (increased ventilatory reserve present) and only borderline abnormalities in resting PFT results make pulmonary disease other than pulmonary vascular disease less likely. The most likely disorder in this young female patient is primary pulmonary hypertension, although chronic thromboembolic disease or combined pulmonary vascular and interstitial lung disease associated with a connective tissue disease could also be present.

Summary of Major Differential Diagnostic Points

Table 6 and the summary below list the main differentiating features in various conditions:

- Cardiac disease: Low AT, steep HR response, no ventilatory limitation, gas exchange normal

(except dead space fraction can be mildly increased as severity of cardiac disease increases).

- COPD: Ventilatory limitation, abnormal gas exchange.
- Interstitial lung disease: Very high maximum RR, abnormal gas exchange, can demonstrate “cardiovascular” abnormal pattern with severe disease.
- Pulmonary vascular disease: Cardiovascular pattern but very abnormal gas exchange, especially a high and sometimes increasing dead space fraction. Abnormal ventilation is present but is not the limiting factor.
- Interstitial lung disease, especially when associated with pulmonary hypertension, can have an overlapping pattern with pulmonary vascular disease.
- Poor effort: no limiting system is identified.

6MWT and Shuttle Walking Test

In contrast with complex CPET, the main subject of this review, the 6MWT is a relatively low complexity test that measures the distance that a patient can quickly walk in a 100-ft hallway in a period of 6 min (the 6-min walk distance [6MWD]). The subject chooses his own intensity, and is allowed to rest and stop. A cone marks the turnaround spot, and standardized phrases are used for encouragement. As most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better

reflect the functional exercise capacity for daily physical activities. The 6MWT was the subject of a recent ATS guideline (see Annotated Bibliography).

Indications for the 6MWT include measuring the response to a medical intervention (pretreatment and posttreatment comparisons for lung transplantation, lung resection, lung volume reduction surgery, pulmonary rehabilitation, COPD, pulmonary hypertension and heart failure); single measurement of functional status (COPD, cystic fibrosis, heart failure, peripheral vascular disease, fibromyalgia); and predictors of morbidity and mortality (heart failure, COPD, primary pulmonary hypertension). The information in the 6MWT is complementary to CPET. The 6MWD and $\dot{V}O_{2\max}$ correlate well ($r = 0.73$) in patients with end-stage lung diseases. The 6MWD may correlate better than CPET with formal quality of life measures.

A slightly more complex walking test is the shuttle-walking test, which uses an audio signal from a tape cassette to tell the patient how fast to walk. The test ends when the patient cannot reach the turnaround point within the required time, as the shuttle speed increases progressively.

Annotated Bibliography

Main Reference

ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167:211–277 and corrections in erratum letter to the editor (Am J Respir Crit Care Med 2003; 167:1451–1452). *The corrected version from the ATS Web site is available and recommended.* Available at: www.thoracic.org/sections/publications/statements/pages/pfet/cardioexercise.html. Accessed April 10, 2006

This is a very long article that is a short textbook on the current consensus on CPET. It serves both as a manual for setting up and supervising an exercise laboratory, and as a textbook for learning concepts. Those not currently interested in setting up a lab can skip the Methodology section if time is short. For a quick review of patterns in diseases, approach to interpretation, and cases, see pages 246–263.

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Wasserman K. Diagnosing cardiovascular and lung pathophysiology from exercise gas exchange. Chest 1997; 112:1091–1101

This relatively brief review emphasizes the utility of the nine-plot graphics in interpretation of CPET tests.

Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1999

The standard reference work and a highly readable text for learning the principles of exercise testing. Includes a section with dozens of case presentations. Uses the 9-plot graphic montage for interpretation as developed by this group at Harbor-UCLA. This is a must-read for those who wish to get active in CPET testing.

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A brief review of where CPET fits in our diagnostic algorithm and the basic patterns seen in common conditions.

Weisman IM, Zeballos RJ. Clinical exercise testing. *Clin Chest Med* 1994; 15:173–451

This is an excellent collection of chapters written by many of the experts in this field.

Weisman IM, Zeballos RJ. Clinical exercise testing. *Clin Chest Med* 2001; 22:679–701

An up-to-date overview of exercise testing ranging from the 6MWT to the CPET.

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A lucid review of exercise testing using a different set of graphic panels than the more widely used nine plot of Wasserman and colleagues.