Cardiopulmonary Exercise Testing

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Objectives:

1. To understand the physiologic mechanisms that support the increased metabolic rate during normal exercise.
2. To review how disease disrupts the coordinated function of several systems that support exercise function.
3. To review the indications for performing cardiopulmonary exercise testing.
4. To understand the measurements performed during cardiopulmonary exercise testing and their use in interpreting exercise tests.
5. 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

The pulmonary function tests performed at rest measure the mechanical and gas exchange physiology of the lung, and are reliable tools for diagnosis and management of respiratory disease. FEV_1 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 that are the subject of this review. I will focus on the symptom-limited, incremental exercise test that is the test protocol used most by pulmonologists. This test involves a continuous ramped increase in workload, with the test continuing until the patient has symptoms (fatigue or dyspnea, most commonly) that cause him to feel he cannot continue to higher workloads. 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 significant tachyarrhythmia, ST segment depression, or fall in systolic blood pressure.

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 workload. In contrast, work on the treadmill depends on gait, grade, and speed, such that a linear incremental work rate test is not usually obtained.

Electrocardiogram (ECG): Used for heart rate, ST segments, and arrhythmia detection.

Collection of All Expired Gases: The primary measurements are from a flow meter, capnometer, and oximeter. From these three measurements, many ventilatory and gas exchange parameters are obtained. These include:

- Tidal volume (V_T)* in mL or L
- Minute volume or minute ventilation ($\dot{V}_E$) in L/min
- Respiratory rate (RR), or breathing frequency (f) in breaths/min

- Rate of carbon dioxide elimination ($\dot{V}CO_2$), in L/min
- Rate of oxygen uptake or consumption ($\dot{V}O_2$)
- Respiratory quotient (R), which is the ratio of $\dot{V}co_2$ to $\dot{V}O_2$, measured simultaneously.
- 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 L/min of ventilation required per liter of O_2 or CO_2 production (an "efficiency" ratio).

Pulse Oximetry: Abbreviated as SpO_2, in contrast to arterial oxygen saturation, SaO_2.

Arterial Catheterization: Blood gases, lactate (optional).

Blood Pressure: Invasive or noninvasive measurement.

*Note on convention: V refers to volume, $\dot{V}$ 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.

Indications for Cardiopulmonary Exercise Testing

Unexplained Exertional Intolerance: Dyspnea or Fatigue

When routine clinical evaluation including history, physical examination, chest radiograph, ECG, and resting pulmonary function tests (PFTs) do not provide an answer, cardiopulmonary exercise testing (CPET) is a useful tool for identifying diseases and factors contributing to the symptoms. CPET 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 echocardiogram, or in disability evaluation, measurement of exercise performance can be helpful.

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.

Preoperative Assessment Before Lung Resection

When resting PFTs indicate a high risk for lung resectional surgery, peak $\dot{V}O_2$ along with perfusion scan data helps 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 tests. The incremental protocol used for other conditions is not ideal for this diagnosis. A treadmill test performed at 80 to 90% of predicted heart rate 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 then resting PFTS in patients with early or mild interstitial lung disease. Patients with COPD and normal or near-normal carbon monoxide diffusing capacity (D_{LCO}) almost never lower their Pa_{O_2} with exercise; conversely, many but not all patients with a $D_{LCO} < 55\%$ develop exercise oxygen desaturation.

Titrate O_2 Flow During Exercise

Oxygen prescription should indicate appropriate flow rates for rest, exercise, and sleep (sleep study not routinely performed).

Pulmonary Rehabilitation Prescription and Assessment of Response

Individually targeted programs can be based on the patient's peak $\dot{V}O_2$, AT, and presence of O_2 desaturation.

Transplant Referral and Prognosis

Functional status and prognosis best correlate with peak $\dot{V}O_2$. Peak $\dot{V}O_2$ of <14 mL/min/kg is often used as a basis for referral for cardiac transplantation. Prognosis in cystic fibrosis is predicted by peak $\dot{V}O_2$ and may be useful for transplant decisions.

Assess Response to Therapy—Medical, Physical, Surgical

CPET probably provides a more clinically meaningful objective endpoint measurement than resting PFTs for evaluation of new therapies.

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 oxygen is consumed), although increasing proportions of the work are done via anaerobic mechanisms later in exercise.

Determinants of O_2 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):

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

Rearrangement of the Fick equation (HR = heart rate in beats/min; SV = stroke volume in mL; Hb = hemoglobin concentration, in g/dL; 1.34 = oxygen-carrying capacity of Hb, in mL of O_2/g/dL of Hb; Sao_2 and $S\bar{v}O_2$ = arterial and mixed venous oxygen saturation, respectively):

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

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

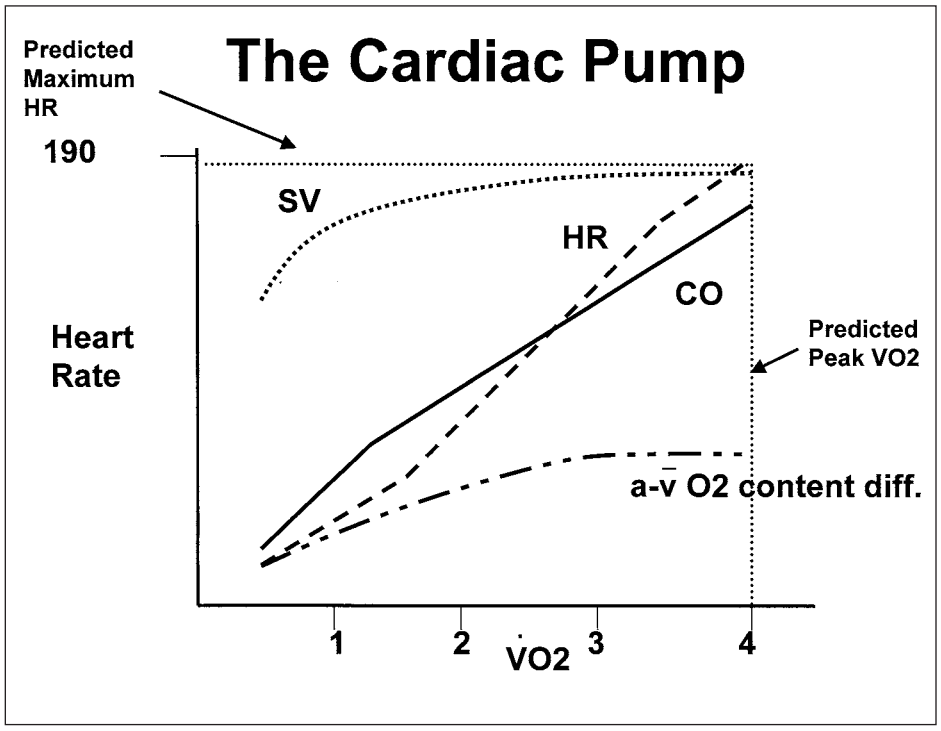

Figure 1. Normal exercise responses in a 30-year-old man. This graphic presentation of the rearranged Fick equation shows the contribution of stroke volume (SV), heart rate (HR), and O_2 extraction in the tissues (arterial-mixed venous oxygen content difference) to the increased O_2 consumption of progressive exercise loads.

From the rearranged Fick equation, we can see that increasing oxygen consumption during steadily increasing exercise depends on the degree to which cardiac output can increase. The maximum level of exercise, and the maximum oxygen consumption, are dependent on the maximum cardiac output, the presence of anemia, the arterial oxygen saturation, and the degree to which the exercising muscles can extract oxygen and lower the mixed venous O_2 (manifested as the a-v O_2 content difference in equation 2, or O_2 saturation difference in equation 3).

The Cardiac Pump

$$CO = HR \times SV$$

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

Changes in CO, HR, SV, and C(a-v)O_2 During Exercise

The role of these factors from the modified Fick equation is show 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. Oxygen extraction in the muscles increases to a maximum value in late exercise.

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. Aging reduces the maximum HR and the muscles' ability to extract oxygen, 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 arterial O_2 content. Anemia and carboxyhemoglobinemia ("functional" anemia) would also reduce arterial O_2 content and reduce peak $\dot{V}O_2$.

HR-$\dot{V}O_2$ Relationship

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 × age in years]). The predicted maximum $\dot{V}O_2$ 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, the normal subject reached the predicted peak $\dot{V}O_2$ when he reached his peak HR. The patient

Table 1. — Determinants of peak $\dot{V}O_2$ due to aging and disease according to how they affect the factors in the modified Fick equation.

Determinants of Peak $\dot{V}O_2$

	$\dot{V}O_2$ peak = [HR x SV]	x	[CaO_2 – CvO_2]
25 y.o. normal	3.5 = [195 x 112]	x	[20 - 4]
70 y.o. normal	2.2 = [160*x 100]	x	[20 - 6*]
Trained	6.2 = [190 x 205*]	x	[20 - 4]
Mitral Stenosis	1.4 = [190 x 43*]	x	[20 - 3]
Arterial Hypoxemia	2.6 = [195 x 112]	x	[15*-3]

* = Major difference from 25-year-old normal

From Dempsey, ATS 1998

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 or $\dot{V}O_2$ by having a higher HR (relative tachycardia). As a result, they reach their peak heart rate sooner and stop exercising due to 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 volume and lower HR at any given level of $\dot{V}O_2$ or work.

O_2 Pulse

This parameter is $\dot{V}O_2/HR$, obtained by dividing these two simultaneous measurements taken during exercise. It is literally the mL of oxygen consumed per beat, although it is often used (with some hedging) as a noninvasive surrogate for stroke volume. A rearrangement of equation 3 explains the significance of the O_2 pulse:

$$\dot{V}O_2/HR = SV \times C(a\text{-}\bar{v})O_2$$

If we assume that arterial PO_2 is normal and that the a-v O_2 difference 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 oxygen 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.

Anaerobic Threshold

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 physiologic capability to do most of the work aerobically, and incremental workloads result in progressive lactic acidosis due to anaerobic metabolism in muscle. This workload is referred to as the lactate or anaerobic threshold (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.

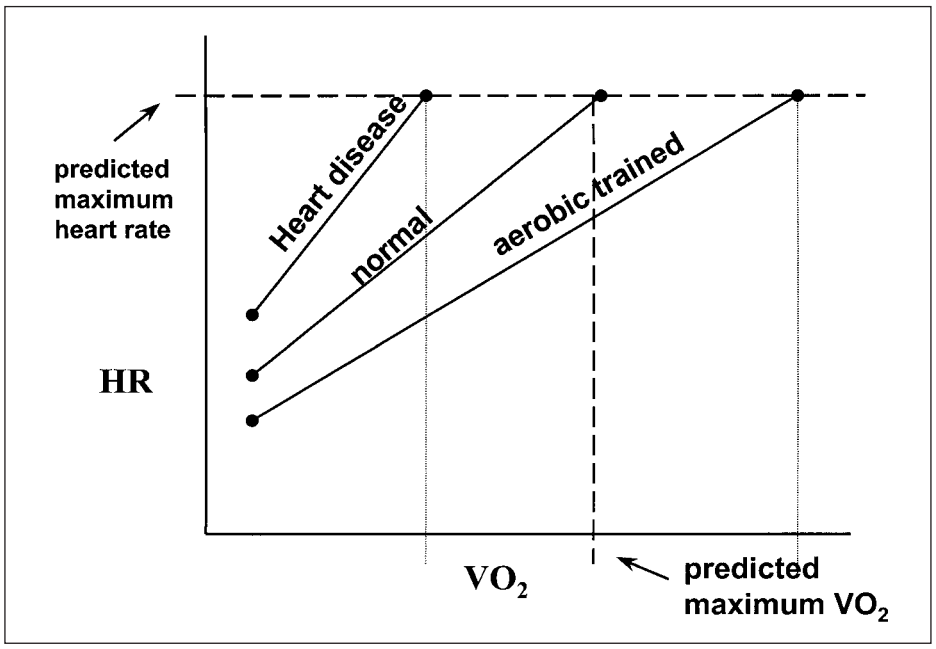

Figure 2. Heart rate (HR) vs oxygen consumption ($\dot{V}O_2$) relationship during exercise.

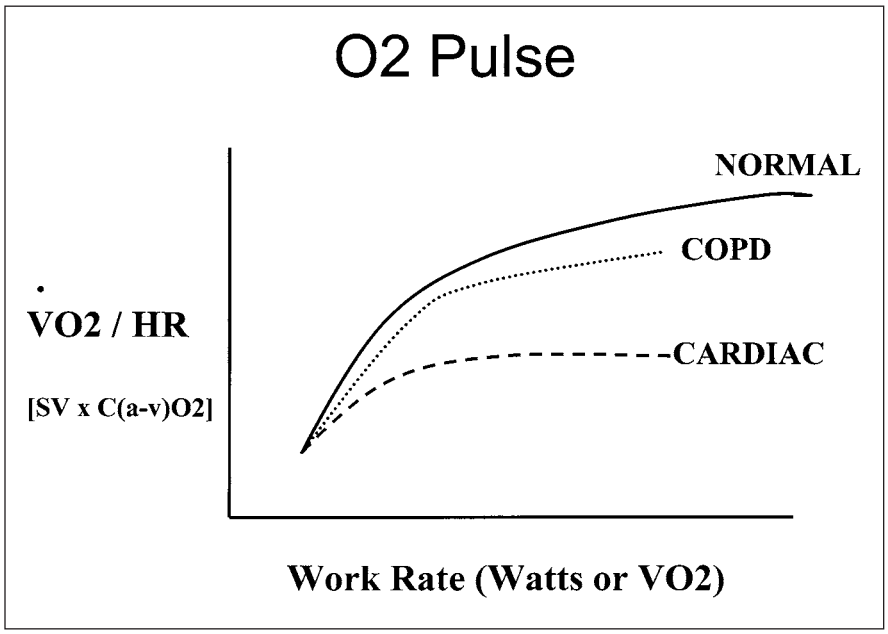

Figure 3. Relationship of O_2 pulse ($\dot{V}O_2/HR$) and work rate during exercise.

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 CO_2 production without O_2 consumption, and characteristic effects on gas exchange parameters:

Aerobic Metabolism: 1 mol of O_2 consumed results in 0.8 mol of CO_2 produced (assuming a normal R of 0.8)

Anaerobic Metabolism:

$[H+] + [lactate–] + [HCO_3^-] \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$

As lactate accumulates, progressively increasing amounts of CO_2 are generated from nonaerobic metabolic sources. This results in an increase in R, and a steepening in the slope of increase of $\dot{V}E$ to maintain a normal $PaCO_2$ in the face of accelerating CO_2 production. AT is identified by inspection of several graphs (Fig 4).

V-Slope Method: In the lower left 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 upper right 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 to tidal volume ratio (V_D/V_T) (mechanism explained below). At AT, the $\dot{V}E/\dot{V}O_2$ inflects upward since V_E is driven upward by the sudden increase in CO_2 production while $\dot{V}O_2$ continues to increase at its previous pace. At the same time,

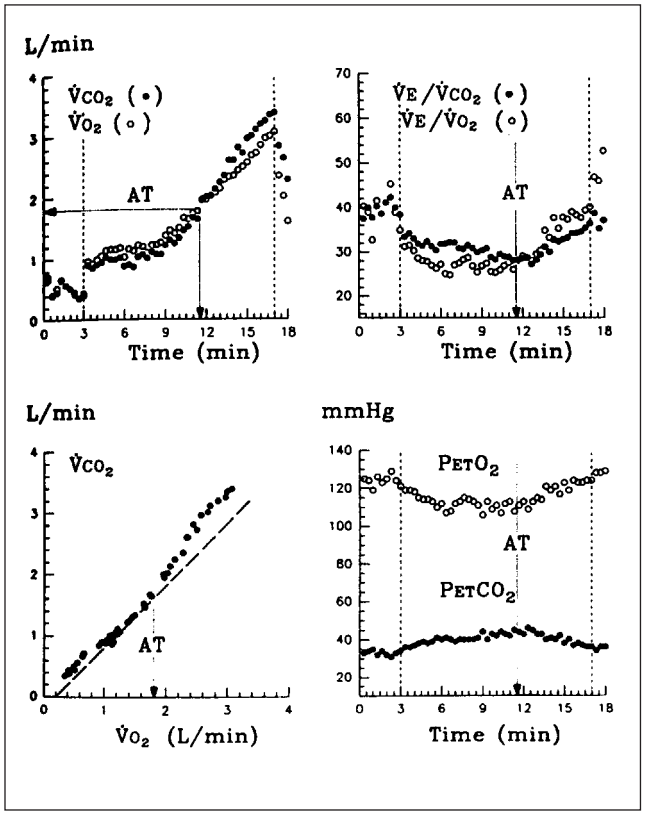

Figure 4. Graphs typically used to identify anaerobic threshold (AT) by gas exchange criteria. See text for details. (From Wasserman et al. Principles of exercise testing and interpretation. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.)

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 P_{ACO_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" 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 and CO_2 (P_{ETO_2} and P_{ETCO_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 (P_{AO_2}), P_{aO_2}, and P_{ETO_2}. The AT is identified by the upward inflection of the P_{ETO_2} curve, which occurs slightly before the downward deflection in P_{ETCO_2} at the respiratory compensation point (Fig 4, lower right panel).

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

From a functional standpoint, peak or maximum $\dot{V}_{O_2}$ ($\dot{V}_{O_2}$ max) defines 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, a maximal $\dot{V}_{O_2}$ is a peak $\dot{V}_{O_2}$ that has been demonstrated to represent a plateau or 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 could 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

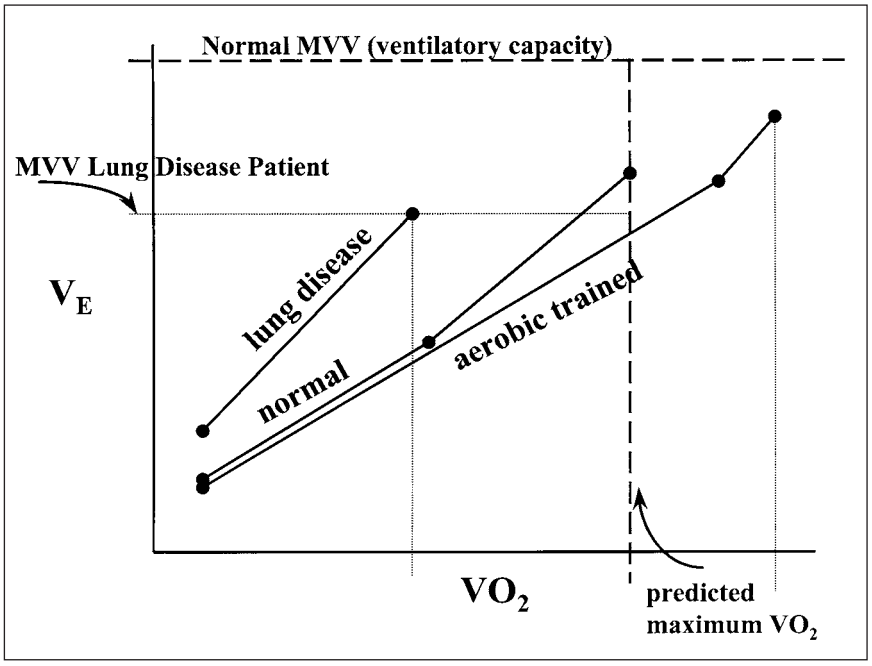

Figure 5. Exercise ventilatory responses. Minute ventilation ($\dot{V}_E$) vs oxygen consumption ($\dot{V}_{O_2}$). The normal subject has a ventilatory reserve. The lung disease subject has a reduced maximal voluntary ventilation (MVV) and an increased ventilatory requirement, leading to early termination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

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 (the 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 about 75% of the MVV when reaching his predicted peak $\dot{V}O_2$. Instead, normal people stop exercising after reaching the maximum achievable HR (Figure 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 FEV_1 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 result 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: $\dot{V}E = \dot{V}A + \dot{V}D$ (minute ventilation = alveolar ventilation + 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, L/min) is the volume per beat (SV) multiplied by the number of beats per minute (HR). The ventilatory pump is analogous:
$\dot{V}E = VT \times RR$ (minute ventilation = tidal volume × respiratory rate)

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 VT. As VT reaches to about 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 percent 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; most normal subjects and patients with obstructive lung disease have maximal exercise respiratory frequencies of < 50.

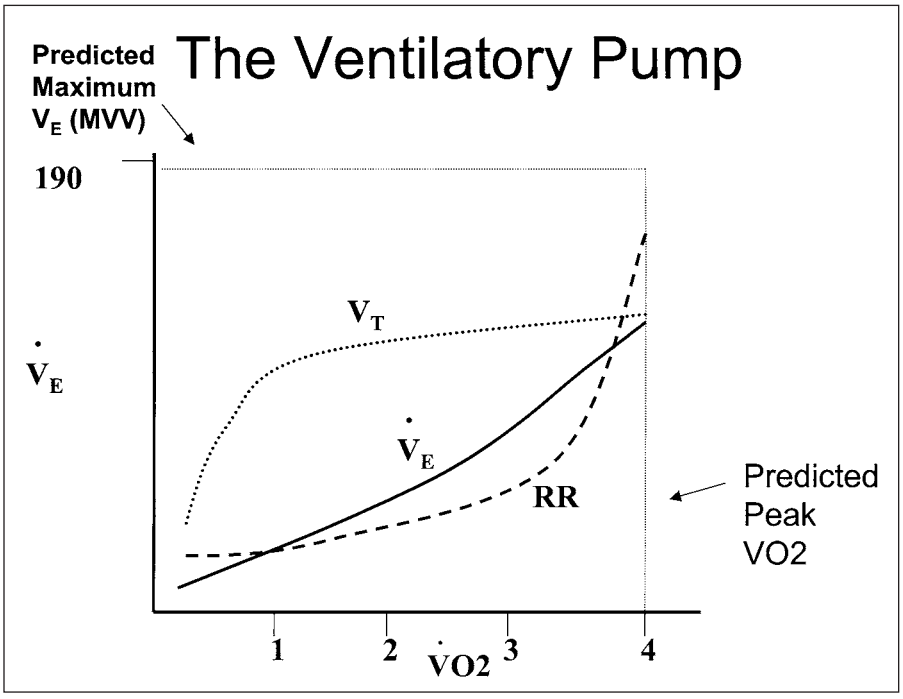

Figure 6. Normal ventilatory responses in a 30-year-old man. Minute ventilation ($\dot{V}E$) vs oxygen consumption ($\dot{V}O_2$) during an incremental exercise test. $\dot{V}E$ increases mostly due to tidal volume (VT) increases early in exercise and mostly due to increase in respiratory rate (RR) later in exercise. There is a ventilatory reserve at maximum exercise. $\dot{V}E$ inflects upward at anaerobic threshold.

Exercise Tidal Flow-Volume Loops

A new way to evaluate patients for ventilatory limitation is to measure tidal breathing at rest and during exercise, and place these loops within the patient's 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 end-expiratory lung volume goes below resting functional residual capacity (FRC) during exercise. 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 tidal volume 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 CO_2 production 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 oxygen 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 not perfused. Increases in the alveolar-arterial oxygen pressure difference [$P(A\text{-}a)O_2$] are due to low $\dot{V}/\dot{Q}$ areas or shunt.

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 minute ventilation ($\dot{V}_E$) is partitioned into two components, the portion participating in gas exchange, alveolar ventilation ($\dot{V}_A$), and the portion going to ventilation of dead space (V_D). The fraction of each breath going to the dead space, the dead space to tidal volume ratio (V_D/V_T), decreases from about 0.30 at rest to 0.18 during maximal exercise. This is easy to remember as a change from approximately 1/3

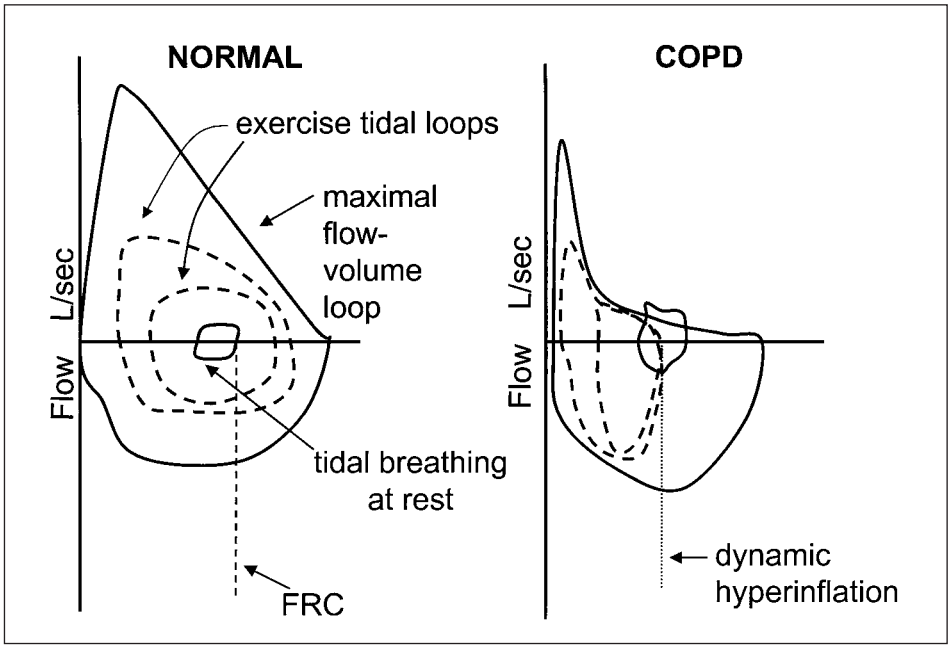

Figure 7. Tidal flow-volume loops measured during exercise can be placed within the maximal flow-volume loop, measured at rest, to identify the development of ventilatory limitation during exercise. This is seen as obliteration of flow and volume reserve.

to 1/5. The decrease is due to two factors: (1) the tidal volume increases during exercise; and (2) perfusion of the upper lung zones increases during exercise as cardiac output 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:

$$V_D/V_T = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}$$

This parameter requires measurement of an arterial blood sample and a measurement of mixed-expired CO_2 ($P\bar{E}_{CO_2}$), 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 $P\bar{E}_{CO_2}$ is to Pa_{CO_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 Pa_{CO_2} of 40. If the average CO_2 concentration (or partial pressure), $P\bar{E}_{CO_2}$, is 30, 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 Pa_{CO_2} is again 40, but the $P\bar{E}_{CO_2}$ is 20. $V_D/V_T = (40 - 20)/40 = 20/40 = 0.5$.

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:

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

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. Pa_{CO_2} remains unchanged if ventilation increases linearly with CO_2 production. 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:

$$\frac{\dot{V}_E}{\dot{V}_{CO_2}} = K \bullet \frac{1}{Pa_{CO_2}\,[1 - (V_D/V_T)]}$$

This equation tells us that only two factors determine the value of $\dot{V}_E/\dot{V}_{CO_2}$: the level of Pa_{CO_2} and V_D/V_T. If we know that a patient had a normal Pa_{CO_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 around 29, with an upper limit of 34.

Oxygen Transfer

Normal values for rest and exercise are shown in Table 2. Although Pa_{O_2} increases slightly at high levels of exercise, the $P(A\text{-}a)O_2$ also increases. While this may seem contradictory, it relates to a larger increase in P_{AO_2} in association with a falling Pa_{CO_2} and increasing R. While it is not always practical to place an arterial catheter to obtain arterial blood gases, it is important to realize that pulse oximetry at rest is accurate ± 2%, but less reliable during exercise.

Interpretation of Cardiopulmonary Exercise Tests

Interpretation of these tests is daunting, in part due to the plethora of data that is 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 includes submaximal data in showing a response over time.

Method of sequential questions:

- Is exercise capacity normal?
  - $\dot{V}_{O_2}$ max
  - Work rate max

Table 2—*Normal Values for Major Parameters in Cardiopulmonary Exercise Testing*

Parameter (Abbreviation, units)	Comments	Predicted	Range
Peak or Max $\dot{V}O_2$, L/min	Highest work rate, also expressed per kg	Based on height, age, sex, habitual activity level, (+/-weight)	Lower limit = 83% of predicted
Maximum Heart Rate (HR) (beats/min)		220-Age in years (alternate: [210-0.65 x Age in years]	+/- 15 beats; >90% predicted
Heart Rate Reserve		Predicted maximum HR— observed = 0	+/- 15 beats
O_2 Pulse ($\dot{V}O_2$/HR) (mL/beat)	At high work loads with maximum stroke volume and O_2 extraction	Predicted Peak $\dot{V}O_2$ / predicted maximum HR	> 80% predicted
Anaerobic Threshold (AT) (L/min $\dot{V}O_2$)	Lactic acid begins to accumulate	50-60% of predicted (not actual)$\dot{V}O_2$ max	> 40% of predicted $\dot{V}O_2$ max
Blood Pressure (mm Hg)		Cuff: rest, 125/80; near exercise max, 200/90 Intra-arterial: rest, 140/85; near exercise max, 205/100	Intra-arterial: Systolic 205 +/- 25 Diastolic 100 +/- 10
Maximum Voluntary Ventilation (MVV) (L/min)	This parameter defines the upper "ceiling" of achievable ventilation	Indirect MVV: FEV-1 x 40 (some use 35) Direct MVV: performed at 60 breaths/min for 12 seconds	We use the higher of the directly and indirectly measured MVV
Ventilatory Reserve (L/min)	MVV— maximum exercise $\dot{V}E$	38	>15
Breathing Reserve ("Dyspnea Index")	Maximum $\dot{V}E$/ MVV	0.70-0.75	0.72 +/-0.15
Maximum Respiratory Rate (breaths/min)		<50	<50
Ventilatory Equivalents for CO_2 and O_2 at AT ($\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$)	A noninvasive index of dead space (unless hyperventilation is present)	$\dot{V}E/\dot{V}CO_2$: 29 $\dot{V}E/\dot{V}O_2$: 26.5	$\dot{V}E/\dot{V}CO_2$: <34 $\dot{V}E/\dot{V}O_2$: <31
Dead Space to Tidal Volume Ratio (V_D/V_T)	Requires arterial sampling of $PaCO_2$	Rest: 0.30 (≈ 1/3) Maximum exercise: 0.18 (≈ 1/5)	Rest: <0.45 Maximum exercise: <0.30
$PaCO_2$ (mm Hg)	Declines during heavy exercise due to lactic acidosis	Stable, 36-42, declining with heavy exercise	
PaO_2 (mm Hg)	Increases slightly with heavy exercise; more sensitive than pulse oximetry	>80, increasing slightly with heavy exercise	
P(A-a) O_2 (mm Hg)	Defines abnormalities of O_2 transfer in the lung	Rest: 10-20 Maximum exercise: 15-30	Rest: <20 Maximum exercise: <35
SaO_2 or SpO_2	Pulse oximetry less reliable during exercise	>95%, no decrease throughout exercise	Drop of < 3% with exercise
Respiratory Quotient (R)	$\dot{V}CO_2/\dot{V}O_2$ ratio	Rest: 0.8 Maximum exercise: 1.21	Rest: 0.6-1.0 Maximum exercise: 1.1-1.3
Decline in HCO_3- (mmol/L)	Due to lactic acidosis above AT	Maximum exercise: younger 6, older 4	Maximum exercise: younger: 4-8, older 2-6

- Is cardiovascular function normal?
  - HR vs $\dot{V}O_2$ graph
  - O_2 pulse ($\dot{V}O_2$/HR)
  - AT
  - $\dot{V}O_2$ vs work rate
- Is ventilatory function normal?
  - $\dot{V}E$/MVV
  - MVV – $\dot{V}E$
  - RR max
  - Increasing $PaCO_2$
  - 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, $P(A\text{-}a)O_2$
  - SpO_2

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 includes 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 R > 1.15.
- SaO_2 drop > 5%.

Exercise Patterns in Common Diseases and Conditions

Major distinguishing features are shown in **bold**.

Cardiomyopathy

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

- The 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 max HR reached). AT normal or indeterminate (may stop before reaching AT; others have blunted ventilatory responses limiting graphic interpretation). O_2 pulse 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).
- **Ventilatory limitation is the characteristic abnormality:** Peak $\dot{V}E$/MVV increased (reduced or absent ventilatory reserve) and may exceed 1.0 in some. $\dot{V}E/\dot{V}CO_2$ at AT 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 abnormal:** Elevated V_D/V_T at rest and less than normal reduction with exercise; abnormal PaO_2 and $P(A\text{-}a)O_2$. Oxygenation may worsen, be stable, or improve with exercise.

Interstitial Lung Disease

- The 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).
- **Ventilatory limitation present: high maximum RR**, ≥ 50; $\dot{V}E$/MVV is increased (reduced or absent ventilatory reserve); $\dot{V}E/\dot{V}CO_2$ increased at AT due to increased V_D/V_T and low $PaCO_2$ setpoint.

- **Gas exchange abnormal:** elevated V_D/V_T at rest and less than normal reduction with exercise. Pa_{O_2} may be normal at rest, but progressively severe abnormalities in Pa_{O_2} and $P(A\text{-}a)O_2$ are seen with exercise.

Pulmonary Vascular Disease

- The exercise capacity is reduced: reduced $\dot{V}_{O_2}$ max.
- **Cardiovascular responses are abnormal** (same as in cardiomyopathy above): Early onset of AT. No HR reserve, as a result of reaching predicted HR early in exercise in association with a steep slope of increase in HR. O_2 pulse has an early plateau and low maximum value.
- **Ventilatory limitation 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:** elevated V_D/V_T at rest with only small decrement with exercise, may actually increase with exercise (obstructed vasculature leads to high $\dot{V}/\dot{Q}$ zones). Pa_{O_2} and $P(A\text{-}a)O_2$ abnormal at rest and progressively abnormal during exercise.

Obesity

- **Decreased exercise capacity: reduced max $\dot{V}_{O_2}$/kg but normal in L/min (based on ideal body weight). High O_2 cost to perform external work ($\dot{V}_{O_2}$ vs work rate in watts shifted up to left).**
- Normal cardiovascular responses.
- No ventilatory limitation based on normal ventilatory reserve ($\dot{V}_E$/MVV); failure to develop normal ventilatory compensation for lactic acidosis in some.
- Normal gas exchange responses: those with low Pa_{O_2} at rest improve with exercise (improved ventilation to bases of lung).

Deconditioned

- Decreased exercise capacity: reduced $\dot{V}_{O_2}$ max.
- **Cardiovascular responses all borderline abnormal; improve with conditioning.** Normal echocardiogram.
- No ventilatory abnormalities.
- Gas exchange normal at rest and exercise.

Malingering/Poor Effort

- Decreased exercise capacity: reduced $\dot{V}_{O_2}$ max.
- **No physiologic limit to exercise identified:** increased HR reserve (predicted HR not achieved); normal or increased ventilatory reserve (no ventilatory limitation); gas exchange normal at rest and exercise.

Psychogenic/Anxiety

- **Nonphysiologic breathing patterns**, especially hyperventilation. If no arterial line, acute hyperventilation noted by high R (unloading excess CO_2 relative to $\dot{V}_{O_2}$).

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.

- Decreased exercise capacity: reduced $\dot{V}_{O_2}$ max.
- **Hypercirculatory response**: steep HR slope; slightly low O_2 pulse; AT low-normal, indeterminate, sometimes frankly low (reflects poor O_2 utilization in peripheral tissues).
- **Hyperventilatory response**: high $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E/\dot{V}_{O_2}$ at peak exercise and at 50% of $\dot{V}_{O_2}$ max, but 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 essentially normal**: Pa_{O_2}, $P(A\text{-}a)O_2$ normal at rest and during exercise; V_D/V_T normal at rest and decreases slightly less than usual, likely due to reduced peak intensity of exercise.

Illustrative Cases

Case 1

A 69-year-old man has COPD, hypertension, and coronary artery disease. He undergoes CPET to clarify the major cause of his exercise intolerance. His FEV_1 is 1.5 L (56% of predicted), FVC is 3.1 (94%), FEV_1/ FVC is 0.48 (predicted, 0.74), and D_{LCO} adjusted for hemoglobin is 12 (52%). His measured MVV was 52, and calculated MVV (FEV_1 × 40) was 60. An echocardiogram shows mild left ventricular dysfunction. ECG was normal throughout exercise. See graphs in Figure 8 and the table below for more data. The patient stopped exercising due to dyspnea. No ECG abnormalities were noted.

Comment: This patient's exercise capacity is moderately reduced and is limited by COPD. He demonstrates a ventilatory limitation to exercise as shown by the two measures of ventilatory reserve, the $\dot{V}_E$/MVV ratio (0.95) and the difference between his MVV and maximal exercise $\dot{V}_E$ (3). This is seen graphically on the $\dot{V}_E$ vs $\dot{V}_{O_2}$ graph, which shows that the patient has 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 lower their Pa_{CO_2} to compensate for lactic acidosis, or even develop hypercapnia 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 is occurring 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 Pa_{O_2} and the widened $P(A\text{-}a)O_2$ with exercise is not consistent with cardiac disease.

Case 2

A 45-year-old man with known cardiomyopathy and obesity is sent for CPET for prognosis and cardiac transplant evaluation. He has no lung disease and normal resting PFT results. An echocardiogram shows severe global hypokinesis, and the nuclear left ventricular ejection fraction is 35%. His height is 170 cm (67 in) and weight is 100 kg (220 lb). The patient

Case 1

Measurement	Predicted	Measured (% predicted)
Peak $\dot{V}_{O_2}$, L/min	1.95	1.21 (62%)
HR maximum, beats/min	151	117 (71%)
Heart Rate Reserve	0	34
O_2 pulse, maximum, mL/beat	12.9	10.9 (80%)
AT, L/min of $\dot{V}_{O_2}$	1.13 (0.92, lower limit)	1.09 (56% of pred $\dot{V}_{O_2}$ max)
BP, rest and exercise, mm Hg	140/85, 205/100	150/80, 200/90
$\dot{V}_E$, maximum	(calculated MVV= 60)	57
Maximum $\dot{V}_E$/MVV	0.70-0.75 (0.87, upper limit)	0.95
Ventilatory Reserve, L/m	> 15	3
Respiratory Rate, maximum	< 50	40
Pa_{O_2}, rest and max exercise	>80, > 80	83, 64
$P(A\text{-}a)O_2$, rest and max exercise	<20, <35	17, 54
Pa_{CO_2}, rest and max exercise	36-42, lower after AT	41, 35
V_D/V_T, rest and max exercise	0.30, 0.18	0.42, 0.32
$\dot{V}_E/\dot{V}_{CO_2}$ at AT	< 34	43

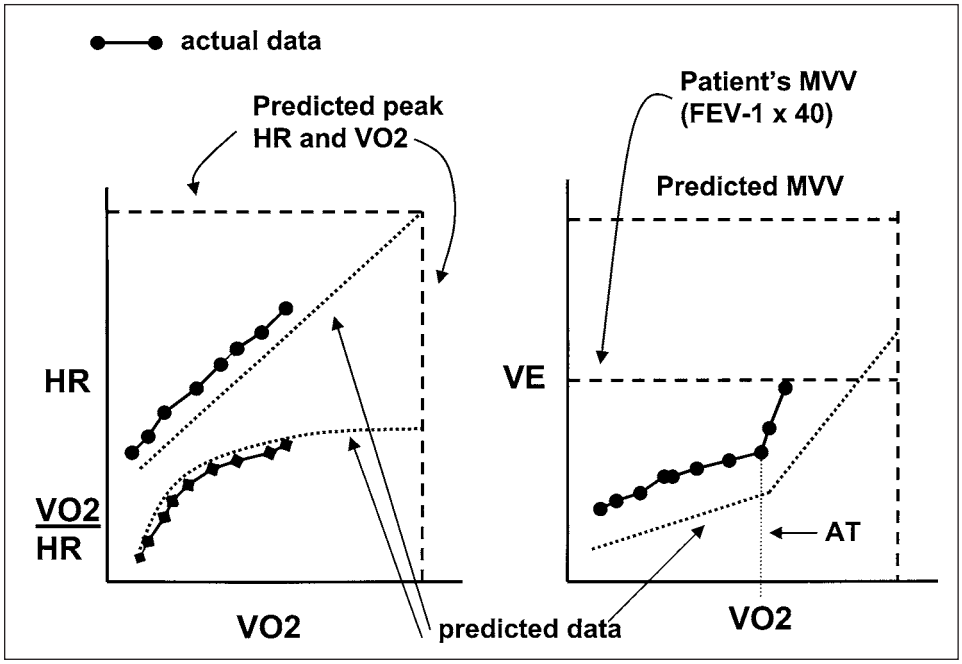

Figure 8. Case 1 data. Heart rate and O_2 pulse ($\dot{V}O_2/HR$) vs. oxygen consumption ($\dot{V}O_2$); Minute ventilation ($\dot{V}E$) vs $\dot{V}O_2$. Anaerobic threshold (AT) and maximum voluntary ventilation (MVV) are labeled.

stopped exercising due to leg and generalized fatigue; dyspnea was present but not an exercise-limiting symptom. ECG showed no arrhythmias or ST-T wave changes. See Figures 9 and 10 and the table below for more data.

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

Case 2

Measurement	Predicted	Measured (% predicted)
Peak workrate, watts	191	90 (47%)
Peak $\dot{V}o_2$, L/min	2.66	1.65 (62%)
Peak $\dot{V}o_2$/kg	34.0	16.5 (49%)
HR maximum, beats/min	175	172 (98%)
Heart rate reserve	0	3
O_2 pulse, maximum, mL/beat	15.1	9.6 (64%)
AT, L/min of $\dot{V}O_2$	1.49 (lower limit, 1.17)	0.98 (37% of pred $\dot{V}O_2$ max)
$\dot{V}E$ maximum	(MVV= 130)	86
Maximum $\dot{V}E$/MVV	0.70-0.75 (upper limit, 0.87)	0.66
Ventilatory reserve, L/m	> 15	44
Respiratory rate, maximum	< 50	34
PaO_2, rest and max exercise	>80, > 80	68, 86
$P(A\text{-}a)O_2$, rest and max exercise	<20, <35	31, 30
$PaCO_2$, rest and max exercise	36-42, lower after AT	41, 34
VD/VT, rest and max exercise	0.30, 0.18	0.35, 0.22
$\dot{V}E/\dot{V}CO_2$ at AT	< 34	31

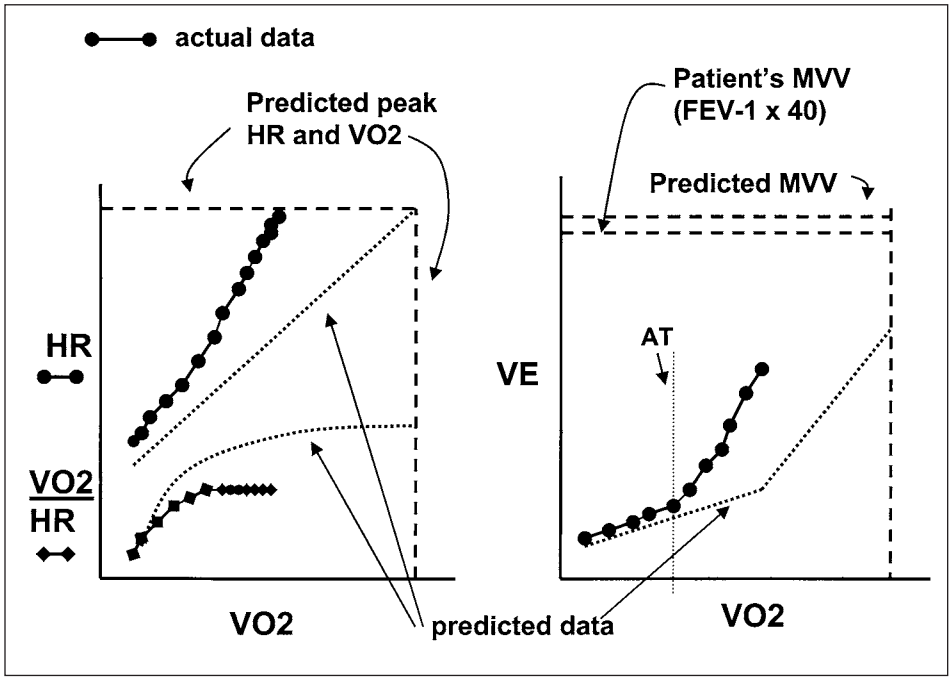

Figure 9. Case 2 data. Heart rate and O_2 pulse (O_2/HR) vs oxygen consumption ($\dot{V}O_2$); Minute ventilation ($\dot{V}E$) vs $\dot{V}O_2$. Anaerobic threshold (AT) and maximum voluntary ventilation (MVV) are labeled.

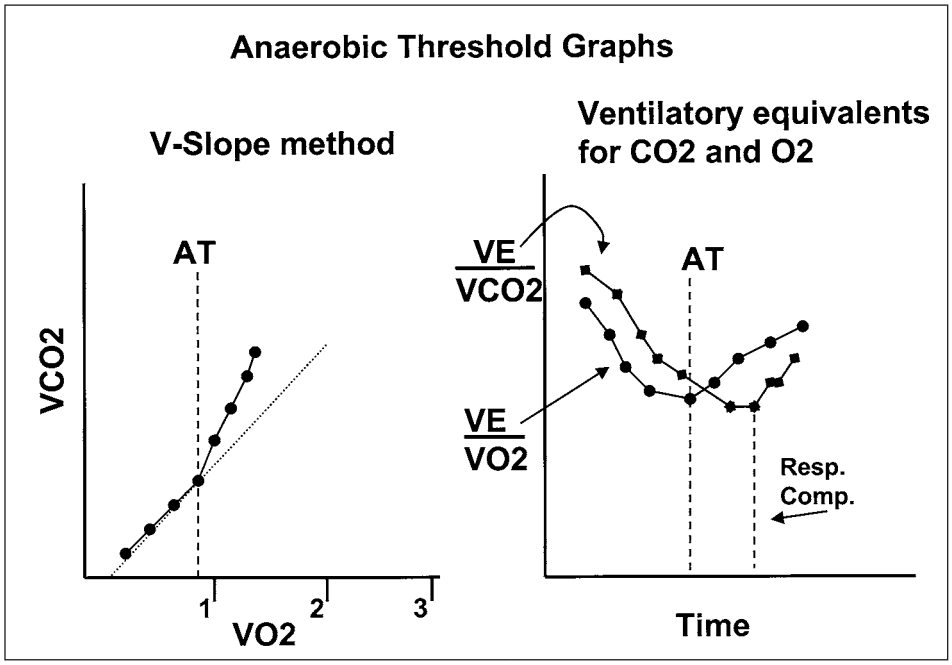

Figure 10. Case 2. Graphs for identifying anaerobic threshold (AT). Carbon dioxide production ($\dot{V}CO_2$) vs oxygen consumption ($\dot{V}O_2$). Ventilatory equivalents for $\dot{V}CO_2$ and $\dot{V}O_2$ ($\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$). AT and the respiratory compensation point for lactic acidosis are identified.

$\dot{V}E$ 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 $P(A\text{-}a)O_2$ 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 CPET for unexplained exertional dyspnea and fatigue. Her resting PFT results were normal except for a borderline low VC and DLCO. Her FEV_1 is 2.40. She stopped exercising due to both dyspnea and leg and global fatigue. Her height is 157 cm (62 in)

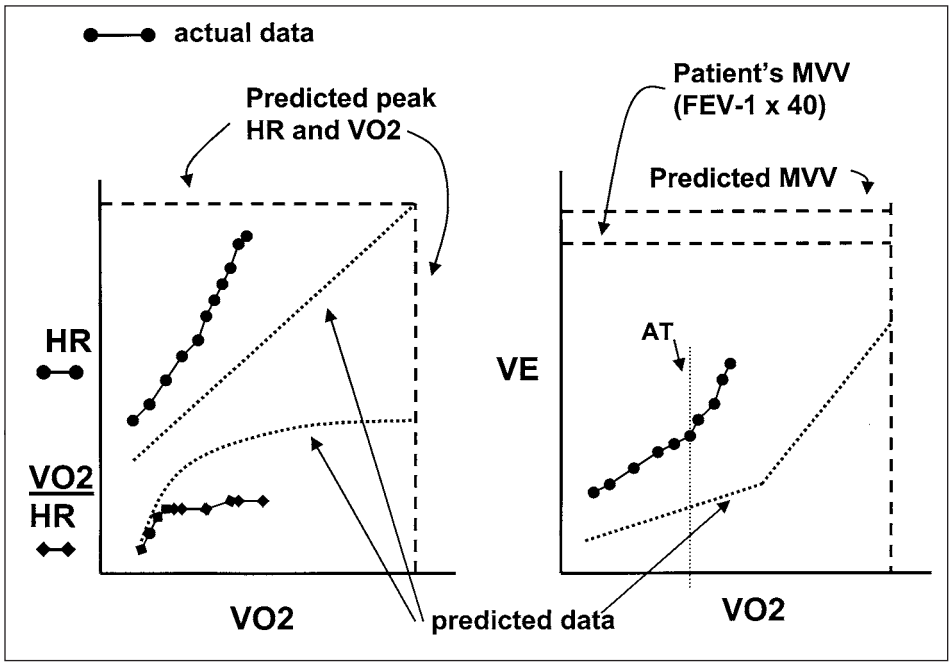

Figure 11. Case 3 data. Heart rate and O_2 pulse ($\dot{V}O_2/HR$) vs oxygen consumption ($\dot{V}O_2$); Minute ventilation ($\dot{V}E$) vs $\dot{V}O_2$. Anaerobic threshold (AT) and maximum voluntary ventilation (MVV) are labeled.

and weight is 60 kg (132 lb). ECG was normal. See Figure 11 and the table below for more data.

Comment: 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 a low work rate, reduced AT, and reduced O_2 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 PaO_2, the widening of the P(A-a)O_2, 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 makes 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

Case 3

Measurement	Predicted	Measured (% predicted)
Peak $\dot{V}O_2$, L/min	1.68	0.85 (51%)
HR maximum, beats/min	182	171 (94%)
Heart rate reserve	0	11
O_2 pulse, maximum, mL/beat	9.2	5.0 (54%)
AT, L/min of $\dot{V}O_2$	0.97 (lower limit = 0.79)	0.65 (39% of pred $\dot{V}O_2$ max)
$\dot{V}E$, maximum	(calculated MVV= 96)	62
Maximum $\dot{V}E$/MVV	0.70-0.75 (<0.87)	0.65
Ventilatory reserve, L/m	> 15	32
Respiratory rate, maximum	< 50	40
PaO_2, rest and max exercise	>80, > 80	81, 56
P(A-a)O_2, rest and max exercise	<20, <35	24, 50
$PaCO_2$, rest and max exercise	36-42, lower after AT	36, 29
V_D/V_T, rest and max exercise	0.30, 0.18	0.35, 0.38
$\dot{V}E/\dot{V}CO_2$ at AT	< 34	42

lung disease associated with a connective issue disease could also be present.

Summary of Major Differential Diagnostic Points

1. 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).
2. COPD: Ventilatory limitation, abnormal gas exchange.
3. Interstitial lung disease: Very high maximum RR, abnormal gas exchange, can demonstrate "cardiovascular" abnormal pattern with severe disease.
4. Pulmonary vascular disease: Cardiovascular pattern but very abnormal gas exchange, especially a high and sometimes increasing dead space fraction. Abnormal ventilation present but not the limiting factor.
5. Poor effort: no limiting system identified.

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An up-to-date overview of exercise testing ranging from the 6-min walk test to CPET.

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A lucid review of exercise testing using a different set of graphic panels than the more widely-used 9-plot of Wasserman and colleagues.

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