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A M E R I C A N C O L L E G E O F
 **C H E S T**
P H Y S I C I A N S

Diagnosing Cardiovascular and Lung Pathophysiology From Exercise Gas Exchange*

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Abbreviations: ATP=adenosine triphosphate; CAD=coronary artery disease; C(a-v)O₂=arterial mixed venous O₂ content difference; CM=cardiomyopathy; COPD-A and COPD-S=physically active (COPD patient) and sedentary (COPD patient), respectively; CPET=cardiopulmonary exercise test; HR=heart rate; IC=inspiratory capacity; LAT=lactic acidosis (anaerobic) threshold; MVV=maximum voluntary ventilation; PAD=peripheral arterial disease; PETCO₂=end-tidal PCO₂; R=respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); RLD=restrictive lung disease; $\dot{V}CO_2$ =carbon dioxide output; $\dot{V}E$ =minute ventilation; $\dot{V}O_2$ =oxygen consumption; $\Delta\dot{V}O_2/\Delta\dot{V}WR$ =increase in $\dot{V}O_2$ relative to increase in work rate; V_D/V_T =physiologic dead space ventilation; \dot{V}/\dot{Q} =ventilation/perfusion ratio; V_T =tidal volume

Exercise testing with gas exchange measurements, added to monitoring of the ECG and BP, has been used to evaluate patients with heart and lung disease since the immediate post-World War II boom in medical research. It was particularly stimulated by the development of right heart catheterization with the interest in measuring cardiac output and stroke volume during exercise by the direct Fick method. However, it was not widely used for routine clinical diagnostic studies because it was time consuming, technically difficult, and expensive. There was also a general lack of appreciation for the information that could be obtained from such measurements.

With the development of rapidly responding electronic gas analyzers to replace the technically more demanding chemical methods for the measurement of respiratory gases, and the development of flowmeters that could measure instantaneous flow and volume, the stage was set to measure gas exchange at the time of exercise testing. This greatly decreased the technical time and therefore the cost to do gas exchange measurements. However, the assimilation of the large amount of data obtained from these tests was laborious. When digital computers became available, this problem was solved, since the large number of measurements obtained and required to ad-

dress questions of cardiovascular and lung function could be reduced to a graphic display.

Because the cardiovascular and pulmonary systems are assessed when gas exchange is measured during exercise, these tests are referred to as cardiopulmonary exercise tests (CPETs). It is now possible to do a CPET with complete graphing output ready for interpretation in 15 min. In 1960, this required 2 days of two technicians, and much time of postdoctoral fellows who had the task of doing final calculations and graphing. The gain in technology was also translated into patient safety and comfort because continuous measurement of function allowed exercise work rate to be progressively increased relatively rapidly to maximum tolerance while simultaneously following the physiologic responses. This replaced tests in which large-step increases in work rate of 3 to 6 min in duration were used, the latter ostensibly to obtain steady-state measurements at each work level. Because of the vast gain in efficiency in measuring gas exchange and data processing, it became possible to extend CPET into the routine of medical practice.

The purposes for which CPETs are currently being applied attest to its growing importance in medicine. They include the following: (1) determining the pathophysiology of exercise limitation, differential diagnosis, and severity of impairment in function; (2) evaluating disability; (3) individualizing prescription for exercise rehabilitation programs; (4) determining risk from major surgery; (5) estimating survival potential in patient candidates for heart transplantation; and (6) determining efficacy of treatment modalities in patients with cardiovascular and respiratory diseases. The latter is done by following parameters of aerobic function with serial testing.

In this review, I shall address the use of exercise gas exchange in evaluating pathophysiology of the organ systems involved in the coupling of external to cellular respiration. I shall refer repeatedly to Figure 1 since it provides the interaction of the physiologic requirements to perform exercise and how interruption or alteration of the integrative response might affect cellular and external respiration.

The basic requirement to sustain muscular exercise is an increase in cellular respiration for regeneration of adenosine triphosphate (ATP). To support the increase

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MUSCLE ACTIVITY $O_2 \nabla \text{ \& } CO_2$ TRANSPORT VENTILATION
 $(\dot{V}_A + \dot{V}_D = \dot{V}_E)$

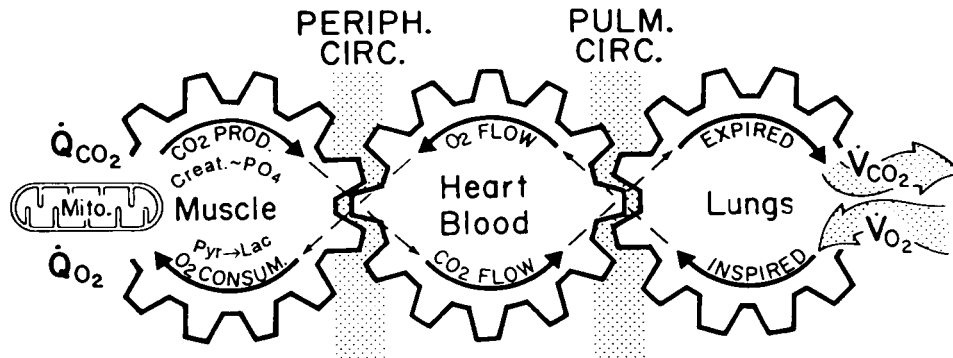


FIGURE 1. Scheme depicting the coupling of external to cellular respiration. \dot{V}_A =ideal alveolar ventilation/time; \dot{V}_D =physiologic dead space ventilation/time; \dot{V}_E =total ventilation measured during expiration/time; \dot{Q}_{O_2} = O_2 consumption; \dot{Q}_{CO_2} = CO_2 production; \dot{V}_{O_2} = O_2 uptake; \dot{V}_{CO_2} = CO_2 output; creat- PO_4 =creatine phosphate; Pyr=pyruvate; Lac=lactate; Mito=mitochondria. See text for description of pathophysiologic states that interfere with the normal coupling of external to cellular respiration.

in cellular respiration, O_2 and CO_2 transport between the cells and the external airway must match the rate of cellular respiration except for transient lags allowed by the capacitances in the transport system, O_2 stores on the venous side of the circulation, and small stores of high-energy phosphate in the form of creatine phosphate in the myocytes. The increase in O_2 and CO_2 transport is a function of the skeletal muscles, peripheral circulation, heart, pulmonary circulation, blood, lungs, and respiratory muscles. The latter provide the ventilation needed to refresh the gas in the alveoli for adding O_2 and removing CO_2 from the blood flowing through the lungs. Any defect in this interactive system can cause exercise limitation.

Pathophysiologic questions appropriate for a physician to ask when caring for a patient with exercise intolerance because of exercise-induced dyspnea or fatigue are shown in Table 1. Using current techniques for making measurements and imposing an exercise stress, CPET provides an efficient way of addressing the questions posed. Examples of disease states that might be present with "yes" answers to the posed questions are also listed in Table 1. By identifying the pathophysiology of exercise limitation, a correct clinical diagnosis accounting for the patient's symptom(s) is possible.

CARDIOPULMONARY EXERCISE TESTING

Which Ergometer?

To stress the cardiorespiratory gas transport system, exercise testing should involve large mus-

cle groups. Practical laboratory ergometers involving large muscle groups are the treadmill and cycle. Although normal untrained subjects can achieve a maximum oxygen consumption (\dot{V}_{O_2max}) on the treadmill that is about 10% higher than they can achieve on the cycle, the cycle ergometer has the major advantage that the work output performed by the patient is known. (The merits of each ergometer have been compared by Wasserman et al.¹) This is of overwhelming importance because considerably more information is learned from CPET about cardiovascular function and gas exchange when the external work performed by the subject is known. Therefore, when the quantitative response to exercise is important in the patient evaluation, we prefer to use the cycle ergometer.

Some physicians seem to think that the cycle is more taxing to the ill patient than walking on a treadmill. This is not the case when using the modern ergometers now available. In the typical, nonobese adult, unloaded cycling at 60 rpm only doubles the resting metabolic rate. This is less cardiovascular stress than walking at zero grade at 2 mph on the treadmill, because the cycle supports the weight of the patient. Reducing the cycling speed reduces the metabolic rate further. Because the work rate increase is known, the normal increase in \dot{V}_{O_2} is predictable. The ability to relate the increase in \dot{V}_{O_2} to the increase in work rate can reveal critically important diagnostic information, such as identifying whether the primary cause of the exercise limitation is due to coronary blood flow or peripheral

Table 1—Questions Addressed by Cardiopulmonary Exercise Testing*

Question	Example of Disorder	Markers for Abnormality
1. Is exercise capacity reduced?	Any disorder	Maximum $\dot{V}O_2$ - panel 3
2. Is the metabolic requirement for exercise increased?	Obesity	$\dot{V}O_2$ -WR relationship - panel 3
3. Is exercise limited by impaired O_2 flow?	Due to ischemic, myopathic, valvular, congenital heart disease?	ECCG; LAT; $\Delta\dot{V}O_2/\Delta WR$; $\dot{V}O_2/HR$ - panels 2,3,5
	Due to pulmonary vascular disease?	$\Delta\dot{V}O_2/\Delta WR$; LAT; $\dot{V}O_2/HR$; $\dot{V}E/\dot{V}CO_2$ - panels 2,3,5,6
	Due to peripheral arterial disease?	BP; $\Delta\dot{V}O_2/\Delta WR$; LAT - panels 3,5
	Due to anemia, hypoxemia, or COHb?	LAT; $\dot{V}O_2/HR$ - panels 2,3,5
4. Is exercise limited by reduced ventilatory capacity?	Lung; chest wall	BR; ventilatory response - panels 1,7,9
5. Is there an abnormal degree of \dot{V}/\dot{Q} mismatching?	Lung; pulmonary circulation; heart failure	P(A-a) O_2 ; P(a-ET) CO_2 ; V _D /V _T ; $\dot{V}E/\dot{V}CO_2$ - panels 4,6,9
6. Is there a defect in muscle utilization of O_2 or substrate?	Muscle glycolytic or mitochondrial enzyme defect	LAT, R, $\dot{V}CO_2$; HR vs $\dot{V}O_2$; lactate; lactate/pyruvate ratio - panels 3,8
7. Is exercise limited by a behavioral problem?	Neurosis	Breathing pattern - panels 7,8
8. Is work output reduced because of poor effort?	Poor effort with secondary gain	HRR; BR; peakR; P(A-a) O_2 ; P(a-ET) CO_2 - panels 2,5,7,8

*Maximum $\dot{V}O_2$ =highest O_2 uptake measured; WR=work rate; BR (breathing reserve)=maximum voluntary ventilation-ventilation at maximum exercise; $\Delta\dot{V}O_2/\Delta WR$ =increase in $\dot{V}O_2$ relative to increase in work rate; V_D/V_T=physiologic dead space/tidal volume ratio; P(A-a) O_2 =alveolar-arterial PO_2 difference; COHb=carboxyhemoglobin; P(a-ET) CO_2 =arterial-end tidal PCO_2 difference; HRR (heart rate reserve)=predicted maximum heart rate-maximum exercise heart rate; $\dot{V}E/\dot{V}CO_2$ =ventilatory equivalent for CO_2 ; Peak R=peak gas exchange ratio.

blood flow in the patient with atherosclerosis. This will be discussed under the heading of “Diagnosis of Exercise Pathophysiology.”

Which Protocol?

Because of the ability to monitor exercise gas exchange continuously, breath by breath or over short periods, it is possible to use progressively increasing work rate protocols, in which the total duration of increasing work rate exercise is only 8 to 12 min, from the lowest work rate to exhaustion. The work rate can be increased under computer control, smoothly in ramp pattern, or in small steps of 1-min duration. Diagnostically, nothing is lost from these non-steady-state, progressive exercise tests and there is considerable gain by being able to determine the $\dot{V}O_2$ at which the lactic acidosis (anaerobic) threshold develops. Additionally, the increase in $\dot{V}O_2$ can be determined as work rate is increased ($\Delta\dot{V}O_2/\Delta$ work rate), a measurement of particular importance when evaluating the cardiovascular function of patients. A grade of work rate is selected to complete the increasing work rate period in the desired time, recognizing that $\dot{V}O_2$ will normally increase 10 mL/min/W. The patient's predicted $\dot{V}O_{2max}$ can be determined by referring to appropriate reference equations. (Multiple sources were reviewed by Wasserman et al.)² While the patient increases work rate to the maximum, he or she exercises at that level for a relatively short period. Thus,

recovery is fast and the exercise test could be repeated at a different rate of increase, or with O_2 breathing if the examining physician thinks it desirable for a more complete patient evaluation.

DATA DISPLAY FOR THE MEDICAL RECORD

CPET studies in recent years have taught us that different defects in the coupling of external (airway) to cellular (mitochondrial) respiration will affect gas exchange in different ways. Thus, the pattern of gas exchange at the airway can be used to diagnose pathophysiology and used to support or refute the correctness of a clinical diagnosis. With an appropriate display of the data, it is possible to determine, noninvasively, the functional status of the cardiovascular system, the ventilatory system, and the uniformity of matching ventilation to perfusion. Because a graphic is much easier to read than a tabular data display, we transformed the CPET data into graphs. To avoid reviewing and interrelating multiple pages of graphs and overburdening the medical record with pages of tedious data, we gradually evolved a single page of nine strategically positioned graphs. These graphs contain 15 plots that systematically assess cardiovascular, ventilatory, ventilation-perfusion matching, and the metabolic responses to exercise (Fig 2). Normal target values such as

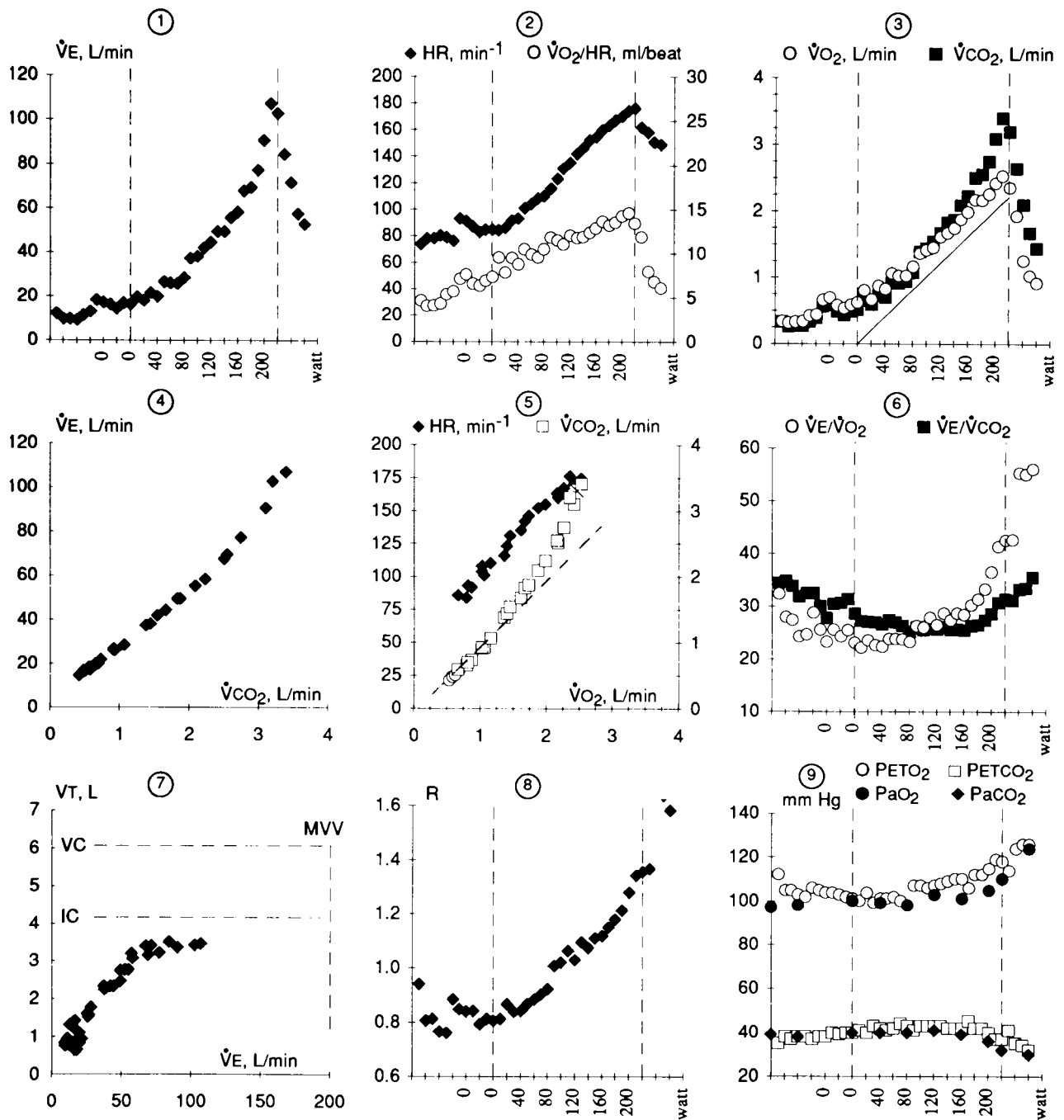


FIGURE 2. Nine-panel graphic array used to describe the cardiovascular, ventilatory, \dot{V}/\dot{Q} matching, and metabolic responses to exercise in the medical record. Study is from a 55-year-old male patient (modified from case 1 of reference 4). The responses are normal. The diagonal line drawn on panel 3 is the normal rate of increase in $\dot{V}O_2$ for the work rate increase (10 mL/min/W). $\dot{V}E$ =minute ventilation; HR=heart rate; R=respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); $PETO_2$ =end-tidal PO_2 ; $PETCO_2$ =end tidal PCO_2 ; PaO_2 =arterial PO_2 ; $PaCO_2$ =arterial PCO_2 ; MVV=maximal voluntary ventilation; IC=inspiratory capacity; VC=vital capacity; watt=unit of power output (work rate).

$\dot{V}O_2$ max and maximum heart rate (HR) are displayed on specific plots. Normal values for all the measurements in the nine-panel graphic array, described by multiple groups for CPET, are summarized elsewhere.²

Evaluation of Systemic Function From the Nine-Panel Graphic Array

The questions that could be asked of exercise tests are shown in Table 1. The answer to the first

question relating to exercise capacity is addressed in panel 3 from the measurement of maximum (peak) $\dot{V}O_2$. If it is reduced, we ask if the reduction is due to a cardiovascular limitation (panels 2, 3, and 5), ventilatory limitation (panels 1, 3, 4, and 7), ventilation-perfusion mismatching (panels 3, 6, and 9), or abnormality in use of metabolic substrate (panels 3 and 8). The nine graphs describe the following physiology.

Panel 1—Minute Ventilation ($\dot{V}E$) vs Work Rate: This normally becomes curvilinear as work rate is increased above the lactic acidosis (anaerobic) threshold (LAT) except when ventilatory work is excessive, eg, some patients with obesity or lung disease.

Panel 2—HR and $\dot{V}O_2$ /HR (Equal to Stroke Volume \times Arteriovenous O_2 Difference) vs Work Rate: HR is high and $\dot{V}O_2$ /HR is low for a given work rate in patients with certain cardiovascular defects except when under rate control or β -adrenergic blockade.

Panel 3— $\dot{V}O_2$ and Carbon Dioxide Output ($\dot{V}CO_2$) vs Work Rate and Slope Showing Predicted Rate of Increase in $\dot{V}O_2$ for the Work Rate Increase (Diagonal Line): This is the first panel to address because it gives global assessment of the presence of exercise limitation. Increase in $\dot{V}O_2$ relative to work rate ($\Delta\dot{V}O_2/WR$) is commonly abnormal in patients with cardiovascular disease, the pattern varying with the defect as described below. $\dot{V}CO_2$ increases above $\dot{V}O_2$ after a lactic acidosis develops and continues to increase steeply despite flattening of $\dot{V}O_2$.

Panel 4— $\dot{V}E$ vs $\dot{V}CO_2$: This is a linear relationship until ventilatory compensation for metabolic acidosis (becomes steeper) or CO_2 retention (becomes more shallow) develops. The slope of the linear part is steep when the exercise physiologic dead space/tidal volume ratio (V_D/V_T) is increased.

Panel 5—HR vs $\dot{V}O_2$ and $\dot{V}CO_2$ vs $\dot{V}O_2$: HR increases linearly with $\dot{V}O_2$ to the predicted maximums in normal subjects. In patients with heart failure or pulmonary vascular disease, the increase may lose its linearity with HR increasing progressively more rapidly than $\dot{V}O_2$. Up to the LAT, $\dot{V}CO_2$ increases linearly with $\dot{V}O_2$ with a slope of one, or slightly less than one. Then $\dot{V}CO_2$ increases more rapidly, the steepening of the slope depending on the rate of buffering of lactic acid. The breakpoint describes the LAT. It will be low in patients with poor cardiovascular function.

Panel 6—Ventilatory Equivalent for O_2 and CO_2 ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$) vs Work Rate: $\dot{V}O_2$ decreases to a nadir at the LAT. $\dot{V}CO_2$ decreases to a nadir at the ventilatory compensation point. Both values are high with pulmonary vascular occlusive disease.

Panel 7— V_T vs $\dot{V}E$: The patient's vital capacity and

inspiratory capacity (IC) are shown on the V_T axis, and actually measured maximum voluntary ventilation (MVV) or FEV_1 times 40 are shown on the $\dot{V}E$ axis. With airflow limitation, maximal exercise $\dot{V}E$ approximates the MVV. Thus, the breathing reserve (MVV- $\dot{V}E$ at maximal exercise) is approximately zero. The breathing reserve cannot be predicted from resting pulmonary function measurements alone. With restrictive lung disease, V_T may approximate the IC at low work rates and respiratory rate may ultimately increase above 50 or 60 breaths per minute.

Panel 8—Respiratory Exchange Ratio ($\dot{V}CO_2/\dot{V}O_2$) (R) vs Work Rate: This usually starts at approximately 0.8 and increases to above 1.0 above the LAT, although these values may be lower after long fasting. Inability or failure to produce an exercise lactic acidosis would mitigate increase to values above 1. Acute hyperventilation at rest and low work rates, as reflected by a decreasing end-tidal PCO_2 ($PETCO_2$), yields an $R > 1$.

Panel 9— $PETCO_2$ and End-Tidal PO_2 vs Work Rate: Low $PETCO_2$ signals either hyperventilation or high ventilation/perfusion ratio (\dot{V}/\dot{Q}) mismatching. R (panel 8) reveals if hyperventilation is acute. Arterial blood gases or knowledge of plasma HCO_3^- differentiates chronic hyperventilation from \dot{V}/\dot{Q} abnormality. Arterial blood gases are plotted on this graph to detect the presence of high and low \dot{V}/\dot{Q} mismatching.

Poor effort is likely to be revealed by a high HR reserve (panel 2), high breathing reserve (panel 7), and a low R (panel 8) at end exercise. In addition, the patient may elicit a chaotic breathing pattern (panel 7) that may cause end-tidal PCO_2 and PO_2 to be quite variable (panel 9), the latter most evident during breath-by-breath monitoring.

Fitting Physiologic Abnormality to Disease Entity

Table 1 describes disorders possible with a positive answer to each of the questions posed and identifies the panels of the nine-panel graphics array that address the question. Panel 3 is always the first panel to examine because of its ability to define if overall function is reduced. The internal relationships of this panel are then reviewed, including the relationship of $\dot{V}O_2$ and $\dot{V}CO_2$ to work rate and each other. The other panels are then systematically reviewed for the purpose of evaluating cardiovascular, ventilatory, \dot{V}/\dot{Q} matching, and metabolic abnormality. Panels 3, 2, and 5 are characteristically abnormal with cardiovascular disease. Lung and chest wall diseases commonly cause abnormalities in panels 1 and 7. When lung and heart diseases are accompanied by \dot{V}/\dot{Q} abnormality, panels 4, 6, and 9 are affected. Panels 3

and 8 are the metabolic plots and help address acute hyperventilation and adequacy of exercise effort.

Obesity, Cigarette Smoking, and Anemia Complicate Interpretation

Three physiologic derangements, not usually considered as diseases of the cardiorespiratory system, may contribute significantly to exercise intolerance due to common cardiorespiratory disorders. These physiologic derangements are (1) obesity, (2) anemia, and (3) carboxyhemoglobinemia secondary to cigarette smoking.

Obesity adds to the O_2 and cardiac output cost of exercise. It also restricts the ventilatory system and increases the work of breathing. These factors become more marked as the $\dot{V}E$ requirement increases.

Anemia reduces the arterial O_2 content and the maximal arteriovenous O_2 difference. Therefore, to achieve a given $\dot{V}O_2$, a greater cardiac output is required than if anemia were not present. Also, because the O_2 content of the arterial blood is reduced, the capillary PO_2 decreases to its critical value, inducing anaerobic metabolism and lactic acidosis to take place at a reduced work rate and $\dot{V}O_2$.

The increased carboxyhemoglobin of the heavy cigarette smoker is about 10 to 12%. This not only reduces the arterial O_2 content to a level that would be found in patients with an arterial PO_2 of about 50 to 55 mm Hg, but also shifts the oxyhemoglobin dissociation curve to the left making it more difficult for O_2 to dissociate from hemoglobin at a given PO_2 . Thus, the capillary PO_2 would fall more rapidly to its critical value, resulting in a lactic acidosis at a reduced level of work.

The net effect of these complicating factors is that the amount of external work that the patient can perform is reduced. However, in obesity, the maximal $\dot{V}O_2$ and LAT are normal or high. With anemia and increased carboxyhemoglobinemia, the maximal $\dot{V}O_2$, LAT, and peak work rate may all be reduced.

DIAGNOSIS OF EXERCISE PATHOPHYSIOLOGY

Exercise requires an increase in gas transport between the airway and mitochondria. Figure 1 illustrates the physiologic mechanisms that must be coupled to achieve this gas exchange. Exercise limitation is caused by any disease state that disrupts the normal gas exchange coupling.

Our approach to diagnosis of exercise pathophysiology has been to use the nine-panel graphic array exemplified by Figure 2. We start with panel 3 because it quantifies the peak $\dot{V}O_2$. We also start with this panel because the pattern of increase in $\dot{V}O_2$ is often abnormal in cardiovascular disorders, with the

abnormal pattern differing depending on the pathophysiologic condition. After reviewing the plots in panel 3, the remaining panels are reviewed to evaluate the physiologic state of coupling at each point in the interactive process schematized in Figure 1.

A flow chart system has been developed to assist the interpreter of exercise tests in selecting the dominant gas exchange pathophysiology limiting exercise.³ Only the nine-panel graphic array for a patient with a normal response is presented herein (Fig 2). It is not possible in this format to discuss the different features of all diseases known to interrupt the normal coupling of external to cellular respiration. Therefore, I have limited this analysis to the pathophysiology of three common cardiovascular disorders, three common pulmonary disorders, and two disorders for which the diagnosis is uniquely made by CPET. See the case presentations with nine-panel graphs in the article by Wasserman et al⁴ for a more comprehensive presentation of examples of cardiorespiratory diseases that impair exercise performance.

Differential Features in Exercise Gas Exchange in Coronary Artery Disease, Cardiomyopathy, and Peripheral Arterial Disease

In this section, the physiologic responses to CPET are contrasted in three different types of cardiovascular disease, including coronary artery disease (CAD), cardiomyopathy (CM), and peripheral arterial disease (PAD). It is important to distinguish the relative importance of the pathophysiology in these three conditions because they are commonly found in the same patient. Knowing the limiting pathophysiology would enable the patient's physician to focus on the therapeutic modality most likely to relieve the patient's symptom(s).

Peak $\dot{V}O_2$ (Cardiac Output) and $\Delta\dot{V}O_2/\Delta WR$ (Panel 3): $\dot{V}O_2$ is equal to cardiac output times arterial-mixed venous O_2 difference ($C[a-v]O_2$). Cardiac output increases linearly with $\dot{V}O_2$ in normal subjects and most heart failure patients with the same slope (approximately 6 L/min cardiac output per liter $\dot{V}O_2$) except for the most severe heart failure patients in whom the slope is more shallow.^{5(p161,181)} $C[a-v]O_2$ also increases approximately linearly with percent of $\dot{V}O_{2max}$ to the same peak value (approximately 80 to 85% extraction) in heart disease patients^{5(p200)} and normal subjects⁶ alike. Therefore, $\dot{V}O_2$ becomes a surrogate measure of cardiac output and stroke volume provided the investigator knows the HR and fraction of the peak $\dot{V}O_2$ value.^{5(p200),6} While peak $\dot{V}O_2$ will be decreased below predicted in patients with myocardial ischemia due to CAD, exercise limitation due to CM, and claudication due to PAD,

the patterns of increase in $\dot{V}O_2$ and $\dot{V}CO_2$ with work rate differ in all three cardiovascular conditions.

In CAD, the myocardial O_2 supply may be adequate to support the O_2 requirement at rest and low work rates. $\dot{V}O_2$ will increase linearly with work rate at a slope of about 10 mL/min/W, parallel to the diagonal line drawn with a slope of 10 mL/min/W on panel 3 of Figure 2. $\dot{V}CO_2$ will be slightly less than $\dot{V}O_2$ and will increase in a similar pattern to $\dot{V}O_2$. However, when exercise drives up the myocardial work as HR and BP increase, the myocardial O_2 (and blood flow) requirement increases. Regions of the myocardium with limited ability to increase their blood flow will be unable to contract. If a large enough area of the myocardium is involved, stroke volume will decrease. As exercise work rate is increased, the falling stroke volume will prevent the cardiac output from sustaining its rate of increase. At that work rate, the slope of rise in $\dot{V}O_2$, the surrogate measure of cardiac output change, abruptly decreases (Fig 3). In our experience, the ECG shows electrical evidence of myocardial ischemia at work rates soon after the abrupt change in $\Delta\dot{V}O_2/\Delta WR$ (slope of increase in $\dot{V}O_2$ relative to work rate increase) in patients with CAD. Chest pain is commonly absent. The decrease in slope signals that the rate of anaerobic ATP regeneration and lactate

accumulation is high in muscle. Reflecting this change in source of ATP regeneration is an increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$, the difference being striking since $\dot{V}CO_2$ continues to increase steeply, while $\dot{V}O_2$ abruptly decreases its rate of rise (Fig 3).

In CM, $\Delta\dot{V}O_2/\Delta WR$ commonly decreases as work rate increases when cardiac output fails to increase linearly with work rate. The change is generally gradual rather than abrupt like that observed when the contracting myocardium becomes ischemic. The decreased $\Delta\dot{V}O_2/\Delta WR$ signals that the rate of anaerobic ATP regeneration and lactate accumulation is high. Reflecting this change in source of ATP regeneration is the increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$, as in CAD. Thus, $\dot{V}CO_2$ continues to increase steeply with work rate in CM, as in CAD, but the pattern of increase in $\dot{V}O_2$ differs.

In PAD, $\dot{V}O_2$ increase will be linear but more shallow than normal during the progressive exercise test (Fig 4), because the high resistance of the conducting arteries leading to the exercising muscle prevents an appropriate increase in muscle perfusion despite local hyperemia. The slow increase in $\dot{V}O_2$ is accompanied by a slow increase in $\dot{V}CO_2$ in contrast to patients with CAD and CM. In PAD, the slope of $\dot{V}CO_2$ vs work rate is usually more shallow than 10 mL/min/W and similar to the $\dot{V}O_2$ vs work rate slope. This contrasts with that observed for CAD and CM

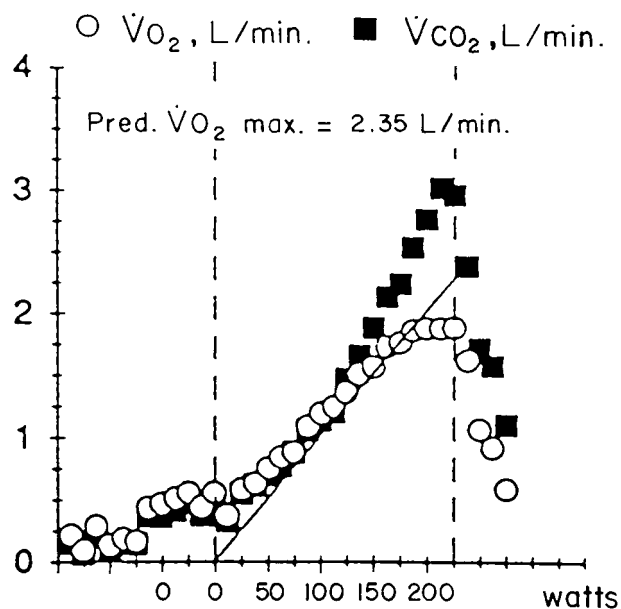


FIGURE 3. Panel 3 of a nine-panel graphic array of a 47-year-old male patient with nonanginal ischemic heart disease. ST segment of ECG showed progressive down-sloping above 150 W reaching 3 mm by the end of exercise in leads II and V_4 by the end of exercise. There was no chest pain. ECG changes resolved by 5 min of recovery. There was no ectopy. Failure for $\dot{V}O_2$ to increase with the slope of the diagonal line past 150 W, despite increasing work rate, is evidence that cardiac output failed to increase normally. Predicted $\dot{V}O_{2max}$ is shown.

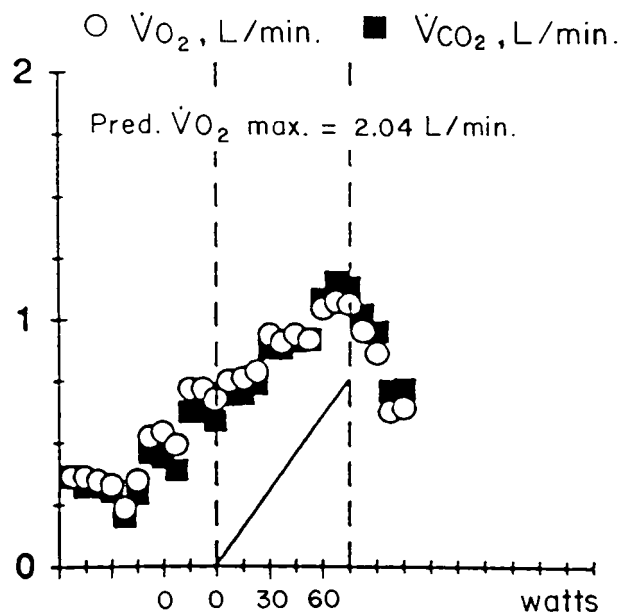


FIGURE 4. Panel 3 of a nine-panel graphic array of a 65-year-old diabetic, cigarette-smoking man with exercise limitation secondary to leg pain characteristic of claudication. ECG was normal during exercise. $\dot{V}O_2$ and $\dot{V}CO_2$ increase at a slower rate than normal (diagonal line) showing that the aerobic response to the imposed work rate was increasing at an inappropriately low rate. Predicted $\dot{V}O_{2max}$ is shown.

patients in whom the $\dot{V}CO_2$ vs work rate slope is >10 mL/min/W. The reduced rate of CO_2 output from the exercising muscle in PAD is likely due to the retention of much of the extra CO_2 produced by anaerobic metabolism in the ischemic muscle along with lactate. Thus, the lactic acidosis cannot be readily reflected in the lung gas exchange in contrast to that observed in CAD and CM patients.

LAT and Stroke Volume (Panel 5 and 2): In CAD, the LAT determined by the breakpoint in the plot of $\dot{V}CO_2$ vs $\dot{V}O_2$ (V-slope plot, panel 5) usually takes place at the $\dot{V}O_2$ where there is myocardial ischemia, slowing the rate of $\dot{V}O_2$ increase with work rate. This commonly takes place above the predicted lower limit of normal for LAT. Therefore, the LAT is usually normal in patients who develop myocardial ischemia during exercise, unless functional myocardial ischemia develops with minimal exercise.

Concurrent with the reduction in $\Delta\dot{V}O_2/\Delta WR$ in CAD is the steepening in HR vs $\dot{V}O_2$ instead of the linear relationship usually observed with increasing work rate (panel 5, Fig 2). The steepening of HR complements the decreasing stroke volume (reflected by the abrupt reduction in rate of increase in $\dot{V}O_2$ vs work rate) as work rate is increased above the LAT. Also the $\dot{V}O_2/HR$ ratio (O_2 -pulse) (panel 2) does not increase normally above the work rate at which myocardial ischemia with dyskinesia occurs. Since the O_2 -pulse measures the product of stroke volume and $C(a-v)O_2$, the unchanging O_2 -pulse suggests that the reduction in stroke volume is offset by an increasing $C(a-v)O_2$.

In contrast to the CAD patient, the patient with significant CM will have a low LAT, depending on the severity of the limitation in forward output (O_2 flow). The HR- $\dot{V}O_2$ relationship is steep but it rarely reaches its predicted maximum because fatigue limits the patient. Thus, there is a significant HR reserve. The O_2 -pulse is low, but in contrast to CAD, the flattening in O_2 -pulse is less abrupt.

In PAD, as in all metabolic states in which ATP is regenerated anaerobically, lactic acid is produced. Since this acid is over 99% dissociated at the pH of cells, it is almost totally buffered by HCO_3^- upon its formation in the exercising muscle. This will result in increased CO_2 production relative to $\dot{V}O_2$. However, this is difficult to assess by the gas exchange methods (eg, V-slope) because much of this buffer-derived CO_2 is retained in the muscle due to the relatively low blood flow through the ischemic limb. Consequently, an accurate assessment of the subject's LAT would be difficult in patients limited by PAD.

The HR vs $\dot{V}O_2$ slope is linear in PAD, but the peak predicted HR is not reached because exercise fatigue and leg pain develop before the central circulation is maximally stressed. Consequent to the

increased resistance to blood flow in the major conducting vessels caused by obstructing atherosclerotic lesions and the nonlimiting cardiac output response, marked BP increases take place at low work rates.

Breathing Reserve and Pattern (Panel 7): $\dot{V}E$ increases during exercise, predominantly by increasing VT at lower work rates and also increasing breathing rate at higher levels of exercise. There is nothing particularly abnormal about the breathing pattern in the CAD and PAD patient, and the maximum exercise ventilation is considerably below the MVV. However, the CM patient generally responds to exercise with a smaller VT and greater breathing frequency for a given exercise ventilation than normal, the altered breathing pattern being more marked, the worse the heart failure.⁷⁻¹⁰

\dot{V}/\dot{Q} Mismatching (Panels 4, 6, and 9): Patients with CAD with exercise myocardial ischemia and/or PAD manifesting claudication have normal uniformity in ventilation relative to perfusion. Thus, panels 4, 6, and 9 are normal in these disorders. In contrast, patients with CM have a high \dot{V}/\dot{Q} mismatching abnormality. Therefore $\dot{V}E/\dot{V}CO_2$ is especially high in these patients. Because of the high \dot{V}/\dot{Q} lung units, PET CO_2 will tend to be low, without evidence of acute hyperventilation as can be deduced from a normal R (panel 8). The contribution of high \dot{V}/\dot{Q} lung units to overall ventilation results in a steep slope in the plot of $\dot{V}E$ vs $\dot{V}CO_2$ (panel 4). The abnormal steepness of the slope is primarily due to a high physiologic dead space ventilation (\dot{V}_D/\dot{V}_T) in these patients. The more abnormal the heart function, the steeper the slope.^{7,8,10}

Differential Features in Exercise Gas Exchange in COPDs, Sedentary and Physically Active, and Restrictive Lung Disease

In this section, I shall illustrate the gas exchange characteristics of three patients with different commonly encountered lung disorders, a physically active COPD patient (COPD-A), a COPD patient who has been sedentary (COPD-S), and a patient characterized by restrictive lung disease (RLD) as seen in patients with idiopathic pulmonary fibrosis, connective tissue disease, or sarcoidosis. In describing these three pulmonary conditions, I shall again refer to Figure 2 to illustrate how the pathophysiology of each condition alters the graphic description of the cardiovascular, ventilatory, \dot{V}/\dot{Q} , and metabolic responses to exercise.

Peak $\dot{V}O_2$ (Cardiac Output) and $\Delta\dot{V}O_2/\Delta WR$ (Panel 3): The patterns of increase in $\dot{V}O_2$ and $\dot{V}CO_2$ differ in the three lung disorders that are the subject of discussion. In the COPD-A patient, $\dot{V}O_2$ will increase linearly

with work rate at a slope of about 10 mL/min/W (parallel to the diagonal drawn on panel 3 of Fig 2). $\dot{V}CO_2$ will be slightly less than $\dot{V}O_2$ and will increase parallel to it, possibly never increasing above $\dot{V}O_2$, depending on the degree of airflow obstruction. In other words, the patient, being physically active, does not develop a significant lactic acidosis before he is forced to stop exercise because of breathlessness from ventilatory limitation (panel 7).

In the COPD-S patient, $\dot{V}O_2$ will increase linearly in the same fashion as in the COPD-A patient because forward output is not impaired by limited heart function or pulmonary vascular resistance. In contrast, $\dot{V}CO_2$ will increase more steeply than $\dot{V}O_2$ at a relatively low work rate because the skeletal muscles of locomotion are deconditioned. Deconditioning results in decreased muscle capillarity and more sparse mitochondrial density in muscle. These factors define the surface area and diffusion distance in the functional muscle unit and therefore dictate the capillary PO_2 needed to achieve the O_2 flow from blood to mitochondria. Detraining would cause a net increase in lactate production in the active muscle at a higher capillary PO_2 and lower $\dot{V}O_2$ than in the trained state. The increase in $\dot{V}CO_2$ and H^+ caused by the lactic acidosis drives ventilation above that of the COPD-A patient. The presence of arterial hypoxemia and/or increased carboxyhemoglobin will further disadvantage the O_2 supply to the muscle during exercise¹¹ and cause $\dot{V}CO_2$ to increase at a still-greater rate than $\dot{V}O_2$.

In the RLD patient, $\Delta\dot{V}O_2/\Delta WR$ may be lower than normal because the high pulmonary vascular resistance limits the patient's ability to increase blood flow through the lung to the extent required to satisfy the increased O_2 requirement of exercise. Thus, in contrast to the COPD-A and COPD-S patient, the increase in $\dot{V}O_2$ with work rate is reduced and often not linear but decreases as the maximum work rate is approached (Fig 5). $\dot{V}CO_2$ relative to $\dot{V}O_2$ is high, indicating that the rate of anaerobic ATP regeneration and lactate accumulation are high. Thus, the patterns of increase in $\dot{V}O_2$ and $\dot{V}CO_2$, when viewed together, differ in these three lung disorders because of the different pathophysiology limiting exercise.

LAT and Stroke Volume (Panel 5 and 2): In the COPD-A patient, the LAT determined by the plot of $\dot{V}CO_2$ vs $\dot{V}O_2$ (V-slope plot) shows either no breakpoint or a breakpoint that is normal. Also, the slope of HR vs $\dot{V}O_2$ is commonly normal reflecting a normal stroke volume. However, the HR at peak exercise is usually low because the patient cannot exercise to a level that stresses their cardiovascular system sufficiently to induce a normal exercise tachycardia.

In the COPD-S patient, the LAT is low and the

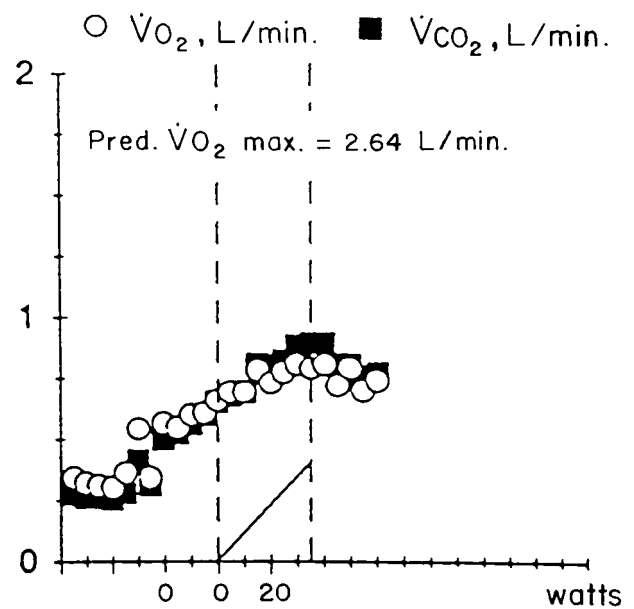


FIGURE 5. Panel 3 of nine-panel graphic array of a 29-year-old man with 6-year history of sarcoidosis with progressively worsening exertional dyspnea. $\dot{V}O_2$ increase became progressively more shallow as work rate increased (see relationship to diagonal line). This contrasts to the finding of the patient with PAD illustrated in Figure 4. Predicted $\dot{V}O_{2max}$ is shown.

HR vs $\dot{V}O_2$ is relatively steep reflecting a low stroke volume. The presence of arterial hypoxemia and high carboxyhemoglobin levels will also cause the slope of HR vs $\dot{V}O_2$ to become steeper than normal because of the decrease in maximal $C(a-v)O_2$. Because of ventilatory limitation, the HR at peak exercise may be below that predicted.

In the RLD patient, the LAT is low and the upper slope of the V-slope plot is exceptionally steep, reflecting the increase in $\dot{V}CO_2$ generated from HCO_3^- buffering of lactic acid when $\dot{V}O_2$ fails to increase normally. The slope of HR vs $\dot{V}O_2$ is very steep and HR commonly reaches its predicted maximum, leaving little or no HR reserve. Impaired ability to increase pulmonary blood flow, rather than the defect in ventilatory mechanics, limits exercise performance in many if not most patients with RLD.¹²

Breathing Reserve and Pattern (Panel 7): The pattern of increase in V_T relative to the increase in $\dot{V}E$ can be visualized in panel 7. $\dot{V}E$ increases during exercise until it reaches the MVV in symptomatic COPD-A and COPD-S patients, leaving no breathing reserve. Note that there is no relationship between resting spirometry measurements and the ventilatory requirement for exercise, because some patients have a very high V_D/V_T and some may have a near normal V_D/V_T . Thus, resting spirometry does not necessarily predict the breathing reserve for a

given level of exercise. In the COPD patient, V_T increases predominantly at low work rates, and then breathing frequency increase becomes progressively more important. V_T generally remains below the IC, as is the case in normal subjects. In the RLD patient, V_T reaches its maximal value at a relatively low exercise level. The upper limit for V_T increase is usually the IC. Thus, respiratory rate increase is usually greater in the RLD patient than in the COPD patient.

\dot{V}/\dot{Q} Mismatching (Panels 4, 6, and 9): Patients with COPD generally have a modestly elevated \dot{V}_E/\dot{V}_{CO_2} at the LAT or maximum work rate because of mismatching of \dot{V}/\dot{Q} . The $PETCO_2$ is low, reflecting the function of the high \dot{V}/\dot{Q} lung units which compensate for the CO_2 retention of the low \dot{V}/\dot{Q} lung units, the net effect usually being arterial eucapnia. In some patients with hypercapnia, \dot{V}_E/\dot{V}_{CO_2} may be normal, with the overall hypoventilation masking the effect of high \dot{V}/\dot{Q} lung units. However, some patients with COPD have a large amount of pulmonary vascular occlusive disease. Thus, high \dot{V}/\dot{Q} lung units (high V_D/V_T) make a large contribution to overall ventilation. This forces ventilation to be high for a given metabolic rate as reflected by an exceptionally high \dot{V}_E/\dot{V}_{CO_2} (panel 6) and a steep slope of \dot{V}_E vs \dot{V}_{CO_2} (panel 4). RLD patients usually have a considerable loss of pulmonary capillary bed relative to loss of airways. This results in a preponderance of high \dot{V}/\dot{Q} lung units. Therefore, \dot{V}_E/\dot{V}_{CO_2} is especially high in RLD patients. Because of the high \dot{V}/\dot{Q} lung units, $PETCO_2$ will tend to be low, without evidence of acute hyperventilation, as deduced from a normal R (panel 8). The greater contribution of high \dot{V}/\dot{Q} lung units to overall ventilation, the steeper will be the plot of \dot{V}_E vs \dot{V}_{CO_2} .

Diagnoses Uniquely Made by Cardiopulmonary Exercise Testing

Severe Pulmonary Vascular Disease Without Pulmonary Hypertension: Most patients limited in exercise because of pulmonary vascular disease have shortness of breath with exercise before they have the resting physical signs of pulmonary hypertension. Once the signs of pulmonary hypertension are present, the patient has occluded most of his or her functional pulmonary circulation, their clinical condition is quite tenuous, and the physician has lost the opportunity to perform simple diagnostic studies or intervene with specific treatment modalities. The test method that should be most sensitive in revealing developing pulmonary vascular occlusive disease is CPET, because the patient's symptoms are present

during exercise. While the pulmonary blood flow may be adequate at rest, these patients have difficulty in increasing pulmonary blood flow appropriately in response to exercise, resulting in exercise-induced symptoms. During exercise, $\dot{V}O_2$ usually fails to continue to increase with a normal slope of 10 mL/min/W, but the slope progressively decreases to the point of fatigue when there may be no further rise (panel 3). The peak $\dot{V}O_2$ (panel 3) and LAT (panel 5) probably provide the best quantitation of severity of the illness. A steep HR response and low O_2 -pulse will be evident in panel 5 and 2, respectively. Panel 6 would show a high value for \dot{V}_E/\dot{V}_{CO_2} at the LAT, reflecting decreased perfusion to ventilated lung (high \dot{V}/\dot{Q}). Arterial blood gases displayed on panel 9 with end-tidal O_2 and CO_2 and calculation of V_D/V_T would further characterize the abnormal physiologic state.

Foramen Ovale Patency With Development of a Right to Left Shunt During Exercise: The anatomy books report that 25% of the population have a potentially patent foramen ovale. However, this is unimportant unless such a person develops right atrial pressures that exceed left atrial pressures. The latter can develop in patients with primary pulmonary vascular disease or pulmonary vascular disease secondary to lung disease. But even with these disorders and a potentially patent foramen ovale, the patient may not shunt venous right atrial blood into the left atrium at rest, only during exercise. If the increase in venous return during exercise exceeds the rate that the right ventricle can pump blood into the pulmonary circulation, right ventricular end-diastolic and therefore right atrial pressure will increase above the resting value. When right atrial pressure exceeds left atrial pressure during exercise, systemic venous blood can enter the left atrium causing rapid systemic arterial oxygen desaturation through a patent foramen ovale. This can take place despite a normal or near-normal arterial oxyhemoglobin saturation at rest. The exercise test repeated during 100% O_2 breathing with arterial blood sampling allows this diagnosis to be confirmed. Panels 3, 4, 6, and 9 would be particularly revealing of this diagnosis. Not only is CPET a specific test for this diagnosis, but it is a test with minimal morbidity and relatively small cost.

CONCLUSION

Evidence has been presented showing how CPET can be used, as a single method, to discriminate among nonanginal myocardial ischemia, CM, and PAD as the major pathophysiology limiting exercise in patients with cardiovascular disease. Similarly, CPET is the only method that can discern if a given pulmonary function impairment limits exercise; it would also seem to be the

best noninvasive method to determine if a patient is likely to benefit from an exercise training program which can be expected to reduce the exercise-induced lactic acidosis. It is also useful for defining the dominant disorder and directing therapy in patients with multiple illnesses. In addition, it is uniquely valuable for making some diagnoses such as the development of a right to left shunt during exercise, demonstrating that pulmonary vascular occlusive disease is limiting exercise and detecting myocardial dyskinesia limiting exercise (increasing work rate and heart rate without an appropriate increase in $\dot{V}O_2$) in ischemic heart disease patients.

In summary, diseases of the cardiovascular system and the lungs translate into abnormal gas exchange during exercise (Fig 1). There is also evidence that peak $\dot{V}O_2$ and the LAT may provide the best quantitation of the degree of impairment in cardiovascular function,¹³⁻¹⁵ and probably at the least cost. Therefore CPET, with measurements of gas exchange, should play a major role in the evaluation of patients with cardiovascular and lung diseases when the cause of exercise intolerance due to dyspnea or fatigue is uncertain. Also, it is likely to be especially valuable in determining the severity of functional limitation. Patients with cardiovascular and/or pulmonary defects commonly go to their physician because of exercise intolerance. Given the fact that the primary roles of the cardiovascular system and ventilatory system are gas exchange between the cells and the air, it is remarkable that so few patients undergo CPET before they undergo much more expensive imaging and invasive tests. It is important for physicians to appreciate that CPET is a powerful diagnostic tool with great decision-making value in guiding the management of patients with cardiovascular and lung diseases.

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