Dyspnea on Exertion

Is It the Heart or the Lungs?

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DYSPNEA is a sensation, a symptom, a complaint on the part of the patient of not being able to breathe enough or having to breathe too much, or, simply, an abnormal, uncomfortable feeling during breathing. Exertional dyspnea is the most common symptom of patients with pulmonary and cardiovascular diseases and the diseases of the pulmonary circulation. Since dyspnea during exercise precedes dyspnea at rest, exercise testing can expose cardiovascular and lung disease at an earlier stage if the patient is examined during exercise.

Our understanding of the factors that cause dyspnea with exercise has greatly improved since measurement of gas exchange and ventilation during exercise has been made reliable and easy by the development of new transducers and minicomputers. Not only has insight been gained into the mechanisms of dyspnea, but we have learned how to use exercise tests to distinguish between its various clinical causes. This review describes the gas-exchange requirements to perform exercise and how their impairment might induce dyspnea.

OVERVIEW OF EXERCISE PHYSIOLOGY

Figure 1 shows the physiological requirements to perform work. Oxygen is consumed in the muscle mitochondria through oxidative processes to produce chemical energy in the form of adenosine triphosphate (ATP) with carbon dioxide (CO_2) as the major by-product. Very little oxygen (O_2) is stored in the tissues. Therefore, muscle blood flow must increase almost immediately to resupply the O_2 consumed. This must be continued to allow ATP generation and exercise to be ongoing. Thus, at the start of exercise, the circulation to the exercising muscles must increase through vasodilation. This dilation seems to be under central sympathetic control initially, but under local humoral control later. The cardiac output is increased at the start of exercise by an increase in stroke volume and heart rate. Stroke volume increases to its maximum as soon as exercise begins, while further increases in cardiac output occur by increasing heart rate as the O_2 requirement is increased. In response to the increase in right ventricular output, the pulmonary circulation dilates primarily by recruiting unperfused or underperfused lung units. This dilation is essential for the normal exercise response of the left ventricle, since without it, the weakly muscled right ventricle could not readily pump the increased venous return through the lungs to the left atrium to effect an increased left ventricular output.

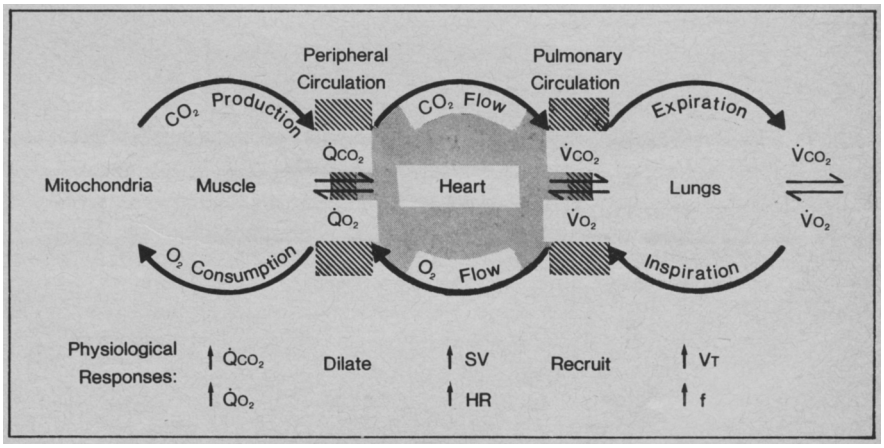
Ventilation increases in proportion to the increased pulmonary blood flow immediately at the start of exercise. This allows gas exchange between the pulmonary capillaries and the alveoli to increase appropriately to reoxygenate the blood and to eliminate the excess CO_2. The increase in ventilation is accomplished, primarily, by increasing tidal volume at low and moderate work rates and breathing frequency at high work rates.

The cardiorespiratory adaptation that occurs at the start of exercise persists as the O_2 uptake approaches a steady state. It is so precisely coupled to cellular metabolism that arterial pH, P_{CO_2}, and P_{O_2} homeostasis is maintained through moderate work levels. The only acid-base disturbance that normally occurs during exercise is a metabolic acidosis seen only during heavy work.

OXYGEN COST OF WORK

The oxygen cost of doing work depends on the work rate. Figure 2 shows an example of the oxygen consumption ($\dot{V}O_2$) for varying levels of

Fig 1.—Physiological responses to exercise. Physiological mechanisms interact to enable oxygen (O_2) uptake ($\dot{V}O_2$) and carbon dioxide (CO_2) output ($\dot{V}CO_2$) to equal muscle O_2 consumption ($\dot{Q}O_2$) and CO_2 production ($\dot{Q}CO_2$). SV indicates stroke volume; HR, heart rate; V_T, tidal volume; and f, frequency.



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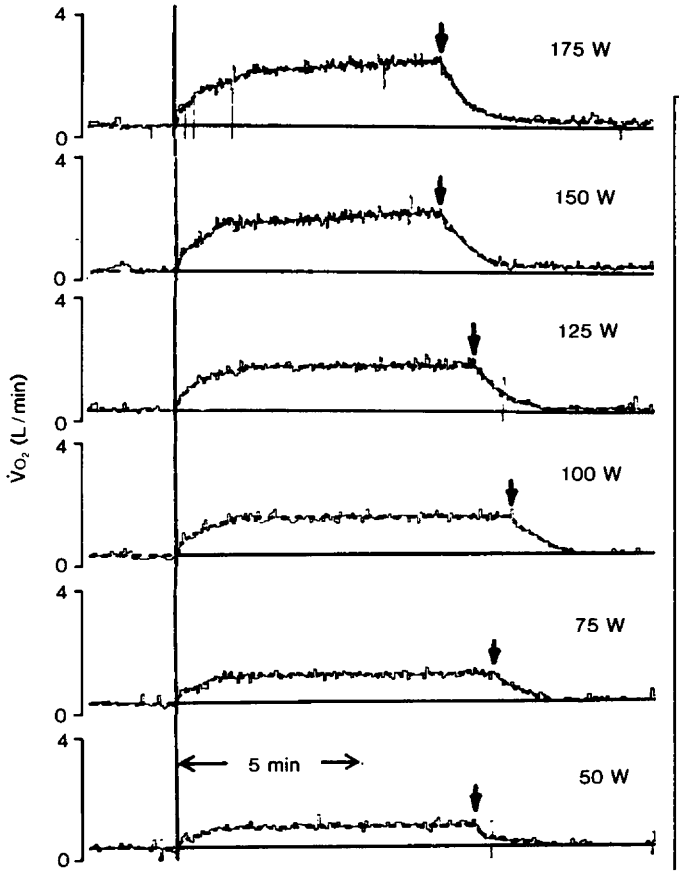
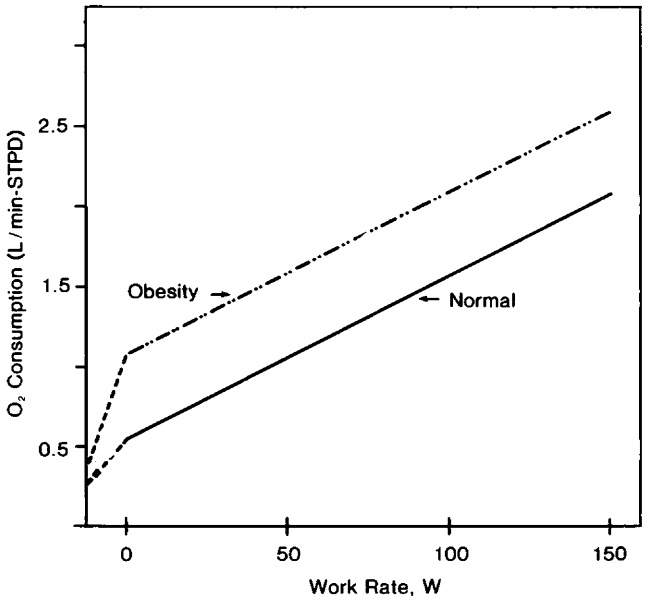


Fig 2.—Oxygen uptake kinetics as related to work rate. Illustration from Whipp and Wasserman,[6] reprinted with permission from the *Journal of Applied Physiology.*

Fig 3.—Oxygen (O_2) cost ($\dot{V}O_2$) of performing cycle ergometer work. Slope of work rate-$\dot{V}O_2$ relationship is same for all people and unaffected by training, age, or gender. However, relation is displaced upward by increasing weight. Predicted $\dot{V}O_2$=5.8×body weight (kg)+151+10.1×watts.[1] STPD indicates standard temperature and pressure, dry.



cycle ergometer work as related to time for a normal person. Note that a steady state is reached by two to three minutes at work rates that are not very intense. At high work rates, $\dot{V}O_2$ continues to increase slowly beyond the initial three minutes (Fig 2).

If the steady-state $\dot{V}O_2$ is plotted against its respective work rate, a linear relationship between $\dot{V}O_2$ and work rate is obtained, as shown in Fig 3. This slope relationship is the same for all normal persons. This means that work efficiency in man is fixed for a given work task. However, while the slope of the $\dot{V}O_2$-work rate relationship is not affected by training, age, or gender, its displacement is dependent on the weight of the subject. Thus, for unloaded cycling, the O_2 cost is for moving the legs.[1]

ANAEROBIC THRESHOLD AND LACTIC ACID PRODUCTION

Exercise requires an increase in O_2 flow to the exercising muscles to enable muscle O_2 utilization to increase sufficiently for walking (×20), jogging (×40), or running (×60). Since 25% of the O_2 is ordinarily removed from the arterial blood by the muscle to support resting muscle metabolism, it is clear that the increased O_2 requirement of exercise could be met only if blood flow to the active muscles was increased. When the oxygen requirement to the exercising muscle cannot be totally supported by oxygen delivery, the aerobic oxidative mechanism must be supplemented by anaerobic mechanisms to the extent to which this is possible. This is accomplished by the conversion of pyruvate to lactate in the cells (Fig 4). The increase in lactic acid is immediately buffered in the cell by bicarbonate ion (HCO_3) with the release of CO_2 (Fig 4). The work level at which anaerobic oxidation becomes evident is usually distinct and at a consistent $\dot{V}O_2$ for a given work task. Therefore, this work-rate threshold, above which the anaerobic mechanisms supplement the aerobic, has been termed the "anaerobic threshold."[2] The shift in the muscle cell oxidation-reduction potential to a more reduced or anaerobic state is reflected not only by an increase in lactate, but also by an increase in the lactate-pyruvate ratio.

The fit subject does not increase his blood lactate level until his working oxygen consumption is quite high (>10 times resting $\dot{V}O_2$). In contrast, sedentary persons start to increase their lactate at work rates that generally just exceed the $\dot{V}O_2$ required for ordinary walking (approximately 4 times rest). On the other hand, patients with New York Heart Association class II to III heart disease increase their lactate levels with minimal activity ($\dot{V}O_2$ <2 times resting).

While the production of lactate benefits the patient by allowing him to walk limited distances at work levels above which the cardiovascular system is capable of supplying the entire oxygen need, it has disturbing effects on breathing in two ways: (1) the added amount of CO_2 produced from the buffering of lactic acid by bicarbonate adds an additional CO_2 load to the respiratory system that must be eliminated to prevent arterial P_{CO_2} from rising, and (2) the increased hydrogen ion concentration caused by the reduction of blood bicarbonate stimulates the respiratory control mechanism (carotid bodies) to cause a further ventilatory increase, thereby lowering arterial P_{CO_2} and providing respiratory compensation for the metabolic acidosis.

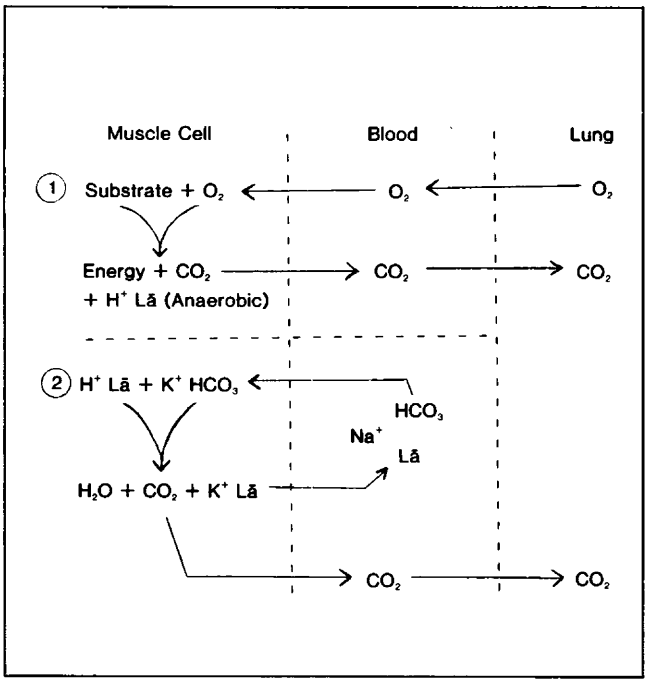


Fig 4.—Effect of exercise above anaerobic threshold on carbon dioxide (CO_2) production and blood bicarbonate. Extra CO_2 is generated from bicarbonate (HCO_3) as lactate (Lā) is produced in cell. Extracellular bicarbonate diffuses into cell by chemical gradient as lactate diffuses out. O_2 indicates oxygen; H^+, hydrogen ion; K^+, potassium ion; Na^+, sodium ion; and H_2O, water.

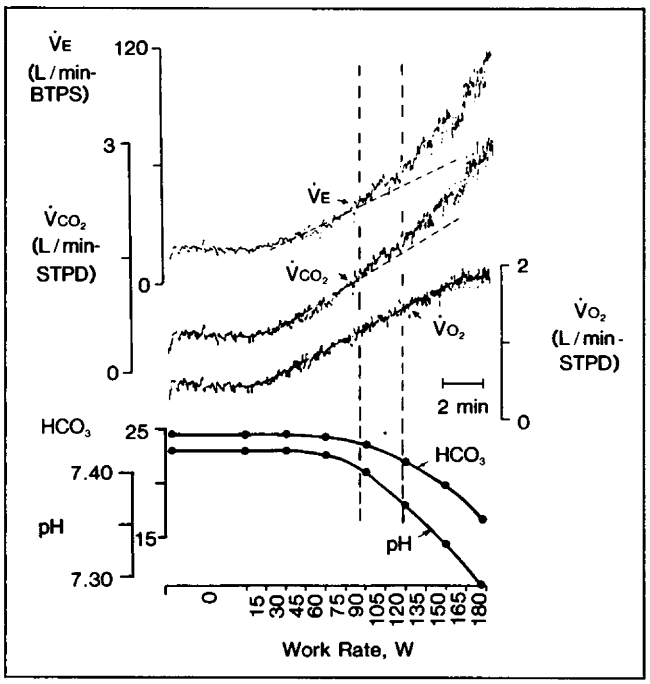


Fig 5.—Gas exchange as work rate is incremented. At anaerobic threshold (left dashed line), carbon dioxide output ($\dot{V}_{CO_2}$) and minute ventilation ($\dot{V}_E$) increase more rapidly than oxygen uptake ($\dot{V}_{O_2}$). After a few minutes (right dashed line), increased acidemia causes $\dot{V}_E$ to increase more rapidly than $\dot{V}_{CO_2}$. BTPS indicates body temperature, pressure, saturated; STPD, standard temperature and pressure, dry; and HCO_3, bicarbonate ion.

Table 1.—Effect of Work Below and Above the Anaerobic Threshold (AT) on Exercise Responses

Measurement	Below AT	Above AT
Exercise duration	Prolonged; limited by joints and substrate	Short; limited by fatigue or dyspnea
$\dot{V}_{O_2}$ steady-state time	<3 min	>3 min or none
$\dot{V}_E$, $\dot{V}_{CO_2}$ steady-state time	<4 min	>4 min or none
pH	Approx 7.4	Metabolic acidosis
P_{aCO_2} ($P_{ET}CO_2$)*	Constant	Decreasing

*$P_{ET}CO_2$ indicates arterial or end tidal carbon dioxide partial pressure on tension.

Figure 5 shows the effect of increasing work rate on ventilation and gas exchange for a cycle ergometer exercise test in which the work rate increments were increased at one-minute intervals after a four-minute pedaling warm-up without load. As the work rates are incremented, oxygen consumption, CO_2 output, and ventilation rate increase linearly until the anaerobic threshold is reached. At work rates above the anaerobic threshold, CO_2 output increases more rapidly than oxygen uptake because CO_2 generated from the bicarbonate buffering of lactic acid is added to the metabolic CO_2 production. Ventilation rate initially tracks the increased CO_2 production. However, as work rate is incremented further, ventilation rate starts to increase even more rapidly than CO_2 output, causing P_{aCO_2} to decrease, thereby providing respiratory compensation for the exercise-induced lactic acidosis. Because the symptom of dyspnea is critically dependent on the ventilatory response to exercise, it is important to evaluate the magnitude of the ventilatory stimulus caused by metabolic acidosis in the dyspneic patient. As demonstrated in Fig 5, the metabolic acidosis contributes a major ventilatory drive.

Methods are now available to determine the anaerobic threshold noninvasively and quickly from gas-exchange methods.[3] It is the best measurement that we have to demarcate the level of work that a patient could sustain for a prolonged period. Thus, work performed below the anaerobic threshold for that task could be done in a steady state and be endured by the patient. Work performed above the anaerobic threshold cannot be endured for long periods. The higher the level of work above the anaerobic threshold, the shorter is the work time. Table 1 contrasts the exercise responses for work above and below the anaerobic threshold.

DYSPNEA-CAUSING SYNDROMES

All causes of dyspnea of an organic basis interfere with O_2 flow to the exercising muscles, CO_2 elimination, or both (Fig 1). Table 2 lists dyspnea-causing syndromes and the primary pathophysiological mechanisms that cause patients with these syndromes to experience exertional dyspnea. In this review, only disorders of the heart and lungs will be discussed. The reader may obtain information on other syndromes from reference 1.

Heart Diseases

Heart diseases (coronary, valvular, or primary myocardial) all have as their basic defect the problem of limited cardiac output (O_2 flow) during physical stress, primarily caused by a reduced stroke volume. To compensate for the relatively low stroke

Table 2.—Disorders Limiting Exercise Performance, Pathophysiology, and Discriminating Measurements*

Disorders	Pathophysiology	Measurements That Deviate From Normal
Pulmonary		
Airflow limitation	Mechanical limitation to ventilation, mismatching of $\dot{V}_A/\dot{Q}$, hypoxic stimulation to breathing	$\dot{V}_E$ max/MVV, expiratory flow pattern, V_D/V_T; $\dot{V}O_2$ max, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E$ response to hyperoxia, (A-a)P_{O_2}
Restrictive	Mismatching $\dot{V}_A/\dot{Q}$, hypoxic stimulation to breathing	
Chest wall	Mechanical limitation to ventilation	$\dot{V}_E$ max/MVV, P_{aCO_2}, $\dot{V}O_2$ max
Pulmonary circulation	Rise in physiological dead space as fraction of V_T, exercise hypoxemia	V_D/V_T, work-rate-related hypoxemia $\dot{V}O_2$ max, $\dot{V}_E/\dot{V}O_2$, (a-ET)P_{CO_2}, O_2-pulse
Cardiac		
Coronary	Coronary insufficiency	ECG, $\dot{V}O_2$ max, anaerobic threshold $\dot{V}O_2$, $\dot{V}_E/\dot{V}O_2$ O_2-pulse, BP (systolic, diastolic, pulse)
Valvular	Cardiac output limitation (decreased effective stroke volume)	
Myocardial	Cardiac output limitation (decreased ejection fraction and stroke volume)	
Anemia	Reduced O_2 carrying capacity	O_2-pulse, anaerobic threshold $\dot{V}O_2$, $\dot{V}O_2$ max, $\dot{V}_E/\dot{V}O_2$
Peripheral circulation	Inadequate O_2 flow to metabolically active muscle	Anaerobic threshold $\dot{V}O_2$, $\dot{V}O_2$ max
Obesity	Increased work to move body; if severe, respiratory restriction and pulmonary insufficiency	$\dot{V}O_2$-work rate relationship, P_{aO_2}, P_{aCO_2}, $\dot{V}O_2$ max
Psychogenic	Hyperventilation with precisely regular respiratory rate	Breathing pattern, P_{CO_2}
Malingering	Hyperventilation and hypoventilation with irregular respiratory rate	Breathing pattern, P_{CO_2}
Deconditioning	Inactivity or prolonged bed rest; loss of capability for effective redistribution of systemic blood flow	O_2-pulse, anaerobic threshold $\dot{V}O_2$, $\dot{V}O_2$ max

*$\dot{V}_A$ indicates alveolar ventilation; $\dot{Q}$, pulmonary blood flow $\dot{V}_E$, minute ventilation; MVV, maximum voluntary ventilation; V_D/V_T, physiologic dead space/tidal volume ratio; O_2, oxygen; $\dot{V}O_2$, O_2 consumption; (A−a)P_{O_2}, alveolar-arterial P_{O_2} difference; and (a−ET)P_{CO_2}, arterial-end tidal P_{CO_2} difference.

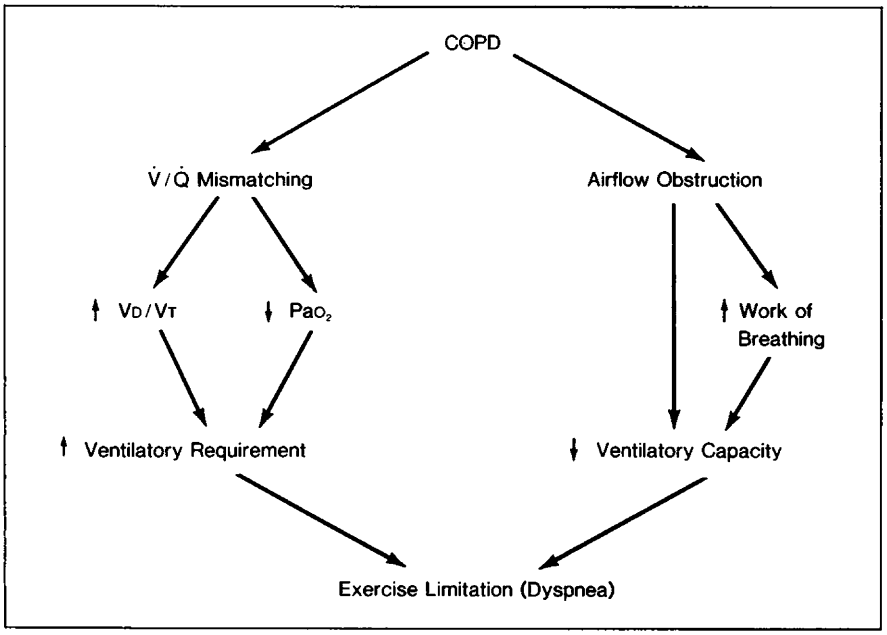


Fig 6.—Pathophysiology of exercise limitation in patients with chronic obstructive pulmonary disease (COPD). V_D/V_T indicates physiologic dead space/tidal volume ratio; $\dot{V}/\dot{Q}$, ratio of ventilation to perfusion in lung gas exchange units. Illustration from Brown and Wasserman,[6] reprinted with permission from WB Saunders Co.

volume, a fast heart rate and a wide arteriovenous O_2 difference (decreased capillary P_{O_2}) generally develop at an inappropriately low work rate. Therefore, the exercising muscles, skeletal and myocardial, have increased difficulty getting an adequate oxygen supply to perform the required work, and dyspnea, fatigue, or pain ensues. The lactic acidosis resulting from the low O_2 delivery to the muscles becomes detectable by noninvasive gas-exchange methods[3] almost immediately after it occurs in the cells (Fig 4). Besides detecting a low anaerobic threshold in the patient with heart disease, abnormalities of heart function could be detected by measuring $\dot{V}O_2$ during exercise. The Fick equation for calculating cardiac output ($\dot{V}O_2 = CO \times [a-v]O_2$) defines that a change in $\dot{V}O_2$ is a measure of a change in cardiac function, since cardiac output (CO) change and arteriovenous O_2 difference ($[a-v]O_2$) change are dependent on cardiac function and are independent of pulmonary function except in some unusual ways in which the lungs might affect cardiac performance. At the start of exercise, CO increases immediately if stroke volume and heart rate increase. The (a−v) O_2 does not start to widen for about 20 s. Therefore, the increase in $\dot{V}O_2$ during the first few seconds of exercise is due to an increase in CO (primarily stroke volume). Since stroke volume is constant after the start of exercise, further increases in $\dot{V}O_2$ are due to the increase in heart rate and (a−v) O_2. If the patient's $\dot{V}O_2$ does not continue to rise as work rate is increased during an incremental exercise test, (a−v) O_2 and CO have reached their maxima.

A failure of $\dot{V}O_2$ to rise in a linear predictable manner as shown in Fig 5 is indicative of cardiac disease. The $\dot{V}O_2$ will rise *linearly* in sedentary or pulmonary patients to its reduced maximum, since neither CO nor (a−v) O_2 limits these patients. While $\dot{V}O_2$ might level off at a subnormal maximal work rate in the cardiac patient (low $\dot{V}O_2$ max), $\dot{V}CO_2$ will continue to increase in an even steeper slope relative to $\dot{V}O_2$ because the increased lactic acid production is buffered immediately by bicarbonate. A low-work-rate metabolic acidosis and decreasing or flattening slope of $\dot{V}O_2$ below the predicted maximum work rate during an incremental exercise test are specific for a cardiovascular and not a pulmonary limitation.

Table 3.—Stimuli That Might Induce Dyspnea
Chemical—pH, $Paco_2$, Pao_2
Cardiovascular pressures—PA, RV, RA*
Mechanoreceptors of the lungs
Mechanoreceptors of the chest wall
Muscle or joint motion (?)
Corticogenic hyperventilation

*PA indicates pulmonary artery; RV, right ventricle; and RA, right atrium.

Primary cardiac limitation to exercise can be detected by (1) evidence of a low anaerobic threshold, (2) the failure of $\dot{V}O_2$ to increase at the start of exercise (no or little increase in stroke volume), (3) a decreasing or flattening of $\dot{V}O_2$ at a submaximal work rate, as work rate is incremented, and (4) a low O_2-pulse ($\dot{V}O_2$ normalized for heart rate [HR], ie, $\dot{V}O_2/HR=SV\times[a-v]O_2$) during exercise, where SV indicates stroke volume.

The ECG is an essential measurement during exercise, in that along with chest pain it provides the best noninvasive evidence of coronary artery disease. However, many cardiac patients are not limited by coronary artery disease, but are limited instead by valvular or cardiomyopathy heart disease, diseases of the pulmonary circulation, or pulmonary causes, and the ECG will not reveal the nature of the patient's defect. Even if the patient has coronary artery disease, measurement of the work level at which O_2 transport becomes limiting and curtails O_2 utilization provides a valuable assessment of the patient's functional limitation and reserve.

Pulmonary Diseases

Disorders of the lungs or chest wall generally prevent external respiration from keeping pace with internal respiration (in the cells) because of mechanical limitations. The symptom limiting exercise in the pulmonary patient is almost always dyspnea, and this is because of the difficulty that the pulmonary patient has in eliminating CO_2 generated by metabolism. Arterial Pco_2 is closely regulated because it so critically affects arterial pH. In contrast, the shape of the oxyhemoglobin dissociation curve allows arterial O_2 content to be well maintained at low Pao_2 levels seen in many pulmonary patients who are still ambulatory (Pao_2 >55 mm Hg). Figure 6 conceptualizes the pathophysiology leading to dyspnea in patients with chronic obstructive pulmonary diseases (COPDs). Dyspnea depends on a balance between how much air must be breathed to eliminate the CO_2 being produced by metabolism and how much can be breathed. The maximum voluntary ventilation (MVV) is used as the measure of ventilatory capacity, and the $\dot{V}E$ at maximal exercise is used as the measure of the ventilatory requirement for that work rate. The breathing reserve is the difference between the $\dot{V}E$ at maximal work and the MVV. This value is close to zero in the patients with COPD. Persons without lung disease have a substantial reserve (approximately 40% of their MVV).

The features of dyspnea-limiting exercise in patients with COPD can be summed up by the two factors diagramed in Fig 6—decreased ventilatory capacity and increased ventilatory requirement. The decreased ventilatory capacity is caused by increased airway obstruction commonly combined with reduced lung elastic recoil and increased work of breathing. The increased ventilatory requirement is primarily caused by mismatching of ventilation to perfusion. The latter causes certain regions of the lungs to be hypoventilated while others are hyperventilated, and this has the effect of increasing the fraction of the breath that is wasted or physiological dead space. Simultaneously, the underventilated areas of the lungs cause arterial hypoxemia, which stimulates ventilation by its action on the carotid bodies. This tends to keep $Paco_2$ at a lower level than would be the case if the carotid bodies were not stimulated.

DYSPNEA-CAUSING STIMULI

The dyspnea-causing stimuli are the same ones that stimulate ventilation[4] and are summarized in Table 3. Only one or several may be active at a time. The patient with pulmonary disease is usually dyspneic from hypoxic or hypercapnic stimuli, while the patient with heart disease usually has a metabolic acidosis-induced hydrogen ion stimulus.

However, the cardiac patient may also have development of high pressures at sites within the heart (right side) or pulmonary circulation that have been shown in experimental animals to contain mechanoreceptors that, when stimulated, might cause breathing to be increased. Receptors in the lung itself, whose afferents run in the vagus, might also stimulate breathing. Receptors in the exercising extremities sensitive to motion or chemical factors are less likely to be important. However, stimuli from the cerebral cortex may induce psychogenic dyspnea associated with bizarre breathing patterns and hyperventilation.

To sense dyspnea, the patient must have the stimulus and a respiratory center that responds to the stimulus despite the patient's inability to provide an adequate ventilatory response because of mechanical limitations.

COMMENT

Exercise stresses both the cardiovascular and ventilatory systems simultaneously. Both organ systems act in concert to provide the external respiration needed to support the internal respiration of the cells. When the cardiovascular system fails to perform adequately, the ventilatory response is changed. The respiratory system is a "window" through which cardiovascular performance can be viewed noninvasively. While dyspnea is a symptom common to patients with either heart or lung diseases, it is usually possible to distinguish between these two large groups of disorders by studying discriminating measurements that are capable of describing the adequacy of the patient's circulation and ventilation in meeting the gas-exchange requirements of exercise.

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References

1. Wasserman K, Whipp BJ: Exercise physiology in health and disease. *Am Rev Respir Dis* 1975;112:219-249.

2. Wasserman K, Whipp BJ, Koyal SN, et al: Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 1973; 35:236-243.

3. Wasserman K, Whipp BJ, Davis JA: Respiratory physiology of exercise: Metabolism, gas exchange and ventilatory control, in Widdicombe JG (ed): *Respiratory Physiology III*, vol 23, in *International Review of Physiology*. Baltimore, University Park Press, 1981, pp 149-211.

4. Guz A: Regulation of respiration in man. *Annu Rev Physiol* 1975;37:303-323.

5. Whipp BJ, Wasserman K: Oxygen uptake kinetics for various intensities of constant-load work. *J Appl Physiol* 1972;33:351-356.

6. Brown HV, Wasserman K: Exercise performance in chronic obstructive pulmonary diseases. *Med Clin North Am* 1981;65:525-547.