Physiology of gas exchange and exertional dyspnoea

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Introduction

Exercise is a problem in gas transport between the cells (predominantly the mitochondria) and the atmosphere. In the adequately nourished patient the cells contain sufficient substrate for energy to support moderate exercise for many hours, but less than a minute's worth of ready-to-use chemical energy and oxygen (for the conversion of substrate into chemical energy). Therefore to perform exercise the increased transport of oxygen to the exercising muscles must be rapid, adequate and sustained. Simultaneously, the carbon dioxide produced in the various decarboxylation steps in the conversion of substrate into chemical energy must be continuously removed to prevent cellular respiratory acidosis and impairment of cellular function. The increased cell respiratory requirements during exercise must be accompanied by appropriate cardiovascular and ventilatory responses to match pulmonary gas exchange with cell respiration. The consequences of inappropriate responses might be anaerobic energy production (lactic acidosis) or carbon dioxide retention or both [1].

Fig. 1 illustrates the coupling of the cardiovascular and respiratory systems to the gas exchange requirements of the cells. Virtually all the oxygen is used in the mitochondria for generation of adenosine triphosphate (ATP) from adenosine diphosphate (ADP), the essential chemical which is capable of immediate transfer of its energy to the muscle contractile elements to achieve muscle contraction. Most of the carbon dioxide is generated by decarboxylation steps in the tricarboxylic acid cycle in the mitochondria. Cardiac output and ventilation rates are remarkably attuned to the rate of oxygen consumption and carbon dioxide production respectively, so that during moderate exercise of even prolonged duration neither a lactic acidosis nor a respiratory acidosis or alkalosis develops [2]. In contrast, work rates of heavy intensity or greater result in a lactic acidosis with a disproportionately increased ventilatory response.

Normal cardiovascular and ventilatory responses

Fig. 1 illustrates, schematically, the coupling of the circulatory and ventilatory functions to muscle metabolism. The performance of both organ systems increased in proportion to the level of the exercise metabolic rate. The cardiac output increases proportionately to the increase in \( V' \), the magnitude being dependent on the change in arterial — venous oxygen difference with increasing level of work. Thus an individual capable of redistributing the cardiac output to the most metabolically active cells would require the smallest increase in cardiac output. The heart rate also increases linearly with metabolic rate, since the stroke volume remains relatively fixed after its initial increase once exercise starts [3].

The ventilatory increase in response to exercise must be precise to maintain pH homeostasis. Thus alveolar ventilation is accurately predicted in normal people for moderate exercise from the carbon dioxide production and the level at which \( PaCO_2 \) is regulated [2]. Minute ventilation is also predictable for normal subjects, because the dead space fraction of the minute ventilation (\( V'd \)) is usually less than 0-20 and varies only slightly with changing levels of work. It is only with high intensity work, when lactic acidosis develops, that ventilation increases disproportionately rapidly relative to metabolic rate. In man this added hyperpnoea in response to the increased H+...
stimulus is known to act through the carotid bodies, allowing partial correction of the acidosis [4].

**Lactic acid production**

Work performed at levels above which blood lactic acid increases is considered to be of heavy work intensity. Obviously, this work level varies from subject to subject according to their relative fitness. Thus in a fit subject the work rate above which blood lactic acid shows a sustained increase would be higher than that for an unfit subject. In patients, with diseases which limit oxygen delivery to the exercising muscles, lactate increases in the blood at lower work levels than for normal people. This work rate is of such great importance that we identify it in all exercise studies, if possible. We refer to this level of oxygen consumption ($\dot{V}O_2$) as the anaerobic threshold.

Above the anaerobic threshold $\dot{V}O_2$, the ventilatory and gas exchange responses do not reach the early steady state that is observed for work rates below the anaerobic threshold $\dot{V}O_2$; hyperventilation ($\dot{P}a\text{,}[\text{CO}_2]$) occurs and the duration for which exercise can be sustained is reduced [5]. Work above the anaerobic threshold is difficult to maintain because the increased $H^+$ concentration stimulates ventilation, causing it to continuously drift upward and $Pa\text{,}[\text{CO}_2]$ downward. Thus the level of work which a subject can perform comfortably for long periods, such as a work shift, is at or below the anaerobic threshold $\dot{V}O_2$. One might attain a steady state in $\dot{V}O_2$ at work rates in small excess of the anaerobic threshold $\dot{V}O_2$ but, when much above it ($>30\%$), a steady state in $\dot{V}O_2$ cannot be achieved.

**Justification for the term 'anaerobic threshold'**

Careful studies of blood lactate concentration during exercise indicate that lactic acid does not show a sustained increase in systemic blood until a work-rate threshold is exceeded [6, 7, 8]. 'Anaerobic' was selected to describe this work-rate threshold because (1) the increase in lactate occurs at a work rate at which the oxygen debt increases disproportionately to work rate and the lactate increase can be equated to this increase in oxygen debt [6], (2) the time to reach a $\dot{V}O_2$ steady state is delayed above this work-rate threshold [1, 9], (3) patients with impaired blood flow (patients with cardiac disease) increase their blood lactate at very low work rates [1], (4) the threshold is related to work capacity and fitness [10, 11], (5) during exercise hyperoxia reduces blood lactate [12] and increases the anaerobic threshold, whereas hypoxia lowers it [13], (6) anaemia (decreased oxygen carrying capacity) created in normal subjects causes the lactate level to increase during exercise [14], (7) the arterial blood lactate increase is accompanied by an increase in the lactate/pyruvate ratio demonstrating that the oxidation-reduction potential is reduced [5, 9] and (8) when a given work rate is below the threshold in one subject and above in another (less fit) the $\dot{V}O_2$ for the less fit subject is reduced compared with the more fit at any time before a steady state is reached (<3 min) [9]. When this work rate is sustained by the less fit subject, $\dot{V}O_2$ continues to increase. The latter phenomenon is best explained by increased...
perfusion of the metabolically active muscles secondary to a local increase in $H^+$, thermal effects, decreased $Po_2$ or other skeletal muscle vasodilators [15].

While the observations described above provide strong evidence that the increase in arterial blood lactate during exercise is related to oxygen supply and the ability to utilize it, there is some controversy over the term 'anaerobic threshold'. Some investigators believe that the increase in arterial blood lactate is dependent on the fibre type contracting during exercise and is unrelated to oxygen supply or utilization [11]. Another argument is that oxygen supply may not be a factor but, rather, oxygen utilization is impaired because of a shortage of mitochondrial enzymes preventing adequate substrate oxidation. This could cause lactate to build up in the blood as a result of increased glycolysis [16].

Lactate is observed to increase during a given form of exercise when the intensity of the work is increased to a critical level, the level being higher the more fit the subject. In the case of the fibre type hypothesis there is no mechanistic basis to suggest that the fast twitch fibres, which are relatively rich in glycolytic pathway enzymes, start to contract at a work-rate threshold when the speed of cycling or walking remain unchanged. Also, the factors described above, which have been shown to affect lactate production, i.e. anaemia, low $Po_2$ etc., should not affect the contracting fibre type.

In the case of the mitochondrial enzyme hypothesis a shortage of mitochondrial enzymes could cause lactate to increase in the blood, but this should be associated with an increase in pyruvate and all other glycolytic intermediaries. However, when pyruvate is increased in the blood during exercise above the anaerobic threshold $Vo_2$, the increase is small; the anaerobic threshold is characterized as an increase in the lactate/pyruvate ratio which parallels the arterial blood lactate increase. The increase in the lactate/pyruvate ratio must be interpreted as a reduction in the cytosol and therefore mitochondrial oxidation-reduction potential.

The anaerobic threshold concept does not deny that lactate may be produced in excess in some muscles, while other muscles with a higher oxidation-reduction potential catabolize it. In fact, the anaerobic threshold concept implies that the net oxidative requirement-capacity balance can become negative during exercise so that the rate of production of lactate surpasses its rate of catabolism thus causing 'overflow' of lactate into the central circulation and a systemic lactic acidosis.

There are tricks that one could play on the glycolytic process to slow and speed glycolysis and change lactate in the blood to small degrees (e.g. pH change) [17]. However, large changes in lactate and the lactate/pyruvate ratio appear to occur with situations of increased oxygen demand such as with exercise, reduced oxygen supply (i.e. circulatory insufficiency) or disorders which impair the function of the cytochrome electron-transport chain [18].

**Anaerobic threshold and maximum $Vo_2$**

The anaerobic threshold $Vo_2$ contrasts with another measure of aerobic capacity, the maximum aerobic capacity ($Vo_2 max.$). These measurements differ in that the former is the maximum $Vo_2$ without an associated lactic acidosis and therefore can be sustained for very long periods, whereas the latter is the maximum oxygen consumption that the subject can possibly perform in spite of increasing work rate (plateau in $Vo_2$ while increasing work rate) and regardless of the lactate level [19]. It can be elicited only by performing very high work intensities, which cannot be sustained for more than a few minutes.

The anaerobic threshold $Vo_2$, like $Vo_2 max.$, can be measured by gas-exchange techniques. However, both measurements can be difficult to assess in certain patients. An anaerobic threshold may not be achieved in the patient forced to stop at a low work level because of airflow limitation, whereas it would be likely to be evident in the patient forced to stop exercise at the same work level from cardiac dysfunction. $Vo_2 max.$ in the sense that it is used by exercise physiologists, also may not be measurable in either the patient or the normal subject because of their unwillingness to push themselves to the associated discomfort and, in the case of the patient, the danger which accompanies exercise of this severity. While the anaerobic threshold $Vo_2$ has the significance of indicating the level above which (a) arterial blood lactate increases, (b) there is a delay steady state in $Vo_2$, $Vco_2$ and $VE$, (c) the maximum duration of work is curtailed and (d) the level of $VE$ becomes excessive for the metabolic requirement (respiratory compensation for metabolic acidosis), the $Vo_2 max.$ defines the maximal oxygen consumption with no specific indication as to whether the physiological limitation is that of the skeletal muscles, peripheral circulation, heart, pulmonary circulation, lungs or chest wall. Any component in the gas transport system can effect a reduction in $Vo_2 max.$ The anaerobic threshold $Vo_2$ is approximately 50% of the $Vo_2 max.$ in normal sedentary subjects; this percentage increases, however, with training [10].
TABLE 1. Disorders limiting exercise performance, pathophysiology and discriminating measurements

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Pathophysiology</th>
<th>Measurements that deviate from normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td></td>
<td>( \dot{V}_E \max./MVV ), expiratory flow pattern, ( \dot{V}_E/\dot{V}T ), ( \dot{V}_O_2 ) max., ( \dot{V}_E/\dot{V}O_2 ), response to hyperoxia, ( Pa,O_2-Pa,O_2 ), ( \dot{V}O_2 )-work rate relationship (oxygen cost of breathing)</td>
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<tr>
<td>Airflow limitation</td>
<td>Mechanical limitation to ventilation, mismatching of ( \dot{V}_A/\dot{Q} ), hypoxic stimulation of ventilation and stroke volume efficiency</td>
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<tr>
<td>Restrictive Alveolar filling</td>
<td>Mismatching ( \dot{V}_A/\dot{Q} ), hypoxic stimulation of ventilation</td>
<td>( \dot{V}_E \max./MVV ), ( Pa,CO_2 ), ( \dot{V}O_2 ) max.</td>
</tr>
<tr>
<td>Chest wall</td>
<td>Mechanical limitation to ventilation</td>
<td>( \dot{V}_E/\dot{V}T ), ( \dot{V}_O_2 ) max., ( \dot{V}_E/\dot{V}_O_2 ), (arterial end tidal) ( Pa,CO_2 ) oxygen pulse</td>
</tr>
<tr>
<td>Pulmonary circulation</td>
<td>Physiological dead space as fraction of ( \dot{V}_A ), exercise hypoxaemia</td>
<td>ECG, ( \dot{V}O_2 ) max., anaerobic threshold ( \dot{V}O_2 ), ( \dot{V}_E/\dot{V}O_2 ), oxygen-pulse, blood pressure (systolic, diastolic, pulse)</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
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<td>Coronary</td>
<td>Coronary insufficiency</td>
<td>Oxygen-pulse, anaerobic threshold ( \dot{V}O_2 ), ( \dot{V}_E/\dot{V}O_2 )</td>
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<tr>
<td>Valvular</td>
<td>Cardiac output limitation (effective stroke volume)</td>
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<tr>
<td>Myocardial</td>
<td>Cardiac output limitation (ejection fraction and stroke volume)</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Reduced oxygen flow to metabolically active muscle</td>
<td></td>
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<tr>
<td>Peripheral circulation</td>
<td>Inadequate oxygen flow to metabolically active muscle</td>
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<tr>
<td>Obesity</td>
<td>Increased work to move body; if severe, respiratory restriction and pulmonary insufficiency</td>
<td></td>
</tr>
<tr>
<td>Psychogenic</td>
<td>Hyperventilation with precisely regular respiratory rate</td>
<td></td>
</tr>
<tr>
<td>Malingering</td>
<td>Hyper- and hypo-ventilation with irregular respiratory rate</td>
<td></td>
</tr>
<tr>
<td>Deconditioning</td>
<td>Inactivity or prolonged bed rest; loss of capability for effective redistribution of systemic blood flow</td>
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Pathophysiology of exertional dyspnoea

It is of immense help to understand the physiology of gas exchange between the air and the mitochondria to appreciate the pathophysiology of exertional dyspnoea. Dyspnoea, functionally, appears to reflect an unsatisfied ventilatory drive. If the ventilatory requirement is not met, the drive to breathe is intensified causing \( \dot{V}_E \) and, particularly, respiratory rate to increase until the subject achieves ventilatory satisfaction (unchanging \( \dot{V}_E \) and respiratory rate) or experiences such breathing discomfort that the subject is finally forced to stop exercising. Many disorders cause exertional dyspnoea and the mechanisms might be quite different in each (see Table 1 for pathophysiology and useful measurements).

Ventilatory limitations

Exercise performance might be abnormal because of a ventilatory disorder involving the airways, the gas exchange parenchyma or both. These disorders cause mismatching of alveolar minute ventilation and perfusion (\( \dot{V}_A/\dot{Q} \)), thereby decreasing the efficiency of gas exchange and increasing the physiological dead space/tidal volume ratio (\( \dot{V}_D/\dot{V}T \)) measurement. The non-uniform \( \dot{V}_A/\dot{Q} \) commonly causes an increase in the alveolar to arterial oxygen tension difference (\( Pa,O_2-Pa,O_2 \)), hypoxaemia and, less commonly, hypercapnia. In addition, mechanical limitations due to disturbances in the lung or chest wall reduce the subject's maximum ability to ventilate during exercise. If the patient becomes hypoxic, the carotid bodies are stimulated to increase \( \dot{V}_E \) still further. Thus the increase in \( \dot{V}_O_2/\dot{V}T \) and the hypoxic stimulus to breathe cause an abnormally high ventilatory requirement, while the ventilatory capacity is simultaneously reduced.

Pulmonary circulation

Defects in the pulmonary circulation cause an increase in the physiological dead-space fraction of the tidal volume because the non-perfused alveoli are not involved in gas exchange. This has the effect of eliminating teeth in the ventilation gear illustrated in Fig. 1, causing it to speed-up relative to that of the circulation and metabolic gears. As a result of the loss of perfusion to alveoli there is an increase in the \( \dot{V}_D/\dot{V}T \) measurement and a relative dilution of carbon dioxide derived from perfused alveoli by gas from non-perfused alveoli causing an increase in (arterial end-tidal) \( Pa,CO_2 \).
Gas exchange and exertional dyspnoea

Cardiovascular limitation

The most common disorder of the heart causing the patient to have a reduced maximum tolerable work rate ($VO_2 \text{ max}.$) is that resulting from inadequate perfusion of the myocardium. Chest pain is commonly the limiting factor. However, this and other disorders involving the heart can result in the lactic acidosis at a relatively low work rate, causing an increased ventilatory drive. Thus the cardiovascular limitations are not always evident as electro-cardiogram (ECG) changes, but might be best described by measurements of gas exchange and ventilation.

Anaemia

When the oxygen carrying capacity is reduced by anaemia, oxygen flow to the metabolically active tissue must be compensated for by increased blood flow. This, of course, is limited and when the anaemia is severe enough, the tissues experience an inadequacy of oxygen supply, at a relatively low work rate. The ensuing metabolic acidosis stimulates ventilation as part of respiratory compensation.

Obesity

Unless obesity is very marked, with associated pulmonary insufficiency secondary to impairment of chest wall function, this disorder is manifested only by an increased $VO_2$ for a given amount of external work. The increase in $VO_2$ is directly proportional to body weight as measured during constant work-rate studies performed on a cycle ergometer [1]. Treadmill work should reflect body weight excess to an even greater degree than cycle ergometry.

Psychogenic dyspnoea and anxiety states

Some patients manifest anxiety reactions by psychogenic dyspnoea. Because this usually becomes evident during exercise, their symptoms might be inseparable from those of someone with lung or heart disease. The patients with hysteria-type psychogenic dyspnoea can be distinguished from the patient with heart or lung disease because they manifest marked hyperventilation and respiratory alkalosis (decreased end-tidal $PCO_2$), with precisely regular breathing rate.

Other anxious patients might breathe quite irregularly at rest but, as exercise is begun and intensified, breathing becomes more regular. Their cardiorespiratory system can be determined to be normal from gas-exchange measurements during an incremental exercise test to tolerance and the $\dot{V_E} - \dot{V_O_2}$, $\dot{V_E} - \dot{V_{CO_2}} - Pa_{CO_2}$ and $\dot{V_O_2} - \text{heart rate relationships}$.

Malingering

Since ventilation is under partial volitional control, patients might attempt to falsify results by hypoventilating or hyperventilating. However, they cannot maintain these factitious responses. Consequently, there are large swings in ventilation rate and end-tidal $PCO_2$, patterns not observed when there is an organic basis for the exercise limitation.

Deconditioning

When individuals become sedentary, they also become deconditioned so that they develop a lactic acidosis at a low work rate. The anaerobic threshold, while low, is usually still at levels which enable the patient to walk at a normal pace without developing a lactic acidosis. This contrasts with patients with significant cardiovascular impairment. In the latter, the lactic acidosis might be present while performing the mildest forms of exercise. The deconditioned state is also reflected by a relatively high heart rate to achieve the metabolic requirement.

Therapeutic considerations

While exercise can be limited due to symptoms of pain, fatigue or dyspnoea, it is dyspnoea which generally limits patients with respiratory disease and many patients with cardiovascular disease.

The factors that determine the ventilatory requirement of the patient are now well defined. They include (1) the metabolic requirement to perform the work, more specifically, carbon dioxide production (since alveolar ventilation is proportional to this function), (2) $V_D/V_T$, i.e. the fraction of the breath requirement to ventilate the functional dead space, and (3) the level at which arterial $PCO_2$ is regulated, alveolar ventilation being hyperbolically related to the $PCO_2$ at a given $VCO_2$ [20].

Exertional dyspnoea can be thought of as a balance between the ventilatory requirement to do work (drive to breathe) and the ventilatory capacity of the patient (Fig. 2). The reflex drives which are thought to be important determinants of ventilation are beyond the scope of this discussion and the reader is referred to the excellent review by Guz [21] for information on this topic. When the ventilatory requirement is high relative to the ventilatory capacity, then the
VENTILATORY REQUIREMENT

VENTILATORY CAPACITY

AT

Fig. 2. Diagram illustrating the importance of the balance between ventilatory requirement and ventilatory capacity in the symptom of dyspnoea. Dyspnoea can be caused by either a decreased ventilatory capacity or an increased ventilatory requirement. Treatment of dyspnoea is directed at increasing ventilatory capacity or reducing the ventilatory requirement or both. AT, Anaerobic threshold.

patient complains of breathlessness. Thus the pathophysiological states which cause the patient to be exercise-limited due to exertional dyspnoea have an excessive ventilatory requirement (drive) or reduced ventilatory capacity or both. The patient with obstructive lung disease exemplifies a disorder with both an increased ventilatory requirement and reduced ventilatory capacity. The ventilatory requirement is increased because of a high $V_D/V_T$ consequent to non-uniform ventilation/perfusion relationships and, commonly, hypoxic stimulation; the ventilatory capacity is reduced because of airflow limitation.

The imbalance in ventilatory requirement and ventilatory capacity appears to be the essential element in the symptom of dyspnoea. Dyspnoea can be reduced, if not eliminated, by therapeutic manoeuvres which increase ventilatory capacity, i.e. bronchodilators or breathing exercises, or reduce the ventilatory requirement, i.e. increase the anaerobic threshold, reduce $V_D/V_T$ or oxygen breathing allowing $P_aCO_2$ to rise during exercise (Fig. 2).

Despite the clear dependency of the ventilatory and cardiovascular responses on the metabolic requirement to perform work, it is remarkable that most hospital exercise laboratories do not measure either oxygen consumption or carbon dioxide production or even ventilation when assessing patients’ exercise limitations. Some extrapolate metabolic performance from heart rate or other indirect means. These indirect methods provide little more than a guess of the true metabolic requirements. The 1980s should see the development of a common exercise laboratory in all hospitals capable of measuring exercise limitation in patients limited by either cardiovascular or respiratory disorders. The difficulties in making the essential measurements in ventilation and gas exchange during exercise have now been overcome with development of reliable transducers and relatively inexpensive microprocessors to do the measurements and computations which heretofore required too much of the physician’s time to perform. Such exercise laboratories will not necessarily be under the purview of the cardiologist or the pulmonary physician, but rather the physician with the broadest appreciation of the physiological requirements of exercise.

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References
Gas exchange and exertional dyspnoea


