Anaerobic threshold and respiratory gas exchange during exercise

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Almost a half-century ago, Hill, Long, and Lupton (12) recognized that “a study of the respiratory quotient, if undertaken with sufficient caution, may throw light, not so much on the bodies being oxidised as on the acid-base changes occurring as a result of exercise and recovery.” Harrison and Pilcher (11) and Pilcher, Clark, and Harrison (23) later demonstrated that patients with heart failure developed metabolic acidosis and, consequently, a high respiratory gas exchange ratio at low work rates. They were also able to induce this phenomenon by exercising patients with heart disease who had limited work capacity but who were not in overt failure at the time. In more recent years Issekutz and Rohdahl (17), Issekutz, Birkhead, and Rohdahl (16), and Naimark, Wasserman and McIlroy (22) were able to compute the gas exchange ratio breath-by-breath during exercise, by measuring expired N₂ and CO₂ concentrations with rapidly responding gas analyzers. Nairnark et al. (22) compared the arterial blood lactate and bicarbonate concentrations with the breath-by-breath changes in R and found the latter to reflect, reliably, the metabolic acidosis of exercise. Wasserman and McIlroy (26) confirmed these observations and applied this technique to the determination of the anaerobic threshold in a group of patients with heart disease. More recently, Cloke and Campbell (6) have attempted to apportion the R increase during exercise, respiratory and blood buffering components.

However, in spite of the potential advantage of detecting the work rate at which a metabolic acidosis occurs during the performance of an incremental exercise test, the anaerobic threshold has not been utilized widely for patient evaluation due, in large part, to technical difficulties with the N₂ analyzer. The introduction of reliable rapidly responding oxygen analyzers and on-line computer processing has enabled us to compute and visualize the anaerobic threshold, as it occurs during the performance of a test. This has expanded our understanding of the disturbances in gas exchange associated with the exercise metabolic acidosis.

It is now evident that the increase in R caused by the buffering of lactic acid by sodium bicarbonate, is transient and occurs only while lactate is increasing and HCO₃⁻ is decreasing in concentration. Furthermore, other bloodless approaches to the measurement of the anaerobic threshold have become evident. End-tidal CO₂ (PET₂) and O₂ tensions (PETₒ₂), when measured simultaneously, have also been found to be sensitive indicators of the anaerobic threshold during incremental work tests. It is also now evident that exercise above the anaerobic threshold results in altered O₂ uptake kinetics, with a delay in the O₂ uptake steady-state time and an increase in the O₂ deficit and debt (1, 28).

We find the anaerobic threshold to be an invaluable concept in understanding changes in gas exchange during exercise and work performance capabilities in normal subjects.
The relationship between oxygen supply and lactic acid production are related by the Hill-Meyerhof concept of inadequacy in O₂ transport (14). Considerations are a) work efficiency is constant, i.e., doubling the work rate requires doubling the high-energy phosphate utilized for muscle contraction (5), b) the work rate determines the number of muscle units contracting (3), and c) control of the local circulation at the exercising muscle level is predominantly determined by the effects of vasodilator metabolites on the vascular resistance (19).

If the local circulation is adequate for the work rate being performed, all of the energy requirements may be supplied by ATPs generated by aerobic mechanisms. However, if the number of muscle units which must contract to generate the required power exceeds the oxygen delivery and exhausts the O₂ stores, the oxygen level will drop to critical levels in each muscle unit and prevent the ATP, which is needed for the muscle contraction, from being generated at an adequate rate by the respiratory enzymes in the mitochondria. This will result in increased anaerobic glycolysis to sustain the availability of ATP. The consequence is an increased rate of lactic acid production.

The physiological changes in respiratory gas exchange resulting from the inadequate O₂ supply for the energy transformations are, as we have measured them, described in Fig. 1. The first consequence of the inadequate O₂ supply is the formation of lactic acid. Because of its low pK, lactic acid will be more than 99% dissociated and buffered predominantly by the bicarbonate system (27). This is a highly effective buffer system because of the volatile nature of the acid component. CO₂ can be readily exhaled into the atmosphere, thereby preventing accumulation of this acid in the body tissues. The additional CO₂ formed by this buffering is exhaled via the lungs, resulting in an increase in VCO₂ and R. A stimulus resulting from the increase in VCO₂ provides an additional ventilatory stimulus. The decrease in local tissue and blood bicarbonate results in a component of respiratory compensation for the metabolic acidosis.

Failure to supply the quantity of O₂ required for the work rate being performed alters O₂ uptake kinetics (28). If the subject could do the work completely aerobically, the steady-state VO₂ would be predicted by the work efficiency and the work rate. However, if all the energy required cannot be provided by reactions involving molecular oxygen, the oxygen uptake would be lower than expected for the work being performed, but it would gradually increase as the circulation readjusts to meet the energy demands. Redistribution of blood flow, which contributes to the increase in VO₂ during work with an anaerobic component, is probably secondary to the regional acidosis and hypoxia of the heavily working muscles (19). Thus, the steady-state time for VO₂ is delayed during a constant work rate above the anaerobic threshold. This contrasts with the VO₂ pattern for the same work rate performed by a subject who is more fit and is able to meet all the energy requirements with reactions involving molecular oxygen (28).

METHODS

Eighty-five normal subjects⁵ between 17 and 91 years of age were given incremental exercise tests. Studies on patients with cardiac disease of functional significance were contrasted with those of the normal subjects.

Expired airflow and CO₂ and O₂ tensions at the mouth were continuously measured and recorded. The expired airflow was measured by use of a Fleisch model 3 pneumotachograph (linear through peak flows of 600 liters/min at normal exercise respiratory frequencies) and Statham model PM97 strain gauge. Expired CO₂ and O₂ were sampled at the mouthpiece and measured with a Beckman model M-211 oxygen analyzer, respectively. There was an 0.08- to 0.12-sec delay in each measurement. The 90% response time of the instrument in the case of CO₂ was 0.160 and 0.200 sec in the case of O₂. More recently, we have used a mass spectrometer (Perkin-Elmer, Pomona, Calif.) with an instrument 90% response time of less than 0.06 sec.

The electrocardiogram was also continuously monitored on an oscilloscope and the heart rate continuously recorded. Some subjects had arterial blood gas and pH measurements using Radiometer equipment (London Company, Cleveland, Ohio) and arterial lactate and pyruvate measurements by enzymatic techniques (4, 15). Blood was sampled as previously described (27).

Sixty-one subjects were studied during an incremental work test in which the initial work rate consisted of 4 min of pedaling on an unloaded ("0") w) cycle ergometer

⁵ These subjects were predominantly sedentary, but included fit subjects as they became available for the study.
(Lanooy, Instrumentation Associates, N.Y.) following which the work rates were incremented 15 w every minute. In the 24 other subjects, 25-w work rate increases were used.

The expired airflow, CO₂ and O₂ tensions, and heart rate measurements were recorded on a Beckman type RM Dynograph and the data simultaneously transmitted to a Varian 620i minicomputer. The computed breath-by-breath Vₑ, VₑCO₂, VₑO₂, and R (2) were displayed on line on the recorder in addition to the directly recorded expired flow, and CO₂ and O₂ tensions in the breath and heart rate. The recorder speed of 10 mm/min permits the investigator to easily view the work rate at which CO₂ production and minute ventilation deviate from linearity as compared with the rate of rise in oxygen consumption as work rate is incremented. This nonlinearity, the associated increase in R, and the decrease in the difference in O₂ tension between inspired and end-tidal values without a comparable change in end-tidal CO₂ (hyperventilation with respect to O₂) were used to detect the anaerobic threshold.

All data were stored on digital tape during the test so that they might be retrieved and displayed on the recorder through the digital-to-analog converter of the computer for more detailed study using scaling factors which might be more appropriate than those used for the on-line test. The processed data can be played back at any speed, but we find that 1 min of study being displayed on 3–12 mm of paper is optimal to recognize those linearity changes of critical significance in detecting the anaerobic threshold. The data processing system is described in a previous report.

All gas analyzers were calibrated before the test with tank gases analyzed by the micro-Scholander method (24). This procedure was repeated routinely immediately after each test to ensure that the calibration factors had not changed during the course of the study.

RESULTS

A. Gas exchange ratio (R) during constant, suprathreshold work. Measurement of R, breath-by-breath, as related to time for work above the anaerobic threshold, after an initial 4-min period of unloaded cycling, is shown in Fig. 2. Note that the gas exchange ratio increases to its peak value at the time that the rate of bicarbonate concentration change is at its maximum. When the bicarbonate concentration no longer changes, or changes minimally, the gas exchange ratio returns to a lower value and stays at this reduced level in spite of the fact that the same work rate is continued. Thus, to see the effects of anaerobic metabolism by studying R, one must look at it during the time of maximal bicarbonate change. R will not remain elevated above the metabolic RQ if the bicarbonate concentration change had already occurred. R should again become equal to the metabolic RQ when the CO₂ stores reach a new steady state. This limits the usefulness of the measurement of R when looking for the anaerobic threshold (AT) during incremental work tests of relatively long duration.

B. Work duration for an incremental work test to detect the anaerobic threshold. In the interest of time and avoiding undue stress to the patient, we concerned ourselves with how short a period we might use for each work rate in an incremental work test, in order to detect the anaerobic threshold. We compared the lactate, lactate/pyruvate ratio, and acid-base parameters for a 1- and 4-min incremental work test (Fig. 3). Note that the magnitudes of the lactate increase and the bicarbonate decrease are less for the 1-min test than for the 4-min test.
FIG. 4. Measurements of ventilatory gas exchange, breath-by-breath, for the 1- and 4-min incremental work tests described in Fig. 3. The respiratory measurements for this same study (Fig. 4) signal the occurrence of metabolic acidosis at the work levels predicted from the lactate and bicarbonate changes. In either the 1- or 4-min incremental work test, the non-linear increase in $\dot{V}E$ and $\dot{V}CO_2$ and the decrease in $\Delta PETCO_2$ (difference between the inspired and end-tidal $O_2$ tensions) without any (1-min test) or a smaller change (4-min test) in PETCO_2 becomes evident at the AT. For the reasons described in section A of RESULTS, the increase in R is greater during the 1-min incremental test than the 4-min incremental test. For this reason, and the obvious advantages of the shorter test, we have elected to use a 1-min incremental work test on a cycle ergometer as a standard work test in our laboratory. Increments of shorter duration (<30 sec) tend to give misleadingly high ATs, presumably because of the availability of $O_2$ stores in tissue and venous blood and high energy phosphates which could transiently support the energetic requirements, as well as transit time delays between the tissue and the lungs.

C. One-minute incremental work test to detect the anaerobic threshold during work. One of the major advantages in measuring the respiratory variables to detect the anaerobic threshold is that it can be determined without blood sampling during the performance of the exercise test. This has special advantages in that the exercise test may be terminated soon after the anaerobic threshold is detected by the investigator. A typical record of expired airflow, $CO_2$, $O_2$, and heart rate and the on-line computed values for $\dot{V}E$, $\dot{V}CO_2$, $\dot{V}O_2$, and R are presented in Fig. 5 for a normal subject. The AT can be detected by the direct recordings of $PETCO_2$ and $\Delta PETCO_2$ in which $\Delta PETCO_2$ is noted to decrease while $PETCO_2$ does not change. The respiratory control mechanism appears to be sensitively set to regulate $CO_2$ so that the nonproportional increase in $VCO_2$ results in a parallel increase in $\dot{V}E$ (Fig. 5). $\dot{V}E$ increases out of proportion to $VO_2$ above the AT with the consequent increase in $PETO_2$ or decrease in $\Delta PETO_2$. While R increases at a faster rate at work rates above the AT, the AT is visualized better from the changes in $PETCO_2$ and $PETO_2$ and the nonlinear increases in $VE$ and $VCO_2$. The reason for this is probably due to the increase in the metabolic RQ as work rate is incremented (1), thus making the additional $CO_2$ from HCO_3~ more difficult to see, particularly when incorporated into the R measurement at high VCO_2.

D. Selected patient studies. Figure 6 shows the results of studies on three patients. The first patient is a 24-year-old laborer with a congenital cyanotic heart lesion (Ebstein's anomaly with an atrioseptal defect). He claimed to have no limitation in exercise capacity. His congenital heart disease was discovered, incidentally, when he visited a doctor for an orthopedic problem. His hematocrit was 80 at the time of the study and his arterial $O_2$ tension was 44 mm Hg and this did not change with this exercise. His anaerobic threshold can be readily determined from the record to be 60 w. This is less than one might expect from a young normal male at his age engaged in physical labor (Fig. 7) and with the high $O_2$ content of his blood (approx 30 vol %). However, it is compatible with only a small reduction in the anaerobic threshold and is in agreement with his class I functional capacity.
The second patient, a 53-year-old female patient with mitral valve disease, who is limited with more than ordinary activity, is of functional class II. Her anaerobic threshold is 30 w.

The third patient is a 33-year-old female patient with mitral stenosis and insufficiency and is limited in performing ordinary household tasks (functional class III). She demonstrates respiratory evidence of metabolic acidosis at the lowest work rates ("0" w) and has a relatively fixed oxygen consumption, even though the work rate is incremented, until her highest work rate is reached. The most likely explanation for her VO2 pattern is her limited cardiac output, similar to that described by Meakins and Long (21). The further increase in VO2, after the relatively flat phase, might be the result of redistribution of her restricted cardiac output as a consequence of tissue hypoxia and acidosis. However, her heart rate parallels the changes in oxygen uptake (she was in normal sinus rhythm at the time of the study). Use of cardiac drugs such as propranolol and digitals might have prevented the normal heart rate response and therefore the VO2 increase.

E. Anaerobic threshold in normal subjects. Values for the anaerobic threshold in 85 normal subjects between the ages of 17 and 91 years of age, range between 45 and 180 w depending on age and physical fitness (Fig. 7), with one exception. This is a 33-year-old male who had a 25-w incremental work test with an AT between 25 and 50 w (plotted at 25 w). The lower limit of normal appears the same for all age groups and both sexes. It is interesting to note that this lower value is equivalent to a VO2 of approxi-
mately 1 liter/min, the $V_O_2$ needed by the typical adult to walk at a normal speed (approx. 2.5 mph) on the level.

**F. Reproducibility of the anaerobic threshold measurement.** The reproducibility of the gas exchange parameters which deviate in association with the metabolic acidosis of exercise are illustrated in Fig. 8 for a subject whose degree of training has been relatively constant. Repeated studies during the same day and over the period of 9 months are virtually identical. In this case, the increase in $R$ is least specific of the gas exchange methods for measuring the anaerobic threshold. The reason for this is that the metabolic $RQ$ increases with work intensity (1) and that the $CO_2$ released from buffering is small compared to the metabolic $CO_2$ in the fit subject, such as used in this study. Several of us have had our AT measured at various times over prolonged periods. Our impression is that considerable deviations in training, or activity, are required to effect a significant change in the anaerobic threshold.

**G. Effect of developing hypoxemia during exercise on the AT measurement.** Since a decreasing arterial $O_2$ tension ($P_aO_2$) during exercise will stimulate breathing over that resulting from the exercise itself, we repeat the 1-min graded exercise study during high oxygen breathing in any patient in whom we suspect arterial hypoxemia during exercise. Such a case is illustrated in Fig. 9. This patient is a 23-year-old male patient with pulmonary alveolar proteinosis. While his resting $P_aO_2$ was 73 while breathing air, prelavage, his $P_aO_2$ progressively decreased during exercise (Fig. 9). His AT would be estimated at 45 w by the criterion of the non-linear increase in $V_E$. However, the decrease in $P_{ET}CO_2$ at this same work rate suggests a non-$CO_2$ stimulus to this hyperpnea. Repeating the incremental test during 100% $O_2$ breathing results in no difference in $V_E$ in this study as compared to the air-breathing study until 45 w is reached (Fig. 9). In contrast to the air-breathing study, $V_E$ is observed to increase linearly until 75 w in the case of $O_2$ breathing. Thus we would attribute the nonlinear hyperpnea between 45 and 75 w of the air breathing study to be due to superimposed arterial hypoxemia, while the “actual” AT is between 60 and 75 w.

Since it is conceivable that 100% $O_2$ might itself increase the AT by a small amount by increasing the $O_2$ content of the blood, probably an inspired $O_2$ tension just high enough to keep the exercise $P_aO_2$ in the 80-120 mm Hg range should be used to unmask the AT from the hypoxic hyperpnea in the patient who develops hypoxemia during exercise. In the case of this patient, we had the opportunity to re-study him (Fig. 9) after treatment with bilateral lung lavage, as previously described (25). Now he no longer experiences exercise arterial hypoxemia and its hyperventilation during air-breathing exercise. Thus, it was possible to confirm his AT at 60–75 w, as was observed during $O_2$ breathing prior to treatment. Also repeating the study during 100% $O_2$ breathing, after lavage, did not measurably influence the AT.

**DISCUSSION**

A great deal of evidence has been accumulated over the last 40 years which demonstrate that the elevation of lactate in the blood during exercise is related to work intensity and that the increase occurs in normal subjects above critical work levels (20, 21). The more fit the subject, the lower the lactate level at a given work rate (Table 1) (8, 9), while patients with limited cardiovascular function have higher lactate concentrations than normal subjects at the same work rate (7, 10, 18, 21). The findings support the original hypothesis of Hill and Lupton (13) that lactic acid is formed during exercise in the presence of tissue hypoxia; this process allows anaerobic mechanisms for ATP generation.

Because of the low $pK$ of lactic acid, it would be almost totally buffered in the blood in the physiological pH range, with bicarbonate decreasing in approximately equimolar
TABLE 1. Δ Lactate, Δ bicarbonate, minute ventilation (VE), change in gas exchange ratio from rest (ΔR), and heart rate at a work rate of 200 w

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<th>Sub</th>
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<th>Δ Bicarbonate, mEq/liter</th>
<th>VE, liters/min</th>
<th>ΔR</th>
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<tr>
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quantities (27). It is because of this buffering that VO₂ increases out of proportion to VO₂.

The sensitivity of the respiratory control mechanism to Paco₂ and pH makes VE one of the prime gas exchange parameters in the study of the AT. As shown in Figs. 4 and 5, VE increases in response to the increase in VCO₂ while maintaining PETCO₂ constant during the 1-min incremental work test. The precision with which ventilation increases to eliminate the increased CO₂ produced from buffering, without letting PETCO₂ change, becomes manifest in a decrease in ΔPETO₂. Thus a simultaneous study of PETCO₂ and PETO₂ is a very sensitive way of detecting the AT. These arc measurements which can be recorded directly from transducers and do not require a computer for special computations.

The simultaneous measurements of PETCO₂ and PETO₂ also permit the investigator to rule out hyperventilation with regard to CO₂ as the cause for an increase in R, since the increase in R during the 1-min incremental work test is associated with an increasing PETO₂ without a concomitant decrease of PETCO₂. However, if the subject is exercised long enough at each work rate above the AT, the bicarbonate decrease becomes more manifest and ventilation is stimulated to a degree which results in a decrease in PETCO₂ and PACO₂ (Figs. 3 and 4).

The extent to which VE might reflect metabolic acidosis and cardiovascular “fitness” is shown by the studies in five subjects between 23 and 27 years of age, reported in Table 1. The measurements listed are the 6th min values for the increase in lactate above the steady state is reached within 2-3 min at low work rates, while at higher work rates the steady state is reached progressively later. Measurements of arterial blood lactate confirm that the VO₂ which reaches a delayed constant value is associated with anaerobic metabolism (28). Previous studies indicate that VO₂ would not reach a steady state until the lactate concentration no longer increases (27). Whipp and Wasserman (28) have found that if the difference in VO₂ between the 3rd and 6th min is zero. The work rate is below the subject’s AT. If the difference is a finite value, the work rate is above the AT, with the extent to which it is above the subject’s AT being estimated by the magnitude of the difference.

Use of the AT in clinical medicine, in large part, has depended upon knowing the normal values for the healthy population. Naimark et al. (22), studying patients with mitral valve disease, and Wasserman and McIlroy (26), studying a variety of other patients with heart disease, found the AT of their patients to be well below that of the lower level of our normal population. Most of their subjects had a VO₂ of less than 500 ml/min at the AT. Our normal subjects who are least fit have an AT VO₂ work equivalent of approximately 1 liter/min. Thus, it would appear that patients with functionally significant heart disease cannot exercise to the level of VO₂ needed for walking at a moderate pace without developing a lactic acidosis.

The incremental work test described here for measuring the anaerobic threshold has advantages over tests previously described because of its short duration and high sensitivity. It can be done with little stress or discomfort to the patient, and it is truly an on-line measurement.

The concept of the anaerobic threshold has been validated in a number of studies in the past. The development of rapidly responding gas analyzers and automated data processing computers has made it possible to apply the physiological knowledge which has gradually accrued, to detecting circulatory insufficiency, by noninvasive techniques. An investigator need not use all five respiratory parameters which we have described to detect the AT (Fig. 1). By far, the easiest technique would be to measure VE during an incremental exercise test and look for the point at which the VE-work rate curve becomes nonlinear.

The AT has widespread application in evaluating physical fitness in normal subjects and in detecting patients with circulatory insufficiency. However, it has limitations. For example, in patients with significant respiratory impairment, an AT may not be present. These patients may not be able to exercise to levels which are associated with lactic acidosis. However, these patients have other characteristics in their work performance test to set them apart from the patients with cardiovascular limitations. Discussion of these characteristics are beyond the scope of this presentation.

Performing an incremental exercise test during oxygen breathing is helpful in distinguishing the hyperventilation from hypoxia in patients with diffusion type abnormalities, pulmonary vascular occlusive disorders, or in other instances of hyperpnea that develop secondary to hypoxic stimulation of the peripheral chemoreceptors rather than to metabolic acidosis, as demonstrated in Fig. 9.

The anaerobic threshold is a useful concept. Its application during exercise testing should considerably increase the information gained regarding cardiovascular function in health and disease.

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References


